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Thyroid Lymphoma: Recent Advances in Diagnosis and Optimal Management Strategies

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Key Words. Primary thyroid lymphoma • Thyroid • Lymphoma • Thyroid surgery • Thyroid malignancy

Learning Objectives

Explain the diagnostic modalities used to diagnose primary thyroid lymphoma.

Describe the role of the endocrine surgeon in the diagnosis and treatment of thyroid lymphoma.

Cite the recent advances in the treatment of primary thyroid lymphoma.

ABSTRACT

Primary thyroid lymphoma is rare, composing approximately 5% of all thyroid malignancies and less than 3% of all extranodal lymphomas. It typically presents as a rapidly enlarging goiter with associated compressive symptoms. Thyroid ultrasound and fine needle aspiration cytology, using flow cytometry and immunohistochemistry, remain the main modalities used to confirm the presence of lymphoma. The increasing use of an ultrasound-guided core biopsy to achieve an accurate diagnosis has further limited the role of surgery. An open surgical biopsy may still be required not only for definitive diagnosis but also to confirm the subtype of lymphoma. There are limited numbers of randomized or prospective trials to guide management, and controversy remains over optimal treatment. Treatment and prognosis of this disease can be dichotomized into two separate groups: pure mucosa-associated lymphoid tissue (MALT) lymphoma and diffuse large B-cell lymphoma (DLBCL) or mixed subtypes. Early stage (stage IE) intrathyroidal MALT lymphomas typically have an indolent course and may be treated with single-modality surgery, radiotherapy, or a combination of both. DLBCLs are more aggressive, and survival outcomes are highest with multimodal therapy incorporating monoclonal antibodies, chemotherapy, and radiotherapy. The prognosis is generally excellent but can be varied because of the heterogeneous nature of thyroid lymphomas. The aim of this paper is to discuss the changes in diagnostic modalities and to focus on the recent alterations in the management of this rare disease, including targeted therapies as well as the more limited role of the endocrine surgeon. ***The Oncologist*** 2013;18:994–1003

Implications for Practice: Primary thyroid lymphoma is a rare malignancy intrinsically associated with Hashimoto's thyroiditis. Presenting with an enlarging goiter and associated pressure symptoms, rapid accurate diagnosis is required. Improvements in fine needle aspiration cytology, its adjuncts, and core biopsy techniques mean that open surgical biopsy is required only if less invasive methods have failed to accurately subtype the lymphoma. Treatment and prognosis are dependent on accurate histological classification. Surgical intervention, although typically incidental in the management of indolent mucosa-associated lymphoid tissue lymphomas, is reserved largely for the emergency preservation of the airway. Multimodal treatment with rituximab, combination chemotherapy, and local radiotherapy provides the highest overall survival rates.

INTRODUCTION

Thyroid cancer is the most common endocrine malignancy, accounting for approximately 1% of all malignancies; however, primary thyroid lymphoma (PTL), lymphoma involving the thyroid gland alone, accounts for only 5% of all thyroid malignancies and approximately 3% of all non-Hodgkin's lymphoma. The annual incidence of PTL is one or two cases per million [1–3]. Typically, it presents in the seventh decade of life, with males being affected 5–10 years earlier than females, despite overall female predominance (female:male ratio of approximately 3:1) [4, 5].

The most common presentation of thyroid lymphoma is a rapidly enlarging, painless goiter. Other symptoms such as dyspnea, dysphagia, and hoarseness may arise as a result of the pressure effects of the mass. Rarely, stridor or superior vena cava obstruction can occur. Cervical lymphadenopathy is present in the majority of cases [6, 7]. Classic B-type symptoms such as weight loss and night sweats occur less commonly and have been reported in approximately 20% of patients [8]. The majority of patients (30%–60%) are biochemically euthyroid at presentation [5, 9].

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The underlying pathogenesis of PTL remains obscure. Links among autoimmune disease, chronic antigenic stimulation, and PTL have been demonstrated, and the major risk factor for PTL is the presence of Hashimoto's thyroiditis (HT). The risk of PTL is between 40 and 80 times higher in patients with HT, which typically develops 20–30 years after the initial diagnosis [5, 10, 11]. Interestingly, although the incidence of HT in patients with PTL approaches 80%, only 0.6% with HT will go on to develop PTL [12]. The association is postulated to result from the development of intrathyroidal lymphoid tissue in HT. This acquired lymphoid tissue resembles mucosa-associated lymphoid tissue (MALT) and may evolve into non-Hodgkin's lymphoma. It has also been postulated that the stimulation of antigens that are specific to the thyroid microenvironment are necessary for the development of PTL [13]. This theory is supported by the fact that more than half of thyroid lymphoma patients have a previous or concurrent diagnosis of chronic lymphocytic thyroiditis, suggesting that chronic antigenic stimulation may play a role in pathogenesis [14–17].

For treatment and prognosis, PTL is divided into two separate clinicopathological entities: diffuse B-cell lymphoma and mixed subtypes and pure MALT lymphomas. Diffuse B-cell lymphomas have an aggressive clinical course and should be considered for multimodal treatment, whereas MALT lymphomas pursue a more indolent course and may be treated adequately with single therapeutic strategies. No trials have compared single versus multimodal therapies for PTL or its subtypes; therefore, data are largely extrapolated from the treatment of extranodal lymphoma.

The overall prognosis of thyroid lymphoma has been described by the British Thyroid Association guidelines as "generally excellent"; however, prognosis is subtype dependent, and 5-year survival rates can be as low at 45% [18]. The management and prognosis of PTL has changed with the advent of multimodal adjuvant therapy and increasing interest in and research into targeted therapies. Correspondingly, the role of the endocrine surgeon has become more restricted, primarily being limited to achieving a definitive diagnosis where less invasive methods have failed, in the urgent management of the obstructed airway or in the incidental excision of MALT lymphomas. The aim of this paper is to focus on the changes in diagnostic modalities and to discuss, in depth, the recent alterations in management of this rare disease, including targeted therapies and the more limited role of the endocrine surgeon.

Classification and Staging of PTL

PTLs are classified based on pathological subtypes, with each carrying a different prognosis. The two most common subtypes are diffuse large B-cell lymphoma (DLBCL) and MALT lymphoma.

DLBCL

DLBCL accounts for up to 70% of all PTLs [4]. DLBCLs are typically positive for MS4A1 (CD20), with 75% also positive for the BCL6 oncogene and up to 50% positive for the BCL2 oncogene [19]. Historically, it is the most aggressive subtype, with 60% of patients exhibiting metastatic disease at first presentation, and was classically associated with poor prognosis. DLBCL itself has now been divided into two major cell-of-origin phenotypes with differing prognoses: a favorable germinal center B-cell-like lymphoma and a more aggressive activated B-cell-like subgroup with overexpression of the activated B-cell immunophenotype markers IRF4 (MUM1) and FOXP1 [19]. A recent study by Niitsu et al. looking at the use of multimodal therapy for DLBCL described a 5-year overall survival (OS) rate of 90% [19]. Interestingly, the authors identified that within this group of patients, those who overexpressed IRF4 (MUM1) with associated high expression of NM23-H1 had a poorer OS rate.

MALT Lymphoma

MALT lymphomas account for majority of the remaining 30% of PTLs. They are considered to be of similar endodermal origin, whether in Waldeyer's ring, the thyroid, or the gastrointestinal tract. MALT lymphomas are characterized by the presence of lymphoepithelial lesions, lymphocytes "stuffing" glandular lumina, representing colonization of the thyroid follicles by the lymphoma cells [20]. MALT is identified by the presence of immunoglobulin light chains, pan-B-cell antigens, and BCL2 and the absence of CD5, CD10, and CD23 [21–23]. Interestingly, there have also been a number of specific chromosomal translocations associated with MALT lymphoma: t [11, 18](q21;21), t [14, 18](q32;q21), t [3, 14](p14.1;q32), and t [1, 14](q32;q21) [21, 24, 25]. MALT lymphoma of the thyroid follows a relatively benign indolent clinical course and thus is more likely to present at an earlier stage and, historically, to demonstrate a better response to treatment [26]; however, transformation to a higher grade, more aggressive lymphoma has been previously documented [5].

Other Subtypes of PTL

Follicular lymphoma is rare, accounting for only 3%–5% of all PTLs [9, 15, 16, 27, 28]. It is a neoplasm of germinal center B cells that, in the majority of cases, shows strong aberrant expression of BCL2 [29, 30]. Follicular lymphoma, although usually presenting with nodal or disseminated disease, has a 5-year OS rate of 87% [31, 32]. Bacon et al. identified two distinct groups of thyroid follicular lymphoma [33]. The first group, although carrying IGH/BCL2 t [14, 18] and/or overexpressing BCL2, was of lower grade but was more likely to have extrathyroidal disease at presentation. These patients had an aggressive clinical course, with five of the seven patients followed having progression or recurrence, and four of those died of PTL. The second group lacked IGH/BCL2 and BCL2 expression and was of higher grade but was less likely to present with extrathyroidal disease. These patients had a more indolent clinical course, with all eight patients in this group alive and disease free at the end of the study.

Classic Hodgkin's lymphoma of the thyroid, which is characterized by the presence of Reed-Sternberg cells mixed with a population of non-neoplastic reactive cells, accounts for 2% of PTL. Small lymphocytic lymphoma is also an uncommon subtype of PTL and affects 3% of PTL patients [4, 34]. Patients with a diagnosis of Hodgkin's lymphoma of the thyroid tend to be younger than patients diagnosed with other subtypes [4]. It carries a female preponderance and is usually associated with a good prognosis [35].

Thyroid lymphomas of T-cell origin are extremely rare, with only approximately 15 reported cases in the literature [36]. Less than half of the cases reported were associated with pre-existing thyroiditis [37]. T-cell lymphomas in general are

Table 1. Pathological diagnosis of primary thyroid lymphoma: fine needle aspiration cytology versus open surgical biopsy

Study	Year	*n*	Results
Matsuzuka et al. [70]	1993	119	78% diagnosed successfully with FNAC
Sangalli et al. [69]	2001	17	Six of 7 diffuse large B-cell lymphomas were diagnosed successfully by FNAC compared with 4 of 10 mucosa-associated lymphoid tissue lymphomas
Cha et al. [55]	2002	23	Prior to 1993, all diagnoses required open surgical biopsy; in the period after 1993, only 4 of 11 required open surgical biopsy
Morgen et al. [56]	2010	70	Diagnosis made in 65% by FNAC alone
Dustin et al. [57]	2012	15	All cases successfully diagnosed by FNAC alone

Abbreviation: FNAC, fine needle aspiration cytology.

associated with a shorter survival time than B-cell lymphomas [38], although a spontaneous regression with no specific treatment has been documented in one case report [37].

Staging

The Ann Arbor criteria, similar to staging of lymphoma at other sites, is used for the staging of PTL [39]. Stage IE applies to disease localized within the thyroid; stage IIE applies to disease confined to the thyroid and regional lymph node basins; stage IIIE applies to disease that involves the thyroid, the lymph node basins on both sides of the diaphragm, and/or the spleen; and stage IVE is used to describe disseminated disease. Approximately 56% of PTLs are stage IE at the time of presentation, with 32% at stage IIE, 2% at stage IIIE, and 11% at stage IVE [4].

Diagnosis

Biochemistry

The definitive diagnosis of PTL is obtained by histological analysis of tissue. Evidence suggests, however, that serum antimicrosomal and antithyroglobulin antibodies are raised in up to 95% of patients with a diagnosis of thyroid lymphoma; therefore, they may lend weight to the diagnosis of thyroid lymphoma [40, 41]. Because of the association between PTL and HT, up to 80% of patients with PTL test positive for circulating antibodies to thyroid peroxidase [42]. It is important to note that this test is not specific for thyroid lymphoma and is not used as a diagnostic tool, but it highlights the association between HT and PTL. Serum lactate dehydrogenase levels are raised in almost one-third of non-Hodgkin's lymphomas and are associated with a higher grade of disease [43]. Levels of β_2 microglobulin have also been shown to be raised in patients with non-Hodgkin's lymphoma and have been used to detect recurrence [44].

Imaging

Ultrasonography is the imaging modality of choice and can typically show one of three patterns: nodular, diffuse, or mixed. When presenting as a solitary mass, the radiological appearance can resemble that of anaplastic thyroid carcinoma but can be distinguished by its homogenous appearance as well as the lack of calcification, necrosis, and cystic degeneration within the nodule [45]. When diffuse lymphoma is identified, it appears as a heterogeneous hypoechoic parenchyma with the presence of structures resembling septae [46]. Ultrasonography is particularly helpful in differentiating between other rapidly enlarging lesions such as anaplastic thyroid carcinoma, subacute thyroiditis, or hemorrhage into a cyst or adenoma.

Radionuclide scanning is extremely nonspecific in the setting of PTL and is not routinely included in the work-up of these patients. Findings may include thyroid enlargement and/or heterogeneity with the presence of cold nodules [42].

Cross-sectional imaging is rarely used in the diagnosis of PTL; however, it is indicated in the presence of symptoms such as stridor, hoarseness, dysphagia, or fixation on physical examination [47]. In these cases, it can be used to assess involvement of surrounding structures, to assist in accurate surgical planning, and to diagnose cervical and mediastinal nodal disease [48]. Magnetic resonance imaging may be more sensitive than computed tomography in the detection of extrathyroidal involvement [49].

Fluorine-18-fluorodeoxyglucose positron emission tomography (FDG-PET) can be useful in staging and restaging or in assessing response to treatment in PTL [50]. Strong evidence supports the use of FDG-PET for lymphoma in general because FDG-PET has superior diagnostic accuracy in lymphoma when compared with computed tomography and magnetic resonance imaging [51]. Although there are no specific studies assessing its usefulness in PTL, several case reports have documented its use in this rare disease [52, 53]. PTL typically demonstrates avid uptake of fluorodeoxyglucose within the thyroid and any associated positive cervical lymphadenopathy [54].

Fine Needle Aspiration Cytology

Fine needle aspiration cytology (FNAC) is the initial technique of choice for pathological assessment of a thyroid lesion. Because PTL is a small cell tumor with few pathogenomic features, it may present diagnostic challenges for the pathologist [31]. Although no randomized clinical trials have assessed the accuracy of thyroid FNAC for the diagnosis of PTL, multiple small retrospective studies have demonstrated an increasing sensitivity and specificity with newer adjuncts to FNAC, such as flow cytometry, immunperoxidase studies, and polymerase chain reaction (PCR) (Table 1).

A study by Cha et al. from John Hopkins Hospital highlights the improvement in the sensitivity of FNAC in recent decades [55]. The authors assessed 23 patients with PTL between the years of 1985 and 2000, and of those diagnosed after 1993 ($n = 11$), 63% were diagnosed with FNAC alone and thus did not require an open surgical biopsy. In contrast, all of the patients diagnosed earlier ($n = 12$) required open surgical bi-

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Focusing on IHC, the realization that PTLs are positive for leucocyte common antigen, MS4A1 (CD20), and λ light chain and negative for cytokeratins on immunohistochemical staining has already improved the sensitivity and specificity of FNAC.

opsy. This improvement was attributed to the introduction of immunophenotyping on FNAC samples that were suspicious for PTL. Similarly, in a larger study by Morgen et al., with 70 patients in total, a diagnosis of thyroid lymphoma was made in 65% using FNAC alone [56]. More encouraging was a recent study by Dustin et al., with all cases of thyroid lymphoma (n = 15) successfully diagnosed with FNAC, showing sensitivity of 100% and positive predictive value of 100% [57]. Multiple authors have suggested that the diagnosis of DLBCL is easier because of the presence of large monotonous atypical cells. In comparison, the diagnosis of MALT is harder because of the presence of large numbers of heterogeneous cells and the associated presence of HT.

To address this issue specifically, Takano et al. described a method of using reverse transcriptase PCR to detect the monoclonality of IGH mRNA in fine-needle aspirates, allowing differentiation between lymphoma and HT in 44% of cases [58]. In a later study, the same group demonstrated that monoclonality was detected in 76% of thyroid lymphoma cases and was not found in benign tissue at all [59]. More recently, Takano et al. published a novel method to detect B-cell monoclonality using a combination of vectorette PCR and the digestion of restriction enzymes in aspiration biopsy nucleic acid diagnosis. The overall sensitivity in this small trial study was 50% [60].

Recent decades have seen vast amounts of research examining methods that could increase the sensitivity of fine needle aspirates for the detection of thyroid lymphoma, such as immunohistochemistry (IHC) and flow cytometry. Focusing on IHC, the realization that PTLs are positive for leucocyte common antigen, MS4A1 (CD20), and λ light chain and negative for cytokeratins on immunohistochemical staining has already improved the sensitivity and specificity of FNAC [61]. A study by Ito et al. identified increased expression of CDC25A and CDC25B, which have oncogenic potential, in 47% and 67% of thyroid lymphomas, respectively, using IHC [62]. A similar study by Sugawara et al. demonstrated increased expression of survivin, a protein intricately associated with the inhibition of apoptosis, in PTL tissue when compared with benign tissue using both IHC and PCR [63].

Generally for lymphoma, which may be extrapolated to PTL, Swart et al. found that the addition of flow cytometry to FNAC analysis produced sensitivity of 97% and specificity of 87% for the detection of B-cell lymphoma [64]; however, 13.7% of the original cohort was excluded as a result of an insufficient number of cells to perform flow cytometry, cytology, or both. Inadequate sampling unfortunately remains a limiting factor for performing flow cytometry. Advantages include quicker turnaround time and the facility to examine a single cell for multiple antigens [65].

Core Biopsy

A core biopsy yields more tissue than FNAC and maintains the architecture of the tissue. It can facilitate the distinction among HT, PTL, and anaplastic carcinoma; this is not always possible with FNAC. Recent studies have shown that a core biopsy can yield sufficient tissue for diagnosis and subtyping in up to 95% of lymphomas in general, but few data regard PTL specifically [66]. A small retrospective study was performed by Ravinski et al. demonstrating that performance of a core biopsy can improve the diagnostic accuracy when compared with FNAC and flow cytometry (82% vs. 93%) [67].

Guidance of the biopsy using imaging such as ultrasonography can minimize the risk of trauma to adjacent structures and can avoid taking cores of necrotic tissue within the mass. Novoa et al. carried out a meta-analysis of the use of ultrasound-guided core biopsy in head and neck malignancies [68]. The sensitivity for the detection of malignancy in the thyroid was 68%, but a subgroup analysis of thyroid lymphoma was not performed. They confirmed that the procedure is safe and minimally invasive, with postprocedure hemorrhage occurring in only 1%. The authors concluded that this technique is useful in patients in whom a diagnosis has not been reached using fine needle aspiration and in whom surgery would not be indicated.

Surgical Open Biopsy

Despite these advances in the diagnostic accuracy of FNAC and core biopsy, a limited role remains for an open surgical biopsy to allow for definitive subtyping that may direct future treatment. The diagnosis of MALT lymphomas specifically can be particularly challenging with less invasive modalities. No prospective studies or randomized trials address the utility of an open surgical biopsy; therefore, the evidence for it is limited to retrospective reviews and expert opinion. Sangalli et al. reported that an open surgical biopsy was required to diagnose PTL in 41% of patients (n = 17), with a higher proportion of MALT lymphomas requiring an open biopsy [69]. In contrast, Cha et al. showed in their study of 23 patients that 63% of those diagnosed after 1993 (n = 11) were diagnosed with FNAC alone and thus did not require an open biopsy [55]. An older paper by Matsuzuka et al. contradicts this by stating that an open biopsy is required for subtyping of disease despite the fact that a diagnosis was reached in 79% of patients with FNAC [70]. Currently, surgical open biopsy is recommended only when less invasive techniques fail to achieve a definitive diagnosis of PTL or identification of the exact subtype so that treatment can be tailored to individual patients.

Treatment

The optimal treatment of PTL remains controversial because of the limited evidence harvested from many small retrospective studies, with significant methodological flaws, in the absence of large prospective trials (Table 2). The treatment for thyroid lymphoma is broadly divided according to lymphoma subtype. As with other lymphomas, PTL is sensitive to both chemotherapy and radiotherapy. The gold standard for management of DLBCL is multimodal because of the typically aggressive clinical course and uses a combination of the monoclonal antibody rituximab, chemotherapy (a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone [CHOP]), and radiotherapy. Conversely, MALT lymphomas may be amenable to single-modality treatment because of the indolent na-

Table 2. Studies comparing treatment modalities for thyroid lymphoma

			Treatment groups							
Study	Year	*n*[a]	S alone	RT alone	CT alone	S plus RT	S plus CT	S plus CT plus RT	CT plus RT	Outcome
Pyke et al. [71]	1992	62		X		X				Complete remission of 88% with S plus RT compared with 85% in those who had biopsy plus RT; no difference in survival
Matsuzuka et al. [70]	1993	119							X	8-year OS of 100% in patients receiving the standard chemotherapy regimen and RT vs. 75% in patients receiving RT and older protocol CT
Laing et al. [78]	1994	45		X						30% recurrence rate with RT alone[b]
Doria et al. [79]	1994	211		X	X				X	RT only had 37.1% recurrence, CT only had 43% recurrence, and CT plus RT had 7.7% recurrence
Sasai et al. [6]	1996	22		X					X	No comparison made because 19 had RT plus CT and only 3 had RT alone; 5-year OS was 85%
Derringer et al. [15]	2000	108	X			X	X	X		No difference in outcome between treatment groups; all 16 MALT lymphomas treated with surgery alone remained disease free
Skacel et al. [28]	2000	53		X	X				X	No difference in outcome with CT alone, RT alone, or combined therapy; breakdown of survival rates not detailed in the paper
Ha et al. [16]	2001	51	X	X	X	X			X	10-year failure-free survival of 25% with S alone, 76% with RT alone, 50% with CT alone, and 91% with combined treatment ($p = .15$)
Thieblemont et al. [9]	2002	26	X		X					All 5 MALT with S alone were disease free at 5 years 5-year OS was 77% for the full cohort
Reyes et al. [84]	2005	11			X				X	In the overall group of 647 patients with aggressive localized lymphoma, 5-year event-free survival was 82% in the group given dose-intensified chemotherapy alone vs. 74% in those given CT plus RT
Graff-Baker et al. [4]	2009	1408	X			X				DFS HR of 0.43 for RT only, 0.59 for S only, and 0.53 for S plus RT (when compared with no surgery or radiation); no information on CT
Mian et al. [80]	2011	48	X	X	X			X		Progression-free survival rate of 64% in those who received S plus CT plus RT and 21% in those who received single-modality treatment only; diffuse large B-cell lymphoma only
Watanabe et al. [12]	2011	171		X	X				X	Event-free survival HR was 6.13 for patients who received CT plus RT, 1.0 for CT alone, and 0.85 for RT alone
Onal et al. [81]	2011	87		X	X				X	5-year OS of 57% for CT alone, 69% for RT alone, and 91% for CT plus RT ($p = .08$, multivariate); 5-year DFS of 49% for CT alone, 63% for RT alone, and 91% for CT plus RT ($p = .1$, multivariate)

[a]Sample size corresponds to the number of primary thyroid lymphoma cases in the study, not the total number of cases.
[b]The standard chemotherapy regimen is a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone, or "CHOP."
Abbreviations: CT, chemotherapy; DFS, disease-free survival; HR, hazard ratio; MALT, mucosa-associated lymphoid tissue; OS, overall survival; RT, radiotherapy; S, surgery.

ture of the disease. Treatment may consist of surgery alone, which typically is performed when the MALT lymphoma is detected incidentally; radiotherapy alone; or a combination of both. In general, surgery has a very limited role in the management of PTL but may be indicated in the urgent management of the airway.

Local Therapy: Surgery Alone, Radiotherapy Alone, or a Combination of Surgery and Radiotherapy

Surgery

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centers supports its use. The potential morbidity of the procedure should be borne in mind, given that surgery does not appear to improve OS, when deciding on a treatment strategy. The largest study examining this issue was performed by Pyke et al. from the Mayo Clinic, with 62 patients with PTL [71]. The combination of debulking surgery and external beam radiotherapy (EBRT) did not demonstrate a survival benefit over a surgical biopsy and radiotherapy (88% vs. 85%) in stage IE or IIE disease. The authors concluded that the addition of extensive surgery to radiotherapy was of no clinical benefit. A study by Ha et al., with a small number of patients, similarly demonstrated no survival benefit with the addition of surgery to radiotherapy when accounting for other prognostic factors [16].

There may be a role for surgical intervention in MALT lymphomas, although its sole use remains debatable. Typically, MALT lymphomas are detected incidentally when the thyroid is removed for another indication and, if confined to the thyroid (stage IE), may not require further adjuvant treatment. A study by Derringer et al. included 16 patients with MALT lymphoma who were treated with surgery alone and showed survival rates of 100% at 7 years [15]. Similarly, Thieblemont et al. included five patients with intrathyroidal MALT lymphoma who were treated successfully with surgery alone and who were 100% disease free after 5 years [9]. Surgery in MALT lymphomas is contraindicated in lymphoma higher than stage IE, in bulky tumors greater than 10 cm, and in mixed tumors. Given that MALT lymphomas do not compose the majority of PTL, surgery is not a mainstay of treatment.

Surgical intervention may be required for palliation in the setting of critical airway obstruction. Intervention in this setting carries high morbidity and should be approached with caution. A small series published by Sippel et al. confirmed the utility of surgery for effective palliation in patients with an obstructive airway [72]. More recent evidence challenges the role of surgery in this setting because patients may be better served with corticosteroids and chemoradiotherapy, which may give rapid relief of pressure symptoms without necessitating surgical intervention. A case report by Myatt et al. described a rapid response to high-dose corticosteroids in a case of critical airway obstruction secondary to thyroid lymphoma [73]. No trials have investigated steroids as an alternative to surgical intervention in the emergency setting. The temporary use of tracheal stents has been proposed as an alternative and, in combination with EBRT, may also provide rapid relief of symptoms [74–77].

Radiotherapy

Like surgery, radiotherapy alone should be considered only for localized stage IE MALT lymphomas. Evidence in this specific group of patients shows that radiotherapy alone, typically to the neck and upper mediastinum, can achieve excellent local control, and the treatment morbidity is considerably less than that of radiotherapy for squamous cell carcinomas [14, 78]. When appropriately selected for radiation alone, patients can achieve local control rates of between 70% and 100%. Currently, there are two regimens of radiotherapy that can be administered to patients with PTL, and there is controversy as to which type is superior. "Involved field radiotherapy" includes the thyroid bed and cervical lymph nodes only, whereas "extended field radiotherapy" also includes the mediastinal nodes and sometimes the axillary lymph nodes. A retrospective review carried out at the Royal Marsden Hospital looked at the efficacy of these two different radiotherapy regimens for the treatment of PTL [17]. The patients who received involved field radiotherapy were significantly more likely to have a local recurrence than those who had extended field radiotherapy (52% vs. 27%). Consequently, it is clear that early stage MALT lymphomas may be treated with radiotherapy alone. In the presence of DLBCL or mixed subtypes, stages higher than IE, or extensive bulky local disease, multimodality treatment is strongly recommended.

Systemic Treatment and Combined Chemoradiotherapy

Chemotherapy

Chemotherapy as a single modality for the treatment of PTL has been demonstrated to be inferior to combination chemoradiotherapy and thus is not recommended [12, 16, 79–81]. Most PTL subtypes, excluding MALT, are treated with combination chemotherapy and radiotherapy. The standard chemotherapy regimen is CHOP [79]. The efficacy of this regimen has been demonstrated in large-scale studies of non-Hodgkin's lymphoma, although its use in PTL is documented only in small retrospective studies [70, 82, 83]. Typically, patients with PTL respond rapidly to combination chemotherapy. A more recent study by Reyes et al. looked at a chemotherapy regimen using a combination of dose-intensified doxorubicin, cyclophosphamide, vindesine, bleomycin, and prednisone [84]. The authors documented the superiority of this regimen of chemotherapy alone when compared with the standard CHOP regimen plus radiotherapy in patients younger than 61 years of age with localized lymphoma. This finding should be considered with caution when treating patients with PTL because only 11 patients in the study cohort had PTL.

Combined Chemoradiotherapy

An expanding body of evidence demonstrates that combined treatment modalities, such as chemotherapy and localized radiotherapy, should be used in both early localized disease as well as more advanced presentations, excluding the more indolent MALT lymphomas [85, 86]. The aim of combination chemotherapy is to reduce the incidence of distant recurrence while EBRT reduces the risk of localized recurrence, thereby offering superior long-term disease control when compared to single-modality treatment. Typically, radiotherapy is administered after the third cycle of CHOP chemotherapy [85]. The standard was set in 1993 when Matsuzuka et al. demonstrated 100% 8-year survival for 16 patients who were treated with a single course of chemotherapy (CHOP), followed by 60

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Gy of local radiotherapy and concluding with a further five cycles of CHOP chemotherapy [70]. Since then, these findings have been supported by a systematic review performed by Doria et al., who found recurrence rates of a 7.7% following chemoradiation therapy, 37.1% following radiotherapy alone, and 43% following chemotherapy alone [79]. A more recent retrospective study by Onal et al. confirmed the survival advantage of multimodality treatment in a cohort of 87 patients with PTL [81]. OS was 91% for patients receiving combined-modality therapy, whereas it was 57% for those who received chemotherapy alone ($p = .01$) and 69% for those who received radiotherapy alone ($p = .03$). These findings were also confirmed by Watanabe et al., who demonstrated an event-free survival hazard ratio of 6.13 with combination treatments versus 1.0 for chemotherapy alone and 0.85 for radiotherapy alone [12].

The literature is not unanimous regarding the use of combined therapy, and some studies have failed to detect superiority of multimodal therapy over chemotherapy alone. A methodologically flawed retrospective study by Skacel et al. detected no survival difference between patients treated by chemotherapy alone, by radiotherapy alone, or by combinations of chemotherapy, radiotherapy, and surgery in patients with either MALT or DLBCL [28]. It is important to note that this was a small ($n = 53$) retrospective study spanning 18 years and several institutions and including six different treatment approaches. The mean follow-up was only 46 months. Consequently, the treatment modalities cannot be accurately compared in this study.

These data show that multimodality treatment is important for patients with PTL, particularly those with more aggressive subgroups and extensive locoregional or distant disease. For patients with MALT lymphomas, the benefit may be outweighed by the risks. This highlights the importance of accurately defining the histological subtype before deciding on a definitive treatment plan.

Targeted Therapies: Rituximab

The introduction of rituximab, a chimeric monoclonal antibody that acts against CD20, which is found on the surface of B cells, represents the most significant advance in the treatment of lymphoma since the introduction of chemotherapy [87]. The addition of rituximab to combination chemotherapy has been shown to improve OS and recurrence-free survival in DLBCL, and its use has subsequently been extended to more indolent and follicular lymphomas [87, 88]. A randomized controlled trial published by Hochester et al. confirmed that maintenance therapy with rituximab after standard chemotherapy significantly improved progression-free survival in patients with advanced-stage indolent lymphoma [89]. Interestingly, the response to rituximab may be subgroup specific. Visco et al. found that patients with overexpression of the BCL2 protein had a poorer response to rituximab in combination with CHOP chemotherapy [90]. A similar study by Winter et al. found that patients with DLBCL who overexpressed the protein BCL6 were less likely to benefit from the addition of rituximab to CHOP chemotherapy [91]. In contrast, Mounier et al. showed that treatment with rituximab could potentially overcome chemotherapy resistance in patients overexpressing BCL2 [92].

Rituximab has been licensed for use in the treatment of DLBCL, but there has been little research into its use specifically for the treatment of PTL [93, 94]. Many regimens for the treatment of DLBCL of the thyroid include rituximab in combination with chemotherapy or chemotherapy followed by maintenance rituximab [95].

Emerging Therapies

The identification of mutations and upregulation of cell-signaling pathways has revolutionized cancer treatment in recent years. Although molecular testing for mutations in the *BRAF* proto-oncogene is now used routinely to aid diagnosis and guide treatment of papillary thyroid carcinoma, protein kinase inhibition has not yet been applied in the management of thyroid lymphoma. A recent study by Aggarwal et al. looked at the expression of *BRAF* mutations in a cohort of 25 patients with DLBCL [96]. *BRAF* mutations were identified in 24% of these patients, with a further 8% having *NRAS* mutations. These findings suggest that the mitogen-associated protein kinase pathway is involved in the development and growth of these aggressive tumors and may be a potential therapeutic target for treatment.

Similarly, there has been increasing interest in the use of the vascular endothelial growth factor inhibitor bevacizumab. The SO515 trial was a phase II trial that looked at the addition of bevacizumab to rituximab plus standard chemotherapy for the treatment of 64 patients with DLBCL [97]. The early results were disappointing (median follow-up: 3.5 years), with no disease-free survival advantage and a high number of cardiac and gastrointestinal toxicities. These results suggest that targeting vascular endothelial growth factor may not a viable strategy in the treatment of PTL, and it has not been routinely incorporated into the treatment paradigm.

Prognosis

The overall prognosis of PTL has been generated from the Surveillance Epidemiology and End Results database [4]. Follow-up of 32 years was obtained for 1,408 patients with PTL, of which 56% were stage IE at diagnosis. The median OS was 9.3 years, and the 5-year survival was 66%. The disease-specific survival of PTL was related to histological subtype. The database estimates 5-year disease-free survival of 96% for MALT lymphoma, 75% for DLBCL, 87% for follicular PTL, and 86% for small lymphocytic lymphoma.

The prognosis of DLBCL can be estimated by using the International Prognostic Index, which uses only clinical parameters [98]. There are two indexes: one for all patients, called the "international index," and one that is age adjusted, called the "age-adjusted international index." The international index score is based on age, tumor stage, serum lactate dehydrogenase concentration, performance status, and number of extranodal disease sites. The age-adjusted international index score is based on tumor stage, lactate dehydrogenase level, and performance status. These indexes stratify patients into four risk groups with specific 5-year survival rates, which, when compared with the Ann Arbor staging system, appear to be more accurate in predicting survival.

One of the main challenges in the search for prognostic indicators for PTL is the small numbers of patients diagnosed with this disease. Rosenwald et al. identified a subgroup of patients with DLBCL, the germinal center B-cell-like lymphoma with *BCL2* translocation and *c-Rel* amplification, who have a

CME

more favorable prognosis when compared with patients without this profile [99]. Further studies, including that by Offit et al., also identified rearrangement of *BCL6* as a predictor of favorable clinical outcome [100–103]. Conversely, Katna et al. studied 37 patients with thyroid lymphoma and carried out a tissue-microarray analysis using stored samples [8]. Tumors were assessed for expression of CD10, the activated B-cell immunophenotyping markers MUM1 and FOXP1, as well as *BCL2* and *BCL6* oncogenes. The authors demonstrated that overexpression of FOXP1 was associated with poor response to treatment and increased mortality; however, given the small sample size, this finding failed to reach statistical significance. More detailed research with larger cohorts of patients needs to be performed prior to establishing these markers as prognostic.

Conclusion

PTL is a rare malignancy intrinsically associated with HT. Presenting with an enlarging goiter and associated pressure symptoms, rapid accurate diagnosis is required. Improvements in FNAC, its adjuncts, and core biopsy techniques mean that open surgical biopsy is required only if less invasive methods failed to accurately subtype the lymphoma. Treatment and prognosis are dependent on accurate histological classification. Surgical intervention, although typically incidental in the management of indolent MALT lymphomas, is reserved largely for the emergency preservation of the airway. Multimodal treatment with rituximab, combination chemotherapy, and local radiotherapy provides the highest OS rates. The management algorithms documented in this paper are largely extrapolated from the treatment of extranodal lymphoma. More specific research with larger cohorts of patients with PTL is required to confirm the roles of these algorithms for management.

Author Contributions

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References

1. Ansell SM, Grant CS, Habermann TM. Primary thyroid lymphoma. Semin Oncol 1999;26:316–323.

2. Green LD, Mack L, Pasieka JL. Anaplastic thyroid cancer and primary thyroid lymphoma: A review of these rare thyroid malignancies. J Surg Oncol 2006; 94:725–736.

3. Fujita A, Tomita N, Fujita H et al. Features of primary extranodal lymphoma in Kanagawa, a human T-cell leukemia virus type 1 nonendemic area in Japan. Med Oncol 2009;26:49–54.

4. Graff-Baker A, Roman SA, Thomas DC et al. Prognosis of primary thyroid lymphoma: Demographic, clinical, and pathologic predictors of survival in 1,408 cases. Surgery 2009;146:1105–1115.

5. Pedersen RK, Pedersen NT. Primary non-Hodgkin's lymphoma of the thyroid gland: A population based study. Histopathology 1996;28:25–32.

6. Sasai K, Yamabe H, Haga H et al. Non-Hodgkin's lymphoma of the thyroid. A clinical study of twenty-two cases Acta Oncol 1996;35:457–462.

7. Ruggiero FP, Frauenhoffer E, Stack BC Jr. Thyroid lymphoma: A single institution's experience. Otolaryngol Head Neck Surg 2005;133:888–896.

8. Katna R, Shet T, Sengar M et al. Clinicopathologic study and outcome analysis of thyroid lymphomas: Experience from a tertiary cancer center. Head Neck 2013;35:165–171.

9. Thieblemont C, Mayer A, Dumontet C et al. Primary thyroid lymphoma is a heterogeneous disease. J Clin Endocrinol Metab 2002;87:105–111.

10. Holm LE, Blomgren H, Lowhagen T. Cancer risks in patients with chronic lymphocytic thyroiditis. N Engl J Med 1985;312:601–604.

11. Pasieka JL. Hashimoto's disease and thyroid lymphoma: Role of the surgeon. World J Surg 2000; 24:966–970.

12. Watanabe N, Noh JY, Narimatsu H et al. Clinicopathological features of 171 cases of primary thyroid lymphoma: A long-term study involving 24553 patients with Hashimoto's disease. Br J Haematol 2011;153:236–243.

13. Rossi D. Thyroid lymphoma: Beyond antigen stimulation. Leuk Res 2009;33:607–609.

14. Tsang RW, Gospodarowicz MK, Sutcliffe SB et al. Non-Hodgkin's lymphoma of the thyroid gland: Prognostic factors and treatment outcome. The Princess Margaret Hospital Lymphoma Group Int J Radiat Oncol Biol Phys 1993;27:599–604.

15. 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.

16. Ha CS, Shadle KM, Medeiros LJ et al. Localized non-Hodgkin lymphoma involving the thyroid gland. Cancer 2001;91:629–635.

17. Harrington KJ, Michalaki VJ, Vini L et al. Management of non-Hodgkin's lymphoma of the thyroid: The Royal Marsden Hospital experience. Br J Radiol 2005;78:405–410.

18. Alzouebi M, Goepel JR, Horsman JM et al. Primary thyroid lymphoma: The 40 year experience of a UK lymphoma treatment centre. Int J Oncol 2012; 40:2075–2080.

19. 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.

20. Rawal A, Finn WG, Schnitzer B et al. Site-specific morphologic differences in extranodal marginal zone B-cell lymphomas. Arch Pathol Lab Med 2007;131:1673–1678.

21. Vega F, Lin P, Medeiros LJ. Extranodal lymphomas of the head and neck. Ann Diagn Pathol 2005;9: 340–350.

22. Isaacson PG. Mucosa-associated lymphoid tissue lymphoma. Semin Hematol 1999;36:139–147.

23. Suh C, Huh J, Roh JL. Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue arising in the extracranial head and neck region: A high rate of dissemination and disease recurrence. Oral Oncol 2008;44:949–955.

24. Ott G, Katzenberger T, Greiner A et al. The t(11; 18)(q21;q21) chromosome translocation is a frequent and specific aberration in low-grade but not high-grade malignant non-Hodgkin's lymphomas of the mucosa-associated lymphoid tissue (MALT-) type. Cancer Res 1997;57:3944–3948.

25. Kerrigan DP, Irons J, Chen IM. bcl-2 gene rearrangement in salivary gland lymphoma. Am J Surg Pathol 1990;14:1133–1138.

26. Hwang YC, Kim TY, Kim WB et al. Clinical characteristics of primary thyroid lymphoma in Koreans. Endocr J 2009;56:399–405.

27. Lam KY, Lo CY, Kwong DL et al. Malignant lymphoma of the thyroid. A 30-year clinicopathologic experience and an evaluation of the presence of Epstein-Barr virus. Am J Clin Pathol 1999;112:263–270.

28. Skacel M, Ross CW, Hsi ED. A reassessment of primary thyroid lymphoma: High-grade MALT-type lymphoma as a distinct subtype of diffuse large B-cell lymphoma. Histopathology 2000;37:10–18.

29. Horsman DE, Gascoyne RD, Coupland RW et al. Comparison of cytogenetic analysis, southern analysis, and polymerase chain reaction for the detection of t(14; 18) in follicular lymphoma. Am J Clin Pathol 1995;103:472–478.

30. Lai R, Arber DA, Chang KL et al. Frequency of bcl-2 expression in non-Hodgkin's lymphoma: A study of 778 cases with comparison of marginal zone lymphoma and monocytoid B-cell hyperplasia. Mod Pathol 1998;11:864–869.

31. Jaffe ES, Banks PM, Nathwani B et al. Recommendations for the reporting of lymphoid neoplasms: A report from the Association of Directors of Anatomic and Surgical Pathology. Mod Pathol 2004;17:131–135.

32. Rohatiner AZ, Lister TA. The clinical course of follicular lymphoma. Best Pract Res Clin Haematol 2005;18:1–10.

33. Bacon CM, Diss TC, Ye H et al. Follicular lymphoma of the thyroid gland. Am J Surg Pathol 2009; 33:22–34.

34. Vailati A, Marena C, Aristia L et al. Primary Hodgkin's disease of the thyroid: Report of a case

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and a review of the literature. Haematologica 1991; 76:69–71.

35. Wang SA, Rahemtullah A, Faquin WC et al. Hodgkin's lymphoma of the thyroid: A clinicopathologic study of five cases and review of the literature. Mod Pathol 2005;18:1577–1584.

36. Yokoyama J, Ito S, Ohba S et al. Problems of primary T-cell lymphoma of the thyroid gland–a case report. World J Surg Oncol 2012;10:58.

37. Okamoto A, Namura K, Uchiyama H et al. Cytotoxic T-cell non-Hodgkin's lymphoma of the thyroid gland. Am J Hematol 2005;80:77–78.

38. Shimoyama M, Oyama A, Tajima K et al. Differences in clinicopathological characteristics and major prognostic factors between B-lymphoma and peripheral T-lymphoma excluding adult T-cell leukemia/lymphoma. Leuk Lymphoma 1993;10:335–342.

39. Graff-Baker A, Sosa JA, Roman SA. Primary thyroid lymphoma: A review of recent developments in diagnosis and histology-driven treatment. Curr Opin Oncol 2010;22:17–22.

40. Yahaya N, Din SW, Ghazali MZ et al. Primary thyroid lymphoma with elevated free thyroxine level. Singapore Med J 2011;52:e173–e176.

41. Gupta N, Nijhawan R, Srinivasan R et al. Fine needle aspiration cytology of primary thyroid lymphoma: A report of ten cases. Cytojournal 2005;2: 21.

42. Sakorafas GH, Kokkoris P, Farley DR. Primary thyroid lymphoma (correction of lympoma): Diagnostic and therapeutic dilemmas. Surg Oncol 2010; 19:e124–e129.

43. Fasola G, Fanin R, Gherlinzoni F et al. Serum LDH concentration in non-Hodgkin's lymphomas. Relationship to histologic type, tumor mass, and presentation features Acta Haematol 1984;72: 231–238.

44. Cooper EH, Bunning R, Illingworth S et al. Serial measurement of beta2 microglobulin, acute phase reactant proteins and the ESR in non-Hodgkin's lymphomas and chronic lymphocytic leukaemia. Biomedicine 1978;29:154–158.

45. Aiken AH. Imaging of thyroid cancer. Semin Ultrasound CT MR 2012;33:138–149.

46. Nam M, Shin JH, Han BK et al. Thyroid lymphoma: Correlation of radiologic and pathologic features. J Ultrasound Med 2012;31:589–594.

47. Loevner LA, Kaplan SL, Cunnane ME et al. Cross-sectional imaging of the thyroid gland. Neuroimaging Clin N Am 2008;18:445–461, vii.

48. Kim HC, Han MH, Kim KH et al. Primary thyroid lymphoma: CT findings. Eur J Radiol 2003;46:233–239.

49. Takashima S, Nomura N, Noguchi Y et al. Primary thyroid lymphoma: Evaluation with US, CT, and MRI J Comput Assist Tomogr 1995;19:282–288.

50. Treglia G, Del Ciello A, Di Franco D. Recurrent lymphoma in the thyroid gland detected by fluorine-18-fluorodeoxyglucose PET/CT. Endocrine 2013;43:242–243.

51. Baba S, Abe K, Isoda T et al. Impact of FDG-PET/CT in the management of lymphoma. Ann Nucl Med 2011;25:701–716.

52. Arabi M, Dvorak R, Smith LB et al. Fluorodeoxyglucose positron emission tomography in primary thyroid lymphoma with coexisting lymphocytic thyroiditis. Thyroid 2011;21:1153–1156.

53. Mehta A, Muthukrishnan A. Stage IE non-Hodgkin's thyroid lymphoma on (18)F-FDG-PET/CT. Hell J Nucl Med 2011;14:186–187.

54. Chander S, Zingas AP, Bloom DA et al. Positron emission tomography in primary thyroid lymphoma. Clin Nucl Med 2004;29:572–573.

55. Cha C, Chen H, Westra WH et al. Primary thyroid lymphoma: Can the diagnosis be made solely by fine-needle aspiration? Ann Surg Oncol 2002;9: 298–302.

56. Morgen EK, Geddie W, Boerner S et al. The role of fine-needle aspiration in the diagnosis of thyroid lymphoma: A retrospective study of nine cases and review of published series. J Clin Pathol 2010;63: 129–133.

57. Dustin SM, Jo VY, Hanley KZ et al. High sensitivity and positive predictive value of fine-needle aspiration for uncommon thyroid malignancies. Diagn Cytopathol 2012;40:416–421.

58. Takano T, Miyauchi A, Matsuzuka F et al. Diagnosis of thyroid malignant lymphoma by reverse transcription-polymerase chain reaction detecting the monoclonality of immunoglobulin heavy chain messenger ribonucleic acid. J Clin Endocrinol Metab 2000;85:671–675.

59. Takano T, Miyauchi A, Matsuzuka F et al. Detection of monoclonality of the immunoglobulin heavy chain gene in thyroid malignant lymphoma by vectorette polymerase chain reaction. J Clin Endocrinol Metab 2005;90:720–723.

60. Takano T, Asahi S, Matsuzuka F et al. Aspiration biopsy-nucleic acid diagnosis of thyroid malignant lymphoma by vectorette PCR: Experience of eight cases. Leuk Res 2008;32:151–154.

61. Daneshbod Y, Omidvari S, Daneshbod K et al. Diffuse large B cell lymphoma of thyroid as a masquerader of anaplastic carcinoma of thyroid, diagnosed by FNA: A case report. Cytojournal 2006;3: 23.

62. Ito Y, Yoshida H, Matsuzuka F et al. Cdc25A and cdc25B expression in malignant lymphoma of the thyroid: Correlation with histological subtypes and cell proliferation. Int J Mol Med 2004;13:431–435.

63. Sugawara M, Matsuzuka F, Fukata S et al. Excessive survivin expression in thyroid lymphomas. Hum Pathol 2002;33:524–527.

64. Swart GJ, Wright C, Brundyn K et al. Fine needle aspiration biopsy and flow cytometry in the diagnosis of lymphoma. Transfus Apher Sci 2007;37: 71–79.

65. Swart GJ, Wright CA. The utilization of fine needle aspiration biopsy (FNAB) and flow cytometry (FC) in the diagnosis and classification of non-Hodgkin B-cell and T-cell lymphomas. Transfus Apher Sci 2010;42:199–207.

66. Demharter J, Muller P, Wagner T et al. Percutaneous core-needle biopsy of enlarged lymph nodes in the diagnosis and subclassification of malignant lymphomas. Eur Radiol 2001;11:276–283.

67. Ravinsky E, Morales C. Diagnosis of lymphoma by image-guided needle biopsies: Fine needle aspiration biopsy, core biopsy or both? Acta Cytol 2005; 49:51–57.

68. Novoa E, Gurtler N, Arnoux A et al. Role of ultrasound-guided core-needle biopsy in the assessment of head and neck lesions: A meta-analysis and systematic review of the literature. Head Neck 2012;34:1497–1503.

69. Sangalli G, Serio G, Zampatti C et al. Fine needle aspiration cytology of primary lymphoma of the thyroid: A report of 17 cases. Cytopathology 2001; 12:257–263.

70. Matsuzuka F, Miyauchi A, Katayama S et al. Clinical aspects of primary thyroid lymphoma: Diagnosis and treatment based on our experience of 119 cases. Thyroid 1993;3:93–99.

71. Pyke CM, Grant CS, Habermann TM et al. Non-Hodgkin's lymphoma of the thyroid: Is more than biopsy necessary? World J Surg 1992;16:604–609, discussion 609–610.

72. Sippel RS, Gauger PG, Angelos P et al. Palliative thyroidectomy for malignant lymphoma of the thyroid. Ann Surg Oncol 2002;9:907–911.

73. Myatt HM. Acute airway obstruction due to primary thyroid lymphoma. Rev Laryngol Otol Rhinol (Bord) 1996;117:237–239.

74. Hopkins C, Stearns M, Watkinson AF. Palliative tracheal stenting in invasive papillary thyroid carcinoma. J Laryngol Otol 2001;115:935–937.

75. Noppen M, Poppe K, D'Haese J et al. Interventional bronchoscopy for treatment of tracheal obstruction secondary to benign or malignant thyroid disease. Chest 2004;125:723–730.

76. Tsutsui H, Kubota M, Yamada M et al. Airway stenting for the treatment of laryngotracheal stenosis secondary to thyroid cancer. Respirology 2008;13:632–638.

77. Lee J, Won JH, Kim HC et al. Emergency dilation by self-expandable tracheal stent for upper airway obstruction in a patient with a giant primary thyroid lymphoma. Thyroid 2009;19:193–195.

78. 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.

79. Doria R, Jekel JF, Cooper DL. Thyroid lymphoma. The case for combined modality therapy. Cancer 1994;73:200–206.

80. Mian M, Gaidano G, Conconi A et al. High response rate and improvement of long-term survival with combined treatment modalities in patients with poor-risk primary thyroid diffuse large B-cell lymphoma: An International Extranodal Lymphoma Study Group and Intergruppo Italiano Linfomi study. Leuk Lymphoma 2011;52:823–832.

81. Onal C, Li YX, Miller RC et al. Treatment results and prognostic factors in primary thyroid lymphoma patients: A rare cancer network study. Ann Oncol 2011;22:156–164.

82. McKelvey EM, Gottlieb JA, Wilson HE et al. Hydroxyldaunomycin (Adriamycin) combination chemotherapy in malignant lymphoma. Cancer 1976; 38:1484–1493.

83. Fisher RI. Treatment of aggressive non-Hodgkin' lymphomas. Lessons from the past 10 years. Cancer 1994;74(suppl):2657–2661.

84. Reyes F, Lepage E, Ganem G et al. ACVBP versus CHOP plus radiotherapy for localized aggressive lymphoma. N Engl J Med 2005;352:1197–1205.

85. 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.

86. 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.

87. Hiddemann W, Kneba M, Dreyling M et al. Frontline therapy with rituximab added to the combination of cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) significantly

improves the outcome for patients with advanced-stage follicular lymphoma compared with therapy with CHOP alone: Results of a prospective randomized study of the German Low-Grade Lymphoma Study Group. Blood 2005;106:3725–3732.

88. Gao G, Liang X, Jiang J et al. A systematic review and meta-analysis of immunochemotherapy with rituximab for B-cell non-Hodgkin's lymphoma. Acta Oncol 2010;49:3–12.

89. Hochster H, Weller E, Gascoyne RD et al. Maintenance rituximab after cyclophosphamide, vincristine, and prednisone prolongs progression-free survival in advanced indolent lymphoma: Results of the randomized phase III ECOG1496 Study. J Clin Oncol 2009;27:1607–1614.

90. Visco C, Tzankov A, Xu-Monette ZY et al. Patients with diffuse large B cell lymphoma of germinal center origin with BCL2 translocations have poor outcome, irrespective of MYC status: A report from an International DLBCL rituximab-CHOP Consortium Program Study. Haematologica 2013;98:255–263.

91. Winter JN, Weller EA, Horning SJ et al. Prognostic significance of Bcl-6 protein expression in DLBCL treated with CHOP or R-CHOP: A prospective correlative study. Blood 2006;107:4207–4213.

92. Mounier N, Briere J, Gisselbrecht C et al. Rituximab plus CHOP (R-CHOP) overcomes bcl-2–associated resistance to chemotherapy in elderly patients with diffuse large B-cell lymphoma (DLBCL). Blood 2003;101:4279–4284.

93. Dai CW, Zhang GS, Pei MF et al. Thyroid diffuse large B cell lymphoma (DLBCL) following thyroid medullary cancer: Long-term complete remission with R-CHOP therapy. Ann Hematol 2009;88:701–702.

94. Jonak C, Troch M, Mullauer L et al. Rituximab plus dose-reduced cyclophosphamide, mitoxantrone, vincristine, and prednisolone are effective in elderly patients with diffuse large B-cell lymphoma of the thyroid. Thyroid 2010;20:425–427.

95. Karlin L, Coiffier B. Improving survival and preventing recurrence of diffuse large B-cell lymphoma in younger patients: Current strategies and future directions. Onco Targets Ther 2013;6:289–296.

96. Aggarwal N, Swerdlow SH, Kelly LM et al. Thyroid carcinoma-associated genetic mutations also occur in thyroid lymphomas. Mod Pathol 2012;25:1203–1211.

97. Stopeck AT, Unger JM, Rimsza LM et al. A phase 2 trial of standard-dose cyclophosphamide, doxorubicin, vincristine, prednisone (CHOP) and rituximab plus bevacizumab for patients with newly diagnosed diffuse large B-cell non-Hodgkin lymphoma: SWOG 0515. Blood 2012;120:1210–1217.

98. A predictive model for aggressive non-Hodgkin's lymphoma. The International Non-Hodgkin's Lymphoma Prognostic Factors Project. N Engl J Med 1993;329:987–994.

99. Rosenwald A, Wright G, Chan WC et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Engl J Med 2002;346:1937–1947.

100. Alizadeh AA, Eisen MB, Davis RE et al. Distinct types of diffuse large B-cell lymphoma identified by gene expression profiling. Nature 2000;403:503–511.

101. Kramer MH, Hermans J, Parker J et al. Clinical significance of bcl2 and p53 protein expression in diffuse large B-cell lymphoma: A population-based study. J Clin Oncol 1996;14:2131–2138.

102. Hermine O, Haioun C, Lepage E et al. Prognostic significance of bcl-2 protein expression in aggressive non-Hodgkin's lymphoma. Groupe d'Etude des Lymphomes de l'Adulte (GELA) Blood 1996;87:265–272.

103. Offit K, Lo Coco F, Louie DC et al. Rearrangement of the bcl-6 gene as a prognostic marker in diffuse large-cell lymphoma. N Engl J Med 1994;331:74–80.