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Original Article

Clinical characteristics, treatment patterns, and survival outcomes of pulmonary mucosa-associated lymphoid tissue lymphoma in the United States

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Abstract: Background: Pulmonary mucosa-associated lymphoid tissue (MALT) lymphoma is a relatively rare disease. We aimed to perform a large-scale study of clinical characteristics and optimal treatment for pulmonary MALT lymphoma patients. Method: Our study extracted data from the Surveillance, Epidemiology, and End Results (SEER) Program. The chi-square test was utilized to compare clinical factors. Overall survival (OS) was compared using the Kaplan-Meier (KM) method and Cox regression analysis. Cancer-specific survival (CSS) was compared by the Fine-Gray test. Propensity score matching (PSM) was used to balance confounders. Results: Females and elderly individuals are more likely to suffer from pulmonary MALT lymphoma. The incidence rate is increasing, and most patients are diagnosed in the early stage without specific symptoms. Patients usually suffer from a favorable survival period, especially patients in the early stage. Patients in stage I-II can obtain a survival advantage from surgery, especially for patients older than 60 years, with unilateral lesions, with single-lung-lobe lesions, in stage I, and without B symptoms. Chemotherapy decreases the risk of death for advanced-stage patients, and males, caucasians, patients with stage IV disease, or patients with only unilateral lung involvement were especially recommended for chemotherapy. Conclusion: Pulmonary MALT lymphoma is an indolent tumor. Patients in different stages had different prognoses, and different treatments were recommended. We will conduct prospective research in the future.

Keywords: Pulmonary mucosa-associated lymphoid tissue lymphoma, clinical characteristics, survival, comprehensive treatment

Introduction

Mucosa-associated lymphoid tissue (MALT) lymphoma is the most frequent subtype of marginal zone lymphoma [1]. Usually, it is considered an indolent lymphoma. It is a B-cell chronic lymphoproliferative disease with unique characteristics, and the most commonly involved organ is the gastrointestinal tract, followed by the lung and parotid gland [2]. Lymphoma occurring primarily in the lungs is a rare malignancy. According to statistics, primary pulmonary lymphoma accounts for 0.4% of lymphomas and 0.5%-1.0% of lung malignancies [3, 4]. MALT is the most frequent lymphoma originating primarily from the lung, accounting for 70%-90% of cases [5].

Infection is a possible cause of MALT lymphoma. The relationship between Helicobacter pylori infection and gastric MALT lymphoma has been verified. For pulmonary MALT, reduplicative pulmonary infection, smoking, autoimmune diseases and other chronic immune system irritants are possible factors leading to the disease [6, 7]. As an extremely rare disease, pulmonary MALT is often misdiagnosed as lung cancer or pneumonia. Most patients are asymptomatic, while atypical clinical manifestations include fever, cough, expectoration, chest pain, dyspnea, and other respiratory symptoms [8]. No specific imaging manifestations can be found on CT imaging. Pathology is the gold standard for a clear diagnosis of lymphoma. Differences in morphology are employed for diagno-

sis and classification. Moreover, cytogenetics, flow cytometry, molecular techniques, and immunohistochemistry (IHC) can help to distinguish lymphoma subtypes [9].

The consensus of pulmonary MALT treatment remains controversial, especially for patients initially diagnosed with the disease or with a large tumor burden. For patients with early-stage MALT, it is recommended to "watch and wait" or to receive surgery and radiotherapy. For advanced-stage MALT, systemic treatment, especially regimens including rituximab, is recommended [10, 11]. However, a large prospective study of MALT is lacking, and the optimal treatment is still unclear. Fortunately, as an indolent lymphoma, the prognosis of MALT lymphoma is favorable. The 5-year overall survival (OS) is more than 90%, while the median survival time is more than 10 years [12]. The number of patients diagnosed with pulmonary MALT is increasing. Compared to 2001 and 2005, the incidence of pulmonary MALT increased by 18% in 2006 and 2009 [13]. Therefore, it is necessary to find the optimal regimen to cure MALT.

Previous studies on pulmonary MALT lymphoma included small patient populations. By extracting information from the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program database, we performed a large-scale retrospective study in the American population to learn the epidemiology, clinical characteristics, treatment and prognosis of pulmonary MALT lymphoma.

Materials and methods

Materials acquisition

We retrieved information from the SEER program. The enrollment criteria were as follows: 1. Patients were initially diagnosed with pulmonary MALT lymphoma between 2000 and 2009, and 2. Patients were diagnosed with MALT lymphoma by pathological methods. For further prognosis and survival analyses, patients with unclear survival and Ann Arbor stage were excluded. Patients considered to have secondary lymphoma were also excluded. We extracted demographic and clinical characteristics, including survival status, survival time, years, sex, race, Ann Arbor stage, lateral lymphoma, B symptoms, and therapeutic experience. Early stage referred to patients in stages I-II, while advanced stage represented patients diagnosed in stages III-IV with diffuse disease.

Overall survival (OS) and cancer-specific survival (CSS) are endpoints of the study. OS means the survival duration from initial diagnosis to all-cause death. CSS duration refers to the period from initial diagnosis to cancer-specific death, and deaths caused by other diseases were called competitive events.

No personal identifying information appeared in the study. It was exempted from review by the ethics committee. Our study protocol was in agreement with the provisions of the Helsinki Declaration as revised in 2013.

Statistical analyses

The flowchart of this study is shown in **Figure 1**. Differences between the clinical characteristics of patients at different stages were compared utilizing the chi-square test. The Kaplan-Meier (KM) method with the log-rank test was employed to compare OS duration for patients in different stages. The Fine-Gray test was carried out to compare CSS prognosis [14]. Furthermore, to balance confounding factors, propensity score matching (PSM) was performed, and 2 cohorts with similar clinical characteristics were obtained. Patients were matched based on the evaluated propensity using 1:1 matching with a 0.05 caliper. Next, we performed the KM method and Cox proportional hazards regression analysis with a forward stepwise procedure to screen prognostic factors for patients in the early stage or advanced stage. The Fine-Gray test was carried out to screen prognostic factors of CSS. For patients in the early stage, we explored the population who may benefit from surgery. For patients in the advanced stage, we explored the population who may benefit from chemotherapy.

A two-sided p value <0.05 was considered significant, while a p value <0.10 was significant by univariate analysis. Statistical analyses were achieved by R (version 4.0.4) and SPSS (version 23.0).

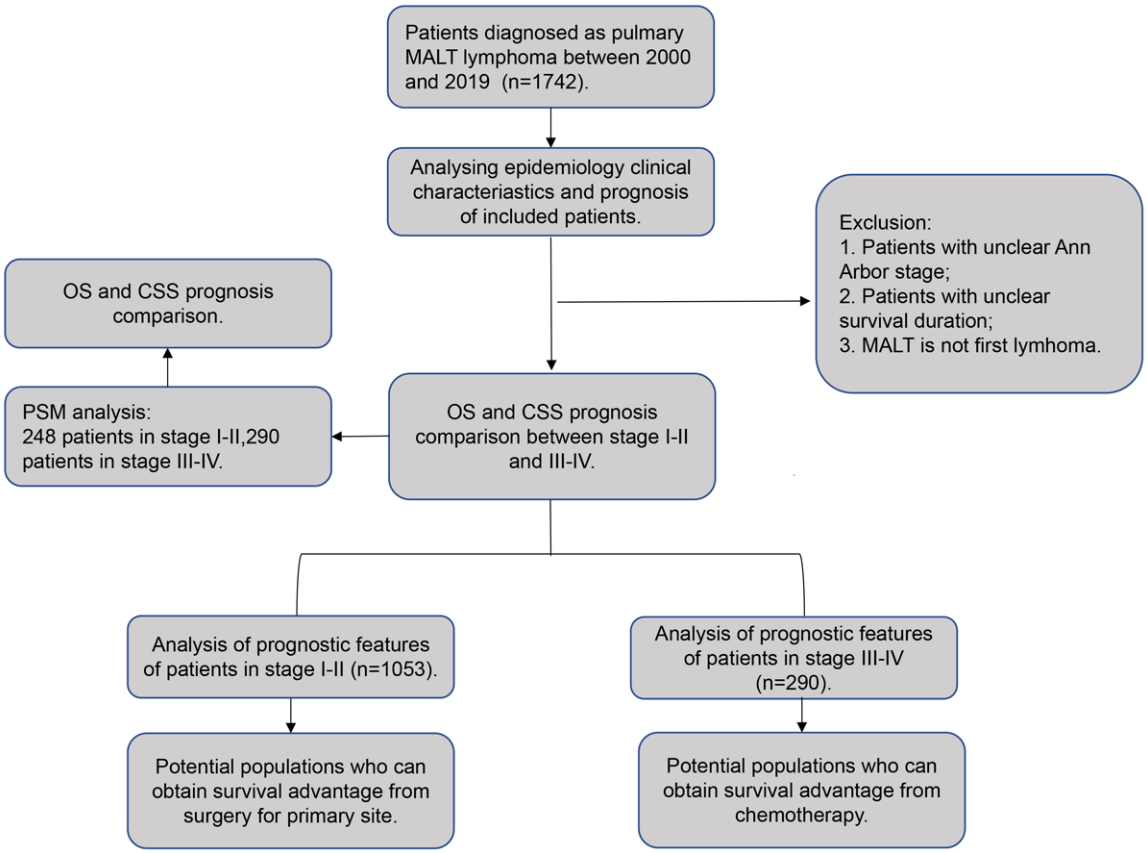

Figure 1. The flowchart of the study.

Results

Epidemiology

There were 1742 patients diagnosed with primary pulmonary MALT lymphoma from 2000 to 2019 in America, accounting for 0.5% of non-Hodgkin lymphoma (NHL), 5.9% of MALT lymphoma, and 46.7% of pulmonary NHL. There were 961,330 patients diagnosed with pulmonary neoplasm during the same period, and MALT lymphoma accounted for a proportion of 0.2%. A total of 58.61% (1021/1742) of patients were female, while 41.39% (721/1742) of patients were male. The ratio of females to males was 1.42:1. The median age of patients diagnosed with pulmonary MALT lymphoma was 68 (IQR 59-77) years old. Patients less than 60 years old accounted for only 25.72%, among whom 6 (0.3%) were younger than 30 years old. A total of 692 (39.7%) patients were diagnosed from 2000 to 2009, while 1050 (60.3%) were diagnosed from 2010 to 2019.

Clinical characteristics

A total of 593 patients were registered with B symptoms. Only 66 (11.1%) were diagnosed with fever, cough, or emaciation, while the other 527 patients (88.9%) were diagnosed without B symptoms. Most patients are diagnosed at an early stage. There were 1343 patients with a clear Ann Arbor stage. The numbers of patients in stage I, stage II, stage III, and stage IV were 872 (64.9%), 181 (13.5%), 25 (1.9%), and 265 (19.7%), respectively. Approximately 70.90% of lymphomas involved only one pulmonary lobe. For patients in the early stage, surgery was the first therapeutic choice. 492 (46.7%) patients received tumorectomy, among whom 21 and 73 patients received postoperative chemotherapy and postoperative radiotherapy, respectively. 111 (10.5%) patients received definitive radiotherapy, while 180 (17.1%) patients received chemotherapy alone. Moreover, 270 (25.6%) patients received no treatment. For patients with advanced-stage disease, 151 (52.1%) patients received chemo-

Table 1. Demographic and clinical features of included patients

Characteristics	Total patients (1742)		Stage I-II (1053)		Stage III-IV (290)		*P* value (Stage I-II vs. Stage III-IV)
	Num.	Percentage	Num.	Percentage	Num.	Percentage	
Age							0.462
<60 y	448	25.72%	292	27.73%	87	30.00%	
≥60 y	1294	74.28%	761	72.27%	203	70.00%	
Sex							0.638
Female	1021	58.61%	620	58.88%	166	57.24%	
Male	721	41.39%	433	41.12%	124	42.76%	
Race							0.647
Asian/AI/Other	122	7.00%	66	6.27%	22	7.59%	
Black	143	8.21%	83	7.88%	25	8.62%	
White	1477	84.79%	904	85.85%	243	83.79%	
Site							<0.001*
Main bronchus	30	1.72%	27	2.56%	3	1.03%	
Single lung lobe	1235	70.90%	982	93.26%	208	71.72%	
Overlapping lesion of lung	123	7.06%	44	4.18%	79	27.24%	
Lateral							<0.001*
Unilateral	1550	88.98%	986	93.64%	222	76.55%	
Bilateral	192	11.02%	67	6.36%	68	23.45%	
B symptom							<0.001*
Yes	101	5.80%	44	4.18%	22	7.59%	
No	773	44.37%	446	42.36%	81	27.93%	
Unknow	868	49.83%	563	53.47%	187	64.48%	
Surgery							0.001*
Yes	705	40.47%	492	46.72%	102	35.17%	
No	1036	59.47%	561	53.28%	188	64.83%	
Chemotherapy							<0.001*
Yes	510	29.28%	272	25.83%	151	52.07%	
No	1232	70.72%	781	74.17%	139	47.93%	
Radiotherapy							<0.001*
Yes	185	10.62%	132	12.54%	10	3.45%	
No	1557	89.38%	921	87.46%	280	96.55%	
Survival							<0.001*
Alive	1098	63.03%	641	60.87%	137	47.24%	
Dead of lymphoma	212	12.17%	123	11.68%	60	20.69%	
Dead of other cause	432	24.80%	289	27.45%	93	32.07%	

OS, overall survival; AI, American Indian; *, p<0.05.

therapy, while 102 (35.2%) patients received pulmonary surgery. Otherwise, the incidence of bilateral pulmonary tumors was 11.1% (193/1743). The demographic and clinical features of the included patients are shown in **Table 1**.

Prognosis

Pulmonary MALT lymphoma is an indolent tumor. The OS probability at 5 years was 75.3%, while it was 52.9% at 10 years. Moreover, the 5-year OS probabilities of patients in the early stage and advanced stage were 78.0% and 71.7%, respectively, while the 10-year OS probabilities were 53.8% and 50.8%, respectively. **Table 2** describes the OS and CSS probabilities of patients at 1 year, 3 years, 5 years, and 10 years.

Compared to patients in stage III-IV, patients in stage I-II were associated with better OS and

Table 2. 1-, 3-, 5-, 10-year OS and CSS rates of included patients

		Total patients (1743)	Stage I-II (1053)	Stage III-IV (290)
OS	1-year	93.8%	94.4%	91.0%
	3-year	84.7%	86.2%	79.9%
	5-year	75.3%	78.0%	71.7%
	10-year	52.9%	53.8%	50.8%
CSS	1-year	96.1%	97.1%	91.9%
	3-year	87.7%	92.4%	83.1%
	5-year	86.4%	88.8%	79.4%
	10-year	75.2%	77.3%	68.9%

OS, overall survival; CSS, cancer specific survival.

CSS (**Figure 2A**, **2B**). Subsequently, Cox proportional hazards regression analysis verified that stage was a prognostic factor of pulmonary MALT lymphoma (P=0.003). Otherwise, PSM was performed to balance confounding factors, and we obtained 2 cohorts of different stages with similar clinical characteristics (**Table 3**). The KM and CSS curves of the 2 balanced cohorts are shown in **Figure 2C**, **2D**. Patients in stage I-II had a prognostic advantage compared to patients in stage III-IV.

Treatment and risk factor analysis

For patients in stage I-II, surgery significantly improved OS prognosis. As shown in **Figure 3A**, the prognosis of patients who underwent surgery was significantly better than that of patients who received radiotherapy alone, chemotherapy alone, or watch and wait. As shown in **Figure 3B**, **3C**, surgery improved the OS and CSS of patients in the early stage. After adjusting for other clinical factors, no surgery obviously increased the OS and CSS risk of patients (OS: HR 1.51, 95% CI 1.24, 1.84; CSS: HR 1.98, 95% CI 1.34, 2.91). The results of the Cox proportional hazards regression analysis are shown in **Table 4**. Except for surgery, age and detailed stage were prognostic factors for OS, while age and B symptoms were prognostic factors for CSS. Subsequently, subgroup analysis demonstrated that patients more than 60 years old, Caucasian patients, patients with unilateral tumors, patients with involvement of a single lung lobe, patients in stage I, patients without symptoms, and patients without chemotherapy received a greater survival advantage from surgery (**Figure 3D**). Notably, the effect of radiotherapy after surgery seemed to improve prognosis.

On the other hand, univariate analysis and Cox proportional hazards regression analysis demonstrated that age and chemotherapy were OS prognostic factors, while only age contributed to CSS prognosis (**Table 5**). Chemotherapy alone significantly improved OS (**Figure 4A**), but not for CSS (**Figure 4B**). After adjusting for other clinical factors, not receiving chemotherapy alone decreased the OS risk of patients (HR 1.32, 95% CI 1.08, 1.70). Subgroup analysis demonstrated that male patients, Caucasian patients, patients with tumors involved in a unilateral lung, and patients at stage IV had a significant survival advantage from chemotherapy (**Figure 4C**).

Discussion

MALT lymphoma is the most common subtype of MZL. Approximately 2/3 of MALT lymphomas occur in the stomach, while the skin, eye/adnexa, lung and thyroid are also relatively common primary sites [2, 15]. MALT lymphoma is an indolent lymphoma subtype with a favorable prognosis compared to other subtypes of lymphomas. However, the morbidity of pulmonary MALT lymphoma is relatively low, and until now, there has been no large-scale research to explore this population. The present study found that pulmonary MALT represented 0.5% of non-Hodgkin lymphoma (NHL) and 5.9% of MALT lymphomas. The data were slightly lower than those of a previous study that evaluated pulmonary MALT lymphoma incidence in the United States from 2000 to 2009 [13]. Otherwise, the incidence was slightly higher in females, with a ratio of 1.42:1, and the median age of initial diagnosis was 68 years old. These results were consistent with previous results [13, 16, 17]. Remarkably, the morbidity during 2010 to 2019 had a 50% increase compared with the period of 2000 to 2009. This may be the result of the aging of the population, and the incidence of carcinoma increases with increasing age. On the other hand, advances in pathology reduce the probability of misdiagnosis and missed diagnosis.

Approximately 30% of pulmonary MALT lymphoma patients are asymptomatic [18, 19]. They are mostly accidentally discovered as pulmonary masses during physical examination. The coexistence of B symptoms is regarded as a sign of aggressive disease. Our study found that 11.1% of pulmonary MALT patients were diagnosed with B symptoms. Specific pulmo-

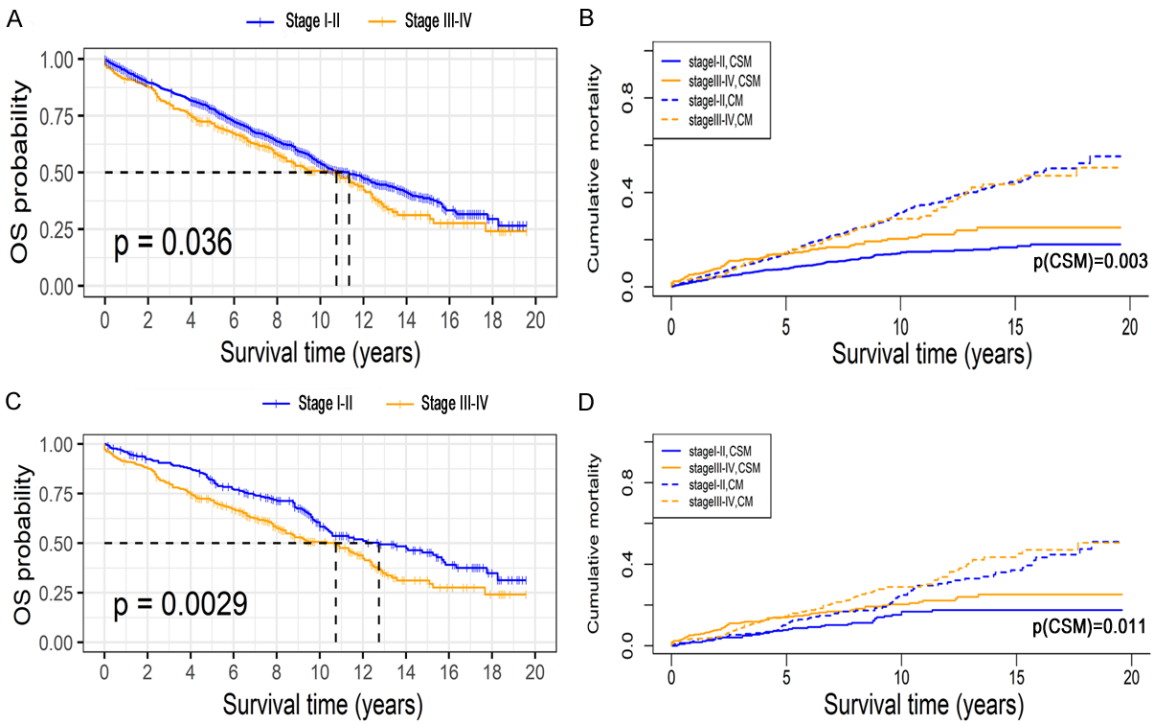

Figure 2. Kaplan-Meier (KM) survival curves and cumulative mortality curves stratified by stages before and after propensity score-matching (PSM) analysis. A. Overall survival (OS) prognosis of patients in stage I-II was superior to that of patients in stage III-IV. B. Cancer-specific survival (CSS) prognosis of patients in stage I-II was superior to that of patients in stage III-IV. C. OS prognosis of patients in stage I-II was superior to that of patients in stage III-IV after PSM analysis. D. CSS prognosis of patients in stage I-II was superior to that of patients in stage III-IV after PSM analysis.

nary symptoms in pulmonary MALT lymphoma patients are usually infrequent [19], such as chest pain, anhelation, and cough. Previous studies indicated that B symptoms presented in 15%-22% of patients, and our findings were close to their conclusions [19-21]. Most patients had involvement of only 1 lung lobe. The Ann Arbor staging system was used in our study because it is widely used in the clinical staging of pulmonary lymphoma [22]. MALT lymphoma progresses slowly with a long course. As a result, most pulmonary MALT lymphomas are diagnosed at an early stage [22], and we found that approximately 80% of patients were diagnosed at stage I-II.

Because of the indolent clinical course, pulmonary MALT lymphoma patients usually have a favorable survival. With a follow-up time of 79 (IQR 44-109) months, the 5-year and 10-year disease-specific survival rates are close to 90% and 70%, respectively, and the median survival time is more than 10 years [20, 23]. We found that the 5-year and 10-year OS rates were 75.3% and 52.9%, respectively. Patients in different stages may obtain different prognostic results. Sammassimo et al. [16] found that the PFS of patients in the early stage was superior to that of patients in the advanced stage, although there was no significant difference in OS. However, the present study demonstrated that the prognosis of early stage was better, regardless of OS or CSS prognosis. Furthermore, to avoid the probability of error and bias, PSM analysis was performed to obtain 2 cohorts with balanced clinical factors, and the final conclusion also supported the previous result.

Until now, the optimal treatment for early-stage pulmonary MALT lymphoma has been controversial. Surgical resection on localized lesions, radical radiation therapy, single-agent chemotherapy, or just watching and waiting were feasible methods [24, 25]. Wang et al. [19] carried out retrospective research and found that surgical resection could not improve OS or PFS, although surgery was an important method for diagnosis. In contrast, Sammassimo et al. [16]

Table 3. Characteristics of patients after PSM

Characteristic	Stage I-II (248)		Stage III-IV (290)		*p* value
	Num.	Percentage (%)	Num.	Percentage (%)	
Age					0.002
<60 y	193	77.8	87	30.0	
≥60 y	55	22.2	203	70.0	
Sex					0.663
Female	137	55.2	166	57.2	
Male	111	44.8	124	42.8	
Race					0.085
Asian/AI/Other	26	10.5	22	7.6	
Black	33	13.3	25	8.6	
White	189	76.2	243	83.8	
Site					0.064
Main bronchus	3	1.2	3	1.0	
Single lung lobe	207	83.5	208	71.7	
Overlapping lesion of lung	38	15.3	79	27.2	
Lateral					0.466
Unilateral	197	79.4	222	76.6	
Bilateral	51	20.6	68	23.4	
B symptom					0.385
Yes	14	5.6	22	7.6	
No	81	32.7	81	27.9	
Unknown	153	61.7	187	64.5	
Surgery					0.181
Yes	102	41.1	102	35.2	
No	146	58.9	188	64.8	
Chemotherapy					0.730
Yes	125	50.4	151	52.1	
No	123	49.6	139	47.9	
Radiotherapy					1.000
Yes	9	3.6	10	3.4	
No	239	96.4	280	96.6	

PSM, propensity score matching; AI, American Indian.

considered that surgery significantly improved the PFS of patients. Additionally, Wang et al. [26] found that radiation would contribute to lower morbidity with the preservation of lung function. Recently, Lin et al. [27] performed a retrospective study of 953 early-stage patients and demonstrated that neither chemotherapy, surgery, nor combination therapy can improve survival prognosis, and they suggested "watch and wait" to be the first choice. Our study verified that age ≥60 years, stage II disease, and surgery were prognostic factors for OS and CSS in patients with localized disease. Compared with watching and waiting, chemotherapy alone, radiotherapy alone, and combined therapy, surgery significantly improved prognosis, especially for patients older than 60 years, with unilateral lesions, with involvement of a single lung lobe, with stage I disease, or without B symptoms. In sum, it seemed that patients with insidious, slowly developing disease could obtain a survival advantage from surgery.

For patients in advanced stages, systemic therapy including rituximab is recommended as the first choice. Compared to chemotherapy alone, the combination of rituximab improved the event-free survival, overall response rate, and PFS of patients [28]. IELSG research reported no difference in OS between watching and

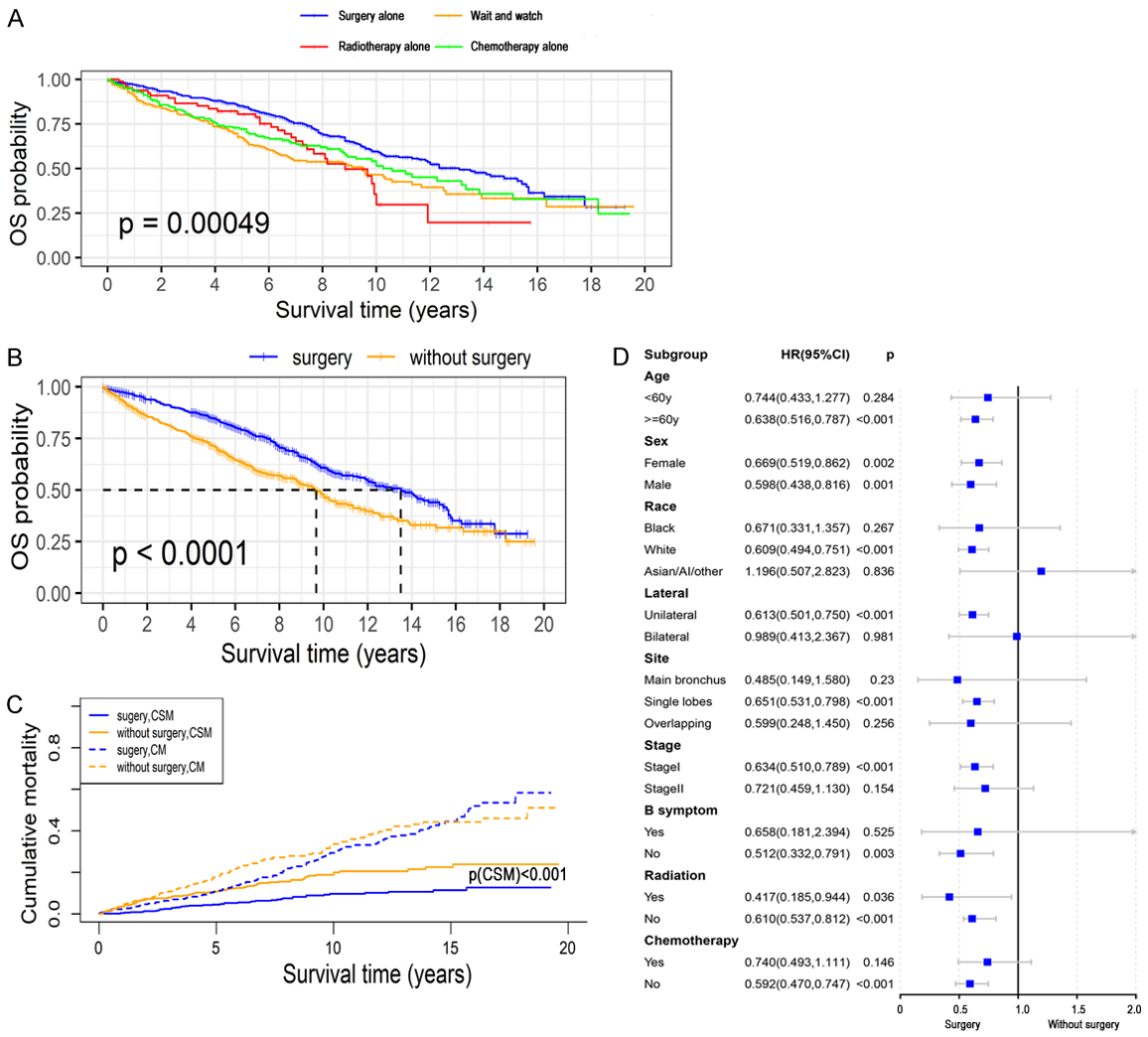

Figure 3. Prognosis comparison of patients in early stage with different treatment modalities. A. Surgery brought the best OS prognosis compared with other treatment modalities. B. Surgery significantly improved OS prognosis. C. Surgery significantly improved CSS prognosis. D. Subgroup analysis to identify optimal populations to receive surgery.

waiting, chemotherapy alone, orimmunochemotherapy [16]. In our study, we found that age and chemotherapy were prognostic factors of OS for advanced-stage patients, while only age was a prognostic factor for CSS. Patients without chemotherapy increased the overall death risk by 32%. For female patients, Caucasian patients, patients in stage IV or patients with only unilateral lung involvement, chemotherapy was necessary.

To our knowledge, our research is the largest retrospective study to explore the clinical characteristics and prognosis of pulmonary MALT lymphoma. However, there were several limitations we should admit. First, we performed this study on the basis of data from the SEER database. Because of the lack of some important clinical information, a degree of bias existed, and some important prognostic factors might be omitted, such as POD24 and IPI score, which were identified as prognostic factors for indolent lymphoma in previous studies [29, 30]. Second, the period from 2000 to 2019 included the pre-rituximab and post-rituximab eras, and specific chemotherapy agents were not registered in the SEER program. We could not further explore the optimal chemotherapy regimen for patients. Third, because of the lack of material, we could not perform an analysis on PFS. Finally, this is a retrospective study, and prospective research on the treatment of pul-

Table 4. Univariate and multivariate analyses for OS and CSS of patients in stage I-II

Variable	OS			CSS		
	Univariate	Multivariate		Univariate	Multivariate	
	p	Hazard ratio (95% CI)	p	p	Hazard ratio (95% CI)	p
Age	<0.001		<0.001	0.018		0.011
<60 y		reference			reference	
≥60 y		3.89 (2.91, 5.21)			1.79 (1.14, 2.79)	
Sex	0.821		-	0.517		-
Race	0.385		-	0.876		-
Site	0.126		-	0.083		0.210
Lateral	0.188		-	0.453		-
Stage	0.024		0.014	0.020		0.290
Stage I		reference				
Stage II		1.36 (1.07, 1.73)				
B symptom	0.213		-	0.009		0.014
Yes					reference	
No					0.35 (0.15, 0.81)	
Unknown					0.64 (0.30, 1.37)	
Surgery	<0.001		<0.001	<0.001		<0.001
Yes		reference			reference	
No		1.51 (1.24, 1.84)			1.98 (1.34, 2.91)	
Chemotherapy	0.573		-	0.006		0.230
Radiation	0.43		-	0.574		

OS, overall survival; CSS, cancer-specific survival; CI, confidence intervals.

Table 5. Univariate and multivariate analyses for OS and CSS of patients in stage III-IV

Variable	OS			CSS		
	Univariate	Multivariate		Univariate	Multivariate	
	p	Hazard ratio (95% CI)	p	p	Hazard ratio (95% CI)	p
Age	<0.001		<0.001	<0.001		<0.001
<60 y		reference			reference	
≥60 y		5.83 (3.46, 9.82)			4.49 (1.94, 10.4)	
Sex	0.082		0.293	0.492		-
Race	0.385		-	0.517		-
Site	0.922		-	0.103		-
Lateral	0.808		-	0.687		-
Stage	0.168		-	0.627		-
B symptom	0.269		-	0.105		-
Surgery	0.043		0.133	0.121		-
Chemotherapy	0.082		0.046	0.571		-
Yes		reference				
No		1.32 (1.08, 1.70)				

OS, overall survival; CSS, cancer-specific survival; CI, confidence intervals.

monary MALT lymphoma with different stages is necessary in the future. However, we believe that our research provides a novel understanding of pulmonary MALT lymphoma and offers a reference for clinical practice.

Conclusion

Pulmonary MALT lymphoma is an indolent lymphoma with a favorable prognosis. The incidence rate in females was slightly higher than

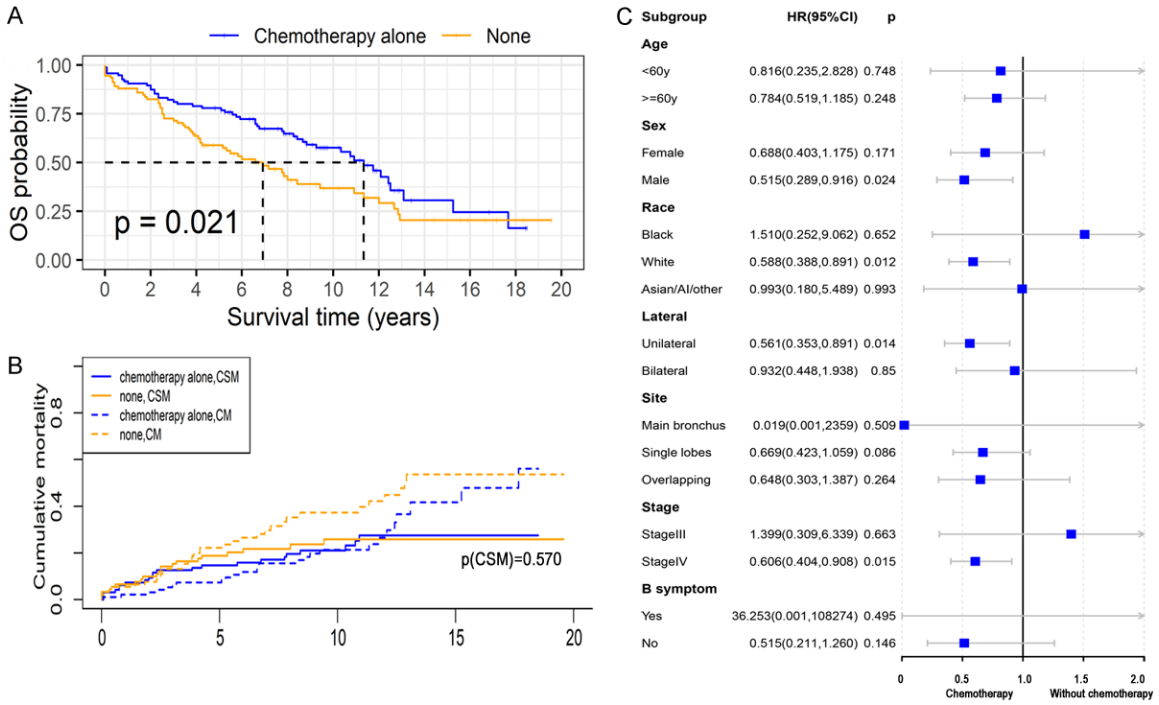

Figure 4. For patients in advanced stage, (A) Chemotherapy significantly improved OS prognosis, but (B) not for CSS prognosis. (C) Subgroup analysis to identify optimal populations to receive chemotherapy.

that in males, and it was more common in elderly patients were. Patients in the early stage had a longer survival period, and localized surgical resection prolonged OS and CSS, especially for patients older than 60 years, with unilateral lesions, with single-lung-lobe lesions, in stage I, and without B symptoms. For patients with diffuse disease, chemotherapy was recommended, especially for males, caucasians, patients in stage IV or patients with only unilateral lung involvement. We look forward to prospective research on the treatment of pulmonary MALT lymphoma in the future.

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Disclosure of conflict of interest

None.

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