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Prognosis of Primary Thyroid Lymphoma: Demographic, Clinical, and Pathologic Predictors of Survival

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PROGNOSIS OF PRIMARY THYROID LYMPHOMA: DEMOGRAPHIC, CLINICAL AND PATHOLOGIC PREDICTORS OF SURVIVAL

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The aim of this study is to assess associations between demographic, clinical and pathologic characteristics of patients with primary thyroid lymphoma (PTL) and survival, using both bivariate and multivariate analyses. We hypothesize that age, stage at diagnosis, and histology will be independent predictors of survival after diagnosis of PTL. Use of surgery to treat PTL will not improve survival.

PTL patients were identified in the SEER database. Bivariate (χ^2, Kaplan-Meier, and log rank) and multivariate (Cox proportional hazards) analyses were used to assess the associations between patient characteristics and survival.

A total of 1,408 patients were identified. Overall, 98% had non-Hodgkin's lymphoma; 68% had diffuse large B-cell, 10% follicular, 10% marginal zone, and 3% small lymphocytic. A total of 88% had stage I or II disease. Median survival was 9.3 years. On bivariate analysis, older age, single marital status, stage II-IV disease, histology (diffuse large B-cell, follicular, or other non-Hodgkin's), earlier year of diagnosis, lack of prior malignancies, and no radiation or surgery predicted worse survival. Age ≥80 years, stage IV disease, no radiation or surgery, and large B-cell or follicular histology predicted worse prognosis in multivariate analysis.

Based on the analysis, we conclude that older age, advanced stage, histologic subtype, and lack of radiation or surgical treatment are associated with worse survival. Thyroid resection offers benefit only for patients with stage I disease.

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A modified version of the work presented in this thesis resulted in two publications, published in *Surgery* in December 2009 (co-authors: Sanziana Roman, Daniel Thomas, Robert Udelsman, and Julie Ann Sosa) and in *Current Opinion in Oncology* in January 2010 (co-authors: Julie Ann Sosa and Sanziana Roman). I also presented this research during a podium presentation at the Annual Meeting of the American Association of Endocrine Surgeons on May 4th, 2009 in Madison, WI.

Finally, I would like to thank my family for their continued love and support. Their confidence and humor have sustained me.

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Introduction

Primary thyroid lymphoma (PTL) is a rare type of thyroid cancer. It has an estimated incidence of 1-5% of thyroid malignancies and 2% of all extranodal lymphomas, with an annual incidence of two per million (1-4). The vast majority of patients are diagnosed with non-Hodgkin's lymphoma of B-cell origin; Hodgkin's lymphoma has been rarely reported. A number of distinct histologic subtypes exist, each with unique diagnostic and prognostic characteristics. Due to the rarity of this malignancy, the literature contains only case reports and single institutional series evaluating PTL. This work represents the first population-based study of PTL in the United States to examine associations among patient demographic, pathologic, and clinical characteristics, including the extent of thyroid resection, and overall and disease-specific survival.

Clinical presentation

The largest study of PTL in the United States to date encompassed 108 patients; it found that PTL most commonly affects women (3:1 predominance) between the ages of 50 and 80 years, with a peak incidence in the late sixties (5). Patients typically present with a rapidly growing thyroid mass and may experience hoarseness, stridor, or, less commonly, dysphagia (6). The rate of thyroid enlargement tends to be more rapid in those with PTL than in patients with other thyroid malignancies, with the exception of anaplastic thyroid carcinoma (7). Patients may also present with "B symptoms", such as fever, night sweats, weight loss, pruritus, or all of the above. Patients with chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) are at increased risk of developing PTL. There is a particularly strong association between Hashimoto's thyroiditis and marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue (MALT), with

an estimated relative risk of 67 (8). At least one-half of patients diagnosed with PTL have a clinical history of Hashimoto's thyroiditis, and an even larger number have either immunologic or pathologic evidence of the disease, with a reported rate as high as 94% in one study (5, 9, 10). Nonetheless, most patients with Hashimoto's thyroiditis do not develop PTL. Hashimoto's thyroiditis is strongly linked to human leukocyte antigen (HLA) haplotype in certain populations, but recent investigations have not found a similar HLA association for patients with PTL (11).

Histologic subtypes

Diffuse large B-cell lymphoma

PTL can be classified by histologic subtype. The most common of these subtypes is diffuse large B-cell lymphoma (DLBCL), which accounts for approximately two-thirds of cases (5). In some patients, DLBCL may arise from a preexisting MALT lymphoma, and a component of MALT lymphoma can be seen in one-third of patients with DLBCL (9). In terms of cellular immunophenotype, thyroid DLBCLs are CD20 positive, and the majority are B-cell lymphoma (Bcl)-6 positive. Approximately half are Bcl-2 positive; CD5, CD10, and CD23 are usually negative (9).

The most aggressive of the histologic subtypes, DLBCL is associated with the worst prognosis and is an independent predictor of death from PTL (5). Positive cytoplasmic staining for nm23-H1 protein and the nongerminal center B-cell type are associated with a poor prognosis (9).

Marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue

The second most common form of PTL, MALT is an indolent, low-grade malignancy. Diagnostic features of thyroid MALT include lymphoepithelial lesions

(LEL), reactivation germinal centers, and frequent plasmacytic differentiation. The utility of LELs as a diagnostic feature of extranodal MALT lymphoma has been questioned due to the presence of LELs in other histologic subtypes, but a recent site-specific analysis reveals that LELs are found in 100% of thyroid MALT, indicating that their presence is important for diagnosis (12). The presence of immunoglobulin light chain, CD20, and Bcl-2 are expected, as are the absence of CD5, CD10, and CD23 (13).

Histologic similarities between thyroid MALT and follicular lymphoma and the frequent association with Hashimoto's thyroiditis present diagnostic challenges (12, 14). Distinguishing MALT from plasma cell neoplasms can be accomplished with expanded immunostaining panels; immunoglobulin-M heavy chain staining in the plasma cell component strongly supports the diagnosis of MALT (12). Prominent plasma cell differentiation, follicular colonization, and presence of LELs may be found in Hashimoto's thyroiditis and PTL, but the diagnosis of MALT can be made on the basis of the presence of centrocyte-like cells on immunohistochemistry and clonal band on PCR for the immunoglobulin heavy chain (14).

Multiple series that evaluated the histologic subtypes of PTL have reported that patients with MALT have longer disease-specific survival than those with DLBCL, although these disparities have not achieved statistical significance in all studies (5, 6, 15) MALT more frequently presents in stage I than DLBCL (15). MALT patients respond well to treatment and are significantly more likely to achieve complete remission when compared to patients with DLBCL (15).

Follicular lymphoma

Thyroid follicular lymphoma is widely reported to be less common than MALT. Due to its rarity, the clinicopathologic features of thyroid follicular lymphoma have only recently been characterized (16). Thyroid follicular lymphomas have neoplastic follicles with typical follicular lymphoma morphology contained within a destructive atypical lymphoid infiltrate. The interfollicular cells are small centrocytic cells, and LELs are found in all cases. Immunohistochemistry commonly shows expression of Bcl-6, CD10 or both within the interfollicular cells. Bcl-2-positive thyroid follicular lymphoma is associated with disseminated disease, whereas Bcl-2-negative neoplasms are more likely to be localized. Follicular lymphoma can be distinguished from MALT by the expression of Bcl-6, the presence of areas with typical follicular lymphoma architecture, and the lack of immunoglobulin heavy chain expression (16).

Other

A number of other histologic subtypes of PTL have been reported, all at very low rates. Hodgkin's lymphoma, small lymphocytic lymphoma, and plasmacytoma each represent less than 5% of PTL, whereas T-cell, mantle cell, Burkitt's, and lymphoblastic histologies are found in less than 1% of cases (3, 17-19)

Pathogenesis

Theories describing the molecular pathogenesis of PTL have been based on the association between Hashimoto's thyroiditis and PTL. It has been postulated that the chronic antigenic stimulation and proliferation of lymphoid tissue in Hashimoto's thyroiditis creates cells that are susceptible to neoplastic transformation, leading to PTL. Recent work by Moshynska et al. (20) supports this theory, by showing clonal similarity

in immunoglobulin heavy chain gene rearrangement sequences in the clonal bands of Hashimoto's thyroiditis and subsequently developed PTL.

The theory of antigenic stimulation does not explain the pathogenesis of PTL entirely, as demonstrated by Takakuwa et al. (21). Aberrant somatic hypermutation, previously attributed to the development of multiple proto-oncogenes in other types of DLBCL, was shown in this study to target thyroid DLBCL, MALT, and particularly follicular lymphoma. Interestingly, the authors also found aberrant somatic hypermutation in two patients of Hashimoto's thyroiditis, leading to them to propose that aberrant somatic hypermutation may represent an early step in the process of thyroid lymphomagenesis in patients with Hashimoto's thyroiditis.

Diagnosis

Despite its rarity, PTL should always be considered in the differential diagnosis of rapidly growing goiter or thyroid nodules. Definitive diagnosis of PTL is not possible based on history, physical examination, thyroid function tests, or imaging alone due to the lack of specificity of any of these for lymphoproliferative disorders. Tissue is necessary for confirmation.

Fine needle aspiration

Fine needle aspiration (FNA) biopsy is an excellent diagnostic test for thyroid disorders as it is minimally invasive and can be performed in the office. Unfortunately, the reported accuracy of FNA is not high enough to rely solely on this test for diagnosis. This is largely due to the histopathological similarities between PTL and Hashimoto's thyroiditis. The lack of marked nuclear atypia in PTL makes the cytological differentiation between the lymphoid infiltrate of Hashimoto's thyroiditis and lymphoma

difficult (14, 15, 22). Several series have reported accurate diagnosis of PTL using FNA in 60% of patients who were later proven to have the malignancy (15, 23). Takano et al. (22) proposed a diagnostic method for non-Hodkin's PTL in which the detection of a monoclonal immunoglobin heavy chain gene in B cells is combined with aspiration biopsy-nucleic acid diagnosis (ABND). ABND uses extracted nucleic acids from leftover cells found within the needle after FNA to allow for the detection of various malignancies using the relatively small number of cells available in the needle. This technique seems promising, but it has not yet shown high enough sensitivity or specificity to replace the current diagnostic techniques.

Core needle and surgical biopsy

Most patients with suspected PTL require either core needle or open surgical biopsy for histopathological confirmation, classification of histologic subtype, and chemotherapeutic treatment planning. In a small study of six patients, ultrasound-guided core needle biopsy was shown to be safe and accurate, suggesting that it may be considered a suitable alternative to open surgical biopsy (24). Nonetheless, the more limited core biopsy specimen may not be representative of the entire tumor, particularly in the case of coexisting MALT and DLBCL histologies. Thus, there continues to be a role for surgical biopsy to ensure that aggressive histologies are not missed (14).

Pretreatment evaluation

A number of laboratory studies are useful in evaluating patients with PTL. In addition to obtaining standard serologic chemistries, serum lactate dehydrogenase and β2 microglobulin levels may be checked, as they have prognostic implications for non-

Hodgkin's lymphoma (25). Thyroid function tests may also be useful due to the high incidence of hypothyroidism in patients with PTL.

Staging

PTL is staged based on the Ann Arbor staging criteria (26), with up to 90% of patients presenting with early stage disease (5, 15). Stage IE (extranodal) PTL is defined as lymphoma limited to the confines of the thyroid gland, stage IIE denotes spread beyond the thyroid to regional lymph nodes, stage IIIE involves lymph nodes on both sides of the diaphragm, and stage IVE indicates systemic dissemination. Prognosis varies by stage at diagnosis; patients who present with higher stage disease far significantly worse than those presenting at earlier stages (5, 6).

Imaging

Cervical ultrasound is a standard initial imaging study in patients with thyroid disease and masses. PTL often presents as a pseudocystic, hypoechoic region that can be mistaken for a benign cyst on sonography (24). Therefore, a clear diagnosis cannot be made on ultrasound alone. However, the use of ultrasound is particularly valuable in guiding appropriate FNA or core needle biopsies. Once the diagnosis of PTL has been established, imaging of the entire body is necessary in order to stage the patient accurately. Computed tomography (CT) of the head, neck, chest, abdomen, and pelvis are commonly employed. The clinical utility of fluorodeoxyglucose-PET (FDG-PET) scanning has been of recent interest (27). In patients with DLBCL, FDG-PET appears to be a sensitive modality for assessing PTL and may lead to earlier identification of disease recurrence than CT scan surveillance (28). FDG-PET scanning is potentially inaccurate in patients with Hashimoto's thyroiditis, in whom inflammation causes diffusely

increased thyroid uptake and false-positive results. FDG-PET is also of limited clinical utility in patients with MALT because the low metabolic rate of the malignancy and the high rates of concurrent Hashimoto's thyroiditis lead to difficulty in detecting residual or recurrent disease.

Treatment

Appropriate treatment for patients with PTL depends on histologic subtype, as the tumor grade and the efficacy of each treatment modality vary by subtype. Thirty years ago, PTL was considered a surgical disease, but the introduction of effective chemotherapeutic regimens has significantly changed the treatment paradigm since then. Currently, chemotherapy or combined chemotherapy and locoregional radiation are the mainstay of treatment for most histologic subtypes. A study of 50 patients evaluating surgical trends in the management of thyroid lymphoma found that fewer patients underwent thyroid resection for therapeutic purposes in the latter half of the 35-year study period and that surgical thyroid resection had no impact on disease-free survival (29).

Localized treatment

Regardless of histologic subtype, there is consensus that the role of locoregional treatments, such as surgical excision and radiation, is limited to patients with stage I or II disease. MALT and follicular lymphomas tend to follow a more indolent course and are frequently treated locally with either surgical excision or radiotherapy. Thyroid resections can be difficult in patients with PTL due to the inflammatory nature of thyroiditis and possible extrathyroidal extension. Some patients may present with a solitary thyroid nodule, which is only diagnosed as PTL after surgical resection. Anecdotal evidence

supports the irradiation of patients with stage I follicular PTL, as this treatment may be curative, but there are no definitive studies in the literature. In MALT lymphomas of the head and neck, chemotherapy does not have a clear effect on either disease-specific or relapse-free survival (13). Patients with indolent histologic subtypes do require close long-term follow-up, as thyroid MALT may be associated with high rates of dissemination and recurrence (13).

DLBCL was once treated primarily with surgical excision, but localized treatments now play less of a role. The rarity of this malignancy has hindered the use of randomized, controlled trials to study the efficacy of surgical excision in stage I disease. Limited radiation does enter the treatment paradigm for patients with bulky disease, as does the use of surgery in cases of airway obstruction. Acute airway compromise in patients with DLBCL due to tumor compression or invasion of the trachea is rare, but can be managed with tracheostomy or with tracheal stents (30).

Chemotherapeutic regimens

To date, no randomized, controlled trials evaluating the efficacy of chemotherapy in PTL exist, but outcomes have been extrapolated from studies of extranodal non-Hodgkin's lymphoma. These studies suggest that the use of chemotherapy, most commonly CHOP (cyclophosphamide, doxorubicin, vincristine, prednisolone), in patients with extranodal lymphomas is both well tolerated and efficacious. Most PTL patients who present with recurrent disease relapse at a distant site, further supporting the case for systemic treatment, either with chemotherapy alone or with combined modality treatment (31).

The U.S. Food and Drug Administration (FDA) approval of rituximab for the treatment of DLBCL has altered the chemotherapeutic approach to patients with PTL. Approved in 2006 for first-line treatment, rituximab is a monoclonal B-cell antibody that selectively binds to the CD20 antigen found on pre-B and mature B lymphocytes (32). In patients with DLBCL, rituximab is approved for use with CHOP or other anthracycline-based chemotherapy regimens. For patients with follicular lymphoma, rituximab improves outcomes when used in conjunction with CHOP or CVP (cyclophosphamide, vincristine, and prednisone) (33).

Recently, a large study of 1222 elderly patients aged 61 to 80 years compared the outcomes of patients with nodal DLBCL treated with either six or eight cycles of rituximab and CHOP or CHOP alone. The addition of rituximab led to significantly improved event-free, progression-free, and overall survival (OS) when compared with CHOP alone, but the additional two cycles of R-CHOP did not, suggesting that elderly patients are best treated with six cycles of R-CHOP (34). As with previous advances in chemotherapy, treatment data from nodal lymphoma have been extrapolated to PTL, and many centers now treat DLBCL PTL patients with rituximab when appropriate.

In summary, PTL is a rare malignancy, with few studies available in the literature that evaluate prognostic factors and significant ongoing controversy regarding optimal treatment paradigms for the various histologic subtypes. This work is the first population-based study of PTL in the United States, and aims to provide insight into the demographic, clinical, and pathologic predictors of overall and disease-specific survival in this malignancy.

Statement of Purpose

The Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute (NCI) is an excellent source for evaluating the prognosis, treatment and outcomes of cancer patients in the United States. The SEER database is the only database of cancer patients in the U.S. that provides information on disease stage at diagnosis and that allows for the calculation of survival rates for each stage (35). Using data from the SEER database, this project will assess associations between demographic, clinical and pathologic characteristics of patients with primary thyroid lymphoma and their overall and disease-specific survival, using both bivariate and multivariate analyses. To our knowledge, this work is the first population-based study of PTL in the U.S. The hypotheses are as follows:

(1) Younger age, lower stage at diagnosis, and radiation treatment will be independent predictors of improved survival after diagnosis of PTL.

(2) When comparing disease-specific survival, patients with the histologic subtype DLBCL will have the worst disease-specific survival, and MALT will be associated with the best disease-specific survival.

(3) In accordance with treatment recommendations, use of surgery in the treatment of PTL will have declined from 1973 to 2005, while the use of other treatment modalities will have increased over the same time period.

Methods

Patients with PTL were identified in the Surveillance, Epidemiology, and End Results (SEER) database of the National Cancer Institute from 1973 to 2005. The SEER database was started in 1973 with 9 sites and currently provides cancer incidence and

survival data from 17 geographic regions (Alaska, Atlanta, greater California, Connecticut, Detroit, rural Georgia, Hawaii, Iowa, Kentucky, Los Angeles, Louisiana, New Jersey, New Mexico, San Francisco-Oakland, San Jose/Monterey, Seattle-Puget Sound, and Utah) representing approximately 26% of the U.S. population. Although the population captured by the database is more urban than the overall population, it is comparable in terms of income level and education (35).

The International Classification of Diseases for Oncology, Third Edition (ICD-O-3) coding system was used to select patients from SEER with primary tumors originating in the thyroid (ICD-O-3 code C73.9), and histology-specific codes (ICD-O-3 codes 9590-9758) were then used to identify those with PTL. All patients with active follow-up were included. Patients examined at death or by autopsy, or who were not followed after the diagnosis, were excluded.

Demographic information included gender, age at diagnosis, year of diagnosis, geographic location, race, and marital status at diagnosis. Age at diagnosis was analyzed as both a continuous and a categorical variable: age <45, 45-59, 60-69, 70-79, and ≥80. Year of diagnosis was analyzed with the following categories: 1973-1987, 1988-1997, and 1998-2005. Geographic location was classified as West, Midwest, Northeast and South. Race was categorized as white, black or other. Marital status was categorized as married, single/divorced/widowed, and unknown.

Clinical characteristics included number of other malignancies (none, 1, or ≥2) and systemic symptoms (asymptomatic, ‘‘B’’ symptoms and/or pruritus). Each patient’s unique SEER patient identification number was used to identify other malignancies in the cohort of PTL patients that were also captured within the SEER database (number and

type of lifetime malignancies, type of prior malignancies, and radiation for prior malignancy). The number of malignancies prior to the diagnosis of thyroid lymphoma represents the sequence of PTL in patient's lifetime history of malignancy, even if the prior malignancy is not represented in the SEER database. Cause of death of patients who died during follow-up was classified as lymphoma, other malignancy, non-malignant medical illness, accident/injury, and other/unknown.

Treatment modality was analyzed (no surgery or radiation, radiation only, surgery only, or both surgery and radiation), as was regional lymphadenectomy (none, limited, modified radical, or radical) and the number of regional lymph nodes examined in conjunction with surgery (none, 1, or >1). Site-specific surgical therapy codes were used to more specifically categorize the type of operation into none (including patients receiving incisional, needle, or aspiration biopsy only), local excision/partial lobectomy, lobectomy, and near-total/total thyroidectomy. Patients who received external beam radiation, with or without radioisotopes, or unspecified radiation therapy were categorized as a single group; patients who only received radioisotopes were categorized separately. SEER does not include information regarding use of chemotherapy; therefore, this treatment modality could not be evaluated in our analysis. Due to the limitations of the database, some clinical characteristics were analyzed over limited time frames. Data for the type of operation and systemic symptoms were only available after 1988; data for regional lymphadenectomy was available only from 1998 to 2002.

Pathologic characteristics examined include histologic subtype and stage at diagnosis. Histologic subtype was analyzed as follows: (1) diffuse large B-cell (DLBCL) (ICD-O-3 9680-9684), (2) follicular (ICD-O-3 9690-9698), (3) MALT (ICD-O-3 9699),

(4) small lymphocytic (ICD-O-3 9670-9671), (5) Hodgkin's (ICD-O-3 9650-9652 and 9663-9667), and (6) other non- Hodgkin's, including mixed, diffuse B-cell (ICD-O-3 9675), mantle cell (ICD-O-3 9673), Burkitt's (ICD-O-3 9687), T-cell (ICD-O-3 9702-9714), lymphoblastic (ICD-O-3 9727), and plasmacytoma (ICD-O-3 9731-9734).

PTL is staged based on the Ann Arbor staging criteria (26). As described in previous studies analyzing lymphoma using SEER (36), information on cancer stage according to the Ann Arbor guidelines was used to analyze PTL stage at diagnosis from 1988 to 2005.

Summary statistics for the entire PTL cohort and for each histologic subtype were obtained for all demographic, clinical, and pathologic characteristics. Variable trends over time were analyzed using broad groups (1973-1987, 1988-1996, and 1997-2005) as well as 3 year intervals. An analysis of variance (ANOVA) was used for continuous variables, and the χ^2 test was used for categorical variables. A bivariate analysis was performed using the Kaplan-Meier method and log-rank test to identify significant prognostic factors and calculate overall and disease-specific survival. The Cox proportional hazards regression model was used to obtain hazard ratios for each independent variable and to conduct multivariate analysis. The strength of association between each variable and survival was reported as a hazard ratio (HR), as well as a 95% confidence interval (CI). Tests were 2-sided, with statistical significance assumed at a p-value of < 0.05. The Statistical Package for Social Sciences software version 16.0 (SPSS Inc., Chicago, IL) was used for data analyses. SEER is a public data set that contains deidentified information; therefore, Institutional Review Board exemption was obtained. All coding of the database and statistical analyses were conducted by the author (Amanda

Graff-Baker), with assistance on the bivariate and multivariate analysis provided by Daniel Thomas, MPH.

Results

Summary statistics

A total of 1408 patients with primary thyroid lymphoma were identified over 32 years of follow-up in the SEER database, with a median follow-up of 3.75 yrs. Seventy-five percent of patients were female and 93% were white (Table 1). Nearly half of the patients were from the West (48%), with the Midwest being the second-most represented region (28%). Mean age at diagnosis was 66 years, with 24% of patients diagnosed between ages 60 and 69 years and 28% diagnosed between ages 70 and 79 years. Men were diagnosed at a younger age than women (63 vs. 68 years, respectively, $p < 0.001$). There was no significant difference in age noted when comparing patients diagnosed with higher and lower stage disease.

Table 1. Demographic Characteristics of Patients with Primary Thyroid Lymphoma, SEER 1973-2005

	All Patients (n=1408)	Histologic Subtype				
		DLBCL (n=846)	MALT (n=120)	Follicular (n=123)	Small lymphocytic (n=40)	Hodgkin's (n=24)
Patient Characteristics	**Percent (%)**					
Female	75	75	71	77	70	79
Age (mean years ± SD)	66.4 ±14.1	68.4 ±13.3	63.8 ±14.3	62.4 ±12.3	68.4 ±13.1	38.2 ±19.6
<45	7	5	8	8	2	67
45-59	23	20	28	31	28	21
60-69	24	24	24	32	20	0
70-79	28	31	22	24	30	8
>80	18	20	18	6	20	4
Race						
White	93	93	84	94	95	91
Black	1	2	0	0	0	9
Other	6	5	16	6	5	0
Marital status						
Married	58	55	63	72	67	58
Single/divorced	42	45	37	28	33	42

SEER, Surveillance, Epidemiology, and End Results Program; SD, standard deviation; MALT, mucosa associated lymphoid tissue

Histologically, 98% of patients had non-Hodgkin's lymphoma. Of the entire cohort, 68% had DLBCL, 10% follicular, 10% MALT, 3% mixed diffuse B-cell, 3% small lymphocytic, 2% Hodgkin's, 1% plasmacytoma. Burkitt's, T-cell, mantle cell, and lymphoblastic lymphomas each accounted for less than 1% patients. Age at diagnosis

varied between histologic subtypes. Approximately one third of patients with DLBCL were diagnosed between the ages of 70-79, with a mean age at diagnosis of 68.4. The mean age at diagnosis for patients with MALT, follicular lymphoma and small lymphocytic lymphoma was also in the 60's. In contrast, two-thirds of patients with Hodgkin's lymphoma were <45 years old and the mean age at diagnosis for those with Hodgkin's was 38 years, significantly younger than the mean age at diagnosis for any of the other histologic subtypes ($p < 0.001$).

Most patients (56%) had stage I disease at diagnosis (Table 2); 32% were diagnosed with stage II disease, 2% were diagnosed with stage III disease and 11% were diagnosed with stage IV disease. Forty percent of patients underwent both surgery and radiation, 28% underwent surgery only, 18% were treated with radiation only, and 15% received neither surgery nor radiation. 70% of patients found to have stage I disease received surgery, compared with 60% of patients with stage II and 56% of patients with stage III/IV disease ($p < 0.001$). Older patients were less likely to receive surgery; 55% of patients over 80 years received surgery, while 66% of patients younger than 45 years, 72% of patients between 45 and 59 years, 73 % of patients between 60 and 69 years, and 67% of patients between 70 and 79 years were operated upon ($p < 0.001$). Operative treatment employed regional lymphadenectomy in only 3%. From 1998 to 2002, the number of regional lymph nodes examined during surgery was recorded for 308 patients, with 10% having one lymph node examined, 5% having more than one, and a majority (85%) having no lymph nodes examined. Patients who did not receive surgery after 1988 overwhelming did not do so because surgery was not recommended (97%). Radiation was used in 58% of patients with stage I disease, 60% of patients with stage II disease,

and 31% of patients with stage III/IV disease. External beam radiation, either with or without additional radioactive isotopes, was used as treatment for 58% of patients. An additional seven patients (0.5%) received therapy with radioactive isotopes only.

Table 2. Clinical and Pathologic Characteristics of Patients with Primary Thyroid Lymphoma, SEER 1973-2005

	All Patients	Histologic Subtype				
		DLBCL	MALT	Follicular	Small lymphocytic	Hodgkin's
Patient Characteristics	**Percent (%)**					
Surgery performed	(n=1400)	(n=840)	(n=119)	(n=122)	(n=40)	(n=24)
	68	65	83	80	80	71
Type of Surgery	(n=682)	(n=406)	(n=98)	(n=73)	(n=20)	(n=9)
Local excision/partial lobectomy	17	19	11	11	15	11
Lobectomy	34	32	39	41	30	56
Near-total/total thyroidectomy	49	49	50	48	55	33
Lymphadenectomy	(n=272)	(n=245)	(n=55)	(n=31)	(n=9)	(n=6)
None	97	98	96	97	100	100
Limited	3	2	4	3	0	0
Modified radical	1	1	0	0	0	0
Radical	0	0	0	0	0	0
Reason for no surgery	(n=312)	(n=205)	(n=18)	(n=18)	(n=4)	(n=40)
Not recommended	97	97	94	100	100	75
Contraindicated	2	2	0	0	0	0
Refused	1	0	6	0	0	25
Radiation therapy used	(n=1352)	(n=812)	(n=117)	(n=121)	(n=39)	(n=24)
	59	58	55	55	56	71

	All Patients	Histologic Subtype				
		DLBCL	MALT	Follicular	Small lymphocytic	Hodgkin's
Patient Characteristics	**Percent (%)**					
Treatment	(n=1357)	(n=806)	(n=116)	(n=120)	(n=39)	(n=24)
No surgery or radiation	14.7	15	10	10	8	4
Radiation only	17.9	20	7	10	13	25
Surgery only	27.7	27	34	34	36	25
Surgery and radiation	39.7	38	48	46	44	46
Systemic symptoms	(n=598)	(n=386)	(n=57)	(n=53)	(n=13)	(n=12)
Asymptomatic	87	86	91	96	92	75
"B" symptoms and/or pruritus	13	14	9	4	8	25
Stage	(n=1062)	(n=666)	(n=115)	(n=91)	(n=25)	(n=12)
I	56	54	72	46	52	42
II	32	33	24	42	40	58
III	2	2	1	4	0	0
IV	11	12	3	8	8	0
Died of PTL	20.5	23	4	19	13	13
Died during follow-up	46.7	49	18	37	60	21

SEER, Surveillance, Epidemiology, and End Results Program; SD, standard deviation; MALT, mucosa associated lymphoid tissue

Patients with DLBCL were significantly less likely to receive surgery than patients with MALT or with follicular lymphoma ($p < 0.001$ for both). The percentage of patients undergoing radiation treatment was similar for all histologic subtypes (58.5% for DLBCL, 54.7% for MALT, 55.4% for follicular, and 56.4% for small lymphocytic), with the exception of patients with Hodgkin's lymphoma. 70.8% of those patients received

radiation. For all histologic subtypes, patients were more likely to receive both surgery and radiation than they were to receive either surgery or radiation alone.

Regardless of histologic subtype, the majority of patients presented with stage I or stage II disease. Patients with MALT were less likely to present with stage III or stage IV disease than those with DLBCL ($p < 0.01$) or follicular lymphoma ($p < 0.01$). More than 10% of patients with DLBCL and Hodgkin's presented with systemic symptoms. Patients with DLBCL were significantly more likely to present with systemic symptoms than those with follicular lymphoma ($p < 0.05$). Very few patients with MALT died of PTL (4.2%).

For 79% of patients, PTL was their only malignancy. Of those patients with other lifetime malignancies, 236 were recorded elsewhere in the SEER database. Common sites of other malignancies were breast (66 patients), colon (37 patients), prostate (30 patients), and lung (29 patients). Of the other malignancies documented in the database, 125 occurred prior to PTL. 29% of those patients received radiation as treatment for their first malignancy.

The use of surgery for PTL has declined over time. 81% of patients underwent surgery from 1973 to 1987, whereas 61% had surgery from 1997 to 2005. A similar trend was observed for radiation, with 69% of patients receiving radiation from 1973 to 1987, compared with 53% from 1997 to 2005. Over time, PTL was diagnosed in patients at an earlier stage; 83% were found to have stage I or stage II disease from 1988 to 1990, whereas 88% were diagnosed at those stages in 2003 to 2005.

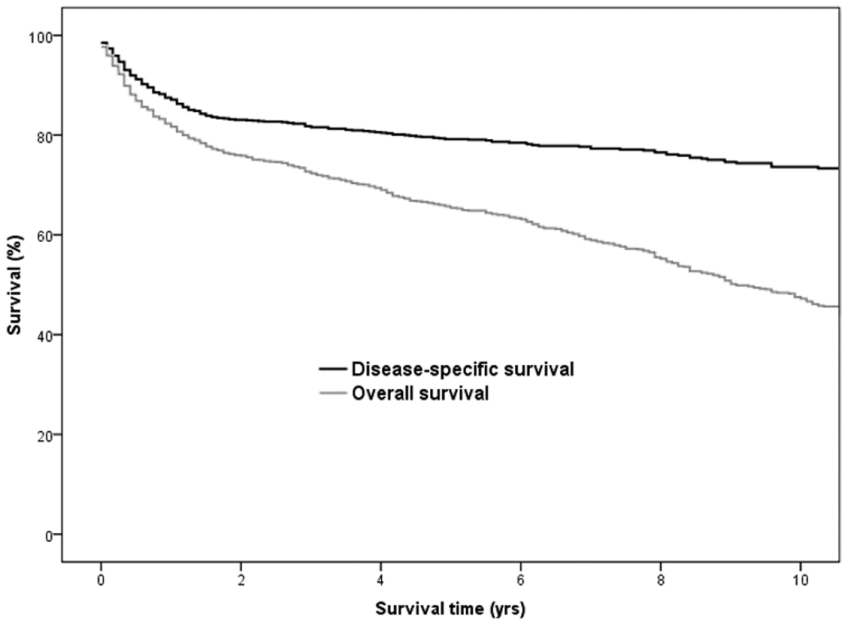
Of the 658 patients who died during follow-up, 44% died from lymphoma, whereas 35% died from a nononcologic cause. Cardiovascular and cerebrovascular

disease were the most common causes of nononcologic death, accounting for 68% of cases. An additional 13% of patients died from non-PTL malignancies; lung cancer was the most common, accounting for 34% of these deaths. Among patients who died from PTL, 58% succumbed within the first year after diagnosis and 88% within the first 5 years.

Kaplan-Meier analysis

Median overall survival of the cohort was 9.3 years. The 5-year overall survival was 66% and the 5-year disease-specific survival was 79% (Fig 1). Older age (age ≥60), single marital status, and more advanced stage were associated with decreased disease-specific survival on bivariate analysis (Table 3). When stratified by stage, patients who were diagnosed at a higher stage had a shorter disease-specific survival (Fig 2). Five years after diagnosis, disease-specific survival was 86% for patients with stage I disease, 81% for patients with stage II disease, and 64% for patients with stage III or IV disease. Receiving operative treatment or radiation was associated with improved survival.

Figure 1. Overall and disease-specific survival from primary thyroid lymphoma. SEER, 1973-2005.



This graph displays the Kaplan-Meier survival curves from PTL for overall and disease-specific survival. Five-year overall survival from PTL was 66% and 5-year disease-specific survival was 79%. Of those who succumbed to PTL, 58% died within the first year.

Table 3. Demographic, Clinical, and Pathologic Characteristics with Associated Hazard Ratios Based on Bivariate Analysis of Disease-Specific Mortality in Patients with Primary Thyroid Lymphoma, SEER 1973-2005

Variable	Hazards Ratio (95% CI)	*p*-value
Gender		
Male	1	*
Female	1.33 (0.99-1.77)	NS

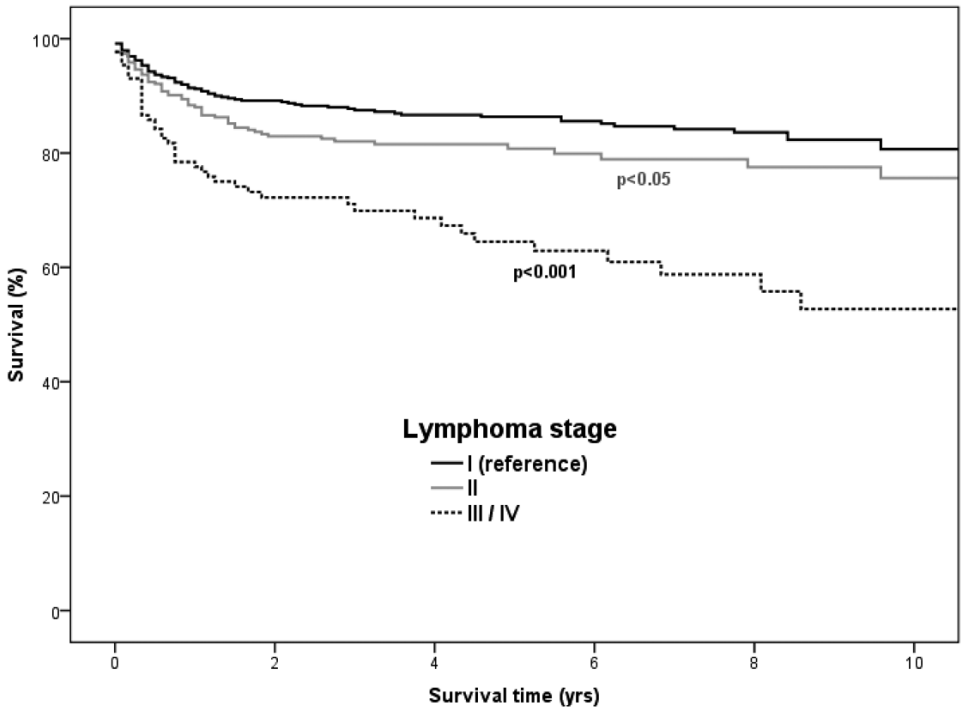
Variable	Hazards Ratio (95% CI)	*p*-value
Age[A]		
<45	1	*
45-59	1.28 (0.59-2.76)	NS
60-69	2.16 (1.03-4.52)	<0.05
70-79	3.27 (1.59-6.73)	0.001
≥80	6.67 (3.23-13.78)	<0.001
Marital Status[A]		
Married	1	*
Not married	1.83 (1.45-2.31)	<0.001
Race		
White	1	*
Black	1.45 (0.60-3.50)	NS
Other	0.73 (0.40-1.34)	NS
Year of Diagnosis[A]		
1973-1987	1	*
1988-1996	0.71 (0.53-0.94)	<0.05
1997-2005	0.58 (0.44-0.77)	<0.001
Treatment[A]		
No surgery or radiation	1	*
Radiation only	0.63 (0.43-0.93)	<0.05
Surgery only	0.57 (0.40-0.81)	<0.01
Surgery and radiation	0.54 (0.39-0.75)	<0.001

Variable	Hazards Ratio (95% CI)	*p*-value
Type of surgery		
None	1	*
Local excision/partial lobectomy	0.82 (0.50-1.33)	NS
Lobectomy	0.49 (0.32-0.77)	<0.01
Near-total/total thyroidectomy	0.79 (0.57-1.10)	NS
Stage[A]		
I	1	*
II	1.41 (1.00-1.97)	<0.05
III	1.38 (0.44-4.39)	NS
IV	3.08 (2.12-4.47)	<0.001
Number of other cancers[A]		
None	1	*
1	0.60 (0.42-0.85)	<0.01
≥2	0.62 (0.30-1.25)	NS
Systemic symptoms		
Asymptomatic	1	*
"B" symptoms and/or pruritus	1.43 (0.82-2.49)	NS
Histologic Subtype[A]		
MALT	1	*
Diffuse large B-cell	5.46 (2.25-13.28)	<0.001
Follicular	3.74 (1.42-9.84)	<0.01
Small lymphocytic	2.61 (0.76-9.03)	NS
Other non-Hodgkin's	3.92 (1.44-10.71)	<0.01
Hodgkin's	2.43 (0.58-10.17)	NS

* reference variable; [A] included in multivariate analysis

SEER, Surveillance, Epidemiology, and End Results Program; 95% CI, 95% confidence interval; NS, not significant; MALT, mucosa associated lymphoid tissue

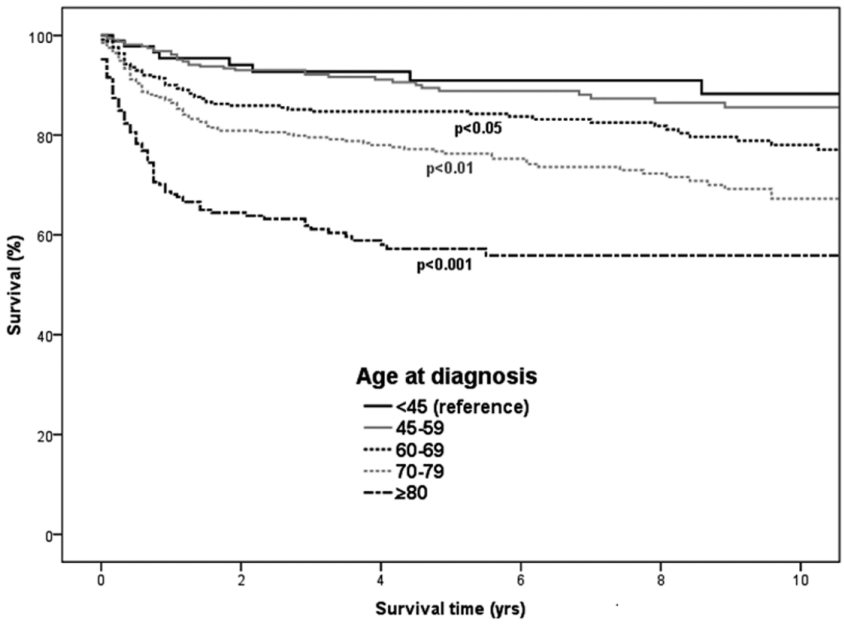
Figure 2. Disease-specific survival from primary thyroid lymphoma by stage. SEER, 1988-2005



Kaplan-Meier analysis was used to generate disease-specific survival curves, stratified by stage. When compared to patients with stage I disease, patients with stage II and stages III/IV disease fared significantly less well ($p < 0.05$ and $p < 0.001$, respectively).

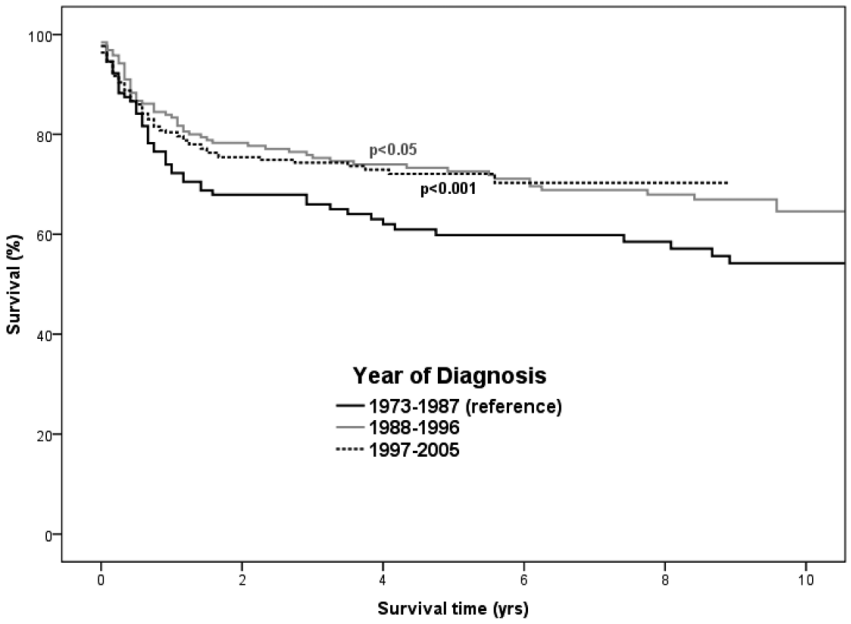
Older age at diagnosis was associated with shorter disease-specific survival (Fig 3). Disease-specific survival at 5 years was more than 90% for patients less than 60 years old, compared with 57% for patients ≥80 years old. There was a significant difference in disease-specific survival for patients whose conditions were diagnosed more than 20 years ago compared with those from the last 2 decades (Fig 4).

Figure 3. Disease-specific survival from primary thyroid lymphoma by age at diagnosis. SEER, 1973-2005.



Survival curves were generated based on age at diagnosis, and a relentless dose-response was associated with each additional ten years of age. With age <45 as the reference, the decrease in survival was significant for all age brackets over 60 ($p < 0.05$ for age 60-69, $p < 0.01$ for age 70-79, $p < 0.001$ for age ≥80.)

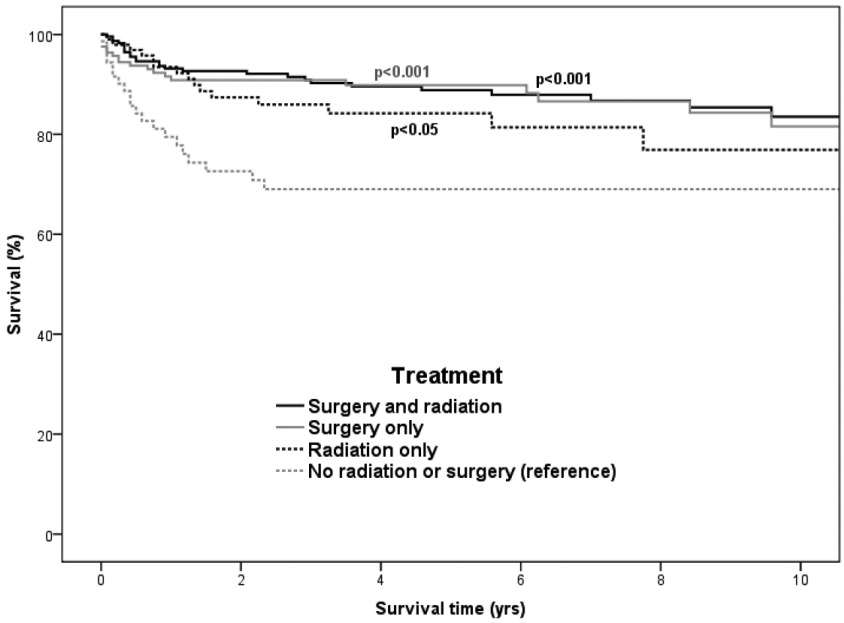
Figure 4. Disease-specific survival from primary thyroid lymphoma by year of diagnosis. SEER, 1973-2005.



Survival curves for year of diagnosis demonstrate a significant difference in survival for patients diagnosed from 1973-1987 when compared with those diagnosed from 1988-1996 ($p < 0.05$) and those diagnosed from 1997-2005 ($p < 0.001$).

When stratified by stage, treatment with surgery and radiation or surgery alone was associated with improved survival for stage I disease ($p < 0.001$ for both), whereas radiation was associated with improved survival for stages I and II ($p < 0.05$ for both) (Fig 5).

Figure 5. Disease-specific survival from stage I primary thyroid lymphoma by treatment. SEER, 1988-2005.



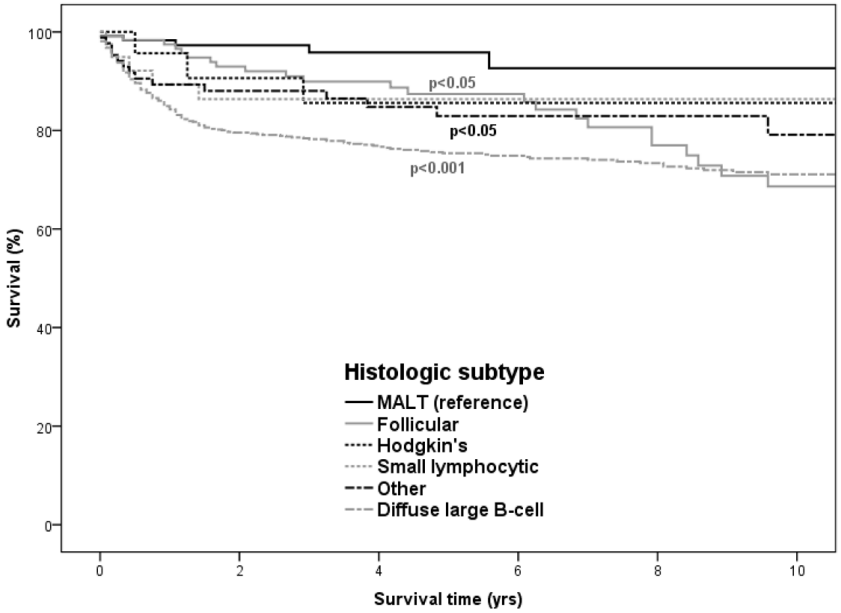
All three groups of patients receiving radiation or surgery had better survival than the no surgery or radiation group ($p<0.05$ for radiation only, $p<0.001$ for surgery only, $p<0.001$ for radiation and surgery). There was no significant difference in prognosis when comparing the three treatment groups. All patients in the no surgery or radiation group who died from PTL did so within the first three years, so the disease-specific survival of that group is unchanged thereafter.

All variables associated with disease-specific survival were also significant for overall survival, with 2 exceptions. Female sex predicted worse overall survival, but it was not significant for disease-specific survival. The number of malignancies was only significant for disease-specific survival.

Histologic subtype analysis

When stratified by histologic subtype, patients with DLBCL, follicular, and other non-Hodgkin's lymphomas had worse disease-specific survival than those with MALT lymphoma (Fig 6). Patients with DLBCL are five times more likely to die from PTL than patients with MALT. The 5-year disease-specific survival rate was 75% for DLBCL, 87% for follicular, 86% for small lymphocytic, 83% for other non-Hodgkin's, and 96% for MALT lymphoma. Disease-specific survival from MALT was significant when compared to patients with DLBCL ($p < 0.001$), follicular lymphoma ($p < 0.01$), and other non-Hodgkin's lymphoma ($p < 0.01$). Overall survival for patients with MALT was significantly better than for patients with DLBCL ($p < 0.001$) and other non-Hodgkin's lymphomas ($p < 0.05$).

Figure 6. Disease-specific survival from primary thyroid lymphoma by histologic subtype. SEER, 1973-2005.



Kaplan-Meier survival curves for each histologic subtype demonstrate significant differences in survival. Patients with MALT had the best disease-specific survival and were used as the reference group. Patients with follicular lymphoma, other non-Hodgkin's lymphoma, and DLBCL all had significantly worse survival ($p < 0.05$, $p < 0.05$, and $p < 0.001$, respectively).

For patients with DLBCL, age, marital status, treatment modality and stage at diagnosis were significant factors affecting disease-specific survival. Age was also significant predictor of survival for patients with MALT ($p = 0.001$) and with Hodgkin's lymphoma ($p < 0.001$). The hazard ratio for disease-specific survival of patients with DLBCL $\geq$ 80 years old was 5.2 when compared to patients <45 years old ($p < 0.001$).

Marriage offered some protection in terms of survival from DLBCL, with a hazard ratio of 1.6 for single patients ($p < 0.001$).

Just as in the overall analysis, DLBCL patients receiving surgery and/or radiation had a significantly better disease-specific survival than patients who did not receive either intervention. DLBCL patients who received neither surgery nor radiation had a 5-year disease-specific survival of 58.7%; less than one-quarter of patients who received surgery and/or radiation for DLBCL had died from PTL at five years (5-year disease-specific survival: 79.9% for radiation only, 74.8% for surgery only, 77.4% for surgery and radiation). The specific type of surgery performed for DLBCL, however, was not significant.

Treatment was also a significant indicator of disease-specific survival for patients with follicular lymphoma. All three groups of patients receiving treatment with surgery and/or radiation had hazard ratios of less than one, indicating improved survival when compared to patients who did not receive either treatment; however, the analysis only reached statistical significance for those patients who received both surgery and radiation ($p < 0.05$). Treatment was not a significant predictor of disease-specific survival on bivariate analysis for any of the other histologic subtypes.

Five-year disease specific survival decreased with increased stage for patients with DLBCL, MALT, follicular lymphoma, and other non-Hodgkin's lymphoma; these decreases reached statistical significance only for DLBCL and MALT (Table 4). For patients with DLBCL, only one in five patients diagnosed with stage I disease will succumb within five years, whereas 40% of patients with stage III or stage IV disease will die from PTL during that time.

Table 4. Five-Year Disease-Specific Survival by Histologic Subtype and Stage in Patients with Primary Thyroid Lymphoma, SEER 1988-2005

Histologic subtype	Disease-specific survival (SE)	*p*-value
Diffuse large B-cell		
Stage I (n=357)	81.7% (2.3%)	*
Stage II (n=217)	75.8% (3.3%)	NS
Stage III/IV (n=92)	60.4% (5.6%)	<0.001
Follicular		
Stage I (n=42)	94.3 % (3.9%)	*
Stage II (n=38)	91.0% (5.0%)	NS
Stage III/IV (n=11)	88.9% (10.5%)	NS
MALT		
Stage I (n=83)	97.5% (1.7%)	*
Stage II (n=28)	95.8% (4.1%)	NS
Stage III/IV (n=4)	50.0% (35.4%)	<0.05
Small lymphocytic		
Stage I (n=13)	82.1% (11.7%)	*
Stage II (n=10)	100%	NS
Stage III/IV (n=2)	100%	NS
Other non-Hodgkin's		
Stage I (n=32)	93.8% (4.3%)	*
Stage II (n=16)	92.3% (7.4%)	NS
Stage III/IV (n=8)	85.7% (13.2%)	NS
Hodgkin's		
Stage I (n=5)	75.0% (21.7%)	*
Stage II (n=7)	100%	NS
Stage III/IV (n=0)	--	NS

* reference variable

SEER, Surveillance, Epidemiology, and End Results Program; SE, standard error; NS, not significant; MALT, mucosa associated lymphoid tissue

When disease-specific survival for each histologic subtype was assessed based on stage and treatment modality, treatment with surgery and/or radiation were associated with improved survival for patients with stage I DLBCL, small lymphocytic, and MALT histologies. Stage II DLBCL treated with radiation had a better prognosis than stage II DLBCL treated with neither surgery nor radiation ($p < 0.05$); treatment of stage II DLBCL with surgery, either with or without radiation, was not associated with improved prognosis. There were no other significant associations between histologic subtype and treatment modality for stages II, III, and IV.

Multivariate analysis

Age, treatment modality, PTL stage, and histologic subtype remained significant predictors of disease-specific survival in multivariate analysis (Table 5). Age ≥80 remained an independent predictor of decreased survival ($p <0.001$). Patients with stage IV disease were 2.2 times more likely to die than those with stage I ($p <0.001$). All treatment groups did better than the no surgery or radiation group. Compared with patients with MALT lymphoma, patients with DLBCL were nearly 5 times more likely to die ($p <0.01$), and patients with follicular histology were 3.5 times more likely to die ($p < 0.05$).

Table 5. Demographic, Clinical, and Pathologic Characteristics with Associated Hazards Ratios Based on Multivariate Analysis of Disease-Specific Mortality in Patients with Primary Thyroid Lymphoma, SEER 1988-2005

Variable	Hazards Ratio (95% CI)	*p*-value
Age		
<45	1	*
46-59	0.65 (0.24-1.76)	NS
60-69	1.03 (0.41-2.63)	NS
70-79	2.18 (0.91-5.25)	NS
≥80	4.57 (1.91-10.96)	0.001
Treatment		
No surgery or radiation	1	*
Radiation only	0.43 (0.26-0.73)	<0.01
Surgery only	0.59 (0.38-0.92)	<0.05
Surgery and radiation	0.53 (0.35-0.80)	<0.01
Stage		
I	1	*
II	1.35 (0.94-1.95)	NS
III	1.76 (0.55-5.71)	NS
IV	2.19 (1.44-3.34)	<0.001

Variable	Hazards Ratio (95% CI)	*p*-value
Histologic Subtype		
MALT	1	*
Diffuse large B-cell	4.87 (1.79-13.26)	<0.01
Follicular	3.55 (1.15-10.96)	<0.05
Small lymphocytic	1.78 (0.33-9.73)	NS
Other non-Hodgkin's	1.89 (0.50-7.12)	NS
Hodgkin's	3.89 (0.40-37.71)	NS

* reference variable
SEER, Surveillance, Epidemiology, and End Results Program; 95% CI, 95% confidence interval; NS, not significant; MALT, mucosa associated lymphoid tissue

Discussion

PTL is a rare malignancy, with an estimated annual incidence similar to that of anaplastic thyroid cancer (3). To our knowledge, this study represents the first population-level analysis of patients with this disease. PTL most commonly affects white women over 60 years old, and most patients are found to have stage I disease. DLBCL is the most common histology and it carries the worst prognosis. The use of surgery and radiation for PTL has declined over time, although a majority of patients continue to receive both surgery and radiation. PTL is more likely to be diagnosed at an earlier stage now than it was 20 years ago. Approximately half of the patients died within 10 years of diagnosis, but less than half of those died from PTL. In our multivariate analysis, age ≥80 years, advanced PTL stage, lack of radiation or surgical treatment, and DLBCL and follicular histology were independently associated with decreased disease-specific survival.

To date, published analyses of PTL have been limited by small sample size, leading to discrepancies in the reported prevalence of histologic subtypes, overall and disease-specific survival, and significant prognostic indicators. Prior to this analysis, the largest study of PTL in the United States analyzed 108 cases (5). In that study, 66% of patients presented with stage I disease. Most patients had DLBCL, whereas approximately one third of patients were found to have MALT lymphoma. Stage, but not treatment, was associated with survival; no patients with stage I disease died during follow-up. No significant differences in survival were found for stages II, III, or IV.

A literature review that included 211 patients concluded that combined chemoradiation therapy should be the mainstay of treatment for PTL (37). Patients treated with both radiation and chemotherapy had significantly lower rates of distant and overall recurrence compared with those who received only one treatment modality. This analysis was limited to radiation and chemotherapy and did not include operative treatment. A more recent analysis of 50 PTL patients by Meyer-Rochow et al. (29) found that 54% of patients presented with stage II disease, with significant differences in survival between stages. No difference in disease-free survival was found when patients underwent resection versus open biopsy, leading the authors to conclude that surgery should be employed only to establish the diagnosis of PTL or to manage severe airway obstruction.

Overall, the demographic characteristics of our large cohort were similar to those described in smaller, single-institution series (5, 9, 17, 18, 29, 38-42). Our study is the first to show a significant disparity between the sexes in the mean age at diagnosis, with men diagnosed at a younger age. However, there was no significant difference between

the sexes with regard to disease-specific survival. Prior studies have found that approximately 90% of patients are found to have early stage PTL (5, 18, 29, 38). This is consistent with the current study. The distribution of patients between stage I and stage II varies widely in the literature, ranging from 31% to 71% for stage I (5, 18, 29, 38-41, 43, 44). Our finding of 56% of patients with stage I disease is within the reported range. There is consensus that DLBCL is the most common histologic subtype (3, 4, 45, 46); in our study, DLBCL accounted for 68% of all PTL. There is no such consensus about the incidence of less common histologies. MALT lymphoma is thought to be the second-most common histology in PTL; most studies have reported rates of 20% to 40% (5, 9, 42) Only 10% of our cohort had MALT and a larger percentage had follicular lymphoma that has been reported in most studies (5, 18, 42).

Reported overall survival from PTL ranges from 56% to 90% (9, 31). Derringer et al. (5) reported a 5-year disease-specific survival of 79%, with 90% of deaths occurring within the first three years after diagnosis. Our findings are similar, with a 5-year disease-specific survival of 79% and 80% of deaths occurring within the first 3 years. While 5-year disease-specific survival for stage I has been reported to be as high as 100% (5, 39), other studies have not found that stage I patients do so well (6, 31); in the current study, 14% of patients with stage I PTL died within 5 years of their diagnosis.

Belal et al. (39) reported that age had no effect on overall or recurrence-free survival; in contrast, DiBiase et al. (31) found that advanced age was associated with shorter overall survival. In the current study, a dose-response association was observed between increasing age and shorter disease-specific survival. Older age was associated

with more aggressive histology; still, age remained an independent predictor of disease-specific survival after adjustment for histology in our multivariate analysis.

Several studies have concluded that PTL stage and histology predict prognosis; that is, patients examined at an earlier stage or with MALT lymphoma have the best outcomes (5, 18, 29). These studies have relied on bivariate comparisons, rather than multivariate analysis, to provide support for these conclusions, as none of the series have been large enough to power a multivariate analysis. Studies that report significant survival differences based on stage have concluded that patients with stage I disease fare significantly better than those with stage IV (5, 6, 29); there is less consensus about prognostic implications of stage II and stage III disease. Our multivariate analysis indicated that patients with stage IV disease were twice as likely to die from PTL as those with stage I disease, but found no significant differences in survival of patients with stage I disease when compared to those with stage II or stage III disease.

Despite concluding that histologic subtype is an important factor in disease-specific survival from PTL, few studies have been large enough to conduct statistical analysis comparing the different histologic subtypes or to assess prognostic factors for each histologic subtype. This is the first study encompassing a large enough number of patients with PTL to allow for such analysis. We found that patients with DLBCL and follicular lymphoma were more likely to present with advanced stage disease than those with MALT. Patients with DLBCL were more likely to present with systemic symptoms than those with follicular lymphoma. The bivariate analyses conducted for each histologic subtype were most robust for DLBCL, where age, marital status, treatment and stage were all found to be significantly associated with disease-specific survival from

DLBCL. Disease-specific survival for patients with DLBCL and follicular lymphoma was significantly worse when compared with MALT lymphoma in multivariate analysis, thus corroborating prognostic value of histologic subtype for PTL.

In our multivariate analysis, the year of diagnosis was not associated with survival, which indicated that patients whose conditions were diagnosed in 2005 did not fare better than those whose conditions were diagnosed in 1988, despite considerable changes in the treatment paradigm for PTL during the last 2 decades. Treatment analysis in SEER was limited by a lack of chemotherapy data and by our inability to extrapolate surgical intent from the database. Still, several treatment-related results were available. Despite a growing consensus over the last decade that PTL is best treated by chemotherapy and/or radiation, depending on the histologic subtype (29, 37, 45), 61% of patients underwent surgery for PTL from 1997 to 2005. Possible reasons for surgical resection include tumor debulking for advanced disease, definitive treatment for stage I, or inappropriate operations. It is also possible that some patients underwent surgery for other thyroid pathology, and the diagnosis of PTL was only appreciated in the postoperative setting. Procedures used for the diagnosis of PTL and acquisition of tissue for immunohistochemical studies prior to the enrollment in chemotherapeutic protocols, such as incisional, needle, and aspiration biopsies, were not considered surgical procedures in our analysis, thus eliminating the possibility that high rates of surgery seen from 1997 to 2005 were a reflection of increased diagnostic testing.

There are no published randomized, controlled trials studying the efficacy of chemotherapy for PTL; therefore, chemotherapy regimens have been extrapolated from studies of extranodal lymphomas (45). Approved by the FDA after the conclusion of the

study period in 2006 as a first-line therapy for non-Hodgkin's lymphoma, rituximab has been used for off-label treatment of non-Hodgkin's PTL for the last several years. We were unable to assess whether any patients captured in the SEER database were treated with rituximab off-label. Patients with DLBCL at most centers receive 6-8 courses of R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine, and prednisone) as an initial treatment (18, 45). A single case report exists describing the treatment of PTL with rituximab. This patient was diagnosed with stage IE DLBCL in the left thyroid lobe after having a right lobectomy 10 years prior for medullary thyroid carcinoma. Treated with six courses of R-CHOP, the thyroid mass completely disappeared, and the patient achieved complete remission for the 34 months of follow-up (47).

Controversy still exists about the role of thyroid surgery for early stage disease (3, 4, 37, 44, 45). Our results suggest that surgery and radiation are associated with improved disease-specific survival for patients with stage I PTL. A study of 62 patients from the Mayo Clinic concluded that thyroidectomy with adjuvant chemotherapy provided long-term cure for PTL contained within the thyroid capsule (48). Other studies provide retrospective evidence for the use of single-modality therapy with surgery or radiation for indolent forms of PTL such as MALT (5, 45). Our data supported an association between surgery and/or radiation and the improved survival for patients with stage I MALT, DLBCL, and small lymphocytic histologies. The recurrence rates for PTL have been shown to be reduced by chemotherapy, but we could not test this finding in SEER.

Limitations of this study include those inherent to any analysis using a large database, such as coding errors, although SEER has been well validated. SEER does not

include imaging or central pathologic review. Information regarding chemotherapy is not available; therefore, the decline in use of surgery and radiation and the rise in the percentage of patients receiving neither surgery nor radiation over time might reflect increasing use of chemotherapy. SEER does not include information about patient comorbidities, so the number of primary tumors was the only available proxy for patient (oncologic) comorbidity. SEER also does not include recurrence or reoperation rates, so measurable outcomes were limited to overall and disease-specific survival.

In conclusion, this represents the largest population-based study of PTL published to date. Patient age, PTL stage and histology, and treatment modality are independently associated with survival. The paucity of data from large studies adequately powered to examine a relatively rare clinical entity such as PTL implies the need for additional research. We propose the creation of a retrospective/prospective multi-institutional thyroid lymphoma database that incorporates centers with experience in oncology, endocrinology, and thyroid surgery. In particular, future study should be committed to examining the role of operative treatment for early stage PTL. Given the importance of early diagnosis for improved survival, education of the public as well as of primary care physicians, endocrinologists, and oncologists should be emphasized.

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