Pergamon

*Oral Oncol, Eur J Cancer*, Vol. 30B, No. 2, pp. 121–125, 1994

0964–1955/94 $6.00 + 0.00

# Primary Extranodal Non-Hodgkin Lymphoma of the Oral Cavity. An Analysis of 34 Cases

**Eppo B. Wolvius, Paul van der Valk, Jacqueline E. van der Wal, Paul J. van Diest, Peter C. Huijgens, Isaäc van der Waal and Gordon B. Snow**

**34 patients with primary extranodal non-Hodgkin lymphoma (PE-NHL) of the oral cavity have been studied with reference to age, sex, clinical symptoms, location of primary tumour, histological subtype, grade of malignancy according to the Working Formulation, stage of disease, treatment and follow-up. The clinicopathological features of these oral PE-NHL correspond with those of PE-NHL in general. Survival was influenced by stage of disease and grade of malignancy.**
*Oral Oncol, Eur J Cancer*, Vol. 30B, No. 2, pp. 121–125, 1994.

## INTRODUCTION

MALIGNANT LYMPHOMAS are a heterogenous group of neoplasms affecting the lymphoid system. Within this group, Hodgkin's lymphoma is a disease, characterised by the presence of typical large bi- or multinucleated, so-called Reed-Sternberg cells in an appropriate background. All other neoplasms of the lymphoid system are called non-Hodgkin lymphoma (NHL). Several classification systems have been used for categorising the various subtypes of NHL. The Working Formulation (WF) for Clinical Usage, an attempt to group together similar categories from different classifications, divides NHLs into three prognostically different groups: low-, intermediate- and high-grade malignancy [1]. It is based on lymphoid proliferations arising in lymph nodes and other lymphoid tissues, such as Waldeyer's ring, thymus and spleen. However, in contrast to Hodgkin's disease, NHL often presents outside the lymphoid system at sites such as the stomach, skin, lung, central nervous system, orbit, salivary glands and oral cavity [2]. Certain types of the primary extranodal NHL (PE-NHL) seem to behave different clinically from nodal NHL [2–5]. For example, it has been reported that small-cell B-cell lymphomas arising in mucosa-associated lymphoid tissue (MALT), so called maltomas, display a distinct clinical behaviour [3].

PE-NHLs form a substantial part of all NHL's throughout the body [2]. Despite the relative high occurrence of extranodal NHL, conceptual knowledge of PE-NHL is available only from a few sites, such as the stomach, skin, lung, thyroid and salivary gland [3, 5–7]. Reports on oral NHLs are rare.

In the present study, a series of 34 cases of PE-NHL of the oral cavity has been reviewed. The clinicopathological findings, including clinical staging and clinical course, have been analysed. Special attention has been paid to whether the system of grading according to the WF proved to be clinically relevant for oral PE-NHL.

Correspondence to I. van der Waal.
I. van der Waal, E.B. Wolvius and J.E. van der Wal are at the Department of Oral & Maxillofacial Surgery and Oral Pathology; P. van der Valk and P.J. van Diest are at the Department of Pathology; P.C. Huijgens is at the Department of Hematology; and G.B. Snow is at the Department of Otorhinolaryngology and Head & Neck Surgery, Free University Hospital, Postbox 7057, 1007 MB Amsterdam, The Netherlands.
Received 20 May 1993; provisionally accepted 22 June 1993; revised manuscript received 21 July 1993.

## MATERIALS AND METHODS

During the period 1 January 1973 to 1 January 1993, a total number of 34 patients with NHL of the oral cavity were registered at the Departments of Oral & Maxillofacial Surgery and Otorhinolaryngology/Head & Neck Surgery of the Free University Hospital, Amsterdam. In all cases the oral cavity was the primary site of the disease, or the first symptoms were caused by a tumour in that area. From the clinical data and radiographs it was determined, whether the tumour was primarily located intraosseously or of soft tissue origin.

33 patients were staged according to the criteria established at the Ann-Arbor conference in 1972 [8]. The staging procedures included at least a physical examination, routine laboratory investigation, a computed tomographic scan of the abdomen, an X-ray of the chest and bone marrow biopsy of the iliac crest. One patient was not staged because of his advanced age and poor physical condition.

Biopsy specimens were re-examined and classified, using the updated Kiel classification (Kiel) [9]. According to Hui *et al.* [10], the centroblastic lymphomas were further subdivided into four morphological variants (monomorphic, polymorphic, multilobated and centrocytoid). In addition, each lymphoma was graded as a low-, intermediate- or high-grade malignancy according to the WF. The monomorphic, multilobated and centrocytoid subtypes of the centroblastic lymphomas were graded as intermediate-grade and the polymorphic subtypes as high-grade malignancy [11]. Besides routine haematoxylin–eosin staining, immunohistochemical methods were used to investigate the origin of the tumour cells. A routine avidin–biotin complex method was used (Vector, Burlingane, California, U.S.A.). Antibodies used were: L26 (CD20, a pan-B-cell marker), CD3 and UCHL1 (CD45RO)

(pan-T-cell markers), from DAKO (Copenhagen, Denmark); MB2 (Biotest, Dreiech, Germany) staining predominantly B-cells, and BerH2 (CD30), also from Dako.

The patients were mainly treated with radiotherapy, chemotherapy or combined radiotherapy and chemotherapy. Radiation doses commonly ranged from 4.000 to 5.000 cGy in 5–6 weeks. For low-grade NHLs chlorambucil with or without prednisone was administered. For intermediate- and high-grade NHLs, CHOP multichemotherapy (cyclophosphamide, doxorabicin, vincristine, prednisone) was given. In stage II to IV disease this was combined with methrotrexate. 12 patients primarily received radiotherapy (11 patients were in stage I, 1 patient was not staged). 14 patients primarily received chemotherapy (7 patients in stage I, 1 in stage II, 1 in stage III and 5 in stage IV). 1 of these patients died of AIDS related causes within 3 months after initial diagnosis of NHL. 5 patients were treated with combined radiotherapy and chemotherapy (2 in stage I, 3 in stage IV). 1 patient with a maltoma on the palate was treated by surgical excision; after 67 months of follow-up no recurrence was reported. One 3-year-old boy with disseminated lymphoblastic lymphoma and a male of 20 years of age with disseminated Burkitt's type lymphoma died within several days after admission. Both were in a too fragile condition to receive any therapy.

Recurrence-free survival was defined as the time elapsing from entering complete remission until first recurrence. Overall survival time was measured from the initial diagnosis until death from disease or end of follow-up. Statistical analysis was carried out with the Biomedical Package, regarding *P*-values below 0.05 as significant. Kaplan–Meier curves were plotted and differences between the curves were analysed with the Mantel–Cox statistic. Multivariate survival analysis was carried out with the Cox regression model using the variables histologic subtype (Kiel), grade of malignancy (WF) and stage of disease (grouped as stage I/II vs. stage III/IV), in order to evaluate the additional prognostic value of these variables. The enter and remove limits were set to 0.10.

## RESULTS

There were 20 men and 14 women with a mean age of 59 years (range 3–88 years). In 24 cases the initial symptom was a diffuse swelling of the soft tissues. 8 patients complained of spontaneously occurring pain. Numbness of the mental nerve was noted in 3 patients. Mucosal ulceration or a red to blue discolouration was reported in 10 cases. Initially, some of these lesions were clinically diagnosed as squamous cell carcinoma. 4 patients showed an oro-nasal fistula on the palate due to destructive growth of the tumour. In 3 cases tumour-related fever, and in 2 cases extensive weight loss within the last 2 months was reported.

The clinical and radiographical findings with reference to initial localisation in soft tissue or bone are listed in Table 1. In 12 cases the tumour arose intraosseously; 5 in the maxilla, 5 in the mandible and 2 in the palate. In 22 cases the tumour arose in the soft tissue; 10 in the palate, 7 in the maxilla, 4 in the cheek and 1 on the lateral border of the tongue. In some cases radiographical examination revealed lowering of the alveolar margin and loss of lamina dura, suggesting periodontitis or periradicular inflammation. In 2 cases radiographical signs suggested osteomyelitis of the mandible. In 3 patients computerised tomography showed destruction of the maxilla, and spreading into the nasal cavity and the maxillary sinus (Fig. 1).

*Table 1. Primary site of 34 oral PE-NHLs*

| | Tissue of origin | | |
|---|---|---|---|
| | Soft tissue | Bone | Total |
| Maxilla | 7 | 5 | 12 |
| Palate | 10 | 2 | 12 |
| Mandible | — | 5 | 5 |
| Cheek/tongue | 5 | — | 5 |
| Total | 22 | 12 | 34 |

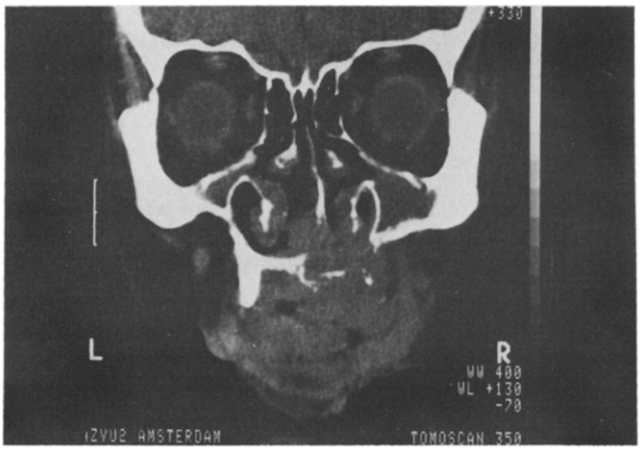


**Fig. 1. Computerised tomography shows a large tumour mass destructing the maxilla, and spreading into the nasal cavity and the maxillary sinus.**

In 4 cases a follicular and in 30 cases a diffuse growth pattern was found. The results of the morphological classifications are listed in Table 2. The most frequent histological subtype (Kiel) was the diffuse centroblastic lymphoma (12 cases) (Fig. 2). In 2 cases, both located on the palate, the lesions were diagnosed as maltoma, with centrocyte-like cells showing invasion of epithelium of salivary gland tissue, forming characteristic lymphoepithelial lesions (Fig. 3).

Finally, histological grading (WF) revealed four low-grade (12%), 19 intermediate-grade (56%), and 11 high-grade lesions (32%).

33 patients were staged according to the Ann-Arbor criteria [8]. 1 patient was not staged. 20 patients were in stage I. 1 patient was in stage II, with involvement of the submandibular lymph nodes. 1 patient was in stage III, showing involvement of paraaortic and inguinal lymph nodes. 11 patients were in stage IV, with involvement of lymph nodes in the abdominal, inguinal, supraclavicular and cervical area. Bone marrow examination showed tumour localisation in 6 cases.

The relationship between clinical stage and histological grade of malignancy (WF) is presented in Table 3. Most of the patients had a localised PE-NHL (stage I/II) of intermediate grade malignancy (WF) (13 patients).

The mean survival time was 38 months. The mean recurrence-free survival time was 31 months. There was no statistically significant difference in survival time between patients with oral PE-NHL located in the bone and in the soft tissue ($P = 0.09$). As to the WF grading, there was a significant

difference in recurrence-free survival time between patients with low-, intermediate-, and high-grade lymphoma ($P=0.007$) (Fig. 4). The difference in overall survival time between the three grades was not significant ($P=0.08$). The overall survival curves (Fig. 5) and recurrence-free survival curves showed both a significant difference between localised disease (stage I and II) and disseminated disease (stage III and IV) ($P=0.0001$ and 0.001, respectively).

Univariate analysis revealed that histological subtype (Kiel) had no significance as prognostic factor. In multivariate analysis using overall survival time, stage of disease (stage I/II vs. stage III/IV) was selected as the most significant variable, closely followed by the grade of malignancy (WF). For recurrence-free survival time, grade of malignancy turned up as most significant, closely followed by stage of disease.

## DISCUSSION

The incidence of PE-NHL of all NHL ranges from 24% [12] to 48% [13]. In a recent Dutch study [2], PE-NHL accounted for 41% of all NHL and 3% of these were initially located in the oral cavity. Extranodal NHL primarily located in the oral cavity appears indeed to be rare. In immunocompromised patients, including patients with AIDS, an increased incidence of NHL has been recognised [14]. Several reports have shown the oral cavity to be the primary site of HIV-associated NHL [15, 16].

The majority of patients with a NHL are over 60 years of age, and almost all subtypes of NHL show a slight or moderate male predominance [11]. The findings for oral PE-NHL correspond with these data [17–24].

Most of the presenting symptoms in the oral cavity are attributable to a local tumour mass, while "B" symptoms (weight loss, fever, night sweats) are uncommon [17, 18, 22, 23]. The clinical features of oral PE-NHL are not characteristic and therefore, these NHL can easily be misdiagnosed. In combination with the radiological sign of local diffuse bone loss they can resemble osteomyelitis [22, 23]. Also radiological findings of lowering of the alveolar margin or disappearance of the lamina dura may result in erroneous diagnoses of periodontitis or periradicular inflammation [25, 26]. NHL can also resemble other malignant diseases, such as squamous cell carcinoma or malignant salivary gland tumours [25, 27]. Thus, the importance of initial histological examination should not be underestimated [17, 23]. Given the possible diagnostic problems with histology [11], the biopsy specimens should be handled carefully. Where possible fresh tissue should be provided for immunohistochemical analysis and gene rearrangement studies.

As previously and currently shown, most PE-NHL are found in the soft tissue of the upper jaw, particularly of the palate [17, 21, 24]. On the other hand, Howell *et al.* [20] have found the vestibules and gingivae to be the most common sites involved. In the present study, no difference in prognosis was found between patients with a lymphoma primarily located in the soft tissue and jaw bone. This is in contrast with previous reports, where a better outcome for patients with a PE-NHL in the jaw bone was suggested [18, 26]. At the same time one should realise that the determination of tumour localisation, being primarily intraosseous or of soft tissue origin, is somewhat subjective. Furthermore, some cases of intraosseous localisation in the palate and the maxilla may actually represent extension from nasal and/or paranasal disease. Although some larger studies on PE-NHL arising in skeletal

*Table 2. Classification of 34 cases of oral PE-NHL according to the updated Kiel classification of B-cell non-Hodgkin's lymphomas and grade of malignancy according to the Working Formulation*

| Updated Kiel classification | | Working Formulation |
|---|---|---|
| Low-grade malignant lymphomas | | |
| Lymphocytic | — | |
| Chronic lymphocytic leukaemia | — | |
| Prolymphocytic leukaemia | — | |
| Hairy cell leukaemia | — | |
| Lymphoplasmacytic/-cytoid (immunocytoma) | — | |
| Plasmacytic | — | |
| Centroblastic-centrocytic | 8 | |
| Follicular ± diffuse | 2 | Low-grade |
| Diffuse | 6 | Intermediate-grade |
| Centrocytic (mantle cell) | 6 | Intermediate-grade |
| Monocytoid, including marginal zone cell | — | |
| High-grade malignant lymphomas | | |
| Centroblastic | 12 | |
| Monomorphic | 3 | Intermediate-grade |
| Polymorphic | 5 | High-grade |
| Multilobated | — | |
| Centrocytoid | 4 | Intermediate-grade |
| Immunoblastic | 1 | High-grade |
| Burkitt's lymphoma | 1 | High-grade |
| Large cell anaplastic (Ki-1+) | 2 | High-grade |
| Lymphoblastic | 2 | High-grade |
| Rare types | — | |

2 cases were diagnosed as a maltoma; according to the Working Formulation these are of low-grade malignancy.

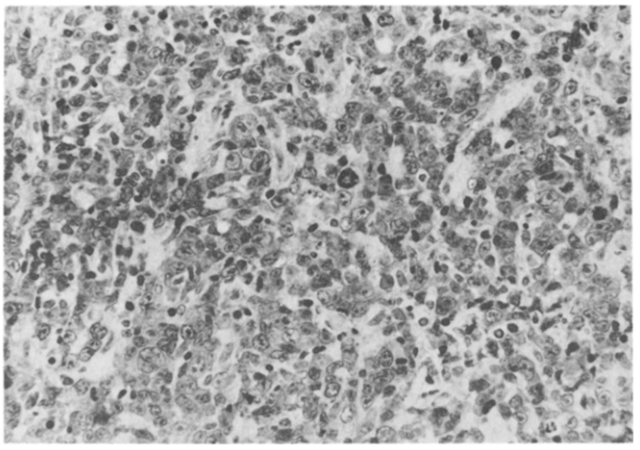

**Fig. 2. Centroblastic lymphoma, polymorphic subtype. Diffuse proliferation of large blastic cells, with prominent nucleoli, sometimes located centrally in the nucleus, sometimes marginally (haematoxylin–eosin stained section, × 330).**

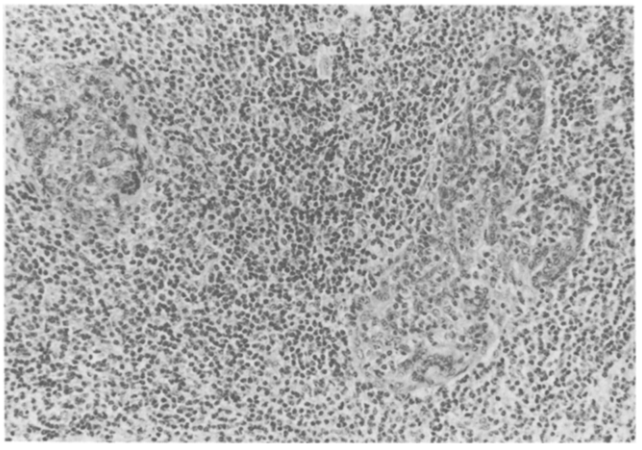

**Fig. 3. Maltoma of minor salivary gland on the palate. Two ducts are seen diffusely infiltrated by the tumour cells: the so-called lymphoepithelial lesions. The areas surrounding the ducts (especially in the upper left corner) show cells slightly larger than small lymphocytes; these proved monotypic with immunochemistry (haematoxylin–eosin stained section, × 330).**

bone do suggest a better prognosis [28], series of oral PE-NHL published so far do not clearly show the prognostic impact of initial tumour localisation [17, 20, 22].

In the series reported by the National Cancer Institute sponsored study of classifications of NHLs [1], a follicular growth pattern of the tumours was noted in 40% of the cases. In contrast, in the current study, a follicular growth pattern was found in only 12% of the cases. A proportionately low occurrence of this type of lymphoma has also been reported by others [17, 21, 24], and for PE-NHL elsewhere in the body [2, 29].

Oral lymphomas are predominantly of B-cell lineage [19–21], unlike those from the nasal area [4]. The appearance of T-cell lymphoma in the oral studies varies from zero [21] to 3% [20]. However, in Japanese populations a relative high incidence of T-cell lymphoma has been reported [18, 24]. In the present study, diffuse centroblastic lymphoma (Kiel) was the most common subtype, and accounted for 35% of all lymphomas. According to the WF, this subtype is classified as diffuse large cell lymphoma [1]. In this respect, the current findings for oral PE-NHL seem to correspond with those reported by others [17, 21, 22, 24]. Furthermore, the relative predominance of this subtype has been shown by studies of PE-NHL in the head and neck region [29], and by larger studies of PE-NHL throughout the body [2]. In the present study, two cases of maltoma on the palate were noted. Although maltomas have been found in the gastrointestinal tract, lungs, thyroid and major salivary glands, this is probably the first report of localisation on the palate [3]. Since minor salivary glands are commonly present in the palatal mucosa, the finding of a maltoma on this site does not seem surprising.

The proportions of low-, intermediate- and high-grade (WF) cases in the series of oral PE-NHL and of PE-NHL in general seem to be similar [2, 18, 22–24], and both differ from those of nodal lymphomas. Due to a relatively low occurrence of follicular lymphoma, the series of PE-NHL contain fewer low-grade cases and most cases are of intermediate-grade malignancy [2]. In this study of extranodal lymphomas the WF had prognostic value. Overall survival of the three different categories only just failed to reach significance, but this could be due to the small number of cases investigated. Though WF grading is not appropriate for all extranodal lymphomas (some gastrointestinal and skin lymphomas categories behave quite different from their nodal counterparts) [3, 5], for oral lymphomas the WF is useful. In the current study, the survival was especially influenced by stage of disease. Patients in stages I and II seem to have a better prognosis than patients in stages III and IV [2, 29].

In the 1970s and early 1980s, patients in stages I and II were treated with local radiotherapy. At present, it is recommended to add chemotherapy to radiotherapy in both stage I and II NHLs of intermediate- and high-grade malignancy [30, 31]. Cabanillas *et al.* [32] found that chemotherapy alone was effective for patients in stage I and II, and recommended radiotherapy following the chemotherapy in stage II patients only in the presence of a bulky tumour. The 11 patients in the current study with high-grade malignant lymphoma had a disappointing recurrence-free survival. This may be partially

*Table 3. Relationship between clinical stage (grouped as stage I/II vs. stage III/IV disease) and histological grade of malignancy (WF) of 34 patients with oral PE-NHL**

| | Low-grade | Intermediate-grade | High-grade | Total |
|---|---|---|---|---|
| Stages I and II | 2 | 13 | 6 | 21 |
| Stages III and IV | 2 | 6 | 4 | 12 |
| Total | 4 | 19 | 10 | 33 |

*1 patient with lymphoma of high-grade malignancy (WF) was not staged.

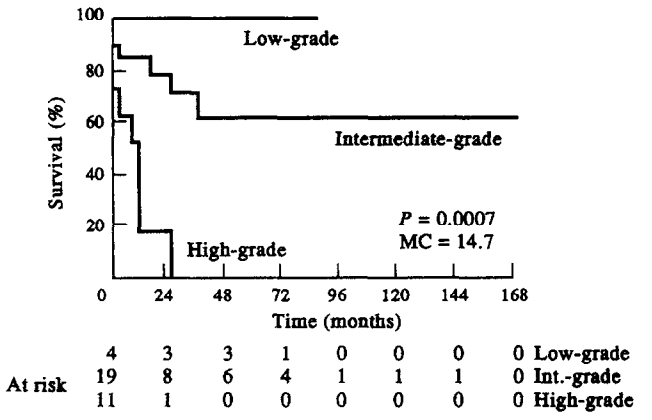


**Fig. 4. Recurrence-free survival curves of 34 patients with low-, intermediate- and high-grade malignancy (WF).**

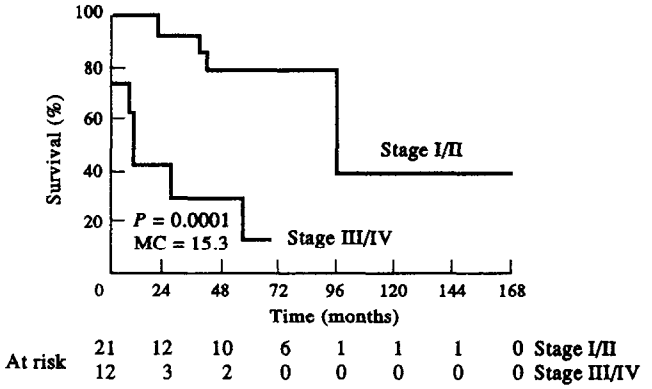


**Fig. 5. Overall survival curves of 34 patients with localised disease (stages I and II) and disseminated disease (stages III and IV).**

due to the initial treatment with radiotherapy insufficient according to modern standards, and to their high clinical stage.

In conclusion, PE-NHL of the oral cavity is a rare finding, with the soft tissue of the palate being the most frequent location. The clinicopathological features of oral PE-NHL seem to correspond with those of PE-NHL in general. In the present study, survival was influenced by stage of disease and histological grade of malignancy (WF).


1. National Cancer Institute sponsored study of classification of non-Hodgkin's lymphoma's. The non-Hodgkin's lymphoma pathologic classification project. Summary and description of a Working Formulation for clinical usage. *Cancer* 1982, **49**, 2112–2135.
2. Otter R, Gerrits WBJ, Sandt MM van der, Hermans J, Willemze R. Primary extranodal and nodal non-Hodgkin's lymphoma. *Eur J Cancer Clin Oncol* 1989, **25**, 1203–1210.
3. Isaacson PG, Spencer J. Malignant lymphoma of mucosa-associated lymphoid tissue. *Histopathology* 1987, **11**, 445–462.
4. Noorduyn LA, Torenbeek R, Valk P van der, Snow GB, Balm AJH. Sinonasal non-Hodgkin's lymphoma and Wegener's granulomatosis: a clinicopathological study. *Virch Arch A Pathol Anat* 1991, **418**, 235–240.
5. Bruin PC de, Beljaards RC, Heerde P van, *et al.* Differences in clinical behaviour and immunophenotype between primary cutaneous and primary nodal large cell anaplastic lymphoma of T- or null cell phenotype. *Histopathology* 1993, **23**, 127–137.
6. Hyjek E, Smith WJ, Isaacson PG, Primary B-cell lymphoma of salivary glands and its relationship to myoepithelial sialadenitis. *Hum Pathol* 1988, **19**, 766–776.
7. Schmid U, Helbron D, Lennert K. Primary malignant lymphomas localized in salivary glands. *Histopathology* 1982, **6**, 673–687.
8. Carbone PP, Kaplan HS, Musshof K, Smithers DW, Tubiana M. Report of the committee on Hodgkin's disease staging classification. *Cancer Res* 1971, **31**, 1860–1861.
9. Stainfeld AG, Diebold J, Kapanci Y, *et al.* Updated Kiel classification for lymphomas. *Lancet* 1988, **2**, 292–293.
10. Hui PK, Feller AC, Lennert K. High-grade non-Hodgkin's lymphoma of B-cell type. I. Histopathology. *Histopathology* 1988, **12**, 127–143.
11. Lennert K, Feller AC. *Histopathology of non-Hodgkin's lymphomas.* (Based on the updated Kiel classification). Berlin, Springer 1992.
12. Freeman C, Berg JW, Cutler SJ. Occurrence and prognosis of extranodal lymphomas. *Cancer* 1972, **29**, 252–260.
13. Banfi A, Bonadonna G, Carnevali G, Oldini C, Salisni E. Preferential sites of involvement and spread in malignant lymphomas. *Eur J Cancer Clin Oncol* 1968, **4**, 319–324.
14. Beral V, Peterman T, Berleman R, Jaffe H. AIDS-associated non-Hodgkin's lymphoma. *Lancet* 1991, **337**, 805–809.
15. Langford A, Dienemann D, Schürman D, *et al.* Oral manifestations of AIDS associated non-Hodgkin's lymphomas. *Int J Oral Maxillofac Surg* 1991, **20**, 136–141.
16. Rubin MM, Gatta CA, Cozzi GM. Non-Hodgkin's lymphoma of the buccal gingiva as the initial manifestation of AIDS. *J Oral Maxillofac Surg* 1989, **47**, 1311–1313.
17. Eisenbud L, Sciubba J, Mir R, Sachs SA. Oral presentations in non-Hodgkin's lymphoma. A review of thirty-one cases. Part I. Data analysis. *Oral Surg Oral Med Oral Pathol* 1983, **56**, 151–156.
18. Fukada Y, Ishida T, Fujimoto M, Ueda T, Aozasa K. Malignant lymphomas of the oral cavity: clinicopathologic analysis of 20 cases. *J Oral Pathol* 1987, **16**, 8–12.
19. Handlers JP, Howell RE, Abrams AM, Melrose RJ. Extranodal oral lymphoma: a review of 31 cases. *Oral Surg Oral Med Oral Pathol* 1986, **61**, 362–367.
20. Howell RE, Handlers JP, Abrams AM, Melrose RJ. Extranodal oral lymphoma. Part II. Relationship between clinical features and the Lukes-Collins classification of 34 cases. *Oral Surg Oral Med Oral Pathol* 1987, **64**, 597–602.
21. Regezzi JA, Zarbo RJ, Stewart JCB. Extranodal oral lymphomas: histologic subtypes and immunophenotypes (in routinely processed tissue). *Oral Surg Oral Med Oral Pathol* 1991, **72**, 702–708.
22. Slootweg PJ, Wittkampf ARM, Kluin PM, Wilde PCM de, Unnik JAM van. Extranodal non-Hodgkin's lymphoma of the oral tissues. *J Maxillofac Surg* 1985, **13**, 85–92.
23. Soderholm A-L, Lindqvist C, Heikinheimo K, Forssell K, Happonen RP. Non-Hodgkin's lymphomas presenting through oral symptoms. *Int J Oral Maxillofac Surg* 1990, **19**, 131–134.
24. Takahashi N, Tsuda N, Tezuka F, Okabe H. Primary extranodal non-Hodgkin's lymphoma of the oral region. *J Oral Pathol Med* 1989, **18**, 84–91.
25. Robbins KT, Fuller LM, Manning J, *et al.* Primary lymphoma of the mandible. *Head Neck Surg* 1986, **8**, 192–199.
26. Eisenbud L, Sciubba J, Mir R, Sachs SA. Oral presentations in non-Hodgkin's lymphoma: a review of thirty-one cases. Part II. Fourteen cases arising in bone. *Oral Surg Oral Med Oral Pathol* 1984, 57, 272–280.
27. Barber HD, Stewart JCB, Baxter WD. Non-Hodgkin's lymphoma involving the inferior alveolar canal and mental foramen: report of a case. *J Oral Maxillofac Surg* 1992, **50**, 1334–1336.
28. Dorosetz DE, Raymond AK, Murphy GF, *et al.* Primary lymphoma of bone. *Cancer* 1982, **50**, 1009–1014.
29. Shima N, Kobashi Y, Tsutsui K, *et al.* Extranodal non-Hodgkin's lymphoma of the head and neck. *Cancer* 1990, **66**, 1190–1197.
30. Ossenkoppele GJ, Mol JJ, Snow GB, *et al.* Radiotherapy versus radiotherapy plus chemotherapy in stage I and II non-Hodgkin's lymphoma of the upper digestive and respiratory tract. *Cancer* 1987, **60**, 1505–1509.
31. Nissen NI, Ersboll J, Sand Hansen H, Walbom-Jorgensen S. A randomized study of radiotherapy plus chemotherapy in stage I–II non-Hodgkin's lymphomas. *Cancer* 1983, **52**, 1–7.
32. Cabanillas F. Chemotherapy as definitive treatment of stage I–II large cell and diffuse mixed lymphomas. *Hematol Oncol* 1985, **3**, 25–31.