Original Article

The impact of age on the efficacy of radiotherapy in pleural mesothelioma patients receiving trimodality therapy: a population-based study of the SEER database

Jun Yang[1,2#], Liang Xia[1#], Hui Jie[1#], Tengyong Wang[1,2], Chenglin Guo[1], Chengwu Liu[1], Hu Liao[1], Jiandong Mei[1], Qiang Pu[1], Lunxu Liu[1]

[1]Department of Thoracic Surgery and Institute of Thoracic Oncology, West China Hospital, Sichuan University, Chengdu, China; [2]West China School of Medicine, Sichuan University, Chengdu, China

Contributions: (I) Conception and design: L Liu; (II) Administrative support: L Liu, Q Pu; (III) Provision of study materials or patients: L Xia, T Wang; (IV) Collection and assembly of data: J Yang, J Mei, C Guo, C Liu, H Liao; (V) Data analysis and interpretation: J Yang, T Wang, H Jie; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Lunxu Liu, MD, PhD, FRCS. Department of Thoracic Surgery and Institute of Thoracic Oncology, West China Hospital, Sichuan University, No. 37, Guoxue Alley, Chengdu 610041, China. Email: lunxu_liu@aliyun.com.

Background: Pleural mesothelioma (PM) is a highly aggressive tumor with poor survival outcomes. The role of additional radiotherapy for PM patients who have received surgery and chemotherapy remains controversial. In this study, we aim to evaluate the impact of age on the effectiveness of additional radiotherapy in order to identify the populations that may benefit from the trimodality therapy.

Methods: We designed a case-control study and retrospectively selected PM patients who underwent surgery and chemotherapy, with or without radiotherapy, from the Surveillance, Epidemiology, and End Results (SEER) database (2000–2019). Kaplan-Meier curves were performed to compare the overall survival (OS) and cancer-specific survival (CSS) between the surgery + chemotherapy group and the trimodality therapy group. Propensity score matching (PSM) was used to balance the clinical characteristics and reduce potential confounding effects.

Results: A total of 745 patients were selected, of which 515 received surgery + chemotherapy and 230 received trimodality therapy. For patients aged 50 to <65 years, additional radiotherapy showed better OS (3-year: 34.78% *vs.* 23.92%, P=0.02) and CSS (3-year: 36.15% *vs.* 25.46%, P=0.04) compared to surgery + chemotherapy. Similar results were observed after PSM (3-year OS: 38.76% *vs.* 26.53%, P=0.02; 3-year CSS: 40.49% *vs.* 26.92%, P=0.02). No significant benefit of radiotherapy was seen for patients aged <50 and ≥65 years, both before and after PSM.

Conclusions: Our findings reveal that trimodality therapy is associated with better OS and CSS compared to surgery + chemotherapy for patients aged 50 to <65 years. These patients might obtain a benefit from additional radiotherapy.

Keywords: Pleural mesothelioma (PM); trimodality therapy; age; Surveillance, Epidemiology, and End Results (SEER)

Submitted Jul 13, 2024. Accepted for publication Sep 06, 2024. Published online Oct 25, 2024.
doi: 10.21037/jtd-24-1111
View this article at: https://dx.doi.org/10.21037/jtd-24-1111

© AME Publishing Company.

Introduction

Pleural mesothelioma (PM) is a highly aggressive tumor arising from the serosal layer of the pleura. Due to the prolonged occult medical history, patients are often diagnosed at an advanced stage, and the median overall survival (OS) is only 8.3 months (1,2). PM is rare with an incidence ranging between 2.4 and 3.5 cases per 100,000 person-years (2). Thus, it is essential to investigate the impact of various treatment patterns on PM patients.

Based on National Comprehensive Cancer Network (NCCN) guideline, for PM patients whose clinical stages are classified as I–IIIA and histological subtypes are epitheloid or biphasic, surgery should be considered as a priority after careful evaluation (3). Many studies have shown that surgical resection can prolong the median OS of patients (4-8), however, the randomized surgical trial MARS dividing the patients into extrapleural pneumonectomy (EPP) group *vs.* no EPP group found no significant differences of OS between the two arms (9). For patients whose tumor are operable, chemotherapy is recommended for preoperative induction or postoperative adjuvant therapy. An analysis based on Surveillance, Epidemiology, and End Results (SEER) database demonstrated that patients who received chemotherapy had a survival benefit, regardless of whether they received surgery (10). Another study has also shown that the combination of surgery and chemotherapy presented a higher survival rate compared to surgery alone (11). For PM patients who are unable to undergo surgery or refuse surgical intervention, chemotherapy alone is considered the first-line treatment. A Phase III clinical trial, CheckMate 743, demonstrated that the combination of Nivolumab and Ipilimumab improved OS in patients with unresectable PM compared to standard chemotherapy regimens of platinum plus pemetrexed.

The addition of adjuvant radiotherapy for PM patients following surgery and chemotherapy is referred to as trimodality therapy. Studies have indicated that adjuvant radiotherapy following surgery can reduce the local recurrence rate in PM patients (12,13). Nevertheless, the role of additional radiotherapy remains controversial, and the data regarding are efficacy is heterogeneous. Several studies have shown survival benefits in patients who received trimodality therapy (14-16). However, a phase II trial, SAKK 17/04, failed to prove the benefit of using hemithoracic radiotherapy after EPP and chemotherapy for PM patients (17). Another study proved that the addition of radiotherapy can improve survival in patients with localized PM, but not for regional or distant PM (18).

To date, clinicopathological factors that influence the efficacy of the additional radiotherapy in PM patients have not been fully investigated. This study aims to assess the effect of age on the efficacy of additional radiotherapy by analyzing data from the SEER database. We present this article in accordance with the STROBE reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1111/rc).

Highlight box

Key findings

- Age is an important factor in the efficacy of trimodality therapy in pleural mesothelioma (PM) patients, and only patients aged 50 to <65 years would benefit from additional radiotherapy.

What is known and what is new?

- The role of additional radiotherapy to PM patients remains controversial and the data are heterogenous.
- In a cohort study of 745 PM patients, we found that patients aged 50 to <65 years received trimodality therapy showed better overall survival (OS) and cancer-specific survival (CSS) compared to patients receiving surgery + chemotherapy, with or without propensity score matching.

What is the implication, and what should change now?

- Our findings suggest that PM patients aged 50 to <65 years may benefit from radiotherapy, but not for other age groups, and this result could provide a reference for clinicians to choose whether to add radiotherapy to patients.

Methods

Data source and study population

The SEER database is an authoritative cancer statistics database based on the American population. Clinical data were downloaded using the SEER Stat 8.4.0 (19). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

We retrospectively selected PM patients from 2000 to 2019. The ICD-O-3 histological codes we used were 9050 for unclear type, 9052 for epithelioid type, and 9053 for biphasic type. The inclusion criteria were: (I) patients aged 18 years or older; (II) patients were pathologically diagnosed; (III) patients received surgery + chemotherapy ± radiotherapy; (IV) the survival record was complete, and patients had a survival duration of more than 0 days. The exclusion criteria were: (I) the left and right sides of the

© AME Publishing Company.

tumor were unclear; (II) uncertain survival duration or survival state; (III) suffering from other malignant tumors; (IV) unclear information on radiotherapy.

Variables and outcomes

The key variables for the selected patients included age, sex, race, year of diagnosis, laterality, extent of disease, extent of surgery, and histological subtype of PM. The outcomes were OS and cancer-specific survival (CSS). The OS was defined as the follow-up duration from diagnosis to the last follow-up or the death due to any reason. And the CSS was defined as the follow-up duration from diagnosis to the last follow up or the death due to the diagnosed PM.

Statistical analysis

Propensity score matching (PSM) was used to balance the clinical characteristics between the surgery + chemotherapy and the trimodality therapy groups to reduce potential confounding effects. R package "MatchIt" was used to implement the "nearest neighbor matching" method. For those aged <50 and ≥65 years, the ratio was 2:1, and for those aged 50 to <65 years, the ratio was 1:1. The matched variables included: sex, race, year of diagnosis, histological subtype, laterality, extent of disease, and surgery extent. Sensitivity analysis was also conducted by excluding patients with certain characteristics.

The mean ± standard deviation and quartile were used to describe normally distributed variables and skewed continuous variables respectively. For appropriate continuous variables, Student's *t* test or Wilcoxon signed rank test was used for analysis, while Chi-squared test was applied for categorical variables. Comparison of outcomes between the surgery + chemotherapy group and the trimodality therapy group was performed using Kaplan-Meier curves, with the log-rank test to assess for significance. The hazard ratio (HR) and 95% confidence interval (CI) were used to describe the results of the univariable and multivariable analyses. Statistical software R (R-4.0.3) was used in this study. All P values were two tailed and P<0.05 was defined as statistically significant.

Results

Baseline characteristics

A total of 745 patients were selected in this study, of whom 515 received surgery + chemotherapy and 230 received trimodality therapy. The median surveillance time was 24 months (interquartile range: 10–30 months). The baseline demographic and clinicopathological characteristics were shown in *Table 1*. The mean age were 65.8±9.6 and 63.6±9.2 years for the surgery + chemotherapy group and the trimodality therapy group, respectively. Patients who received trimodality therapy were younger (P<0.001) and were diagnosed more recently (P=0.04) than those who received surgery + chemotherapy. In addition, patients who received trimodality were more likely to undergo extensive surgery than patients who received surgery + chemotherapy (47.4% *vs.* 33.0%, P<0.001). Except for the aforementioned differences, there were no significant differences in other baseline characteristics between the two groups.

Survival analysis of all patients who received surgery + chemotherapy vs. trimodality therapy

There was no statistical difference in CSS (P=0.32) and OS (P=0.10) between surgery + chemotherapy group and trimodality therapy group when all patients were included in the analysis (*Figure 1*). The 1-year OS for surgery + chemotherapy and trimodality therapy groups is 66% and 77%, respectively. However, 3 years after the diagnosis of PM, the survival rates of patients in the two groups dropped rapidly, becoming 21% and 26%, respectively. And by the fifth year the survival rates were only 11% and 13%, respectively.

Survival analysis stratified by age before PSM

All patients were divided into three age groups: <50, 50 to <65 and ≥65 years, and the baseline characteristics of each age group are presented in *Table 2*. As shown in the table, compared with the <50 group or the ≥65 group, more patients in the 50 to <65 group underwent radiotherapy (proportion: <50 *vs.* 50 to <65 years: 25.0% *vs.* 40.1%, P<0.001; ≥65 *vs.* 50 to <65 years: 25.4% *vs.* 40.1%, P<0.001). The results of survival analysis are shown in *Figure 2*, and patients who received trimodality therapy were associated with significantly better OS and CSS compared to surgery + chemotherapy management in the 50 to <65 group (3-year OS: 34.78% *vs.* 23.92%, P=0.02; 3-year CSS: 36.15% *vs.* 25.46%, P=0.04; *Figure 2C*,*2D*). However, this benefit was not observed in the <50 group (*Figure 2A*,*2B*) or the ≥65 group (*Figure 2E*,*2F*).

© AME Publishing Company.

Table 1 Baseline and clinicopathological characteristics of patients received surgery + chemotherapy or trimodality therapy

Characteristics	Surgery + chemotherapy (n=515)	Trimodality therapy (n=230)	P value
Age (years)			<0.001
<50	33 (6.4)	11 (4.8)	
[50, 65)	167 (32.4)	112 (48.7)	
≥65	315 (61.2)	107 (46.5)	
Mean ± SD	65.8±9.6	63.6±9.2	0.009
Sex			0.88
Female	119 (23.1)	55 (23.9)	
Male	396 (76.9)	175 (76.1)	
Race			0.23
White	466 (90.5)	214 (93.0)	
Black	28 (5.4)	6 (2.6)	
Others[†]	21 (4.1)	10 (4.3)	
Year of diagnosis			0.04
2000–2004	72 (14.0)	46 (20.0)	
2005–2009	129 (25.0)	59 (25.7)	
2010–2014	147 (28.5)	71 (30.9)	
2015–2019	167 (32.4)	54 (23.5)	
Laterality			0.50
Right	302 (58.6)	128 (55.7)	
Left	213 (41.4)	102 (44.3)	
Extent of disease			0.16
Localized	42 (8.2)	10 (4.3)	
Regional	156 (30.3)	69 (30.0)	
Distant	317 (61.6)	151 (65.7)	
Surgery extent[‡]			<0.001
Incomplete	252 (48.9)	68 (29.6)	
Complete	93 (18.1)	53 (23.0)	
Extended	170 (33.0)	109 (47.4)	
Histological subtype			0.13
Epithelioid	315 (61.2)	147 (63.9)	
Biphasic	79 (15.3)	43 (18.7)	
NOS	121 (23.5)	40 (17.4)	

Values are numbers (percentages) unless otherwise stated, and percentages may not total 100 because of rounding. [†], others include American Indian/AK Native, Asian/Pacific Islander. [‡], incomplete surgeries are code 30: simple/partial surgical removal of primary site and code 50: surgery stated to be "debulking"; complete surgery is code 40: total surgical removal of primary site; extended surgery is code 60: radical surgery and partial or total removal of the primary site with a resection in continuity with other organs. NOS, not otherwise specific.

© AME Publishing Company.

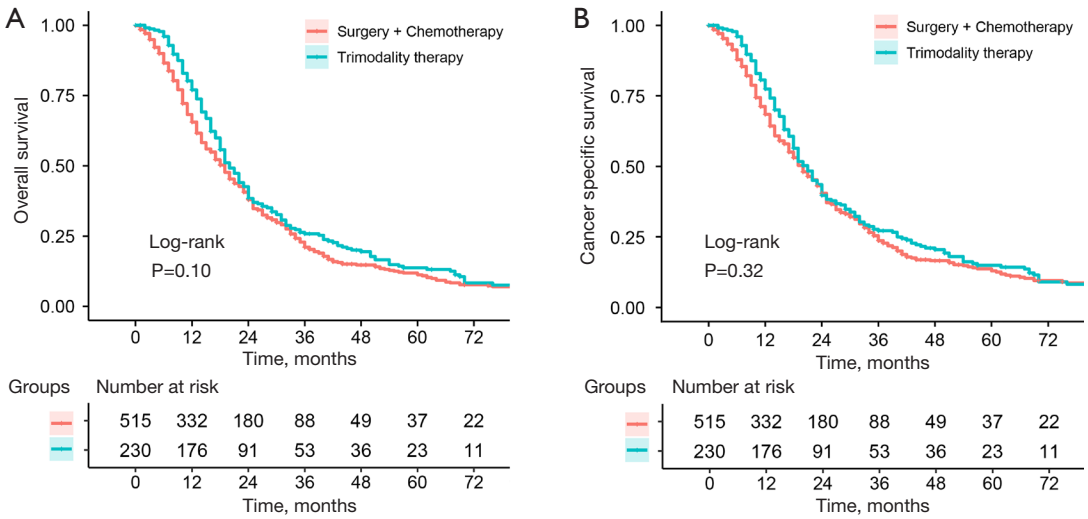

Figure 1 Survival analysis for all patients with pleural mesothelioma who received surgery + chemotherapy *vs.* trimodality therapy.

Survival analysis stratified by age after PSM

Before PSM, we conducted a comprehensive analysis of all relevant clinical factors to investigate whether there were potential clinicopathological factors that might influence the effectiveness of additional radiotherapy, summarizing the results in a forest plot (Figure S1). The results indicated that additional radiotherapy was a protective factor in patients aged 50 to <65 years (HR: 0.75, P=0.04), which aligns with our previous results.

After PSM, there were no statistically significant differences between the surgery + chemotherapy and trimodality therapy groups in baseline characteristics in each age group (Table S1, Figure S2). The results shown in *Figure 3* still favored trimodality therapy in patients aged 50 to <65 years when compared to surgery + chemotherapy management (3-year OS: 38.76% *vs.* 26.53%, P=0.02; 3-year CSS: 40.49% *vs.* 26.92%, P=0.02; *Figure 3C,3D*). Similarly, this result was still not observed in patients aged <50 years (*Figure 3A,3B*) or ≥65 years (*Figure 3E,3F*).

Sensitivity analysis

Given that biphasic patients undergo surgery only when the sarcomatoid component is <10%, and the database does not contain this specific data, we performed a sensitivity analysis by excluding biphasic patients from the analysis of matched patients. We found consistent results with the previous findings. Patients in the 50 to <65 years age group experienced survival benefits from trimodality therapy (OS: P=0.02, CSS: P=0.04; Figure S3), whereas no significant benefits were observed in other age groups.

To investigate the impact of surgery extent on our finding, we categorized all patients into complete and incomplete surgery groups and compared the survival between patients undergoing surgery + chemotherapy or trimodality therapy across different ages within the groups. The complete surgery group comprised both previously defined complete and extended surgeries; and PSM was also utilized (Tables S2,S3). The results of the survival analysis are shown in Figure S4. In the complete surgery group, additional radiotherapy demonstrated consistent benefits in patients aged 50 to <65 years (P=0.03; Figure S4B), while in the incomplete surgery group, no benefit of additional radiotherapy was observed across all age groups (Figure S4D-S4F). Notably, in the age group below 50 years in the complete surgery group, additional radiotherapy indicated unfavorable survival outcomes (P=0.02; Figure S4A). However, given the small sample size, caution is advised in interpreting this result.

Interaction analysis of additional radiotherapy and age

In order to more clearly explain the influence of age on the efficacy of trimodality therapy, patients were subdivided into <50, 50–54, 55–59, 60–64, 65–69, 70–74, and ≥75 years, for a total of seven age groups. The interaction between

© AME Publishing Company.

Table 2 Baseline characteristics of patients stratified by age

Characteristics	Age groups (years)			P value		
	<50	[50, 65)	≥65	<50 *vs.* [50, 65)	<50 *vs.* ≥65	[50, 65) *vs.* ≥65
Sex				0.01	<0.001	0.002
Female	21 (47.7)	78 (28.0)	75 (17.8)			
Male	23 (52.3)	201 (72.0)	347 (82.2)			
Race				0.001	0.001	0.22
White	33 (75.0)	258 (92.5)	389 (92.2)			
Black	6 (13.6)	14 (5.0)	14 (3.3)			
Others[†]	5 (11.4)	7 (2.5)	19 (4.5)			
Year of diagnosis				0.75	0.14	0.006
2000–2004	11 (25.0)	52 (18.6)	55 (13.0)			
2005–2009	11 (25.0)	81 (29.0)	96 (22.7)			
2010–2014	11 (25.0)	80 (28.7)	127 (30.1)			
2015–2019	11 (25.0)	66 (23.7)	144 (34.1)			
Laterality				0.78	0.80	>0.99
Right	24 (54.5)	162 (58.1)	244 (57.8)			
Left	20 (45.5)	117 (41.9)	178 (42.2)			
Extent of disease				0.14	0.15	0.74
Localized	0 (0.0)	20 (7.2)	32 (7.6)			
Regional	16 (36.4)	79 (28.3)	130 (30.8)			
Distant	28 (63.6)	180 (64.5)	260 (61.6)			
Surgery extent[‡]				0.42	0.62	0.20
Incomplete	21 (47.7)	108 (38.7)	191 (45.3)			
Complete	6 (13.6)	57 (20.4)	83 (19.7)			
Extended	17 (38.6)	114 (40.9)	148 (35.1)			
Radiotherapy				0.08	>0.99	<0.001
Surgery + chemotherapy	33 (75.0)	167 (59.9)	315 (74.6)			
Trimodality therapy	11 (25.0)	112 (40.1)	107 (25.4)			
Histological subtype				0.17	0.10	0.91
Epithelioid	24 (54.5)	174 (62.4)	264 (62.6)			
Biphasic	5 (11.4)	45 (16.1)	72 (17.1)			
NOS	15 (34.1)	60 (21.5)	86 (20.4)			

Values are numbers (percentages), and percentages may not total 100 because of rounding. [†], others include American Indian/AK Native, Asian/Pacific Islander. [‡], incomplete surgeries are simple/partial surgical removal of primary site and surgery stated to be "debulking"; complete surgery is total surgical removal of primary site; extended surgery is radical surgery and partial or total removal of the primary site with a resection in continuity with other organs. NOS, not otherwise specific.

© AME Publishing Company.

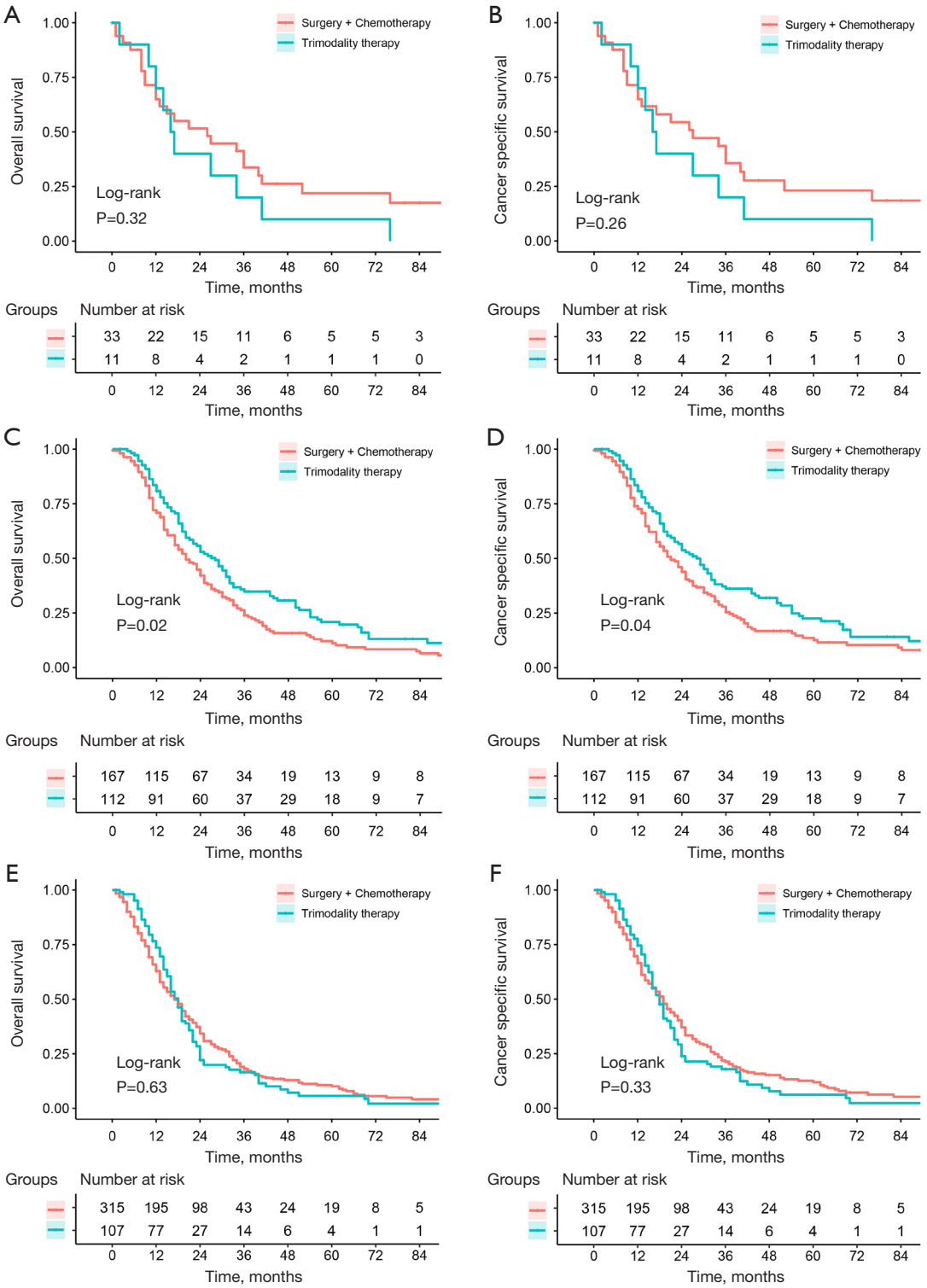

Figure 2 Survival comparison of pleural mesothelioma patients who received surgery + chemotherapy *vs.* trimodality therapy in different age groups before matching. (A,B) <50 years group; (C,D) 50 to <65 years group; (E,F) ≥65 years group.

© AME Publishing Company.

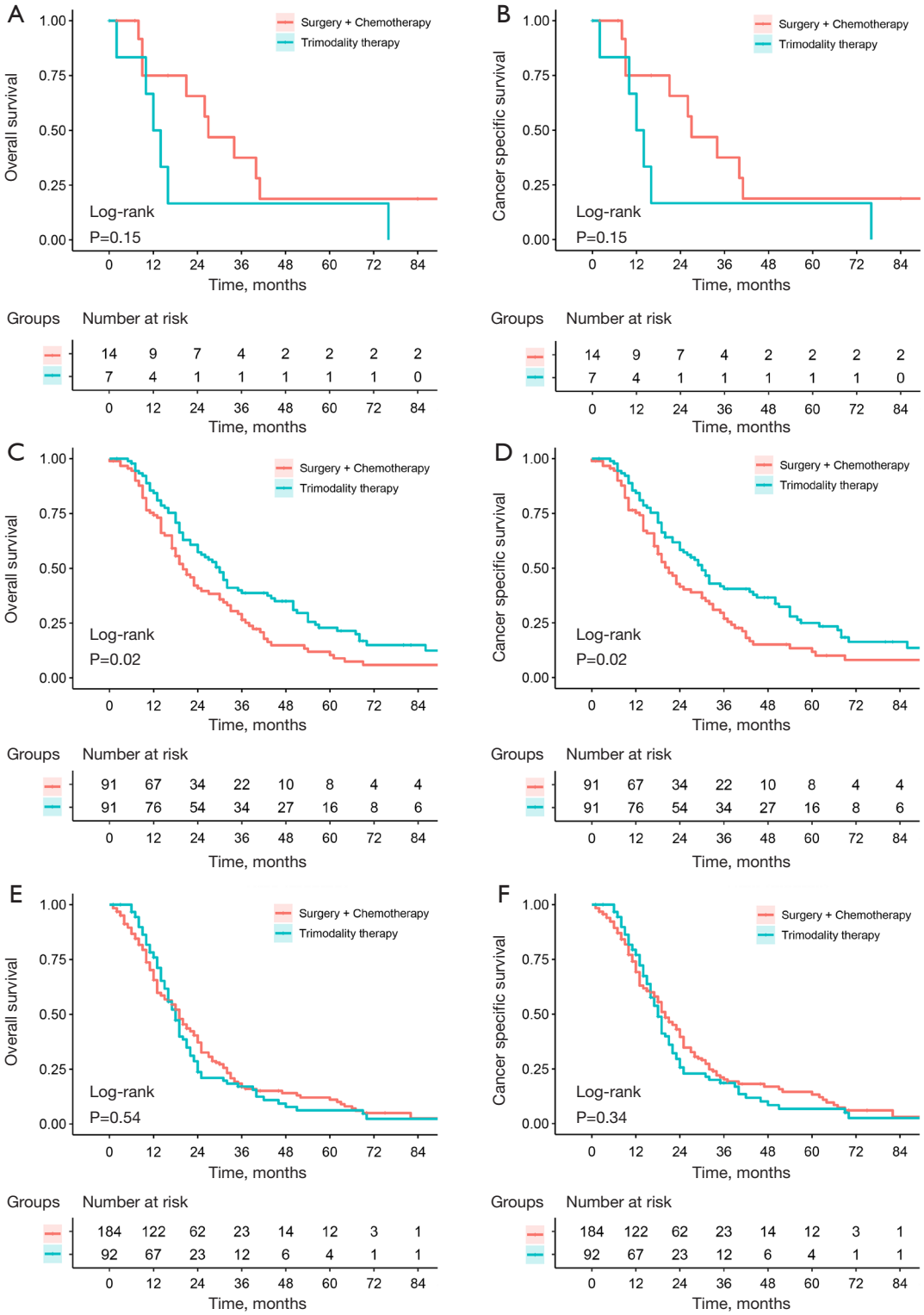

Figure 3 Survival comparison of pleural mesothelioma patients who received surgery + chemotherapy *vs.* trimodality therapy in different age groups after match. (A, B) <50 years group; (C, D) 50 to <65 years group; (E,F) ≥65 years group.

© AME Publishing Company.

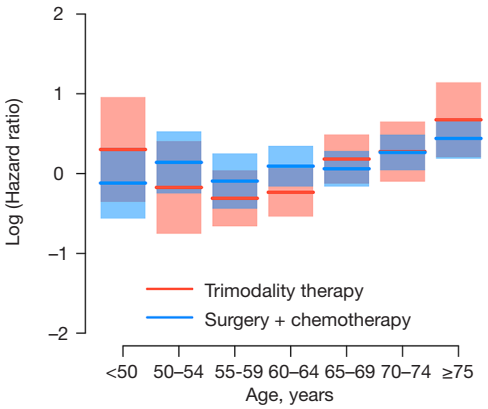

Figure 4 Results of the interaction analysis of additional radiotherapy and age.

additional radiotherapy and age was analyzed using multifactor Cox regression analysis (where all variables listed in *Table 1* were included). As shown in *Figure 4*, the addition of radiotherapy only brought potential survival benefits to the 50–54 group, the 55–59 group, and the 60–64 group.

Discussion

PM is a relatively rare tumor with long latency period and poor prognosis. There is currently controversy over whether to add radiotherapy to the treatment regimen for operable PM patients. In this study, we investigated the effect of age on efficacy of the additional radiotherapy in conjunction with surgery and chemotherapy. We found that in the 50 to <65 years group, patients who received trimodality therapy had a better OS and CSS than those who received surgery + chemotherapy. This result was still observed after performing PSM to reduce potential confounding bias. However, we did not prove the same benefit in <50 group nor ≥65 group, regardless of whether PSM was performed.

The latest NCCN guideline recommends PM patients whose clinical stages are I–IIIA and histological subtypes are epithelioid or biphasic to undergo surgical treatment and chemotherapy, and radiotherapy should be considered as needed (20-23). However, the guidelines do not specify which patients will benefit from radiation therapy. We investigated this issue in PM patients of different ages based on a large cohort from SEER database. Surgery is not recommended for patients of sarcomatoid subtype, we excluded patients of sarcomatoid subtype to reduce the influence of confounding factors. In PSM, we only included patients whose ICD-O-3 histological codes were 9052 (epithelioid type) and 9053 (biphasic type) and excluded patients with an ICD-O-3 histological code of 9050 (unclear pathologic classification) to make our result after PSM more reliable.

With the completion of the MARS 2 trial, the necessity of surgery for PM patients has become a topic worth discussing. The MARS 2 trial found that the risks of extended pleurectomy decortication for operable PM patients are higher than those of chemotherapy alone (24). However, the MARS 2 team assessed PM patients for surgical resection solely using computed tomography (CT), while current guidelines recommend a comprehensive evaluation including imaging and performance status (3). This might lead to unsuitable patients being deemed eligible for surgery. Additionally, some researchers have claimed that the MARS 2 trial's statistical analysis of certain subgroups was biased and that the data were inadequate to support the conclusion that surgery results in worse survival rates (25).

Unnecessary or excessive surgery can lead to poorer prognoses for PM patients (26); however, at this stage, many researchers believe that the role of surgery cannot be denied (25,27). In the current context where systemic therapy remains the primary approach, more precise and personalized resection plans are crucial for PM patients. A more comprehensive and in-depth exploration of whether surgery is necessary is needed to provide stronger evidence for clinical decision-making.

A phase III clinical trial, CheckMate 743, demonstrated that the combination of Nivolumab and Ipilimumab improved OS in patients with unresectable PM compared to standard chemotherapy regimens of platinum plus pemetrexed (28). The results of a meta-analysis also demonstrated the safety and efficacy of immunotherapy (29). According to the latest guidelines, the chemotherapy regimen of platinum plus pemetrexed is still recommended for operable PM patients (3). Therefore, we consider that future research is needed to investigate whether the combination of nivolumab and ipilimumab can replace the role of chemotherapy in the trimodality therapy for operable PM patients, and whether there will be changes in the characteristics of PM patients who could benefit from the trimodality therapy after modifying the regimen.

The role of radiotherapy in PM remains controversial. The phase II IMPRINT trial evaluated the safety of

© AME Publishing Company.

hemithoracic intensity modelled radiotherapy (IMRT) given to patients with PM after induction chemotherapy and surgery. In IMPRINT trial, with a total of 27 participants, radiation pneumonia was reported in 30% of patients (6 patients with grade 2 and 2 patients with grade 3) and was reversible with corticosteroids, no grade 4 or 5 radiation-related toxicities were observed (30). Based on IMPRINT trial, the NCCN recommended that hemithoracic IMRT should be considered after induction chemotherapy and pleurectomy/decortication (P/D) by qualified professionals. Another phase III SMART trial compared prophylactic radiotherapy with delayed radiotherapy to evaluate recurrence rates in patients undergoing PM surgery (31). In SMART trial, 203 eligible patients were randomly assigned to immediate radiotherapy or delayed radiotherapy in a 1:1 ratio, with data showing no difference in surgical band recurrence between the prophylactic radiotherapy (RT) group and the delayed RT group. Thus, prophylactic radiotherapy was no longer routinely recommended to prevent instrumental tract recurrences after pleural intervention.

To date, there is no randomized controlled trial that elucidates the therapeutic effect of additional therapy in conjunction with surgical treatment and chemotherapy. SKK 17/04 trial is considered one of the most important trials regarding the therapeutic effect of additional radiotherapy. In the SKK 17/04 trial, participants received three cycles of cisplatin/pemetrexed chemotherapy and EPP, then 54 participants with complete macroscopic resection were randomly assigned (1:1) to receive high-dose radiotherapy or standard care (17). No significant difference in survival was observed and the trial did not support the routine use of hemithoracic radiotherapy. However, many researchers argued that the result of this trial failed to support the benefit of additional hemithoracic radiotherapy because of slow enrollment of patients, poor macroscopic clearance and high postoperative mortality rates (1,18,32-34). Besides the clinical trials, there are still many studies exploring the effect of radiotherapy in postoperative treatment of PM. Many studies have confirmed that the use of radiotherapy after EPP, P/D or chemotherapy has survival advantages (13,14,16,35-37). A recent SEER analysis found that the addition of radiotherapy only improved survival for PM patients with localized tumors and did not find the benefit in patients with regional or metastatic disease (18). In our study, we found different treatment outcomes of trimodality therapy for PM patients in different age groups. Our findings suggest that PM patients aged 50 to <65 may obtain a potential benefit from the addition of radiotherapy and could provide a reference for clinicians to decide whether to include radiotherapy in their treatment plan.

How to accurately deliver radiation to the entire pleural surface without damaging radiosensitive organs such as the lungs and heart is a major challenge in radiotherapy for PM (38). Due to the age-related degeneration, patients over 65 years have poorer cardiopulmonary function, lower performance status score, and poorer renal function than patients between 50 and 65 years of age, leading to their lower tolerance to radiation exposure. We speculated that this might be the reason why additional radiotherapy did not bring a survival benefit to PM patients over 65 years old. Asbestos exposure is the most significant risk factor for PM, and patients usually have a history of asbestos exposure for more than 40 years (39). We speculated that PM patients younger than 50 years might be caused by high exposure to asbestos over a short period of time or with the harboring of driver mutations of PM (40,41), and the condition of those PM patients was too severe, potentially overshadowing the benefits of the trimodality therapy.

There are also some limitations in this study. First, our data might have selection bias and information bias due to the retrospective design. Second, because the SEER database does not provide details of surgery and radiotherapy dosage, we could not further validate our findings according to these details and although we identified age as a key factor influencing the efficacy of radiation therapy, the absence of patient response data to radiation therapy, including complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD), limits our ability to establish a predictive nomogram. Third, smoking information is missing from the SEER database, therefore we could not evaluate the effect of smoking on the results. Fourth, in the interaction analysis, due to the small sample size of each age group after subdividing patients into seven age groups, our result could only show the trend of the influence of age on the efficacy of radiotherapy, so further studies with larger sample size might provide more details about this finding. Finally, although we conducted PSM and sensitivity analyses, there is some heterogeneity in the treatment methods in our article, necessitating further exploration and validation through well-designed prospective studies.

Conclusions

In conclusion, we found improved survival for trimodality

© AME Publishing Company.

therapy versus surgery + chemotherapy in the PM patients aged between 50 and 65 years, but not in the younger and older age groups. Although the SEER database has inherent limitations, our analysis showed that patients aged 50 to <65 years may derive potential benefit from additional radiotherapy. The influence of other factors on additional radiotherapy still needs to be further explored to improve the understanding of trimodality therapy in the future.

Acknowledgments

We express our gratitude to the National Cancer Institute and the SEER Program tumor registries for their dedicated contributions in constructing the SEER database. The authors take full responsibility for interpreting the data.
Funding: This work was supported by 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYJC21002 to L.L.); and the Science and Technology Project of the Health Commission of Sichuan Province, China (No. 21PJ008 to L.X.).

Footnote

Reporting Checklist: The authors have completed the STROBE reporting checklist. Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1111/rc

Peer Review File: Available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1111/prf

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://jtd.amegroups.com/article/view/10.21037/jtd-24-1111/coif). L.X. receives funding from the Science and Technology Project of the Health Commission of Sichuan Province, China (No. 21PJ008). L.L. receives funding from 1.3.5 Project for Disciplines of Excellence, West China Hospital, Sichuan University (No. ZYJC21002). The other 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. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013).

Open Access Statement: This is an Open Access article distributed in accordance with the Creative Commons Attribution-NonCommercial-NoDerivs 4.0 International License (CC BY-NC-ND 4.0), which permits the non-commercial replication and distribution of the article with the strict proviso that no changes or edits are made and the original work is properly cited (including links to both the formal publication through the relevant DOI and the license). See: https://creativecommons.org/licenses/by-nc-nd/4.0/.

References

1. Janes SM, Alrifai D, Fennell DA. Perspectives on the Treatment of Malignant Pleural Mesothelioma. N Engl J Med 2021;385:1207-18.
2. van Kooten JP, Belderbos RA, von der Thüsen JH, et al. Incidence, treatment and survival of malignant pleural and peritoneal mesothelioma: a population-based study. Thorax 2022;77:1260-7.
3. National Comprehensive Cancer Network. (NCCN) Clinical Practice Guidelines in Oncology. Mesothelioma: Pleural, Version 1. 2024. Available online: https://nccn.medlive.cn/guide/detail/500. Accessed 5 Aug 2024.
4. Bovolato P, Casadio C, Billè A, et al. Does surgery improve survival of patients with malignant pleural mesothelioma?: a multicenter retrospective analysis of 1365 consecutive patients. J Thorac Oncol 2014;9:390-6.
5. Lang-Lazdunski L, Bille A, Lal R, et al. Pleurectomy/decortication is superior to extrapleural pneumonectomy in the multimodality management of patients with malignant pleural mesothelioma. J Thorac Oncol 2012;7:737-43.
6. Treasure T, Waller D, Tan C, et al. The Mesothelioma and Radical surgery randomized controlled trial: the Mars feasibility study. J Thorac Oncol 2009;4:1254-8.
7. Cao C, Tian D, Park J, et al. A systematic review and meta-analysis of surgical treatments for malignant pleural mesothelioma. Lung Cancer 2014;83:240-5.
8. Taioli E, Wolf AS, Camacho-Rivera M, et al. Determinants of Survival in Malignant Pleural Mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) Study of 14,228 Patients. PLoS One 2015;10:e0145039.
9. Treasure T, Lang-Lazdunski L, Waller D, et al. Extra-pleural pneumonectomy versus no extra-pleural pneumonectomy for patients with malignant pleural mesothelioma: clinical outcomes of the Mesothelioma and Radical Surgery (MARS) randomised feasibility study. Lancet Oncol 2011;12:763-72.
10. Beebe-Dimmer JL, Fryzek JP, Yee CL, et al. Mesothelioma in the United States: a Surveillance, Epidemiology,

and End Results (SEER)-Medicare investigation of treatment patterns and overall survival. Clin Epidemiol 2016;8:743-50.
11. Nelson DB, Rice DC, Niu J, et al. Long-Term Survival Outcomes of Cancer-Directed Surgery for Malignant Pleural Mesothelioma: Propensity Score Matching Analysis. J Clin Oncol 2017;35:3354-62.
12. Rice DC, Stevens CW, Correa AM, et al. Outcomes after extrapleural pneumonectomy and intensity-modulated radiation therapy for malignant pleural mesothelioma. Ann Thorac Surg 2007;84:1685-92; discussion 1692-3.
13. Gomez DR, Hong DS, Allen PK, et al. Patterns of failure, toxicity, and survival after extrapleural pneumonectomy and hemithoracic intensity-modulated radiation therapy for malignant pleural mesothelioma. J Thorac Oncol 2013;8:238-45.
14. Rea F, Marulli G, Bortolotti L, et al. Induction chemotherapy, extrapleural pneumonectomy (EPP) and adjuvant hemi-thoracic radiation in malignant pleural mesothelioma (MPM): Feasibility and results. Lung Cancer 2007;57:89-95.
15. Flores RM, Krug LM, Rosenzweig KE, et al. Induction chemotherapy, extrapleural pneumonectomy, and postoperative high-dose radiotherapy for locally advanced malignant pleural mesothelioma: a phase II trial. J Thorac Oncol 2006;1:289-95.
16. Casiraghi M, Maisonneuve P, Brambilla D, et al. Induction chemotherapy, extrapleural pneumonectomy and adjuvant radiotherapy for malignant pleural mesothelioma. Eur J Cardiothorac Surg 2017;52:975-81.
17. Stahel RA, Riesterer O, Xyrafas A, et al. Neoadjuvant chemotherapy and extrapleural pneumonectomy of malignant pleural mesothelioma with or without hemithoracic radiotherapy (SAKK 17/04): a randomised, international, multicentre phase 2 trial. Lancet Oncol 2015;16:1651-8.
18. Thompson AB, Quinn TJ, Siddiqui ZA, et al. Addition of radiotherapy to surgery and chemotherapy improves survival in localized malignant pleural mesothelioma: A Surveillance, Epidemiology, and End Results (SEER) study. Lung Cancer 2020;146:120-6.
19. Surveillance Research Program, National Cancer Institute SEER*Stat software. Available online: http://www.seer.cancer.gov/seerstat, version 8.4.0. Accessed 1 January 2023.
20. Kaufman AJ, Flores RM. Surgical treatment of malignant pleural mesothelioma. Curr Treat Options Oncol 2011;12:201-16.
21. Kondola S, Manners D, Nowak AK. Malignant pleural mesothelioma: an update on diagnosis and treatment options. Ther Adv Respir Dis 2016;10:275-88.
22. Raynaud C, Greillier L, Mazieres J, et al. Management of malignant pleural mesothelioma: a French multicenter retrospective study (GFPC 0802 study). BMC Cancer 2015;15:857.
23. van Thiel ER, Surmont VF, van Meerbeeck JP. Malignant pleural mesothelioma: when is radiation therapy indicated? Expert Rev Anticancer Ther 2011;11:551-60.
24. Lim E, Waller D, Lau K, et al. Extended pleurectomy decortication and chemotherapy versus chemotherapy alone for pleural mesothelioma (MARS 2): a phase 3 randomised controlled trial. Lancet Respir Med 2024;12:457-66.
25. Gulati S, Wolf AS, Flores RM. Should Treatment of Mesothelioma Include Surgery? MARS2 Fails to Land. Semin Thorac Cardiovasc Surg 2024;S1043-0679(24)00050-9. [Epub ahead of print]. doi: 10.1053/j.semtcvs.2024.07.001.
26. Taioli E, Wolf AS, Flores RM. Meta-analysis of survival after pleurectomy decortication versus extrapleural pneumonectomy in mesothelioma. Ann Thorac Surg 2015;99:472-80.
27. Nakamura A, Hashimoto M, Kuroda A, et al. Impact of Operation on Disease Progression and Survival of Patients With Pleural Mesothelioma. Ann Thorac Surg 2024;118:216-23.
28. Baas P, Scherpereel A, Nowak AK, et al. First-line nivolumab plus ipilimumab in unresectable malignant pleural mesothelioma (CheckMate 743): a multicentre, randomised, open-label, phase 3 trial. Lancet 2021;397:375-86.
29. Tagliamento M, Di Maio M, Remon J, et al. Meta-Analysis on the Combination of Chemotherapy With Programmed Death-Ligand 1 and Programmed Cell Death Protein 1 Blockade as First-Line Treatment for Unresectable Pleural Mesothelioma. J Thorac Oncol 2024;19:166-72.
30. Rimner A, Zauderer MG, Gomez DR, et al. Phase II Study of Hemithoracic Intensity-Modulated Pleural Radiation Therapy (IMPRINT) As Part of Lung-Sparing Multimodality Therapy in Patients With Malignant Pleural Mesothelioma. J Clin Oncol 2016;34:2761-8.
31. Clive AO, Taylor H, Dobson L, et al. Prophylactic radiotherapy for the prevention of procedure-tract metastases after surgical and large-bore pleural procedures in malignant pleural mesothelioma (SMART): a multicentre, open-label, phase 3, randomised controlled

© AME Publishing Company.

trial. Lancet Oncol 2016;17:1094-104.
32. Riesterer O, Ciernik IF, Stahel RA, et al. Pattern of failure after adjuvant radiotherapy following extrapleural pneumonectomy of pleural mesothelioma in the SAKK 17/04 trial. Radiother Oncol 2019;138:121-5.
33. Nicolini F, Bocchini M, Bronte G, et al. Malignant Pleural Mesothelioma: State-of-the-Art on Current Therapies and Promises for the Future. Front Oncol 2019;9:1519.
34. de Perrot M, Wu L, Wu M, et al. Radiotherapy for the treatment of malignant pleural mesothelioma. Lancet Oncol 2017;18:e532-42.
35. de Perrot M, Feld R, Cho BC, et al. Trimodality therapy with induction chemotherapy followed by extrapleural pneumonectomy and adjuvant high-dose hemithoracic radiation for malignant pleural mesothelioma. J Clin Oncol 2009;27:1413-8.
36. Minatel E, Trovo M, Bearz A, et al. Radical Radiation Therapy After Lung-Sparing Surgery for Malignant Pleural Mesothelioma: Survival, Pattern of Failure, and Prognostic Factors. Int J Radiat Oncol Biol Phys 2015;93:606-13.
37. Chance WW, Rice DC, Allen PK, et al. Hemithoracic intensity modulated radiation therapy after pleurectomy/decortication for malignant pleural mesothelioma: toxicity, patterns of failure, and a matched survival analysis. Int J Radiat Oncol Biol Phys 2015;91:149-56.
38. Ashton M, O'Rourke N, Currie S, et al. The role of radical radiotherapy in the management of malignant pleural mesothelioma: A systematic review. Radiother Oncol 2017;125:1-12.
39. Bibby AC, Tsim S, Kanellakis N, et al. Malignant pleural mesothelioma: an update on investigation, diagnosis and treatment. Eur Respir Rev 2016;25:472-86.
40. Carbone M, Adusumilli PS, Alexander HR Jr, et al. Mesothelioma: Scientific clues for prevention, diagnosis, and therapy. CA Cancer J Clin 2019;69:402-29.
41. Louie BH, Kurzrock R. BAP1: Not just a BRCA1-associated protein. Cancer Treat Rev 2020;90:102091.

Cite this article as: Yang J, Xia L, Jie H, Wang T, Guo C, Liu C, Liao H, Mei J, Pu Q, Liu L. The impact of age on the efficacy of radiotherapy in pleural mesothelioma patients receiving trimodality therapy: a population-based study of the SEER database. J Thorac Dis 2024;16(10):6462-6474. doi: 10.21037/jtd-24-1111

© AME Publishing Company.