

Surgical treatment of primitive thyroid lymphoma

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ABSTRACT

Aims and background. Primitive thyroid lymphoma, although rare, is becoming more frequent. Its incidence is increasing, from 0.5% in the sixties to 1-5% of all thyroid neoplasms today. The diagnosis of such neoplasms is not always straightforward. In fact, it is often the result of pathologic findings on a gland resected for an apparently benign disease. Surgical dissection may prove more complicated than in standard cases of thyroidectomy for the possible tight adhesions existing between the gland's capsule and the surrounding structures. In cases of capsular infiltration, postoperative external local radiotherapy is indicated.

Methods. A retrospective observational analysis was performed to establish whether patients with incidental thyroid lymphomas who underwent total thyroidectomy for another pathology had major surgical complications and worse prognostic results than patients with an accurate preoperative diagnosis.

Results. Six cases of thyroid lymphoma were retrospectively reviewed: 4 diffuse large B-cell lymphomas and 2 MALT lymphomas. Of these, 2 were correctly preoperatively identified by fine-needle aspiration biopsy and 4 were an unexpected finding at histology: 3 cases of total thyroidectomy carried out for huge hypothyroid goiter in patients affected by Hashimoto's thyroiditis and in 1 case of total thyroidectomy carried out for anaplastic carcinoma in a patient affected by Hashimoto's thyroiditis.

Conclusions. In our experience, a correct preoperative diagnosis was extremely difficult (33%). In patients who underwent fine-needle aspiration, a correct diagnosis was made in 66% of cases. All patients with stage IE lymphoma who underwent total thyroidectomy had equivalent surgical complications and prognosis.

Key words: Hashimoto's thyroiditis, preoperative diagnosis, thyroidectomy.

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Introduction

Primitive thyroid lymphoma (PTL), although rare, is becoming more frequent. The incidence of the lymphoma is increasing, from 0.5% of the sixties¹ to 1-5% of all thyroid neoplasms today^{2,3}. A Danish epidemiologic study reported an annual incidence of 2.1 cases per million⁴. The occurrence of the disease must always be considered in the study of thyroid masses, due to the specific diagnostic approach and variable prognosis.

The aim of the present study was to establish whether patients with incidental thyroid lymphomas who underwent total thyroidectomy for another pathology had major surgical complications and worse prognostic results than patients with an accurate preoperative diagnosis.

Materials and methods

A retrospective observational analysis has been performed. From January 1986 to September 2008, 9,324 patients underwent surgery for thyroid disease at the Endocrine Surgical Unit of Perugia and Terni, University of Perugia Medical School, Italy. Pathologic diagnosis was: well-differentiated thyroid carcinoma – 958 cases (90%); medullary carcinoma – 67 cases (6.3%); insular carcinoma – 11 cases (1%); anaplastic carcinoma – 19 cases (1.8%); PTL – 6 cases (0.5%); plasmacytoma – 2 cases (0.2%); angiosarcoma – 2 cases (0.2%). The follow-up lasted until January 31, 2009. A data base and data forms were set up for the detailed collection of the data on pathology, radiologic examinations, surgical techniques, related complications and follow-up.

The 6 patients affected by PTL had an average age of 71 years. There were 5 females and 1 male. They were all affected by Hashimoto's thyroiditis, diagnosed more than 20 years before. Only 1 patient complained of fever and excessive perspiration. The most common clinical presentation is that of a rapidly enlarging thyroid mass (Table 1). Histology was as follows: large B-cell lymphoma, 4 cases; MALT (mucous-associated lymphoid tissue) lymphoma, 2 cases.

Diagnosis was obtained preoperatively in 2 patients affected by Hashimoto's thyroiditis, in which a rapidly growing thyroid mass appeared. In these cases, a diagnosis was yielded by cytology on fine-needle aspiration (FNA) samples. Such patients were staged to rule out a secondary thyroid lymphoma, a much more frequent occurrence. The PTL was an unexpected finding at pathology in 3 cases of thyroidectomy carried out for huge hypothyroid goiter in patients affected by Hashimoto's thyroiditis (Figures 1-4). The PTL was an unexpected finding at pathology in a thyroid gland resected for suspect anaplastic carcinoma in a patient affected by Hashimoto's thyroiditis. Preoperative diagno-

sis had been obtained by cytology on FNA samples (Table 2).

Local staging, based on ultrasound and computerized tomography, did not demonstrate extracapsular invasion, so total thyroidectomy was carried out. The surgical procedure proved more difficult than in other clinical settings for the existence of tight inflammatory adhesions between the thyroid capsule and surrounding structures due to Hashimoto's thyroiditis and the lardaceous consistency of the thyroid neoplasm. Lymphomatous tissue is more friable than the tissue of a gland affected by chronic thyroiditis, and in such cases extracapsular thyroidectomy is more difficult to perform.

Hemostasis was enhanced using reabsorbable hemostatic products. Since 2001, dissection has been aided by the application of a harmonic scalpel (Ultracision, Ethicon, Johnson and Johnson). As a rule, lymphoadenectomy was not carried out systematically, but according to the "node picking" technique, in case of enlarged nodes. No surgical complications or surgical mortality were registered.

In the 4 cases in which PTL was discovered starting with a different preoperative diagnosis (1 anaplastic carcinoma, 3 cases of Hashimoto's thyroiditis in a huge hypothyroid goiter), technical difficulties were all related to tight inflammatory adhesions between the thyroid capsule and surrounding structures and parenchymal infiltration by lymphomatous tissue. In such cases, the harmonic scalpel and hemostatic products were also employed. No postoperative complications were observed.

In one case, a median sternotomy was required to resect a huge goiter descending into the mediastinum. Two patients, for which capsular infiltration was detected at pathology, were submitted to postoperative local external radiotherapy (Table 3).

In the 5 patients submitted to thyroidectomy through cervical incision, postoperative day 1 drainage always

Table 1 - Demographics and clinical characteristics of patients

Patient	Sex	Age	Hashimoto's thyroiditis diagnosed over 20 years before	Clinical presentation			Vitiligo	LT4 therapy	Hormonal and biochemical values		
				Rapidly enlarging thyroid mass	Fever	Excessive perspiration			TSH	Unbound T ₄	TPO antibodies
A	Female	79	Yes	Yes	No	Yes	No	Yes	Elevated (> 3.5 mU/L)	Low	Yes
B	Female	76	Yes	Yes	Yes	Yes	No	Yes	Low (0.06-1 mU/L)	Elevated	Yes
C	Female	61	Yes	Yes	No	Yes	Yes	Yes	Low (0.06-1 mU/L)	Normal	Yes
D	Female	70	Yes	Yes	No	Yes	No	Yes	Low (0.06-1 mU/L)	Elevated	Yes
E	Female	67	Yes	Yes	No	Yes	No	Yes	Low (0.06-1 mU/L)	Normal	Yes
F	Male	73	Yes	Yes	No	Yes	No	Yes	Low (0.06-1 mU/L)	Normal	Yes

TSH, thyroid-stimulating hormone; TPA, thyroid peroxidase antibody.

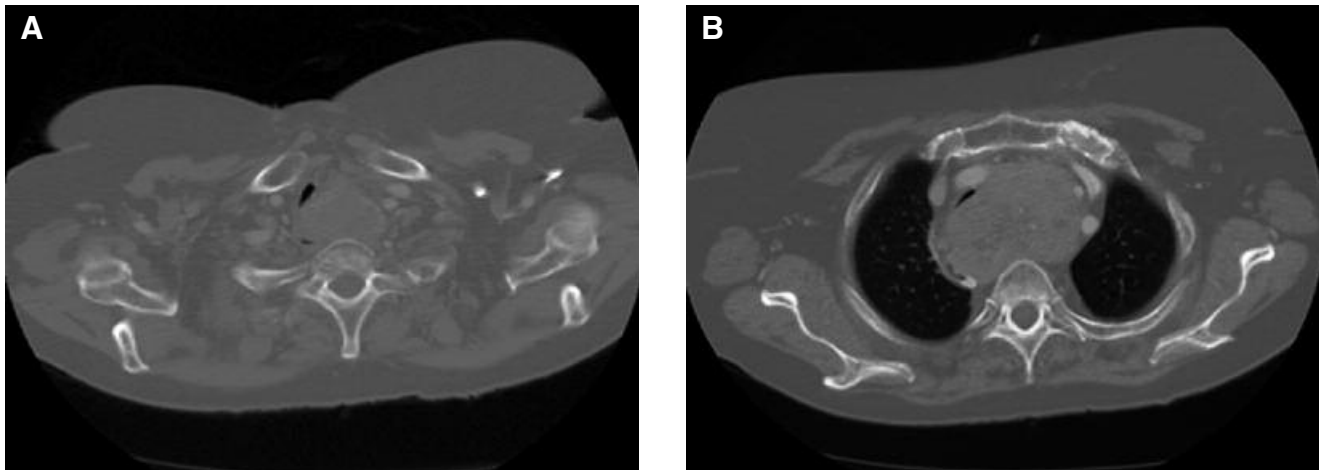


Figure 1 - CT chest-neck: non-Hodgkin lymphoma diffuse large B-cells in colloid goiter intratoracic multinodulare-cystic.

exceeded 80 ml, so the surgical drain was removed in one of the following days (on the average, on postoperative day 3).

All patients entered a follow-up program of at least 3 years. Local recurrences occurred only in the patients presenting capsular invasion and appeared at neck ultrasound after 25 and 32 months from thyroidectomy. Overall survival at 3 years was 66%, and disease-free survival at 3 years was 50% (Table 4).

Results

Six cases of thyroid lymphoma were reviewed retrospectively. A preoperative diagnosis of PTL is extremely difficult. In our experience, a correct preoperative diagnosis was made in only 33% of cases (2/6 patients). FNA was performed only in 3 patients and correctly identified only 2 diffuse large B-cell lymphomas. Only 1 diffuse large B-cell lymphoma was not identified in this manner (preoperative diagnosis was an anaplastic carcinoma in a patient affected by Hashimoto's thyroiditis). In the other patients, 1 diffuse large B-cell lymphoma and 2 MALT lymphomas were an unexpected finding at pathology in total thyroidectomy carried out for huge hypothyroid goiter in patients affected by Hashimoto's thyroiditis.

In the two groups (preoperative FNA and incidental specimen diagnosis of thyroid lymphoma), the localization was only the thyroid gland and there was no cervical or thoracic lymph node involvement. There was capsular infiltration in one patient of each group.

No intraoperative or postoperative complications were present in these patients. Only adjuvant local external radiotherapy was required in 2 patients with capsular infiltration.

Overall survival was 66% in each group. Disease-free survival was better in patients in whom the diagnosis

was incidental. The only local recurrence appeared in a case with a preoperative FNA diagnosis.

Discussion

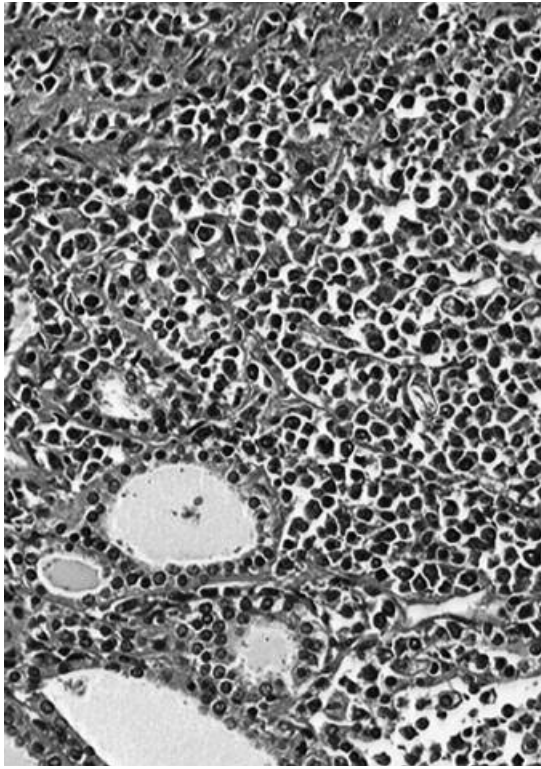
The increase in incidence of PTL has paralleled the increase in Hashimoto's thyroiditis. Such a strict correlation can be explained by the fact that thyroid lymphomas are more frequent in women (M/F ratio, 2:1-14:1)^{4,5}, the gender that presents the greatest incidence in Hashimoto's thyroiditis.

Hashimoto's thyroiditis coexists in 83% of patients with PTL⁶. In patients affected by chronic autoimmune thyroiditis, the probability of developing a PTL is 20 times greater than in the general population⁷. A longer duration of the autoimmune disease correlates with an increased risk of developing a PTL.

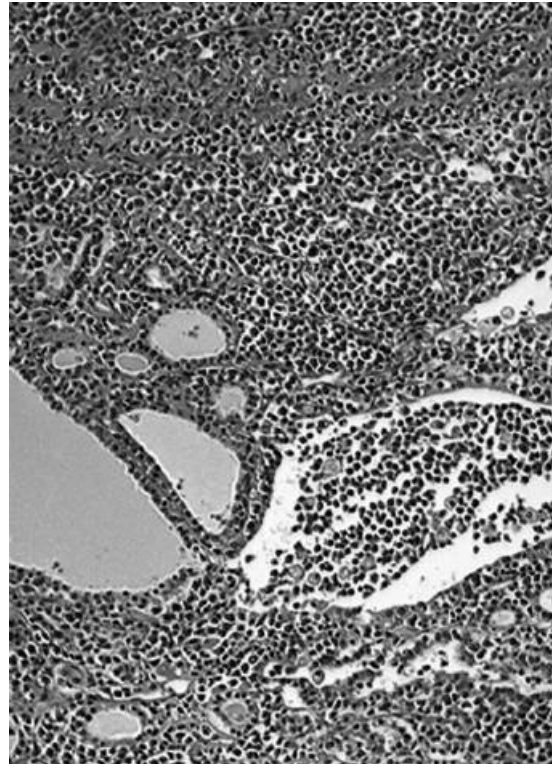
PLT represents 2-7% of all extranodal primitive lymphomas^{3,8}. Non-Hodgkin lymphoma is the most common PLT (93%)⁸ and is divided in two subtypes^{4,9}: B-cell lymphoma and T-cell lymphoma (6-27%)¹⁰. The B-cell lymphoma group includes large-cell high-grade lymphoma (very aggressive) and MALT lymphoma (low grade). Large-cell lymphomas derive from transformation of MALT lymphomas^{4,9}.

Various classifications have been proposed for such diseases, resulting in much confusion in the literature¹¹. According to the National Cancer Institute Working Formulation, about 70% of PTL is intermediate grade¹²⁻¹⁵. If Kiel's classification is used, 65% is low grade, 30% is high grade, and the grade is impossible to define in 5% of cases⁶.

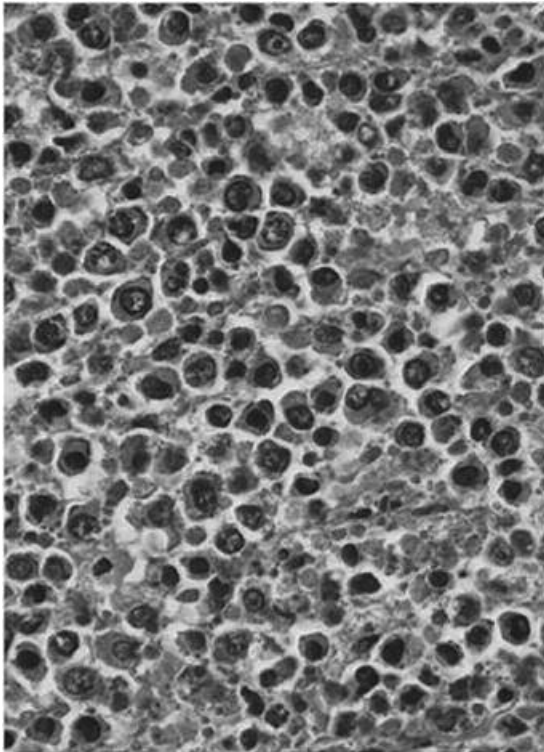
Large B-cell thyroid lymphoma presents as an asymptomatic fast-growing mass; MALT lymphoma instead grows slowly¹⁶. PTL generally infiltrates the surrounding structures, inducing dysphagia, hoarseness or dyspnea in roughly 25% of cases¹⁷. Hypothyroidism occurs in 10-



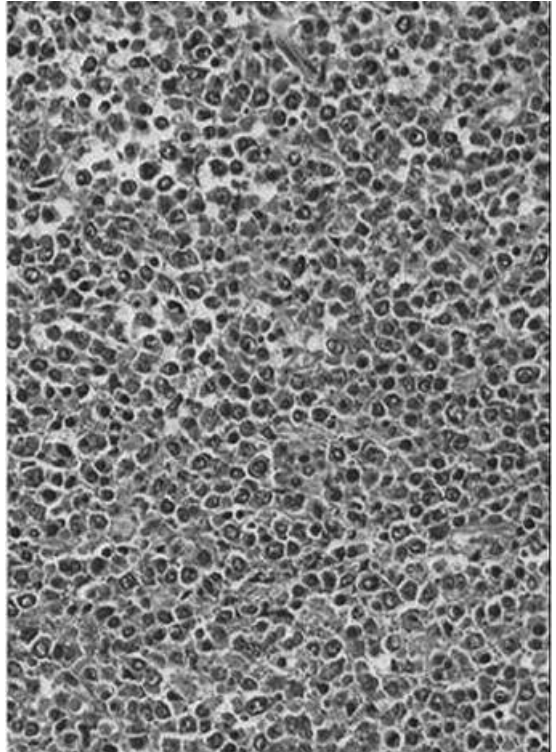
A



B



C



D

Figure 2 - Non-Hodgkin lymphoma diffuse large B-cells in colloid goiter multinodulare-cystic: follicular thyroid and lymphoid infiltration.

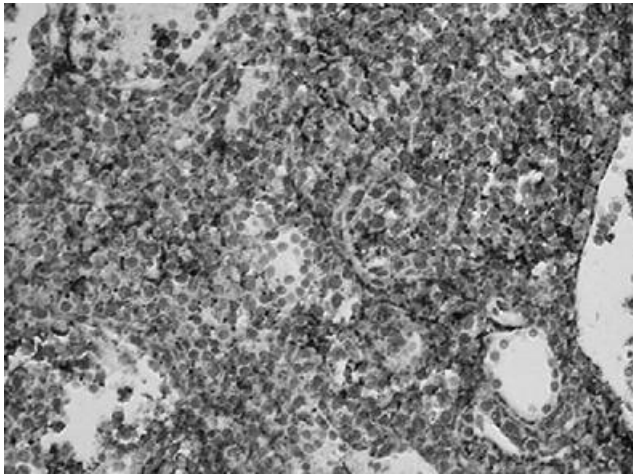


Figure 3 - Non-Hodgkin lymphoma diffuse large B-cells in colloid goiter multinodulare-cystic. Immunohistochemistry: antibodies anti CD20 for B lymphocytes.

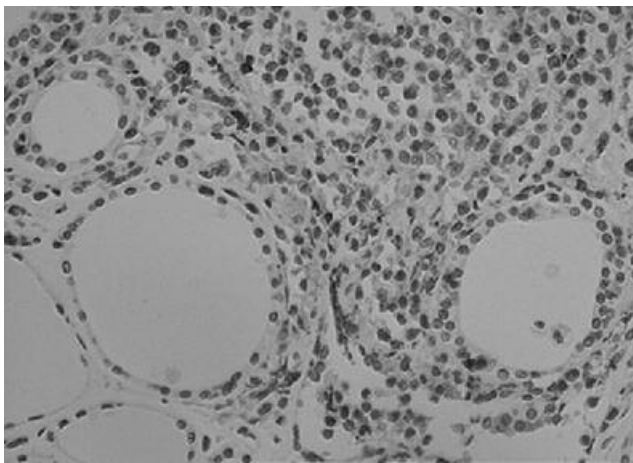


Figure 4 - Non-Hodgkin lymphoma diffuse large B-cells in colloid goiter multinodulare-cystic. Immunohistochemistry: antibodies anti-CD5 for T lymphocytes.

Table 2 - Histological and diagnostic characteristics of patients

Patient	Histology	FNA performed	Correctly histology identified with FNA	Different preoperative diagnosis
A	Large cell B lymphoma	Yes	Yes	-
B	Large cell B lymphoma	Yes	Yes	-
C	MALT	No	-	Huge hypothyroid goiter
D	Large cell B lymphoma	Yes	No	Anaplastic carcinoma
E	Large cell B lymphoma	No	-	Huge hypothyroid goiter
F	MALT	No	-	Huge hypothyroid goiter

FNA, fine needle agobiopsy; MALT, mucosa-associated lymphoid tissue.

Table 3 - Surgical and complementary treatments

Patient	Treatment	Neoplastic capsular infiltration	Post-operative external local radiotherapy
A	Thyroidectomy through cervical incision	No	No
B	Thyroidectomy through cervical incision	Yes	Yes
C	Thyroidectomy through cervical incision	No capsular infiltration	No
D	Thyroidectomy through cervical incision and median sternotomy	No capsular infiltration	No
E	Thyroidectomy through cervical incision	Capsular infiltration	Yes
F	Thyroidectomy through cervical incision	No capsular infiltration	No

Table 4 - Follow-up at 3 years

	Overall survival	Disease free survival
Total thyroidectomy for thyroid lymphoma	66%	33%

40% of cases^{12,17}, whereas hyperthyroidism is extremely rare^{18,19}. General symptoms associated with lymphomas, such as fever, excessive perspiration and weight loss, are present in only 10-20% of patients²⁰. Physical examination reveals a diffusely hypertrophied thyroid gland, fixed to surrounding structures. Cervical lymphadenopathy coexists in 40-50% of cases^{11,17}.

Specific laboratory tests are lacking. In most cases, thyroid function values are altered (increased TSH) due to hypothyroidism, together with autoimmune disease indicators (increase in antithyroglobulin and antiperoxidase antibodies)¹¹.

Radiologic studies and scintiscan are of fundamental importance in defining the extension of disease, in planning therapy and in the differential diagnosis of lymphoma from other thyroid neoplasms or thyroiditis^{21,22}. Computerized tomography scanning for lymphomas presents some peculiarities, not sufficient anyway to reach the definitive diagnosis based only on imaging²³ (Table 5). A characteristic finding at computerized tomography in thyroid lymphoma is the “donut sign”, caused by the tendency of the neoplasm to completely encircle the trachea²². Radioiodine scintiscan is not useful, as lymphocytes do not have the capability of concentrating iodine. Gallium-67 instead highlights an uptake defect in 90% of patients²⁴⁻²⁶.

PET scanning shows an aspecific uptake in Hashimoto's thyroiditis and large B-cell lymphoma^{27,28}. The ex-

Table 5 - CT findings in thyroid neoplasms

	Calcification	Necrosis	Local Invasion
Papillary carcinoma	+/-	+++/-	- -/+
Follicular carcinoma	- - -/+	- - - - -/+	- - -/+
Medullary carcinoma	+/-	- - - - -/+	- - -/+
Anaplastic carcinoma	+++/-	+++/-	+++/-
Lymphoma	- - - - -/+	- - - - -/+	+/-

amination therefore is not useful in the diagnosis of PTL²⁹. However, MALT lymphoma generally induce false-negative results at PET¹¹.

A preoperative diagnosis of PTL may be reached during the workup of patients presenting with a solitary thyroid nodule, a nodule in multinodular goiter, or a nodule in Hashimoto's thyroiditis. A preoperative diagnosis is often formulated at cytology on FNA: it is very easy in the case of diffuse large B-cell lymphomas³⁰⁻³². More complex is the definition of MALT lymphomas in patients affected by chronic autoimmune thyroiditis. In such cases, immunohistochemical studies are often necessary³³ (Table 6). Needle biopsy is utilized only in rare cases, when FNA is not diagnostic.

Once a diagnosis is made, total body CT scan completes staging, according to the Ann Arbor classification (Table 7). In our experience, a correct preoperative diagnosis was extremely difficult (33%). In the patients who underwent FNA, a correct diagnosis was made in 66%.

In the literature, in about 50% of patients the disease is confined to the gland (stage IE), and in another 45% the gland and regional lymph nodes are involved (stage IIE). Only 5% of cases show lymph node involvement above and below the diaphragm (stage IIIE) or extranodal disease (stage IV)^{4,11,34-36}. PTL is easily curable if diagnosed early and correctly treated.

Table 6 - A cytologic diagnosis of primitive thyroid lymphomas (PTL) by fine needle agobiopsy (FNA)

Diagnosis by FNA	
Cha 2002	7/8 (88%)
Sangalli 2001	10/17 (59%)
	40% in MALT (4/10) vs 86% (6/7) in large B cells lymphomas

MALT, mucosa-associated lymphoid tissue; FNA, fine needle agobiopsy.

Table 7 - Ann Arbor classification of primitive thyroid lymphomas

Stage	Disease localization
IE	Only thyroid
II E	Thyroid and cervical lymph-nodes
III E	Thyroid and lymph-nodes above and below diaphragm
IV	Thyroid and extension to extranodal sites

Conclusions

At present, no significant advantage in survival has been demonstrated in patients at stage IE-IIE submitted to radical surgery³⁷⁻³⁹. Some surgeons never take the surgical option into consideration in the presence of PTL⁴⁰. Others propose treating only stage IE with total thyroidectomy followed by radiotherapy^{41,42}. The best results after thyroidectomy have been obtained in the treatment of MALT lymphomas⁴³.

Thyroidectomy performed in patients affected by lymphoma presents a higher incidence of complications than procedures carried out for goiter or differentiated neoplasms. The reason is the important pericapsular edema that hampers the correct individuation of anatomical structures. In such cases, the most frequent complications are bleeding, parathyroid ablation and recurrent laryngeal nerve injury⁴⁴. If the procedure is performed by a dedicated surgeon, the complication rate does not change significantly in the different clinical settings⁴⁵.

According to the NCCN Guidelines, surgery embodies only one of the therapeutic options for stage IE and does not afford a better prognosis than radio- and/or chemotherapy⁴⁶. Radiotherapy is frequently the treatment of choice for stages IE-IIE. A systematic review of the literature found only 3 randomized controlled studies demonstrating that chemo-radiotherapy is the best treatment⁴⁷⁻⁴⁹. For more advanced stages (IIIE or IV), the therapy of choice is chemotherapy (CHOP – cyclophosphamide, doxorubicin, vincristin, prednisone).

The prognosis is related to lymphoma extension. Five-year survival rates are 55-80% for tumors confined to the gland (IE) and 20-50% for lesions with extracapsular invasion (IIE). For stages IIIE and IV, the rates are 15-35%^{4,13,14,34,39,42,50}.

Surgery for palliation is rarely indicated: in such cases, treatment consists of debulking and tracheostomy carried out for tracheal invasion.

On the basis of the scanty and controversial clinical evidence present in the literature^{51,52}, we can affirm that PTL requires an accurate multidisciplinary approach in order to choose the most appropriate therapy case by case. In our retrospective observational analysis, patients with incidental thyroid lymphomas who underwent total thyroidectomy for other pathologies had surgical complications and prognostic results similar to those with an accurate preoperative diagnosis.

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