

Survival of Patients With Marginal Zone Lymphoma

Analysis of the Surveillance, Epidemiology, and End Results Database

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BACKGROUND. Prognostic factors and outcomes in patients with marginal zone lymphoma (MZL) have been studied in small cohort studies, which may not reflect the population at large. **METHODS.** Clinical characteristics and survival outcomes of adult patients with MZL who were diagnosed between 1995 and 2009 were evaluated using the Surveillance, Epidemiology, and End Results (SEER) database. The authors generated clinical prognostic models for subtypes of MZL and compared survival during the periods of 1995 through 2000, 2001 through 2004, and 2005 through 2009. **RESULTS.** The prognosis was significantly better for patients with mucosa-associated lymphoid tissue (MALT) lymphoma (5-year relative survival rate of 88.7%; $P < .0001$) compared with those with the splenic MZL (SMZL) or nodal MZL (NMZL) subtypes (5-year relative survival rates of 79.7% and 76.5%, respectively). There was evidence of improved outcomes in patients with NMZL and MALT lymphomas between 1995 and 2009 ($P < .0001$), with no difference noted in patients with SMZL ($P = .56$). Advancing age and the presence of B symptoms had prognostic significance in all MZL subtypes. Male sex and stage of disease were significant only for the NMZL and MALT categories. Survival in patients with MALT lymphomas varied depending on the site of origin, with a worse prognosis noted in those with gastrointestinal and pulmonary locations of origin (5-year incidence rate of lymphoma-related death, 9.5%-14.3%) compared with ocular, cutaneous, and endocrine sites (4.5%-7.8%; $P < .0001$). **CONCLUSIONS.** The survival for patients with SMZL is similar to that for those with NMZL, and unlike the NMZL and MALT subtypes, it has not improved over the past decade. The prognosis of patients with MALT lymphoma varies according to the anatomical site of origin. *Cancer* 2013;119:629-38. © 2012 American Cancer Society.

KEYWORDS: marginal zone B-cell lymphoma, mucosa-associated lymphoid tissue (MALT), lymphoma, Surveillance, Epidemiology, End Results (SEER), program, epidemiology.

INTRODUCTION

Marginal zone lymphoma (MZL) is an indolent, mature B-cell neoplasm recognized by the World Health Organization (WHO) classification as 3 entities: nodal (NMZL), splenic (SMZL), and extranodal MZL of mucosa-associated lymphoid tissue (MALT) type.¹ The subtypes share a similar immunophenotype, but differ with regard to clinical characteristics and prognosis. NMZL had been reported to confer a worse prognosis, whereas SMZL is considered to be particularly indolent.^{2,3} Because of the rarity of MZL, prognostic factors and therapy have been studied in small cohort studies, often originating from tertiary centers, which may not be representative of the general population.⁴

Based on retrospective reviews, splenectomy had been the favored treatment of SMZL.^{5,6} In patients with NMZL, treatment typically follows the guidelines for follicular lymphoma.⁷⁻⁹ MALT lymphomas are associated with infections of specific sites and treatment paradigms vary by tumor site and stage. Rituximab alone or in combination with chemotherapy is reported to provide high response rates in patients with MZL and has been advocated for those with disseminated or recurrent disease.^{10,11}

The purpose of the current study was to evaluate the clinical characteristics and survival of patients with MZL subtypes in the unselected population included in the Surveillance, Epidemiology, and End Results (SEER) database.¹²

MATERIALS AND METHODS

Data Source and Cohort Selection

The SEER program collects cancer incidence, treatment, and survival information from 18 areas in the United States, representing 28% of the population. We used tables of incidence rates, relative survival, and case listings extracted by SEER*-Stat software. Our initial query included all adult patients with *International Classification of Diseases for Oncology, 3rd*

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We acknowledge the efforts of the Applied Research Program, National Cancer Institute; Information Management Services, Inc; and the Surveillance, Epidemiology, and End Results (SEER) program tumor registries in the maintenance of the SEER database as a research resource.

DOI: 10.1002/cncr.27773, **Received:** April 29, 2012; **Revised:** July 9, 2012; **Accepted:** July 13, 2012, **Published online** August 14, 2012 in Wiley Online Library (wileyonlinelibrary.com)

Table 1. Characteristics of Patients with Splenic MZL and Extranodal MZL Originating in the Spleen or Other Primary Tumor Sites

Variable		Splenic MZL	Extranodal MZL: Splenic	Extranodal MZL: Other Sites
ICD-O-3 code		9689	9699	9699
No. of cases		915	383	9886
Median age, y		68	69	67
Y of diagnosis, %	1995-2001	1.4	25.1	21.8
	2002-2004	38.5	27.9	33.3
	2005-2009	60.1	47.0	44.9
Race, %	White non-Hispanic	82.7	83.3	71.1
	White Hispanic	6.3	8.4	10.5
	Black	5.2	4.2	7.5
	Asian/other	4.3	3.9	9.1
	Unrecorded	1.5	0.2	1.8
Female sex, %		53.0	54.1	55.4
B symptoms, %		21.8	25.1	8.0
Stage, %	I	18.9	30.3	65.5
	II	6.2	6.5	10.0
	III/IV	70.8	59.8	15.5
	Unrecorded	4.1	3.4	9.1
Radiation, %		1.2	1.3	29.0
Lymphoma-related deaths at 5 y, %		17.3	17.7	8.9

Abbreviations: ICD-O-3, International Classification of Diseases for Oncology, 3rd edition; MZL, marginal zone lymphoma.

edition (ICD-O-3) codes 9689 (“splenic MZL”), 9699 (“MZL [not otherwise specified] NOS”), 9760 (“immunoproliferative disease, NOS”), and 9764 (“immunoproliferative small intestinal disease”) who were diagnosed between 1995 and 2009. We excluded cases with non-B-cell histology (49 cases), those identified through autopsy/death certificate (13 cases), those alive with no recorded survival time (198 cases), and those with duplicate records (31 patients). There was no selectivity of these exclusions with regard to MZL categories or period of diagnosis. Patients aged < 22 years were excluded from the analysis.

Definition of Variables

The database contains variables indicating a patient’s age at the time of diagnosis, year of diagnosis, and race and ethnicity, as well as information regarding socioeconomic status by county, histology, anatomical site and extent of malignancy, survival time, and cause of death. Treatment information is limited to surgery and radiotherapy. We established the subset of individuals with Hispanic ethnicity separate from the white population using the North American Association of Central Cancer Registries (NAACCR) Hispanic Identification Algorithm.¹³ Staging was based on the 7th edition of the American Joint Committee on Cancer manual for staging.

The MZL subtypes were designated using the International Lymphoma Epidemiology Consortium (InterLymph) classification, with 1 adaptation.¹⁴ The InterLymph schema declares ICD-O-3 code 9699 histology to be MALT lymphoma except for cases originating

in the lymph nodes. However, the profile of cases with the spleen as the primary tumor site differed from other MALT lymphomas and mirrored SMZL, and therefore they were categorized as SMZL (Table 1). The incidence rates were evaluated within the period between 2001 and 2009 to maintain homogeneous nomenclature. In cases of MALT lymphoma, we grouped the primary sites into the following categories: ocular, salivary gland, thyroid, other head/neck, lung, gastric, other gastrointestinal tract, genitourinary, cutaneous, breast, connective tissue, central nervous system, and other/unknown. Very rare or uncertain MALT sites (241 cases) were omitted from the survival analysis by anatomical origin.

Survival Endpoints

Lymphoma-specific survival (LSS) and overall survival (OS) were the outcomes of interest in the current study. In SEER, cause-specific survival is assigned only for the first malignancy occurring in each patient. Cancer-related death is determined by virtue of an algorithm incorporating death certificate, number, sequence, and sites of neoplasms and comorbidities.¹⁵ For the definition of lymphoma-related death, we used cause-specific events and all fatalities caused by any lymphoma/leukemia. This definition may overcome misattribution of causes on death certificates. When possible, we used relative survival, adjusted to age, sex, and race, because it is an estimate that is comparatively immune to death certificate inaccuracies. For trend comparison, the study was divided

Table 2. Patient Characteristics

Characteristic		All Patients	Lymphoma Subtype			P
			SMZL	NMZL	MALT	
No. of cases	No.	15,908	1298	4724	9886	
	%	100	8.2	29.7	62.1	
Clinical characteristics (% by lymphoma subtype)						
Mean age (SD), y		66 (14.3)	67.4 (12.7)	67.7 (13.5)	65.1 (14.8)	
Median (IQR)		68 (56-77)	69 (58-77)	69 (58-78)	67 (55-77)	.0001
Age groups, %	22-39 y	4.5	1.8	2.8	5.6	
	40-49 y	9.4	7.2	7.3	10.7	
	50-59 y	17.9	19.4	17.1	18.1	
	60-69 y	23.0	24.5	23.7	22.6	
	70-79 y	26.2	28.0	28.8	24.8	
	>80 y	19.0	19.2	20.5	18.2	
Race, %	White non-Hispanic	74.2	82.9	78.1	71.1	<.0001
	White Hispanic	9.6	6.9	8.5	10.5	
	Black	7.0	4.9	6.7	7.5	
	Asian/other	7.5	4.2	5.1	9.1	
	Unrecorded	1.7	1.2	1.6	1.8	
Sex	Women	54.4	53.3	52.8	55.4	.01
	Men	45.6	46.7	47.2	44.7	
B symptoms, %	Present	11.3	22.7	14.9	8.0	<.0001
	Absent	48.6	42.5	43.9	51.6	
	Unrecorded	40.2	34.8	41.2	40.4	
Stage, %	I	47.3	22.3	16.1	65.5	<.0001
	II	10.1	6.3	11.4	10.0	
	III/IV	33.6	67.6	62.2	15.5	
	Unrecorded	9.0	3.9	10.4	9.1	
		20.8	1.2	9.2	29.0	<.0001
Radiotherapy, %		20.8	1.2	9.2	29.0	<.0001
Median follow-up (IQR), mo		42 (17-77)	35 (15-65)	35 (14-66)	47 (20-83)	.0001
Deceased, %		28.4	29.8	33.7	25.7	<.0001
Lymphoma-related death, %		12.2	16.3	18.3	8.8	<.0001
NHL as first malignancy, %		82.0	81.7	79.7	83.1	<.0001
Subsequent DLBCL, %		0.8	1.6	0.9	0.7	.004
Temporal and geographic distribution (% by row)						
Y of diagnosis, no.	1995-2000	2999	3.6	24.5	71.8	<.0001
% by epoch	2001-2004	5242	8.8	28.4	62.8	
	2005-2009	7667	9.5	32.6	57.9	
Region, no., % by region	East	4933	8.3	31.0	60.7	<.0001
	Northern Plains	1731	10.3	28.5	61.2	
	Pacific Coast	8597	7.5	29.6	62.9	
	Southwest	647	9.7	24.7	65.5	
Type of geographic area, no., % by area	Rural	197	8.6	24.4	67.0	.02
	Urban	1396	9.9	27.3	62.8	
	Metropolitan	14,309	8.0	30.0	62.0	

Abbreviations: DLBCL, diffuse large B-cell lymphoma; IQR, interquartile range; MALT, mucosa-associated lymphoid tissue; NHL, non-Hodgkin lymphoma; NMZL, nodal marginal zone lymphoma; SD, standard deviation; SMZL, splenic marginal zone lymphoma.

into the periods of 1995 through 2000, 2001 through 2004, and 2005 through 2009.

Statistical Analysis

The Kruskal-Wallis and chi-square tests for multiple proportions were used to analyze differences between MZL subtypes. OS was analyzed using the Kaplan-Meier method. Because of the high percentage of deaths unrelated to lymphoma, competing-risk analysis was used for cause-specific death.¹⁶ Differences between cumulative incidence function curves were evaluated using the Gray test stratified by age quintiles and OS estimates using the

stratified log-rank test.¹⁷ Multivariate Cox regression models using backward selection with a criterion of $P < .05$ for retention were used to study prognostic factors for LSS. Cause-specific hazards regression was chosen as being more suitable to assess the “pure” biological effect of covariates on the malignancy outcome. Conversely, competing risk regression models take into account the impact of confounders on other causes of death.¹⁸ Model assumptions were tested with log-log plots, observed-to-expected plots, and Schoenfeld residuals. Variables violating the proportional hazards assumption were modeled using time interaction. All statistical tests are reported

with 2-tailed P values and 95% confidence intervals (95% CIs), at an α level of .05 or lower, using Stata statistical software (version 11.2; StatCorp LP, College Station, Tex) and R software (version 2.15.0; R Foundation for Statistical Computing, Vienna, Austria) with *cmprsk* library.¹⁹

RESULTS

Patient Characteristics

A total of 15,908 patients with a median age of 68 years were included in the study. MALT lymphoma was the most common subtype, with an incidence rate of 1.59 per 100,000 adults, followed by NMZL (0.83 per 100,000 adults), and SMZL (0.25 per 100,000 adults). There was a significant increase in the incidence of reported MZL over the course of the decade, particularly NMZL (increase of 41% between 2001 and 2009; $P < .0001$). Because no reciprocal net decrease among other nodal indolent B-cell lymphomas was observed, a biological phenomenon may underlie this change, although increasing recognition of histological subtypes may have contributed.²⁰ MALT lymphomas constituted 5%, NMZL contributed 2.4%, and SMZL contributed 0.7% of all B-cell lymphomas.

Table 2 summarizes the patient characteristics. There was a higher percentage of SMZL/NMZL in white patients (odds ratio [OR], 1.56; 95%CI, 1.42-1.71 [$P < .0001$]), with a particular excess of MALT lymphomas reported in Asians (OR, 1.93; 95%CI, 1.68-2.21 [$P < .0001$]) and Latinos (OR, 1.42; 95%CI, 1.27-1.59 [$P < .0001$]) compared with non-Hispanic white patients). MALT lymphomas were primarily localized, whereas NMZL/SMZL cases presented at advanced stages. Approximately 51% of patients with SMZL underwent splenectomy; however, diagnostic and therapeutic procedures could not be distinguished. Secondary diffuse large B-cell lymphomas (DLBCLs) were recorded in 137 cases, more frequently in patients with SMZL.

Survival Analysis

The 15,908 patients included in the survival analysis corresponded to a cumulative time at risk of 66,855 person-years. Overall, 4522 patients (28%) died, with 43% of events being related to lymphoma (55% of events in SMZL, 54% in NMZL, and 34% in MALT lymphomas). Other competing causes of death included cardiovascular disease (20%), other malignancies (14%), and lung pathology (5%). The incidence of lymphoma-related death and OS were found to be significantly better in patients with MALT lymphoma (Fig. 1) (Table 3). There were no

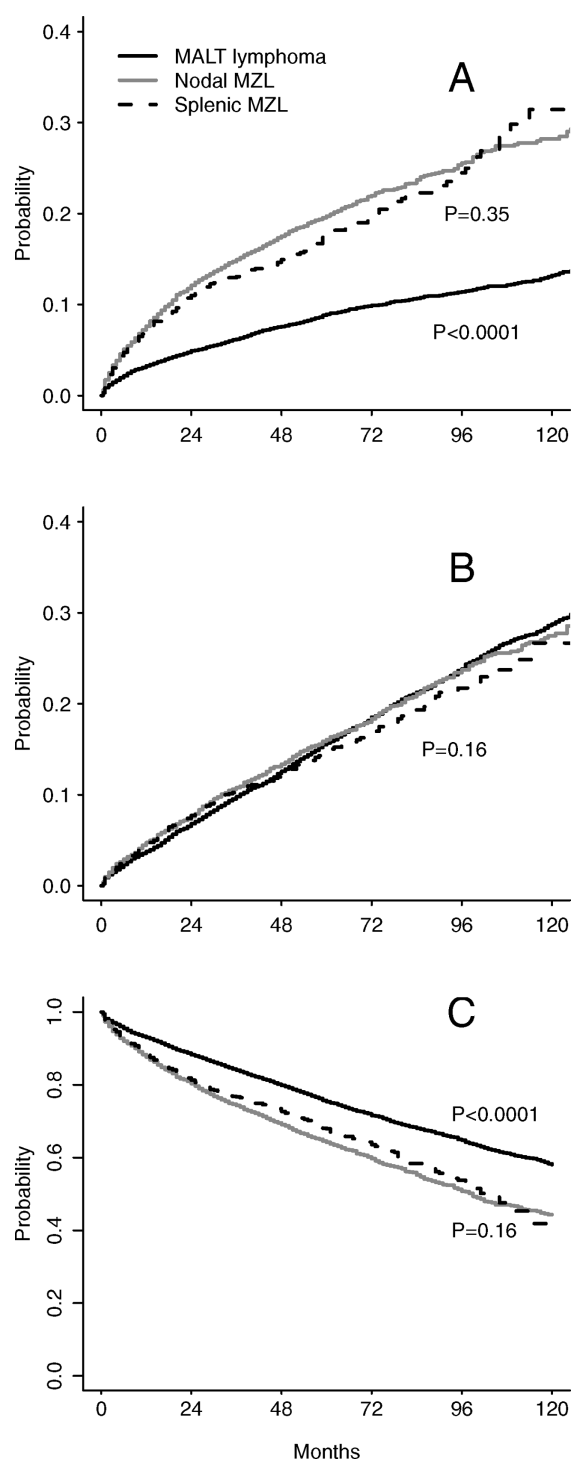


Figure 1. Survival outcomes are shown for the subtypes of marginal zone lymphoma (MZL). The cumulative incidence function for (A) lymphoma-related death and (B) competing causes of death is shown. (C) The Kaplan-Meier estimate of overall survival is shown. MALT indicates mucosa-associated lymphoid tissue.

significant differences noted with regard to deaths from competing causes. The median OS was 8.6 years for patients with SMZL, 8.3 years for patients with NMZL,

Table 3. Survival Endpoints in MZL Subgroups

Lymphoma Subtype	5-Year Survival (95% CI), %	10-Year Survival (95% CI), %	<i>P</i> ^a
Lymphoma-specific survival (Kaplan-Meier)			
All MZL	86.3 (85.6-86.9)	78.7 (77.5-79.8)	
Splenic	81.0 (78.2-83.6)	62.7 (54.3-69.9)	
Nodal	78.6 (77.2-80.0)	67.3 (64.6-69.8)	.32
MALT	90.4 (89.6-91.0)	84.7 (83.4-85.9)	<.0001
Relative survival (actuarial)^b			
All MZL	84.4 (83.4-85.4)	75.1 (73.1-76.9)	
Splenic	79.7 (75.8-83.1)	57.9 (46.8-67.4)	
Nodal	76.5 (74.5-78.4)	62.8 (58.9-66.5)	.22
MALT	88.7 (87.5-89.8)	81.4 (79.0-83.5)	<.0001
Overall survival			
All MZL	71.5 (70.7-72.3)	53.3 (52.0-54.7)	
Splenic	67.9 (64.7-70.9)	41.9 (34.6-49.0)	
Nodal	64.2 (62.5-65.8)	44.3 (41.7-46.9)	.17
MALT	75.4 (74.3-76.3)	58.0 (56.4-59.6)	<.0001

Abbreviations: 95% CI, 95% confidence interval; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.

^a*P* values for lymphoma-specific and overall survival were based on stratified log-rank comparisons of MALT versus non-MALT lymphoma and splenic versus lymph node MZL.

^bRelative survival *P* value is based on the *z* statistic test at 5 years.

and 12.6 years for patients with MALT lymphoma. A subsequent diagnosis of DLBCL was associated with worse LSS in patients with the MALT subtype (univariate hazards ratio [HR], 2.95; 95%CI, 1.97-4.43 [*P* < .0001]) but not for those with the SMZL (HR, 0.70; 95%CI, 0.22-2.20 [*P* = .54]) or NMZL (HR, 1.57; 95%CI, 0.95-2.63 [*P* = .08]) subtypes.

The analysis by disease stage revealed the influence of stage distribution on the survival discrepancies noted in patients with MZL subcategories (Fig. 2). Patients with SMZL demonstrated similar outcomes in stage I, II, and III/IV disease, with 5-year incidence rates of lymphoma-related death of 15.3%, 19.5%, and 18.3%, respectively. In contrast, the corresponding values were 10.7%, 16.8%, and 22.9%, respectively, for patients with NMZL and 6.1%, 13.6%, and 17.6%, respectively, for patients with MALT lymphoma.

When comparing survival trends, we noted a significant improvement in the probability of lymphoma-related death for patients with NMZL and MALT lymphoma that was diagnosed after 2000, with further improvement observed after 2005 in patients with MALT lymphoma. Conversely, there was no demonstrable improvement noted in SMZL (Fig. 3). Similar findings were apparent with regard to relative survival and OS. The 2-year relative survival rate for patients with MALT lymphoma steadily increased from 91.5% between 1995 and 2000 to 94.2% between 2001 and 2004 and 96.0% after 2005. In patients with NMZL, the respective values were 82.5%,

87.2%, and 87.4%, respectively. In patients with SMZL, there was no evident trend noted with values of 87.4%, 86%, and 87.5%, respectively. The significance of these trends was confirmed in regression models adjusting for multiple factors (Table 4). A sensitivity analysis limited to 13 registries reporting in both decades demonstrated similar results. There was also no evidence of a significant stage shift for patients with SMZL (*P* = .06) and MALT lymphoma (*P* = .59), whereas the percentage of disseminated NMZL cases increased over the study period (*P* < .0001).

To evaluate prognostic factors for LSS, separate Cox proportional hazard models were fitted for each MZL subtype (Table 4). The variables included age, sex, race, year of diagnosis, geographical region and type of area, poverty level, stage of disease, presence of B symptoms, prior malignancy, and receipt of surgery or radiotherapy. Gender and stage of disease were not found to be significant in the case of SMZL. Receipt of surgery or radiotherapy was not found to be statistically significant, with the exception of radiotherapy in patients with stage I MALT lymphoma, which was modeled as a stratifying factor.

Survival in MALT Lymphoma Depends on the Site of Origin

There were significant differences noted with regard to MALT lymphomas depending on the anatomical site of origin (Table 5). Gastric, ocular, bowel, pulmonary, and salivary gland sites were the most common. Women had more breast, thyroid, and salivary gland tumors, but

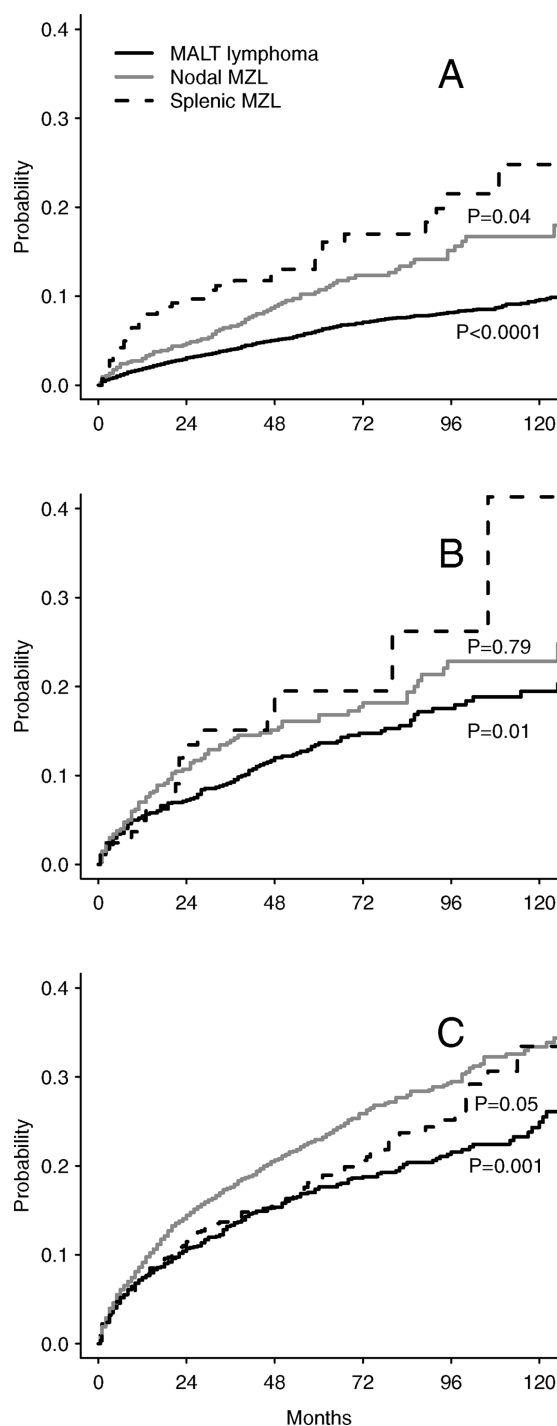


Figure 2. Cumulative incidence of lymphoma-related death is shown in marginal zone lymphoma (MZL) subtypes by stage: (A) stage I, (B) stage II, and (C) stage III/IV. *P* values correspond to Gray test comparisons between splenic MZL versus nodal MZL and non-mucosa-associated lymphoid tissue (non-MALT) versus MALT lymphomas.

fewer skin lymphomas. Noteworthy findings with regard to the racial distribution were relatively higher rates of salivary gland MALT lymphomas observed in white Lat-

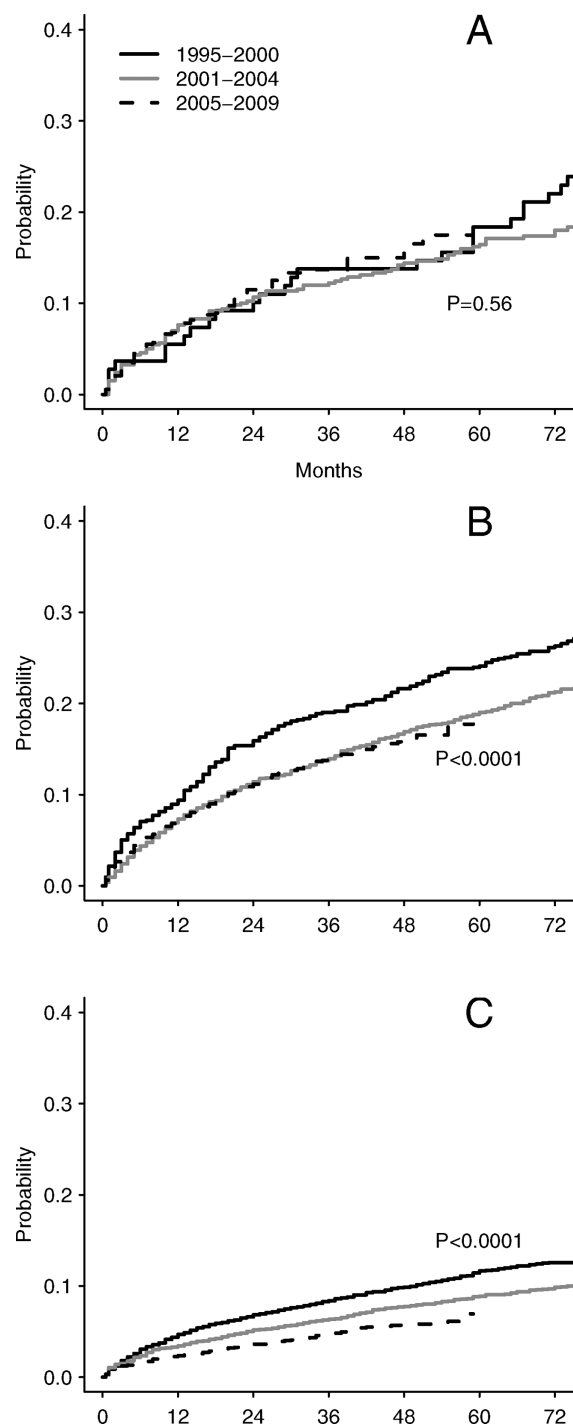


Figure 3. Trends in the cumulative incidence of lymphoma-related death are shown for 3 periods during the study for: (A) splenic marginal zone lymphoma (MZL), (B) nodal MZL, and (C) extranodal mucosa-associated lymphoid tissue lymphoma.

inos, lower rates of cutaneous MALT reported among black patients, and a higher frequency of ocular and bowel tumor locations noted in Asian individuals ($P < .0001$).

Table 4. Prognostic Models for Lymphoma-Specific Survival in MZL Subtypes

Variable	Patients, %	HR (95% CI)	P
Splenic MZL (n = 1236)			
Age (10-y increments)		1.70 (1.49-1.94)	<.0001
Male sex	47	1.13 (0.85-1.49)	.40
Race			
White non-Hispanic	83	Reference	
White Hispanic	7	1.10 (0.65-1.86)	.71
Black	5	1.46 (0.76-2.79)	.25
Asian	4	1.03 (0.52-2.01)	.94
Stage			
I	23	Reference	
II	7	1.59 (0.87-2.90)	.13
III/IV	70	1.33 (0.94-1.89)	.11
B symptoms	23	1.81 (1.27-2.59)	.001
Y of diagnosis			
2001-2004	35	0.81 (0.54-1.23)	.33
2005-2009	56	0.91 (0.58-1.42)	.67
Nodal MZL (n = 4188)			
Age (10-y increments)		1.58 (1.49-1.68)	<.0001
Male sex	47	1.19 (1.04-1.37)	.014
Race			
White non-Hispanic	79	Reference	
White Hispanic	9	1.43 (1.12-1.82)	.004
Black	7	1.22 (0.89-1.67)	.21
Asian	5	1.00 (0.71-1.39)	.98
Stage			
I	18	Reference	
II	13	1.72 (1.27-2.33)	.0001
III/IV	69	2.25 (1.77-2.85)	<.0001
B symptoms	15	2.25 (1.86-2.72)	<.0001
Y of diagnosis			
2001-2004	32	0.67 (0.56-0.80)	<.0001
2005-2009	53	0.59 (0.48-0.72)	<.0001
MALT lymphoma (n = 8871)			
Age (10-y increments)		1.76 (1.65-1.87)	<.0001
Male sex	45	1.31 (1.14-1.51)	.0002
Race			
White non-Hispanic	72	Reference	
White Hispanic	11	1.40 (1.11-1.77)	.004
Black	8	1.31 (1.00-1.72)	.05
Asian	9	1.49 (1.18-1.87)	.001
Stage			
I	72	Reference	
II	11	2.39 (1.96-2.92)	<.0001
III/IV	17	3.02 (2.57-3.55)	<.0001
B symptoms	8	1.81 (1.46-2.25)	<.0001
High-risk site ^a	64	1.83 (1.41-2.38)	<.0001
Interaction with time		0.99 (0.99-1.00)	.008
Y of diagnosis			
2001-2004	33	0.76 (0.65-0.90)	.001
2005-2009	45	0.53 (0.43-0.65)	<.0001

Abbreviations: 95% CI, 95% confidence interval; HR, hazards ratio; MALT, mucosa-associated lymphoid tissue; MZL, marginal zone lymphoma.

^aAll anatomical sites except skin, ocular, thyroid, breast, connective tissue, and salivary.

Table 5. Clinical Features and Survival in MALT Lymphomas of Different Anatomical Origin

Site ^a	No. of Patients		Median Age, Years	Stage IE, %	Radiotherapy, %	5-Year Lymphoma-Related Death (95% CI), %	5-Year OS (95% CI), %
	No.	%					
Skin	680	6.9	58	84.5	42.8	4.5 (2.9-6.5)	87.9 (84.5-90.6)
Ocular	1323	13.4	65	82.2	61.5	4.9 (3.6-6.4)	83.3 (80.8-85.6)
Thyroid	210	2.1	65	72.4	45.7	5.7 (2.7-10.3)	84.5 (77.7-89.4)
Connective tissue	221	2.2	66	64.4	37.6	6.3 (3.3-10.6)	78.5 (71.5-84.0)
Breast	304	3.1	68	66.0	31.9	7.7 (4.6-11.8)	78.8 (72.6-83.7)
Salivary glands	818	8.3	63	67.4	38.1	7.8 (5.8-10.2)	81.8 (78.4-84.7)
Gastric	3596	36.4	69	80.5	21.4	9.5 (8.5-10.6)	71.0 (69.3-72.7)
Pulmonary	860	8.7	68	58.3	7.4	10.3 (8.1-12.8)	72.7 (68.9-76.1)
Other head and neck	425	4.3	66	58.8	39.3	11.2 (8.0-14.9)	75.3 (70.0-79.8)
Genitourinary tract	153	1.6	70	62.4	20.3	12.4 (6.7-19.9)	75.6 (65.6-83.1)
GI tract (excluding stomach)	991	10.0	67	62.7	9.6	14.3 (12.0-16.9)	69.1 (65.7-72.3)
CNS	61	0.6	58	78.3	55.7	17.3 (8.4-29.0)	71.3 (56.7-81.8)

Abbreviations: 95% CI, 95% confidence interval; CNS, central nervous system; GI, gastrointestinal; MALT, mucosa-associated lymphoid tissue; OS, overall survival.

^aExcluding 2 cases with the adrenal glands as the primary tumor site; 36 cases with an unknown primary tumor site; and 203 cases with the primary tumor site recorded as the blood, bone marrow, or hematopoietic system.

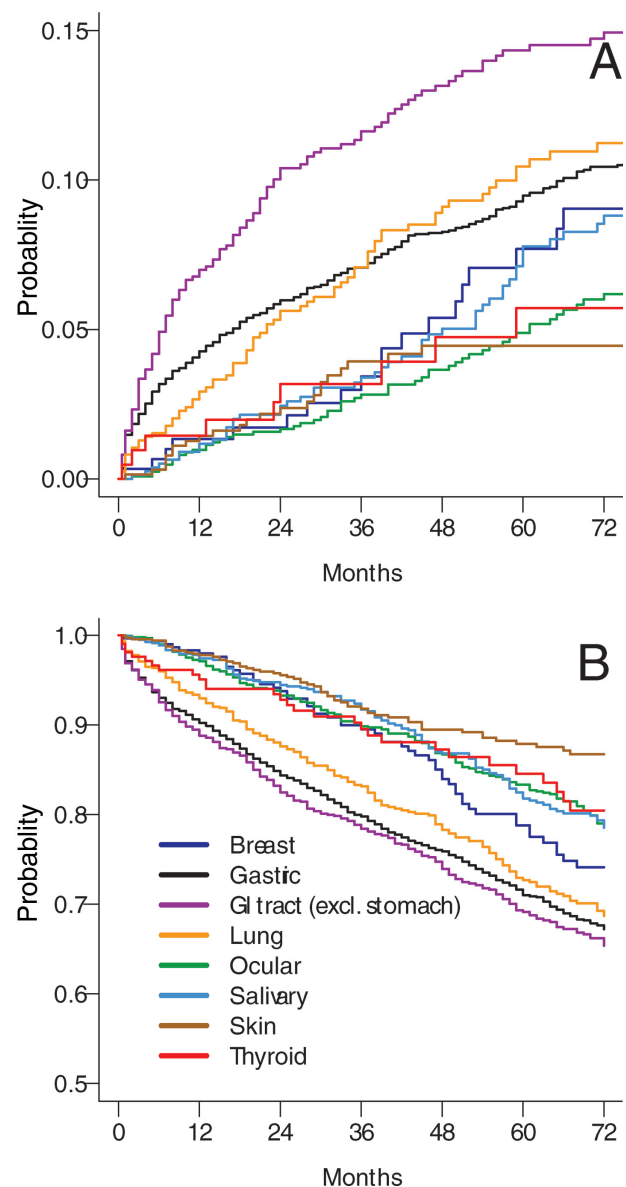


Figure 4. Survival outcomes are shown in patients with mucosa-associated lymphoid tissue lymphomas of the most common primary sites. (A) The cumulative incidence of lymphoma-related death is shown. (B) Overall survival is shown. GI indicates gastrointestinal; excl, excluding.

Survival curves revealed a worse prognosis for patients with respiratory and gastrointestinal MALT lymphomas compared with those with disease at adnexal and endocrine sites ($P < .0001$) (Fig. 4). The high-risk location retained statistical significance after adjusting for age, stage of disease, and receipt of radiotherapy. The improvements noted over the past decade were driven principally by the high-risk locations (stomach [$P = .001$] and bowel [$P = .008$]), with nonsignificant differences reported for other sites.

DISCUSSION

The current study evaluated survival outcomes in a large cohort of patients with MZL, confirming significant differences between subtypes. We noted an opportunity for further refinement in the InterLymph classification, because MZL originating in the spleen should be designated as SMZL rather than MALT lymphoma. The higher incidence of MALT lymphoma in Asian men was noted previously, although the increase noted in Latinos is a novel finding.²¹ It may indicate a genetic predisposition or exposure to infectious agents, because the etiology of MZL is influenced by innate host immunity and its dysfunction.²²

Previous single-institution series have reported excellent long-term survival for patients with SMZL.²³ In contrast, the results of the current study demonstrated a prognosis that is comparable to NMZL, whereas both subtypes displayed significantly worse outcomes than MALT lymphoma. The selectively lower age and comorbidity status of patients evaluated at tertiary institutions may explain this discrepancy. In addition, the differences were significantly influenced by the distribution of disease stage. The prognosis of patients with SMZL was relatively stage independent, consistent with its systemic nature. Patients with stage IE MALT lymphomas had an excellent prognosis, with the poorest outcomes noted in patients with advanced NMZL.

The reasons for the significant survival improvement observed in patients with NMZL and MALT lymphomas over time while no improvement was noted in patients with SMZL remain uncertain. Unlike in some solid tumors, there was no consistent stage shift. The impact of the WHO classification is also not explicatory, because the percentage of splenic B-cell lymphomas designated as SMZL increased between 1995 and 2004 (from 38% to 69%), but remained the same (71%) after 2005. Divergent treatment paradigms (high rate of splenectomy in patients with SMZL, the increased use of rituximab in patients with other subtypes) might play a putative role. However, it should be emphasized that our observational data do not permit inferences regarding treatment effects or conclusions for the management of individual patients.

The results of the current study suggest a distinct biology for MALT lymphomas arising from the gastrointestinal or respiratory tracts compared with those originating in the adnexal and endocrine sites. Previous series reported inconsistent prognostic statistics for MALT lymphoma locations.²⁴⁻²⁶ In a series of 167 patients who were treated with radiotherapy, thyroid and gastric MALT lymphomas were reported to have a significantly better prognosis (10-year recurrence-free survival rate of >

90%) than other sites, particularly the salivary glands and orbits (68%).²⁷ However, to the best of our knowledge, to date there is very little information regarding the comparative benefits of surgery, radiotherapy, and chemoimmunotherapy, despite encouraging retrospective data.²⁸

One weakness of the current analysis is the lack of a central pathology review in the SEER database, which was exacerbated by evolving classifications, with a potential contamination with other indolent lymphomas and immunoproliferative disorders. We attempted to compensate for those issues by appraising the nominal site of origin. However, the differentiation between some lymphoma subtypes may require particular expertise or the use of molecular markers.²⁹⁻³¹ Nevertheless, SEER data reflect the prevalent diagnostic pattern, which remains informative for practicing clinicians.

The limitations of the current study database did not allow us to examine laboratory values of potential prognostic significance or associations with infections, comorbidities, or performance status. The interpretation of the results was also affected by absence of data concerning the use of medical therapy with antibiotics, interferon, rituximab, or chemotherapy. We reported the available clinical prognostic factors for MZL subtypes. Although the International Prognostic Index or Follicular Lymphoma International Prognostic Index could not be constructed from the data, such models have not been validated comparatively for prognosis in patients with MZL.^{32,33} For example, the Integruccio Italiano Linfomi series of SMZL cases identified anemia, hypoalbuminemia, and elevated lactate dehydrogenase as poor prognostic factors.³⁴ The scarce studies of NMZL were too small to categorize significant prognostic factors.^{35,36} One series of MALT lymphomas found no survival difference between patients with localized versus disseminated disease, whereas other studies reached opposite conclusions.³⁷⁻³⁹ The strength of statistical significance in the current analysis suggests a true prognostic relevance for age, the presence of B symptoms, and (for NMZL and MALT only) male sex and advanced stage of disease. Using the lymphoma-specific hazard model rather than OS ensured that the effect of age was biologically significant as a prognostic factor for MZL.

In summary, the current study has described survival outcomes in patients with SMZL, NMZL, and extranodal MZL of MALT type. We believe the analysis of this large cohort has uncovered discrepancies with previous prognostic assertions and opened the field for further research concerning different treatment modalities in patients with MZL and the biology of various anatomical sites of MALT lymphomas.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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