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CASE SERIES

A Retrospective Study of 341 Cases of Primary Extranodal Non-Hodgkin Lymphoma of the Head and Neck

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Abstract:
Aims: Our goal was to obtain comprehensive and accurate information about primary extranodal non-Hodgkin lymphomas of the head and neck region to contribute to the advancement of medical knowledge in this field.
Materiels and methods: We conducted a retrospective study of 341 patients with primary extra-nodal, non-Hodgkin lymphomas of the head and neck, over a period of 7 years from January 2016 to December 2022, in the departments of ENT and Head and Neck Surgery and Hematology, with the help of the department of anatomical pathology of the university hospital Mohammed VI of Marrakech.
Results: 341 patients, with primary extra-nodal, non-Hodgkin lymphomas of the head and neck, was included, with an average age of 57 years, and a sex ratio male/female of 2.21 . in more than half of the cases; Waldeyer's ring was concerned; especially palatine tonsils. Type B NHL was the most frequent and involved 308 patients. Diffuse large B-cell lymphoma was the commonly observed histological type, found in 214 patients; followed by a Follicular Lymphoma and Extra-Nodal NK/T-Cell Lymphoma, Nasal Type. Following the extension workup; patients were all staged according to the ANN ARBOR classification; with a 77.8% of them were localized stages I and II, and of the therapeutically evaluable cases, complete remission was achieved in 112 patients.
Conclusion: Our study focused on all extra-nodal localizations of NHL in the head and neck region. Due to the very heterogeneous nature of these tumors, most of the current studies are limited to a specific site of involvement. Nevertheless, our study provides an overall picture; which those specific studies can be based. The management of NHL has evolved considerably in recent years, insisting on the multidisciplinary character to a better management of these patients.
Keywords: Non-Hodgkin Lymphoma; Primary extra-nodal Lymphoma; head and neck neoplasm.

Introduction:

Lymphoma is the third most common malignant tumor in the head and neck region, after squamous cell carcinoma and thyroid cancer, and comprises 12% of all tumor[1,2] , they are generally divided into Hodgkin lymphoma (HL) and non-Hodgkin lymphoma (NHL); the latter group affect around 11% to 33% of patients ,in the head and neck region[3] . In cases of NHL, in the head and neck region, around 65% of instances involve the lymph nodes, while extranodal sites account for 25% to 30% of cases [1,3]. Primary extranodal lymphomas are characterized as lymphomas that present as a solitary extranodal site, either with or without involvement of adjacent lymph nodes at the time of diagnosis, or when the predominant mass of the disease is situated in an extranodal location [4], in the head and neck , the] primary extra-nodal NHL (PE-HL) can affect : Waldeyer's ring (oropharyngeal wall, base of the tongue, palatine tonsils , and nasopharynx), the oral cavity (palate, maxilla, gingiva, and tongue), salivary glands, thyroid, larynx, nasal cavity and paranasal sinuses, the ear cavities,and skin [5].

The aim of our work is to describe primary extra-nodal non-Hodgkin lymphoma of the head and neck, to examine their clinicopathological and epidemiological features, as a way to help lay the groundwork for predicting prognosis and customizing treatment for individual patients.

Materials and methods:

A retrospective descriptive and analytic study was conducted to assess patients with Primary Extranodal Non-Hodgkin of the head and neck region. Spread over a period of seven years, from January 2016 to December 2022. The study was carried out in the departments of ENT and Head and Neck Surgery, as well as Hematology, with the help of the department of anatomical pathology of the university hospital Mohammed VI of Marrakech. We included all patients with a confirmed histological diagnosis of primary extranodal non-Hodgkin lymphoma of the head and neck region whom gave a clear consent to participate in this study, excluding patients with incomplete medical records.

To collect the maximum amount of epidemiological, clinical/paraclinical, histological, therapeutic, and evolutionary data from the patients, we developed an exploitation sheet based on the data available in the literature. The collected data was analyzed, and the results were expressed as percentages or averages according to the variables studied.
Throughout the study, we maintained strict confidentiality of the patients' files and the information collected for this study.

Results:

After a thorough search of medical records, we were able to identify a total of 341 patients, with primary extra-nodal, non-Hodgkin lymphomas of the head and neck, whom met our inclusion criteria and did not meet any of our exclusion criteria.
The age of the patients ranged from 22 to 85 years with an average of 57 years. The most represented decades were the 5th, 6th and 7th decade figure (1).

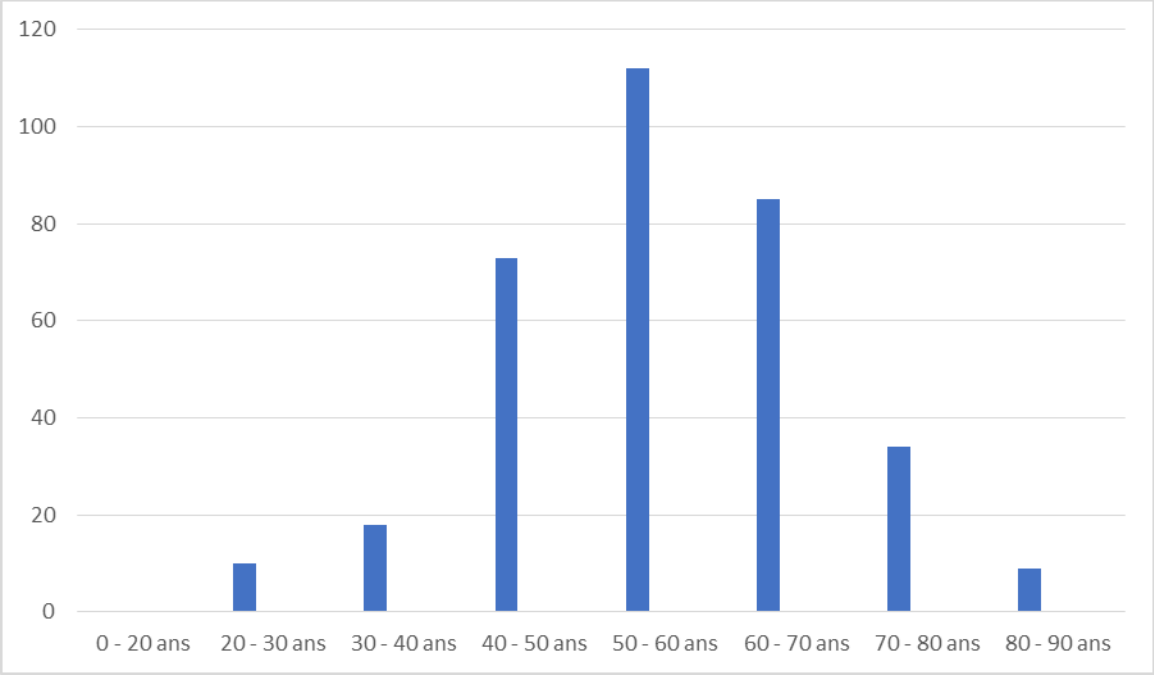

Figure1: Age distribution of patients

Sex distribution of patients, demonstrated a higher prevalence of males, with 235 men (69%) and 106 women (31%), and a sex ratio male/female of 2.21.

The etiology of lymphomas is far from being identified. In our study, some factors were analyzed: 108 cases with chronic smoking, including 66 alcohol-smokers, 77 cases with immunodepression following a chronic infection, 48 cases with a history of Helicobacter Pylori gastritis (HP), and 20 cases with viral hepatitis C, 18 cases with a history of pulmonary tuberculosis, 10 case with notion of toxic exposure; farmer exposed to fungicides and pesticides; 10 case with a family history of tumor; a father followed for gastric lymphoma, 9 case with notion of significant sun exposure, and 15 cases with positive EBV serology. The length of time between the onset of symptoms and the specialist consultation varied in our study between 1 month and 2 years. In our series, about 43% of the patients consulted between 3 and 6 months of evolution.

Extra-nodal involvement of NHL; in our series; concerned in more than half of the cases, Waldeyer's ring, followed by salivary glands and the nasal sinuses. The clinical symptoms displayed varied depending on the site of involvement table (1).

Table 1: illustration of the symptoms of discovery, according to the location of the PE-NHL.

Localisation	**Nomber Of Cases**	**Symptoms**
• Palatine Tonsils	160	• Dysphagia • Dysphonia • Odynophagia
• Nasopharynx	95	• Nasal Obstruction • Epistaxis • Rhinolalia • Hypoacusis
• Nasal Cavity And Paranasal Sinuses	16	• Tumor Mass • Nasal Obstruction • Ophthalmic Signs • Cerebral Signs
• Gingiva	6	• Gingivorrhagia • Tumor Mass
• Base Of The Tongue	4	• Dyspnea • Odynophagia
• Cheek	2	• Tumor Mass • Dysphagia
• Palate	9	• Ulceration Of The Hard Palate • Gingivorragia
• Sub-Maxillary Gland	16	• Swelling • Sjogren's Syndrome
• Thyroid Gland	12	• Cervical Swelling • Dysphonia/ Dyspnea • Dysphagia
• Parotid Gland	7	• Parotid Swelling • Facial Nerve Palsy • Pus Flow Through Stenon's Canal
• Tongue	3	• Dysphagia • Odynophagie
• Ear	4	• Otorrhea • Otalgia
• Skin	7	• Tumor Mass • Ulceration

General signs, such as unexplained fever (higher than 38.5 °c), night sweats, generalized fatigue and weight loss (10% of the initial weight in six months); testifying to the evolution of the disease; were found in 25.54% of patients.

The clinical findings varied from location to another one. Tonsil involvement revealed a budding mass usually in the left tonsillar space, with deep infiltration, bleeding on contact and/or indurated on touch. The volume of this mass varied from small to a large one that could filled almost the entire oropharynx. When the nasophaeynx is infiltrated, the nasofibroscopy showcased a budding process, with bulging of the posterior wall of the nasopharynx. Patients with nasal Cavity and paranasal sinuses involvement present a hard, inflammatory and painless swelling of the face with diffuse palpebral edema, hemorrhagic budding mass. Palate NHL, include hard palatal process, an ulcerated with irregular margins, a raspberry appearance of the mucosa, bleeding on contact.

Blood workup; performed systematically in all patients; included a complete blood count, a sedimentation rate (SR) , a blood ionogram, a liver and kidney workup, an LDH assay, a Beta2 microglobulin, a protein electrophoresis, as well as HIV, Syphilis, hepatitis B and C serology and 3 BK sputum tests. Table (2) shows the different biological abnormalities encountered in our series:

Table2: different biological abnormalities

Biological Abnormality	**Nb Of Cases**
Anemia	23
Pancytopenia	11
Elevated SR	112
Elevated LDH	35
Disturbed Kidney Function	10
Hypergammaglobulinemia	12
Disturbed Liver Function	5
Ionogram Disturbed	19
Cvh Positive	3
Elevated Beta2 Microglobulin	134

In all our documented cases, the immunohistochemical study was performed after biopsy or excisional biopsy, using a panel of antibodies including:

*CD20, CD5, CD10, BCL-2 and BCL-6 for NHL type B

*CD3, CD5, CD30, CD56, Granzyme B for T-type NHL

*Ki-67+ tumor proliferation marker.

According to the WHO classification, our patients were divided into the following histological phenotypes figure (2):

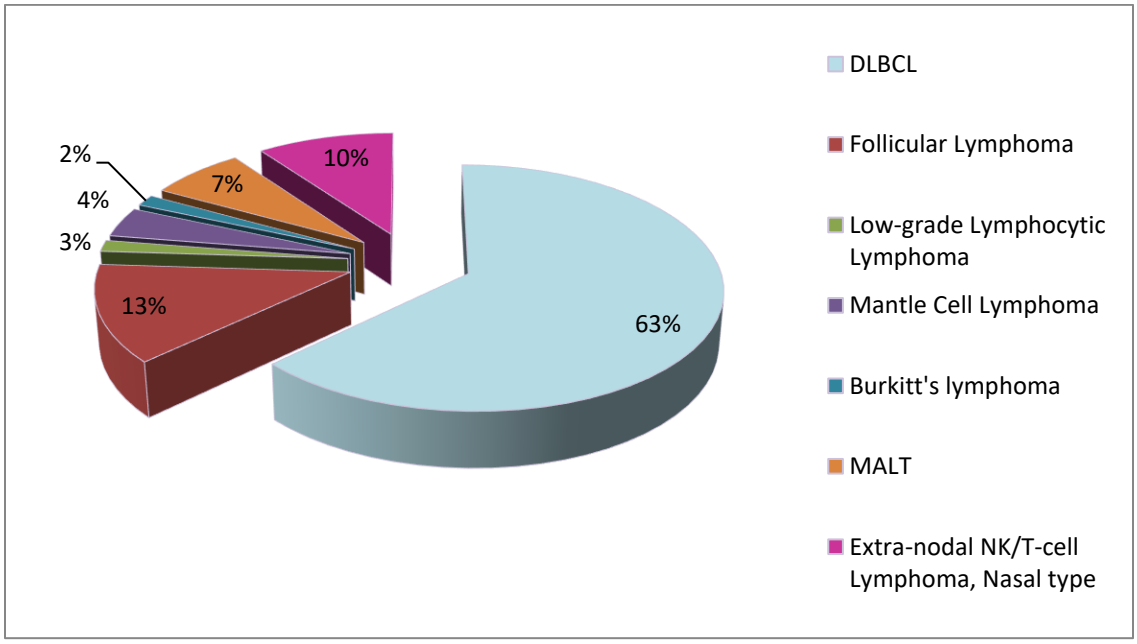

Figure 2: Histological distribution of PE-NHL

*Type B NHL was the most frequent and concerned 308 patients, about 90% of cases. Diffuse large B-cell lymphoma (DLBCL) was the commonly observed histological type, found in 214 patients (63%). Other B-cell lymphomas were detected, including a Follicular Lymphoma (FL) in 13%, Low-grade Lymphocytic Lymphoma in 2% of the cases, Mantle cell lymphoma in its blastoid variant in 13 cases, and Burkitt's Lymphoma in 2% of the patients, and mucosal Associated Lymphoid Tissue (MALT) lymphoma in 7% of the cases.

*Type T NHL involved 33 patients, translating to 10% of the cases; mainly concerning the Extra-Nodal NK/T-Cell Lymphoma, Nasal Type Table (3).

Following the extension workup; that was performed, and included cervical and abdominal ultrasound, body CT scan, CT and MRI of the parotid gland and PET scan; patients were all staged according to the ANN ARBOR classification figure (3); Which translate to; a 77.8% of Localized stages (I, II), and 22.2% of Disseminated stages.

Table 3: Distribution of lymphomas in head and neck sites

Localisation	**Histological type**	%
• Waldeyer ring	• DLBCL • Follicular lymphoma • Burkitt lymphoma • Mantle cell lymphoma • Extranodal NK-/T-cell lymphoma, nasal type	70 12 10 5 3
• Nasal Cavity And Paranasal Sinuses	• Extranodal NK-/T-cell lymphoma, nasal type • DLBCL • Follicular lymphoma • Low-grade lymphocytic lymphoma	70 22 6 2
• Oral cavity	• DLBCL • Follicular lymphoma • MALT lymphoma • Mantle cell lymphoma • Low-grade lymphocytic lymphoma • Burkitt lymphoma	61 16 15 2 2 4
• Thyroid Gland	• DLBCL • MALT lymphoma	55 45
• Salivary glands	• MALT lymphoma • DLBCL • Follicular lymphoma • Low-grade lymphocytic lymphoma • Extranodal NK-/T-cell lymphoma, nasal type • Burkitt lymphoma	30 30 25 5 5 5
• Ear	• DLBCL	100
• Skin	• DLBCL	100

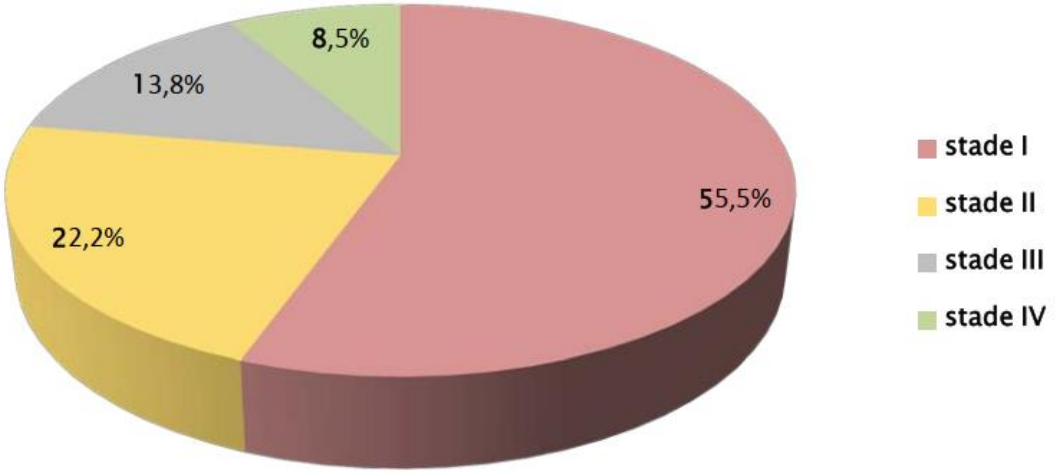

Figure3: Distribution of PE-NHLs according to the ANN ARBOR classification

All patients in our series received treatment, except for 11 cases that refused treatment, and 33 cases that were lost to follow-up after the start of treatment. Therapeutic means varied from surgical treatment involving; bilateral tonsillectomy, sub maxillectomy, total thyroidectomy, and parotidectomy with preservation of the facial nerve, and a wide excision of the cheek mass.

Chemotherapy was the reference protocol in our series. The number of courses varied according to the localized stages between 4 and 6 courses, and the advanced stages between 6 and 8 courses. Immunotherapy was used in 47 cases. The product used was Rituximab, often combined with CHOP or mini-CHOP. Radiotherapy was used in patients with nasal NK T- NHL. External radiotherapy was preceded by 6 courses of CHOEP.

The follow-up was based on the clinical, biological and radiological examinations. The duration of follow-up varied from 2 to 48 months with an average of 25 months. Among the 341 patients with NHL in the department, only 247 patients, i.e. 72%, were evaluable therapeutically. For therapeutic evaluation, we retained only those patients who had received at least two courses of chemotherapy. The remaining 94 cases were not therapeutically evaluable for several reasons: 25 were lost to follow-up, 21 died during treatment, 3 patients refused treatment and 45 cases are under evaluation.

Of the therapeutically evaluable cases, complete remission was achieved in 112 patients or 46%, partial remission was achieved in 65 patients or 26%. Therapeutic failure was observed in 70 patients or 28% figure (4).

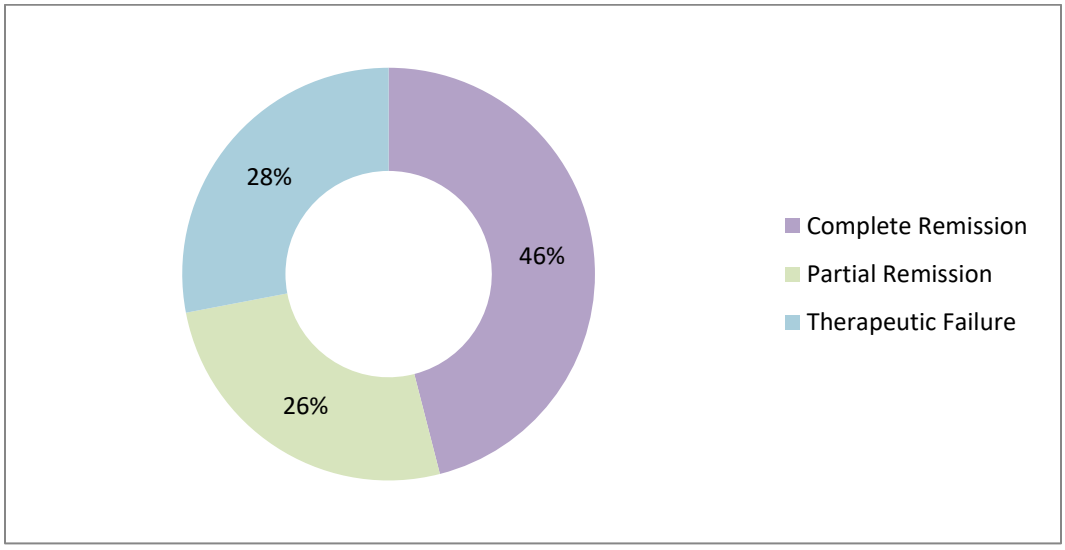

Figure4: Distribution of patients by therapeutic outcome

Discussion:

non-Hodgkin lymphomas represent a diverse array of lymphoproliferative malignancies, there key pathogenetic mechanisms include immunosuppression, particularly regarding T-cell activity, loss of control of latent EBV (Epstein-Barr virus) infection, and persistent and chronic antigen stimulation [5], some of our patients had been exposed to some of these risk factors but others didn't.

When reviewing the literature, PE-NHL of the head and neck region typically affects patients in their 50s to 60s, with an evident male predominance. Jacobs et al [6]; reported PE-NHL with a mean 53 years old, and a male to female ratio of 1.5:1. Economopoulos et al [7] demonstrates a median age at diagnosis of 55 years old, and a sex ratio of 1.9:1. Shima et al [8]; showcased a mean age of 56.7 years, and male: female ratio of 1.5:1; which aligns with the age and sex distribution found in our sample.

Around 50% of extranodal sites in the head and neck region are found within Waldeyer's ring. Among all of those cases, the tonsils are the most commonly affected site [5.7]. The findings in our sample are consistent with these data.

Patients initially present a local, nonspecific symptoms due to the involvement of a distinguish site in the head and neck region. The most reported one is local mass [6.8]. Systemic complaints such as; unexplained weight loss, generalized fatigue, unexplained fever and night sweats were uncommon reported only in 4% of the patients by Jacobs et al [6].

Diffuse large B-cell lymphoma is the most frequently reported clinical histological type in the literature; in extra-nodal sites; in the head and neck region; representing about 50% to 68 % [6.7.9]. DLBCL is frequently found in the tonsils, palate, maxilla, mandible, and parotid glands, affecting both soft tissues and bones [9, 10]. In our study, DLBCLs are the most common histological subtype of PE-NHL (63%), followed by FL (13%).

Diffuse large B-cell lymphoma is the most histological type present in Waldeyer ring lymphoma; accounting for 50% to 60% of patients, and the majority of cases (50% to 70%) are diagnosed at stage I or II [3].in our sample the most common histological type found in this site is DLBCL (70%), followed by FL (12%). This extra-nodal site lymphomas typically appear on CT scans as a submucosal isodense mass with a homogeneous appearance. Enlarged lymph nodes in the neck are often present as well. Unlike carcinomas, irregular margins and ulceration are not typically observed [3].

Lymphomas occurring in the oral cavity account for only about 2% of all extranodal lymphomas [3]. The preferred sites for these lymphomas are the palate, maxilla, and gingiva [11]. Patients with HIV infection are more likely to develop lymphomas in the oral cavity [12]. Oral cavity lymphomas can be of various types, but approximately half of them are DLBCL [3.6]. The next most common type is follicular lymphoma, followed by marginal-zone B-cell lymphoma [6.12]; which is consistent with our data.

Lymphomas in the nasal cavity may be secondary to an extension from lymphomas originating in the paranasal sinuses; or , in a smaller percentage of cases, they can arise primarily [3]. The most frequently encountered lymphomas in this context are extranodal NK-/T-cell lymphoma of the nasal type, which were previously known as midline granuloma, polymorphic reticulosis, and angiocentric lymphoma[13,14]. Between 6.4% and 13% of extranodal NHLs in the head and neck develop in the paranasal sinuses, with DLBCL being the most common subtype [13]. In our study; extra-nodal NK-/T-cell lymphoma of the nasal type was found in 70% of the nasal cavity and paranasal sinuses sites, followed by DLBCL in 22%.

Salivary gland lymphomas comprise 2% to 5% of salivary gland neoplasms, with the parotid gland involved in 70% of cases [15.17]. Histopathologically, these lymphomas are extranodal marginal zone B-cell lymphomas of the MALT type in approximately one third of cases, follicular lymphomas in one third of cases, and diffuse large B-cell lymphomas in the remaining one third of cases [3.15].

Salivary gland lymphomas account for approximately 2% to 5% of all salivary gland neoplasms, with the parotid gland being involved in 70% of cases [15, 17]. Histopathologically, these lymphomas are MALT type in one third of cases, FL in another third of cases, and DLBCL in the remaining cases [3,15]. Our results are in accordance with those conclusions.

The majority of the NHLs occurring in the thyroid are classified as marginal-zone B-cell lymphomas, diffuse large B-cell lymphomas, or marginal-zone lymphomas with areas of progression to large B-cell lymphoma. Other types of lymphoma are relatively uncommon [17]. The tumor may concern the entire thyroid gland; in a diffuse manner; or present as a solitary mass in about 80% of cases, or as

multiple nodules in about 20% of cases [3]. Our results are in line with this observation.

In our sample; 77.8% of patients at the diagnosis were classified in stages I and II. This is in agreement of the most studies reported in the literature [6.7.8.18].

The treatment of PE-NHL involves various therapeutic approaches, and the use of newer drugs in combination with chemotherapy and in maintenance therapy has led to better rates of remission and survival. The introduction of rituximab-based chemoimmunotherapy, in particular, has resulted in significant improvement in patients with diffuse large B-cell lymphomas [5].

Conclusion:

A multi-disciplinary approach and early diagnosis are essential components in the management of primary extranodal non-Hodgkin lymphomas of the head and neck. Due to their rarity and diagnostic challenges, these lymphomas are often misdiagnosed as other benign conditions like infections or, more commonly, malignancies such as squamous cell carcinoma. Increased awareness and research in this field have contributed to the identification of risk factors and causation pathways.

Declarations

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Consent to publish:

The authors affirm that human research participants provided informed consent for publication of the images in all Figures.

Conflicts of Interest:

Authors have no conflict of interest to declare

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