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ORIGINAL RESEARCH

Initial Treatment Strategies Show No Survival Difference in Early-Stage Salivary Gland Mucosa-Associated Lymphoid Tissue Lymphoma

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Purpose: Given the indolent nature of mucosa-associated lymphoid tissue (MALT) lymphoma, immediate intervention is not always necessary, and a consensus on the optimal treatment modality remains elusive. This study aimed to evaluate survival outcomes of different initial treatments for early-stage (stage I–II) salivary gland MALT lymphoma.

Methods: Using data from the Surveillance, Epidemiology, and End Results program, we included patients diagnosed between 2000 to 2021. Initial treatments included surgery alone, radiotherapy alone, surgery combined with radiotherapy, chemotherapy alone, or observation. The chi-square test, Kaplan-Meier method, and multivariate Cox proportional-hazards models were used for statistical analyses.

Results: A total of 892 patients were included. Tumor location was known for 859 patients, with 740 (86.1%) located in the parotid gland, 116 (13.5%) in the submandibular gland, and 3 (0.3%) in the sublingual gland. Of the patients, 237 (26.6%) underwent surgery alone, 202 (22.6%) received radiotherapy alone, 170 (19.1%) underwent surgery combined with radiotherapy, 53 (5.9%) received chemotherapy alone, and 230 (25.8%) with observation. Submandibular gland tumor patients were more likely to receive radiotherapy alone, chemotherapy alone, or observation, while parotid gland tumor patients preferred surgery or surgery combined with radiotherapy ($P<0.001$). Over time, the proportion of observation cases increased ($P=0.004$). The median follow-up time was 92 months. The 8-year cancer-specific survival rates for patients undergoing surgery alone, radiotherapy alone, surgery combined with radiotherapy, chemotherapy alone, and observation were 96.1%, 94.9%, 97.0%, 92.1%, and 95.5%, respectively ($P=0.827$). The 8-year OS rates for these groups were 79.7%, 84.5%, 86.3%, 77.7%, and 79.5%, respectively ($P=0.132$). Multivariate analysis showed that initial treatment modality did not significantly affect survival outcomes. Sensitivity analyses also showed similar outcomes for the five treatment groups across different subgroups. Age and gender were independent prognostic factors associated with survival outcomes.

Conclusion: Our study highlights that early-stage salivary gland MALT lymphoma is characterized by a female predominance and an increasing trend toward observation as a management strategy. The lack of significant survival differences across treatment modalities suggests that the choice of initial treatment may be less critical than patient-specific factors such as age and gender. These findings advocate for personalized treatment approaches and underscore the importance of further research to better understand the underlying mechanisms driving gender disparities and the long-term outcomes of conservative management strategies.

Keywords: mucosa-associated lymphoid tissue, salivary gland, surgery, radiotherapy, chemotherapy

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Introduction

Mucosa-associated lymphoid tissue (MALT) lymphomas, an indolent subtype of extranodal B-cell non-Hodgkin lymphoma, represent approximately 8% of all lymphoma cases.[1,2] This malignancy typically emerges in response to chronic microbial infections or autoimmune disorders, developing in extranodal sites that normally lack lymphoid tissue.[3–5] Gastric MALT lymphoma is the most extensively studied among the various subtypes, primarily linked to chronic Helicobacter pylori gastritis.[6] In contrast, salivary gland MALT lymphoma is less common and often associated with chronic inflammation and lymphoid hyperplasia due to autoimmune conditions like Sjogren syndrome (SS) or hepatitis C virus infection.[1,7–9] Despite their shared classification, extra-gastric forms, particularly those involving the salivary glands, remain poorly characterized, especially concerning optimal therapeutic approaches.[10–12] Histologically, salivary gland MALT lymphomas are marked by slow progression and localized growth, yet their management is complicated by anatomical intricacies, potential functional deficits, and a paucity of high-quality evidence on treatment efficacy.

Given the indolent nature of MALT lymphoma, immediate intervention is not always necessary, and a consensus on the optimal treatment modality remains elusive. For stage I–II extranodal MALT lymphoma, the National Comprehensive Cancer Network (NCCN) guidelines propose involved site radiation therapy (ISRT), surgery, or rituximab as potential treatment options.[13] Active surveillance (watch-and-wait) is a viable strategy for asymptomatic patients.[2,14] However, while local surgery or radiotherapy is recommended for primary sites such as the lung, breast, thyroid, and colon/small bowel, specific guidelines for salivary gland MALT lymphoma are lacking.[13] Early-stage (I–II) MALT lymphoma is generally considered curable, with treatment strategies focusing on localized interventions to balance oncological control with functional and cosmetic preservation. Nonetheless, significant controversy persists regarding the most effective approach.[15] This study aimed to systematically evaluate survival outcomes associated with initial treatment strategies, including surgery alone, radiotherapy alone, combined treatment, chemotherapy alone, or observation in early-stage salivary gland MALT lymphoma. By addressing these knowledge gaps, the findings could refine personalized treatment algorithms, reduce unnecessary therapies, and enhance patient care for this understudied lymphoma subtype.

Patients and Materials

Patients

This study investigated the incidence, initial treatment patterns, and survival outcomes of patients diagnosed with salivary gland MALT lymphoma between 2000 and 2021 using the Surveillance, Epidemiology, and End Results (SEER) database.[16] The SEER database, a comprehensive cancer registry in the United States, was utilized to identify cases of MALT lymphoma (International Classification of Diseases for Oncology [ICD-O-3] code 9699/3). Inclusion criteria comprised: 1) a diagnosis of stage I–II salivary gland MALT lymphoma based on the Ann Arbor staging system; 2) availability of data on initial treatment modalities, including surgery, radiotherapy, chemotherapy, or observation (no recorded treatment). Exclusion criteria included patients with unknown staging, secondary primary malignancies, or unspecified radiotherapeutic methods. The study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (approval number XMFHIIT-2025SL156), and informed consent was waived due to the retrospective nature of the study.

Variables

The analysis incorporated the following variables: age, gender, race/ethnicity, Ann Arbor stage, tumor location, presence of B symptoms, and initial treatment modalities (surgery alone, radiotherapy alone, surgery combined with radiotherapy, chemotherapy alone, and observation). Survival outcomes were assessed using cancer-specific survival (CSS) and overall survival (OS). CSS was defined as the time from MALT lymphoma diagnosis to death attributable to lymphoma, while OS was measured from diagnosis to death from any cause.

Statistical Analysis

Baseline patient characteristics across treatment groups were compared using the Chi-square test or Fisher's exact test. Survival outcomes were evaluated using the Kaplan-Meier method, with Log rank tests employed to compare survival

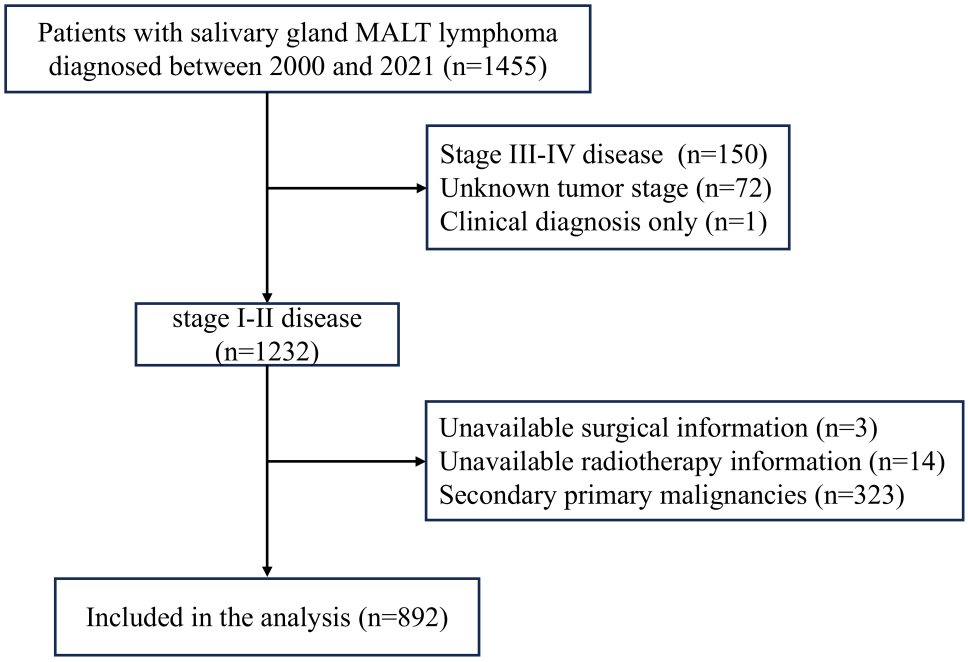

Figure 1 Flowchart of patient selection.

curves. Multivariate Cox proportional-hazards models were used to identify independent prognostic factors for CSS and OS. Sensitivity analyses were conducted to assess the impact of initial treatment modalities on CSS and OS, stratified by gender, race, age, tumor location, tumor stage, and B symptoms. All statistical analyses were performed using the IBM SPSS version (SPSS Inc., Chicago, IL, USA), with a significance threshold of $P < 0.05$.

Results

Patient Characteristics

A total of 892 patients met the inclusion criteria (Figure 1), with a median age at diagnosis of 59 years. The baseline characteristics of the patients are summarized in Table 1. The majority were female (n=651, 73.0%), Non-Hispanic White (n=528, 59.2%), and had stage I disease (n=649, 72.8%). Tumor location was known for 859 patients, with 740 (86.1%) located in the parotid gland, 116 (13.5%) in the submandibular gland, and 3 (0.3%) in the sublingual gland. Among 432 patients with recorded B symptoms, 31 (7.2%) presented with B symptoms.

Table 1 Baseline Characteristics of the Study Cohort

Variables	N	S (%) (n=237)	RT (%) (n=202)	S + RT (%) (n=170)	C Alone (%) (n=53)	O (%) (n=230)	P
Gender							
Male	241	61 (25.7)	55 (27.2)	49 (28.8)	17 (32.1)	59 (25.7)	0.846
Female	651	176 (74.3)	147 (72.8)	121 (71.2)	36 (67.9)	171 (74.3)	
Age at diagnosis (years)							
<50	264	65 (27.4)	53 (26.2)	67 (39.4)	17 (32.1)	62 (27.0)	0.008
50-64	276	76 (32.1)	63 (31.2)	55 (32.4)	21 (39.6)	61 (26.5)	
≥65	352	96 (40.5)	86 (42.6)	48 (28.2)	15 (28.3)	107 (46.5)	

(*Continued*)

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Table 1 (Continued).

Variables	N	S (%) (n=237)	RT (%) (n=202)	S + RT (%) (n=170)	C Alone (%) (n=53)	O (%) (n=230)	P
Race/ethnicity							
Non-Hispanic White	528	152 (61.1)	124 (61.4)	100 (58.8)	28 (52.8)	124 (53.9)	0.545
Non-Hispanic Black	71	14 (5.9)	20 (9.9)	15 (8.8)	5 (9.4)	17 (7.4)	
Hispanic (All Races)	182	47 (19.8)	37 (18.3)	34 (20.0)	12 (22.6)	52 (22.6)	
Other	111	24 (10.1)	21 (10.4)	21 (12.4)	8 (15.1)	37 (16.1)	
Tumor location							
Parotid gland	740	220 (92.8)	159 (78.7)	156 (91.8)	40 (75.5)	165 (71.4)	<0.001
Submandibular gland	116	16 (6.8)	31 (15.3)	14 (8.2)	10 (18.9)	45 (19.6)	
Sublingual gland	3	0 (0)	2 (1.0)	0(0)	0(0)	1 (0.4)	
Others	33	1 (0.4)	10 (5.0)	0(0)	3 (5.7)	19 (8.3)	
Ann Arbor stage							
I	649	176 (74.3)	151 (74.8)	140 (82.4)	26 (49.1)	156 (67.8)	<0.001
II	243	61 (25.7)	51 (25.2)	30 (17.6)	27 (50.9)	74 (32.2)	
Chemotherapy							
No	761	193 (81.4)	182 (90.1)	156 (91.8)	0 (0)	230 (100)	<0.001
Yes	131	44 (18.6)	20 (9.9)	14 (8.2)	53 (100)	0 (0)	
B symptoms							
No	401	90 (38.0)	103 (51.0)	172 (42.4)	18 (34.0)	118 (51.3)	0.009
Yes	31	8 (3.4)	11 (5.4)	3 (1.8)	3 (5.7)	6 (3.6)	
Unknown	460	139 (58.6)	88 (43.6)	95 (55.9)	32 (60.4)	106 (46.1)	

Abbreviations: S, surgery; RT, radiotherapy; C, chemotherapy; O, observation.

Treatment Patterns

Of the patients, 237 (26.6%) underwent surgery alone (included 44 patients receipt of chemotherapy), 202 (22.6%) received radiotherapy alone (included 20 patients receipt of chemotherapy), 170 (19.1%) underwent surgery combined with radiotherapy (included 14 patients receipt of chemotherapy), 53 (5.9%) received chemotherapy alone, and 230 (25.8%) had no recorded treatment information (observation). Patients aged >65 years were more likely to undergo surgery alone, chemotherapy alone, or observation, and less likely to receive surgery combined with radiotherapy or chemotherapy alone (P<0.001). Patients with tumors in the submandibular gland were more likely to receive radiotherapy alone, chemotherapy alone, or observation, while those with tumors in the parotid gland were more likely to undergo surgery or surgery combined with radiotherapy (P<0.001). Additionally, patients with stage II disease were more likely to receive chemotherapy or observation (P<0.001) (Table 1). In earlier years of diagnosis, surgery or surgery combined with radiotherapy was the predominant treatment, while in recent years, the proportion of patients undergoing observation has significantly increased (P=0.004) (Figure 2).

Survival Analysis

The median follow-up time for all patients was 92 months (range, 0–262 months). During this period, 209 patients died, including 47 deaths attributed to lymphoma-related causes. The 8-year cancer-specific survival (CSS) and overall survival (OS) rates were 95.6% and 81.8%, respectively. The treatment modality did not significantly affect CSS or OS. The 8-year CSS rates for patients undergoing surgery alone, radiotherapy alone, surgery combined with radiotherapy, chemotherapy alone, and observation were 96.1%, 94.9%, 97.0%, 92.1%, and 95.5%, respectively (P=0.827) (Figure 3A). The 8-year OS rates for these groups were 79.7%, 84.5%, 86.3%, 77.7%, and 79.5%, respectively (P=0.132) (Figure 3B).

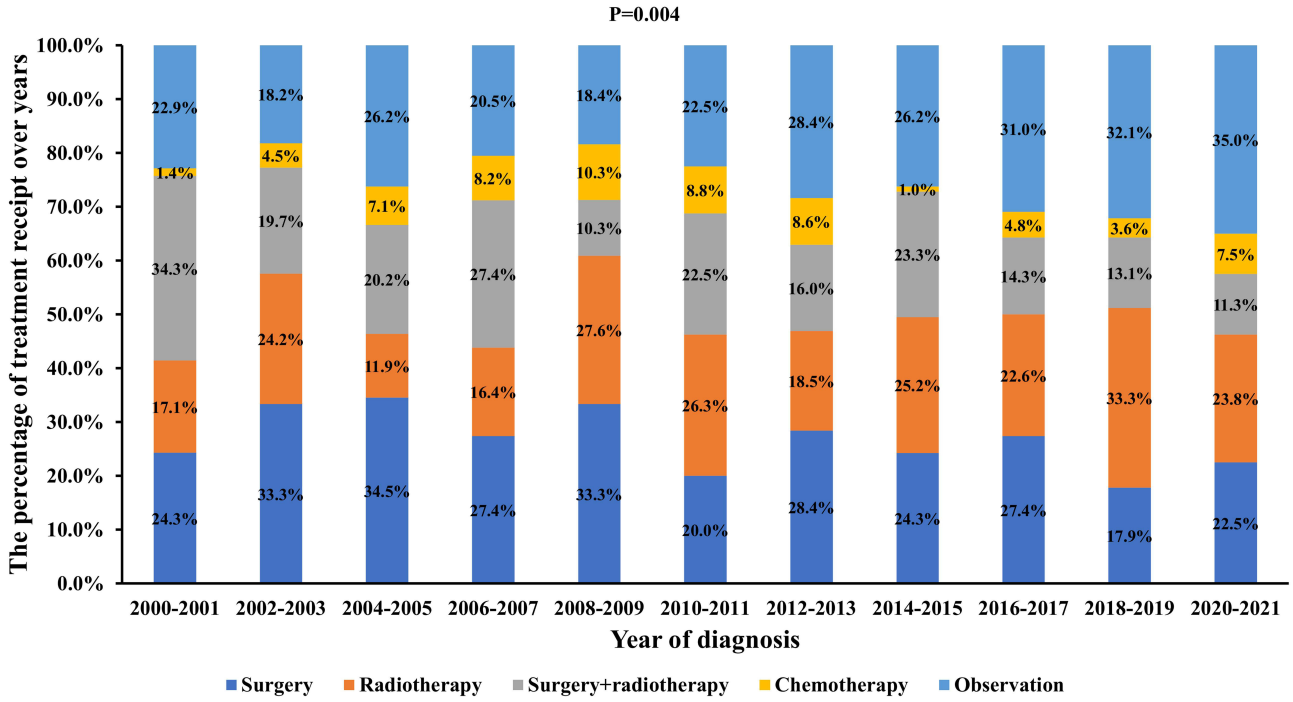

Figure 2 The percentage of the receipt of initial treatment strategies over the years.

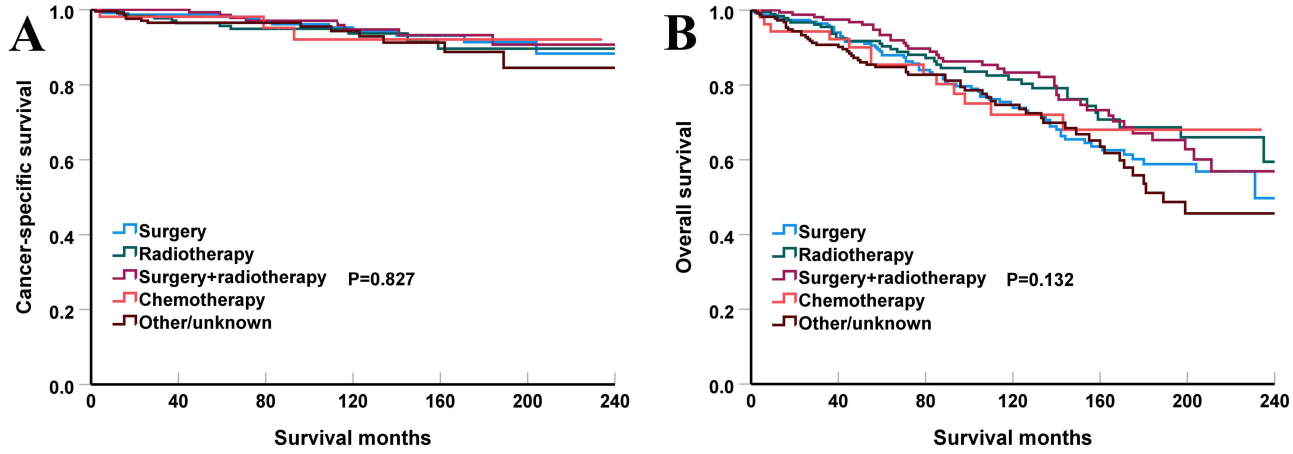

Figure 3 The effect of initial treatment strategies on cancer-specific survival (**A**) and overall survival (**B**).

Prognostic Analysis

Multivariate analysis was performed to identify independent prognostic factors for CSS and OS (Table 2). Age was identified as an independent prognostic factor for CSS, with patients aged 50–64 years having significantly better CSS than those aged >65 years (hazard ratio [HR] 0.366, 95% confidence interval [CI] 0.190–0.704, P=0.003) (Figure 4A). However, initial treatment modality, gender, race/ethnicity, tumor location, and tumor stage did not significantly affect CSS. For OS, multivariate analysis indicated that gender and age were independent prognostic factors. Female patients had significantly better OS than male patients (HR 0.723, 95% CI 0.531–0.984, P=0.039). Additionally, patients aged 50–64 years (HR 0.018, 95% CI 0.006–0.048, P<0.001) and those aged <50 years (HR 0.221, 95% CI 0.159–0.311, P<0.001) had significantly better OS than patients aged >65 years (Figure 4B).

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Table 2 Multivariate Cox Proportional-Hazards Analysis of Prognostic Factors for Cancer-Specific Survival and Overall Survival

Variables	CSS			OS		
	HR	95% CI	P	HR	95% CI	P
Gender						
Male	1			1		
Female	0.621	0.331–1.162	0.136	0.723	0.531–0.984	0.039
Age at diagnosis (years)						
≥65	1			1		
<50	—	—	0.916	0.018	0.006–0.048	<0.001
50-64	0.366	0.190–0.704	0.003	0.221	0.158–0.311	<0.001
Race/ethnicity						
Non-Hispanic White	1			1		
Non-Hispanic Black	1.032	0.313–3.399	0.958	1.240	0.699–2.197	0.462
Hispanic (All Races)	0.459	0.162–1.302	0.143	0.702	0.454–1.086	0.112
Other	0.469	0.143–1.531	0.209	0.679	0.409–1.127	0.134
Tumor location						
Parotid gland	1			1		
Submandibular gland	0.811	0.337–1.955	0.641	0.694	0.449–1.075	0.102
Sublingual gland	—	—	0.992	1.621	0.215–12.227	0.639
Others	0.376	0.050–2.822	0.341	0.653	0.300–1.422	0.283
Ann Arbor stage						
I	1			1		
II	1.161	0.605–2.227	0.654	1.025	0.710–1.419	0.881
Initial treatment						
Surgery	1			1		
Radiotherapy	1.490	0.646–3.434	0.350	0.856	0.563–1.301	0.467
Surgery + radiotherapy	1.125	0.456–2.776	0.799	0.954	0.636–1.431	0.819
Chemotherapy	1.467	0.408–5.275	0.557	1.019	0.607–2.025	0.737
Observation	1.725	0.767–3.882	0.188	1.248	0.862–1.808	0.241

Abbreviations: CSS, cancer-specific survival; OS, overall survival; HR, hazard ratio; CI, confidence interval.

Sensitivity Analysis

Sensitivity analysis was conducted to evaluate the impact of different initial treatment modalities on CSS and OS. The results showed that, regardless of gender, race, age, tumor location, tumor stage, or B symptoms, initial treatment modality did not significantly affect CSS or OS (Tables 3 and 4).

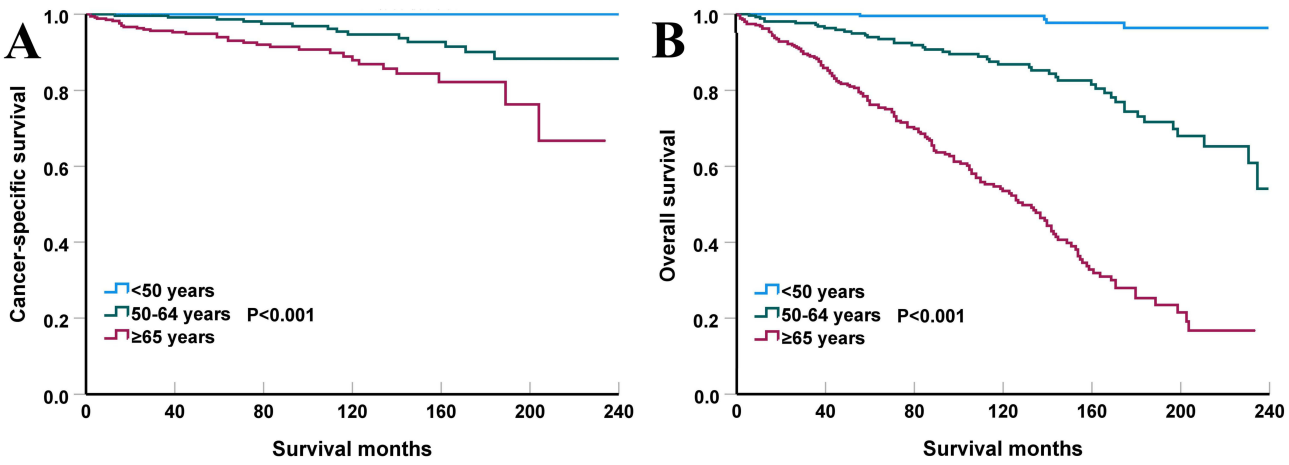

Figure 4 The effect of age on cancer-specific survival (**A**) and overall survival (**B**).

Table 3 Sensitivity Analysis to Evaluate the Impact of Different Initial Treatment Modalities on Cancer-Specific Survival According to Different Patient Characteristics

Variables	Treatment	HR	95% CI	P	Variables	Treatment	HR	95% CI	P
Male	S	1			Parotid gland	S	1		
	RT	0.871	0.234–3.247	0.837		RT	1.483	0.629–3.495	0.367
	S+RT	0.421	0.082–2.170	0.301		S+RT	0.803	0.311–2.072	0.65
	C	1.596	0.305–8.364	0.580		C	0.549	0.071–4.260	0.567
	O	0.514	0.099–2.678	0.429		O	1.657	0.717–3.829	0.237
Female	S	1			Other tumor sites	S	1		
	RT	1.433	0.502–4.088	0.501		RT	0.617	0.039–9.889	0.733
	S+RT	1.176	0.395–3.500	0.770		S+RT	1.512	0.093–24.707	0.772
	C	0.719	0.088–5.851	0.758		C	3.315	0.300–36.673	0.328
	O	2.052	0.794–5.300	0.138		O	0.549	0.034–8.806	0.672
Non-Hispanic White	S	1			Stage I disease	S	1		
	RT	1.588	0.613–4.118	0.341		RT	1.145	0.474–2.766	0.764
	S+RT	1.227	0.445–3.384	0.693		S+RT	0.773	0.300–1.994	0.594
	C	2.254	0.595–8.533	0.232		C	0.625	0.081–4.851	0.653
	O	1.924	0.758–4.887	0.169		O	0.780	0.288–2.114	0.625
Other race/ethnicity	S	1			Stage II disease	S	1		
	RT	0.603	0.110–3.298	0.559		RT	2.389	0.216–26.373	0.477
	S+RT	0.268	0.030–2.405	0.240		S+RT	1.589	0.099–25.593	0.744
	C					C	4.463	0.404–49.304	0.222
	O	0.762	0.170–3.420	0.723		O	6.722	0.826–54.680	0.072
<65 years	S	1			No B symptoms	S	1		
	RT	0.823	0.196–3.445	0.789		RT	—	—	0.986
	S+RT	0.677	0.162–2.834	0.593		S+RT	1.135	0.071–18.175	0.929
	C	1.925	0.370–10.017	0.436		C	—	—	0.994
	O	0.309	0.036–2.646	0.284		O	—	—	0.987
≥65 years	S	1			B symptoms and unknown B symptoms	S	1		
	RT	1.667	0.596–4.660	0.330		RT	1.517	0.644–3.572	0.340
	S+RT	1.385	0.437–4.387	0.580		S+RT	0.781	0.284–2.150	0.633
	C	0.740	0.091–6.025	0.778		C	1.383	0.380–5.036	0.623
	O	1.935	0.755–4.957	0.169		O	1.451	0.527–3.998	0.472

Abbreviations: S, surgery; RT, radiotherapy; C, chemotherapy; O, observation; HR, hazard ratio; CI, confidence interval.

Table 4 Sensitivity Analysis to Evaluate the Impact of Different Initial Treatment Modalities on Overall Survival According to Different Patient Characteristics

Variables	Treatment	HR	95% CI	P	Variables	Treatment	HR	95% CI	P
Male	S	1			Parotid gland	S	1		
	RT	0.632	0.289–1.380	0.249		RT	0.868	0.562–1.339	0.521
	S+RT	0.790	0.384–1.628	0.524		S+RT	0.749	0.496–1.133	0.171
	C	1.098	0.404–2.989	0.854		C	1.023	0.523–2.000	0.946
	O	0.800	0.373–1.716	0.567		O	1.138	0.762–1.699	0.528
Female	S	1			Other tumor sites	S	1		
	RT	0.788	0.488–1.271	0.328		RT	0.513	0.138–1.913	0.32
	S+RT	0.709	0.437–1.149	0.163		S+RT	0.539	0.104–2.793	0.461
	C	0.841	0.398–1.779	0.651		C	1.036	0.247–4.347	0.961
	O	1.298	0.865–1.946	0.207		O	1.087	0.371–3.190	0.879
Non-Hispanic White	S	1			Stage I disease	S	1		
	RT	0.798	0.506–1.261	0.334		RT	0.737	0.466–1.164	0.190
	S+RT	0.678	0.420–1.094	0.112		S+RT	0.735	0.476–1.133	0.163
	C	1.168	0.592–2.304	0.654		C	0.622	0.249–1.557	0.311
	O	1.238	0.818–1.876	0.312		O	1.055	0.698–1.594	0.801

(*Continued*)

Table 4 (Continued).

Variables	Treatment	HR	95% CI	P	Variables	Treatment	HR	95% CI	P
Other race/ethnicity	S	1			Stage II disease	S	1		
	RT	0.253	0.253–1.555	0.313		RT	0.848	0.341–2.110	0.722
	S+RT	1.020	0.479–2.171	0.959		S+RT	0.717	0.248–2.072	0.538
	C	0.686	0.197–2.391	0.554		C	1.633	0.656–4.065	0.292
	O	1.238	0.609–2.516	0.555		O	1.572	0.742–3.330	0.237
<65 years	S	1			No B symptoms	S	1		
	RT	0.592	0.224–1.562	0.289		RT	1.150	0.466–2.836	0.762
	S+RT	1.174	0.551–2.501	0.677		S+RT	0.864	0.321–2.323	0.772
	C	2.412	0.910–6.394	0.077		C	0.475	0.060–3.775	0.482
	O	1.192	0.522–2.723	0.677		O	0.948	0.385–2.336	0.908
≥65 years	S	1			B symptoms and unknown B symptoms	S	1		
	RT	0.830	0.528–1.303	0.418		RT	0.686	0.430–1.092	0.112
	S+RT	0.827	0.509–1.342	0.442		S+RT	0.730	0.470–1.132	0.160
	C	0.644	0.292–1.420	0.275		C	1.009	0.541–1.884	0.977
	O	1.002	0.675–1.488	0.992		O	1.302	0.884–1.920	0.182

Abbreviations: S, surgery; RT, radiotherapy; C, chemotherapy; O, observation; HR, hazard ratio; CI, confidence interval.

Discussion

This study offers a detailed evaluation of the influence of various treatment modalities on survival outcomes in 892 patients with stage I–II salivary gland MALT lymphoma, representing one of the largest cohorts to address regional treatment variations. Our findings demonstrate an exceptionally favorable prognosis in this patient subset, with no statistically significant differences in survival outcomes observed across initial treatment strategies.

Salivary glands are the most commonly affected extra-gastric site for MALT lymphoma, accounting for approximately 10% of cases.[17,18] While lymphomas constitute only 5–10% of all salivary gland tumors,[9,19] MALT lymphoma is the predominant subtype, representing 50–77.5% of salivary gland lymphomas.[12,20] Similar to MALT lymphoma in other sites,[21–23] salivary gland MALT lymphoma is characterized by a high OS rate. A previous study reported a median OS of 18.3 years and a progression-free survival (PFS) of 9.3 years following initial treatment.[24] In our cohort, with a median follow-up of 92 months, the 8-year CSS and OS rates were 95.6% and 81.8%, respectively. Notably, B symptoms were present in only 7.2% of patients with documented symptoms, consistent with findings from a study of primary SS-associated lymphoma, where 76.0% of cases were MALT lymphomas and only 3.2% exhibited B symptoms.[25] These results underscore the indolent nature and favorable prognosis of salivary gland MALT lymphoma. The indolent progression pattern of this lymphoma subtype implies that immediate aggressive treatment may not always be necessary. This slow-growing characteristic is crucial in understanding why active surveillance is a viable strategy for a significant proportion of patients. As time passed, we observed an increasing proportion of cases under observation, which might be due to the recognition of this indolent behavior.

The female predominance (73.0%) observed in our cohort aligns with prior studies, likely reflecting the higher incidence of SS and hepatitis C virus infection among women, both of which are risk factors for MALT lymphoma.[18,26] For instance, non-Hodgkin lymphomas develop in 5–10% of primary SS patients, with 70% of these being MALT lymphomas, predominantly affecting the parotid glands.[10,12,27] Although the SEER database does not capture autoimmune disease status, previous systematic reviews and multicenter studies have reported that 69.5–75% of salivary gland MALT lymphoma patients are female, with 41–80.2% having concurrent autoimmune disorders, most commonly SS.[12,24] This gender disparity may be attributed to the higher prevalence of SS in women and the established association between SS and salivary gland MALT lymphoma. Further research is needed to elucidate the underlying mechanisms driving this gender imbalance.

In our study, 131 patients (14.7%) received chemotherapy. Among them, the percentages of patients who received chemotherapy in the groups of surgery alone, radiotherapy alone, and surgery combined with radiotherapy were 18.6%,

9.9%, and 8.2%, respectively. However, several studies have indicated that the rate of patients initially treated with systemic therapy ranges from 25.8% to 37%.[24,28] The relatively low chemotherapy acceptance rate in this study may be associated with the disease stages of patients, as all the patients included in our study were in stages I–II. In a study by Zhang et al, for 105 patients with head and neck MALT lymphoma (53 cases occurred in the parotid gland), the rate of patients in stages I–II receiving chemotherapy and/or rituximab was lower than that of patients in stages III–IV (21.9% vs 59.4%).[29] Additionally, the SEER database does not record the status of patients receiving rituximab, which may also lead to an underestimation of systemic therapy.

The indolent nature of salivary gland MALT lymphoma has led to a lack of consensus on optimal treatment strategies. For stage I–II extranodal MALT lymphoma, the NCCN guidelines suggest ISRT, surgery, rituximab, or active surveillance as viable options.[13] However, specific recommendations for salivary gland MALT lymphoma remain undefined. In our study, 45.7% of patients underwent surgery with or without radiotherapy, 22.6% received radiotherapy alone, 5.9% were treated with chemotherapy alone, and 25.8% were managed with observation. A prior systematic review of 374 parotid gland MALT lymphoma cases reported treatment distributions of 13.3% surgery alone, 42.7% chemotherapy alone, 18.7% radiotherapy alone, 8.0% combined chemotherapy and radiotherapy, and 17.3% watchful waiting.[12] Similarly, a multicenter international cohort of 248 patients found that 57% received surgery, radiotherapy, or both, 37% underwent systemic therapy, and 6% were observed.[24] These variations highlight the absence of a standardized treatment approach. Interestingly, our study noted a significant increase in the proportion of patients managed with observation in recent years (P=0.004), reflecting a potential shift toward more conservative strategies. This trend may be driven by the indolent nature of the disease, concerns about overtreatment, and a growing emphasis on preserving quality of life. Advances in diagnostic accuracy and surveillance protocols may also contribute to increased clinician confidence in deferring immediate intervention. However, the long-term implications of this approach, particularly regarding disease progression and survival outcomes, warrant further investigation.

Our investigation reveals that the absence of significant disparities in CSS and OS across various treatment modalities (surgery alone, radiotherapy alone, surgery combined with radiotherapy, chemotherapy alone, and observation), implies that the initial treatment choice may not be a pivotal factor in determining survival outcomes for stage I–II salivary gland MALT lymphoma. This observation aligns with the indolent nature of MALT lymphoma, characterized by slow disease progression, where survival is predominantly influenced by patient-specific factors such as age and gender rather than the treatment modality employed. Another reason might be that the early-stage nature of this disease in our study plays a role. In early-stage salivary gland MALT lymphoma, the tumor may be more localized and less invasive, and thus different treatment modalities may have similar effectiveness in achieving oncological control. The uniformly high survival rates across all groups (8-year CSS: 92.1%-97.0%; 8-year OS: 77.7–86.3%) further underscore the generally favorable prognosis of early-stage disease, irrespective of the therapeutic approach. Consistent with our findings, Jackson et al reported a median OS of 18.3 years and a median progression-free survival (PFS) of 9.3 years following primary therapy, with no significant differences in outcomes between patients receiving local (surgery, surgery plus radiotherapy, or radiotherapy alone) or systemic therapy in first-line management of stage I–II disease.[24] Similarly, Wen et al included 84 patients with salivary gland MALT lymphoma and found no significant difference in PFS between surgical and conservative treatment groups.[30] Parallel outcomes have been documented in MALT lymphomas affecting other anatomical sites. For instance, studies on colon MALT lymphoma also indicate no substantial survival differences among patients treated with local therapy, chemotherapy, or observation.[21] Nonetheless, close follow-up is essential, as approximately 31% of patients may experience disease progression post-treatment, including recurrence in the ipsilateral salivary gland or neck (29.4%), contralateral salivary gland (31.4%), and distant sites (39.2%).[24] Another study indicated that in MALT patients with primary SS, the 5-year and 10-year event-free survival rates were 63.6% and 45.5%, respectively.[25] Moreover, antibiotic therapy emerges as a viable treatment option. In a study of 28 patients with extranodal MALT lymphoma treated with antibiotics as first-line therapy, including four with parotid gland MALT lymphoma, only one patient experienced disease progression after five years, while the remaining three remained disease-free during a follow-up period of 5.0–7.7 years.[31] These findings collectively highlight a universal survival advantage for localized salivary gland MALT lymphoma, regardless of the initial management strategy.

Given the excellent outcomes across all treatment strategies, it is imperative to consider the side-effect profile and potential long-term complications when tailoring treatment to individual patients. MALT lymphomas originating from the orbit and ocular adnexa may adversely affect the cosmetic outcomes of the ocular and surrounding tissues with local surgical treatment. In contrast, radiotherapy may offer advantages in preserving the organs and mitigating potential cosmetic adverse effects, while also demonstrating excellent local control rates (5-year local control rate of 98%).[32] Nonetheless, in cases of intestinal MALT, surgical procedures continue to be crucial for acquiring biopsy samples and enabling accurate pathological assessment.[33] Parotidectomy, often performed for diagnostic purposes, was considered curative in about one-fifth of surgical cases, with no further treatment required. For localized MALT lymphomas, unimodal treatment is often deemed sufficient.[34,35] Both surgery and radiotherapy are equally effective in our study and previous research.[34,35] However, it is crucial to recognize that a significant proportion of patients with salivary gland MALT lymphomas also suffer from SS. For non-gastric MALT lymphomas, ISRT at doses of 20–24 Gy is recommended.[14,36] Regarding the functional impairments of different treatment modalities, irradiation of the salivary gland may exacerbate gland dysfunction, leading to xerostomia and associated complications such as altered appetite, impaired swallowing, increased dental caries, and permanent dietary modifications.[37,38] In our study, a substantial number of patients received radiotherapy either alone or in combination with surgery. Therefore, the potential long-term local toxicities must be carefully weighed against the side effects of cytotoxic therapy, especially given the prolonged survival expected in most patients. Future research should quantify the incidence and severity of xerostomia and other functional impairments associated with radiotherapy and other treatment methods. This information can help in making more informed treatment decisions, especially when balancing the potential benefits of treatment against its side effects.

Multivariate analysis in our study identified age and gender as independent prognostic factors for survival outcomes, with younger patients and females demonstrating superior survival rates. The protective effect of younger age may be attributed to better overall health and treatment tolerance, while the superior OS in females could be linked to hormonal or immunological factors. These findings underscore the necessity for personalized treatment strategies informed by tumor biology and patient-specific risks. Jackson et al found that age <60 years and a low to intermediate international prognostic index were associated with improved OS and PFS, and the presence of SS was linked to better OS.[24] Conversely, Zhang et al reported that patients without SS had prolonged recurrence-free survival compared to those with SS.[28] Additionally, several studies have implicated Trisomy 18 in predicting tumor relapse.[28,39] Interestingly, tumor stage did not significantly impact CSS or OS, further emphasizing the importance of patient-specific factors in determining outcomes.

Several limitations of this study should be acknowledged. First, its retrospective nature introduces potential biases, including selection bias and unmeasured confounding factors. Second, the lack of detailed data on Sjögren's syndrome status, treatment regimens, dosages, and compliance limits the ability to assess the impact of specific therapeutic approaches. Third, the long follow-up period (median 92 months) may have introduced variability in treatment practices over time, particularly with the increasing use of observation. Future prospective studies are needed to validate the long-term safety of observation strategies in this patient subset. Additionally, the relatively small number of patients in certain subgroups (eg, chemotherapy alone, n=53) may have limited the statistical power to detect differences in survival outcomes. Finally, the absence of data on recurrence rates, long-term toxicity, or quality-of-life metrics may still influence treatment decisions.

Conclusions

In conclusion, this study highlights that stage I–II salivary gland MALT lymphoma is characterized by a female predominance and an increasing trend toward observation as a management strategy. The lack of significant survival differences across treatment modalities suggests that the choice of initial treatment may be less critical than patient-specific factors such as age and gender. However, further clarification is required regarding the selection criteria for the observation group, particularly whether these patients were primarily low-risk cases, as this could significantly influence the interpretation of the findings. Additionally, the potential impact of treatment selection bias, evidenced by the notably lower utilization of chemotherapy in our cohort compared to other studies, necessitates further investigation to ensure the

generalizability and robustness of our results. Furthermore, the growing adoption of the observation strategy highlighted in this study should be substantiated with functional outcome data, such as quality of life assessments, to provide a more comprehensive evaluation of its clinical benefits and potential limitations. These findings advocate for personalized treatment approaches and underscore the importance of further research to better understand the underlying mechanisms driving gender disparities and the long-term outcomes of conservative management strategies. Future prospective studies with standardized treatment protocols and detailed patient data are warranted to refine treatment guidelines, prioritizing both efficacy and the minimization of treatment-related harms for this rare malignancy.

Data Sharing Statement

The datasets used and/or analyzed during the current study are available from the corresponding author Dr. San-Gang Wu upon reasonable request.

Ethics Approval and Consent to Participate

The study was approved by the Ethics Committee of the First Affiliated Hospital of Xiamen University (approval number XMFHIIT-2025SL156), and informed consent was waived due to the retrospective nature of the study.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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The authors declare that they have no competing interests in this work.

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