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Characteristics of 40 primary extranodal non-Hodgkin lymphomas of the oral cavity in perspective of the new WHO classification and the International Prognostic Index

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Abstract. Non-Hodgkin lymphomas (NHLs) are often present outside the lymph nodes. Although primary extranodal NHLs (PE-NHL) form a substantial part of all NHLs, reports on oral PE-NHLs are rare.

Forty patients with PE-NHL of the oral cavity have been studied for the distribution of gender, age, oral subsite and presenting complaint, histological subtype according to the WHO classification, clinical stage, treatment, and follow-up. The data are reviewed against the background of the literature. Furthermore, the International Prognostic Index has been taken into consideration.

All patients had a lymphoma of B-cell lineage. Two-thirds of patients presented with locoregional disease. Mean survival time was 38 months, with a mean recurrence-free survival time of 31 months. There was no statistically significant difference in survival time between patients with bone versus soft tissue localisation of the PE-NHL.

In view of the rarity of PE-NHL involving the oral region multicenter studies are needed for evaluation of the usefulness of the International Prognostic Index for non-Hodgkin lymphoma in this particular part of the body.

Key words: non-Hodgkin lymphoma; oral cavity; WHO classification.

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Lymphomas are a heterogeneous group of clonal malignant diseases that share the single characteristic of arising as the result of a somatic mutation in a lymphocyte progenitor. The progeny of the affected cell usually carries the phenotype of a B-, T-, or natural killer-cell as determined by immunophenotyping and/or gene rearrangement studies.[8] A lymphoma may arise in lymph nodes or any organ, either by spread from lymphatic sites or as a manifestation of primary extranodal disease.[8]

While there is a preadolescent peak in lymphoma incidence in Hodgkin's disease, there is generally a logarithmic

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increase with age in non-Hodgkin's lymphoma.[7] Generally, a moderate male preponderance is noted. Variations in racial incidence, histology, and immunological subtypes of lymphomas are found throughout the world.[7,18]

Within the lymphoma group, Hodgkin's lymphoma is defined by the presence of the Reed–Sternberg cells in an appropriate cellular background.[8] All other neoplasms of the lymphoid system are called non-Hodgkin's lymphoma (NHL). The classification of the subtypes of lymphomas, such as the revised European–American classification of lymphoid neoplasms (REAL)[10] that has recently been incorporated with minimal change in the World Health Organisation (WHO) classification of haematopoietic and lymphoid neoplasms[14] (Table 1), is aimed at combining clinical aspects, histomorphological features, immunological phenotype and genetic features.[8] Because the Ann Arbor staging system[2] (Table 2) was inconsistent in predicting outcome, the International Prognostic Index (IPI), incorporating several parameters (Table 3), has been developed and validated to provide prognostic information for a variety of types of lymphoma.[3,12] The IPI is used within the histological subtypes to stratify patients into different prognostic groups.

As opposed to Hodgkin's disease, NHL often presents outside the lymph nodes at sites such as the stomach, skin, lung, central nervous system, orbit, salivary glands, and oral cavity.[17] In the present study, a series of six cases of PE-NHL of the oral cavity is presented and put in perspective of a review of the literature together with 34 cases of our Institute that have been published earlier.[21]

Table 1. WHO REAL classification of non-Hodgkin lymphomas according to clinical aggressiveness[14]

Indolent lymphomas
B-cell neoplasms
Small lymphocytic lymphoma/B-cell chronic lymphocytic leukaemia
Lymphoplasmocytic lymphoma (± Waldenström's macroglobulinaemia)
Plasma cell myeloma/plasmacytoma
Hairy cell leukaemia
Follicular lymphoma (grades I and II)
Marginal zone B-cell lymphoma
Mantle cell lymphoma
T-cell neoplasms
T-cell large granular lymphocytic leukaemia
Mycosis fungoides
T-cell prolymphocytic leukaemia
Natural killer cell neoplasms
Natural killer cell large granular lymphocytic leukaemia
Aggressive lymphomas
Follicular lymphoma (grade III)
Diffuse large B-cell lymphoma
Peripheral T-cell lymphoma
Anaplastic large cell lymphoma, T-null cell
Highly aggressive lymphomas
Burkitt lymphoma
Precursor B lymphoblastic leukaemia/lymphoma
Adult T-cell lymphoma/leukaemia
Precursor T lymphoblastic leukaemia/lymphoma
Special group of localized indolent lymphomas
Extranodal marginal zone B-cell lymphoma of MALT type*
Primary cutaneous anaplastic large cell lymphoma

* MALT = mucosa-associated lymphoid tissue.

Table 2. Ann Arbor staging system[2]

Stage	Defining status
Stage I*	Restricted to single lymph node region (I) or a single extranodal site (I-E)
Stage II*	Two or more areas of nodal involvement on same side of the diaphragm (II) or one or more lymph node regions with an extranodal site (II-E)
Stage III*	Lymphatic involvement on both sides of the diaphragm (III), possibly with an extranodal site (III-E), the spleen* (III-S), or both (III-SE)
Stage IV	Liver, marrow, or other extensive extranodal disease
Substage	
Substage E	Localised, extranodal disease
Substage A	Absence of systemic signs
Substage B	Presence of unexplained weight loss (≥10% in 6 months), and/or unexplained fever, and/or night sweats

* The spleen is considered nodal.

Patients and methods

In the studied period 1 January 1997 to 1 January 2002, 263 new cases of oral malignant tumours of which six NHLs were identified at the VU University medical centre, Amsterdam, The Netherlands. In all cases, oral lesions were the primary manifestation of the disease. The patient data, including gender, age, oral site of presentation, clinical stage according to the Ann Arbor conference,[2] the IPI, primary mode of treatment and follow-up results, were retrospectively retrieved via the medical records. The performance status of the IPI was classified as 0 (the patient had no symptoms) or 1 (the patient had symptoms, but was ambulatory), 2 (the patient was bedridden less than half the day), 3 (the patient was bedridden half the day or longer), and 4 (the patient was chronically bedridden and required assistance with the activities of daily living). The data of the six new patients were supplemented with those of the previously reported 34 patients.[21]

Table 3. International Prognostic Index for NHLs[3,12]

Parameters
Age ≥60 years
Advanced stage (III or IV)
Extranodal involvement of >1 site
Performance status ≥2
Serum lactate dehydrogenase level raised (above normal)
Risk group stratification (according to total number of above-listed features)
0–1: Low risk
2: Low intermediate risk
3: High intermediate risk
4–5: High risk

Biopsy specimens were reviewed and classified using the recent WHO/REAL classification.[14] Beside routine haematoxyline–eosine stainings, immunohistochemical methods were used to investigate the origin of the tumour cells. Antibodies used were L26 (CD20, a pan-B-cell marker), CD79a (the immunoglobulin anchoring molecule, thus a B-cell marker), CD3 and UCHL1 (CD45RO) (both pan-T-cell markers), BerH2 (CD30), and MB2 (staining predominantly B-cells). For the differential diagnosis with epithelial malignancies keratin antibodies AE1/AE3 and CAM5.2 were used.

The patients were treated with radiotherapy, chemotherapy, or a combination of these modalities. Radiotherapy was administered in stage I patients with indolent NHL or if age precluded polychemotherapy. When radiotherapy was applied, cumulative radiation doses of 28–40 Gy fractionated over 2–4 weeks. Chemotherapy regimes for the indolent NHLs consisted most often of chlorambucil with or without prednisolone. Aggressive NHLs were treated with poly-

Table 4. Data of six patients with an oral PE-NHL

Case	Sex	Age	Oral site of presentation	Histologic type of NHL[14]	Clinical stage	IPI	Rx	Follow-up	Outcome
1	M	61	Maxillary gingival	DLBCL	I-E	2	Chemo	72 mos	A & W
2	M	61	Mandible	DLBCL	IV	3	Chemo	14 mos	A & W
3	F	28	Mandible	DLBCL	I-E	1	Chemo	49 mos	A & W
4	F	53	Palate	Plasmacytoma	I-E	n.a.	RT	70 mos	A & W
5	M	86	Palate	DLBCL	I-E	2	RT	6 mos	DOD
6	M	75	Tongue	DLBCL	III	3	Chemo	18 mos	DOD

DLBCL: diffuse large B-cell lymphoma; n.a.: not applicable.

chemotherapy (CHOP; cyclophosphamide, doxorubicin, vincristine, and prednisolone).

Results

The data of the six new patients, including gender, age, oral site of presentation, histological subtype of NHL according to the WHO/REAL classification,[14] clinical stage according to the Ann Arbor conference,[2] the IPI, primary mode of treatment and follow-up results are summarised in Table 4.

These six patients taken together with the earlier described 34 PE-NHL patients, accumulate to a total of 40 PE-NHLs, 24 men and 16 women, with a mean age of 59 years (range 3–88). None of the patients had a medical history of irradiation, immune deficiencies, or long-term immunosuppressive therapy. The duration of oral signs and symptoms ranged from 14 days to 4 months, often with sudden onset and rapid progression. In 29 cases the initial symptom was a diffuse, non-tender swelling of the soft tissues, ulcerating in 14 of these patients. Nine patients complained of spontaneously occurring pain, whereas mental nerve numbness was noted in three patients. In four patients, computerised tomography showed destruction of the palate, and spread into the nasal cavity, the maxillary sinus, and—sometimes—the orbit. Six patients presented with 'B' symptoms: three had fever, and another three had extensive weight loss.

The primary oral sites, with reference to initial localisation in soft tissue or bone following clinical and radiographical investigations, are listed in Table 5. Using the WHO/REAL classification and Ann Arbor system, patients were categorised as shown in Tables 6 and 7, respectively. All patients had a B-cell lineage lymphoma. One patient did not undergo staging because of poor physical condition and advanced age.

Mean survival time in the earlier described group of 34 patients was 38 months, with a mean recurrence-free survival time of 31 months.[21] There was no statistically significant difference in survival time between patients with bone versus soft tissue localisation of the PE-NHL. Locoregional disease, i.e. stages I and II, and disseminated disease, i.e. stages III and IV, showed significant differences both for overall survival ($P = 0.0001$) and recurrence-free survival ($P = 0.001$). Furthermore, there was a significant difference in recurrence-free survival time between patients with low-, intermediate-, and high-grade lymphoma using the Working Formulation ($P = 0.007$); however, the difference in overall survival between the three grades was not significant ($P = 0.08$).[21] The six patients registered in the period between 1997 and 2002 could not statistically be evaluated for mean recurrence-free survival time and overall survival due to the limited number of patients and the limited mean follow-up period.

Table 5. Primary site of 40 oral PE-NHLs

	Tissue of origin		
Oral subsite of presentation	Soft tissue	Bone	Total
Upper jaw	20	7	27
Lower jaw	–	7	7
Buccal mucosa and tongue	6	n.a.	6
Total	26	14	40

Table 6. WHO/REAL subtype of 40 oral PE-NHLs

Stage	B-cell neoplasms	Cases
I	Precursor B-cell neoplasm	–
	B-cell lymphoblastic lymphoma	2
II	Peripheral B-cell neoplasms	–
	Plasmacytoma/plasma cell myeloma	1
	Burkitt lymphoma (including Burkitt-like lymphoma)	1
	Extranodal marginal zone B-cell lymphoma of MALT type	2
	Mantle cell lymphoma	6
	Follicular lymphoma	8
	Diffuse large B-cell lymphoma	20
Total		40

Table 7. Clinical stage of 40 oral PE-NHLs

Stage	Number of patients
I-E	24
II-E	1
III-E	2
IV	12
Unstaged	1
Total	40

Discussion

Lymphoma is the second most common neoplasm of the head and neck following squamous cell carcinoma.[6] Most occur in Waldeyer's ring, i.e. the tonsils, pharynx, and the base of the tongue, whereas lymphomas arising within the oral cavity account for 3.5% of all oral malignancies.[6] The reported percentage of PE-NHL of all NHLs ranges from 24[9] to 48.[1,13] Dutch study, PE-NHLs accounted for 41% of all NHLs, 3% of which were primarily located in the oral cavity.[17]

The clinical characteristics of the six new PE-NHL patients taken together with the earlier described are in accordance with those reported in the literature.[15,21] In the present single institution series of 40 patients, there was a slight male predomi-

nance (24 men, 16 women; male–female ratio of 1.5) and a mean age of 59 years (range 3–88).

In the oral cavity, lymphomas usually present as an extranodal, soft-elastic, asymptomatic lesion,[6] hardly ever being accompanied by 'B' symptoms.[5,20] In our study oral PE-NHLs arose in two-thirds of patients (26/40) from soft tissues, 77% of these located in the upper jaw (20/26). Although lymphoma sites of the upper jaw are commonly separately indicated as palate and maxilla, in clinical practice this subdivision is often not clear-cut. Hence, we prefer the more realistic term upper jaw. In the remaining one-third of patients (14/40), the lesions originated from the bone, equally distributed over the mandible (7/14) and the upper jaw (7/14). On radiographical investigations, lymphoma with bone involvement predominantly causes diffuse bone destruction, leading to disappearance of the lamina dura of the teeth or appearing as a solitary radiolucent defect. In our patients, NHLs of the upper jaw most often originate from soft tissue (20/27), whereas NHLs of the lower jaw all arise in bone (7/7).

Most PE-NHLs are of B-cell lineage, the cause of which is unknown. In our series it was striking that all patients had a B-cell lineage lymphoma (Table 6). Diffuse large B-cell lymphomas (DLBCLs) represent approximately 40% of adult lymphomas[8] and, in our series, comprised 50% of oral PE-NHLs (20/40). Furthermore, as has been reported in the literature,[3,8] most of these DLBCLs presented with locoregional disease, i.e. stages I or II.

Mean survival time was 38 months in the earlier described group of 34 patients, with a mean recurrence-free survival time of 31 months.[21] Although PE-NHL arising in skeletal bone,[4] and reports on small series of oral PE-NHL suggested a better prognosis for bone localisation, reported larger series of oral PE-NHL do not show this prognostic impact of primary tumour localisation.[5,19] Follow-up of the newly included six PE-NHL patients was too short to include for statistical analysis, but in our previous study,[21] as in other studies[5,19] there was no statistically significant difference in survival time between patients with bone versus soft tissue localisation of the PE-NHL. Besides, determination of tumour localisation, primarily having an intraosseous or soft tissue origin, carries some subjectivity. Furthermore, cases of intraosseous localisation in the upper jaw, i.e. palate and maxilla, may represent local extension from nasal and/or paranasal sinus processes and vice versa. Locoregional disease, i.e. stages I and II, and disseminated disease, i.e. stages III and IV, showed significant differences both for overall survival ($P = 0.0001$) and recurrence-free survival ($P = 0.001$).[21] In the International Prognostic Index advanced stage (III or IV) is, indeed, one of the parameters.

The value of the IPI could not be tested on the presently reported six patients because of a too short follow-up period. Since the IPI includes information on performance status, this index could not reliably be applied in retrospect on our previously reported series of 34 patients registered in the period 1973–1993 either. Probably the majority of these 34 cases would fall in the IPI low risk or low intermediate risk group, as the six recently added cases did (Table 4).

Initially, the IPI was developed to predict outcome in patients with aggressive non-Hodkin lymphoma. Apparently, the IPI is also applicable for patients with lymphomas that are histologically more indolent.[11] Using the IPI index ranging from low risk to high risk, the increased risk of death is due to both a lower rate of complete response and a higher rate of relapse from complete response.[12] It has been emphasized that prognostic factors as defined by the IPI must be combined with the histological diagnosis for appropriate clinical decisions.[16]

In order to be able to apply statistical analyses on relapse-free survival and overall survival of PE-NHL located in the oral cavity, larger number of patients are required than can be provided by single institutions.

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