PhD THESIS ABSTRACT

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ORAL AND MAXILLOFACIAL LYMPHOMAS

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2016
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KEY WORDS:

This doctoral thesis comprises 224 pages, being illustrated by numerous figures (144) and tables (163). Documentation is made based on a deep study of 551 bibliographical references.

The Abstract includes a limited number of figures and tables, maintaining the same numbering and table of contents of the Thesis.
Introduction

Lymphomas are considered, in terms of frequency, as the second neoplasia found at the level of the oral and maxillofacial territory after carcinomas. They are lymphoid malignancies with unpredictable variations from morphological, clinical evolution, therapeutic response and prognosis point of view, with a strong impact on patients` survival.

Lymphomas represent the most common haematological malignancy that covers the head and neck regions, in most cases the damage being not limited only to this anatomic area, but involving also a disseminated tumour process, with multiple locations at the level of the body.

The two main categories are the Hodgkin Lymphoma and Non-Hodgkin`s Lymphoma. In most of the cases, the Hodgkin Lymphomas have nodal location, affecting mainly the laterocervical ganglia. Non-Hodgkin`s Lymphomas are more frequent, presenting an extranodal location in 40% of cases. The most frequent sub-type of lymphoma covering the oral and maxillofacial territory is the Diffuse Large B-Cell Lymphoma - DLBCL (Vega et al. 2005).

Due to their complexity and multitude of histopathological subtypes, the classification of lymphomas has been a real challenge. The classifications proposed in the area are numerous, the international consensus being achieved when the World Health Organization has completed and published the Lymphoid Tumours Classification, the 4th edition.

Clinically, lymphomas have the same symptoms and signs as the malignant oral-maxillofacial tumours from various locations (oral cavity, oropharynx, paranasal sinuses, salivary glands, head and neck chains of ganglia, cervico-facial teguments), the differential diagnosis being often pretty difficult.

Certain diagnosis is established after anatomopathological examination, the biopsy being the essential gesture of the oral and
maxillofacial surgeon who faces the lymphoma diagnosis suspicion. The specification of the proliferating cell origin (T or B cell, with their sub-populations), by using the immunophenotyping analysis and subsequent to the antigenic profile obtained will help us to figure out the subtype of lymphoma.

Staging of the disease requires both clinical, biological and imaging evaluation. Ann Arbor system, which has firstly been introduced for the Hodgkin Lymphoma and subsequently for Non-Hodgkin`s Lymphoma, is the most widely used staging system.

Treatment of lymphomas of the oral & maxillofacial territory is of multidisciplinary nature, and in most of the cases non-surgical, the surgeon`s role being more active in the diagnostic stage. The aim of treatment is to achieve complete remission of the disease through the application of therapeutic protocols and by using immunotherapy, radiotherapy and surgery treatment.

The Doctoral research comprises two studies: the first study is conducted over a period of 5 years on patients with lymphomas, diagnosed in the Oral & Maxillofacial Surgery Iasi, and a second study is conducted exclusively on patients with parotid lymphoma, diagnosed and treated over a period of 65 for years.

The objectives of the first study aim to determining: the clinico-epidemiological specific features and histopathological profile of lymphomas with oral & maxillofacial localization, the prognostic value of Ki-67 antigen in Non-Hodgkin`s Lymphomas and also evaluation of the multimodal therapy used, particularly the role of surgical intervention performed.

The second study that has been conducted exclusively on patients with parotid lymphomas aims to figure out the clinico-epidemiological and histopathological profile of the parotid gland lymphomas, the most common subtypes present at this level, and to analyze the tumour formation location in the architecture of parotid gland correlated both with the type of parotidectomy practiced and the postoperative facial nerve disorders.
OWN ORIGINAL CONTRIBUTIONS

Chapter 3
Reasoning and Objectives of the Study

Lymphomas are the most common haematological malignancy, representing 3% of all malignancies and 5% of head and neck neoplasia, respectively. (Marcus, Sweetenham and Williams 2014) (Hermans 2006). About 25% of extranodal lymphomas affect head and neck regions (Harris and Weisman 2007), representing, in terms of frequency, the second location after the gastrointestinal one. (Vega et al. 2005). Lymphomas constitute a heterogeneous group of neoplasia, being, after carcinomas, the most frequent malignant disease at the level of the oral & maxillofacial territory. (Guevara-Canales et al. 2011)

The epidemiological data highlight the importance of lymphomas in oral and maxillofacial pathology, given their increasing incidence, especially in developed countries (Zapater et al. 2010), (Razmpa and Saed 2009).

The pathological, clinical and evolutionary characteristics, together with immunosuppression, various infectious agents or with autoimmune diseases reveal the complexity of lymphomas in terms of diagnosis and therapeutic approach. Moreover, the diagnosis of extranodal lymphomas involves differences in prognosis and therapeutic management compared to the nodal locations (Thakral, et al. 2015).

Due to the anatomical complexity of the oral & maxillofacial territory, it is most likely to find both common and rare cancers affecting all cell lines, and therefore the differential diagnosis of lymphoma becomes a challenge that proves to be extremely difficult.
Lymphomas Localized in the Oral & Maxillofacial Territory

Also, we must bear in mind that in some cases due to diagnostic errors, lymphomas may rapidly evolving towards mortality. Early diagnosis is essential in all cases.

In the management of lymphomas, the oral and maxillofacial surgeon is involved especially in the first two stages of the four: recognition, diagnosis, staging and treatment (Marx and Stern 2012). It is therefore important that in case of lymphoma diagnosis suspicion, the oral and maxillo-facial surgeon should provide, following the biopsy, a correct and necessary tissue material to the anatomopathologist in order to establish the diagnosis of certainty (Zapater et al. 2010). In particular cases with unique nodal or extranodal tumour location, the excisional biopsy is the method of choice for sampling tissue material, and thus the oral and maxillo-facial surgeon contributes to diagnosis and even to the treatment of lymphomas, although in the vast majority of cases, the treatment is non-surgical. After the treatment application, the surgeon plays an essential role in the periodic assessment of patients for early diagnosis of possible recurrence.

The surgeon may intervene as well, in the management of lymphomas treatment complications arising in the oral and maxillofacial territory, such as: stomatitis, xerostomia (dry mouth) or post-radiotherapy oral thrush, drug-induced avascular necrosis or osteoradionecrosis of the jaw bones (Marx and Stern 2012).

Management of lymphomas with location in the oral and maxillofacial territory involves a multidisciplinary team, consisting of a surgeon, anatomopathologist, hematologist, oncologist and radiotherapist. The success of collaboration between the oral and maxillofacial surgeon and the other specialists depends on both knowledge of this pathology and awareness of his/her essential role in the recognition and early diagnosis of the disease, often by taking biopsy material.

Lymphomas with location in the oral and maxillofacial territory are an important component of the oral and maxillofacial pathology, with an increasing incidence and multiple clinical presentations, having a variable evolving and requiring multimodal
Lymphomas Localized in the Oral & Maxillofacial Territory

Treatment. Under these circumstances, lymphomas represent a pathology of real interest for the oral and maxillofacial surgeon, which is actively involved in the various stages of the patient`s multidisciplinary management.

The objectives of the Doctoral Study are as follows:

- figuring out the epidemiological features of the lymphomas localized in the oral and maxillo-facial territory;
- ascertaining the clinical and morphological profiling of cervicofacial lymphomas;
- highlighting the histopathological subtypes and immunohistochemical profile of lymphomas with oral and maxillofacial location;
- determining the prognostic value of antigen Ki-67 in Non-Hodgkin`s cervicofacial lymphomas;
- figuring out the clinical and morphological profiling of parotid lymphomas and evaluation of the surgical treatment outcome;
- assessing the outcomes of multimodal treatment and the rate of survival in lymphomas localized in the oral and maxillofacial territory.
Chapter 4
Clinical and Morphological Features of Lymphomas Localized in the Oral & Maxillofacial Territory. Retrospective Analysis (2010-2014)

4.1 Introduction

The incidence of lymphomas is in a continuous growth in the last four decades (Razmpa and Saed 2009), becoming an important component of the oro-maxillo-facial tumor pathology.

Non-Hodgkin`s lymphomas are the most frequent, accounting for about 75% of the lymphomas located in the oro-maxillo-facial territory (Boring, et al. 1994). Extranodal localization of Hodgkin lymphoma is very rare (Kobler and Borce 2005). 23% of Non-Hodgkin's lymphomas and only 4% of Hodgkin lymphomas from head and neck are extranodal (Picard et al. 2015).

Lymphomas of the oro-maxillo-facial territory form a heterogeneous group of malignant tumors with various histological subtypes and multiple clinical presentations. Diagnostic errors occur when clinical manifestations and/or imaging appear in the form of epithelial neoplasia or infections, and in such cases the diagnosis of lymphoma should also be considered because it requires specific treatment (Picard et al. 2015).

4.2. The Purpose of the Study

The aim of this study is to assess the clinico-epidemiological and morphological features of the lymphomas located in the oro-maxillo-facial territory, including the research of histopathological forms involved and anatomical sites affected. It has also been analyzed their progress and response to treatment, as well as the patients` rate of survival.
4.3. Material and Method

The clinico-statistical retrospective study of the cervicofacial lymphomas has been conducted within the Department of Oral and Maxillofacial Surgery – “Sf. Spiridon” Iasi County Emergency Clinical Hospital and the Department of Hematology – Iasi Regional Oncology Institute, for a period of 5 years (from 2010 to 2014), analyzing the data recorded in the Patient Observation Recording Sheet and the Patient Anatomopathological Analysis Reports for the inpatients diagnosed initially in Department of Oral and Maxillofacial Surgery.

In the group of patients under study, there is a single case diagnosed with classic Hodgkin lymphoma of nodular sclerosis type - Grade II, the rest of lymphomas being Non-Hodgkin`s lymphomas. In order to obtain statistical relevance, the Hodgkin lymphoma case is excluded from the statistical analysis.

Subsequently, the patients were looked after at the Department of Hematology – Iasi Regional Oncology Institute, their response being assessed as positive (complete or partial disease remission) or negative (no response to treatment, fast evolving disease).

4.4 Outcomes

In the period 2010-2014 in the Clinic of Oral and Maxillofacial Surgery Iasi were hospitalized and diagnosed a total of 47 patients with lymphoma presenting a cervicofacial tumoral location. 46 of the cases were Non-Hodgkin`s lymphomas with various subtypes and a single case diagnosed with classic Hodgkin lymphoma of nodular sclerosis type - Grade II (mentioned previously as excluded from the statistical analysis) (Fig. 4.1, 4.2).
Out of the group of 46 patients diagnosed with Non-Hodgkin lymphomas, 27 are males and 19 females, the ratio men/women amounting to a value of 1.42 (Fig. 4.3, 4.4).

Most cases of Non-Hodgkin lymphomas are diagnosed in patients between the ages of 70-79 years, namely a number of 21 patients (Fig. 4.7)
Lymphomas Localized in the Oral & Maxillofacial Territory

Out of those 46 Non-Hodgkin’s lymphomas, 26 are Diffuse Large B-cell Lymphomas (the most of the cases), accounting for 56.5% of the cases. (Fig. 4.9)

The majority of patients are in Ann Arbor stage IV of disease, constituting a total of 21 cases which represents 45.7% of all Non-Hodgkin’s lymphomas (Fig 4.11).

Out of those 46 Non-Hodgkin’s lymphomas, a number of 24 have extranodal location, representing 52.2% of the cases, while 22 have nodal location (Fig. 4.14). The case of Hodgkin lymphoma has classic nodal localization.
The multimodal treatment administered to those 46 patients with Non-Hodgkin’s lymphomas consists of chemotherapy, radiotherapy, surgical therapy, which has been applied as a single therapy method or a combination thereof. Chemotherapy is the most used therapeutic method, applied in the treatment of 33 patients (both single and in combination with the radiotherapy and/or surgery treatment) (Figure 4.15).

Response to treatment: favorable in 21 patients with Non-Hodgkin`s lymphoma; partial remission in 19 cases, and complete remission of the disease in 2 cases (Fig. 4.17).
Upon completion of the study, a number of 23 patients diagnosed with Non-Hodgkin`s lymphomas died, representing 50% of the cases.

Extranodal Non-Hodgkin`s lymphomas are mostly Diffuse Large B-cell Lymphomas, representing 58.3% of the cases (Fig. 4.25).
Extranodal locations of lymphomas in the oro-maxillo-facial territory are as follows: most of the cases of such lymphomas are located at the parotid gland level, namely 10 (ten), then, 5 (five) cases of such lymphomas are located at the jaw and palate level. Cervicofacial teguments are affected in 4 (four) cases, while 2 (two) patients have tumor lesions at the level of mandibular gingival fibro mucosa.
Lymphomas Localized in the Oral & Maxillofacial Territory

Out of the 24 patients with extranodal non-Hodgkin's lymphoma, a number of 11 persons have survived, representing 45.8% of the cases. (Figure 4.31)

![Fig 4.31 – Decease Ratio in Extranodal Non-Hodgkin’s Lymphomas Patients](image)

Fig. 4.31 – Decease Ratio in Extranodal Non-Hodgkin’s Lymphomas Patients

Altering of the ganglionar stations of the oro-maxillo-facial territory is highly variable and difficult to classify from statistical point of view, containing many variables. The most frequent anatomopathologic subtype is the Diffuse Large B-cell Lymphoma, namely in 12 of the cases (Fig. 4.36).

![Figura 4.36 – Subtypes of Nodal Non-Hodgkin’s Lymphomas in OMF Territory](image)

Figura 4.36 – Subtypes of Nodal Non-Hodgkin’s Lymphomas in OMF Territory
Out of those 22 patients with nodal Non-Hodgkin`s lymphoma, a number of 10 persons died, while survival ratio rises up to 54.5%.

4.5. Discussions

A very frequent location of nodal and extranodal lymphomas is the head and neck region. While nodal lymphomas show same characteristics with the lymphoganglionar lymphomas, having any systemic location, the extranodal lymphomas of the oro-maxillo-facial territory show specific characteristics. (Thakral, et al. 2015)

Boring et al report that Hodgkin lymphomas represent up to 25% of the head and neck lymphomas, while non-Hodgkin`s lymphomas represent more than 70% thereof. (Boring, et al. 1994)

In our study, we have a single case of nodal Hodgkin lymphoma, which by reference to the total number of cases it is consistent with the literature data. Non-Hodgkin lymphomas are the vast majority in this study. Extranodal forms are in a higher ratio but consistent with the data reported in the literature, accounting for over 50% of the cases.

Etemad-Moghadam et al. reports that the most common location of extranodal Non-Hodgkin`s lymphomas following Waldayer ring is the salivary gland (Etemad-Moghadam, Tirgary, et al. 2010). In our study, the most common location of extranodal Non-Hodgkin`s lymphomas is at the level of the parotid glands.

Scherfler et al reports that 69% of the patients with head and neck lymphomas showed a disseminated disease with multiple locations (Scherfler et al. 2012). These data are consistent with the data obtained in the own study, most of the patients (namely 68% of the cases) being diagnosed in stage III and IV of the disease (predominantly in stage IV).

The use of chemotherapy, preferably in combination with radiotherapy, represents the treatment of choice for patients with head and neck lymphomas (Guevara-Canales et al. 2011).
In our study, the current therapeutic method applied is chemotherapy, due to the high number of patients in an advanced stage disease. The surgical treatment has been used in combination (or not) with chemotherapy in a relatively high number of cases. Although, in our study, the most cases presented are in stage IV of the disease, it has been achieved a favorable response to treatment in 46% of the cases. Patients’ survival assessment is made one year later (after the end of the review period), namely in 2015, and the outcome shows a survival rate of 50%.

4.6. Conclusions

Oro-maxillo-facial lymphomas are in 98% of the cases Non-Hodgkin`s lymphomas.

In 50% of the cases they are of extranodal forms, diagnosed in advanced stages of disease (Ann Arbor stage III and IV).

The most common histopathological subtype in oro-maxillo-facial territory is the Diffuse Large B-cell Lymphoma (DLBCL), representing 56% of the total number of cases.

The most frequent extranodal location is the parotid gland, followed, in terms of frequency, by the jaws and palate.

The most common method of treatment is chemotherapy in combination with surgical treatment or radiotherapy.

Surgical treatment is used as a single therapy method or in combination with chemotherapy and/or radiotherapy.

In the most cases of oro-maxillo-facial lymphomas, the response to treatment proves to be unfavorable. Patients’ death is recorded in 50% of the cases.
Chapter 5
Anatomopathological Study of Lymphomas Localized in the Oral & Maxillofacial Territory. Retrospective Analysis (2010-2014)

5.1 Introduction

The histological examination made using standard hematoxylin eosin staining may reveal abnormal lymphoid architecture and presence of atypical lymphoid cells in the tumoral tissue. Complementary examinations of immunohistochemistry, flow cytometry or cytogenetic and molecular studies provide important diagnostic information. Immunohistochemical assays and flow cytometry determine the origin of lymphoid infiltrate cell line and also detect the presence of monoclonal populations. Marked dominance of B or T cells will determine the subtype of Non-Hodgkin’s lymphoma, namely B or T cells subtype (Lam 2013).

The anatomopathological examination provides, besides its fundamental role in establishing the diagnosis of certainty, important data related to prognosis (Schultz and Ersbøll 1989). Thus, lymphomas can be classified according to the degree of malignancy and the patients may be assigned to a particular group of prognostic, taking advantage of an optimal multimodal treatment (Ekström Smedby-2006).

5.2. The Purpose of the Study

The purpose of the study: making the anatomopathological profile of oro-maxillo-facial lymphomas, setting the subtypes of lymphomas occured at both nodal and extranodal sites, and also determining how the pathological form of lymphoma has influenced the disease stage, response to treatment and patients’ survival.
5.3. Material and Method
The study is conducted on a sample of 47 patients diagnosed with oro-maxillofacial lymphomas, and hospitalized between 2010-2014 in the Department of Oral and Maxillofacial Surgery Iasi.

All the patients in the study experienced complete anatomopathological diagnostic including immunohistochemistry tests. For each patient we recorded data on age, sex, tumor location, histopathological subtype, disease stage, treatment, therapeutic response and survival.

5.4. Outcomes
Out of the 46 Non-Hodgkin`s lymphomas localized in the oro-maxillo-facial territory, 24 of them have extranodal and 22 nodal location.

We have identified a number of 7 (seven) subtypes of Non-Hodgkin`s lymphoma in the patients under study, namely: Diffuse Large B-cell Lymphoma, Follicular Lymphoma, Mantle Cell Lymphoma, Marginal Zone Lymphoma, Lymphocytic Lymphoma, Plasmablastic Lymphoma and NOS Lymphoma (Lymphoma Not Otherwise Specified)

Diffuse Large B-cell Lymphoma is the most frequent subtype of Non-Hodgkin`s lymphoma, both in nodal and extranodal sites, namely 56,5% (fig 5.2).

Figura 5.2 – Subtypes of Non-Hodgkin`s Lymphomas located in OMF Territory
Lymphomas Localized in the Oral & Maxillofacial Territory

Those 24 extranodal lymphomas are localized at the level of cervicofacial tegments, jaws sinuses, parotid gland, orbits, jaw/palate, mandible (gingival fibromucosa) and oral floor (Figure 5.3).

![Figure 5.3 – Distribution of the Subtypes of Extranodal Non-Hodgkin’s Lymphomas based on the location of the tumour in the OMF Territory](image)

The immunohistochemical profile of those 26 Diffuse Large B-cell Lymphomas is presented in table 5.1.

**Table 5.1 – Immunohistochemical Profile of Diffuse Large B-cell Lymphomas**

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<tbody>
<tr>
<td>1</td>
<td>CD20+,BCL6 +, ki67+, CD3-,CD10-</td>
</tr>
<tr>
<td>2</td>
<td>CD 0+,BCL6 +, ki67+, CD3-,CD10-</td>
</tr>
<tr>
<td>3</td>
<td>CD20+,BCL6 +, ki67+, CD5-,CD10+,CD6+,BCL2-</td>
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<td>4</td>
<td>CD45+,CD20+,ki67+,BCL6+, CD3-,Vimentin-,AE1/AE3+</td>
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<td>CD20+,CD3+, CD5+,CD23-, CyclinaD1-,Ki67+</td>
</tr>
<tr>
<td>8</td>
<td>CD20+,CD3+,BCL6+,AE1/AE3-, S100,-Ki67+</td>
</tr>
<tr>
<td>9</td>
<td>CD20+, BCL6+,AE1/AE3-,CD3-,CD10,-ki67+</td>
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<td>AE1/AE3-,CD20+,CD3-,BCL6+,CD10,-Ki67+</td>
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<td>11</td>
<td>CD20+,BCL6 +, ki67+, CD3-,CD10-</td>
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<td>CD20+,CD3+,AE1/AE3-, HMB45-,LCA+,Ki67+</td>
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<td>14</td>
<td>CD20+,CD3-,CD5-,BCL6+,ALK1-, ki67+</td>
</tr>
<tr>
<td>15</td>
<td>CD20+,CD3-,BCL6+,AE1/AE3-, ki67+</td>
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Lymphomas Localized in the Oral & Maxillofacial Territory

<table>
<thead>
<tr>
<th></th>
<th>CD20+, CD3-, CD10+, BCL6+, MUM 1+</th>
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<tbody>
<tr>
<td>16</td>
<td>CD20+, CD3-, Ck5-, LCA+, Ki67+</td>
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<tr>
<td>17</td>
<td>CD20+, BCL6+, CD3+, CD10-, ki67+</td>
</tr>
<tr>
<td>18</td>
<td>CD45+, CD20+, CD3-, CD5-, Ki67+</td>
</tr>
<tr>
<td>19</td>
<td>CD20+, LCA+, CD79a+, ALK1-, BCL2+, CD10-, CD5-, CD3-, CD23-, CD30+, CD15+, S100-, HMB45-, AE1/AE3-, Ck20-, Ki67+</td>
</tr>
<tr>
<td>20</td>
<td>AE1/AE3-, LCA+, Vimentin-, Desmin-, SMA-, S100-, Ck20-, Cromogranin-, Sinaptozin-, CD20+, CD3, Pax5+, Tdt-</td>
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<td>21</td>
<td>AE1/AE3-, CD20+, CD3-, ki67+</td>
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<td>CD20+, CD3-, BCL6+, Cyclina D1-, ki67+</td>
</tr>
<tr>
<td>23</td>
<td>AE1/AE3-, Synaptozifina-, S100-, SMA-, Vimentin-, Desmin-, HMB45, LCA+, CD20+, CD3+, Ki67+</td>
</tr>
<tr>
<td>24</td>
<td>CD20+, CD3-, BCL6+, Cyclina D1-, Ki67+</td>
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<tr>
<td>25</td>
<td>CD20+, CD3-, BCL6+, Cyclina D1-, Ki67+</td>
</tr>
<tr>
<td>26</td>
<td>CD20+, BCL6+, ki67+, CD3-, CD10-</td>
</tr>
</tbody>
</table>

The immunohistochemical profile of the Follicular Lymphomas is presented in table 5.II.

**Tabel 5.II – Immunohistochemical Profile of Follicular Lymphomas**

<table>
<thead>
<tr>
<th></th>
<th>CD20+, CD3+, BCL2++, CD6+, CD10+, CD23+, Cyclina D1-</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD20+, CD3-, BCL2+, CD23+, Ki67+</td>
</tr>
<tr>
<td>2</td>
<td>CD20+, CD3-, BCL2+, CD23+, Ki67+</td>
</tr>
<tr>
<td>3</td>
<td>CD20+, CD3-, CD23+, BCL2+, Ki67+</td>
</tr>
<tr>
<td>4</td>
<td>CD20+, CD10+, BCL2+, CD21-, CD3-, BCL6+, ki67+</td>
</tr>
<tr>
<td>5</td>
<td>CD20+, CD3-, BCL2+, CD23+, Ki67+</td>
</tr>
</tbody>
</table>

The single case of marginal zone lymphoma cells shows the following immunohistochemical profile: CD20+, CD79a+, CD3+, AE1/AE3-, chains K/λ >10.

The immunohistochemical profile of those 4 cases of Mantle Cell Lymphomas is presented in table 5.III.

**Tabel 5.III – Immunohistochemical Profile of Mantle Cell Lymphomas**

<table>
<thead>
<tr>
<th></th>
<th>CD20+, CD3-, CD5+, CD23-, Cyclina D1+</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD20+, CD3-, Cyclina D1+, CD5+, ki67+</td>
</tr>
<tr>
<td>2</td>
<td>CD20+, CD3-, Cyclina D1+, CD5+, ki67+</td>
</tr>
<tr>
<td>3</td>
<td>CD20+, CD3, CD5+, CD23, Cyclina D1, ki67+</td>
</tr>
<tr>
<td>4</td>
<td>CD20+, CD5+, CD23+, Cyclina D1+, Ki67+</td>
</tr>
</tbody>
</table>
The Plasmablastic lymphoma, diagnosed in a single case, shows the following immunohistochemical profile: CD20+, CD3-, CD5-, BCL6, CD30+, CD138+, vs38C+, CD79a+, AE1/AE3, ki67+.

Table 5.IV presents the immunohistochemical profile of NOS lymphomas, diagnosed in 4 cases.

<table>
<thead>
<tr>
<th></th>
<th>Immunohistochemical Profile of NOS Lymphomas</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>AE1/AE3, LCA-, CD3-, S100+, CD99-, HMB45-, ki67+</td>
</tr>
<tr>
<td>2</td>
<td>CD20+, CD3+ BCL6+, AE1/AE3-, ki67+</td>
</tr>
<tr>
<td>3</td>
<td>CD45+, CD3+, CD20+, CD10-, CD5-, CD23+, BCL2+, BCL6-, ki67+</td>
</tr>
<tr>
<td>4</td>
<td>AE1/AE3, CD68+, LCA+, CD20+, CD5, Cyclina D1, BCL6, CD10, CD23, Ki67+</td>
</tr>
</tbody>
</table>

Lymphocytic lymphoma, diagnosed in 3 cases, presents the following immunohistochemical profile. (Table 5.V)

<table>
<thead>
<tr>
<th></th>
<th>Immunohistochemical Profile of Lymphocytic Lymphomas Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CD20+, CD3-, CD5-, CD23+, Cyclina D1-, BCL2+, CD10+</td>
</tr>
<tr>
<td>2</td>
<td>CD5+, CD3+, Cyclina D1-, CD23+, BCL2+, CD20+, CD10-, Ki7+</td>
</tr>
<tr>
<td>3</td>
<td>CD20+, CD3+, CD5+, CD23+, Cyclina D1-, CD10-, CD10+, Ki67+</td>
</tr>
<tr>
<td>4</td>
<td>CD20+, CD3-, CD5+, CD23+, Cyclina D1-, BCL6-, CD10-, ki67+</td>
</tr>
<tr>
<td>5</td>
<td>CD3+, CD5+, CD10-, Cyclina D1-, CD20+, ki67+</td>
</tr>
</tbody>
</table>

Analyzing stage IV patients, we note that Diffuse Large B-cell Lymphomas are diagnosed in 66.7% of the cases. Follicular lymphomas represent 14.3% of the cases. Mantle Cell Lymphomas, NOS Lymphomas, Lymphocytic Lymphomas and Plasmablastic Lymphomas are representing each 4.8% of the cases.

Diffuse Large B-cell Lymphoma is commonly associated with stage IV of disease, while the marginal zone lymphomas are associated with stage I.

Diffuse Large B-cell Lymphomas respond unfavorable to treatment in most of the cases, while the follicular lymphoma presents a favorable therapeutic response.
We find that the deceased patients were diagnosed with Diffuse Large B-cell Lymphoma in 73.9% of the cases. Follicular lymphoma is associated with the survival of all diagnosed patients.

### Case no 1. Diffuse Large B-cell Lymphomas

Fig 5.4 - HE, x 400, proliferation with large cells with immunoblasts or centroblast morphology

Fig 5.5 – Diffuse Large B-cell Lymphoma
CD20, x400, positive diffuse

Fig 5.6 Diffuse Large B-cell Lymphoma
Ki67, positive in over 90% of the cells

Fig 5.7 Diffuse Large B-cell Lymphoma
MUM1, positive in variant with activated B-cells

### 5.5. Discussions

In our study, the ratio of extranodal lymphomas rises up to 54%. Our outcome (namely, a higher number of cases with
extranodal Non-Hodgkin's lymphoma compared to the cases with nodal location) is consistent with the study carried out by Scherfler et al. on a number of 42 cases. (Scherfler, et al. 2012)

According to other previous studies, most of the head and neck lymphomas are B-cell lymphomas (Picard et al. 2015), just as it comes out from our study, less a single case, which is a T-cell lymphoma NOS.

With reference to the subtypes of lymphomas, most studies show that the most common subtype found at the level of head and neck is the Diffuse Large B-cell Lymphoma. Once more, our study data are consistent with those reported in the literature, the Diffuse Large B-cell Lymphoma being the main subtype diagnosed in 56.4% of the cases.

Diffuse Large B-cell Lymphoma is considered an aggressive malignancy, treatable, with a variable evolution. Post-chemotherapy initial remission is reported to be in percentage of 60%-80% (Kumar, Fausto, et al., Robbins and Cotran Pathologic Basis of Disease 2005) (Shipp 1994). The retrospective studies report a rate of survival of 50% at 5 years (Vose 2008). In our study, more than 70% of the patients with Diffuse Large B-cell Lymphoma had an unfavorable response to the treatment and died.

Immunohistochemically, the expression of pan-markers CD20 and CD79a up is common with the variable presence of germinal center markers CD10 and Bcl-6 (Jaffe et al. 2001). This immunohistochemical profile corresponds to that shown in our study.

5.6. Conclusions

Diffuse Large B-cell Lymphoma is the most common subtype of lymphoma found in oro-maxillo-facial territory, both in nodal and extranodal forms.

Extranodal location is found mostly at parotid glands level, then, the second rated location is at the jaw/palate level.
Large B-cell Lymphoma occurs more frequently in patients older than 75 years, while Follicular Lymphoma is more frequent in patients under the age of 74 years.

Large B-cell Lymphoma has more often been associated with stage IV of the disease, with a negative response to treatment and with a low rate of survival.

Follicular Lymphoma is diagnosed in stages I and II of the disease and presents a favorable therapeutic response, with the survival of all patients.
Chapter 6
Complex Therapeutic Approach in Lymphomas Localized in the Oral & Maxillofacial Territory (2010-2014)

6.1 Introduction

Treatment of lymphomas located in the oro-maxillo-facial territory implies a multidisciplinary approach, involving hematologists, radiotherapists and oral and maxillofacial surgeons.

The role of surgery in the head and neck lymphoma is many times restricted to biopsy necessary for diagnosis. In certain cases of indolent and limited lymphomas in terms of localization, surgical intervention with curative visa can be practiced (Kemp et al. 2008).

The therapeutic strategy will vary from case to case and should be individualized depending on various factors, including the histological subtype of lymphoma, stage of disease, patient age, performance status and a number of other prognostic factors (Miron et al. 2008).

6.2. The Purpose of the Study

The Purpose of the Study is to determine the therapeutic methods used in oro-maxillo-facial lymphomas, assess the outcome and therapeutic efficacy, as well as to find out the factors that influence the response to treatment and survival of patients.

6.3. Material and Method

The study has been conducted on a sample of 47 patients diagnosed with lymphomas localized in the oro-maxillofacial territory, hospitalized during 2010-2014 in the Department of Oral and Maxillofacial Surgery – “Sf. Spiridon” Iasi County Emergency Clinical Hospital. The patients were subsequently treated in the
Only one case is diagnosed with Hodgkin Lymphoma, while all the others are Non-Hodgkin`s Lymphoma, and it is excluded from further statistical analysis in order to maintain its relevance.

For each patient we have recorded the data related to age, sex, tumor location, histopathological subtype, disease stage, treatment, therapeutic response and survival. A number of patients refuse the treatment. Despite this, these patients are still kept in the study to assess their disease evolution, with and without treatment.

**6.4. Outcomes**

Treatment methods used for those 46 patients with Non-Hodgkin`s Lymphomas are as follows: chemotherapy, radiotherapy and surgical treatment, which have been applied either as a single therapy method or a combination thereof. Only four (4) patients did not follow any treatment after diagnosis. (Fig. 6.1)
The surgical methods have curative visa in 19 of the cases, while in 27 of the cases they are used only for diagnostic purposes by biopsy sampling. (Fig 6.3)

Curative surgical treatment is applied in 6 cases of Nodal Non-Hodgkin Lymphoma and in 13 cases of Extranodal Non-Hodgkin Lymphoma (Fig. 6.4).

The surgical treatment with curative visa applied in 19 cases of Non-Hodgkin`s Lymphomas is shown in Figure 6.5 in terms of surgical procedures. The surgical procedure of lymphadenopathy block removal is practiced in all cases of nodal lymphomas.

CHOP Regimen (Cyclophosphamide, Doxorubicin, Vincristine, Prednisone) is used in 18 patients with Non-Hodgkin`s Lymphomas and in 14 cases it is associated with Rituximab.
The therapeutic response of those 46 patients with Non-Hodgkin’s Lymphomas located in the oro-maxillo-facial territory is as follows: favorable response in 21 cases, with partial or complete remission, out of which only two (2) cases of complete remission of the disease; unfavorable response in 25 cases (Fig 6.6).

We have examined whether the type of treatment (surgery, chemotherapy or the combination thereof) influences the therapeutic response and implicitly the patients’ rate of survival. To this end,
we have created a new variable, namely, the treatment type with four categories: 1. no surgical treatment or chemotherapy; 2. only surgical treatment; 3. only chemotherapy; and 4. surgical treatment in combination with chemotherapy.

Chemotherapy tends to be more effective than surgery, but their combination (surgical treatment and chemotherapy) has better results than individual application. On the other hand, we find out that the percentage of subjects who respond favourably to treatment tends to change from surgery to chemotherapy, reaching, although, the highest level only if they are applied in combination.

Chemotherapy is more effective than the surgical treatment, and a combination thereof leads to a higher survival rate rather than individual application of these therapeutic methods.

We have also examined whether the application of treatment in an initial (stage I or II) or advanced stage (stage III or IV) influences the response to treatment and patients' survival.

In patients whose treatment has been lately applied, in stages III or IV, there is a percentage of 80% of cases with unfavorable response to treatment and only a percentage of 20% of cases with favorable response. Therefore, early treatment application influences definitely the favorable therapeutic response.

In patients receiving early treatment (stage I or II), there is a high percentage of survival, namely 88.9% of the cases. In contrast, in patients receiving late treatment (stage III or IV), there is a majority of 80% of patients who died.

Therefore, applying early treatment influences, as expected, the patients' survival.

6.5. Discussions

Treatment of head and neck lymphomas is multimodal and complex due to the many variables involved in terms of the status of the patient, lymphoma subtype or stage of disease extension (Sunaba, et al. 2000).
The therapeutic methods from the studies reported in the literature are the same as those used in the patients included in our study, namely: chemotherapy, radiotherapy and surgical treatment. They are used in combination or as a single therapeutic method.

Early diagnosis leads to treatment in early stages, and therefore to a better prognosis of the patients (Epstein, et al. 2001).

In our study we have noticed that applying the treatment in stages I and II leads to a positive therapeutic response with a high survival rate.

Also, combination of the therapeutic methods, and in particular combination of chemotherapy with irradiation treatment or with surgical treatment leads to a positive therapeutic response, and therefore to a higher survival rate.

In our study, the majority of lymphomas are highly aggressive, the combination of the therapeutic means resulting in superior therapeutic effects, particularly in the combination of chemotherapy with irradiation treatment.

6.6. Conclusions

In most of the cases, treatment of Non-Hodgkin Lymphomas located in the oro-maxillo-facial territory means chemotherapy in the form of R-CHOP regimen.

Application of the surgical treatment in stages I and II is correlated with a positive therapeutic response and with a high survival rate.

Chemotherapy treatment is the most eligible for use (71% of the cases) both as single therapy and in combination with surgery and/or radiotherapy.

The combination of treatment methods, especially chemotherapy with surgical treatment, or chemotherapy with radiotherapy shows a higher therapeutic efficiency than the individual use of those means.
Lymphomas Localized in the Oral & Maxillofacial Territory

The most frequently applied surgical treatment with curative visa is represented by the different types of parotidectomy applied, only in the cases of parotid lymphomas with single location.

The therapeutic response is relatively favorable in 45% of the cases, registering partial or complete remission of the disease in the period of time under study.

Half of the patients died by the completion of the study, the death rate being caused by the underlying disease, associated comorbidities (most patients are of older age) and possible by side effects of chemotherapy.
Chapter 7
Peculiarities of Diagnosis and Surgical Treatment of Parotid Lymphomas.
Retrospective Analysis 1950-2014

7.1. Introduction

Most of the salivary glands lymphomas cover the parotid glands. Parotid lymphomas may originate both in the intraparotid ganglions and in the glandular tissue, so that a differential diagnosis between a nodal and extranodal lymphoma becomes difficult to be performed, especially in the case of nodal parotid lymphoma with extension over the parotid glandular parenchyma (Barnes, et al. 2005).

Biopsy is the essential gesture in the diagnosis of lymphoma. This should provide enough tissue material for making the anatomopathological examination and immunohistochemistry tests.

Incisional biopsy is contraindicated to parotid lymphomas with a single tumor location and no other available sites, due to the presence of the facial nerve and possible salivar complications (cutaneous salivary fistulas) of this procedure. Tumor extirpation by parotidectomy will be the one to provide the necessary tissue material for histopathological examination in this situation.

7.2 The Purpose of the Study

The Purposes of the Study are multiple. We aim to achieve the clinical and epidemiological profile of parotid gland lymphomas and establish their weight in the parotid tumor pathology. By analyzing the subtypes of lymphoma that interest parotid gland we intend to figure out its anatomopathological profile and determine the most common forms located at this level. The analysis made regarding the location of the tumoral formation in the architecture of the gland has been correlated with both the type of parotidectomy
practiced by the surgeon and postoperative facial nerve disorders. We have also put emphasis on the patients’ survival rate, over a period of 15 years (2000-2014).

7.3. Material and Method

The clinico-statistical retrospective study of the parotid lymphomas has been performed within the Department of Oral and Maxillofacial Surgery – “Sf. Spiridon” Iasi County Emergency Clinical Hospital for a period of 65 years (1950 to 2014), analyzing the data recorded in the Patient Observation Recording Sheet and the Patient Anatomopathological Analysis Reports for the patients hospitalised in the aforementioned ward and diagnosed after the surgical treatment made herein.

For each patient we have recorded the following data: age, sex, and tumoral formation location in the architecture of parotid gland, type of surgical treatment applied, lymphoma anatomopathological form and postoperative complications in relation to the facial nerve. The period under study has been divided per decades, less the last 15-year period, from 2000 to 2014, which is analyzed as a whole, due to statistical considerations.

All the parotid lymphomas have showed, both clinically and imagistically, a single tumoral site with no other occurrence for sampling tissue material for the anatomopathological examination, being considered as Ann Arbor stage I tumors, except for a single case that presents double location, at parotid and lacrimal level, which has been excluded from statistical analysis due to its peculiarities.

7.4. Outcomes

There are 59 parotid lymphomas diagnosed in our study, representing 4.85% of the total parotid tumors hospitalized in Department of Oral and Maxillofacial Surgery, 5.07% of the parotid tumors undergoing surgical intervention and 13.17% of the parotid gland malignant tumors.
By histopathological point of view, those 59 parotid lymphomas are divided in 10 Hodgkin Lymphomas and 49 Non-Hodgkin`s Lymphomas, which, in their turn are divided as follows: 19 MALT Lymphoma, 18 Diffuse Large B-Cell Lymphoma, one Lymphocytic Lymphomas and 11 lymphomas that are not definable in any subtype of Non-Hodgkin`s Lymphoma (Fig. 7.12).

Out of those 59 cases of lymphomas with parotid location, 39 of them occur in males and 20 cases in females. The value of male/female ratio accounts to 1.95, showing an incidence almost doubled for males.

Parotid lymphomas of MALT type have the highest incidence in patients aged between 41 and 50 years (10 cases, out of a total of 19 cases), while parotid lymphomas of Diffuse Large B-cell type are diagnosed more frequently in patients aged between 61 and 70 years (7 cases) and 31-40 years (5 cases).

Distribution in time of parotid lymphomas has been reported per decades. The period between 2000 and 2014 is analysed as a whole in order to assess the incidence of parotid lymphoma in the recent years. Starting with 1950, the incidence of parotid lymphomas has gradually increased (especially Non Hodgkin`s Lymphomas), reaching the highest values during 2000 and 2014 (Fig. 7.21).
Lymphomas Localized in the Oral & Maxillofacial Territory

**Figure 7.21 – Incidence of Parotid Lymphomas per decades, during 1950 – 2014**

MALT Lymphoma and Diffuse Large B-Cell Lymphoma show the highest incidence during 2000 and 2014 (Fig. 7.22).

**Fig. 7.22 – Incidence of Non-Hodgkin’s Lymphomas per decades, during 1950 – 2014**

Most of the parotid lymphomas are localized at the level of the superficial lobe of the parotid gland, representing 48 of cases and respectively 81.40% of the total parotid lymphomas.

With reference to the surgical methods, we mention they imply superficial total or expanded parotidectomies, with or without all or part facial-nerve sacrifice. The surgical procedure applied in most of the cases is the superficial parotidectomy (Fig 7.26).
Integral conservation of the facial nerve during surgery is performed in 43 cases, accounting for 73% out of the total parotid lymphomas. Facial nerve partial conservation is practiced in 16.90% of the parotidectomies, namely in 10 cases of parotid lymphomas. Facial nerve total conservation is performed in 10.10% of the patients, namely a total of 6 cases.

Postoperatively, we note a healing process without neurological complications in 35 patients who underwent a parotidectomy surgical procedure for removal of lymphomas, representing 59% of the cases.
Evaluation of the adjuvant radio and chemotherapy treatment and survival of patients with parotid lymphomas has not been possible for the entire period of time included in the study due to poor or lack of some parts of the archived documentation, therefore the analysis has been limited to cases diagnosed in the last years of the study, namely from 2000 to 2014.

In 6 patients with MALT parotid lymphoma it is practiced only surgical treatment by parotidectomy. In 17 cases of parotid lymphoma, the surgical treatment is performed in combination various chemotherapy cures (R-CHOP, R-CNOP, R-COP, CEOP, COP), the most administered cure being the R-CHOP treatment. Two (2) cases of parotid lymphoma with large B-cell received postoperative chemo radiotherapy. Other two (2) patients refused the postoperative adjuvant cancer treatment (Fig. 7.31).

Survival rate of the patients diagnosed with parotid lymphomas, Hodgkin's and Non-Hodgkin's Lymphomas, during 2000 and 2014 rises up to 67%.
7.5. Discussions

Parotid gland lymphomas are rare tumors, representing between 1.7% and 3.1% of the salivary gland neoplasms and between 0.6% and 5% of the parotid gland tumors (Mehl et al. 1993). Parotid gland lymphomas show, however, a progressive growth in incidence in the recent decades, thanks to better means of diagnostics and more suitable resources for patients’ hospitalization, but also due to increased average lifespan of patients (Schusterman, et al. 1998). In our study, increase of parotid lymphomas incidence is progressive, with a threefold increase during 2000 and 2014.

Clinical forms of the parotid lymphomas are similar with the forms of manifestation of various malignant or benign tumor formations. Aspiration puncture with a fine needle together with the imaging evaluation should be conducted routinely (Shum et al. 2014).

Cho et al describe a nondiagnostic rate of 12.2% in the puncture biopsy (Cho and Kim 2011). In this situation, tumor extirpation by parotidectomy will be the one to provide the necessary tissue material for the histopathological examination.

In the study undertaken in this Thesis, the parotidectomy has had both a diagnostic and therapeutic role.

Studies outcomes are comparable to those reported in the literature, lymphomas accounting for 4.85% of the parotid tumor pathology, the most frequent being Non-Hodgkin lymphomas in a percentage of more than 80%. Out of these, the most common have been MALT lymphomas, accounting for 32.20% of the cases.

Feinstein et al. report a 10-year survival rate of 60%, by analyzing a sample of 2140 patients diagnosed with parotid lymphomas (Feinstein et al. 2013). These data are consistent with those obtained in our study; therefore, we may state that analyzing the period from 2000 to 2014 we noted a survival rate of 67% for.
7.6. Conclusions

Lymphomas with parotid location are rare salivary gland tumors, accounting for 4.85% of the total parotid tumors diagnosed within 65 years.

Out of the many histopathological forms of the lymphomas, at parotid-level we found only three types: Hodgkin Lymphomas, MALT Lymphomas and Diffuse Large B-cell Lymphomas. The most frequent are the MALT Lymphomas.

The anatomical peculiarities and relatively high amount of tumoral tissue necessary for the anatomopathological examination require removal of the tumoral formation by parotidectomy in the cases where there is only one tumoral site.

The treatment has primarily been surgical (because of the impossibility of taking a biopsy, dictated by anatomical peculiarities and unique tumor localization) involving removal of the tumoral formation by parotidectomy with the facial-nerve sacrifice or preserving, allowing thus to establish the histopathologic diagnosis of certainty. In the cases of parotid lymphomas, the parotidectomy holds dual role of diagnosis and therapeutic, respectively.

Survival rate of the patients with parotid lymphomas has been assessed only for the period 2000 to 2014, accounting for 67%.

Lymphomas are located mostly on the superficial lobe of the parotid gland, the superficial parotidectomy being the most frequent surgical procedure used therein. Facial-nerve preservation has been possible in almost all the cases, with restitutio ad integrum of the neurological function after a certain time. Patients’ postoperative prognosis has been favorable.
Chapter 8
Clinico-Statistical Analysis Regarding the Prognostic Value of Ki-67 Antigen in Cervicofacial Non-Hodgkin`s Lymphomas

8.1 Introduction

Although prognostic factors based on clinicopathological characteristics are widely used in assessing the survival of patients with Non-Hodgkin lymphomas, including Ann Arbor Staging and International Prognostic Index (IPI), the predictive specific factors of survival based on biological markers yet are still missing (Sattar and Griffeth 2006).

Cell proliferation is the main characteristic of tumor development. In the case of lymphomas, this is measured by the immunohistochemical analysis of Ki-67 nuclear antigen (Urruticoechea and Smith 2005).

Ki-67 is a nonhistonic nuclear protein that is synthesized from early cell proliferation. The role of Ki-67 is that of tumoral marker of cell proliferation due to its presence in the active phases of the cell cycle, represented by phases G1, S, G2 and mitosis (Scholzen and Gerdes 2000).

8.2. The Purpose of the Study

The purpose of the study aims to demonstrate that between the value of Ki-67 proliferative index and the response to treatment of patients with Non-Hodgkin lymphoma with at least one cervicofacial location there is a close connection, so that the clinician can assess broadly and early, soon after the anatomopathological diagnosis and the analysis of Ki-67 proliferative index value, the evolution and response to treatment of the patient. Establishing the relationship between the Ki-67 proliferative index and the survival of patients diagnosed and treated for non-Hodgkin lymphomas with oro-maxillo-facial component, it has
been an important element in assessing the evolution and prognosis of the disease.

8.3. Material and Method

Clinico-statistical retrospective analysis has been performed on patients with non-Hodgkin lymphomas diagnosed in the Clinic of Oral and Maxillofacial Surgery Iasi, for a period of 5 years, from 2010 to 2014, following the anatomopathological examination and immunohistochemistry tests (value of Ki-67 proliferative index).

The response to treatment of the patients included in the study has been considered as favorable (partial or total remission of the disease) or unfavorable (lack of therapeutic response).

8.4. Outcomes

The minimum value of Ki-67 proliferative index amounts to 10% while the maximum value reaches a percentage of 100%, the average indicating a percentage of 68% (standard deviation 23.97).

We have checked out if the value of Ki-67 proliferative index is correlated with the patients’ response to treatment and survival. Thus, the high levels of Ki-67 proliferative index are associated with adverse response to treatment and reduced survival.

8.5. Discussions

The clinician needs a predictive factor for the evolution and response to treatment of patients with non-Hodgkin lymphomas, immediately after histopathologic diagnosis to better individualize the therapy.

Cell proliferation is an important factor in human malignancy grading, in assessing both the clinical development and post-therapeutic outcome (Broyde, et al. 2009).
Ki-67 antigen is present only in proliferating cells. The value of Ki-67 proliferative index allows the assessment of the tumor growth, being a diagnosis and prognosis tumoral marker in non-Hodgkin's lymphomas, used also in other cancers (Gerdes et al. 1984), (Miller, et al. 1994), (Dzięgiel, et al. 2005).

Most studies have shown a correlation between the value of Ki-67 proliferative index and the histopathological subtype of the tumor that determines the degree of malignancy and influences the survival rate (Szczuraszek, et al. 2008).

The values of Ki-67 proliferative index vary in the different sub-types of non-Hodgkin's lymphomas. Also, the average values of Ki-67 proliferative index increase in direct proportion to the degree of aggressiveness of the tumor.

The high levels of Ki-67 are correlated with a survival of short duration and with a negative response to treatment.

We believe that the values recorded in our study are alarming, since the final data are driven us to the same correlation, according to which high levels of Ki-67 are associated with the patients adverse response and reduced survival rate.

In our study, diffuse large B-cell lymphomas, which are a majority as histopathological subtype, have shown an average value of Ki-67 of 81%, which may explain also the 50% survival rate.

In the study, the response to treatment is correlated both with the lymphoma histopathological subtype and value of Ki-67 proliferative index. If histopathological subtype only partially influences the treatment response, then value of Ki-67 proliferative index remains the only valid parameter in anticipating the effectiveness of treatment and implicitly of the prognosis, while high values of Ki-67 proliferative index are associated with an unfavorable response to treatment.

**8.6. Conclusions**

Ki-67 proliferative index can be obtained by relatively facile methods of immunohistochemistry. This is a predictive factor to which
the clinician has access immediately after diagnosis, having the possibility to use it together with other predictive factors for an optimal post-therapeutical outcome.

The statistical study shows that the variable which explains significantly the probability of a favorable response to treatment is the Ki-67 value.

Ki-67 proliferative index has a definite influence, from statistics point of view, in determining the probability that a patient to record a positive evolution after the treatment administered. The lower the value the better prognosis is.

Diffuse Large B-cell Lymphomas present the highest values of Ki-67 and are the majority in the oro-maxillofacial territory, the clinician facing very often a patholgye with a high degree of aggressiveness.

**General Conclusions**

Lymphomas with location the in oro-maxillo-facial territory are rare malignancies presenting high diversity in terms of clinical manifestation, histopathological subtype, evolution and response to treatment. They mostly affect male patients. Patients address to the doctor, on average, about 4 months after onset of the disease, moment that coincides with setting of the diagnosis of certainty.

In oro-maxillo-facial territory, the most frequent diagnosed lymphomas are non-Hodgkin lymphomas, namely in 98% of the cases.

Extranodal lymphomas are more frequent than nodal lymphomas, while the prevalent histological subtype is diffuse large B cell lymphoma.

Most of the cases have been diagnosed in stage IV of extension of the disease, joining an unfavorable therapeutic response and a death rate of 50% out of the total patients.

Diffuse Large B-cell Lymphoma has been associated in most of the cases with stage IV of extension of the disease, with a negative therapeutic response and reduced survival of patients.
Chemotherapy is the most commonly used therapeutic method to treat patients with lymphomas localized in the oro-maxillofacial territory, the R-CHOP regimen being the most commonly applied. The most effective therapeutic results and high patients’ survival rate have been obtained as a result of combination of chemotherapy to surgery, in the tumoral forms with single location.

Extranodal lymphomas are the most common lymphomas of the parotid glands, which presented stage I of extension in all cases. The histological subtype diagnosed most commonly in the parotid glands is the extranodal lymphoma with cells from the marginal area MALT type, followed with a close frequency by Diffuse Large B-cell Lymphoma.

The most frequent used surgical treatment for lymphomas with oro-maxillo-facial location is represented by different types of parotidectomies performed, due to their predominant localization in the parotid glands.

Single tumoral localization and the tumoral site peculiarity at the level of parotid gland, with the impossibility of making biopsy to establish the diagnosis (increased risk of injury to the facial nerve, occurrence of chronic cutaneous salivary fistula) led to the application of surgical treatment in all cases of parotid lymphoma.

Most parotid lymphomas are localized to the superficial lobe of the parotid gland, the superficial parotidectomy being the most frequently surgical procedure applied. Preservation of facial nerve is achieved in most cases of parotid lymphoma.

Ki-67 proliferation index is a definite prognostic value, statistically proven, so that, the lower the value the higher the chances of a favorable response are. Diffuse Large B-cell Lymphomas show the highest values of Ki-67 proliferation index and they associate the highest rate of negative response to treatment with an increased number of deceased patients.

The role of the surgeon is very important, being indispensable both by practicing the biopsy for setting the diagnosis of certainty
Lymphomas Localized in the Oral & Maxillofacial Territory

and in terms of extirpation of the tumor in lymphomas with single oro-maxillo-facial location.

**Elements of Originality and Perspectives Opened by the Phd Thesis**

The Thesis addresses to research a topical pathology, rare but with different forms of clinical presentations that requires multimodal complex treatment and significantly affects the survival of patients diagnosed and treated.

The clinico-morphological study of the patients with oro-maxillo-facial lymphomas, diagnosed in the Department of Oral and Maxillofacial Surgery – “Sf. Spiridon” Iasi County Emergency Clinical Hospital is the only study of its kind conducted in the population of Moldavia.

The clinico-statistical retrospective study of patients with parotid lymphomas diagnosed and treated in the Department of Oral and Maxillofacial Surgery has been conducted over a period of 65 years and it is the only study of this amplitude conducted in our country.

Assessing the multidisciplinary complex treatment applied to patients diagnosed with oro-maxillo-facial lymphoma, we found out the indispensable role of chemotherapy and value of biopsy, and implicitly of the surgical treatment applied by first intention or in combination with chemotherapy, especially for parotid lymphomas.

The need for assessing the patients’ prognosis immediately after setting the diagnosis of certainty based on the histopathological examination, has led to detailed research of the prognostic value of Ki-67 antigen in non-Hodgkin lymphomas located in the oro-maxillo-facial territory. The study demonstrated the usefulness of Ki-67 proliferation index in assessing patients’ prognosis.

Making the study’s outcomes available to public will be of great help to the clinicians involved in the therapeutic management of this category of patients.
SELECTIVE BIBLIOGRAPHY


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