*Clinical Review*

# Thyroid Lymphoma

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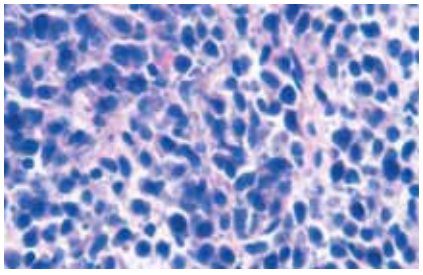
This article reviews the clinical presentation, prognosis, therapeutic strategies, and outcomes of thyroid lymphomas.

Primary thyroid lymphoma is an uncommon cancer and includes < 5% of extranodal non-Hodgkin lymphoma and < 5% of all thyroid cancers.[1,2] In the past, it was often difficult to correctly diagnose by fine-needle aspiration cytology (FNAC). Development of immunocytochemical lymphoid markers has improved the success rate of an accurate diagnosis of thyroid lymphoma. Although thyroid lymphoma is not a common cancer, it is very important to distinguish primary thyroid lymphoma from anaplastic thyroid carcinoma since the prognosis is very different; few patients with anaplastic thyroid carcinoma survive beyond 2 years; while primary thyroid lymphoma generally has a favorable outcome. This article reviews the clinical presentation, prognosis, therapeutic strategies, and outcomes of thyroid lymphomas.

## EPIDEMIOLOGY

Primary thyroid lymphoma is rare and represents 2% to 5% of extranodal non-Hodgkin lymphoma. Thyroid lymphomas constitute < 5% of all thyroid cancers. Thyroid lymphoma is 2 to 4 times more common in women compared with men. Lymphomas of the thyroid are typically seen in the elderly in the seventh decade of life, although the age range can vary from 31 years to 82 years. Almost all thyroid lymphomas are B-cell non-Hodgkin lymphoma and are often associated with Hashimoto's thyroiditis. Hodgkin lymphoma and T-cell lymphomas of the thyroid are rare.

**Figure 1.**



Pathologic image of thyroid lymphoma showing diffuse infiltration of atypical cells consistent with B-cell lymphoma with no normal thyroid tissue present.

## PATHOLOGY

Malignant tumors of the thyroid are largely divided into 2 categories based on the classification of the World Health Organization: tumors that originate from the thyroid gland proper and extraordinary tumors that appear as a thyroid gland malignancy (such as thyroid lymphoma, which commonly develop in organs other than the thyroid gland).

**Table 1. Histologic subtypes of thyroid lymphoma[1,3]**

| |
|---|
| • Diffuse large B-cell lymphoma |
| • MALT lymphoma |
| • Follicular lymphoma |
| • Hodgkin disease |
| • Small lymphocytic |

MALT = mucosa-associated lymphoid tissue lymphoma.

Thyroid lymphoma (Figure 1) is a heterogeneous and diverse disease entity and not a single disease. The majority of thyroid lymphomas are of B-cell origin, and 5 distinctive histologic subtypes are recognized (Table 1).[1,3] The most common and predominant histologic subtype is diffuse large B-cell lymphoma (DLBCL), which has a relatively monotonous architecture of large, abnormal lymphoid cells and displays the most aggressive clinical course. The second common subtype of histology is mucosa-associated lymphoid tissue lymphoma (MALT), which shows small lymphocytes with plasmacytoid features and has a relatively benign clinical course. MALT lymphomas are often associated with Hashimoto's thyroiditis. The development of MALT lymphoma from Hashimoto's thyroiditis takes a long time, sometimes as long as 30 years.[2] MALT

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lymphoma is generally characterized by an indolent clinical course, although transformation from MALT lymphoma to aggressive lymphoma may occur in some cases.[4] Follicular lymphomas usually show a predominantly follicular pattern and oftentimes a clinically protracted course of disease; the response to therapy is short-lived, resulting in frequent recurrences. Hodgkin disease and small lymphocytic lymphoma are extremely rare and are not covered in this discussion.

The diagnosis of DLBCL is relatively easy because of clear-cut pathologic features of large, monotonous atypical high-density cells. In contrast, diagnosis of MALT lymphoma is somewhat tricky, because of a more heterogeneous overall picture in addition to difficulty in demarcating this entity from unmixed Hashimoto's thyroiditis. Furthermore, sampling errors of tiny specimens could result in higher chances of false negative reports, because many MALT lymphomas occur in concert with Hashimoto's thyroiditis within a thyroid gland. The presence of a lymphoepithelial lesion is not a specific finding of MALT lymphoma, although once it was considered to be a diagnostic finding of thyroidal MALT lymphoma. In order to distinguish DLBCLs from MALT lymphomas and also MALT lymphomas from Hashimoto's disease, immunohistochemical stains, flow cytometry analysis of biopsy tissue, fine-needle aspiration (FNA) sampling, and molecular genetic analysis may be needed to aid in the diagnosis.

## CLINICAL PRESENTATION

The most common presenting symptom is a painless enlargement of the neck (thyroid gland), which is typically seen in 30% to 50% of cases. Some patients may feel a pressure sensation in the anterior neck region. The neck mass is usually smooth, bulky, and rubbery. Thyroid lymphomas frequently present on 1 side of the thyroid gland. Hoarseness, dysphagia, dyspnea, and stridor are also common presenting symptoms. The presence of constitutional symptoms (lymphoma's B symptoms) are not frequent, and few patients experience B symptoms, such as fever, night sweats, and weight loss (Table 2). The characteristic fever is a cyclic fever over an average period of 1 or 2 weeks, and it is specifically called Pel-Ebstein fever when associated with lymphoma.

**Table 2. B symptoms of lymphomas**

- Pel-Ebstein fever
- Night sweats
- > 10% unintentional weight loss

According to Sarinah and Hisham, 65% of their thyroid lymphoma patients were euthyroid, and 29% were hypothyroid. The majority of their patients had a palpable goiter (Table 3).[5] Four of 17 patients had clinically palpable cervical lymph nodes. However, imaging studies showed the presence of cervical lymph nodes in 11 patients.[5]

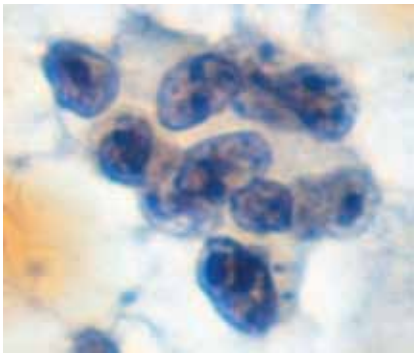
## DIAGNOSIS

Due to its rareness, thyroid lymphomas often create diagnostic and therapeutic difficulties. Until fine-needle aspiration biopsy (FNAB) was developed in the late 1970s, thyroid lymphoma was frequently diagnosed postoperatively, subsequent to thyroidectomy for presumed thyroid cancer. An ultrasound-guided FNAB of an hypoechoic or pseudocystic lesion is the preferred procedure since a blind FNAB is often unable to differentiate malignant lymphoma from chronic lymphocytic thyroiditis. The sufficient tissue sampling is very important for appropriate interpretation of the histopathologic examination. Recent advancement in immunocytochemical staining techniques and cytopathologic knowledge has enhanced the capacity to make an accurate diagnosis of this rare entity.

**Table 3. Presenting symptoms and signs of thyroid lymphoma[5]**

- Neck mass (82%-88%)
- Goiter (70%)
- Dyspnea (65%)
- Dysphagia (21%-53%)
- Hoarseness (25%-35%)

**Figure 2.**



Cytologic image of thyroid lymphoma showing undifferentiated malignant neoplastic cells with no normal thyroid tissue identified.

## CYTOLOGY

Cytologic diagnosis of thyroid lymphoma requires careful analysis of morphologic, clinical, and immunophenotypic information. Fine-needle aspiration biopsy shows the replacement of the thyroid with neoplastic lymphocytes by Papanicolaou stains (Figure 2). Certain characteristic pathogenetic findings of large-cell lymphoma are large, monotonous ab-

**Table 4. International Prognostic Index (IPI)**

| Factors | Description |
|---|---|
| Age | > 60 years |
| Performance status | ECOG ≤ 2 |
| Serum lactate dehydrogenase | Abnormal |
| Tumor stage | III – IV |
| Involved sites (No.) | > 1 |

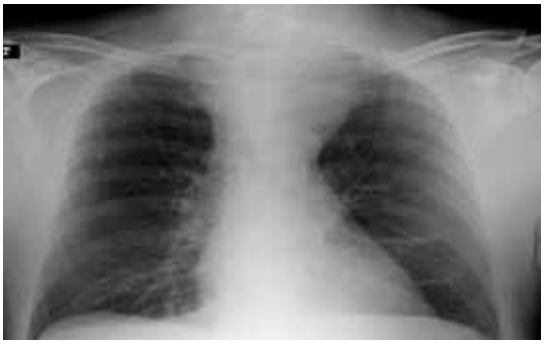
Source: *N Engl J Med.* 1993;329(14):987-994.
ECOG = Eastern Cooperative Oncology Group Performance Status.

**Table 5. Prognostic group (IPI score)**

| Risk group | IPI scores |
|---|---|
| Low | 0-1 |
| Low-intermediate | 2 |
| High-intermediate | 3 |
| High | 4-5 |

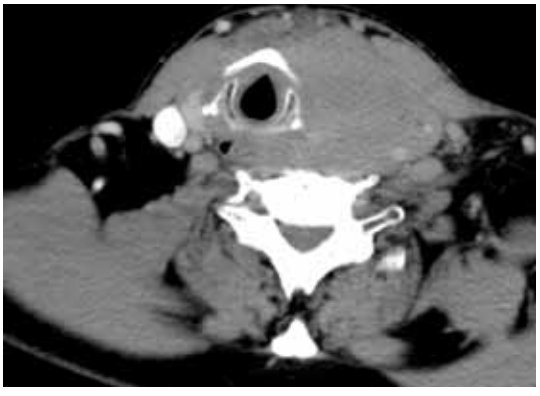
Source: *N Engl J Med.* 1993;329(14):987-994.

**Figure 3.**



Chest X-ray showing soft tissue density projecting over the medial aspect of the left upper lung, representing an underlying mass involving the lower neck and upper mediastinum.

**Figure 4.**



CT scan showing a large soft tissue mass in the left side of the neck and superior mediastinum, which surrounds and arises from the left lobe of the thyroid gland.

normal cells in a background of lymphoglandular features, predominant plasmacytoid lymphocytes, and specific immunophenotyping findings. The diagnosis of thyroid lymphoma can be made accurately by FNAC in a majority of patients, in correlation with flow cytometry and immunohistochemical analysis technique. In some difficult cases, however, a large-bore needle biopsy or excisional biopsy may still be required for an accurate diagnosis, especially in small lymphocytic or MALT lymphomas in the setting of Hashimoto's disease.

Continuous progress in immunophenotypic techniques, such as immunohistochemistry and flow cytometry, have remarkably improved the accuracy of FNA for the diagnosis of lymphoma (Table 4). Cha and colleagues pioneered immunophenotyping in combination with FNA in diagnosing thyroid lymphoma.[6] Of their 4 patients, none had a correct diagnosis when immunophenotyping was not applied, while 88% of cases (7 of 8 patients) were correctly diagnosed utilizing immunophenotyping along with FNA. For example, MALT lymphoma can be linked to 4 translocations and t(11;18) is the most common chromosomal translocation in MALT lymphoma.

In cases of difficult morphologic problems, surface markers can provide a valuable objective basis for resolving diagnostic dilemma. Markers, such as CD-22, CD-19, and CD-20 are immunophenotypes of B-cell lymphomas. Characteristic markers of follicular center cell lymphoma are CD-5-, CD-10+, and CD-23 +/- phenotypes; while the CD5-, CD10-, and CD23- phenotypes are typical markers of MALT lymphoma.

## IMAGING STUDY

A chest X-ray can show a mediastinal mass or tracheal deviation (Figure 3). Computed tomography and magnetic resonance imaging (MRI) are the most useful imaging studies for diagnosis and staging of thyroid lymphomas (Figure 4). According to a study by Takashima and colleagues, MRI was superior in correctly assessing the extent of tumor infiltration to lymph nodes, surrounding muscles, esophagus, internal jugular vein, and carotid artery.[7] Ultra-

sound is also a very useful imaging study in revealing a thyroid nodule that often clearly distinguishes from normal thyroid tissue and is also a helpful tool in the successful localization and FNA procedures, compared with random blind biopsies. However, an ultrasound is not a reliable test in identifying lymphoma invasion to surrounding structures such as lymph nodes, the esophagus, and carotid artery.

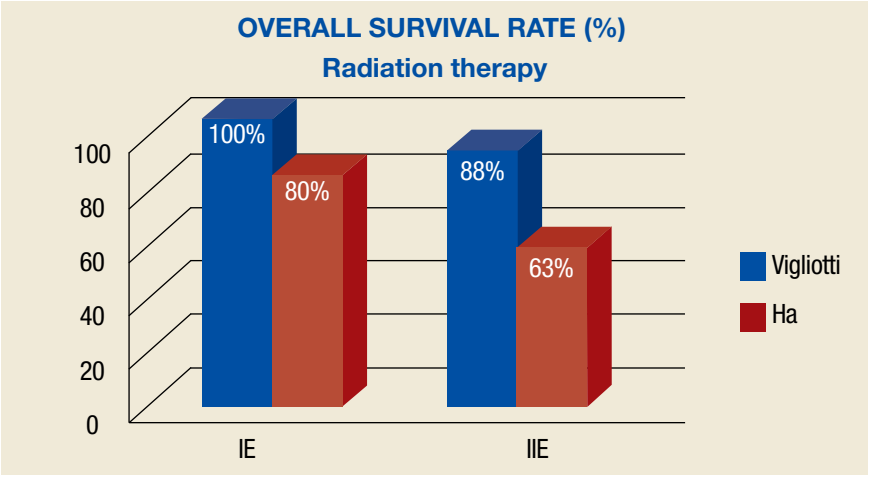
## THERAPEUTIC STRATEGY

The therapeutic strategy for this tumor is somewhat contentious. In the past, surgical resection was the primary therapy. As malignant lymphomas are very sensitive to both chemotherapy and radiotherapy, radiation treatment alone or combination chemotherapy and radiation therapy has become the standard of thyroid lymphoma treatment. The management of low-grade lymphomas can be radiation therapy and oral or intravenous chemotherapy. The management of DLBCL should be combined-modality therapy with radiation and chemotherapy, using the cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) regimen.[8] Surgical resection of the thyroid mass is no longer a routine part of the management strategy.

### SURGERY

In the past, surgery was the major therapeutic strategy for thyroid lymphoma treatment. However, surgery is now playing a minor role as chemotherapy and radiation therapy became more effective. Although the role of surgery has become less important, surgery still plays certain imperative roles; specifically, in surgical biopsy for establishing a correct diagnosis and a potential role in the local control of selected indolent disease, as well as in palliating critical symptoms associated with large obstructive lymphomas. Past experience indicates a certain subgroup of early, localized stage IE thyroid lymphomas showed good response to surgery or radiation. In selected and ideal situations, surgery may be recommended as a primary therapy of early stage lymphoma and favorable thyroid lymphomas, such as MALT subtype stage IE, only if the tumor can be completely resected with minimal morbidity.[9]

**Figure 5.**




Overall survival rates (stage IE vs IIE) after radiation therapy.[16,17]

### RADIATION THERAPY

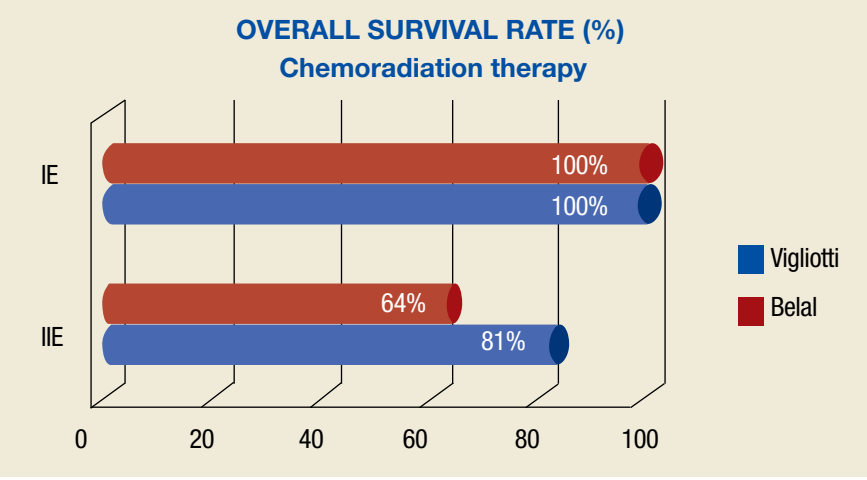
In a report by Blair and colleagues, from the Mayo Clinic, of 38 patients treated with radiation therapy, overall disease-free survival at 5 years was 59%.[10] Fourteen patients experienced a recurrence, and 71% (10 patients) recurred in 2 or more sites. Patients received a radiation dose of 4,000 cGy (2,400-6,000 cGy) to the neck only or neck and mediastinum. They did not recommend a split course of therapy because of higher failure rates.[10]

Tsang and colleagues reviewed 103 cases with stage IE and IIE MALT lymphomas of various presenting sites (stomach, orbit, salivary glands, thyroid glands, etc) in patients who received radiation therapy (median radiation dose of 3,000 cGy).[11] Eighty-four of 85 patients showed a complete response to radiation alone. No recurrences were observed in patients with thyroid lymphoma.[11] The more indolent lymphomas, MALT lymphomas when localized to the thyroid (stage IE), responded well to local therapy alone.

### CHEMORADIATION THERAPY

Currently, primary thyroid lymphoma is usually treated nonsurgically once the diagnosis is established. For aggressive thyroid lymphomas, a combined approach with chemotherapy and radiation therapy is now a common approach for successful outcomes as systemic chemotherapy reduces risk of distant recurrences. Diffuse large B-cell lymphoma, treated with aggressive therapy, is the most common and major subtype, comprising roughly 70% of thyroid lymphomas, and displays a more aggressive clinical

**Figure 6.**




Overall survival rates (stage IE vs IIE) after chemoradiation therapy.[15,16]

course. Furthermore, almost 60% of these lymphomas present with disseminated disease at the time of initial diagnosis. Accordingly, these lymphomas should be treated with combined modality of chemotherapy and radiation.

Previously, a popular combination of multiagent chemotherapy was CHOP, but recently rituximab has been added to the CHOP combination (R-CHOP). The current standard regimen for chemotherapy is R-CHOP. Sarinah and Hisham reported their experience with 15 patients treated with R-CHOP with or without radiation therapy.[5] All patients showed an excellent response to therapy, and tumor size was rapidly decreased. At the time of their report, 14 patients were still alive with no evidence of recurrence, and the overall survival (OS) rate was 82%.

Doria and colleagues reviewed 211 cases of stage IE and stage IIE thyroid lymphoma in patients who were treated with a combined modality of therapy and found that distant and overall failure rates were significantly lower when patients were treated with combined therapy.[12] They also found that thyroid lymphomas confined to the neck only had similar outcomes when treated with either combined modality or radiation alone.

## SEQUELAE OF THERAPY

The most common adverse effects (AEs) of radiotherapy are acute and transient skin and mucosal reactions, erythematous skin changes, sore throat, esophagitis, dysphagia, and rarely dry or moist desquamation. Late AEs include hypothyroidism and pneumonitis if mini-mantle field is used. In the worst-case scenario, fibrosis, mild skin atrophy, pigmentation or telangiectasis, and neck edema could develop, but are extremely unlikely. Myelosuppression is the main AE of chemotherapy. When used, cardiotoxicity can be an important sequela of doxorubicin, depending on the accumulated total dose. As a long-term sequela, second malignancy can be related with therapy.

## PROGNOSIS AND OUTCOMES

According to a study reported by Onal and colleagues, age, tumor size, stage, lymph node involvement, B symptoms, and treatment modality were all prognostic factors in the univariate analysis for OS, disease-free survival, and local control.[13] In multivariate analysis, OS was affected by age, B symptoms, lymph node involvement, and tumor size, while disease-free survival and local control were adversely related with B symptoms and tumor size. Combined modality treatment resulted in a better 5-year OS, disease-free survival, and local control, compared with single modality therapy. In contrast, Niitsu and colleagues found no significant differences in either the OS or disease-free survival according to age, stage, lactic acid dehydrogenase level, or presence of bulky mass.[14] As to the International Prognostic Index (IPI), the low-intermediate risk cases showed significantly poorer prognosis than did the low-risk cases in both overall and disease-free survivals. A clinical IPI was developed using 5 factors (Table 4) and has become the standard for assessing clinical prognosis and treatment stratification. One point was allocated for each factor and categorized into 4 prognostic groups; namely, low, low-intermediate, high-intermediate, and high (Table 5).

Niitsu and colleagues reported an 84% and 90% 5-year progression-free survival rate and OS rate, respectively, with a median follow-up period of 62 months in their study of 32 patients with stage I/IIE thyroid DLBCL treated with combined therapy. A retrospective analysis of stage I and stage II thyroid lymphomas by Onal and colleagues reported a 74% and 71% 5- and 10-year OS rates and 68% and 64% disease-free survival rates, respectively.[13,14] In conclusion, multimodality combined therapy demonstrated better outcomes for patients with aggressive lymphoma but failed to improve OS and local control

in indolent lymphoma patients. Selected survival rates reported in the literature for stage IE and stage IIE lymphomas are shown in Figures 5 and 6.[15-17]

The presence of histopathologic features of MALT are associated with a statistically significant factor in survival of patients as well as a favorable prognostic factor for high-grade lymphomas. In the meantime, non-MALT associated lymphomas have a poorer prognosis according to Laing and colleagues.[18] The overall cause-specific survival at 5 years for patients with non-Hodgkin lymphomas of MALT origin was 90% compared with 55% for those without evidence of MALT origin.

## FOLLOW-UP AND SURVEILLANCE

Most treatment failures seem to develop within the first 2 years after therapy, although late recurrences can occur. Regular follow-up is required for early detection of recurrent disease, as well as prompt and appropriate management of hypothyroidism and hypocalcemia. Serum calcium and parathyroid hormone should be monitored. Prolonged, lifelong follow-up seems reasonable as late relapses and second malignancies have been reported. At each follow-up visit, a careful history and a complete physical examination should be performed. The first follow-up visit should be 4 to 6 weeks after completion of treatment and then patients should be followed every 3 to 4 months for the first year. After the first year, patients should be seen every 6 months for the next 2 to 3 years, and then annually thereafter.

## SUMMARY

Thyroid lymphoma is a rare cancer of the thyroid gland that tends to be prevalent in the elderly and women. Often, thyroid lymphoma patients have had a prior history of Hashimoto's thyroiditis. Fine-needle aspiration cytology has an established role in the diagnosis and management of thyroid lymphoma. Clinically, it can be confused with anaplastic thyroid carcinoma because of similar clinical characteristics of a rapid growing neck mass. Although thyroid lymphoma is not a common cancer, it is very important to distinguish thyroid lymphoma from anaplastic thyroid carcinoma since the prognosis is very different.

Most thyroid lymphomas are B-cell origin lymphomas and mostly DLBCL. The second most common histologic subtype is MALT lymphoma. The choice of treatment is based on the histologic subtype, stage, and tumor bulkiness. Fortunately, the majority of thyroid lymphoma presents with stage I and stage II disease. The 5-year survival rate is about 80% for stage IE, 50% for stage IIE, and < 36% for stage IIIE and stage IVE. Several studies reported an advantage of multimodality using combined chemotherapy and radiation therapy, which is the mainstay of thyroid lymphoma management. ●

### *Author disclosures*

*The authors report no actual or potential conflicts of interest with regard to this editorial.*

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