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Prognostic Nomogram and Competing Risk Analysis of Death for Primary Thyroid Lymphoma

A Long-term Survival Study of 1638 Patients

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Background: Primary thyroid lymphoma (PTL) is such a rare malignancy that there are no large-scale prognostic proofs to create a consensus on optimal management. This study aimed to determine the survival outcomes of PTL and specify associated factors by building a prognostic nomogram and to analyze competing risks of death to balance the hazards and benefits of different therapeutic approaches.

Method: A total of 1638 PTL patients from 2000 to 2018 were identified from the Surveillance, Epidemiology, and End Results (SEER) database. Cox proportional hazard regression and competing risk analysis were applied.

Results: We have identified through Cox analysis that age in years, diffuse large B-cell lymphoma (DLBCL) pathology, lymph node dissection, radiation, and chemotherapy were independent prognostic factors for disease-specific survival (DSS). Based on these findings, we built a nomogram for predicting 5- and 10-year DSS and analyzed the overall survival (OS) by calculating cumulative incidence of death. The overall cumulative incidences of the 5- and 10-year PTL-specific cumulative death probabilities were 14.0% (95% CI: 12.3%–15.9%) and 16.3% (95% CI: 14.4%–18.4%), respectively, while the 5- and 10-year cumulative death probabilities from other causes were 12.4% (95% CI: 10.6%–12.3%) and 24.7% (95% CI: 22.1%–27.4%). Results from the competing risk hazards regression analysis revealed that older age and Ann Arbor grading were associated with a greater probability of death from other causes and death from PTL. Radioactive therapy by external beam radiation was associated with death from other causes only. DLBCL histology, lymph node dissection, and chemotherapy were correlated with death from PTL. Cumulative incidence curves demonstrated that the pathological type of lymphoma is the factor determining the likelihood of dying from PTL versus other causes.

Conclusion: Patients' age, Ann Arbor stage, pathological type of lymphoma, and the use of specific therapy regimen should all be taken into consideration when devising individualized treatment strategies for PTL. Decision models based on our findings may help clinicians make better decisions by taking into account the competing risk of death from causes other than PTL.

Keywords: thyroid lymphoma, nomogram, competing risk analysis, cumulative incidence function, survival outcome, prognostic analysis

Primary thyroid lymphoma (PTL) is a rare malignancy constituting only 1% to 2% of all extranodal lymphomas[1] and less than 8% of all thyroid malignancies.[2–7] PTLs are almost always non-Hodgkin lymphomas of B-cell origin, while T-cell PTL is extremely rare.[8] Hashimoto's thyroiditis (HT) is comorbid with up to 90% of cases and is an independent risk factor for developing PTL[6]: the risk is 60 to 67 times higher in those with thyroiditis compared with those without.[1,9] Accordingly, the incidence and prevalence of PTL are higher in areas with higher rates of thyroiditis. Females are far more susceptible to both HT and PTL than males, with a male-female ratio of prevalence for both conditions of approximately 1 to 4.[10] A rapidly enlarging thyroid mass, neck adenopathy and compressive symptoms are the most frequently occurring clinical features of PTL. Patients occasionally report symptoms of B-cell lymphoma including fever, night sweats, and weight loss, as well as symptoms of coexisting HT such as fatigue, cold intolerance, constipation, and menstrual irregularities.[10,11] Rarely, some patients may have symptoms of hyperthyroidism due to the destruction of the thyroid follicles by the lymphoma.[12]

Due to rarity of PTL, it is difficult to conduct randomized or prospective trials to guide management. As a result, the optimal management of PTL remains controversial.[13] An open surgical biopsy is required not only for definitive diagnosis but also to confirm the pathological subtype of lymphoma.[14] Sometimes surgeries are also performed to relieve compressive symptoms.[15] Combined modality treatment with chemotherapy and radiotherapy is preferred over chemotherapy alone for limited-stage diffuse large B-cell lymphoma (DLBCL), and is associated with a higher 5-year survival rate.[16] Early stage (stage IE) intrathyroidal mucosa-associated lymphoid tissue (MALT) lymphomas may be

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treated with single-modality surgery, radiotherapy, or a combination of both.[17] The role of surgery in management of extranodal lymphomas is site sensitive,[18] and extranodal lymphomas can originate from almost any organ. Whether thyroidectomy or lobectomy should be done in PTL has not been discussed.

The overall prognosis of PTL has been described as generally excellent.[16] However, the prognosis is subtype dependent, 5-year survival rates for overall PTL can be as low as 45%,[19] and the prognostic factors of PTL are not well determined.

In addition, on average, most PTL patients are diagnosed in their late 60s, and patients in this age group tend to have a higher prevalence of comorbidities than younger patients.[20,21] Considering most PTL patients receive radiation, chemotherapy or combined modality treatments, which may cause mortality-threatening complications, they are at risk of dying from both thyroid lymphoma itself and from other causes related to treatments, comorbidities, or aging. Therefore, the potential risks and costs must be balanced against the benefits of PTL treatment.

Given the lack of clarity surrounding prognosis, we sought to engage data from Surveillance, Epidemiology, and End Results (SEER) to conduct a large-scale survival analysis of PTL: (1) to determine the survival outcomes of PTL and specify associated factors by building a prognostic nomogram and (2) to analyze competing risks of death in PTL, in order to clarify the hazards and benefits of therapeutic approaches, and the likelihood that patients will die from lymphoma versus other etiologies and associated factors.

MATERIALS AND METHODS

Data Sources

The study cohort initially diagnosed with PTL were extracted from the SEER program, which recodes cancer incidence and mortality data from 18 population-based cancer registries covering approximately 27.8% of the US population.[22] Institutional Review Board approval was not required because SEER is an open-access public database with deidentified data. SEER registries collect data concerning patient demographics, tumor morphology, stage at diagnosis, primary tumor site, the first course of treatment, and follow-up for vital status. Our selected database is cited as "Incidence—SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018)—Linked To County Attributes—Total U.S., 1969–2019 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2021, based on the November 2020 submission."

Study Population

Using the selected database, we identified a consecutive cohort of 1638 patients diagnosed between 2000 and 2018 with lymphoma originating from the thyroid (lymphoblastic, Burkitt, DLBCL. NK/T-cell, MALT, Hodgkin, and other lymphomas). The clinical data were extracted regarding demographics, tumor staging, and therapy: age, gender, race, primary site of tumor, pathology, stage of lymphoma, primary surgery, lymph node dissection, radiotherapy,

TABLE 1.

Demographic and Clinical Characteristics of Primary Thyroid MALT Lymphoma and DLBCL

	Total	MALT	DLBCL	*P*
	N = 1495	n = 380	n = 1115	
Age (years), mean ± SD/median	65.4 ± 14.0/67.0	62.42 ± 13.44/63.0	66.41 ± 13.99/68.00	<0.001
Sex, n (%)				0.895
Female	1007 (67.4%)	257 (67.6%)	750 (67.3%)	
Male	488 (32.6%)	123 (32.4%)	365 (32.7%)	
Race, n (%)				<0.001
White	1315 (88.0%)	308 (81.0%)	1007 (90.3%)	
Black	32 (2.1%)	12 (3.2%)	20 (1.8%)	
Other	148 (9.9%)	60 (15.8%)	88 (7.9%)	
Stage, n (%)				<0.001
Unknown	562 (37.6%)	128 (33.7%)	434 (38.9%)	
IE	533 (35.7%)	186 (49.0%)	347 (31.1%)	
IIE	375 (25.1%)	66 (17.3%)	309 (27.7%)	
IIIE/IIIS/IIIES	25 (1.7%)	0 (0.00%)	25 (2.3%)	
Primary Surgery, n (%)				<0.001
No surgery	684 (45.8%)	82 (21.6%)	602 (54.0%)	
Lobectomy	438 (29.3%)	133 (35.00%)	305 (27.4%)	
Total thyroidectomy	373 (24.9%)	165 (43.4%)	208 (18.6%)	
Lymph node dissection, n (%)				<0.001
None	786 (62.4%)	187 (55.6%)	599 (64.9%)	
Yes	136 (10.8%)	58 (17.3%)	78 (8.5%)	
Unknown	337 (26.8%)	91 (27.1%)	246 (26.6%)	
Radiation, n (%)				0.014
None/Unknown	836 (55.9%)	233 (61.3%)	603 (54.1%)	
EBRT	659 (44.1%)	147 (38.7%)	512 (45.9%)	
Chemotherapy, n (%)				<0.001
None/unknown	511 (34.2%)	301 (79.2%)	210 (18.8%)	
Yes	984 (65.8%)	79 (20.8%)	905 (81.2%)	
Systemic therapy, n (%)				<0.001
No	663 (68.3%)	216 (76.3%)	447 (65.0%)	
Yes	308 (31.7%)	67 (23.7%)	241 (35.0%)	
Disease-specific death, n (%)				<0.001
Censored	910 (60.9%)	281 (73.9%)	629 (56.4%)	
Other causes	355 (23.7%)	84 (22.1%)	271 (24.3%)	
Primary thyroid lymphoma	230 (15.4%)	15 (4.0%)	215 (19.3%)	
Overall death, n (%)				<0.001
Alive	910 (60.9%)	281 (73.9%)	629 (56.4%)	
Dead	585 (39.1%)	99 (26.1%)	486 (43.6%)	
Survival months, mean ± SD/median	78.1 ± 63.7/ 68.0	86.14 ± 59.21/ 80.00	75.30 ± 64.96/ 63.00	<0.001

MALT, mucosa-associated lymphoid tissue; EBRT, external beam radiation therapy.

chemotherapy, systemic therapy, survival months, cause-specific death classification, and survival status. The Ann Arbor criteria is used for the staging of PTL.[23,24] Stage IE applies to disease localized within the thyroid; stage IIE applies to disease confined to the thyroid and regional lymph node basins; stage IIIE/IIIS/IIIES applies to disease that involves the thyroid, the lymph node basins on both sides of the diaphragm, and/or the spleen; and stage IVE is used to describe disseminated disease.[25]

Outcome Definition

Cause of death was used to determine whether each patient died as a result of their PTL or another cause, or whether they were alive at the end of the follow-up period. In our study, the primary outcome was disease-specific survival (DSS), which was defined as the time between initial diagnosis and PTL-specific death. As the secondary outcome, overall survival (OS) was measured as the time between initial diagnosis and death from any cause, and included an analysis of competing risks between PTL-specific death and other causes of death.

Disease-specific Survival Analysis and Nomogram Development

Prognostic factors were determined by univariate Cox proportional hazards regression and Kaplan-Meier curves. Subsequently,

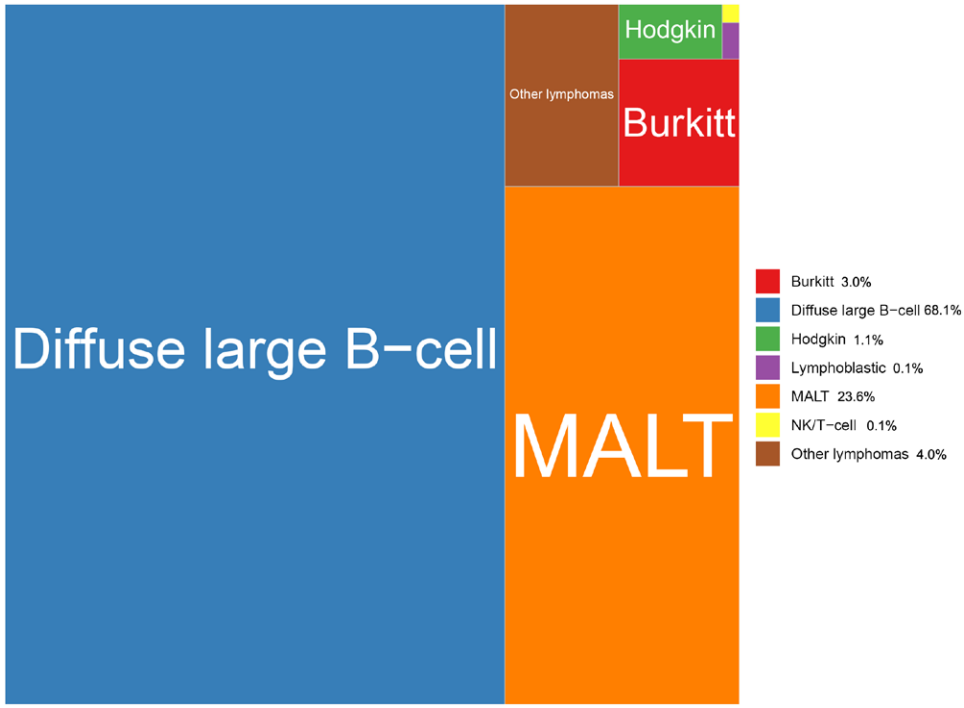

FIGURE 1. Tree map of histological distribution in the primary thyroid lymphoma population. MALT, mucosa-associated lymphoid tissue.

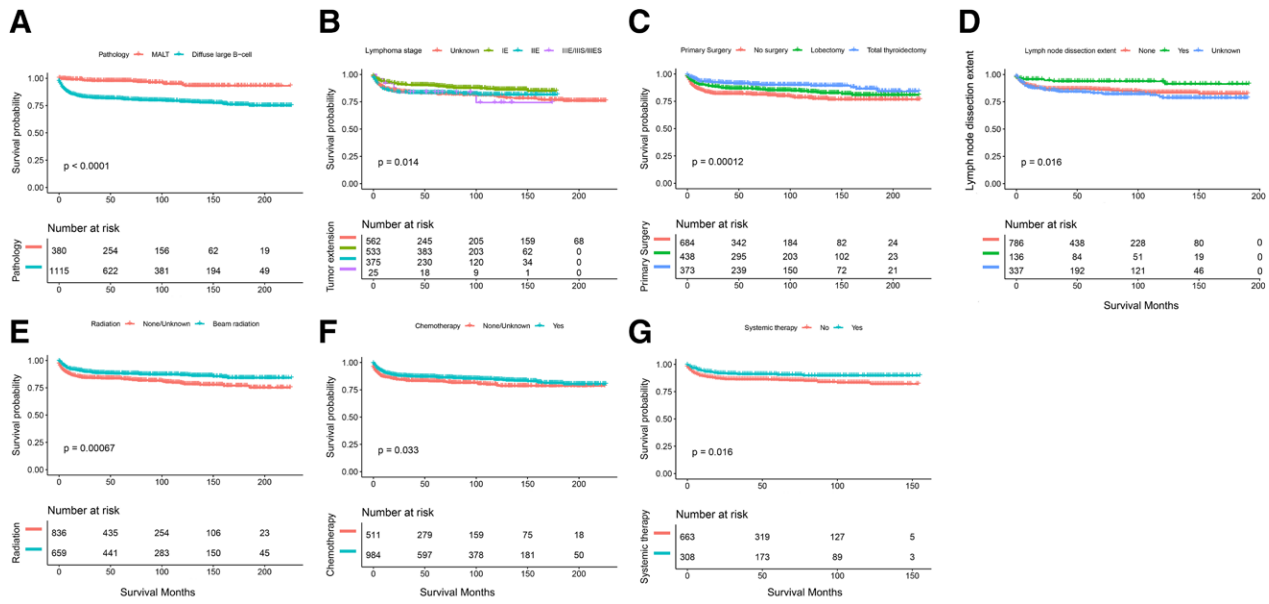

FIGURE 2. Kaplan-Meier survival curves of disease-specific survival based on A, pathology; B, stage; C, primary surgery; D, lymph node dissection; E, radiation; F, chemotherapy; and G, systemic therapy. MALT, mucosa-associated lymphoid tissue.

significant factors screened by the univariate analysis ($P < 0.05$) were further included in multivariate Cox proportional hazards models. The best Cox model was selected by a backward selection process (entry criterion: $P < 0.05$, elimination criterion: $P > 0.10$). Multivariate Cox proportional hazard regression analysis was performed to identify variables that significantly affected the DSS of patients with PTL. Furthermore, the nomogram was built upon variables selected from the multivariate Cox regression ($P < 0.05$). The whole population was included as the training cohort. Finally, we incorporated the chosen prognostic factors to develop the nomograms for predicting 5- and 10-year DSS rates in PTL patients using the R software package "cmprsk."

Competing Risk Analysis of All-cause Deaths

In the competing risk model, deaths from any other causes rather than PTL were regarded as a competing event for PTL. First, we computed the cumulative incidence function (CIF) for PTL and other causes. Subgroup analysis was then carried out according to age, sex, pathology, Ann arbor grading of lymphoma, primary surgery, lymph node dissection, radiation therapy, chemotherapy, and systemic therapy. Corresponding CIF curves were plotted for these variables. The significant differences in CIF values among subgroups were evaluated by Gray's test.[26] Second, variables that were considered significant in the univariate CIF analysis ($P < 0.1$) were introduced into a stepwise competing risk regression model. Subsequently, the optimal regression model was fitted when incorporating the predictive variables selected by the stepwise regression procedure. Finally, we calculated the subdistribution hazard ratio (SHR) of the included variables for PTL patients based on the multivariate competing risk model with the aid of the R package "riskRegression."

Statistical Analysis

We presented descriptive statistics in Table 1 for the entire study cohort and compared the results between the top 2 leading pathological types (DLBCL and MALT lymphoma). Continuous and categorical variables were assessed with the Kruskal-Wallis test and Pearson chi-square test, respectively. Continuous variables were expressed as the mean ± standard deviation/median. Categorical variables were displayed as number (percentage). All statistical analyses were carried out employing the R studio version 4.0.4. A two-tailed $P < 0.05$ was considered statistically significant.

RESULTS

A total of 1638 PTL patients from 2000 to 2018 were identified from the SEER database. Rare pathology types (2 lymphoblastic lymphomas, 49 Burkitt lymphomas, 1 NK/T-cell lymphomas, 18 Hodgkin lymphomas, and 66 other lymphomas) in a total of 143 patients were excluded from the current study. Finally, 1495 patients eligible for our analysis were included. The histological composition was illustrated with a tree map in Figure 1. The demographic portrait of the PTL population was a group of elderly (median age at diagnosis is 67 years, range from 13 to 85), White (1315, 88.0%), and female (1007, 67.4%) patients. The dominating histology type of PTL was DLBCL (1115, 74.6%). MALT lymphoma comprised approximately

TABLE 2.

Univariate and Multivariate Cox Proportional Hazard Regression for Analyses of Primary Thyroid Lymphoma Patients for Disease-specific Survival

	Univariate			Multivariate		
	HR	**95% CI**	***P***	**HR**	**95% CI**	***P***
Age						
Each increase in one year	1.08	1.06–1.10	<0.001	1.07	1.05–1.09	<0.001
Sex						
Female	1	Reference				
Male vs female	1.24	0.84–1.83	0.282			
Race						
White	1	Reference		1	Reference	
Others	1.18	0.65–2.14	0.582	1.21	0.67–2.19	0.526
Pathology						
MALT	1	Reference		1	Reference	
DLBCL	11.85	5.27–26.65	<0.001	12.00	5.38–26.76	<0.001
Stage						
Unknown	1	Reference		1	Reference	
IE	0.57	0.34–0.99	0.045	0.62	0.37–1.04	0.070
IIE	1.19	0.72–1.97	0.507	1.25	0.76–2.05	0.373
IIIE/IIIS/IIIES	1.00	0.38–2.69	0.993	1.08	0.41–2.88	0.872
Primary surgery						
No surgery	1	Reference				
Lobectomy	1.43	0.79–2.57	0.235			
Total thyroidectomy	0.98	0.48–2.01	0.961			
Lymph node dissection						
No	1	Reference		1	Reference	
Yes	0.37	0.14–0.97	0.043	0.37	0.15–0.93	0.034
Unknown	1.46	0.98–2.19	0.066	1.47	0.99–2.20	0.058
Radiation						
None/unknown	1	Reference		1	Reference	
Yes	0.55	0.37–0.82	0.004	0.54	0.36–0.81	0.003
Chemotherapy						
None/unknown	1	Reference		1	Reference	
Yes	0.31	0.19–0.51	<0.001	0.29	0.19–0.43	<0.001
Systemic therapy						
None/unknown	1	Reference				
Yes	0.87	0.45–1.69	0.673			

DLBCL, diffuse large B-cell lymphoma; EBRT, external beam radiation therapy; MALT, mucosa-associated lymphoid tissue.

1/4 (380, 25.4%) of the cohort. Most patients were diagnosed with Ann Arbor stage IE (533, 35.7%), followed by stage IIE (375, 25.1%), and stage IIIE/IIIS/IIIES (25, 1.7%). The stages of the remaining 37.6% of the patients were not indicated in the database. Therapy wise, more than half of the population was given surgery (438 lobectomy and 373 thyroidectomy, 811 in total, 54.2%), radiation (659, 44.1%), and chemotherapy (984, 65.8%). Systemic therapy was not favored (663, 68.3%), and most records of lymph node dissection (786, 62.4%) cannot be identified from the database. Table 1 shows the characteristics of the study population and a comparison between DLBCL and MALT lymphoma, including demographics, tumor characteristics, and therapeutic approaches.

The median follow-up of the study cohort was 68 months (range from 1 to 226 months). In total, 585 (39.1%) patients died during the whole follow-up period, of whom 230 (15.4%) died due to PTL and 355 (23.7%) died due to non-PTL causes. Overall, the 5- and 10-year DSS was 85.5% (CI: 83.6%–87.4%) and 82.6% (CI: 80.4%–84.8%), respectively, while the 5- and 10-year OS was 73.6% (CI: 71.3%–76.0%) and 59.0% (CI: 56.1%–62.0%).

For DSS analysis, all variables were applied using an unadjusted Kaplan-Meier method. The significant survival curves were drawn in Figure 2 for initial detection of significant factors. Then, univariate and multivariate Cox proportional hazard models were adopted in sequence to determine significant DSS prognostic factors for the study population. In the univariate Cox analysis, age in years (HR = 1.08, 95% CI: 1.06–1.10, $P < 0.001$), DLBCL pathology (vs MALT, HR = 11.85, 95% CI: 5.27–26.65, $P < 0.001$), IE stage (vs unknown stage, HR = 0.57, 95% CI: 0.34–0.99, $P = 0.045$), lymph node dissection (vs no dissection, HR = 0.37, 95% CI: 0.14–0.97, $P = 0.043$), radiation (vs none/unknown, HR = 0.55, 95% CI: 0.37–0.82, $P = 0.004$), and chemotherapy (vs none/unknown, HR = 0.31, 95% CI: 0.19–0.51, $P < 0.001$) were prognostic factors for DSS. However, gender, race, surgical treatment, and systemic therapy were not statistically relevant to DSS. Furthermore, we incorporated these significant prognostic factors into a multivariate Cox proportional hazard regression for adjustment and found that age in years (HR = 1.07, 95% CI: 1.05–1.09, $P < 0.001$), DLBCL pathology (vs MALT, HR = 12.00, 95% CI: 5.38–26.76, $P < 0.001$), lymph node dissection (vs no dissection, HR = 0.37, 95% CI: 0.15–0.93, $P = 0.034$), radiation (vs none/unknown, HR = 0.54, 95% CI: 0.36–0.81, $P = 0.003$), and chemotherapy (vs none/unknown, HR = 0.29, 95% CI: 0.19–0.43, $P < 0.001$) were independent prognostic indicators, which are shown in Table 2 and visualized by forest plot in Figure 3A. Thus, the prognostic nomogram was developed to predict the 5- and 10-year DSS rates based on independent Cox proportional prognostic risk factors (Figure 3B).

Subsequently, we analyzed the OS by calculating the cumulative incidence of death. The overall cumulative incidences of the 5- and 10-year PTL-specific cumulative death probability were 14.0% (95% CI: 12.3%–15.9%) and 16.3% (95% CI: 14.4%–18.4%), respectively, while the 5- and 10-year cumulative probabilities of death from other causes were 12.4% (95% CI: 10.6%–12.3%) and 24.7% (95% CI: 22.1%–27.4%). To separately evaluate the risks affecting OS, the 5- and 10-year cumulative incidences of mortality rates of PTL and other causes by pathological category and therapeutic approaches are displayed in Supplemental Table 1 (http://links.lww.com/AOSO/A188), and the corresponding CIF curves are presented in Figure 4.

Supplemental Figure 1 (http://links.lww.com/AOSO/A189) shows the cumulative incidence curves demonstrating competing risks of death in different pathological categories of PTL. Supplemental Figure 1A (http://links.lww.com/AOSO/A189) demonstrates that a higher proportion of patients die from DLBCL initially, but after 7.5 years, the proportion dying from other causes is higher. In contrast, for patients with MALT lymphoma (Supplemental Figure 1A, http://links.lww.com/AOSO/A189), a higher proportion of patients die of other causes over time. The likelihood of death from other causes versus PTL differs by specific pathological type of lymphoma.

Results from the competing risk hazards regression analysis are shown in Table 3. Older age and Ann Arbor grading were associated with both a greater probability of death from other causes (e.g., 70–80 years of age vs younger than 50 years, SHR = 8.41, 95% CI: 2.88–24.55, $P < 0.001$; IIE vs stage unspecified, SHR = 3.49, 95% CI: 1.73–7.05, $P < 0.001$) and death from PTL (e.g., 70–80 years of age vs younger than 50 years, SHR = 9.52, 95% CI: 2.66–34.13, $P < 0.001$; IIE vs stage unspecified, SHR = 2.03, 95% CI: 1.08–3.80, $P = 0.027$). Therapy by external beam radiation (vs none/unknown, SHR = 0.56, 95% CI: 0.38–0.84, $P = 0.005$) was associated with death from other causes. DLBCL histology (vs MALT lymphoma, SHR = 13.04, 95% CI: 4.41–38.84, $P < 0.001$), lymph node dissection (vs no dissection, SHR = 0.12, 95% CI: 0.02–0.95, $P = 0.044$), and chemotherapy (vs none/unknown, SHR = 0.30, 95% CI: 0.17–0.54, $P < 0.001$) were correlated with death from PTL.

DISCUSSION

Due to the rarity of PTL, very little literature addresses the optimal management of the disease. An initial objective of our study was to answer the question of how to optimally manage PTL

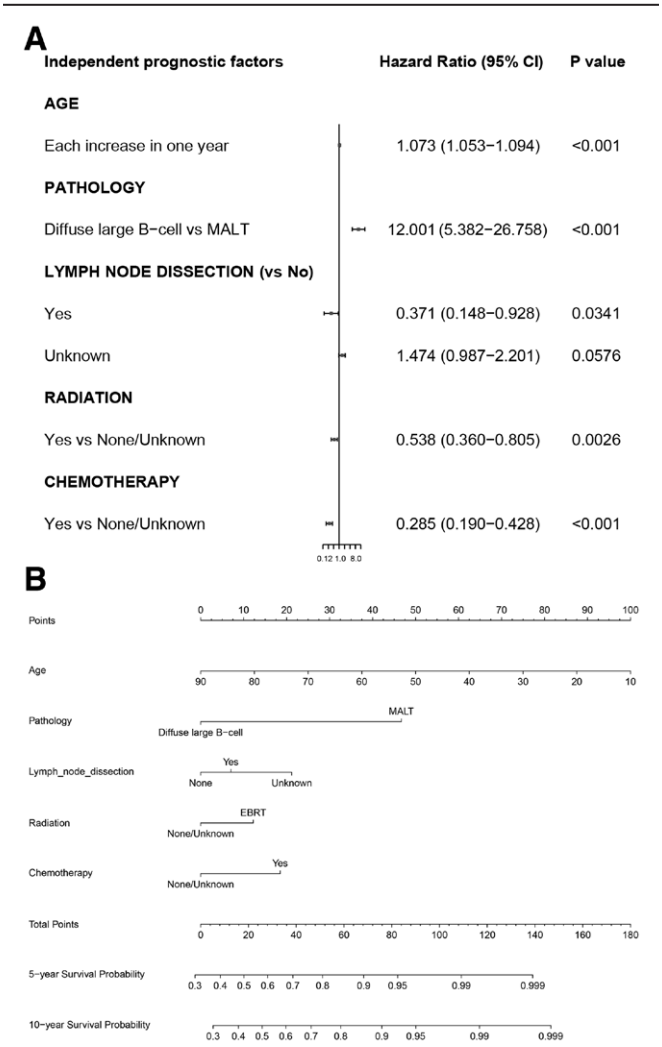

FIGURE 3. Cox proportional hazard analysis of disease-specific survival in primary thyroid lymphoma patients: A, visualized forest plot of multivariate analysis in predicting disease-specific survival; B, nomogram predicting the 5- and 10-year disease-specific survival.

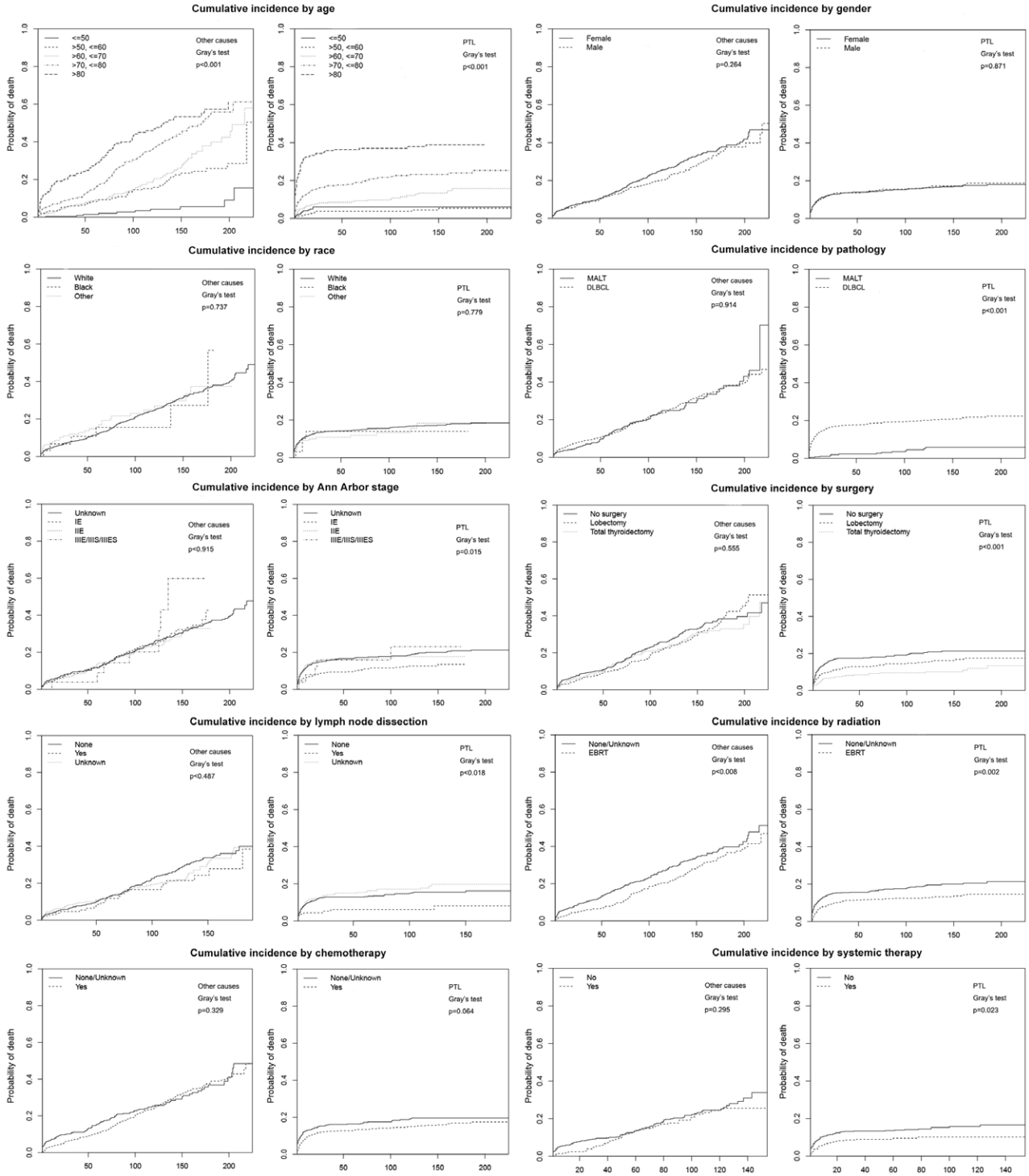

FIGURE 4. Cumulative incidence curves of death for patients with primary thyroid lymphoma by different variables. DLBCL, diffuse large B-cell lymphoma; MALT, mucosa-associated lymphoid tissue; EBRT, external beam radiation therapy.

by clarifying prognostic factors among the clinicopathologic characteristics and therapeutic approaches. In the present study, both Cox proportional hazard regression and competing risk analysis were performed to investigate the predictive factors for patients with PTL from the SEER database.

In the study cohort, PTL is more common in females and has a female-male ratio of 2 to 1 with a median age of 67 years at diagnosis, which is similar to previous reports.[10,20,21] Interestingly, all patients diagnosed with stage IIIE fall into the DLBCL pathological type, which has a much more aggressive biological behavior than MALT. About twice as many MALT PTL patients (87.4%) received partial or complete thyroid removal, compared with those diagnosed with DLBCL (46.0%). There is a preference for more aggressive chemotherapy and radiotherapy for DLBCL (81.2% and 45.9%) compared with MALT lymphoma (20.8% and 38.7%), which is also in accordance with previous reports.[16,26]

Cox regression revealed that age in years, DLBCL pathology, lymph node dissection, radiation, and chemotherapy were independent DSS predictive factors after adjustments, consistent

TABLE 3.

Competing Risk Hazard Regression for Death in Primary Thyroid Lymphoma Patients

	Death from other causes			Death from primary thyroid lymphoma		
	SHR	95% CI	*P*	SHR	95% CI	*P*
Age at diagnosis (years)						
<50	1	reference		1	reference	
50–60	5.01	(1.66–15.17)	0.004	1.23	(0.25–6.08)	0.802
60–70	5.36	(1.82–15.74)	0.002	2.05	(0.51–8.16)	0.310
70–80	8.41	(2.88–24.55)	<0.001	9.52	(2.66–34.13)	<0.001
≥80	17.07	(5.72–50.95)	<0.001	11.38	(3.15–41.06)	<0.001
Pathology						
MALT	1	reference		1	reference	
DLBCL vs MALT	0.90	(0.54–1.49)	0.674	13.08	(4.41–38.84)	<0.001
Grading						
Unknown	1	reference		1	reference	
IE	3.99	(2.03–7.87)	<0.001	0.85	(0.42–1.72)	0.654
IIE	3.49	(1.73–7.05)	<0.001	2.03	(1.08–3.80)	0.027
IIIE/IIIS/IIIES	4.31	(1.49–12.48)	0.007	1.10	(0.27–4.52)	0.891
Primary surgery						
No surgery	1	reference		1	reference	
Lobectomy	0.93	(0.49–1.78)	0.833	1.44	(0.69–3.03)	0.331
Total thyroidectomy	1.63	(0.88–3.04)	0.121	1.29	(0.55–3.01)	0.562
Lymph node dissection						
No	1	reference		1	reference	
Yes	0.79	(0.39–1.60)	0.515	0.12	(0.02–0.95)	0.044
Unknown	0.845	(0.54–1.31)	0.450	1.26	(0.76–2.06)	0.3701
Radiation						
None/unknown	1	reference		1	reference	
Yes	0.56	(0.38–0.84)	0.005	0.72	(0.45–1.16)	0.176
Chemotherapy						
None/unknown	1	reference		1	reference	
Yes	1.10	(0.61–1.98)	0.757	0.30	(0.17–0.54)	<0.001
Systemic therapy						
None/unknown	1	reference		1	reference	
Yes	1.12	(0.58–2.15)	0.738	1.05	(0.46–2.39)	0.912

DLBCL, diffuse large B-cell lymphoma; EBRT, external beam radiation therapy; MALT, mucosa-associated lymphoid tissue; SHR, subdistribution hazard ratio.

with previous reports.[6,17,27] We also computed a DSS nomogram based on traditional Cox proportional hazard analysis, which has been proven to be a simple and pragmatic clinical tool[28,29] for predicting the individual probabilities of DSS for patients with PTL and many other cancers.[30-35] When assessing the prognosis for patients and making clinical decisions, it is imperative to take into account individual risk profiles. A prognostic nomogram enables clinicians to plan treatment strategies and evaluate outcomes more conveniently.

The results of competing risk analysis of PTL patients demonstrate that the risk of death is almost 13 times higher in those with DLBCL histology compared with those with MALT histology (SHR = 13.04, 95% CI: 4.41–38.84, $P < 0.001$). Lymph node dissection (vs no dissection, SHR = 0.12, 95% CI: 0.02–0.95, $P = 0.044$) and chemotherapy (vs none/unknown, SHR = 0.30, 95% CI: 0.17–0.54, $P < 0.001$) can effectively reduce PTL-specific death risk by 88% and 70%, respectively. As for survival hazards induced by other causes, older age (e.g., 70–80 years of age vs younger than 50 years, SHR = 8.41, 95% CI: 2.88–24.55, $P < 0.001$) and advanced Ann Arbor stage (e.g., IIE vs stage unspecified, SHR = 3.49, 95% CI: 1.73–7.05, $P < 0.001$) lead to the greatest increases in non-PTL death risk. External beam radioactive therapy has a major impact, as it significantly lowers non-PTL death risk by 44% (vs none/unknown, SHR = 0.56, 95% CI: 0.38–0.84, $P = 0.005$).

After reviewing and comparing the results, the most intriguing finding is that each therapy regimen for PTL improves survival outcomes by reducing a different type of mortality risk. For example, chemotherapy and lymph node dissection contribute to better survival outcomes by reducing PTL-specific mortality risks, or in other words, "treating the lymphoma itself." In contrast, radioactive therapy benefits PTL patients by lowering non-PTL death risks, or "boosting the overall condition against risk factors of other causes." Advanced age (age over 70) enhances the risk of both PTL-specific and non-PTL mortality. And since radiation can significantly decrease non-PTL death risk, this evidence supports a stronger recommendation for elderly PTL patients to receive this therapy.

Another important finding was that the likelihood of death from other causes versus death from PTL is determined by the pathological type of lymphoma (see Supplemental Figure 1, http://links.lww.com/AOSO/A189). Importantly, the likelihood of dying of other causes correlated with patient characteristics such as age, lymphoma stage, and radiation, while the likelihood of dying from PTL-specific causes correlated with tumor pathology, chemotherapy, and lymph node dissection. We were particularly interested in the beneficial effect of lymph node dissection because this finding suggests that this intervention should be offered to the entire cohort of PTL patients to improve their prognosis, which is not the current standard of treatment.[28–30]

Strengths of our study include a large sample size and the use of competing risk model to perform survival analysis. In general, the SEER database offers a sufficient sample to investigate predictive factors and further develop a model-based prognostic nomogram. Moreover, findings derived from the analysis of a population-based database are more generalizable and representative than those from single-center studies. In addition, the competing risk model fully takes into consideration other competing events, which renders a unique view of the correlation between mortality and the choice of treatments.

Admittedly, there are also several limitations to our study. For instance, some known prognostic variables, such as comorbidities, targeting therapy, and more specified treatment modality were not recorded in the SEER database. Further study is

warranted to incorporate these variables, and another external validation cohort should be included to ensure the accuracy of the nomogram. In the meantime, the nomogram should be used with caution.

In spite of these limitations, we have conducted the first study using a competing risk model to evaluate the cumulative incidence of PTL patients and constructed a nomogram based on Cox hazard proportional regression. These findings can guide personalized medical decision making and highlight the importance of considering patient context when balancing the benefits and harms of PTL management.

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