



Faculty of Medicine

**Descriptive epidemiology, trends in incidence  
and survival analysis in extranodal head and  
neck lymphoma from 1994 to 2013 in Girona,  
Spain: a population-based study**

Final degree project

**Pathology service**

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## **SUMMARY**

**Introduction:** an epidemiological study is presented, focused on extranodal lymphomas that arise in the head and neck region, including B-cell lymphomas, T-cell lymphomas, Hodgkin's lymphomas and not otherwise specified (NOS) lymphomas.

**Methodology:** descriptive epidemiology, incidence and its trends and survival are analyzed for extranodal head and neck lymphomas registered in the Cancer Registry of Girona, Spain, from January 1<sup>st</sup> 1994 to December 31<sup>st</sup> 2013.

**Results:** 122 cases of extranodal head and neck lymphomas were identified. Of these, 108 were B-cell lymphomas, 5 T-cell lymphomas, 3 Hodgkin's lymphomas, and 6 malignant lymphomas, NOS. The most frequent histological type was diffuse large B-cell lymphoma, which accounted for 47.5% of all extranodal head and neck lymphomas. In men the most common region for the lymphoma's presentation were the tonsils (14.7% among all the cases) followed by the nasopharynx (9.8%). In women the most common region were the salivary glands (15.6%) followed by the tonsils (10.6%). In men, a decreasing tendency of incidence was observed for diffuse large B-cell, marginal zone and total B-cell lymphoma, and an increasing tendency was observed for those classified with other B-cell lymphomas. A decreasing incidence of total lymphomas was observed in both sexes. For both sexes, and among all B-cell lymphomas, OS at 5 years was 61.6, being 63.4 for men and 59.6 for women, but there was no significant difference between sexes.

**Conclusions:** extranodal head and neck lymphomas are rather rare. As observed in other reports, incidence increases with the age, and men are the most affected ones. Like these reports, the tonsils obtained the largest number of cases and the most common morphology was diffuse large B-cell lymphoma. The incidence tended to diminish as years passed, and survival was slightly better compared to other reports, which also detected a better survival for women unlike this study.

## **KEY WORDS**

- Extranodal lymphoma
- Head and neck neoplasm
- Epidemiology
- Incidence
- Survival
- Population-based cancer registry

## **1.- INTRODUCTION**

### **1.1.- About lymphomas**

Hematological malignancies are a heterogeneous group of malignant diseases that begin in the cells of blood-forming tissue. They can originate from two different cell lines (1):

- Lymphocytes or their precursors, leading to lymphoid neoplasms.
- Myeloid precursors, leading to myeloid neoplasms.

The present study focuses on lymphomas, a heterogeneous group of hematological malignancies, which belong to the first group, and that at the same time are subclassified in Hodgkin's Lymphoma (HL) (marked by the presence of a type of cell called Reed-Sternberg cell) and non-Hodgkin's Lymphoma (NHL) which includes a large, diverse group of cancers of immune system cells (2). Both of these subtypes can occur in children and adults, men and women. Together with their subtypes, HL and NHL have a particular clinical presentation. Their behavior and response to treatment are different in each type and, like the prognosis, it will depend on the stage and type of cancer (3).

So HL and NHL share a common origin: the lymphocyte in any of its different maturation stages. But this first approach can be more accurate with the use of immunohistochemical analysis, that allows to identify specific antigens, cytogenetic alterations or products of expression for each type of lymphoma (1). In this way, the different lymphomas can be properly categorized to make a diagnostic and therapeutic suitable approach for each type.

Furthermore, from the viewpoint of the location, it is important to distinguish two different entities:

- Nodal lymphomas: originated in the lymph nodes or other lymphoid organs.
- Extranodal lymphomas: originated in other anatomical structures (skin, stomach, intestine, thyroid gland, lung, spleen, tonsil...) and can also secondarily extent to lymph nodes or other lymphatic organs (4).

At least one quarter of NHL arise from tissues other than lymph nodes and even from sites which normally contain no lymphoid tissue, while in HL primary extranodal disease is thought rarer (5).

Thus, different types of lymphomas have distinctive morphological characteristics, from a histopathological point of view as well as from their distribution in the body, allowing in most cases their identification. The currently used classification of lymphomas is the one that WHO drafted in 2008, based on an update of the REAL system - Revised European-American Lymphoma Classification - from 1994. This classification has been updated to the present day, and in fact the last revision corresponds to 2016 (6). This recognizes three main categories of lymphoid neoplasms based on morphology and cell lineage:

- B-cell neoplasms.
- T-cell and NK-cell neoplasms.
- Hodgkin's lymphoma.

Within the categories of B and T lymphocytes, two subdivisions are recognized: neoplasms of precursor cells, corresponding to the earliest stages of differentiation, and neoplasms of mature cells differentiated. The lymphoid neoplasms classification proposed by the WHO in 2008 is detailed on annex 1.

It is important to notice, as commented earlier, that this classification criteria includes morphological, clinical, genetical and immunophenotypical features.

### **1.2.- Epidemiology of lymphomas**

NHL is the most prevalent hematopoietic neoplasm; it represents approximately 2.7% of all cancer diagnoses and it ranks as the tenth most in frequent cancer worldwide (see figure 1). NHL is more than five times more common than HL (7). In 2012 there were 385,741 cases of NHL and 65,950 cases of HL worldwide, with an incidence of 5.5 for NHL and 0.9 for HL. In Spain 5,130 cases of NHL and 1,150 of HL were recorded, representing an incidence of 13.1 and 2.5 respectively (7).

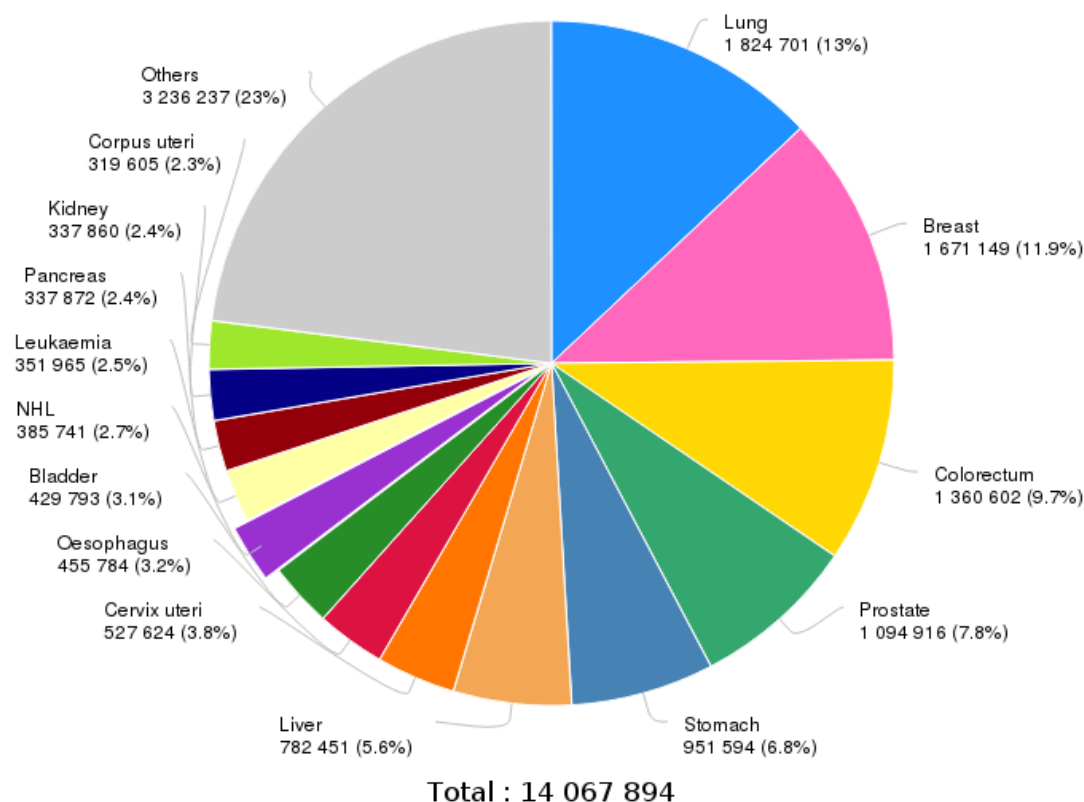


Fig. 4: Top 15 cancer sites incidences, worldwide, both sexes (7). In purple, estimated incidence of NHL, 2012

Incidence varies depending on age, sex and region. People who live in more developed countries have a higher risk of HL and NHL than those who live in less developed regions. For HL, citizens who present a greater risk are the Europeans, followed by the Americans, while the region of less risk is Western Pacific. In the case of NHL the first risky region is America, the second one is Europe, and the last one is South-East Asia. See figures 2-5.

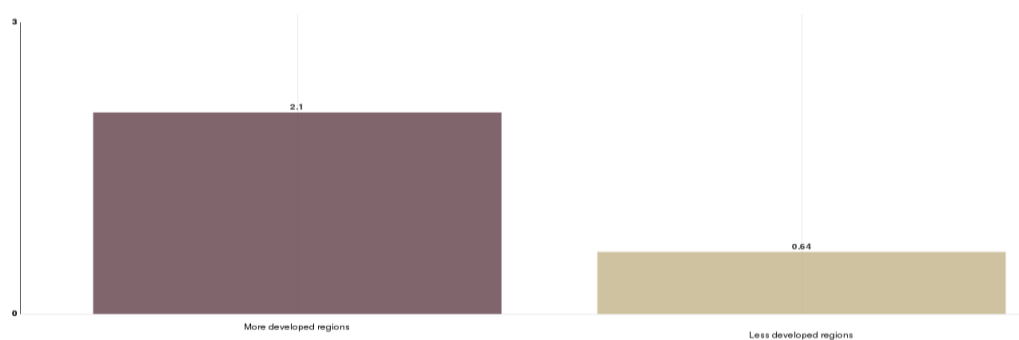


Fig. 5: Estimated age-standardized rates of HL by region level development, worldwide, both sexes, 2012 (7)



Fig. 6: Estimated age-standardized rates of NHL by region level development, worldwide, both sexes, 2012 (7)

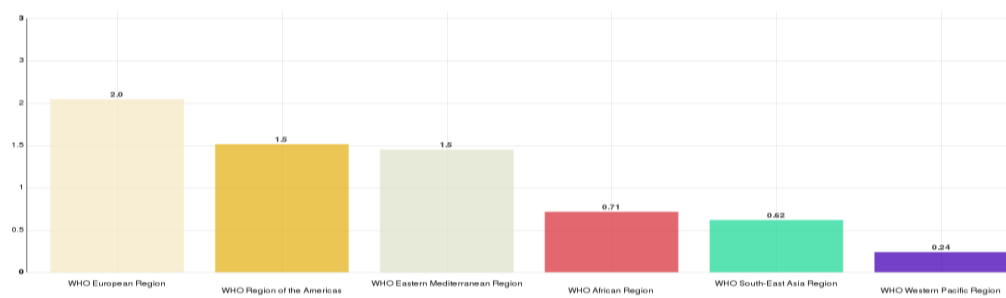


Fig. 4: Estimated age-standardized rates of HL by WHO region, both sexes, 2012 (7)

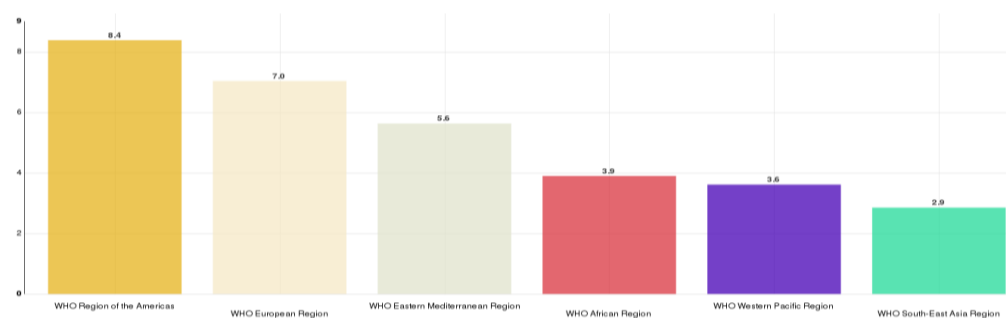


Fig. 5: Estimated age-standardized rates of NHL by WHO region, both sexes, 2012 (7)



In general, the incidence of NHL is slightly higher in men than in women, with a male:female ratio of approximately 1.2-1.4:1 (8,9), however, the ratio may vary depending on the subtype of NHL. The age at which most subtypes of NHL are becoming more prevalent is older than 50, so NHL incidence is strongly related to age, with the highest incidence rates being in older males and females. Around 50% of cases are diagnosed in people aged 70 and over. Age-specific incidence rates rise steeply from around age 50-54, reaching an overall peak in the 80-84 age group for both males and females, and subsequently dropping. Incidence rates are higher for males than females for those aged between 5-9 and 10-14, and 30-34 and over, and this gap is widest at the ages of 5 to 9, when the male:female ratio of age-specific incidence rates is around 2.7:1 (10). See figure 6.

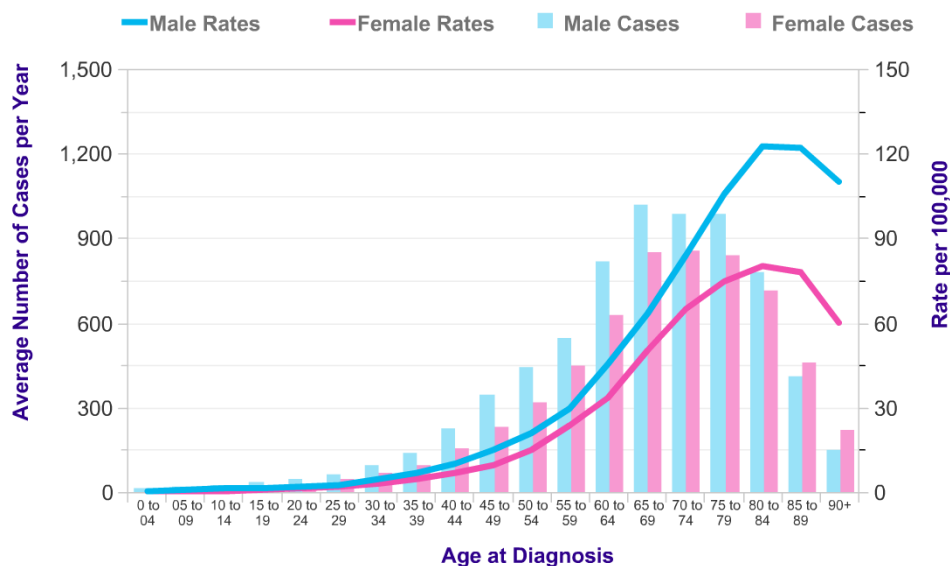


Fig. 6: NHL average number of new cases per year and age-specific incidence rates, UK, 2011-2013 (10)

As mentioned, and according to a study by the Research Network Hematologic Malignancy in the UK (11), the incidence by sex and age of lymphomas varies greatly by the type of lymphoma that is being analyzed. Thus, in under 39 years old it has been found that the most common is the classic HL, with a male: female ratio ranging from 2.2:1 (under 15 years old) to 1.3-1.4:1 (between 15 and 24 years old, and between 25 and 39 years old, respectively). From age 40 the most common type is diffuse large B-cell NHL, which goes increasing in proportion with the age, and presents the same male:female ratio already commented (1.2-1.4:1). See figure 7.

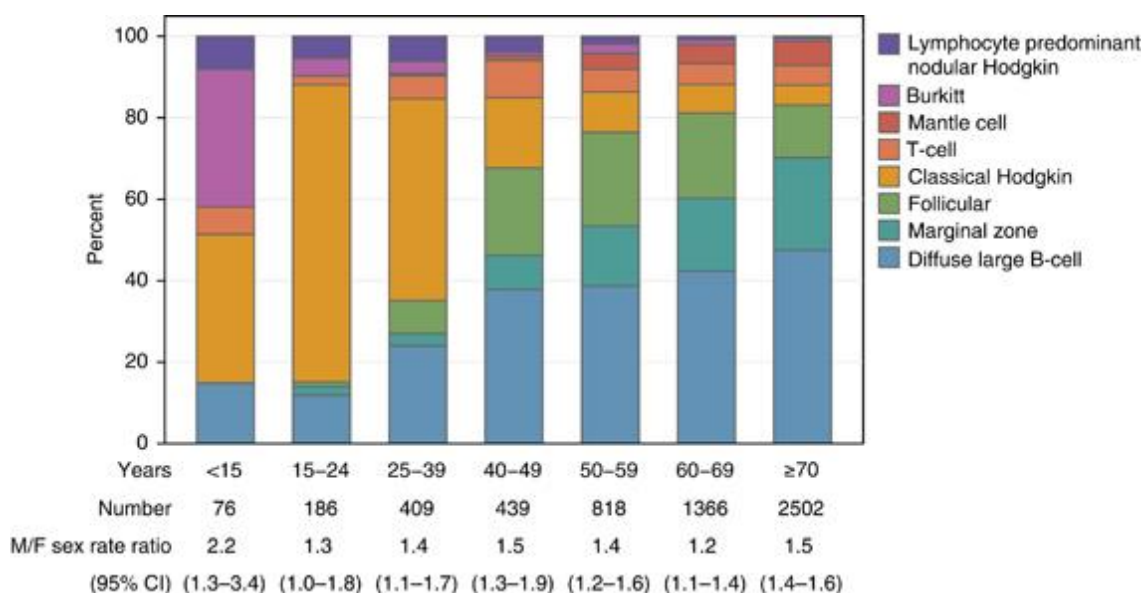


Fig. 7: Numbers of cases of lymphomas and sex-rate ratios by sub-type and age (11)

About 56% of new cases of HL happens in males, and 44% in females, giving a male:female ratio of around 1.3:1. HL incidence shows a clear bimodal age distribution, with the first peak in incidence rates in young adults, and the second peak in older males and females. Approximately 50% of cases are diagnosed in people aged 45 and over. Age-specific incidence rates rise sharply during childhood and peak first in young adults aged 20-24. For females this is the highest peak. Rates then decrease until middle age before rising again to reach a second peak in males and females aged 75-79. For males this is the highest peak. Incidence rates are higher for males than for females aged 0-4 and 30-34 to 70-74 and this gap is widest at the age of 0-4, when the male:female incidence ratio of age-specific rates is around 10.6:1 (10).

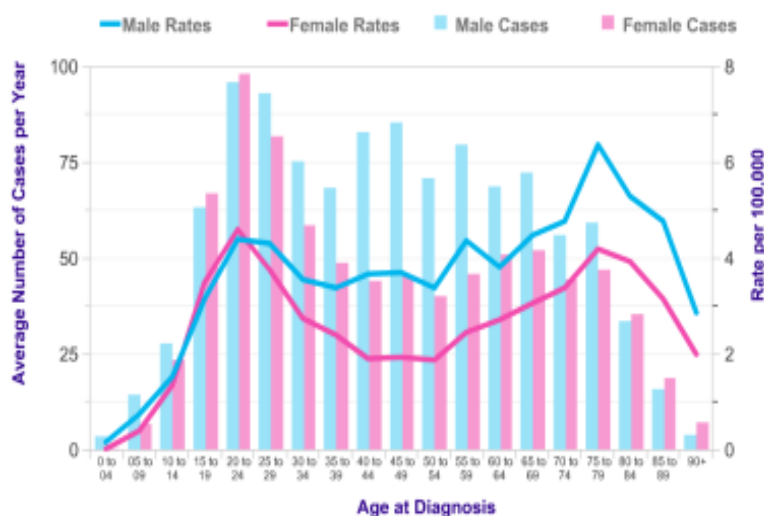


Fig. 8: HL average number of new cases per year and age-specific incidence rates, UK, 2011-2013 (10)

On trends in the incidence, there has been an increase in the number of cases per year of NHL since 1975 until 2009, when reaching the maximum level of incidence and begins to descend until 2013. For HL, the rate of incidence has been stable during all these years. In the figure 9 is seen a graphic that shows this trend for both lymphoid neoplasms (12).

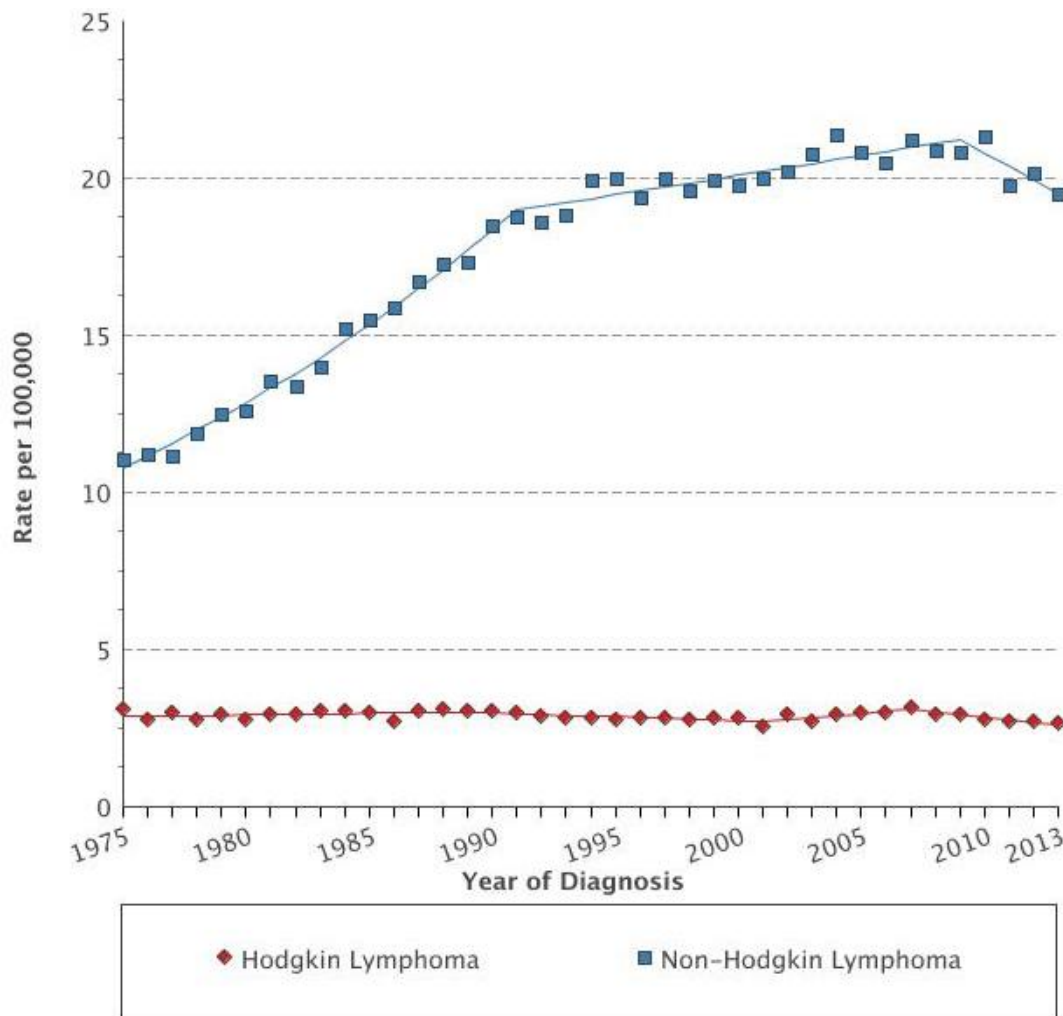


Fig. 9: Age-adjusted SEER incidence rates for NHL and HL, all ages, all races, both sexes, 1975-2013 (12)

### **1.3.- Staging of lymphomas**

Lymphomas are staged with the Ann Arbor classification system. The use of diagnostic findings allows to produce groups of patients who require similar treatment and have similar expected outcomes. Ann Arbor staging system was developed in 1971 in a Michigan city with the same name, and a modification was applied after a revision in 1989. Although it was firstly developed for the staging of HL, it was subsequently applied to NHL as well (1,13). The stage depends on two characteristics of the lymphoma:

- Place where the malignant tissue is located (as located with biopsy, CT or PET).
- Systemic symptoms due to the lymphoma (fever, night sweats, weight loss) known as B-Symptoms.

On annex 2 is detailed the Ann Arbor staging system with its clusters, and figures for its illustration (14).

For the purpose of staging, consideration of what is nodal or extranodal might be taken (13):

- Nodal or lymphatic site: lymph nodes, Waldeyer's ring, thymus, spleen.
- Extranodal or extralymphatic site: bone marrow, gastrointestinal tract, skin, bone, central nervous system, lung, ocular adnexa, liver, kidney, uterus, etc.

### 1.4.- Extranodal lymphomas

Extranodal lymphoma is a well-recognized entity: the lymphomas that appear at places other than lymph nodes, Waldeyer's ring, spleen or thymus, with no, or only regional, lymph node involvement after staging are classified as extranodal lymphomas; whereas the lymphomas that appear in lymph nodes, Waldeyer's ring, spleen or thymus, with no, or only minor, extranodal involvement after staging are categorized according to the Ann Arbor classification as primary nodal lymphomas. While the majority of lymphomas arise in the lymph nodes or other lymphatic tissues such as the spleen, Waldeyer's ring and thymus, approximately one quarter of them originate in extranodal sites. In the study of Groves FD et. al. 27% of all NHL cases were extranodal (15) , and in the study of AlShemmari SH et. al. 23% were extranodal as well (16).

The place of presentation can be very varied, being the skin, the digestive tube, the head and neck, the brain and the lungs the most frequent extra nodal lymphomas locations. However, different studies have shown that the frequency of topographic affectionation is not uniform (see table 1):

**Tab. 1: Most frequent distribution of extranodal NHL according four different studies**

	AlShemmari SH et. al. (2008) (16)	Wu X-C et. al. (2009) (17)	Greiner TC et. al. (1995) (18)	Groves FD et. al. (2000) (15)
<b>First most frequent distribution</b>	GIT–stomach, small and large bowel	Skin (men), stomach (women)	Skin (men), stomach (women)	Skin
<b>Second most frequent distribution</b>	<b>Head and neck</b>	Stomach (men), skin (women)	Stomach (men), skin (women)	Stomach
<b>Third most frequent distribution</b>	Skin	<b>Head and neck</b> (men and women)	<b>Head and neck</b> (men and women)	Brain
<b>Fourth most frequent distribution</b>	Brain and CNS	Small intestine (men), brain (women)	Small intestine (men and women)	Small intestine
<b>Fifth most frequent distribution</b>	Bone	Brain (men), eye and orbit (women)	Brain and CNS (men and women)	Lung

It is important to say that there is a dearth of information in the literature on features of extranodal lymphomas. Few studies deal with this type of lymphoma and those that do so are usually small reports, retrospective case-series concerning extranodal manifestations in various organs. In the few studies that look at the frequency of each type of extranodal lymphoma according to histology the same order of frequency for each subtype of lymphoma is appreciated, but the percentages may appear slightly different: 78% for B-cell lineage and 15.6% for T-cell lineage in the study

of Wu X-C et. al. (17), while 89% for B-cell lineage and 10.2% for T-cell lineage in AlShemmari SH et. al. study (16), with a big difference of almost 30% for diffuse large B-cell. See table 2.

Tab. 2: Most frequent histological subtype distribution of extranodal NHL according two different studies

	AlShemmari SH et. al. (2008) (16)	Wu X-C et. al. (2009) (17)
Total B-cell lineage	89%	78%
Diffuse large B-cell	71.1%	40.1%
Follicular	6.2%	12.2%
Marginal zone B-cell	7.2%	7.6%
Other B-cell	5.2%	5.8%
Total T-cell lineage	10.2%	15.6%
Others / Unclassifiable	0.8%	6.4%

As can be observed in studies, the same frequency percentages for each histological type are given in men and women, and the same again if the distribution is made by age (15–22).

### 1.5.- Extranodal head and neck lymphomas

Concerning extranodal lymphomas of the head and neck region, and according to “Oral manifestations of lymphoma: a systematic review” (23) that includes the presentation of 982 cases reported in 73 scientific papers, the tonsils were the most affected in the head and neck region, appearing in 12.12% of the cases, followed by salivary glands with 11.01% of the cases, while the maxilla was the most affected bone region, with 9.16% of the cases reported. See figure 10.

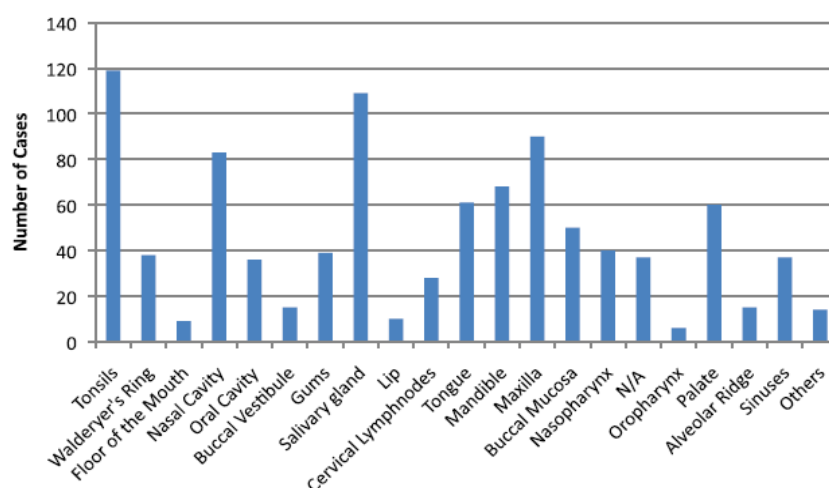


Fig. 10: Most frequent location of lymphomas in head and neck region (23)

In terms of lymphoma types, diffuse large B-cell non-Hodgkin's lymphoma was the most frequent, followed by marginal zone B-cell lymphoma and follicular lymphoma.

### **1.6.- Risk factors for lymphomas**

The lymphoid malignant proliferation is a consequence of a lymphogenesis that has been accumulating genetic injuries that result in a clonal malignant expression. As a lymphoid precursor cell is differentiating there exists an important genetic instability status. This makes the cell very vulnerable to external agents such as viruses or toxics and increases the risk that some kind of translocations take place, which can activate oncogenes or inactivate tumoral suppressor genes. In short, the consequences of these processes are:

- Alterations in the regulation of the growth cell.
- Changes in routes of transmission of signals.
- Changes of apoptosis.

Although there may be some forms of genetic susceptibility, the increase in the incidence of lymphoid neoplasms in all geographic areas of the world would make us think much more on environmental factors in its etiology. Nowadays several factors have been found that may affect the chance of getting HL or NHL. Some of these risk factors are:

- Age: as showed in figure 6 NHL incidence is strongly related to age, with the highest incidence rates being in older males and females. Figure 8 shows that HL incidence presents a bimodal age distribution, with the first peak in incidence rates in people aged 20-24, and the second peak in people aged 75-79.
- Gender: overall, the risk of non-Hodgkin lymphoma is higher in men than in women. In general, women have a 30% lower overall incidence of NHL (9). The only exception is follicular lymphoma: Morton LM et. al. (24) and Smith A et. al. (25) found it to be more common in women than in men.
- Geography: as seen in figures 2 and 3, both HL and NHL are more prevalent in more developed regions; HL in Europe and NHL in USA.
- Immunosuppression / Human immunodeficiency virus (HIV): the association of diseases that cause decreased function of immune system with increased susceptibility to present lymphomas is well known. The most frequent case is the HIV infection and, secondly, transplanted patients. Patients with primary immune

system disorders have a probability of more than 25% of developing tumors, which share a number of common characteristics: high-grade B diffuse histology, extranodal involvement (especially CNS and gastrointestinal), aggressive course and association with EBV. Patients infected with HIV are 60 to 200 times more likely to develop NHL than the general population. Since the introduction of highly active antiretroviral treatments there has been a very significant decrease in the incidence of AIDS-related lymphomas (1,26,27).

- Autoimmune diseases: some autoimmune diseases are linked with an increased rate of non-Hodgkin lymphoma. Patients with Sjögren's syndrome have a relative risk between 4 and 40 to develop MALT lymphoma of the parotid gland. The fact of having rheumatoid arthritis or lupus erythematosus implies that patients are most likely to present a NHL. Patients with celiac disease have six times more risk of lymphoma, especially T extranodal lymphomas in the small intestine (1,28–30).
- Infections:
  - Epstein-Barr virus (EBV): if an organism is infected by EBV and subsequently undergoes a state of immunosuppression, EBV (that has remained dormant) will reactivate, producing a greater risk of malignant transformation lymphoid (31). This is especially important for African endemic Burkitt lymphoma, almost 100% of cases of which present EBV infection (31). In immunocompetent individuals, it appears that those with high levels of antibodies to EBV are more likely to develop HL and NHL (32,33). It seems that EBV can be considered a cofactor, but not the principal agent in the etiology of most NHL.
  - Human herpesvirus 8 (HHV-8) or Kaposi sarcoma-associated herpes virus (KSHV): HHV-8 is an endemic virus from the Mediterranean and Sub-Saharan Africa. It can infect lymphocytes, leading to a rare type of lymphoma called primary effusion lymphoma that is almost exclusive in patients who are infected with HIV, and that affects pleura and peritoneum (34).
  - Human T-cell Lymphotropic Virus I (HTLV-1): a human retrovirus associated with T-cell lymphoma in areas of the Caribbean and Japan, where the infection is endemic (35). Less than 5% of the infected develop lymphoma, and this is much more frequent when the individual is infected in his or her early life (36).



- Hepatitis C virus (HCV): currently available epidemiological data have confirmed that about 20% of B-cell NHLs are associated with HCV infection. Unlike lymphomas that appear in immunodeficiency states in HCV infected patients, there is a predominance of indolent forms (1). The highest proportion of HCV-positive patients occurred within the group of MALT lymphomas, diffuse large-cell and follicular NHLs (37). Its importance as a cause of NHL is discussed, and it seems that it is more important in countries where there is more prevalence of HCV infection.
- Helicobacter pylori (HP): the serological studies of Parsonnet et. al. confer a risk of gastric MALT lymphoma six times more than the general population, for patients with IgG against HP (38).
- Chemical and radiation exposure: it has been demonstrated that chemicals such as benzene and certain herbicides and insecticides (weed and insect killing substances) may be linked with a higher risk of non-Hodgkin lymphoma (39).

This consideration takes special interest with regard to occupational diseases. Studies of survivors of atomic bombs and nuclear reactor accidents have shown that they have an increased risk of developing several types of cancer, including NHL. Patients treated with radiation therapy for some other cancers, such as HL, have a slightly higher risk of developing NHL later in life. This risk is greater for patients treated with both radiation and chemotherapy (40).

### **1.7.- Population-based Girona Cancer Registry (GCR)**

GCR is a population-based registry located northeast of Catalonia and covering a population of 761,632 residents in the province of Girona according to the census of 2013. GCR main objective is to record all cases of cancer diagnosed annually affecting the people of Girona, whether diagnosed within the territory covered by GCR (province of Girona) or outside it. Through this population registry it is possible to perform analysis of incidence, survival and mortality of a particular tumor to have better control over the impact of cancer at the level of population. The sources of information used by population-based Girona Cancer Registry (GCR) to record all cases of the province of Girona cancer come from:

- Hospital discharges of the hospitals in the province of Girona.
- Results of hematology and pathology department and laboratory results of other reference centers located outside the province. If there is not available microscopic verification, GCR records detected tumors by exploratory techniques (clinical or surgical, image technics or laboratory) if they provide a high degree of safety about the tumor's malignancy in question.
- Information obtained from death certificates, in those cases for which no information source other than a death certificate mentioning cancer can be found, which are consequently registered as death certificate-only (DCO).

In order to act according the “Ley Orgánica 15/1999, de 13 de diciembre, de Protección de Datos de Carácter Personal (41)”, confidentiality agreement regarding personal data must be signed in order to access all this information, as well as an accreditation for clinical appraisalment as being accredited to enter medical records.

All cases included in GCR are recorded following the recommendations of the European Network for Cancer Registries (ENCR) and encoded by morphology and topography using the International Classification of Diseases for Oncology (ICD-O). The second edition of ICD-O (ICD-O-2) published 1990 was used to record cases diagnosed until 1997 and the third edition (ICD-O-3) is used to record cases since 1998 to the present.

The RCG was established in 1994 as an extension of the monograph registration of breast cancer and female genital that was in operation from 1980 until 1989. The responsible for carrying it out is the “Unitat d’Epidemiologia i Registre del Càncer del Pla Director d’Oncologia”. The GCR is a member of the International Agency for Cancer Registries (IACR) and their data are regularly published in the monographs of Cancer Incidence in Five Continents; the last volume was published in 2007 and refers to the data for the period 1998 -2002. He is also a member of the "European Network of Cancer Registries" (ENCR) (42).

### **1.8.- Institut d’estadística de Catalunya (IDESCAT)**

IDESCAT is the statistical body of the Government of Catalonia (Generalitat de Catalunya). It is an independent administrative part of the Economy and Hacienda department of Government of Catalonia. The mission of this organization is the management of the statistical system of Catalonia through planning, standardization of business statistics and statistical technical assistance activities included in the annual performance statistics compiled by the institute and approved by the Government of Catalonia. It produces official economic, demographic and social statistics and also keeps track of other statistical activities that are spreading in the region and the official results. It is also responsible for the creation and management of the Population Register of Catalonia (43). Figure 11 consists in a population pyramid showing the demographic age-distribution in Girona for the year 2013, according IDESCAT data.

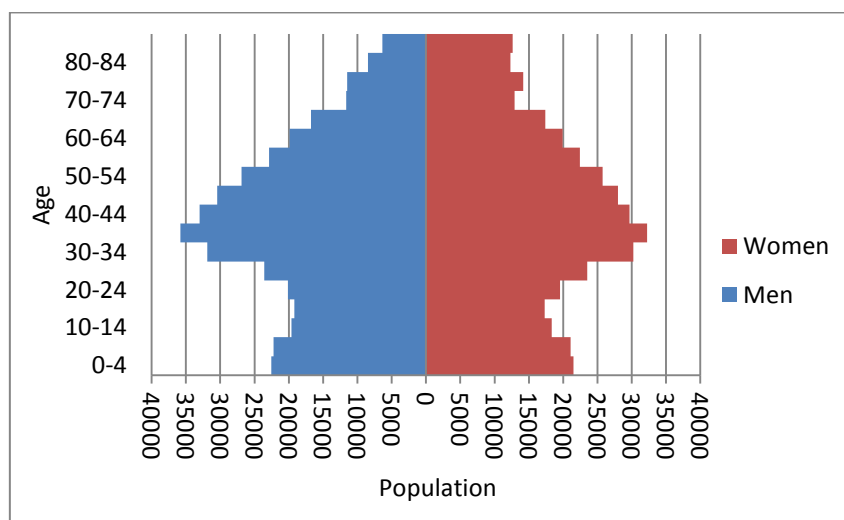


Fig. 11: Population pyramid. Province of Girona, 2013

### **1.9.- International Classification of Diseases for Oncology (ICD-O)**

ICD-O was designed as a classification system, providing a system of diagnostic codes for classifying malignancies. It has been used for more than 35 years, mainly in tumor or cancer registries, for coding the site (topography) and the histology (morphology) of the neoplasm, usually obtained from a pathology report.

By agreement with the College of American Pathologists, the morphology section of ICD-O is incorporated into the Systematized Nomenclature of Medicine (SNOMED) classification as the neoplasm section of the morphology field.

In some categories, the acronym “NOS” (Not Otherwise Specified) is printed after topographic or morphologic terms. It is used when a diagnostic is made in a general sense, without specifying the subclassification of the disease within its group (44,45).

For the purpose of this study, the third edition of ICD-O was used (ICD-O-3). The morphological codes for lymphomas and topographic codes for head and neck region are detailed on annex 3.

## **2.- JUSTIFICATION**

Approximately one quarter of lymphomas are specified as extranodal, meaning that each year about 97,500 cases are diagnosed around the world. Thus, it follows that approximately 0.69% of the total of cancers diagnosed worldwide correspond to extranodal lymphomas. While there is extensive literature on the epidemiology of lymphomas in general because it is a rather common tumor, there is a lack of information about extranodal lymphomas, although, overall, they represent a fairly significant percentage.

Making this distinction between extranodal and nodal lymphomas is important because some studies have reported that there is a difference in the prognosis of both entities (46–48).

Since no such analysis has been done previously in the province of Girona, this study aims to shed light on the epidemiology of extranodal lymphomas to assess the impact they may have on the health of its population.

The choice of the studied region, head and neck, has not been random either. This area stands as the second or third where extranodal lymphomas most frequently arise (the order varies with studies, see table 1), and it also presents a rather complex anatomy. This implies that two extranodal lymphomas that arise in different sites in this region may have a very different prognosis.

Surely, it would have been very interesting, and useful for medicine, to perform a study of extranodal lymphomas throughout the whole human body. Unfortunately there was not as much time as this undertaking requires. However, this can be the starting point to carry out such a feat, allowing to assess the situation of extranodal lymphomas that are treated in the hospitals in our province of Girona.

### **3.- HYPOTHESIS**

In Girona, between January 1<sup>st</sup> 1994 to December 31<sup>st</sup> 2013:

- Histological type and site of presentation of extranodal head and neck lymphomas is not different from those observed in the rest of the World.
- Incidence and its trends of extranodal head and neck lymphomas are not different from those observed in the rest of the World.
- Survival of extranodal head and neck lymphomas is not different from those observed in the rest of the World, and there are no significant differences between men and women.

### **4.- OBJECTIVES**

- To describe the histological and topographic presentation of extranodal head and neck lymphomas diagnosed in Girona between January 1<sup>st</sup> 1994 to December 31<sup>st</sup> 2013.
- To evaluate the incidence of extranodal head and neck lymphomas diagnosed in Girona between January 1<sup>st</sup> 1994 to December 31<sup>st</sup> 2013 and analyze its tendency.
- To analyze the survival of extranodal head and neck lymphomas diagnosed in Girona.

## **5.- METHODOLOGY**

### **5.1.- Study design**

This cohort study is a descriptive, retrospective review performed in patients with extranodal head and neck lymphoma diagnosed in the province of Girona between January 1<sup>st</sup> 1994 to December 31<sup>st</sup> 2013.

### **5.2.- Population in study**

This review focuses on patients with extranodal head and neck lymphoma followed at any hospital in the province of Girona and recorded in the population-based Girona Cancer Registry (GCR), from January 1<sup>st</sup>, 1994 to December 31<sup>st</sup>, 2013.

### **5.3.- Inclusion criteria**

- Patients diagnosed with extranodal head and neck lymphoma between January 1<sup>st</sup>, 1994 to December 31<sup>st</sup>, 2013 and histologically confirmed by a pathologist.
- Patients recorded in the population-based Girona Cancer Registry (GCR) encoded as: C00-C14;C30-C32 for topography, and 9590-9729 for morphology.

### **5.4.- Exclusion criteria**

- Patients with a less than three-month period between a first diagnosis of extranodal head and neck lymphoma and a second one of other lymphoma that arise in a different location non-adjacent to the first found.
- Patients with unknown date of birth or date of diagnosis, or those whose follow-up was lost.

### **5.5.- Data**

Data for descriptive epidemiology, incidence and survival analysis were extracted from the GCR. Population data used for the statistical analysis were provided by IDESCAT. Cases were registered applying the rules of the International Classification of Diseases for Oncology (ICD-O). A quality control of cases was done by reviewing the medical records of each lymphoma, obtained from the pathology laboratory of Dr. Josep Trueta University Hospital of Girona, and ensuring that the data recorded in the

CRG were correct. If any inconsistency between clinical history and CGR registration was detected, the case was discarded from the study.

The sample consisted in 64 men (53.3% of the total) with a median age of 58.73, and 57 women (46.7% of the total) with a median age of 65.09. They all had microscopical verification, and no case was diagnosed with a death certificate only (DCO).

Unless otherwise indicated, all statistical analysis was performed using the software package SPSS v.23.0 (49).

### **5.6.- Incidence rates**

Extranodal head and neck lymphoma incidence rates, crudes and age-adjusted, for the period 1994-2013 in Girona were calculated using the computer program EPIDAT (50). These rates were estimated by sex, age, period of time of diagnosis and by histological type of lymphoma in those cases with enough number of patients.

Age-adjusted rates were calculated using the direct standardization method, in which those are obtained by applying the age-specific rates observed in the study population to a single standard population. This was necessary in order to eliminate the effect of differences in population age structures when comparing crude rates for different population sub-groups. When rates were age-standardized, it was possible to know that differences in the rates over sex and periods of time did not simply reflect variations in the age structure of the populations. This is important when looking at cancer rates because it is a disease that predominantly affects the elderly.

The data obtained from IDESCAT for the period 1994-2013 were used to calculate both crude and age-adjusted rates, which were expressed by 100,000 habitants/year.



### **5.7.- Tendency of the incidence**

The changes over time in the incidence rates were evaluated applying a log-linear regression using the age-adjusted incidence rate as dependent variable with Joinpoint Regression Program (51). This software allowed to calculate the annual percent change and analyze changes in the trend of incidence.

### **5.8.- Survival**

To analyze observed survival, follow-up time was calculated between the date of diagnosis and the date of death (obtained by the Mortality Register of Catalonia and by the Spanish National Death Index) or, if the patient was alive when the study period ended, the end of follow-up study. Lymphoma specific mortality was not available. A Kaplan-Meier curve of percentage of patients that survived had been done for total B-cell lymphoma and for diffuse large B-cell lymphoma.

## **6.- ETHICAL CONSIDERATION**

This study has been performed in accordance with the ethical principles that are reflected in the Declaration of Helsinki (52) and with their practical applications to the discipline of Pathologic Anatomy (53). Both CRG and the pathology laboratory of Dr. Josep Trueta University Hospital of Girona have ensured the confidentiality principle (derived from the principles of autonomy and non-maleficence), and the pathology laboratory of Dr. Josep Trueta University Hospital of Girona has also ensured the principle of informed consent (derived from the autonomy principle) and the principle of sample excess (derived from the principle of beneficence).

## 7.- RESULTS

### 7.1.- Descriptive epidemiology:

122 cases of extranodal head and neck lymphomas were identified in the CGR database during the period 1994-2013. Out of these, 108 were B-cell lymphoma, 5 T-cell lymphoma, 3 Hodgkin's lymphoma, 4 malignant lymphoma, NOS, and 2 malignant lymphoma, non-Hodgkin, NOS.

B-cell lymphomas accounted for 88.5% of all extranodal head and neck lymphoma cases for the whole period. Out of these, 45.9% were men and 42.6% women, and they were diagnosed at a median age of 58.87 in men and 63.81 in women.

The distribution of the different morphologies of B-cell lymphoma in different parts of head and neck region can be seen on Table 3. The most frequent histological type was diffuse large B-cell lymphoma, accounted for 47.5% of all extranodal head and neck lymphoma cases for the whole period, with a male/female ratio of 1.07. The second most frequent was marginal zone B-cell lymphoma, which represents the 27.8% of the cases. A 6.5% of the cases were diagnosed as follicular lymphoma, making it the third most frequent over the population in study. In men the most common location for the lymphoma's presentation were the tonsils (14.7% among all the cases) followed by the nasopharynx (9.8%). In women the most common location were the salivary glands (15.6%) followed by the tonsils (10.6%).

**Tab. 3: Distribution of B-cell head and neck lymphoma. Girona, 1994-2013. N (%)**

	Diffuse large B-cell		Follicular		Marginal zone B-cell		Other B-cell <sup>2</sup>		Total B-cell	
	Men	Women	Men	Women	Men	Women	Men	Women	Men	Women
Oral cavity	3 (2.4)	3 (2.4)		1 (0.8)	1 (0.8)			1 (0.8)	4 (3.2)	5 (4.0)
Salivary glands	2 (1.6)	2 (1.6)	1 (0.8)	1 (0.8)	6 (4.9)	15 (12.3)		1 (0.8)	9 (7.3)	19 (15.6)
Tonsils	14 (11.4)	11 (9.0)	2 (1.6)	1 (0.8)	2 (1.6)			1 (0.8)	18 (14.7)	13 (10.6)
Nasopharynx	2 (1.6)	7 (5.7)			7 (5.7)	1 (0.8)	3 (2.4)		12 (9.8)	8 (6.5)
Nasal cavity	1 (0.8)	2 (1.6)		1 (0.8)	1 (0.8)		2 (1.6)		4 (3.2)	3 (2.4)
Others <sup>1</sup>	8 (6.5)	3 (2.4)		1 (0.8)	1 (0.8)				9 (7.3)	4 (3.3)
Total	30 (24.5)	28 (22.9)	3 (2.4)	5 (4.0)	18 (14.7)	16 (13.11)	5 (4.0)	3 (2.4)	56 (45.9)	52 (42.6)
Total (both sexes)	58 (47.5)		8 (6.5)		34 (27.8)		8 (6.5)		108 (88.5)	

1: Including tongue, gums, palate, oropharynx, hypopharynx, Waldeyer's ring and sinuses

2: Including lymphocytic lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma, immunoblastic lymphoma and Burkitt lymphoma

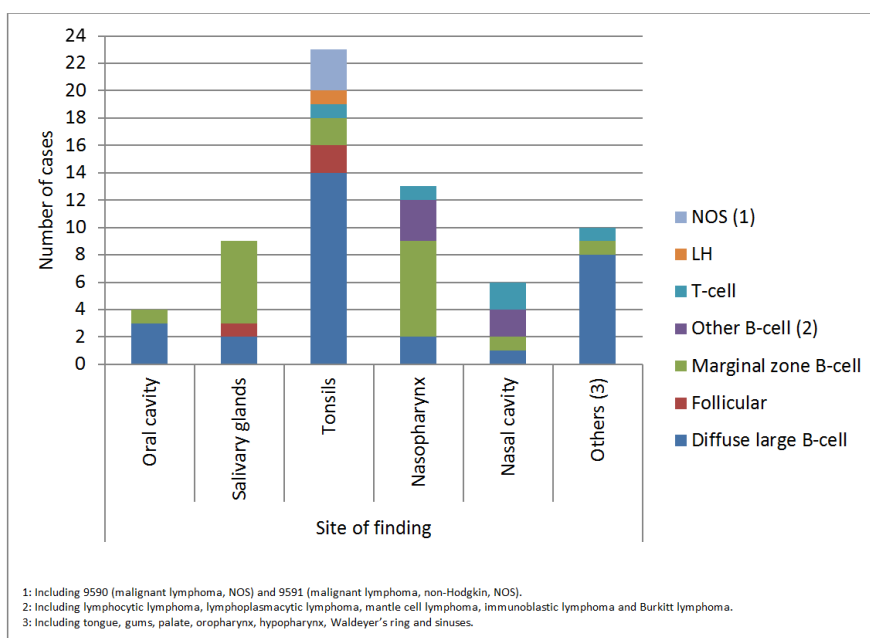
T-cell lymphoma, which was found only in men, represented a 4% of the whole and was diagnosed at a median age of 58. HL represented only 2.4% of the population in study and the median age of diagnosis was 63.67. Finally, those specified with NOS (9590 and 9591) accounted for 4.9% of all extranodal head and neck lymphoma, and were diagnosed at a median age of 72. Table 4 shows the distribution of the T-cell

lymphoma, HL and NOS lymphoma for different parts of head and neck region, according to ICD-O-3.

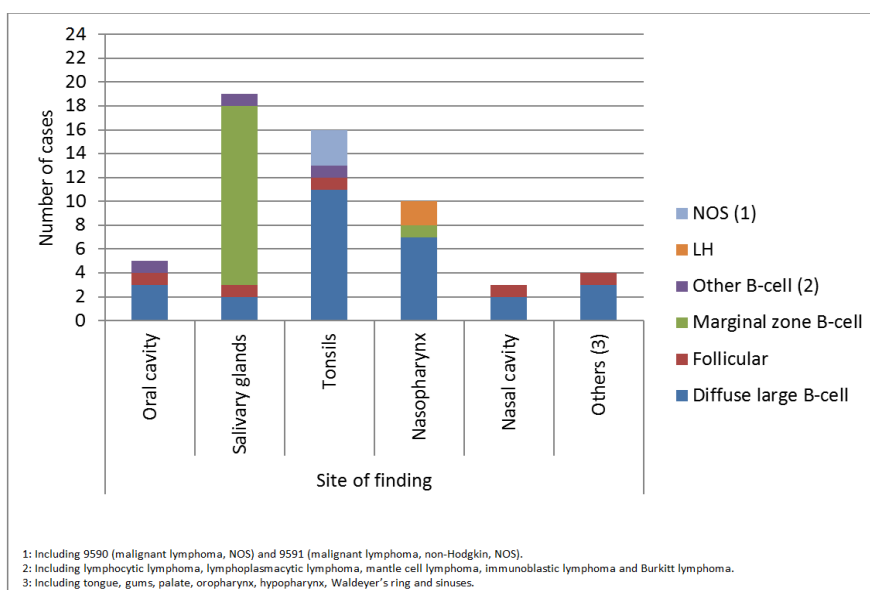
**Tab. 4: Distribution of T-cell, HL and NOS lymphoma in head and neck region. Girona, 1994-2013. N (%)**

	T-cell		HL		NOS	
	Men	Women	Men	Women	Men	Women
Tonsils	1 (0.8)		1 (0.8)		3 (2.4)	3 (2.4)
Nasopharynx	1 (0.8)			2 (1.6)		
Nasal cavity	2 (1.6)					
Sinuses	1 (0.8)					
Total	5 (4.0)		1 (0.8)	2 (1.6)	3 (2.4)	3 (2.4)
Total (both sexes)		5 (4.0)		3 (2.4)		6 (4.9)

For a more visual understanding of the epidemiology that is being analyzed, figures 12 and 13 show graphs consisting in a contingency analysis of the histological type depending on the site of finding of the lymphoma.



**Fig. 12: Contingency analysis of the histological type depending on the site of finding of the lymphoma, men. Girona, 1994-2013.**



**Fig. 13: Contingency analysis of the histological type depending on the site of finding of the lymphoma, women. Girona, 1994-2013.**

Additionally, the prevalence of B-cell lymphomas varies according to the age of the patients. Grouping patients into 5 years age intervals, it has been seen that B-cell lymphomas begin to be diagnosed in the age group 10-14, but it is in the 55-59 group where they start to become more prevalent. The maximum is for 80-84, and from here the prevalence decreases. Figure 14 shows a graph in which the age-specific rates of B-cell lymphomas are represented by age of patients grouped in periods of 5 years. Observed age-specific rates are represented in blue bars. The trend of this variable has been modeled and is represented in a red line.

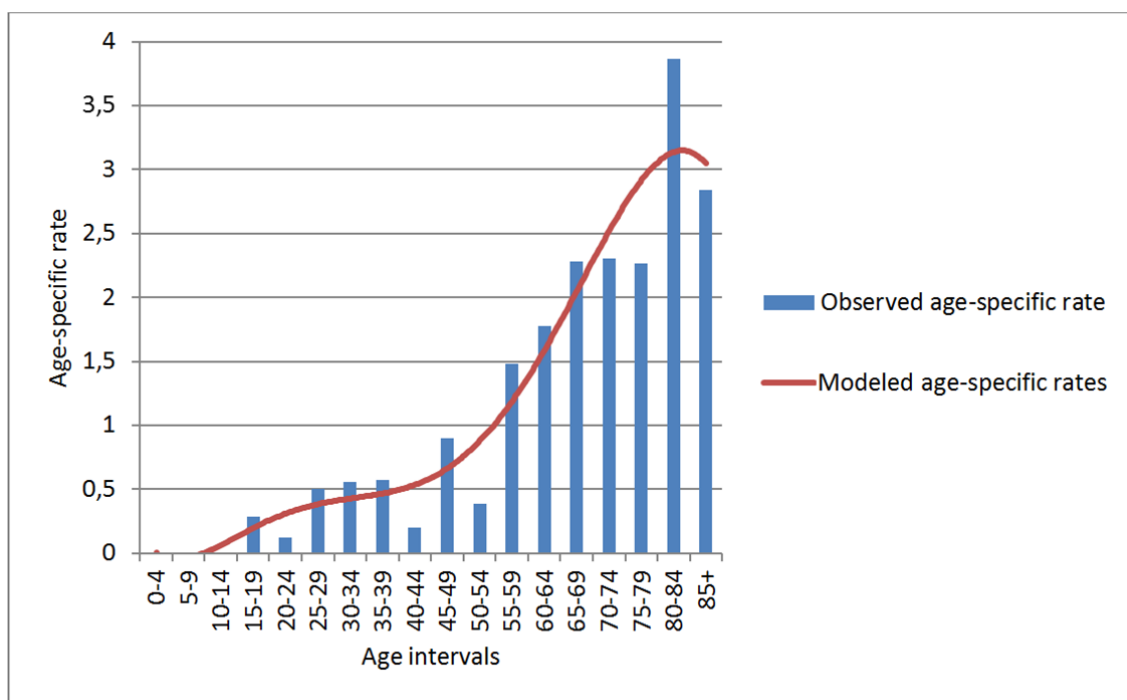


Fig. 14: Age-specific rates of B-cell lymphoma according 5-year-intervals of age. Girona, 1994-2013

## 7.2.- Incidence

Table 5 summarizes the incidence of different B-cell lymphoma, grouped into 5-year periods. The annual percent of change (APC) for these categories of lymphoma are shown in Table 6. For lymphomas others than B-cell lymphoma the incidence was not analyzed because of the small number of patients.

**Tab. 5: Incidence of B-cell head and neck lymphoma by 5-years period time. Girona, 1994-2013**

Period of time		Men				Women				Both sexes			
		N	CR	ASRe	CI 95%	N	CR	ASRe	CI 95%	N	CR	ASRe	CI 95%
Diffuse large B-cell	1994-1998	6	0.46	0.59	(0.1; 1.1)	7	0.52	0.55	(0.1; 1.0)	13	0.49	0.56	(0.3; 0.9)
	1999-2003	9	0.64	0.71	(0.2; 1.2)	3	0.21	0.17	(0.0; 0.4)	12	0.42	0.42	(0.2; 0.7)
	2004-2008	7	0.41	0.46	(0.1; 0.8)	14	0.92	0.91	(0.4; 1.4)	21	0.62	0.71	(0.4; 1.0)
	2009-2013	8	0.42	0.53	(0.2; 0.9)	4	0.24	0.24	(0.0; 0.5)	12	0.32	0.36	(0.2; 0.6)
Follicular	1994-1998	2	0.15	0.15	(-0.1; 0.4)	1	0.07	0.08	(-0.1; 0.2)	3	0.08	0.08	(0; 0.2)
	1999-2003					1	0.07	0.06	(-0.1; 0.2)	1	0.04	0.03	(0; 0.1)
	2004-2008					3	0.18	0.21	(0.0; 0.5)	3	0.09	0.11	(0; 0.2)
	2009-2013	1	0.05	0.06	(-0.1; 0.2)					1	0.03	0.03	(0; 0.1)
Marginal zone B-cell	1994-1998	7	0.41	0.46	(0.1; 0.8)	2	0.15	0.18	(-0.1; 0.4)	9	0.61	0.67	(0.2; 1.2)
	1999-2003	4	0.28	0.33	(0; 0.7)	9	0.63	0.69	(0.2; 1.1)	13	0.28	0.33	(0; 0.7)
	2004-2008	3	0.18	0.23	(0; 0.5)	1	0.06	0.05	(-0.1; 0.2)	4	0.18	0.23	(0; 0.5)
	2009-2013	3	0.16	0.19	(0; 0.4)	4	0.21	0.25	(0; 0.5)	7	0.16	0.19	(0; 0.4)
Other B-cell <sup>1</sup>	1994-1998	2	0.15	0.14	(-0.1; 0.3)	1	0.07	0.07	(-0.1; 0.2)	3	0.11	0.11	(0; 0.2)
	1999-2003	1	0.07	0.06	(-0.1; 0.2)	1	0.07	0.07	(-0.1; 0.2)	2	0.07	0.07	(0; 0.2)
	2004-2008												
	2009-2013	2	0.10	0.13	(-0.1; 0.3)	1	0.05	0.06	(-0.1; 0.2)	3	0.08	0.10	(0; 0.2)
Total B-cell	1994-1998	17	1.30	1.44	(0.7; 2.1)	11	0.82	1.96	(0.6; 3.3)	28	1.06	1.15	(0.7; 1.6)
	1999-2003	14	0.99	1.10	(0.5; 1.7)	14	0.98	1.49	(0.6; 2.4)	28	0.99	1.03	(0.6; 1.4)
	2004-2008	10	0.59	0.69	(0.2; 1.1)	18	1.08	1.84	(0.8; 2.8)	28	0.83	0.95	(0.6; 1.3)
	2009-2013	14	0.73	0.91	(0.4; 1.4)	9	0.48	1.11	(0.4; 1.9)	23	0.61	0.70	(0.4; 1.0)

N: number of cases; CR: crude rate; ASRe: European age standardized rate.

1: Including lymphocytic lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma, immunoblastic lymphoma and Burkitt lymphoma.

Incidence rates vary depending on sex, histological type of lymphoma and period of time. Considering total B-cell lymphoma, for men and women, the period of more incidence was 1994-1998 followed by 1999-2003. When only men are considered, the period of more incidence was 1999-2008 for diffuse large B-cell lymphoma and 1994-1998 for follicular lymphoma and for marginal zone B-cell lymphoma. For women, the period of more incidence was 2004-2008 for diffuse large B-cell lymphoma and for follicular lymphoma, and 1999-2003 for marginal zone B-cell lymphoma. Thus, it must be therefore concluded that extranodal head and neck lymphomas, in Girona, were diagnosed in earlier periods of time in men rather than in women.

**Tab. 6: APC of B-cell head and neck lymphoma in incidence rates. Girona, 1994-2013**

	Men				Women				Both sexes			
	N	APC	CI 95%	P value	N	APC	CI 95%	P value	N	APC	CI 95%	P value
Diffuse large B-cell	30	-4.9	(-7.6; -2.2)	<0.01	28	3	(-1.9; 8.3)	0.2	58	0.4	(-3.9; 5)	0.8
Follicular	3	-1.2	(-3.5; 1.3)	0.3	5	3.6	(-0.9; 1.7)	0.1	8	-2.9	(-6.9; 1.3)	0.2
Marginal zone B-cell	17	-4.2	(-6.9; -1.5)	<0.01	16	-3.1	(-7.6; 1.6)	0.2	33	-4.1	(-9.1; 1.1)	0.1
Other B-cell <sup>1</sup>	5	3.3	(1.2; 5.5)	<0.01	3	-1	(-3.4; 1.4)	0.4	8	1.5	(-0.7; 3.9)	0.2
Total B-cell	55	-3.4	(-6.4; -0.3)	<0.01	52	-0.6	(-5.6; 4.6)	0.8	107	-3	(-5.6; -0.3)	<0.01

N: number of cases; APC: annual percent of change.

1: Including lymphocytic lymphoma, lymphoplasmacytic lymphoma, mantle cell lymphoma, immunoblastic lymphoma and Burkitt lymphoma.

In bold, significant data (p < 0.01)

About the tendency of the incidence, it is important to notice, for the whole period 1994-2013, that the only significant data ( $p$  value  $< 0.01$ ) obtained corresponded to the APC of diffuse large B-cell, marginal zone B-cell and others B-cell lymphomas, and only for men. For the total B-cell lymphomas, a significant data was obtained for men and for both sexes, but no for women. Thus, focusing on men, a decreasing tendency of incidence was observed for diffuse large B-cell, marginal zone B-cell and total B-cell lymphoma, and an increasing tendency was observed for those classified with other B-cell lymphoma. Also, a decreasing incidence of total lymphomas was observed in both sexes.

Figure 15 consists in a scatter plot that shows the tendency of the incidence for total B-cell head and neck lymphoma in both sexes. Observed age-adjusted rates are represented in blue diamonds. The trend of this variable has been modeled and is represented in a red line. It can be seen how age-adjusted rates decrease, since 1994 to 2013, from 1.2 some to 0.6 some.

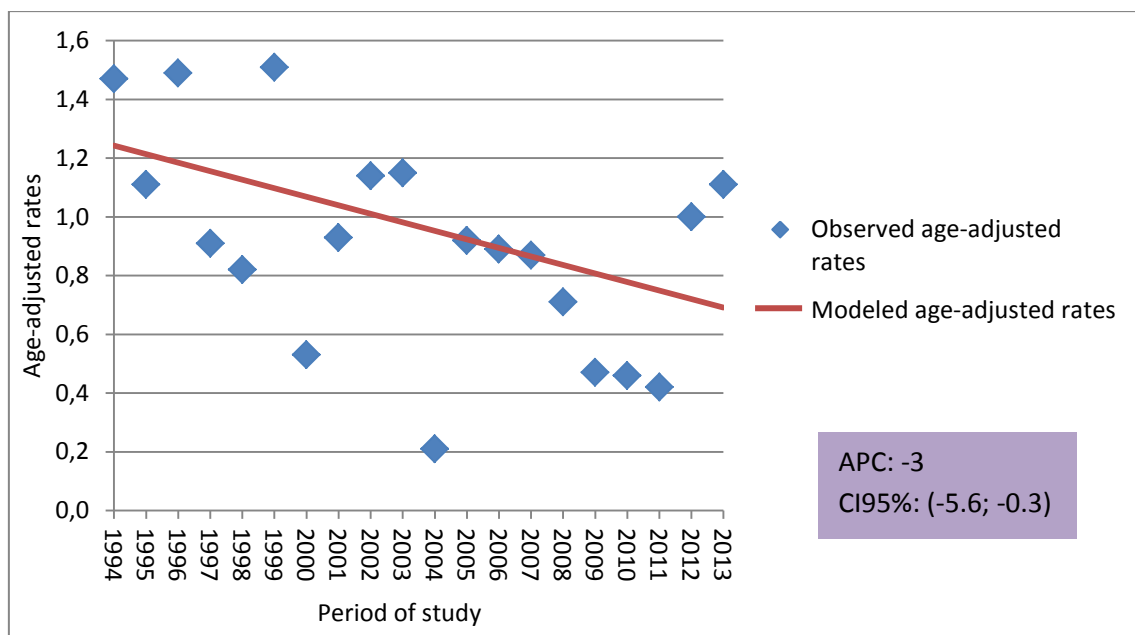


Fig. 15: Tendency of age-adjusted rates of B-cell head and neck lymphoma. Girona, 1994-2013

### 7.3.- Survival

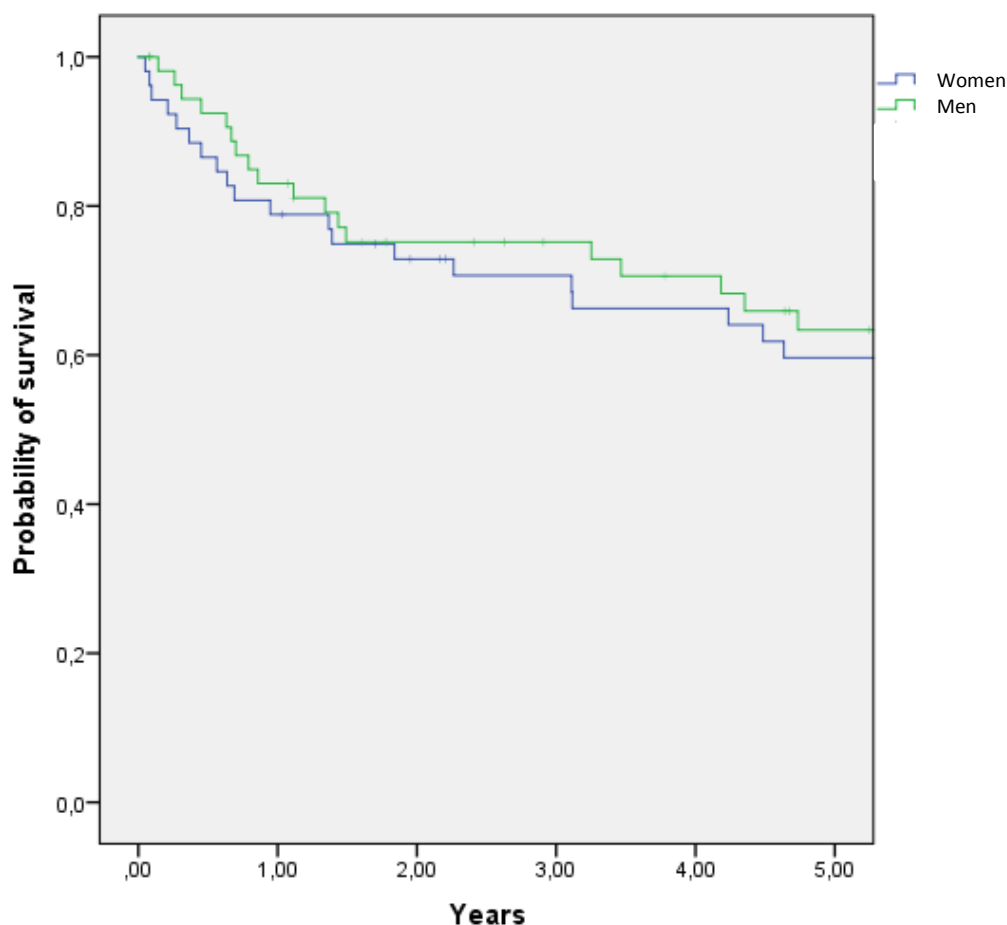
Observed survival (OS) at 3 and 5 years for diffuse large B-cell, marginal zone B-cell and total B-cell lymphomas is shown at Table 7. For lymphomas others than these survival was not analyzed because of the small number of patients.

**Tab. 7: Observed survival (OS) of B-cell head and neck lymphomas. Girona, 1994-2013**

Table 4. Observed survival (%) of B-cell non-Hodgkin's lymphoma: Diffuse large B-cell, 1997-2010										
Period of time	Men			Women			Both sexes			
	N	OS	CI 95%	N	OS	CI 95%	N	OS	CI 95%	
Diffuse large B-cell	3 years	18	67.5	(50.14; 84.85)	14	59.6	(41.08; 78.13)	31	63.7	(51.03; 76.38)
	5 years	12	54.5	(35.19; 73.8)	12	51.1	(31.80; 70.41)	24	52.9	(39.25; 66.55)
Marginal zone B-cell	3 years	15	83.3	(66.14; 100.46)	14	87.5	(71.32; 103.69)	29	85.3	(73.41; 97.20)
	5 years	11	70.9	(68.75; 73.04)	11	80.2	(60.115; 100.28)	22	75.3	(60.48; 90.12)
Total B-cell	3 years	38	75.2	(63.5; 86.9)	36	72.9	(60.81; 84.99)	68	73	(64.42; 81.58)
	5 years	25	63.4	(49.75; 77.05)	27	59.6	(45.95; 73.25)	52	61.6	(51.85; 71.35)

N: number of patients at risk; OS: observed survival.

For both sexes, and among all B-cell lymphomas, OS at 5 years was 61.6, being 63.4 for men and 59.6 for women. The comparison between these two groups obtained a p-value of 0.96, so the survival difference is not significant. A Kaplan-Meier curve representing the survival of total B-cell lymphoma is shown in figure 16.



**Fig. 16: Kaplan-Meier curve for total B-cell head and neck lymphoma. Girona, 1994-2013**



## **8.- DISCUSSION**

Extranodal head and neck lymphomas are rather rare: 3,171 tumors of head and neck have been registered in GCR since 1994 to 2013; of this, 122 were extranodal lymphomas. That represents a 3.8% of the total. More or less, this result matches those of single-center retrospective studies published since 1994 (54–59).

Regarding the distribution of the incidence of lymphomas on population, the results agree with the rest of the literature: lymphomas have been more frequent among men (except for follicular lymphoma, which was diagnosed mostly in women), and more cases were diagnosed as age increase from 55 to 80 years old.

In this study the tonsils have found to be the most affected place, and the salivary glands the second one (see tables 3 and 4). This coincides with the review of Silva TDB et. al. (23), but they found that the third most frequent affected region was the nasal cavity, while in this study was the nasopharynx, as there was only 9 cases of extranodal lymphomas in the nasal cavity. The reason of this difference is unclear, but it can be suspected that it is due to the anatomical classification criteria used by different authors.

Concerning the morphology of the lymphomas, it is described in the articles that diffuse large B-cell lymphoma is the most frequent, followed by marginal zone B-cell lymphoma and by follicular B-cell lymphoma. Tumors others than B-cell lymphoma, including T-cell and Hodgkin's disease are rare, with only isolated cases. This also matches the results of the present study (see table 3).

In the literature, it has been reported that from 1975 to 1990 the incidence of NHL has been doubling. Since 1990 it has increased less, until 2009 when it begins to decrease (see figure 9). In this study, however, a decrease in the incidence of head and neck lymphomas has been observed since 1994 (see figure 15). These years coincide with the introduction of highly active antiretroviral therapy (HAART) to treat HIV. In their review Cobucci et. al. described that treatment with HAART lowers the risk of most NHL in HIV-infected patients (60). Being this disease a risk factor for developing lymphoma, it is very likely that this decrease in the annual number of lymphomas in Girona is due to these treatments.

Studies analyzing the APC for lymphomas of the head and neck were not found, so there is no possibility of comparing the results of this study with those obtained by other authors. Nevertheless, the observed APC of -3 reinforces the theory of the intervention of antiretrovirals.

Hanna et. al. (61), Shima et. al. (62) and Shidnia et. al. (63) reported a 5 years OS between 40% and 60%. In the present study, survival was slightly higher (see table 7). It is important to note, however, that the studies that are being compared are somewhat old, and that they could stratify according to the tumor stage or treatment. The advance in the treatment of lymphomas, as well as the impossibility to stratify the patients in our study, can explain this difference in survival.

In Girona it has not been found a statistically significant difference in OS at 5 years among both sexes, although men seem to have a slightly higher survival. However, the study of Shima et. al. showed an improved survival for women, with a significant difference of 30%. Reasons for these differences may include relatively small numbers of patients, differences in diagnosis and international treatment, ethnic factors and variations in reported sites of involvement.

## **9.- CONCLUSIONS**

Out of a total of 3,171 head and neck tumors registered in the CRG, 3.8% were extranodal lymphomas. As in the rest of the world, these have been more prevalent as age increases, and most of them have been diagnosed in men. The most affected region were the tonsils, and the most common morphology diffuse large B-cell lymphoma, being this equal to other studies consulted. Lymphomas others than B-cell have found to be rare. It has been described an APC of -3% between 1994 and 2013, indicating a decreasing trend of the incidence, and attributing this to the introduction of HAART treatments for HIV-positive patients. It has been observed an OS at 5 years slightly higher compared to studies in the 80s and early 90s, without differences between sexes.

## **10.- LIMITATIONS**

The first limitation that has affected the study, and certainly the most important, has been the limited number of the samples. It has been difficult to make a statistical analysis that allows variable stratify with only 122 cases. The incidence has been calculated only for B-cell lymphomas, and the trend of it only for some subtypes of lymphoma in men and for total B-cell lymphomas in both sexes. Something similar has happened for survival: it was calculated for diffuse large B-cell, marginal zone B-cell and total B-cell lymphomas (which were the groups with most number of cases) but the difference between them, if stratified by sex, was not significant.

It should be emphasized that this study covers a period of 20 years, and this has allowed to evaluate the impact of extranodal lymphomas over a long time. But it must be considered that the immunohistochemical techniques applied today to classify lymphomas have evolved over the years. Because of this, it is possible that some of the cases diagnosed in earlier years, today had a different diagnoses. This can cause a bias instrument, altering the outcome of the study.

In addition, it has not been possible to obtain information about the stages of the lymphomas, because very few cases were registered in the CRG. If this information had been obtained, it would have been possible to study the survival of lymphoma by stage, but that required more time than possible to review each case in the pathology laboratory.

Finally, it has not been possible to obtain information on risk factors either, especially about HIV and EBV infections, that are the most relevant ones. It could have been possible to review every medical record of patients, but again, there was not the necessary time that this task required.

## **11.- SCHEDULE**

The process of this work began on September 19<sup>th</sup> 2016 and ended on October 30<sup>th</sup> 2016. The steps, according to weeks, were as follows:

- September 19<sup>th</sup> – September 25<sup>th</sup>: Meetings with CRG and the pathology laboratory of Dr. Josep Trueta University Hospital of Girona to clarify all the objectives aimed by the study.
- September 26<sup>th</sup> – October 2<sup>nd</sup>: Bibliographic research and training at CRG about how it works and how to perform statistical analysis.
- October 3<sup>th</sup> – October 9<sup>th</sup>: Introduction writing.
- October 10<sup>th</sup> – October 16<sup>th</sup>: Cases selection at CRG, quality control with the medical records obtained at the pathology laboratory of Dr. Josep Trueta University Hospital of Girona and statistical analysis.
- October 17<sup>th</sup> – October 23<sup>th</sup>: Interpretation of the results of the statistical analysis and writing of the results chapter.
- October 24<sup>th</sup> - October 30<sup>th</sup>: Writing of the methodology and discussion chapters and other parts of the study.

There could be a possibility of having this study published. Dedicating an extra time on the study it would be possible to correct some of the limitations discussed above and include more variables in the study (like stage of lymphoma and HIV, EBV or other viruses infection). That would require a pathologist to review each case to obtain information about the stadium and to ensure that the diagnoses made at previous dates are correct, and a researcher should study each medical history to check for HIV and EBV infection.

The main landmarks of the study, if it is published, are described below, and a chronogram is presented next for an easy visualization of the whole process. The following sequence of activities should be carried out by the researchers:

- PHASE 1: Preparation and coordination (2 months).
  - 1.1: Protocol elaboration and evaluation by the Ethical Committee.
  - 1.2: Coordination of the research team with the statistical consultant and data manager to clarify all the objectives aimed by the study.
- PHASE 2: Data collection (3 months).
  - 2.1: Revision of each case by the pathologists, ensuring the diagnosis of older cases and obtaining data about the stage of the lymphoma.
  - 2.2: Revision of each clinical history of every patient by a researcher, in search of infection by HIV, EBV and other viruses.
  - 2.3: Creation of the database by the data manager, or updating of the existing data in the CRG.
- PHASE 3: Data analysis and final evaluation (1 month).
  - 3.1: Statistical analysis performed by the statistician.
  - 3.2: Meeting of the investigation team in order to interpret the preliminary results.
- PHASE 4: Publication and dissemination of the results (2 months).
  - 4.1: Preliminary writing of the article, presenting the results and the possible associations with the variables explained earlier.
  - 4.2: Presentation of the results in both a national and international congress.
  - 4.3: Publication of the article.

CRONOGRAM		2016				2017			
		Nov	Dec	Jan	Feb	Mar	Apr	May	Jun
Phase 1	Protocol elaboration	Researcher							
	Ethical evaluation	Committee							
	Meeting with the team to clarify the objectives		Whole team						
Phase 2	Revision of cases (ensuring and staging)			Pathologist					
	Revision of cases (HIV and EBV information)			Researcher					
	Creation/actualization of the database					Data manager			
Phase 3	Statistical analysis						Statistician		
	Interpret the preliminary results						Researcher		
Phase 4	Preliminary article writing							Researcher	
	Article writing, publication and dissemination								Researcher

## 12.- BUDGET

The development of this study has generated virtually no costs. However, the following budget is proposed in case the study is published. Costs are divided between personnel costs and dissemination of the result costs:

Personnel costs	Data manager (20 hours)	40€/hour	800€
	Statistical consultant (15 hours)	40€/hour	600€
	Training of members (3 persons)	200€/person	600€
	Revision of the cases by a pathologist (60 cases)	50€/history	3,000€
	Revision of the clinical histories by a researcher (120 cases)	50€/history	6,000€
Dissemination of the results costs	Congress (3 days)		
	- Travel (2 persons)	100€/person	3,200€
	- Accommodation (2 persons)	300€/person	
	- Registration (2 persons)	400€/person	
	Article writing		60€
	English editor	1.5€/1000 characters	90€
	Article publication to open access journal	1,500€/article	1,500€
Total amount claimed			15,850€

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**ANNEX 1:** Lymphoid neoplasms classification proposed by the WHO in 2008**1. B-Cell neoplasms****1.1. Precursor B-cell neoplasm**

- 1.1.1. Precursor B-lymphoblastic leukemia/lymphoma (precursor B-cell acute lymphoblastic leukemia)

**1.2. Mature (peripheral) B-cell neoplasms**

- 1.2.1. B-cell chronic lymphocytic leukemia/small lymphocytic lymphoma
- 1.2.2. B-cell prolymphocytic leukemia
- 1.2.3. Lymphoplasmacytic lymphoma
- 1.2.4. Splenic marginal zone B-cell lymphoma (+/- villous lymphocytes)
- 1.2.5. Hairy cell leukemia
- 1.2.6. Plasma cell myeloma/plasmacytoma
- 1.2.7. Extranodal marginal zone B-cell lymphoma of MALT type
- 1.2.8. Nodal marginal zone B-cell lymphoma (+/- monocytoid B cells)
- 1.2.9. Follicular lymphoma
- 1.2.10. Mantle-cell lymphoma
- 1.2.11. Diffuse large B-cell lymphoma
- 1.2.12. Mediastinal large B-cell lymphoma
- 1.2.13. Primary effusion lymphoma
- 1.2.14. Burkitt's lymphoma/Burkitt cell leukemia

**2. T-cell and NK-cell neoplasms****2.1. Precursor T-cell neoplasm**

- 2.1.1. Precursor T-lymphoblastic lymphoma/leukemia (precursor T-cell acute lymphoblastic leukemia)

**2.2. Mature (peripheral) T-cell neoplasms**

- 2.2.1. T-cell prolymphocytic leukemia
- 2.2.2. T-cell granular lymphocytic leukemia
- 2.2.3. Aggressive NK-cell leukemia
- 2.2.4. Adult T-cell lymphoma/leukemia (HTLV1+)



- 2.2.5. Extranodal NK/T-cell lymphoma, nasal type
- 2.2.6. Enteropathy-type T-cell lymphoma
- 2.2.7. Hepatosplenic gamma-delta T-cell lymphoma
- 2.2.8. Subcutaneous panniculitis-like T-cell lymphoma
- 2.2.9. Mycosis fungoides/Sezary syndrome
- 2.2.10. Anaplastic large-cell lymphoma, T/null cell, primary cutaneous type
- 2.2.11. Peripheral T-cell lymphoma, not otherwise characterized
- 2.2.12. Angioimmunoblastic T-cell lymphoma
- 2.2.13. Anaplastic large-cell lymphoma, T/null cell, primary systemic type

### **3. Hodgkin's lymphoma (Hodgkin's disease)**

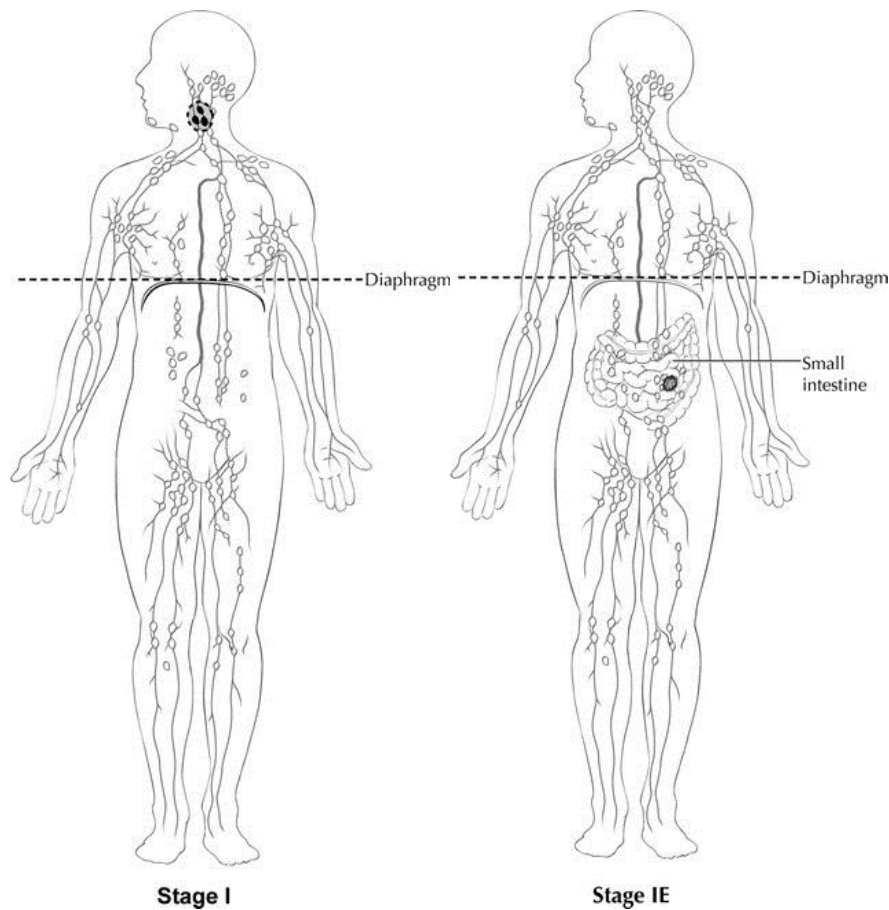
#### **3.1. Nodular lymphocyte-predominant Hodgkin's lymphoma**

#### **3.2. Classical Hodgkin's lymphoma**

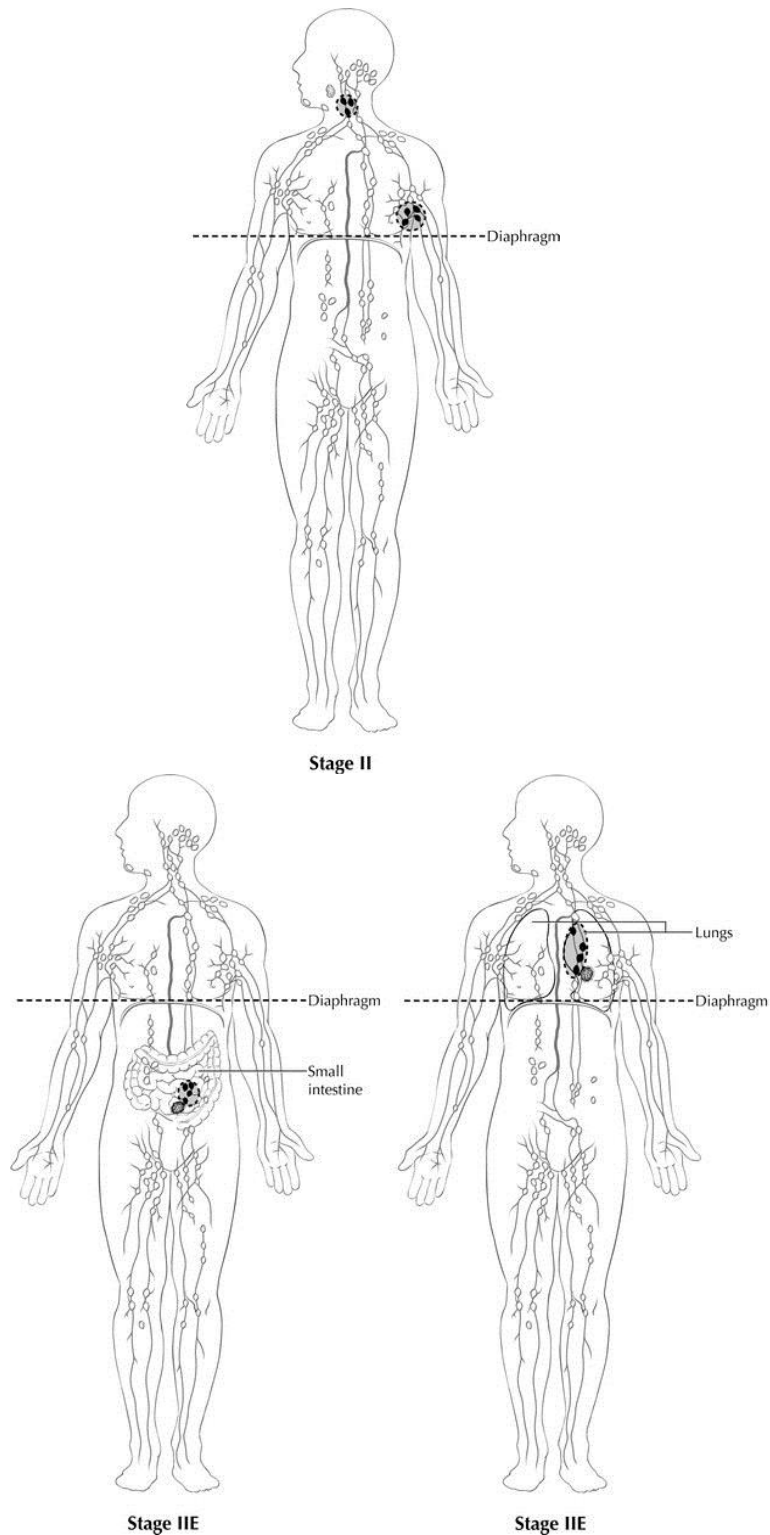
- 3.2.1. Nodular sclerosis Hodgkin's lymphoma (grades 1 and 2)
- 3.2.2. Lymphocyte-rich classical Hodgkin's lymphoma
- 3.2.3. Mixed cellularity Hodgkin's lymphoma
- 3.2.4. Lymphocyte depletion Hodgkin's lymphoma

**ANNEX 2:** Ann Arbor staging system for lymphomas

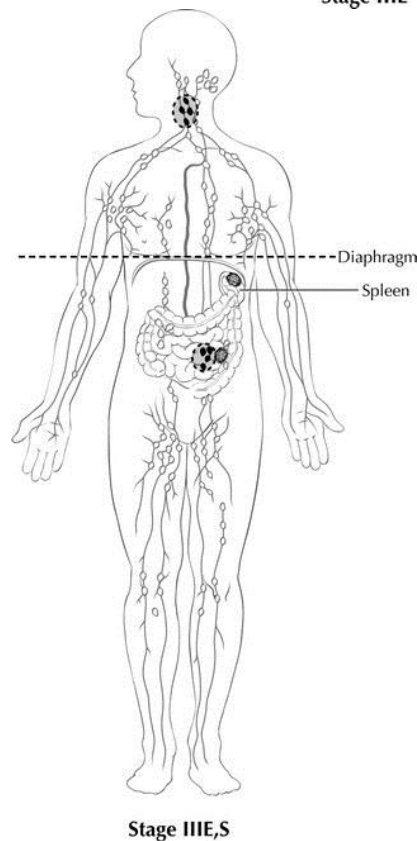
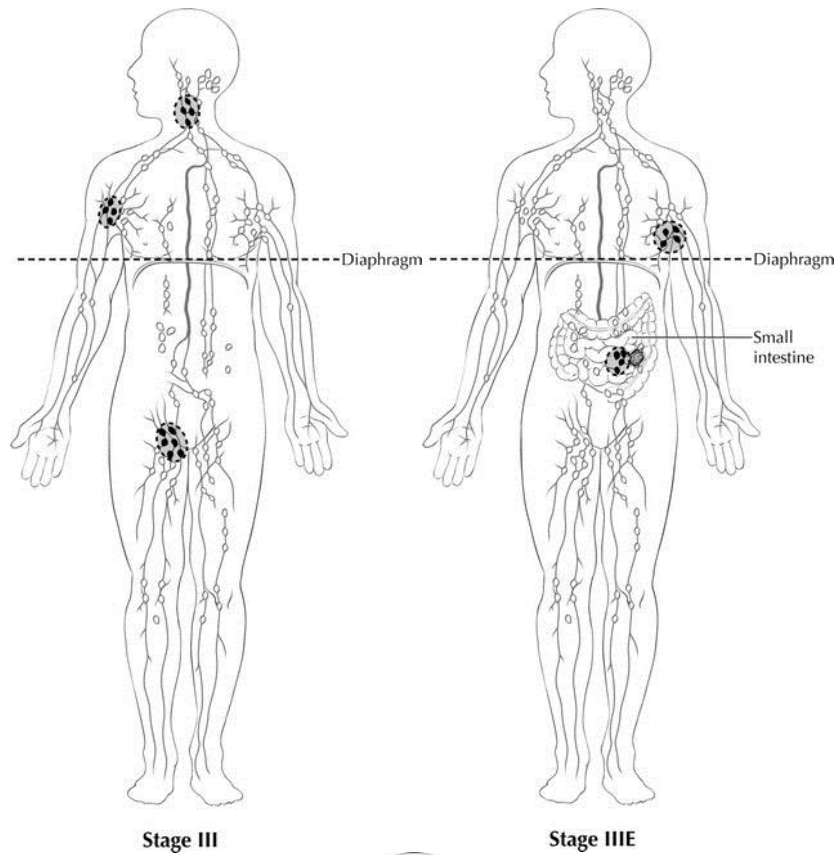
- **I:** Involvement of a single lymphatic site (i.e. nodal region, Waldeyer's ring, thymus or spleen) (I); or localized involvement of a single extralymphatic organ or site in the absence of any lymph node involvement (IE) (rare in Hodgkin lymphoma).



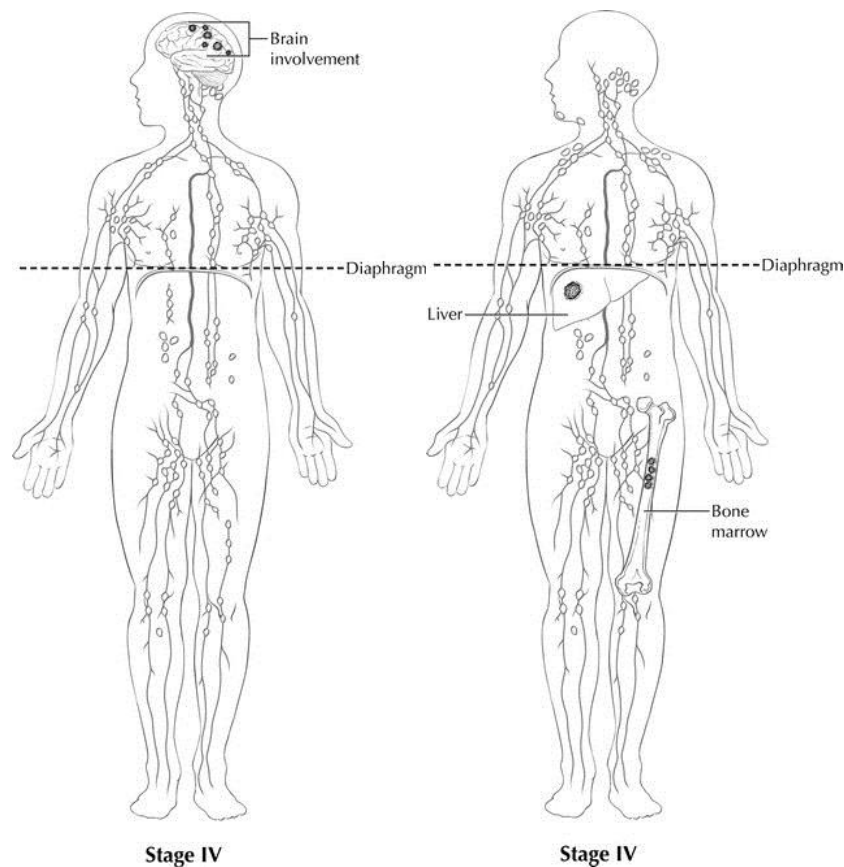
- **II:** Involvement of two or more lymph node regions on the same side of the diaphragm (II); or localized involvement of a single extralymphatic organ or site in association with regional lymph node involvement with or without involvement of other lymph node regions on the same side of the diaphragm (IIE). The number of regions involved may be indicated by a subscript, as in, for example, II3.



- **III:** Involvement of lymph node regions on both sides of the diaphragm (III), which may also be accompanied by extralymphatic extension in association with adjacent lymph node involvement (IIIE) or by involvement of the spleen (IIIS) or both (IIIE,S).



- **IV:** Diffuse or disseminated involvement of one or more extralymphatic organs, with or without associated lymph node involvement; or isolated extralymphatic organ involvement in the absence of adjacent regional lymph node involvement, but in conjunction with disease in distant site(s). Stage IV includes any involvement of the liver or bone marrow, lungs (other than by direct extension from another site), or cerebrospinal fluid.



Some letters can have to be appended to some stages, modifying them:

- A or B: the absence of constitutional (B-type) symptoms is denoted by adding an "A" to the stage; the presence is denoted by adding a "B" to the stage.
- S: is used if the disease has spread to the spleen.
- E: is used if the disease is "extranodal" (not in the lymph nodes) or has spread from lymph nodes to adjacent tissue.
- X: is used if the largest deposit is >10 cm large ("bulky disease"), or in case the mediastinum is wider than  $\frac{1}{3}$  of the chest on a chest X-ray.

The term “lymph node region” refers to a group of lymph nodes found in different parts of the body. The currently accepted classification of core nodal region is as follows(13):

- Cervical (including cervical, supraclavicular, occipital and periauricular) lymph nodes.
- Axillary lymph nodes.
- Infraclavicular lymph nodes.
- Mediastinal lymph nodes.
- Hilar lymph nodes.
- Para-aortic lymph nodes.
- Mesenteric lymph nodes.
- Pelvic lymph nodes.
- Inguinofemoral lymph nodes.
- Epitrochlear lymph nodes (only in NHL).
- Popliteal lymph nodes (only in NHL).
- Internal mammary lymph nodes (only in NHL).
- Occipital lymph nodes (only in NHL).
- Submental lymph nodes (only in NHL).
- Preauricular lymph nodes (only in NHL).

**ANNEX 3:** Lymphoma morphological codes and head and neck topographic codes according to ICD-O-3

Lymphoma morphological codes:

- **959 MALIGNANT LYMPHOMAS, NOS OR DIFFUSE**
  - 9590/3 Malignant lymphoma, NOS
  - 9591/3 Malignant lymphoma, non-Hodgkin, NOS
  - 9596/3 Composite Hodgkin and non- Hodgkin lymphoma
  - 9597/3 Primary cutaneous follicle centre lymphoma
- **965-966 HODGKIN LYMPHOMA**
  - 9650/3 Hodgkin lymphoma, NOS
  - 9651/3 Hodgkin lymphoma, lymphocyte-rich
  - 9652/3 Hodgkin lymphoma, mixed cellularity, NOS
  - 9653/3 Hodgkin lymphoma, lymphocyte depletion, NOS
  - 9654/3 Hodgkin lymphoma, lymphocyte depletion, diffuse
  - 9655/3 Hodgkin lymphoma, lymphocyte depletion, reticular
  - 9659/3 Hodgkin lymphoma, nodular lymphocyte predominance
  - 9661/3 Hodgkin granuloma
  - 9662/3 Hodgkin sarcoma
  - 9663/3 Hodgkin lymphoma, nodular sclerosis, NOS
  - 9664/3 Hodgkin lymphoma, nodular sclerosis, cellular phase
  - 9665/3 Hodgkin lymphoma, nodular sclerosis, grade 1
  - 9667/3 Hodgkin lymphoma, nodular sclerosis, grade 2
- **967-969 MATURE B-CELL LYMPHOMAS**
  - 9670/3 Malignant lymphoma, small B lymphocytic, NOS
  - 9671/3 Malignant lymphoma, lymphoplasmacytic
  - 9673/3 Mantle cell lymphoma
  - 9675/3 Malignant lymphoma, mixed small and large cell, diffuse
  - 9678/3 Primary effusion lymphoma
  - 9679/3 Mediastinal large B-cell lymphoma
  - 9680/3 Malignant lymphoma, large B-cell, diffuse, NOS
  - 9684/3 Malignant lymphoma, large B-cell, diffuse, immunoblastic, NOS
  - 9687/3 Burkitt lymphoma, NOS
  - 9688/3 T-cell/histiocyte rich large B-cell lymphoma
  - 9689/3 Splenic marginal zone B-cell lymphoma
  - 9690/3 Follicular lymphoma, NOS
  - 9691/3 Follicular lymphoma, grade 2
  - 9695/3 Follicular lymphoma, grade 1
  - 9698/3 Follicular lymphoma, grade 3
  - 9699/3 Marginal zone B-cell lymphoma, NOS

- **970-971 MATURE T- AND NK-CELL LYMPHOMAS**

- 9700/3 Mycosis fungoides
- 9701/3 Sezary syndrome
- 9702/3 Mature T-cell lymphoma, NOS
- 9705/3 Angioimmunoblastic T-cell lymphoma
- 9708/3 Subcutaneous panniculitis- like T-cell lymphoma
- 9709/3 Cutaneous T-cell lymphoma, NOS
- 9712/3 Intravascular large B-cell lymphoma
- 9714/3 Anaplastic large cell lymphoma, T cell and Null cell type
- 9716/3 Hepatosplenic T-cell lymphoma
- 9717/3 Intestinal T-cell lymphoma

- 9718/3 Primary cutaneous CD30+ T-cell lymphoproliferative disorder
- 9719/3 NK/T-cell lymphoma, nasal and nasal-type

- **972 PRECURSOR CELL LYMPHOBLASTIC LYMPHOMA**

- 9724/3 Systemic EBV positive T-cell lymphoproliferative disease of childhood
- 9725/3 Hydroa vacciniforme-like lymphoma
- 9726/3 Primary cutaneous gamma- delta T-cell lymphoma
- 9727/3 Precursor cell lymphoblastic lymphoma, NOS
- 9728/3 Precursor B-cell lymphoblastic lymphoma
- 9729/3 Precursor T-cell lymphoblastic lymphoma

Head and neck topographic codes:

- **C00 LIP**

- C00.0 External upper lip
- C00.1 External lower lip
- C00.2 External lip, NOS
- C00.3 Mucosa of upper lip
- C00.4 Mucosa of lower lip
- C00.5 Mucosa of lip, NOS
- C00.6 Commissure of lip
- C00.8 Overlapping lesion of lip
- C00.9 Lip, NOS

- **C01 BASE OF TONGUE**

- C01.9 Base of tongue, NOS

- **C02 OTHER AND UNSPECIFIED PARTS OF TONGUE**

- C02.0 Dorsal surface of tongue, NOS
- C02.1 Border of tongue
- C02.2 Ventral surface of tongue, NOS
- C02.3 Anterior 2/3 of tongue, NOS
- C02.4 Lingual tonsil
- C02.8 Overlapping lesion of tongue
- C02.9 Tongue, NOS



- **C03 GUM**
  - C03.0 Upper gum
  - C03.1 Lower gum a
  - C03.9 Gum, NOS
- **C04 FLOOR OF MOUTH**
  - C04.0 Anterior floor of mouth
  - C04.1 Lateral floor of mouth
  - C04.8 Overlapping lesion of floor of mouth
  - C04.9 Floor of mouth, NOS
- **C05 PALATE**
  - C05.0 Hard palate
  - C05.1 Soft palate, NOS
  - C05.2 Uvula
  - C05.8 Overlapping lesion of palate
  - C05.9 Palate, NOS
- **C06 OTHER AND UNSPECIFIED PARTS OF MOUTH**
  - C06.0 Cheek mucosa
  - C06.1 Vestibule of mouth
  - C06.2 Retromolar area
  - C06.8 Overlapping lesion of other and unspecified parts of mouth
  - C06.9 Mouth, NOS
- **C07 PAROTID GLAND**
  - C07.9 Parotid gland
- **C08 OTHER AND UNSPECIFIED MAJOR SALIVARY GLANDS**
  - C08.0 Submandibular gland
  - C08.1 Sublingual gland
  - C08.8 Overlapping lesion of major salivary glands
  - C08.9 Major salivary gland, NOS
- **C09 TONSIL**
  - C09.0 Tonsillar fossa
  - C09.1 Tonsillar pillar
  - C09.8 Overlapping lesion of tonsil
  - C09.9 Tonsil, NOS
- **C10 OROPHARYNX**
  - C10.0 Vallecula
  - C10.1 Anterior surface of epiglottis
  - C10.2 Lateral wall of oropharynx
  - C10.3 Posterior wall of oropharynx
  - C10.4 Branchial cleft
  - C10.8 Overlapping lesion of oropharynx
  - C10.9 Oropharynx, NOS
- **C11 NASOPHARYNX**
  - C11.0 Superior wall of nasopharynx
  - C11.1 Posterior wall of nasopharynx
  - C11.2 Lateral wall of nasopharynx
  - C11.3 Anterior wall of nasopharynx
  - C11.8 Overlapping lesion of nasopharynx
  - C11.9 Nasopharynx, NOS
- **C12 PYRIFORM SINUS**
  - C12.9 Pyriform sinus
- **C13 HYPOPHARYNX**
  - C13.0 Postcricoid region
  - C13.1 Hypopharyngeal aspect of aryepiglottic fold
  - C13.2 Posterior wall of hypopharynx

- C13.8 Overlapping lesion of hypopharynx
- C13.9 Hypopharynx, NOS
- C14 OTHER AND ILL-DEFINED SITES IN LIP, ORAL CAVITY AND PHARYNX
- C14.0 Pharynx, NOS
- C14.2 Waldeyer ring
- C14.8 Overlapping lesion of lip, oral cavity and pharynx
- **C30 NASAL CAVITY AND MIDDLE EAR**
  - C30.0 Nasal cavity
  - C30.1 Middle ear
- **C31 ACCESSORY SINUSES**
  - C31.0 Maxillary sinus
  - C31.1 Ethmoid sinus
  - C31.2 Frontal sinus
  - C31.3 Sphenoid sinus C31.8 Overlapping lesion of accessory sinuses
  - C31.9 Accessory sinus, NOS
- **C32 LARYNX**
  - C32.0 Glottis
  - C32.1 Supraglottis
  - C32.2 Subglottis
  - C32.3 Laryngeal cartilage
  - C32.8 Overlapping lesion of larynx
  - C32.9 Larynx, NOS