original article

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Treatment results and prognostic factors in primary thyroid lymphoma patients: a Rare Cancer Network study

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Background: This study analyzed prognostic factors and treatment outcomes of primary thyroid lymphoma.
Patients and Methods: Data were retrospectively collected for 87 patients (53 stage I and 34 stage II) with median age 65 years. Fifty-two patients were treated with single modality (31 with chemotherapy alone and 21 with radiotherapy alone) and 35 with combined modality treatment. Median follow-up was 51 months.
Results: Sixty patients had aggressive lymphoma and 27 had indolent lymphoma. The 5- and 10-year overall survival (OS) rates were 74% and 71%, respectively, and the disease-free survival (DFS) rates were 68% and 64%. Univariate analysis revealed that age, tumor size, stage, lymph node involvement, B symptoms, and treatment modality were prognostic factors for OS, DFS, and local control (LC). Patients with thyroiditis had significantly better LC rates. In multivariate analysis, OS was influenced by age, B symptoms, lymph node involvement, and tumor size, whereas DFS and LC were influenced by B symptoms and tumor size. Compared with single modality treatment, patients treated with combined modality had better 5-year OS, DFS, and LC.
Conclusions: Combined modality leads to an excellent prognosis for patients with aggressive lymphoma but does not improve OS and LC in patients with indolent lymphoma.
Key words: chemotherapy, combined modality treatment, non-Hodgkin's lymphoma, prognostic factors, radiotherapy, thyroid lymphoma

introduction

Primary thyroid lymphoma (PTL) is a rare malignancy, accounting for 2%–5% of all thyroid malignancies, 1%–2.5% of all malignant lymphomas, and 2.5%–7% of all extranodal lymphomas [1, 2]. PTL is predominantly seen in middle- to older-aged women and usually presents as a painless mass in the neck region requiring a biopsy for tissue diagnosis [3]. The presence of B symptoms is uncommon [4]. The thyroid gland contains no native lymphoid tissue although in autoimmune thyroid disease, notably in Hashimoto's thyroiditis, the thyroid gland accumulates lymphatic cells [5]. The relative risk of developing a malignant thyroid lymphoma has been estimated to be 40–80 times greater in patients with Hashimoto's thyroiditis than in the general population, with lymphoma typically manifesting 20–30 years after the diagnosis of thyroiditis [6]. This evolution from Hashimoto's thyroiditis to lymphoma [typically a mucosa-associated lymphoid tissue (MALT) lymphoma] occurs in 0.5% of cases and is generally characterized by an indolent course. In some cases, however, transformation from MALT lymphoma to aggressive lymphoma may occur, with a poor prognosis [7]. Most thyroid lymphomas are B-cell-type non-Hodgkin's lymphomas (NHLs), and Hodgkin's and T-cell lymphomas are extremely rare [6].

The optimal strategy for managing PTL remains somewhat controversial. Up to 20 years ago, local surgery was used as a primary management strategy because of the difficulty in distinguishing histologically between malignant lymphoma and anaplastic thyroid carcinoma, especially based on preoperative biopsy [8]. Now, diagnosis can be accomplished using fine-needle aspiration biopsy (FNAB) or by core or open biopsy. Although complete surgical resection improves prognosis over incomplete resection [8, 9], malignant lymphomas are very sensitive to radiotherapy (RT), making this the mainstay

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treatment, either alone or in combination with chemotherapy (ChT) [8, 10]. To diminish the likelihood of local and systemic relapses, multiagent ChT, generally consisting of cyclophosphamide, adriamycin, vincristine, and prednisone (CHOP) and more recently including rituximab (R-CHOP), followed by involved-field radiotherapy (IFRT), has become more frequently used for aggressive lymphomas [11, 12]. Treatment with RT alone is typically reserved for cases with an indolent histology [8, 13], whereas combined modality treatment (CMT) with ChT and RT is preferred for aggressive lymphomas. Due to its rarity, very few studies have investigated the optimal treatment of PTL, and many reviews are based on studies including small numbers of patients. The goal of this Rare Cancer Network (RCN) study was to retrospectively collect a sufficient number of patients to identify prognostic factors that affect disease-free survival (DFS) and overall survival (OS) in PTL patients.

materials and methods

patient characteristics

Between 1986 and 2006, 93 patients with PTL were treated in nine member institutions of the RCN: China, 30 patients from one center; USA, 27 patients from one center; The Netherlands, 11 patients from one center; Turkey, 13 patients from three centers; Greece, 7 patients from one center; and Switzerland, 5 patients from two centers. Information on patient demographics, clinical presentation, staging examinations, pathological characteristics, treatment parameters, recurrence, survival outcomes, and treatment-related morbidity was obtained. The inclusion criteria were histologically proven NHL of the thyroid gland, localized disease, age ≥18 years, and minimum follow-up of 6 months. Only patients with lymphoma primarily involving the thyroid gland were included. Eighty-seven patients were eligible for the study and seven were excluded; three for incomplete data, two did not finish the planned treatment schedule, and one with secondary metastatic cancer.

Staging investigations included medical history and physical examination, complete hematologic profile, blood chemistry, and chest radiograph of all patients. The following tests were carried out: bone marrow aspiration and biopsy (61%), thoracic computed tomography (CT) (49%), erythrocyte sedimentation rate (43%), β2-microglobulin (36%), and positron emission tomography scan (5%). Infradiaphragmatic staging was carried out with abdominal CT (51%), abdominal ultrasonography (38%), or both (11%). According to the Ann Arbor Classification [14], 53 patients (61%) were stage I and 34 (39%) were stage II.

The main findings were a painless, rapidly enlarging thyroid mass in 69 patients (79%) and aerodigestive tract symptoms, including dyspnea and dysphagia, in 41 (47%). Six patients (7%) had thyroid enlargement together with hypothyroidism. Lymphadenopathy was present in the neck in 20 patients (23%) and at the level of the mediastinum in 10 patients (11%); 4 patients (5%) had both cervical and mediastinal lymph node involvement.

FNAB was carried out in 8 patients (9%), core biopsy in 24 (28%), and surgical excision in 55 (63%). In eight patients with FNAB, additional immunohistochemical analysis was carried out for accurate diagnosis. Patients were mostly diagnosed surgically at earlier dates with a substitution toward biopsy in more recent patients. World Health Organization classification was used to identify histological subtypes. The majority of patients had diffuse large B-cell histopathology (56 patients; 64%), while 18 (21%) had MALT lymphoma, 9 (10%) had follicular lymphoma, and 4 (5%) had other lymphoma subgroups (2 lymphoblastic lymphomas, 1 T-cell lymphoma, and 1 mantle cell lymphoma).

treatment modalities

Fifty-five patients (64%) underwent thyroid resection: 42 (48%) hemithyroidectomy and 13 (16%) total thyroidectomy. A tracheostomy was required to relieve airway obstruction symptoms before treatment in eight patients (9%). Surgery was carried out primarily for diagnosis, and all patients with thyroid resection were treated postoperatively: 16 (19%) with RT alone, 17 (20%) with ChT alone, and 22 (25%) with both RT and ChT as CMT. Thirty-two patients (37%) were treated definitively with RT (5 patients; 6%), ChT (12 patients; 14%), or CMT (15 patients; 17%).

Among the 66 patients (76%) receiving ChT (with or without RT and/or surgery), 46 were treated with the CHOP regimen, 14 with CHOP and rituximab, and 6 with other ChT regimens. The median number of ChT cycles was seven (range 1–13).

For the 58 patients who received RT, the median dose was 40 Gy (range 20–54), with a median daily dose of 2 Gy (range 1.5–3). Thirty-four patients received a radiation dose to the primary region of ≥40 Gy. Radiation was delivered with a linear accelerator (6–8 MV) in 51 patients and by ^{60}Co gamma rays in the remaining 7 patients. Twenty patients were treated with IFRT, including the thyroid bed and cervical lymph nodes, and 38 received extended-field radiotherapy (EFRT) that included thyroid, cervical, and upper mediastinal lymph nodes. Treatment was delivered with parallel opposing anterior–posterior fields: 38 patients were treated using conventional techniques, 14 had two-dimensional treatment planning, and 6 had three-dimensional conformal RT.

Patients with follicular lymphoma were treated with single modality therapy, either ChT (five patients; 56%) or RT (four patients; 46%). Patients with other histological types had either single or combined treatment modalities.

clinical end points and follow-up

This study analyzed OS as the primary end point. DFS was calculated from the time of diagnosis to the time of first relapse for DFS and OS from diagnosis to time of death or last follow-up. For DFS, treatment failure was defined as any form of disease recurrence or death from any cause.

statistical analysis

The basic characteristics of patients with indolent and aggressive lymphomas were compared using Fisher's exact test. Survival curves were obtained by the Kaplan–Meier method, and comparisons were made using log-rank tests. Factors found to be significant by univariate analysis were considered for multivariate analysis. Cox proportional hazards models were developed for the multivariate analysis of survival, and P values <0.05 were considered statistically significant.

results

treatment outcome

The median follow-up was 51 months (range 6–239) for the whole group and 76 months (range 6–239) for surviving patients. Median age was 65 years (range 15–92) with a male : female ratio of 1 : 2. Sixty patients (69%) had aggressive lymphoma and 27 (31%) had indolent lymphoma, either MALT lymphoma (18 patients; 21%) or follicular lymphoma (9 patients; 10%). Characteristics of patients with indolent and aggressive lymphomas are summarized in Table 1. Majority of patients (53 patients; 61%) had stage I disease, whereas 34 patients (39%) patients had stage II disease. Of 56 patients with diffuse large B-cell lymphoma (DLBCL), 35 patients (63%) had stage I and 21 patients (37%) had stage II disease. Likewise, 10 of 18 patients with MALT lymphoma and

Table 1. Characteristics of patients with indolent or aggressive lymphoma

	Indolent lymphoma, *n* (%)	Aggressive lymphoma, *n* (%)	*P*
Sex			
Male	7 (26)	22 (37)	0.46
Female	20 (74)	38 (63)	
Age (years)			
≤60	12 (44)	38 (63)	0.10
>60	15 (56)	22 (37)	
Tumor size (cm)			
<5	16 (59)	21 (35)	0.08
5–10	7 (26)	30 (50)	
>10	4 (15)	8 (15)	
Stage			
I	16 (59)	37 (62)	0.81
II	11 (41)	23 (38)	
Palpable mass			
Absent	7 (26)	22 (37)	0.46
Present	20 (74)	38 (63)	
B symptoms			
Absent	24 (89)	55 (92)	0.39
Present	3 (11)	5 (8)	
Thyroiditis			
Absent	20 (74)	47 (78)	0.58
Present	7 (26)	13 (22)	
Aerodigestive tract compression			
Absent	16 (59)	29 (48)	0.36
Present	11 (41)	31 (52)	
Lymph node involvement			
Absent	3 (11)	9 (15)	0.86
Present	24 (89)	51 (85)	
Treatment modality			
Single modality	15 (56)	36 (60)	0.81
Combined modality	12 (44)	24 (40)	
Treatment			
ChT alone	9 (33)	21 (35)	0.87
RT alone	6 (22)	15 (25)	
ChT and RT	12 (45)	24 (40)	

ChT, chemotherapy; RT, radiotherapy.

6 of 9 patients with follicular lymphoma had stage I disease. The remaining two patients with lymphoblastic lymphoma had stage II disease, and one patient with T-cell lymphoma and one with mantle cell lymphoma had stage I disease each.

A total of 65 patients (75%) were alive at last follow-up: 58 with no evidence of disease and 7 with disease. Twenty-two patients (25%) died during follow-up; 15 from causes related to PTL and 7 from other causes (2 with coronary heart disease, 2 due to pneumonia, 1 after gastrointestinal bleeding, 1 with tumor uterine sarcoma, and 1 due to an unknown cause).

overall survival

The actuarial 5- and 10-year OS rates for the whole group were 74% and 71%, respectively (Figure 1). The 5- and 10-year OS rates were 80% and 74%, respectively, for indolent lymphoma and 73% and 71% for aggressive lymphoma. The prognostic factors for OS on univariate and multivariate analyses are summarized in Tables 2 and 3, respectively, whereas Tables 4 and 5 show univariate and multivariate analysis of prognostic factors in indolent and aggressive lymphomas. For the whole group, CMT significantly improved OS compared with single modality with either ChT or RT (91% versus 57%, $P = 0.01$, and versus 69%, $P = 0.03$, respectively) (Figure 3). There was no significant difference between treatment with ChT or RT alone ($P = 0.8$). In indolent lymphoma, CMT did not significantly improve OS compared with single modality, and treatment with either RT or ChT alone did not differ significantly (Table 4). In aggressive lymphoma, CMT significantly improved OS compared with single modality treatment with RT alone ($P = 0.005$) or ChT alone ($P = 0.02$), although the results of treatment with either RT alone or ChT alone did not differ significantly (Table 5). There was a trend toward statistical significance for higher RT doses (>40 Gy) compared with doses ≤40 Gy (86% versus 73%, $P = 0.09$). On multivariate analysis, B symptoms ($P = 0.007$), tumor size ($P = 0.02$), and lymph node involvement ($P = 0.02$) were all found to be significant prognostic factors for survival. Treatment modality was close to the level of significance ($P = 0.08$).

local control

The crude local recurrence rate was 17% (15 of 87 patients, 12 of whom died of disease). The actuarial LC rates were 77% and 73% at 5 and 10 years, respectively. The results of univariate analysis are summarized in Table 2. While CMT improved 5-year LC rates compared with either ChT or RT alone (95% versus 56%, $P < 0.001$, and versus 69%, $P = 0.001$), single treatment modality with either ChT or RT did not differ significantly ($P = 0.5$). In patients treated with RT, doses ≥40 Gy significantly improved LC rates compared with lower RT doses (94% versus 78%, $P = 0.04$), whereas EFRT did not significantly improve LC compared with IFRT. On multivariate analysis, a significantly worse LC was found for patients with B symptoms [hazard ratio (HR) 3.7, $P = 0.03$] and for stage II disease (HR 2.8, $P = 0.04$). Treatment modality did not significantly improve LC.

disease-free survival

The 5- and 10-year actuarial DFS rates were 68% and 64%, respectively (Figure 2). The 5- and 10-year DFS rates were 70% and 67% for indolent lymphoma and 63% and 54% for aggressive lymphoma. The prognostic factors affecting DFS are summarized in Tables 2 and 3 for the whole population and in Tables 4 and 5 according to indolent and aggressive lymphomas. CMT significantly improved DFS compared with ChT alone ($P < 0.001$) and RT alone ($P < 0.001$). The 5-year DFS rate was 49% for ChT alone, 45% for RT alone, and 91% for CMT ($P = 0.04$) (Figure 4). Treatment with ChT alone or RT alone did not differ significantly ($P = 0.2$). DFS rates in patients with indolent and aggressive lymphomas were significantly better in the CMT arm (Table 3); however, there was no difference between treatment with RT alone or ChT alone in either indolent or aggressive lymphoma. In patients

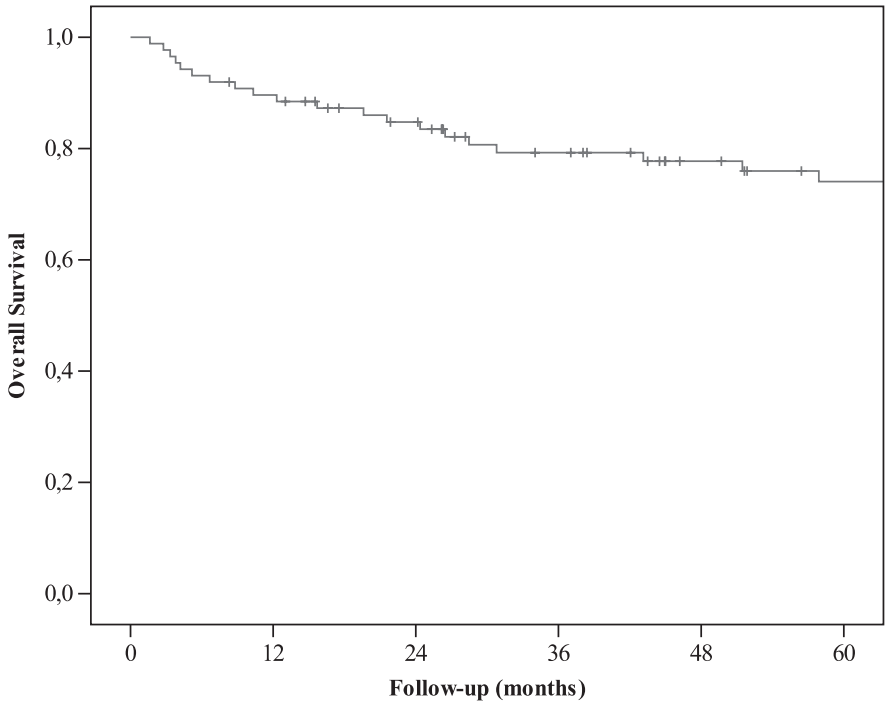


Figure 1. Overall survival of the total patient group.

treated with RT, doses ≥40 Gy had borderline significance for DFS compared with lower RT doses (94% versus 76%, $P = 0.05$). Patients treated with EFRT had higher DFS compared with patients treated with IFRT (93% versus 67%, $P = 0.01$). On multivariate analysis, presence of B symptoms ($P = 0.001$), large tumor ($P = 0.02$), and single modality treatment ($P = 0.01$) were found to be negative significant prognostic factors for DFS (Table 3). Although lymph node involvement did not show significance on LC, there was a trend toward a negative impact (HR 3.3, 95% confidence interval 1.0–11.3, $P = 0.05$).

patterns of relapse

Locoregional and distant relapse was seen in 15 patients (17%) and 9 patients (10%), respectively, while 2 patients (2%) presented with both locoregional and distant relapse. Distant relapses were mainly seen in the abdomen (six patients), with two patients having either pulmonary relapse or paranasal sinus relapse.

early and late toxic effects

Due to the retrospective nature of the study and because data were collected from different centers, early and late toxic effects were assessed only through patient chart review and cannot be considered a complete assessment of toxicity. Eighteen patients (21%) had grade 2 and two (2%) had grade 3 acute toxicity, including dysphagia, dyspnea, and skin reactions. Severe late (grade 3–4) effects included clinical hypothyroidism (seven patients), neck fibrosis (one patient), hemiparesis (one patient), polyneuropathy and lung fibrosis (one patient), pneumonia (one patient), and brain necrosis and abscess (one patient). Infield secondary cancer (papillary thyroid cancer and breast cancer) was observed in two patients.

discussion

Our data from patients treated for PTL over a prolonged period of time provide valuable insight into the management of this uncommon disease. Although published results from smaller series failed to isolate significant prognostic factors, we collected enough data to identify several factors that have prognostic value with respect to OS, DFS, and LC. We also demonstrated the superiority of CMT for DFS and LC in all subgroups and for OS for patients with aggressive lymphoma.

PTL is most commonly observed in middle-to older-aged females [15]. The main presenting findings are a mass in the thyroid gland or diffuse enlargement that causes symptoms related to compression, such as hoarseness, dysphagia, and dyspnea. The majority of our patients (68 of 86) had thyroid enlargement at diagnosis. Age has been shown to be a significant factor determining OS rates among PTL patients, especially those >60 years of age, in agreement with our results [15, 16].

Approximately 80% of patients with thyroid lymphoma present with stage I or II disease [2, 15]. Although the staging for NHL is adopted from the Ann Arbor system, difficulties and controversies can arise in staging especially extranodal NHL [17]. In view of this, Dawson et al. [18] proposed that specific staging of primary NHL at any extranodal site should be restricted to disease with the main manifestation at the extranodal site, with or without regional lymph node involvement. This essentially limits the staging of primary NHL of the thyroid gland to stage I or II disease [18]. For this reason, in our study, stage I patients had localized involvement of the thyroid only, whereas in stage II patients the major site of involvement was the thyroid gland but associated with regional lymph node involvement.

Table 2. Univariate analysis of prognostic factors for OS, LS, and DFS

Factor	*n* (%)	5-Year OS (%)	*P*	5-Year LC (%)	*P*	5-Year DFS (%)	*P*
Age (years)							
≤60	29 (33)	84	0.02	85	0.2	78	0.8
>60	58 (67)	66		71		65	
Sex							
Male	37 (43)	68	0.6	74	0.7	61	0.7
Female	50 (57)	77		79		71	
Pathology							
Aggressive	60 (69)	73	0.8	74	0.7	63	0.8
Indolent	27 (31)	80		79		70	
Tumor size (cm)							
<5	38 (44)	88	0.01	87	0.03	77	0.01
5–10	38 (44)	70		77		68	
>10	11 (12)	46		47		36	
Stage							
I	53 (61)	80	0.02	91	0.001	75	0.02
II	34 (39)	65		56		55	
Lymph node involvement							
Absent	10 (12)	81	0.01	78	0.03	79	0.03
Present	77 (88)	50		54		55	
Palpable mass							
Absent	28 (32)	80	0.3	83	0.3	79	0.2
Present	59 (68)	71		75		69	
B symptoms							
Absent	81 (93)	79	<0.0001	82	<0.0001	76	<0.0001
Present	6 (7)	33		31		25	
Thyroiditis							
Absent	66 (76)	70	0.4	62	0.02	65	0.1
Present	21 (24)	87		83		80	
Aerodigestive compression							
Absent	46 (53)	77	0.4	78	0.4	76	0.4
Present	41 (47)	71		73		68	
Treatment modality							
Single modality	50 (58)	61	0.009	62	0.001	53	0.008
Combined modality	37 (42)	92		95		83	
Treatment							
ChT alone	21 (24)	57	0.01	56	0.001	49	0.04
RT alone	29 (33)	69		69		63	
ChT and RT	37 (43)	91		95		91	

OS, overall survival; LC, local control; DFS, disease-free survival; ChT, chemotherapy; RT, radiotherapy.

Table 3. Multivariate analysis of prognostic factors for OS (Cox model)

Factor	OS exp(B) [95% CI for exp(B)]	DFS exp(B) [95% CI for exp(B)]	LC exp(B) [95% CI for exp(B)]
B symptoms (present versus absent)	4.2 [1.7–13.0], $P = 0.002$	5.6 [1.9–16.6], $P = 0.003$	3.6 [1.1–11.6], $P = 0.04$
Tumor size (<5 versus ≥5 cm)	2.4 [1.2–5.4], $P = 0.03$	2.1 [1.3–4.1], $P = 0.03$	1.8 [0.7–4.0], $P = 0.2$
Stage (I versus II)	1.2 [0.4–3.6], $P = 0.6$	1.8 [0.8–4.9], $P = 0.09$	2.5 [1.1–7.6], $P = 0.04$
Lymph node involvement (present versus absent)	4.4 [1.6–13.5], $P = 0.02$	3.4 [1.2–11.3], $P = 0.05$	3.2 [0.6–9.2], $P = 0.2$
Treatment modality (combined versus single modality)	2.9 [0.9–10.6], $P = 0.08$	4.2 [1.3–16.1], $P = 0.03$	3.8 [1.1–19.8], $P = 0.1$

OS, overall survival; CI, confidence interval; DFS, disease-free survival; LC, local control.

PTL is predominantly of B-cell origin and is commonly associated with Hashimoto's thyroiditis. Williams et al. [19] reported a causal relationship between Hashimoto's thyroiditis and development of lymphoma, although other studies do not support this [20, 21]. Although worse outcomes have been reported for malignant lymphomas arising from autoimmune disease, this is not supported by our findings or some other studies [20, 21]. Belal et al. [20] demonstrated relapse-free survival rates of 94% in patients with preexisting thyroiditis compared with 47% in patients without known thyroiditis; however, in our series, we found that DFS, OS, and LC rates were better in patients with preexisting thyroiditis, which may be attributable of coexistence of thyrioditis with MALT lymphoma and DLBCL related to MALT lymphoma, which has an indolent behavior than DLBCL. Since there exists an observed association with MALT lymphoma and thyroiditis in a substantial number of cases, it is unfortunately difficult to differentiate the reason of hypothyroidism seen in our seven cases, either treatment-related or preexisting thyroiditis. Although hypothyroidism seen after treatment, this condition is relatively easy to manage. Most thyroid lymphomas are DLBCL, although up to 25% of the lesions may be indolent lymphomas, including follicular lymphoma and MALT lymphoma. The most common B-cell lymphoma is the diffuse

Table 4. Univariate analysis of prognostic factors for OS and DFS among indolent and aggressive lymphoma

Features	Indolent lymphoma		Aggressive lymphoma	
	P		*P*	
	OS	DFS	OS	DFS
Age	0.02	0.008	0.24	0.91
Sex	0.21	0.67	0.81	0.97
Tumor size	0.02	0.01	0.03	0.02
Stage	0.11	0.05	0.07	0.03
Lymph node involvement	<0.001	<0.001	<0.001	<0.001
Palpable mass	0.47	0.54	0.81	0.76
B symptoms	0.01	0.009	<0.001	<0.001
Thyroiditis	0.51	0.25	0.39	0.56
Aerodigestive compression	0.91	0.42	0.47	0.67

OS, overall survival; DFS, disease-free survival.

Table 5. Multivariate analysis of prognostic factors for OS and DFS by Cox proportional hazards analysis

Prognostic factors	OS exp(B) [95% CI for exp(B)]		DFS exp(B) [95% CI for exp(B)]	
	Indolent	Aggressive	Indolent	Aggressive
Age (>60 years)	5.7 [0.5–31.7], $P = 0.2$	1.9 [0.5–6.1], $P = 0.3$	7.0 [1.1–25.5], $P = 0.04$	1.2 [0.7–2.2], $P = 0.4$
B symptoms	3.3 [0.4–25.0], $P = 0.4$	7.8 [1.4–22.9], $P = 0.02$	3.6 [0.5–22.6], $P = 0.3$	10.1 [1.9–34.5], $P = 0.007$
Tumor size (≥5 cm)	2.1 [0.4–10.7], $P = 0.4$	2.4 [0.9–6.6], $P = 0.09$	1.7 [0.6–4.9], $P = 0.4$	2.1 [0.9–4.7], $P = 0.08$
Stage II	2.5 [0.4–10.6], $P = 0.4$	1.2 [0.3–4.7], $P = 0.7$	2.5 [0.5–11.7], $P = 0.2$	1.1 [0.3–3.9], $P = 0.8$
Treatment modality	1.6 [0.7–15.4], $P = 0.7$	4.3 [1.9–10.0], $P = 0.04$	3.1 [0.4–18.1], $P = 0.4$	5.4 [1.2–15.5], $P = 0.03$

OS, overall survival; CI, confidence interval; DFS, disease-free survival.

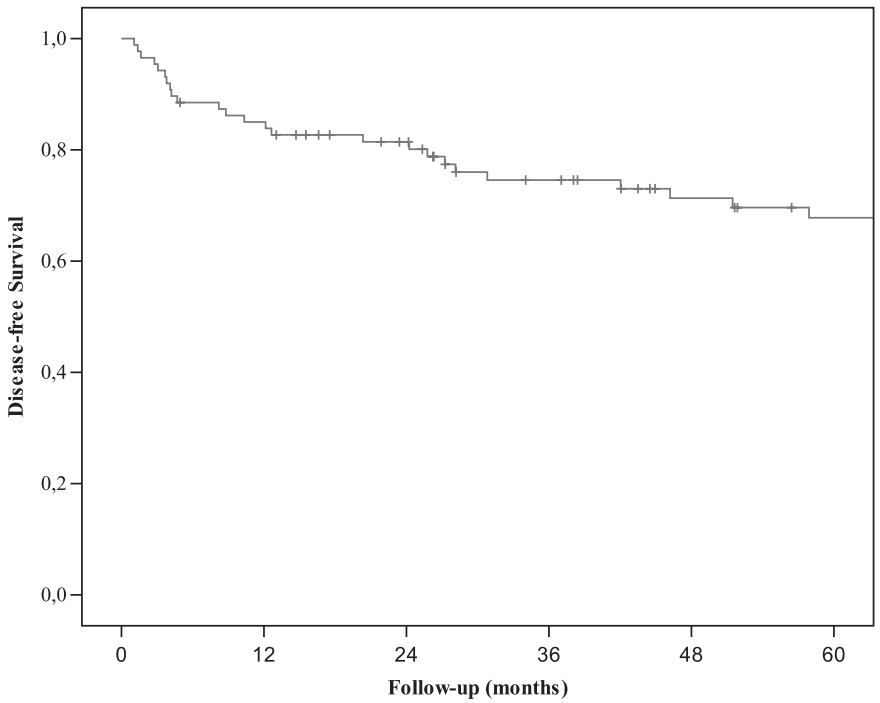
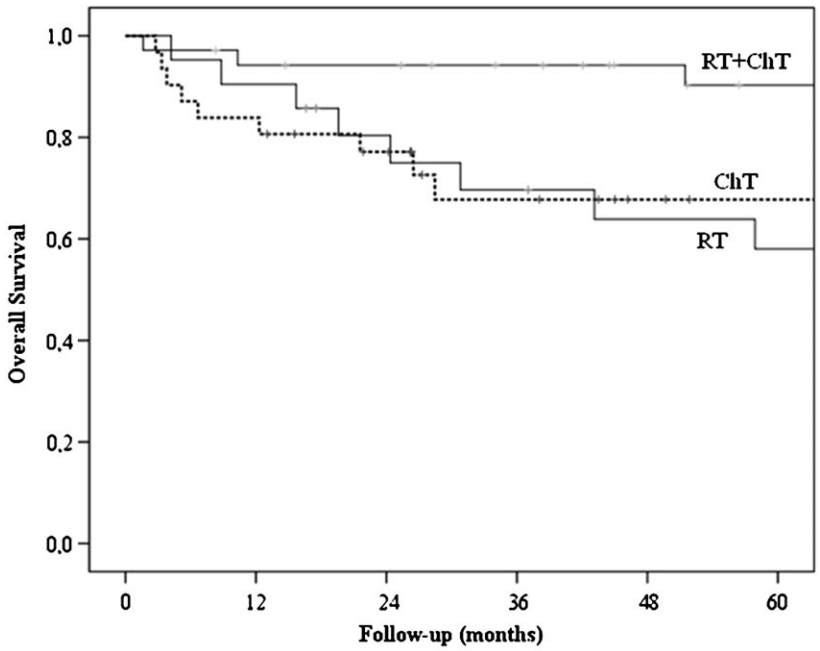


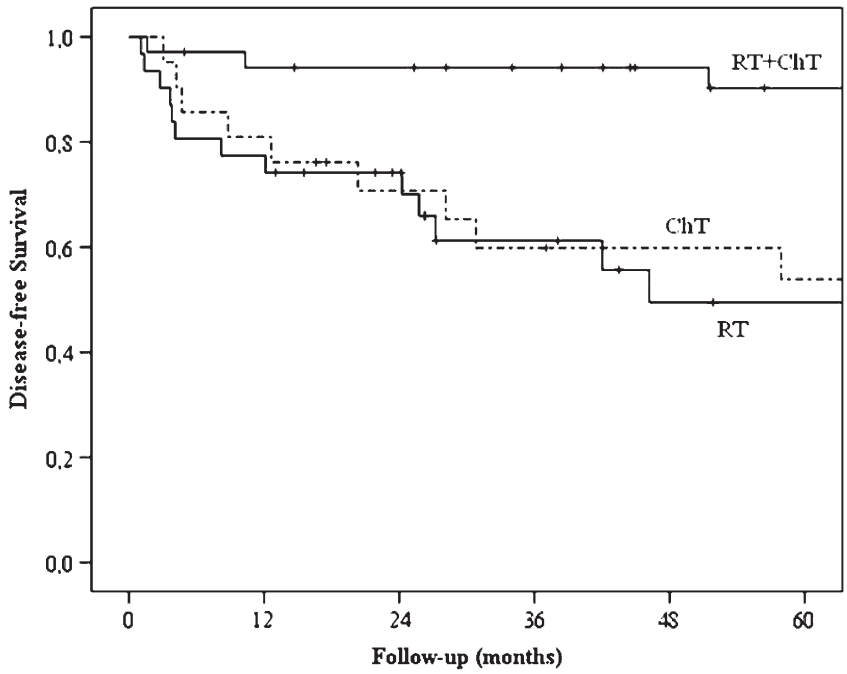
Figure 2. Disease-free survival of the total patient group.



Patients at risk

RT+ChT	35	32	31	28	24	21
ChT	31	25	20	14	10	8
RT	21	19	15	13	11	10

Figure 3. Overall survival according to treatment modality.



Patients at risk

RT+ChT	35	32	31	28	24	21
ChT	31	24	19	12	8	7
RT	21	17	13	11	10	9

Figure 4. Disease-free survival according to treatment modality.

Table 6. Survival analysis according to treatment modality among lymphoma subgroups

Group	*n* (%)	5-Year OS	*P*	5-Year DFS	*P*	5-Year LC	*P*
Aggressive lymphoma	60						
Single modality	32 (57)	60	0.005	54	0.001	57	0.001
Multimodality	24 (43)	90		89		92	
Indolent lymphoma	27						
Single modality	15 (56)	72	0.1	53	0.02	64	0.04
Multimodality	12 (44)	91		90		91	

OS, overall survival; DFS, disease-free survival; LC, local control.

large cell accounting for 50%–70% of all lymphomas, as was in our series [21–23]. Other rare subtypes include follicular lymphoma (12%), Hodgkin's disease (7%), small lymphocytic lymphoma (4%), and Burkitt's lymphoma (4%). Thyroid DLBCL at a localized stage generally has a good prognosis, but it is heterogeneous with respect to the pathological subtype and some types have a poor prognosis [24, 25]. MALT is recognized as a distinct lymphoma with unique clinicopathologic features. MALT lymphomas generally arise in lymphoid tissue that has developed as a result of chronic inflammation, such as seen in Hashimoto's thyroiditis. Pure MALT lymphomas of the thyroid make up 23%–30% of primary lymphomas [21, 26]. The incidence of aggressive lymphomas was 96% in the series of Rosen et al. [27] and 100% in that of Belal et al. [20], and several other studies have reported a similar incidence [13, 15, 22]. In our series, 36% of patients had indolent lymphoma, which seems higher than previously published findings. The recruitment of patients mainly through radiation oncology departments may have led to an overrepresentation of these cases. Unfortunately, the treatment results of indolent lymphoma were found to be worse than those in other anatomical sites, and further research is needed to determine whether there is a distinct biological background of PTL.

Because of the rarity of PTL, no randomized controlled trials have compared the efficacy of multimodality versus single modality treatment. In a retrospective series by Ha et al. [28], they found that the 5-year OS and DFS rates are 64% and 76%, which is in concordance with our findings. And they concluded that prognosis for patients with localized NHL involving the thyroid gland have good outcome, especially when CMT was used. However, it seems reasonable to extrapolate treatment of this disease based on the results of randomized trials for other sites of nodal and extranodal lymphoma. In the Eastern Cooperative Oncology Group 1484 study, Horning et al. [29] demonstrated improved DFS in 172 patients with early-stage aggressive lymphoma treated with CHOP and low-dose RT (30 Gy) but without any OS benefit. In a multicenter trial of 401 similar patients, Miller et al. [30] reported a 5-year progression-free survival of 77% for CHOP plus RT versus 64% for CHOP alone and an estimated 5-year OS of 82% versus 72%, and CMT has subsequently been considered the standard of care for early-stage aggressive lymphomas. In a review of 211 patients with thyroid lymphoma, Doria et al. [31] demonstrated that addition of ChT to RT significantly lowered distant and overall recurrence rates compared with RT alone (overall recurrence 8% versus 37%; distant recurrence 5% versus 31%). Our findings clearly demonstrated that CMT significantly improved DFS, OS, and LC for aggressive lymphoma and DFS and LC for other types of lymphoma (Table 6). Similar to published findings, the addition of rituximab, a chimeric anti-CD20 immunoglobulin G1 monoclonal antibody, to CHOP improved OS (92% versus 71%, $P = 0.06$) [11, 12, 32, 33].

Given the retrospective nature of our review (i.e. retrospective, multi-institutional study over the years, many pathologists) and variation in the treatment methods employed, patient selection bias may have impacted the results of our study. However, all patients were treated with conventionally fractionated RT and conventional ChT, and relatively few patients received single modality treatment. Without data from randomized studies, the results of retrospective reviews such as ours provide a valuable contribution to our understanding of the clinical behavior and treatment of PTL. Based on the results of our retrospective series and extrapolated evidence of two randomized controlled trials for mainly nodal aggressive lymphomas [29, 30], we recommend CMT for the treatment of PTL. The use of better staging procedures, improvement of ChT by the addition of rituximab to CHOP, limited use of surgery, and advanced RT delivery techniques will improve results for patients with PTL with respect to DFS and side-effects.

conclusions

Since PTL is a rare disease, it is difficult to carry out prospective randomized trials to evaluate prognostic factors and optimal treatment combinations. Our multivariate analysis of data obtained from a large number of patients identified the following independent prognostic factors: age, B symptoms, lymph node involvement, and treatment modality for OS; B symptoms and treatment modality for DFS; and B symptoms, lymph node involvement, and treatment modality for LC. Patients with aggressive lymphoma are good candidates for CMT involving ChT and RT.

disclosure

The authors have declared no conflicts of interest.

references

1. Austin JR, el-Naggar AK, Goepfert H. Thyroid cancers. II. Medullary, anaplastic, lymphoma, sarcoma, squamous cell. Otolaryngol Clin North Am 1996; 29: 611–627.

2. Aozasa K, Tsujimoto M, Sakurai M et al. Non-Hodgkin's lymphomas in Osaka, Japan. Eur J Cancer Clin Oncol 1985; 21: 487–492.
3. Singer JA. Primary lymphoma of the thyroid. Am Surg 1998; 64: 334–337.
4. Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. Semin Oncol 1999; 26: 316–323.
5. Kato I, Tajima K, Suchi T et al. Chronic thyroiditis as a risk factor of B-cell lymphoma in the thyroid gland. Jpn J Cancer Res 1985; 76: 1085–1090.
6. Pedersen RK, Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: a population based study. Histopathology 1996; 28: 25–32.
7. Laing RW, Hoskin P, Hudson BV et al. The significance of MALT histology in thyroid lymphoma: a review of patients from the BNLI and Royal Marsden Hospital. Clin Oncol (R Coll Radiol) 1994; 6: 300–304.
8. Klyachkin ML, Schwartz RW, Cibull M et al. Thyroid lymphoma: is there a role for surgery? Am Surg 1998; 64: 234–238.
9. Tupchong L, Hughes F, Harmer CL. Primary lymphoma of the thyroid: clinical features, prognostic factors, and results of treatment. Int J Radiat Oncol Biol Phys 1986; 12: 1813–1821.
10. Blair TJ, Evans RG, Buskirk SJ et al. Radiotherapeutic management of primary thyroid lymphoma. Int J Radiat Oncol Biol Phys 1985; 11: 365–370.
11. Coiffier B, Lepage E, Briere J et al. CHOP chemotherapy plus rituximab compared with CHOP alone in elderly patients with diffuse large-B-cell lymphoma. N Engl J Med 2002; 346: 235–242.
12. Sehn LH, Donaldson J, Chhanabhai M et al. Introduction of combined CHOP plus rituximab therapy dramatically improved outcome of diffuse large B-cell lymphoma in British Columbia. J Clin Oncol 2005; 23: 5027–5033.
13. Scholefield JH, Quayle AR, Harris SC, Talbot CH. Primary lymphoma of the thyroid, the association with Hashimoto's thyroiditis. Eur J Surg Oncol 1992; 18: 89–92.
14. Carbone PP, Kaplan HS, Musshoff K et al. Report of the committee on Hodgkin's disease staging classification. Cancer Res 1971; 31: 1860–1861.
15. DiBiase SJ, Grigsby PW, Guo C et al. Outcome analysis for stage IE and IIE thyroid lymphoma. Am J Clin Oncol 2004; 27: 178–184.
16. Logue JP, Hale RJ, Stewart AL et al. Primary malignant lymphoma of the thyroid: a clinicopathological analysis. Int J Radiat Oncol Biol Phys 1992; 22: 929–933.
17. Tsang RW, Gospodarowicz MK, Pintilie M et al. Stage I and II MALT lymphoma: results of treatment with radiotherapy. Int J Radiat Oncol Biol Phys 2001; 50: 1258–1264.
18. Dawson IM, Cornes JS, Morson BC. Primary malignant lymphoid tumours of the intestinal tract. Report of 37 cases with a study of factors influencing prognosis. Br J Surg 1961; 49: 80–89.
19. Williams ED. Malignant lymphoma of the thyroid. Clin Endocrinol Metab 1981; 10: 379–389.
20. Belal AA, Allam A, Kandil A et al. Primary thyroid lymphoma: a retrospective analysis of prognostic factors and treatment outcome for localized intermediate and high grade lymphoma. Am J Clin Oncol 2001; 24: 299–305.
21. Thieblemont C, Mayer A, Dumontet C et al. Primary thyroid lymphoma is a heterogeneous disease. J Clin Endocrinol Metab 2002; 87: 105–111.
22. Derringer GA, Thompson LD, Frommelt RA et al. Malignant lymphoma of the thyroid gland: a clinicopathologic study of 108 cases. Am J Surg Pathol 2000; 24: 623–639.
23. Wirtzfeld DA, Winston JS, Hicks WL Jr, Loree TR. Clinical presentation and treatment of non-Hodgkin's lymphoma of the thyroid gland. Ann Surg Oncol 2001; 8: 338–341.
24. Niitsu N, Okamoto M, Nakamura N et al. Clinicopathologic correlations of stage IE/IIE primary thyroid diffuse large B-cell lymphoma. Ann Oncol 2007; 18: 1203–1208.
25. Tilly H, Dreyling M. Diffuse large B-cell non-Hodgkin's lymphoma: ESMO clinical recommendations for diagnosis, treatment and follow-up. Ann Oncol 2009; 20 (Suppl 4): 110–112.
26. Tsang RW, Gospodarowicz MK, Pintilie M et al. Localized mucosa-associated lymphoid tissue lymphoma treated with radiation therapy has excellent clinical outcome. J Clin Oncol 2003; 21: 4157–4164.
27. Rosen IB, Sutcliffe SB, Gospodarowicz MK et al. The role of surgery in the management of thyroid lymphoma. Surgery 1988; 104: 1095–1099.
28. Ha CS, Shadle KM, Medeiros LJ et al. Localized non-Hodgkin lymphoma involving the thyroid gland. Cancer 2001; 91: 629–635.
29. Horning SJ, Weller E, Kim K et al. Chemotherapy with or without radiotherapy in limited-stage diffuse aggressive non-Hodgkin's lymphoma: Eastern Cooperative Oncology Group study 1484. J Clin Oncol 2004; 22: 3032–3038.
30. Miller TP, Dahlberg S, Cassady JR et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Engl J Med 1998; 339: 21–26.
31. Doria R, Jekel JF, Cooper DL. Thyroid lymphoma. The case for combined modality therapy. Cancer 1994; 73: 200–206.
32. Persky DO, Unger JM, Spier CM et al. Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group study 0014. J Clin Oncol 2008; 26: 2258–2263.
33. Bari A, Marcheselli L, Sacchi S et al. Prognostic models for diffuse large B-cell lymphoma in the rituximab era: a never-ending story. Ann Oncol 2010; 21: 1486–1491.