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INVITED MEDICAL REVIEW

Malignant lymphoma of the head and neck

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Malignant lymphomas represent approximately 5% of all malignant neoplasms of the head and neck area. They are classically divided into two subgroups, Hodgkin's lymphomas (HLs) and non-Hodgkin's lymphomas (NHLs). We describe the clinical characteristics of head and neck lymphomas and the methods to establish the diagnosis. The World Health Organization classification of lymphoid tissues describes more than 50 different histological types, and we analyse the most common staging system for lymphomas, the Ann Arbor staging system. Finally, the different therapeutic approaches are discussed.

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Introduction

The main cells of the immune system are the T and B lymphocytes, which originate in the thymus and the bone marrow respectively. Once these cells have matured, they pass into the circulatory system and are localised in the lymphoid organs (lymphatic nodes and spleen) and mucosa-associated lymphoid tissue (MALT). MALT is found in the gastrointestinal tract, thyroid, breast, lung, salivary glands, eye and skin. Lymphomas are malignant neoplastic mutations of normal lymphoid cells. A number of factors contributing to this mutation have been identified, including infectious agents [Epstein–Barr virus (EBV), human immunodeficiency virus (HIV), human T-cell leukaemia virus 1, *Helicobacter pylori* infection, hepatitis C and others] and deregulation of the cell cycle, as well as host susceptibility factors (congenital or acquired) (Jaffe *et al*, 2008).

Malignant lymphomas represent approximately 5% of all malignant neoplasms of the head and neck area (Boring *et al*, 1993). This heterogeneous group of tumours is classically divided into two subgroups, Hodgkin's lymphomas (HL) and non-Hodgkin's lymphomas, depending on the presence or absence of Reed-Sternberg cells. These are cells with two or more nuclei, which are found in HL tissue biopsies. Prognosis is poorer in NHL, as it is in most cases widely disseminated at the time of diagnosis (Urquhart and Berg, 2001).

There are several reasons why malignant lymphoma (ML) is becoming more prevalent in developed countries. For example, the proportion of elderly people in the population is increasing, and this is the age group most frequently affected by NHL (Urquhart and Berg, 2001). ML is considered an 'opportunistic neoplasm,' as it frequently affects immunocompromised patients. The prevalence of these patients has increased considerably with the increased frequency of organ transplantation and improved AIDS survivorship. Kaposi's sarcoma is the only so-called malignant tumour that occurs more frequently than NHL in these patients (Moran, 1990). For this reason, the diagnosis of extranodal NHL should exclude AIDS (Zapater *et al*, 1996).

The current classification of malignant lymphomas is that proposed by the World Health Organization (WHO), which was developed by the Society for Hematopathology and the European Association of Hematopathologists using a combination of morphology, immunotyping, genetic features and clinical syndromes (Swedlow *et al*, 2008). The goal was to define clinically relevant disease entities involving B cells, T cells and natural killer (NK) cells that could be recognised by pathologists. To ensure clinical relevance, a clinical advisory committee of oncologists with American and European co-chairs reviewed and discussed the proposed WHO classification. The proponents of all major lymphoma and leukaemia classifications agreed that if a reasonable consensus emerged from this effort, they would accept the WHO classification of haematological malignancies as the standard. A comprehensive listing of subtypes and variants was presented in a formal WHO publication (Table 1). The main changes of this updated classification in comparison to the previous version include the recognition of

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Table 1 WHO classification of mature B-cell, T-cell and NK-cell neoplasms (2008)

Precursor lymphoid neoplasms
B lymphoblastic leukaemia/lymphoma NOS
B lymphoblastic leukaemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukaemia/lymphoma with t(9;22); bcr-abl1
B lymphoblastic leukaemia/lymphoma with t(v;11q23); MLL rearranged
B lymphoblastic leukaemia/lymphoma with t(12:21); TEL-AML1 & ETV6-RUNX1
B lymphoblastic leukaemia/lymphoma with hyperploidy
B lymphoblastic leukaemia/lymphoma with hypodiploidy
B lymphoblastic leukaemia/lymphoma with t(5;14); IL3-IGH
B lymphoblastic leukaemia/lymphoma with t(1;19); E2A-PBX1 & TCF3-PBX1
T lymphoblastic leukaemia/lymphoma
Mature B-cell neoplasms
Chronic lymphocytic leukaemia/small lymphocytic lymphoma
B-cell prolymphocytic leukaemia
Splenic marginal zone lymphoma
Hairy cell leukaemia
Lymphoplasmacytic lymphoma/Waldenström macroglobulinaemia
Heavy chain disease
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Extranodal marginal zone B-cell lymphoma of mucosa-associated lymphoid tissue (MALT) type
Nodal marginal zone lymphoma
Follicular lymphoma
Primary cutaneous follicular lymphoma
Mantle cell lymphoma
Diffuse large B-cell lymphoma, NOS
(T-cell/histiocyte-rich type; primary CNS type; primary leg skin type and EBV + elderly type)
Diffuse large B-cell lymphoma with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK + large B-cell lymphoma
Plasmablastic lymphoma
Large B-cell lymphoma associated with HHV8 + Castleman disease
Primary effusion lymphoma
Burkitt's lymphoma
B-cell lymphoma, unclassifiable, Burkitt's-like
B-cell lymphoma, unclassifiable, Hodgkin's lymphoma-like
Mature T- and NK-cell neoplasms
T-cell prolymphocytic leukaemia
T-cell large granular lymphocytic leukaemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK cell leukaemia
Systemic EBV + T-cell lymphoproliferative disorder of childhood
Hydroa vacciniforme-like lymphoma
Adult T-cell lymphoma/leukaemia
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous CD30 + T-cell lymphoproliferative disorder
Primary cutaneous gamma/delta-positive T-cell lymphoma
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK + type
Anaplastic large cell lymphoma, ALK-type
Hodgkin's lymphoma (Hodgkin's disease)
Nodular lymphocyte-predominant Hodgkin's lymphomas
Classical Hodgkin's lymphoma
Nodular sclerosis Hodgkin's lymphoma
Lymphocyte-rich classical Hodgkin's lymphoma
Mixed cellularity Hodgkin's lymphoma
Lymphocyte depletion Hodgkin's lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia
Infectious mononucleosis-like PTLD
Polymorphic PTLD
Monomorphic PTLD (B and NK/T-cell types)
Classical HD-type PTLD
Histiocytic and dendritic cell neoplasms
Histiocytic sarcoma
Langerhans cell histiocytosis
Langerhans cell sarcoma
Interdigitating dendritic cell sarcoma
Follicular dendritic cell sarcoma
Fibroblastic reticular cell tumour
Indeterminate dendritic cell sarcoma
Disseminated juvenile xanthogranuloma

small clonal lymphoid populations and the identification of diseases characterised by the involvement of specific anatomical sites or by other clinical features, such as age (Jaffe *et al*, 2008).

Non-Hodgkin's lymphoma (NHL) is the most frequent type of tumour of the head and neck, representing about 75% of lymphomas in this area (Boring *et al*, 1993). Some types of NHL are especially common in this area. The common B-cell neoplasms are precursor B-lymphoblastic leukaemia/lymphoma, chronic lymphocytic leukaemia/small lymphocytic lymphoma, extranodal marginal-zone B-cell lymphoma of MALT, follicular lymphoma, mantle cell lymphoma, diffuse large B-cell lymphoma, and Burkitt's lymphoma/leukaemia. The most frequent T-cell and NK cell NHL is the extranodal NK/T-cell lymphoma, nasal type (Harris *et al*, 1994).

Clinical evaluation

The timing of diagnosis differs considerably depending on the type of lymphoma. HL is diagnosed more frequently in patients 20–30 years of age, whereas NHL is diagnosed more frequently between 70 and 80 years of age (Urquhart and Berg, 2001). In childhood, extranodal NHL may mimic other clinical entities, such as inflammatory disease, polymorphic reticulosis or rhabdomyosarcoma (La Quaglia, 1994). There are no gender differences between HL and NHL in the head and neck. Generalised symptoms, such as fever, weight loss, night sweats, fatigue or pruritus (Urquhart and Berg, 2001), are more frequent in HL than NHL (41% *vs* 27% respectively). Thus, taking into account the minor frequency of HL in the head and neck, systemic symptoms are not common in this area.

Nodal lymphoma

Cervical lymphadenopathy is the most frequent head and neck presentation in both HL and NHL. These are multiple painless nodes with specific characteristics that facilitate differential diagnosis from epidermoid metastatic nodes. These lesions are not as hard as metastatic nodules in squamous cell carcinoma and they usually do not adhere to either the skin or the deep planes. There may also be nodes in other locations, such as the axilla or groyne. The most common location of HL nodes is the lower cervical or supraclavicular region. HL usually arises in a single node or chain of nodes and spreads to a contiguous node or chain. Mediastinal or hilar nodes are frequently involved at presentation. Abdominal involvement is unusual unless the patient has systemic symptoms. NHL spreads more commonly to non-contiguous nodes (Weber *et al*, 2003). Mediastinal involvement is rare, whereas abdominal involvement is more common.

Extranodal lymphoma

The head and neck region is the second most frequent anatomical site of extranodal lymphomas after the gastrointestinal tract (Vega *et al*, 2005). Primary extranodal Hodgkin's disease is rare. Lymphomas may originate in any region containing lymph tissue. NHL in the head and neck is usually submucosal rather than ulcerative, as seen in squamous cell carcinoma (Nathu *et al*, 1999).

Half of the extranodal lymphomas of the head and neck are located in Waldeyer's ring, which is a ring of lymphoid tissue arising in the nasopharynx, palatine tonsils, base of the tongue and the oropharyngeal wall. Lymphoma of Waldeyer's ring is associated with an increased incidence of spread to the gastrointestinal tract, which is found in 10% of patients. The most common pathological forms presenting in Waldeyer's ring are diffuse large B-cell, follicular, Burkitt's and mantle cell lymphomas (Weber *et al*, 2003). The palate tonsil is the most common site of involvement. Patients complain of dysphagia and sore throat, and the asymptomatic enlargement of one tonsil is common (Figure 1). Therefore, some authors consider routine excision of abnormally large asymmetrical tonsils to be advisable (Oluwasanmi *et al*, 2006). The first symptom of rhinopharyngeal lymphoma is usually an enlarged neck node, although presentation may be in the form of increasing nasal obstruction (Anselmo *et al*, 2002; Kochbati *et al*, 2006). This is one of the reasons why a patient presenting with an enlarged neck node should be examined using endoscopic techniques to check the head and neck location for any possible primary tumour. Neck nodes should not be operated upon without adequate examination. Presentation may also be in the form of hearing loss as a consequence of otitis media with effusion produced by dysfunction of the Eustachian tube. The base of the tongue is a very rare location of lymphoma, with very few reported cases. Lymph node involvement is usually the first sign leading to diagnosis. (Talmon *et al*, 2007; Jovanovic, 2008).

Oral lymphomas occur more frequently in patients with HIV infection. Symptoms typically consist of oral swelling, pain and ulcers. Lymphomas may present either as a tumour or ulcerated lesion located anywhere in the mouth, but they are most common on the gingivae, palate and tongue (Kemp *et al*, 2008) (Figure 2). The lesions usually show rapid growth and

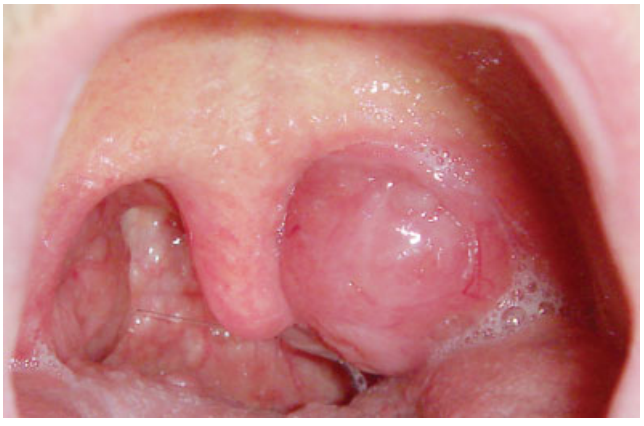

Figure 1 Enlargement of left tonsil because of a malignant lymphoma

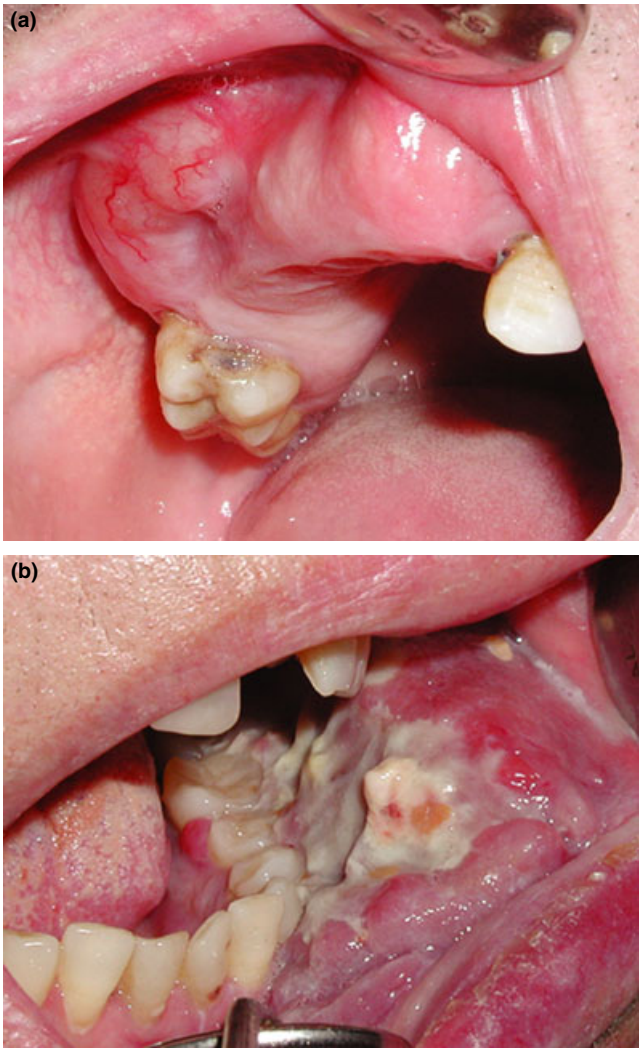

Figure 2 Oral lymphomas in the gingivae (**a**) and buccal mucosa (**b**)

can affect the underlying jaw bones. Lytic bone destruction can be caused by highly aggressive mature B-NHL (Feinberg *et al*, 2007). These lesions represent the most rapidly dividing lymphoma, and one of the most rapidly growing types of tumour in humans (Levine, 1992). The initial clinical manifestations in the mandible and maxilla are swelling and loosening of the teeth. Most bone lymphomas are of the diffuse large B-cell type (Weber *et al*, 2003).

Lymphoma of the salivary glands accounts for approximately 2–5% of salivary gland neoplasms. The parotid gland is the most frequently affected, and facial paresis is infrequent in comparison to other parotid malignant neoplasms. The most frequent histopathological forms are marginal-zone B-cell lymphoma of the MALT type (which arises in the parotid parenchyma), follicular lymphomas (which usually involve intra parotid lymph nodes), and diffuse large B-cell lymphomas (Weber *et al*, 2003). Salivary gland lymphomas are frequently associated with Sjögren's syndrome (Lima *et al*, 2008).

Thyroid lymphoma is associated with Hashimoto's thyroiditis in 80% of the cases. The only clinical peculiarity in comparison to other thyroid neoplasms is the absence of cystic degeneration. Patients usually present with a rapidly enlarging anterior neck mass, which may be associated with hoarseness and/or dysphagia. The most frequent pathological forms are diffuse large B-cell and MALT lymphomas (Coltrera, 1999).

Laryngeal lymphoma is usually located in the supraglottic region, and the symptoms are similar to those of laryngeal carcinoma: hoarseness, dysphagia and dyspnoea. Tracheostomy may be necessary in cases complicated by narrowing of the laryngeal lumen. Examination reveals a submucosal tumour with a smooth surface. The most frequent histopathological forms are the same as those in the thyroid gland, and laryngeal lymphoma is reportedly associated with rheumatoid arthritis (Patiar *et al*, 2005).

Limited knowledge regarding the pathology of lymphomas arising in the nasal cavity has resulted in controversies regarding nomenclature, with a variety of terms being used, such as polymorphic reticulosis, pseudolymphoma, midline granuloma syndrome, and lethal midline granuloma. In virtually all cases, neoplastic cells contained the Epstein–Barr virus. The median age at presentation is 50 years, with male predominance. NK/T-cell lymphoma is the most frequent pathological form, and has been designated lymphoma of nasal type (Cheung *et al*, 1998). The tumour causes obstruction, discharge and epistaxis, and presents some other signs with its evolution, such as facial swelling and visual disturbance. These are very aggressive tumours that cause bone destruction and may extend into the paranasal sinuses, alveolar bone, hard palate, cheek, buccinator space, para-nasopharyngeal space, infra-temporal fossa, nasopharynx, the orbit, and intracranial cavity. The clinical outcome is poor, with multiorgan involvement and a high mortality rate (Cuadra-García *et al*, 1999) (Figure 3).

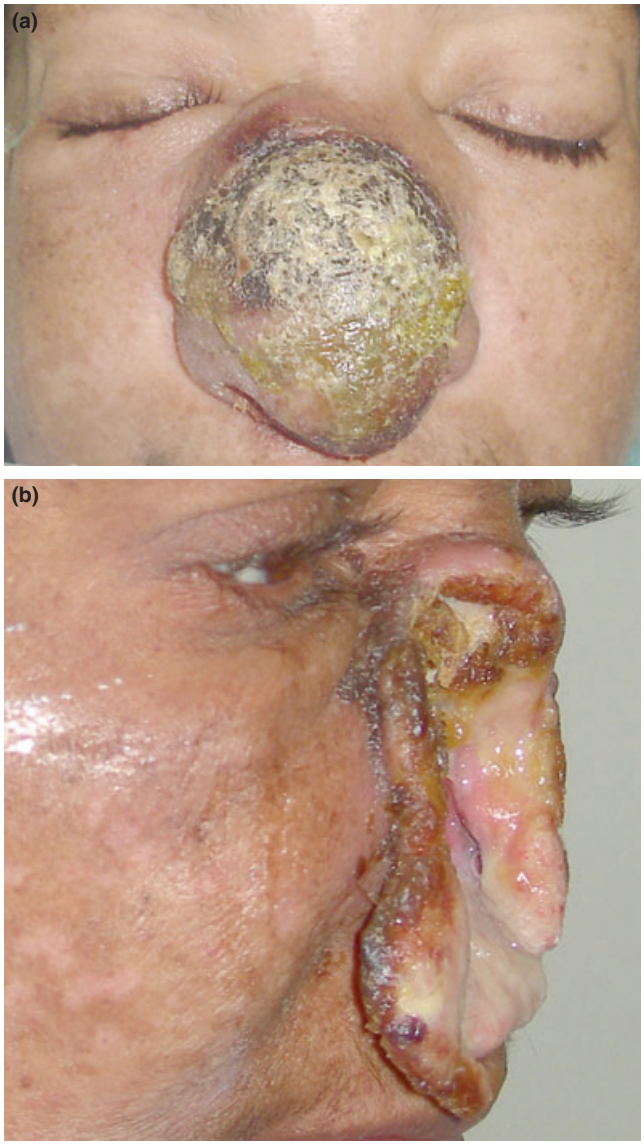

Figure 3 (**a**) Natural killer/T-cell lymphoma arising in the nasal pyramid. (**b**) Recurrence posttreatment

Diffuse large B-cell lymphoma is the most frequent pathological form in the paranasal sinuses. This is a moderately aggressive tumour that commonly extends into the orbit (Cuadra-García *et al*, 1999). The usual form of presentation consists of sinusitis symptoms. Subsequently, diplopia and exophthalmos may occur with the spread of the tumour.

The skin of the head and neck region develops specific types of lymphoma, including primary cutaneous follicle-centre lymphoma, cutaneous marginal zone B-cell lymphoma, and some subtypes of diffuse large B-cell lymphoma (Willemze *et al*, 2005). Follicle-centre cell lymphoma, when presenting in the head and neck, is predominantly located on the scalp or forehead. The lymphoid infiltrate involves the dermis and sometimes the epidermis, and macroscopically may exhibit either a solitary plaque or a group of plaques. A clear-cut follicular growth pattern is common (Santucci *et al*,

1991). Cutaneous marginal zone lymphoma does not affect the epidermis and presents as a red papule (Willemze *et al*, 2005) (Figure 4). Diffuse large B-cell lymphoma arising in the head and neck is usually a cutaneous manifestation of systemic lymphoma (Li *et al*, 2001). Table 2 summarises the main characteristics of lymphomas according to anatomical location.

Diagnosis

The diagnosis of lymphoma is based on the results of pathological examination. In the case of extranodal lesions, a deep biopsy should be taken, similar to the procedure performed in squamous cell carcinoma tumours. This can usually be performed under local anaesthesia, except in some locations, such as the paranasal sinuses, salivary glands, some laryngeal lesions and the thyroid gland. In these cases, there are no typical clinical signs permitting their differentiation from other tumours, and therefore extemporaneous analysis can be performed to determine the appropriate surgical procedure. In the case of parotid lesions, it is usually necessary to perform partial parotidectomy with facial preservation. Some supraglottic lesions can be biopsied under local anaesthesia unless there is limited ventilation. In such cases and in those with glottic lesions, it is necessary to apply general anaesthesia with tracheostomy if intubation is difficult or if swelling of the lesion is likely to produce dyspnoea. Future decannulation will be possible if the treatment response is good. In thyroid lesions, the minor surgical procedure is a hemithyroidectomy. Extemporaneous analysis will avoid more invasive surgical procedures indicated for different histopathological forms.

In nodal disease, fine-needle aspiration is a useful tool for diagnosis, but it is possible to obtain both false positive and negative results by this method. Cytodiagnosis of HL is generally thought to be easier than that of NHL. Appropriate interpretation of cytological features, together with the use of immunocytochemical parameters, can aid in reducing the margin of error in cytodiagnosis (Das *et al*, 2009; Siddiqui *et al*, 2009). However, histopathological examination of the node via complete adenectomy is necessary to establish a definitive diagnosis. Appropriate selection of the node is important, which should be as undistorted as possible. Resection can usually be performed under local anaesthesia. However, in cases in which the nodules are very deep, computed tomography (CT) and magnetic resonance imaging (MRI) are useful to identify the nodule to be resected, which is then usually removed under general anaesthesia.

Biopsy material should be processed fresh, rather than fixed in formaldehyde, as this allows immunohistochemical staining to be performed. Such treatment can distinguish between lymphomas and anaplastic neoplasms and also permits differentiation among the different forms of lymphoma. Pan-leucocyte antibodies are specific for lymphomas (Harris *et al*, 1994; Aisenberg, 1995).

The main task of otorhinolaryngologists and oral and maxillofacial surgeons consists of diagnosis, with staging and treatment of patients usually performed by haematologists or oncologists. Therefore, it is important

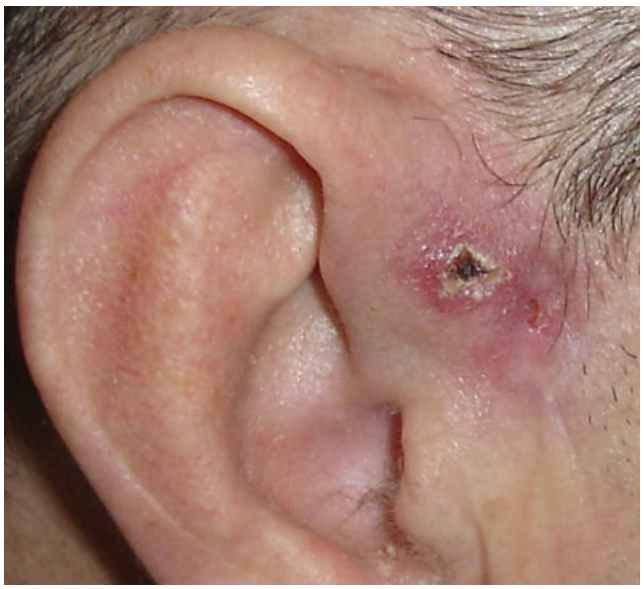

Figure 4 Low-grade cutaneous marginal zone lymphoma

Table 2 Main characteristics of head and neck lymphomas according to location

Disease location	*Main characteristics*
Nodal	Painless Elastic consistency HL usually involves mediastinal or hilar nodes NHL usually spreads to non-contiguous nodes and abdominal involvement is common
Palatine tonsil	The most frequent extranodal lymphoma in the head and neck. Asymptomatic enlargement of one tonsil is frequently seen
Rhinopharynx	A neck node is the most common form of presentation Others: nasal obstruction, hearing loss
Base of tongue	Few reported cases Neck node is the first sign
Oral cavity	Form of presentation: swelling, pain and ulceration Locations: palate, gingiva and maxilla
Salivary glands	The parotid gland is the most frequently affected site Frequently associated with Sjögren's syndrome
Thyroid	Frequently associated with Hashimoto's thyroiditis Absence of cystic degeneration
Larynx	Most frequently supraglottic Usually submucosal
Nasal cavity	Neoplastic cells positive for Epstein–Barr virus NK/T-cell lymphoma is the most common Very aggressive
Paranasal sinuses	Sinusitis is the most common form of presentation Commonly extends into the orbit
Skin	The most frequent pathological forms are: follicle-centre cell, cutaneous marginal zone, and diffuse large B-cell

to suspect the disease to obtain a biopsy specimen as soon as possible, and it is also necessary to obtain a clinical specimen in an appropriate manner (*i.e.*, a complete node that is fresh rather than fixed). Following treatment, otorhinolaryngologists and stomatologists will also participate in regular examination of patients to detect any possible recurrence.

Complementary examination

Blood analysis can detect anaemia and quantitative alterations in leucocyte number. Liver and kidney functions should also be examined. Serum levels of creatinine, transaminases, lactate dehydrogenase and β2-microglobulin can yield information regarding the involvement of these organs. Increases in serum alkaline phosphatase and calcium levels may indicate bone infiltration. It is also necessary to screen for AIDS, as NHL may be the first clinical manifestation of this disease (Zapater *et al*, 1996).

Imaging evaluation is necessary for staging of the disease. However, such examination cannot reliably distinguish between HL and NHL. Contrast-enhanced CT is routinely performed, including the head and neck, chest, abdomen and pelvis, and is especially useful to detect bone destruction when extranodal lymphoma arises in areas close to the bone (*e.g.,* the skull base, paranasal sinuses, mandible or maxilla). MRI is preferred for the evaluation of soft tissue extension, such as the para-pharyngeal space, infra-temporal fossa, tongue and intracranial or intraspinal invasion.

Both HL and NHL typically show multiple homogeneous nodes ranging in size from 2 to 10 cm (Figure 4). Nodal necrosis preceding treatment and extranodal spread are observed more frequently in clinically aggressive lymphomas (Aiken and Glastonbury, 2008). As mentioned above, HL usually spreads contiguously, whereas NHL is typically non-contiguous and more commonly shows extranodal involvement. HL tends to arise in the jugular chain, whereas NHL should be suspected in cases in which the lesion is located in the retropharyngeal, parotid, occipital or submandibular nodes (Figure 5).

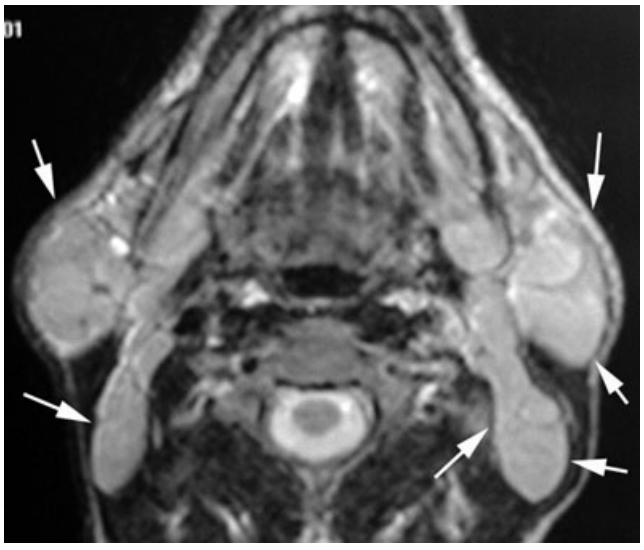

Figure 5 IRM of a patient with a NHL of oral mucosa showing multiple lymph nodes (arrows)

Extranodal lymphomas usually present as submucosal lesions that may show postcontrast enhancement. Ulceration and irregular margins are infrequent. The enhancement is usually slight, but may be marked depending on inflammation or increased vascularity (Weber *et al*, 2003). Bony destruction is not as frequent as in carcinomas, although clinically aggressive lymphomas, such as Burkitt's, diffuse large B-cell and NK/T-cell lymphomas are characterised by destruction of the maxillae, mandibles and paranasal sinus walls.

When extranodal lymphoma arises in Waldeyer's ring, it frequently shows gastrointestinal involvement, and therefore barium studies are necessary for the staging of the disease. Tonsillar lymphoma usually presents as homogeneous enlargement with intensity similar to that of normal tissue, associated with ipsilateral lymphadenopathy (Harris *et al*, 1994). Lymphoma arising in the nasopharynx may mimic carcinoma, but it has some specific characteristics: bony erosion is rare and it tends to spread in an exophytic manner to fill the airway, rather than infiltrating the deep tissues or bone. Deep tumour infiltration, when it occurs, is found in patients with primary NHL and is usually limited (King *et al*, 2003). Tongue lymphoma also tends to be more homogeneous and is less likely to be necrotic than tongue carcinoma (Aiken and Glastonbury, 2008).

Upon CT, Burkitt's lymphoma appears as a large osteolytic lesion near the angle of the mandible, with an associated soft tissue mass without osteoid or cartilaginous matrix (Aiken and Glastonbury, 2008). Burkitt's lymphoma may also affect the maxilla.

Sinonasal NHL can mimic various clinical entities, such as Wegener's granulomatosis, aesthesioneuroblastoma and squamous carcinoma. However, MRI of NHL shows a more homogeneous tumour and less intense enhancement than that observed in carcinoma. Furthermore, NHL tends to remodel rather than destroy bone, although it may erode adjacent bone (Aiken and Glastonbury, 2008).

Parotid lymphoma cannot be distinguished from carcinoma based on radiological patterns, and may present as diffuse parotid infiltration or as bilateral multifocal masses in cases of disseminated disease (Mehle *et al*, 1993).

Thyroid lymphoma imaging mimics anaplastic carcinoma. It usually presents as a solitary rapidly enlarging mass, although multiple nodules may also be observed. These lesions are usually homogeneously hypointense on T1- and T2-weighted images. Thyroid lymphoma tends to be more homogeneous than carcinoma, and calcification, cystic degeneration and necrosis are rare (Widder and Pasieka, 2004).

Laryngeal lymphoma tends to be homogeneous on MRI and usually involves the hypopharynx. Superior extension to the oropharynx and even nasopharynx may occur (King *et al*, 2003).

Table 3 Ann Arbor staging system for lymphomas

Stage I	Involvement of a single lymph node region (I) or localised involvement of a single extralymphatic organ site (IE)
Stage II	Involvement of two or more lymph node regions on the same side of the diaphragm (II) or localised involvement of an extralymphatic organ or site and one or more lymph node regions on the same side of the diaphragm (IIE)
Stage III	Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by localised involvement of an associated extralymphatic organ or site (IIIE), by involvement of the spleen (IIIS), or both (IIIS + E)
Stage IV	Diffuse or disseminated involvement of one or more extralymphatic organs or tissues, with or without associated lymph node involvement, or isolated extralymphatic organ involvement with distant (non-regional) nodal involvement

Positron emission tomography complements CT and MRI findings, as it provides information regarding metabolic activity. Positron emission tomography (PET) has been shown to be more reliable than CT and MRI in detecting residual or recurrent disease, as well as in distinguishing posttreatment fibrosis from active residual tumours (Cremerius *et al*, 1998).

Following imaging evaluation, other diagnostic procedures may be indicated to complete staging of the disease. A bone marrow biopsy is necessary, as approximately 20% of NHLs show bone involvement (Aisenberg, 1995). This procedure is usually performed at the posterior iliac crest.

Lumbar puncture is indicated in all patients with HIV infection, in patients with specific histological subtypes, such as Burkitt's lymphoma and lymphoblastic lymphoma, and in cases showing symptoms of neurological disease. Lumbar puncture is also indicated for any lymphoma involving the paranasal sinuses to detect possible destruction of the skull base. Staging laparotomy or laparoscopy may be needed in cases with suspected occult splenic or liver disease or infiltration of retroperitoneal nodes.

Clinical classification

The WHO classification of lymphoid tissues describes more than 50 different histological types, which are too complex from a clinical viewpoint. It is necessary to clinically organise the different histological entities in terms of aggressiveness and prognosis. The following three terms have been defined for the lymphomas: indolent, in which the survival of patients with untreated disease is measured in years; aggressive, in which the survival of patients with untreated disease is measured in months; and highly aggressive, in which the survival of patients with untreated disease is measured in weeks. The relevance of this clinical classification, which is not part of the WHO classification, is derived from the following considerations. Indolent lymphomas are generally associated with reasonably long survival (years) even if left untreated, but they are usually not curable with conventional treatment. On the other hand, the aggressive and highly aggressive variants are curable, but rapidly fatal (weeks to months) if untreated or unresponsive to therapy. Patients with indolent lymphomas may have prolonged survival even if treatment results in only a partial response, while in the case of aggressive and highly aggressive lymphomas, only those patients who show a complete response to treatment can expect reasonable survival or cure. HL, although a lymphoid malignancy, is considered to be a distinct entity and generally has an excellent prognosis.

The most common staging system for lymphoma is the Ann Arbor staging system, which was developed in 1971 for HL and adapted for staging NHL (Table 3) (Moormeier *et al*, 1990). This staging system focusses on the number of tumour sites (nodal and extranodal), location and the presence or absence of systemic ('B') symptoms. Stage I refers to NHL involving a single lymph node region (stage I) or a single extralymphatic organ or site (stage IE). Stage II refers to two or more involved lymph node regions on the same side of the diaphragm (stage II) or with localised involvement of an extralymphatic organ or site (stage IIE). Stage III refers to lymph node involvement on both sides of the diaphragm (stage III), or with localised involvement of an extralymphatic organ or site (stage IIIE) or the spleen (stage IIIS), or both (stage IIIES). Stage IV refers to the presence of diffuse or disseminated involvement of one or more extralymphatic organs (*e.g.*, liver, bone marrow or lung), with or without associated lymph node involvement. The presence or absence of systemic symptoms should be noted with each stage designation (A, asymptomatic; B, presence of fever, sweats or weight loss $>10\%$ of body weight) (Cheson, 2008).

The whole range of complementary examinations for staging disease should be performed only in those cases where a change in stage would require modification to the initial therapy. For example, a positive biopsy from the posterior iliac crest constitutes pathological stage IV, which obviates other staging measures as treatment will not be modified. Lymphoma presenting in the head and neck tends to be associated with an earlier stage.

Prognostic factors

A number of studies have demonstrated that prognosis is far more dependent upon histopathology, being influenced only secondarily by clinical parameters such as age, presence of extranodal disease, performance status and stage (I/II *vs* III/IV). Determining prognosis for each of the NHL variants is related to multiple differences in tumour cell biology (*e.g.*, cytogenetics, immunophenotype, growth fraction, LDH level and β2-microglobulin production) found within each of the specific disease variants. The second group of variants depends on tumour burden, which is clearly an important prognostic factor in lymphoma, and may also affect the overall treatment strategy. The survival of

lymphoma patients has improved markedly over the last several years and large numbers of cases can be cured with new treatment modalities. However, a substantial proportion of the patients experiences very serious disease evolution or is not curable. The development of prognostic systems is imperative to identify these patients at diagnosis, so that appropriate treatment approaches can be applied. Such adapted therapy will spare those with favourable prognoses from increased toxicity caused by unnecessary therapy (Johnston and Salles, 2008).

Well-validated prognostic systems are essential to identify patient risk groups and compare new treatment strategies among these groups. The two most useful scores are the International Prognostic Index (IPI) for aggressive lymphoma and the Follicular Lymphoma International Prognostic Index (FLIPI) for indolent disease, especially follicular lymphoma.

Institutions in the United States, Canada and Europe participated in the International Non-Hodgkin's Lymphoma Prognostic Factors Project, which was intended to elaborate upon the IPI. Patients with aggressive lymphomas were evaluated for pretreatment features, which predicted survival following treatment with doxorubicin-containing chemotherapy regimens. The following factors were found to be significantly correlated with shorter overall or relapse-free survival: age >60, serum LDH concentration greater than normal, Eastern Cooperative Oncology Group (ECOG) performance status ≥ 2, Ann Arbor clinical stage III or IV, and number of involved extranodal disease sites >1. In this system, one point is given for each of the above characteristics for a total score ranging from 0 to 5, representing increasing degrees of risk: low risk, IPI score 0 or 1; low intermediate risk, IPI score 2; high intermediate risk, IPI score 3; high risk, IPI score 4 or 5. When applied to the initial group of 2031 patients with aggressive NHL, the 5-year overall survival rates for patients with scores of 0/1, 2, 3 or 4/5 were 73%, 51%, 43% and 26% respectively (Hermans *et al*, 1995).

Follicular Lymphoma International Prognostic Index for indolent disease is based on an international study of long-term survival in 4167 patients with follicular lymphoma diagnosed between 1985 and 1992. Five adverse prognostic factors were identified: age >60 years, Ann Arbor stage III or IV, haemoglobin level <12.0 g dl^{-1}, number of involved nodal areas >4, and serum LDH level greater than the upper limit of normal. The following three risk groups and their corresponding 5- and 10-year overall survival rates were identified: low risk (0 or 1 adverse factors), 91% and 71%; intermediate risk (two adverse factors), 78% and 51%; high risk (three or more adverse factors), 52% and 36% (Solal-Celigny *et al*, 2004).

Treatment

The prognosis for patients with lymphoma has improved over the last several years attributable to advances in precise diagnosis, staging and definition of risk groups, and the development of effective combinations of chemotherapy, radiotherapy and monoclonal antibodies. The actual management of lymphomas begins with an accurate diagnosis involving immunophenotyping and cytogenetics. The second point is to determine the patient's risk profile based on the prognostic score. However, age, comorbidities and histological subtype should be determined regardless of whether there is a reasonable chance for cure or only a palliative approach.

Management of indolent B lymphomas

Low-grade lymphomas have a slow growth rate and a long clinical course. Bone marrow involvement is usually present at diagnosis. Stage I–II can be treated with immunochemotherapy [rituximab plus cyclophosphamide, adriamycin, vincristine and prednisone (R-CHOP)] and consolidation field irradiation. These patients can be cured, although the relapse rate is high. The advanced stages III–IV cannot be cured by immunochemotherapy/radiation therapy, and are only treated if active disease is present. The current combination therapy for advanced disease includes rituximab (an anti-CD20 monoclonal antibody) with chemotherapy, such as CHOP, fludarabine/cyclophosphamide or bendamustine (Hiddemann *et al*, 2007; Cheson and Leonard, 2008; Peinert and Seymour, 2008; Tan and Horning, 2008; Zucca *et al*, 2008).

Management of aggressive B lymphomas

The standard therapy for aggressive B lymphomas is the combination therapy R-CHOP. Radiotherapy is used only in early stages and for the residual bulky mass. Patients with advanced disease are currently treated only with immunochemotherapy. However, patients with high risk scores have recently been included in clinical trials examining the feasibility of intensive chemotherapy regimens followed by autologous stem cell transplantation (Friedberg and Fisher, 2008; Fu *et al*, 2008; Persky *et al*, 2008).

Management of highly aggressive B lymphomas

Very aggressive lymphomas (*e.g.*, lymphoblastic and Burkitt's lymphoma) are closely related to acute lymphoblastic leukaemia and are treated similarly with multiple courses of combined chemotherapy and central nervous system (CNS) prophylaxis because of the high rates of CNS involvement. Maintenance therapy with methotrexate and mercaptopurine is mandatory for lymphoblastic lymphoma. Patients with very high risk scores may be considered for stem cell transplantation (Thomas *et al*, 2006; Aldoss *et al*, 2008; Fielding, 2008; Sweetenham, 2008; Gökbuget and Hoelzer, 2009).

Management of NK/T-cell lymphomas

This type of lymphoma is rare and heterogeneous with many histological subtypes. Treatment based on the CHOP regimen produces a response rate of about 50–60%, but with very poor long-term disease-free survival rates. The more intensive chemotherapy protocols do not result in better prognosis. New agents (purine analogues, gemcitabine and bortezomib) and

immunological agents (anti-CD24 and -CD52) have been shown to be active, but new alternatives and combinations are currently being explored.

The recommended treatment for localised nasal NK/T-cell lymphoma typically involves radiation with anthracycline-based chemotherapy and intrathecal prophylaxis. Localised presentation has a 5-year overall survival rate of 40%, but the very aggressive forms of the disease show a 5-year overall survival rate of only 9%.

Younger patients may be candidates for autologous or allogeneic stem cell transplantation, and some success has been achieved in such cases. As these diseases are rare and heterogeneous, there is no standard therapeutic regimen, and it is very important to include such cases in clinical trials of new agents (Savage, 2008; Suzuki *et al*, 2008; Vose, 2008).

Management of Hodgkin's lymphoma

The standard chemotherapy for patients with HL is adriamycin, bleomycin, vinblastine and dacarbazine in combination with limited field irradiation of the initial sites of bulky disease. The goal of current strategies is to provide each patient with the best probability of cure and the minimum long-term toxicity. Early stages are treated with a short course of chemotherapy (2–4 cycles) and consolidation field radiotherapy. Patients in advanced stages are treated with chemotherapy (6–8 cycles) and complementary irradiation only in bulky areas or in cases with active residual tumours (Evens *et al*, 2008).

References

Aiken A, Glastonbury C (2008). Imaging Hodgkin and non-Hodgkin lymphoma in the head and neck. *Radiol Clin North Am* **46:** 363–378.

Aisenberg AC (1995). Coherent view of non-Hodgkin's lymphoma. *J Clin Oncol* **13:** 2656–2675.

Aldoss IT, Weisenburger DD, Fu K *et al* (2008). Adult Burkitt lymphoma: advances in diagnosis and treatment. *Oncology* **22:** 1508–1517.

Anselmo AP, Cavalieri E, Cardarelli L *et al* (2002). Hodgkin's disease of the nasopharynx: diagnostic and therapeutic approach with a review of the literature. *Ann Hematol* **81:** 514–516.

Boring CC, Squires TS, Tong T (1993). Cancer statistics. *CA Cancer J Clin* **43:** 7–26.

Cheson BD (2008). Staging and evaluation of the patient with lymphoma. *Hematol Oncol Clin North Am* **22:** 825–837.

Cheson BD, Leonard JP (2008). Monoclonal antibody therapy for B-cell non-Hodgkin's lymphoma. *N Engl J Med* **359:** 613–626.

Cheung MM, Chan JK, Lau WH *et al* (1998). Primary non-Hodgkin's lymphoma of the nose and nasopharynx: clinical features, tumor immunophenotype, and treatment outcome in 113 patients. *J Clin Oncol* **16:** 70–77.

Coltrera MD (1999). Primary T-cell lymphoma of the thyroid. *Head Neck* **21:** 160–163.

Cremerius U, Fabry U, Neuerburg J, Zimny M, Osieka R, Buell U (1998). Positron emission tomography with ^{18}F-FDG to detect residual disease alter therapy for malignant lymphoma. *Nucl Med Commun* **19:** 1055–1063.

Cuadra-García I, Proulx GM, Wu CL *et al* (1999). Sinonasal lymphoma: a clinicopathologic analysis of 58 cases from the Massachusetts General Hospital. *Am J Surg Pathol* **23:** 1356–1369.

Das DK, Francis IM, Sharma PN *et al* (2009). Hodgkin's lymphoma: Diagnostic difficulties in fine-needle aspiration cytology. *Diagn Cytopathol* **37:** 564–573.

Evens AM, Hutchings M, Diehl V (2008). Treatment of Hodgkin lymphoma: the past, present, and future. *Nat Clin Pract Oncol* **5:** 543–556.

Feinberg SM, Ou SH, Gu M, Shibuya TY (2007). Burkitt's lymphoma of the base of the tongue: a case report and review of the literature. *Ear Nose Throat J* **86:** 356–360.

Fielding A (2008). The treatment of adults with acute lymphoblastic leukemia. *Hematology* **1:** 381–389.

Friedberg JW, Fisher RI (2008). Diffuse large B-cell lymphoma. *Hematol Oncol Clin North Am* **22:** 941–952.

Fu K, Weisenburger DD, Choi WW *et al* (2008). Addition of rituximab to standard chemotherapy improves the survival of both the germinal center B-cell-like and non-germinal center B-cell-like subtypes of diffuse large B-cell lymphoma. *J Clin Oncol* **26:** 4587–4594.

Gökbuget N, Hoelzer D (2009). Treatment of adult acute lymphoblastic leukemia. *Semin Hematol* **46:** 64–75.

Harris NL, Jaffe ES, Stein H, Isaacson PG (1994). A revised European–American classification of lymphoid neoplasm: a proposal from the International Lymphoma Study Group. *Blood* **84:** 1361–1392.

Hermans J, Krol AD, van Groningen K *et al* (1995). International prognostic index for aggressive non-Hodgkin's lymphoma is valid for all malignancy grades. *Blood* **86:** 1460–1463.

Hiddemann W, Buske C, Dreyling M, Weigert O, Lenz G, Unterhalt M (2007). Current management of follicular lymphomas. *Br J Haematol* **136:** 191–202.

Jaffe ES, Harris NL, Stein H, Isaacson PG (2008). Classification of lymphoid neoplasms: the microscope as a tool for disease discovery. *Blood* **112:** 4384–4399.

Johnston A, Salles G (2008). Prognostic Systems for lymphoma. *Hematol Oncol Clin North Am* **22:** 839–861.

Jovanovic MB (2008). An exophytic localized lymphoma of the tongue base. *Otolaryngol Head Neck Surg* **139:** 468–469.

Kemp S, Gallagher G, Kabani S, Noonan V, O'Hara C (2008). Oral non-Hodgkin's lymphoma: review of the literature and World Health Organization classification with reference to 40 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* **105:** 194–201.

King AD, Lei KI, Richards PS, Ahuja AT (2003). Non-Hodgkin's lymphoma of the nasopharynx: CT and MR imaging. *Clin Radiol* **58:** 621–625.

King AD, Yuen EH, Lei KI, Ahuja AT, Van Hasselt A (2004). Non-Hodgkin lymphoma of the larynx: CT and MR imaging findings. *Am J Neuroradiol*. **25:** 12–15.

Kochbati L, Chraïet N, Nasr C *et al* (2006). Hodgkin disease of the nasopharynx: report of three cases. *Cancer Radiother* **10:** 142–144.

La Quaglia MP (1994). Non-Hodgkin's lymphoma of the head and neck in childhood. *Semin Pediatr Surg* **3:** 207–215.

Levine AM (1992). Acquired-immunodeficiency syndrome-related lymphoma. *Blood* **80:** 8–20.

Li S, Griffin CA, Mann RB, Borowitz MJ (2001). Primary cutaneous T-cell-rich B-cell lymphoma: clinically distinct from its nodal counterpart? *Mod Pathol* **14:** 10–13.

Lima I, Carneiro AS, Amorim CA, Santiago MB (2008). Hodgkin lymphoma as a complication of primary Sjögren's syndrome. *Mod Rheumatol* **18:** 200–202.

Mehle ME, Kraus DH, Wood BG, Tubbs R, Tucker HM, Lavertu P (1993). Lymphoma of the parotid gland. *Laryngoscope* **103:** 17–21.

Moormeier JA, Williams SF, Golomb HM (1990). The staging of non-Hodgkin's lymphomas. *Semin Oncol* **17:** 43–50.

Moran EM (1990). Lymphoma in AIDS. *JEPTO* **10:** 326–330.

Nathu RM, Mendenhall NP, Almasri NM, Lyunch JW (1999). Non-Hodgkin's lymphoma of the head and neck: a 30-year experience at the University of Florida. *Head Neck* **21:** 247–254.

Oluwasanmi AF, Wood SJ, Baldwin DL, Sipaul F (2006). Malignancy in asymmetrical but otherwise normal palatine tonsils. *Ear Nose Throat J* **85:** 661–663.

Patiar S, Ramsden JD, Freeland AP (2005). B-cell lymphoma of the larynx in a patient with rheumatoid arthritis. *J Laryngol Otol* **119:** 646–649.

Peinert S, Seymour JF (2008). Indolent lymphomas other than follicular and marginal zone lymphomas. *Hematol Oncol Clin North Am* **22:** 903–940.

Persky DO, Unger JM, Spier CM *et al* (2008). Phase II study of rituximab plus three cycles of CHOP and involved-field radiotherapy for patients with limited-stage aggressive B-cell lymphoma: Southwest Oncology Group Study 0014. *J Clin Oncol* **26:** 2258–2263.

Santucci M, Pimpinelli N, Arganini L (1991). Primary cutaneous B-cell lymphoma: a unique type of low-grade lymphoma. Clinicopathologic and immunologic study of 83 cases. *Cancer* **67:** 2311–2326.

Savage KJ (2008). Prognosis and primary therapy in peripheral T-cell lymphomas. *Hematology Am Soc Hematol Educ Program* **2008:** 280–288.

Siddiqui MT, Pitelka LA, Gattuso P (2009). Extranodal lymphomas: review of clinicopathologic and cytologic features. *Diagn Cytopathol* **37:** 220–229.

Solal-Celigny P, Roy P, Colombat P *et al* (2004). Follicular lymphoma international prognostic index. *Blood* **104:** 1258–1265.

Suzuki R, Takeuchi K, Ohshima K, Nakamura S (2008). Extranodal NK/T-cell lymphoma: diagnosis and treatment cues. *Hematol Oncol* **26:** 66–72.

Swedlow SH, Campo E, Harris NL *et al* (2008). Eds. *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edn. WHO/International Agency for Research on Cancer: Lyon.

Sweetenham JW (2008). Highly aggressive lymphomas in adults. *Hematol Oncol Clin North Am* **22:** 965–978.

Talmon Y, Gilbey P, Falah R, Samet A, Cohen H, Khoury J (2007). Primary B cell lymphoma of the tongue. *IMAJ* **9:** 755–756.

Tan D, Horning SJ (2008). Follicular lymphoma: clinical features and treatment. *Hematol Oncol Clin North Am* **22:** 863–882.

Thomas DA, Faderl S, O'Brien S *et al* (2006). Chemoimmunotherapy with hyper-CVAD plus rituximab for the treatment of adult Burkitt and Burkitt-type lymphoma or acute lymphoblastic leukemia. *Cancer* **106:** 1569–1580.

Urquhart A, Berg R (2001). Hodgkin's and non-Hodgkin's lymphoma of the head and neck. *Laryngoscope* **111:** 1565–1569.

Vega F, Lin P, Medeiros J (2005). Extranodal lymphomas of the head and neck. *Ann Diagn Pathol* **9:** 340–350.

Vose JM (2008). Peripheral T-cell non-Hodgkin's lymphoma. *Hematol Oncol Clin North Am* **22:** 997–1005.

Weber A, Rahemtullah A, Ferry JA (2003). Hodgkin and non-Hodgkin lymphoma of the head and neck: clinical, pathologic, and imaging evaluation. *Neuroimaging Clin N Am* **13:** 371–392.

Widder S, Pasieka JL (2004). Primary thyroid lymphomas. *Curr Treat Options Oncol* **5:** 307–313.

Willemze R, Jaffe ES, Burg G *et al* (2005). CJ WHO-EORTC classification for cutaneous lymphomas. *Blood* **105:** 3768–3785.

Zapater E, Bagán JV, Campos A, Armengot M, Abril V, Basterra J (1996). Non-Hodgkin's lymphoma of the head and neck in association with HIV infection. *Ann Otolaryngol Chir Cervicofac* **113:** 69–72.

Zucca E, Bertoni F, Stathis A, Cavalli F (2008). Marginal zone lymphomas. *Hematol Oncol Clin North Am* **22:** 883–901.