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EXTRANODAL NON-HODGKIN'S LYMPHOMA IN THE HEAD AND NECK

Irradiation and clinical course

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The natural history of non-Hodgkin's lymphoma (NHL) has not yet been clarified, but it seems important to differentiate extranodal NHL from nodal NHL. Criticism has been expressed concerning the treatment of early extranodal NHL using extended fields such as mantle or inverted Y fields which often are used for Hodgkin's disease. In addition, tumors originating from extranodal sites in the head and neck region tend clinically to behave somewhat differently from nodal lymphomas.

In the present report, results of irradiation for early extranodal NHL related to the head and neck region and the behaviour of the disease after local irradiation are analysed for the various extranodal sites in the head and neck region including Waldeyer's ring, in order to assess the appropriate treatment fields and the value of prophylactic lymph node irradiation. The value of systemic examinations for staging purposes is also discussed.

Materials and Methods

During the 25-year period from 1955 to 1979, 218 NHL patients were referred to this University Hospital, 188 of these had lesions within the head and neck region, either localized or as part of a disseminated disease. Excluding the cases with lesions located in the neck lymph nodes, nodal NHL, 113 patients were clinically considered to have NHL from extranodal sites including Waldeyer's ring.

As the purpose was to analyse the clinical behaviour of localized extranodal NHL, the main subjects were patients with stage I and II lymphomas. However, patients classified as stage III and IV were also evaluated in order to analyse the clinical behaviour of the disease and the value of different staging procedures.

Site of involvement. The involvement of NHL in extranodal sites of the head and neck region could mainly be divided into 3 groups: Waldeyer's ring, the oral cavity or maxillary sinus, and the nasal cavity. The patients in these groups numbered 47, 44 and 19, respectively. The remaining three patients had lesions in the orbit, the parotid gland, and the thyroid. Among the oral cavity or sinus cases, 24 patients had lesions in the upper gum, palate or maxillary sinus, 15 patients in the lower gum including the mandible, 2 patients in the floor of the mouth, and one patient in the lip, buccal mucosa and tongue.

In the localized stage I and II patients it seems likely that the lesions started from the sites mentioned, in the stage III and IV patients, the disease may have originated from other sites, the initial sites in advanced cases having been estimated from their clinical courses alone.

Histopathologic re-evaluation. Most of the patients had been classified according to earlier classi-

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fication types, such as reticulum cell sarcoma or lymphosarcoma. Accordingly, the pathologist in the team (R.K.) re-evaluated the available histopathologic material and reclassified the subjects according to the RAPPAPORT classification (1966). Original material could not be obtained for 16 of the 113 patients, who therefore were excluded from the analysis. In addition, among the remaining 97 patients, 10 were regarded as having a different histopathologic diagnosis such as Hodgkin's lymphoma, lymphoepithelioma, or Wegener's granulomatosis. Therefore, only 87 patients were reclassified as NHL in this retrospective review (Table 1). The sex distribution of these 87 patients was 46 males and 41 females, and the average age was 46 years with a minimum of 2 and a maximum of 82. The diffuse type of NHL was predominant (82 of 87, 94%); only 5 patients had a nodular type.

The relationship between the subtypes of NHL and the extranodal sites is shown in Table 2. About half of the lesions in Waldeyer's ring were of the diffuse histiocytic (DH) type, and two thirds in the nasal cavity diffuse mixed lymphocytic and histiocytic (DM) type. In the oral cavity or sinus, no subtype predominated. In 2 other patients lesions of the diffuse, lymphocytic, poorly differentiated (DLPD) type and the Burkitt type were found located in the parotid gland and in the orbit, respectively.

Table 1

Histopathologic re-classification of 87 patients with extranodal non-Hodgkin's lymphoma in the head and neck. Numbers in parentheses represent patients with localized disease (stage I, II)

	Nodular	Diffuse
Lymphocytic, well differentiated	0	3 (3)
Lymphocytic, poorly differentiated	3 (3)	17 (9)
Mixed (lymphocytic and histiocytic)	2 (1)	26 (23)
Histiocytic	0	31 (26)
Burkitt	0	5 (2)
Total	5	82

Staging procedures. Staging of NHL was performed according to the Ann Arbor classification for Hodgkin's disease (CARBORN et coll. 1971). The decision regarding staging was based upon the diagnostic evaluation including the patient's history, physical examination, blood chemistry and results of radiologic examinations. Bipedal lymphangiography and bone marrow needle biopsy have been performed during the past 10 years, while bone scintigraphy with $^{99}\text{Tc}^{\text{m}}$ -MDP and examination of the gastrointestinal tract have been undertaken in the past few years. Diagnostic laparotomy was not employed as a staging procedure, similar to the practice in most Japanese institutions. Among 50 pa-

Table 2

Histopathologic subtype and extranodal site of the disease. Percentage given in parentheses

	Total No. of patients	Nodular (all)	DLWD	DLPD	DM	DH	DB
Waldeyer's ring	34	3 (8.8)	0	4 (11.8)	7 (20.6)	19 (55.9)	1 (2.9)
Nasal cavity	15	0	0	2 (13.3)	10 (66.7)	3 (20.0)	0
Oral cavity or sinus	36	2 (5.6)	3 (8.3)	10 (27.8)	9 (25.0)	9 (25.0)	3 (8.3)
Others	2			1			1
Total	87	5 (5.7)	3 (3.4)	17 (19.5)	26 (29.9)	31 (35.6)	5 (5.7)

DLWD: diffuse lymphocytic well differentiated.
DLPD: diffuse lymphocytic poorly differentiated.
DM: diffuse mixed (lymphocytic and histiocytic).
DH: diffuse histiocytic.
DB: diffuse Burkitt type.

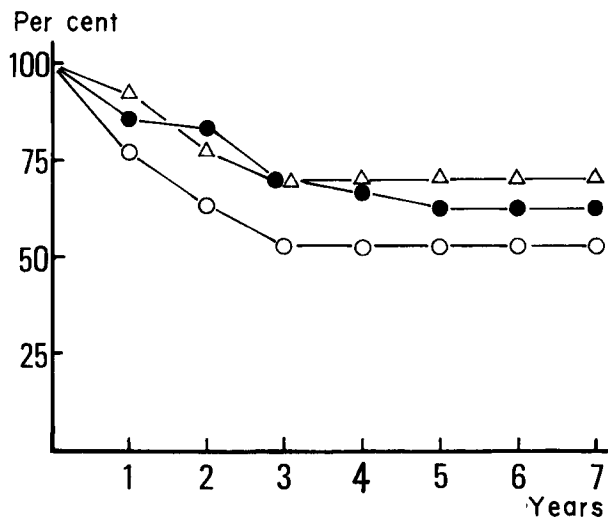


Fig. 1. Actuarial survival rates of localized extranodal non-Hodgkin's lymphoma (stage I and II). Nasal cavity $n=14$ (Δ). Waldeyer's ring, $n=30$ ($\bullet$). Oral cavity or sinus, $n=22$ ($\circ$).

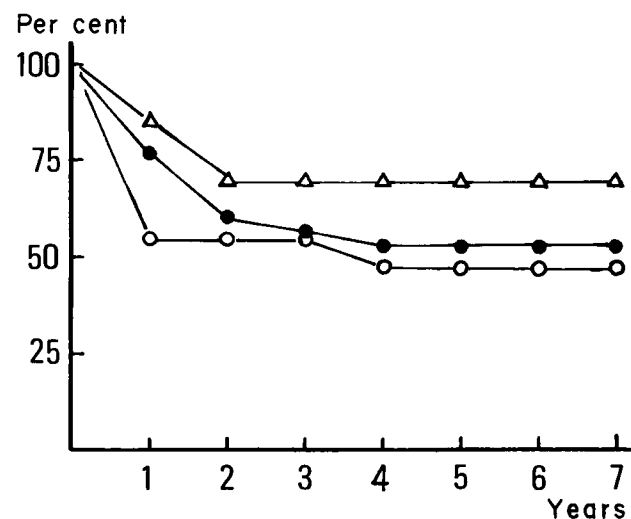


Fig. 2. Disease-free survival rates of localized extranodal non-Hodgkin's lymphoma (stage I and II). Symbols as in Fig. 1.

Table 3

Stage classification and extranodal non-Hodgkin's lymphoma in the head and neck (histopathologically reviewed cases only)

Site of lesion	Total No. of patients	Stage			
		I	II	III	IV
Waldeyer's ring	34	15	15	3	1
Nasal cavity	15	14	0	0	1
Oral cavity or sinus	36	9	13	3	11
Others	2	1	0	0	1
Total	87	39	28	6	14

tients from the past 10 years, lymphangiography was performed in 74 per cent, bone marrow examination in 66, and bone scintigraphy in 40 per cent. Staging within the different sites of involvement is listed in Table 3. All these patients were re-confirmed as NHL.

Most of the patients whose extranodal lesions were located within the head and neck region were referred for radiation therapy from head and neck surgeons (ENT or oral surgeons) after biopsy and histopathologic diagnosis. The lesions had initially been thought to be localized (stage I or II), before the more systematic staging examination, except in a small number of advanced stage III or IV patients who were referred for palliative treatment. However, as shown in Table 3, many stage III or IV

patients were found during the staging examination, especially among those with oral cavity or sinus lesions, i.e. 14 out of 36 (38.9%). The usefulness of the different diagnostic measures will be discussed later.

Radiation therapy. For stage I and II patients whose lesions were located in extranodal sites in the head and neck region with or without regional neck node involvement, only the affected areas were irradiated and prophylactic regional lymph node irradiation was not used, except for lesions localized to Waldeyer's ring. In patients with a lesion in Waldeyer's ring, irradiation of the primary tumor and the neck nodes down to the clavicles was given irrespective of regional neck node involvement.

The irradiation was administered by an orthovoltage 250 kV machine (before 1965) or a ^{60}Co telecurie unit (after 1965), and in a few cases a high-energy electron beam from a betatron. Doses ranged from 30 to 50 Gy with a daily dose of 1.8 to 3.0 Gy in patients with localized lesions. When irradiation was given for a purely palliative purpose in patients with advanced disease the doses were modified according to the condition of each patient.

Results

Survival rate. Actuarial survival rates for stage I and II patients with localized lesions appear in Fig. 1 according to the sites of the involvement. As mentioned, no patient with a lesion localized to the nasal cavity was classified as stage II. In other

words, no patient with regional lymphadenopathy belonged to the nasal cavity group.

The actuarial 5-year survival rate for the nasal cavity group was 70.0 per cent and this figure was stable from 3 to 7 years. Also for lesions from the oral cavity or sinus, the actuarial survival rate was stable from 3 to 7 years (52.2%). For Waldeyer's ring involvement the 5- and 7-year survival was 62.7 per cent. No definite differences in the survival figures were observed between stage I and stage II patients with involvement of Waldeyer's ring or the oral cavity or sinus.

Disease-free survival rates appear in Fig. 2. In the nasal cavity, no relapse occurred after 2 years. As for the oral cavity or sinus all relapses occurred within one year except for one patient who developed lesions in the femoral soft tissue after three and a half years and was controlled with surgery and adjuvant chemotherapy for more than 4 years thereafter. In Waldeyer's ring, the majority of relapses developed within 2 years. In one patient relapse occurred after 3 years and in another after 4 years, however. Disease-free survival rates were the same from 4 to 7 years for all the sites mentioned, i.e. 70.0 per cent for nasal cavity, 47.2 for oral cavity or sinus, and 53.1 per cent for Waldeyer's ring.

Initial relapse after irradiation. The type of relapse from localized (stage I, II) extranodal NHL was rather characteristic for the different original sites. The site of the first relapse observed clinically after irradiation of patients with localized stage I or II lesions appears in Table 4. Among cases with a Waldeyer's ring lesion, 13 patients had relapse after irradiation and 12 of these relapses developed in distant areas outside the radiated volume. The majority of these relapses first occurred in the gastrointestinal tract, i.e. 7 in the stomach and one in the ileocaecal junction. In one patient lymph node relapse developed in the right axilla 3 months after the initial irradiation. No local recurrence occurred in cases with lesions initially located in the oral cavity or sinus. Among the 8 patients with relapse in this group, one patient in stage I and one in stage II developed lymph node relapse located in the neck and the axilla, respectively. However, 4 of these 8 patients developed widespread bone or soft tissue lesions located in the humerus, the femur and the pelvic bone. Of these cases with widespread relapses 3 were originally classified as stage I and one as stage II. In one of the oral and sinus cases the first relapse occurred in the upper abdomen, and

Table 4

First relapse after irradiation in patients with initially localized disease (stage I, II)

	Waldeyer's ring (13/30)	Nasal cavity (4/14)	Oral cavity or sinus (8/22)
Marginal relapse	1	1	0
Lymph node	1	1	2
Abdomen			
Upper	7	0	1
Lower	1	0	0
Bone or soft tissue	2	2	4
Others	1	0	1
Intercurrent death or death of unknown cause	1	1	4

one patient became leukaemic after 6 months. The relapse occurred within 6 months in 7 of these patients and the remaining patient developed soft tissue lesions in the right thigh after 3 and a half years.

Of the cases with lesions originally located in the nasal cavity only 4 developed relapse, one of these in the margin of the irradiated volume, in another patient a cervical node involvement was associated with an upper abdominal mass, and the remaining 2 patients developed lesions in the spine and in the soft tissues, respectively.

Dose-time relationship. The relationship between the total dose, the treatment time in days, and the effect of irradiation in stage I and II patients, are shown in Fig. 3. Local tumor control was quite good at doses ranging from 30 to 50 Gy; lesions that had disappeared completely did not recur locally except in 2 patients in whom marginal recurrences developed as already described. No correlation was found between the total dose, the treatment time, and the result of treatment within the dose range of 30 to 50 Gy. However, relapses in distant regions without local recurrence were frequently observed.

Discussion

Opinions as to whether NHL originating from Waldeyer's ring, rather frequently occurring in Japan, should be classified as nodal lymphoma or as extranodal lymphoma have differed. Lesions with this site have, however, been classified as nodal disease according to the recommendations by the Ann Arbor International Conference for Hodgkin's

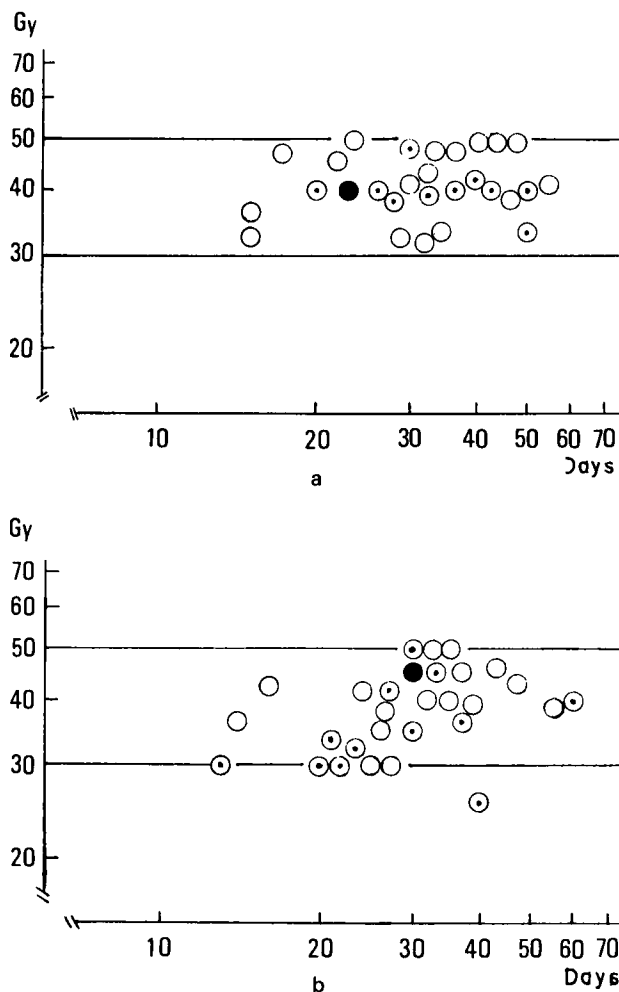


Fig. 3. Dose-time scattergrams for stage I and II patients. a) Waldeyer's ring. b) Nasal cavity and oral cavity or sinus. No evidence of disease more than 2 years later ($\circ$). Relapse to distant areas without local recurrence ($\odot$). Marginal relapse ($\bullet$).

disease (CARBORN et coll.). In some reports (KIM et coll. 1978, FRASER et coll. 1979) NHL arising from Waldeyer's ring has nevertheless been regarded as extranodal lymphoma. Several Japanese reports (IKEDA et coll. 1977, HAYABUCHI 1980, YAMASHITA et coll. 1980) recommended that lesions of Waldeyer's ring should be separated from other extranodal lesions as the treatment results are better in the former group and as the clinical behaviour of Waldeyer's ring lesions are somewhat different from other nodal and extranodal NHL. BANFI et coll. (1972) stated concerning the natural history of malignant lymphoma of Waldeyer's ring, that recurrences might develop simultaneously in Waldeyer's ring and in other parts of the gastrointestinal tract, especially the stomach, or might develop later in the gastrointestinal tract. In the present series, 8 of 13

relapses from lesions of Waldeyer's ring were first observed in the gastrointestinal tract. Although the involvement of NHL in the gastrointestinal tract may be unnoticed at the beginning of the treatment, careful examination of the gastrointestinal tract is important both during the initial staging and during the follow-up period.

In NHL of the oral cavity or sinus, many of the relapses occurred as multiple bone or soft tissue lesions. In patients temporarily classified as stage I, further staging examinations sometimes disclosed occult involvement of bone or bone marrow and therefore these patients could finally be classified as stage IV.

Malignant lymphoma of the oral cavity and paranasal sinuses is often extensive and involves multiple sites, but it tends to remain localized (WANG 1971). Moreover, unlike malignant lymphoma of Waldeyer's ring, spread to the regional nodes is rather uncommon. In another report it was also stated that lymphoma of the paranasal sinuses is strikingly dissimilar to nodal lymphomas, and the incidence of para-aortic node lesions seemed to be low (SOFFERMAN et coll. 1975). In the present series, initial lymph node involvement was not found in NHL of the nasal cavity. In NHL of the oral cavity or sinus the incidence of regional lymph node involvement was comparable to that of NHL in Waldeyer's ring.

The methods for diagnosis and staging of lymphoma have improved with time during the past 20 years. Concerning patients treated after 1971 in whom lymphangiography, bone marrow biopsy and bone scintigraphy were routinely applied during the initial staging, the value of various examinations was evaluated. In the group with NHL in the oral cavity or sinus, 2 patients of 7 who initially appeared to be in stage I could be classified as stage IV; in both of them, bone marrow biopsy and bone scintigraphy revealed pathologic findings. Three of 10 patients initially thought to be in stage II were reclassified to stage III (one patient) and stage IV (2 patients); all these 3 patients had pathologic findings at lymphangiography, one of them a pathologic bone scintigraphy, and one a pathologic liver scintigraphy. In none of the cases with NHL in Waldeyer's ring initially classified as stage I did the stage have to be changed. Two of the 9 patients initially classified as stage II had to be reclassified to stage III and IV due to findings at ^{67}Ga scintigraphy and bone marrow biopsy. In the staging of extranodal

NHL, lymphangiography is now routinely used, as well as bone marrow biopsy, scintigraphy of bone and liver, and examination of the gastrointestinal tract.

If the extent of the disease has been determined as accurately as possible by means of the methods mentioned, prophylactic irradiation of uninvolved volumes seems to be unnecessary and useless as the sites of relapse are not predictable in extranodal NHL. Local irradiation of early extranodal NHL appears to be effective. Prophylactic irradiation of the cervical and supraclavicular regions has been proposed based on observations that 40 per cent of the initial failures occurred in untreated cervical nodes while such failures occurred in only 6 per cent of these cases when the neck was irradiated (FRASER et coll.). Similar experiences were previously reported regarding reticulum cell sarcoma in Waldeyer's ring (HORIUCHI et coll. 1976). Therefore, in patients with NHL in Waldeyer's ring the whole neck down to the clavicles is at present irradiated irrespective of clinical neck node involvement. As regards other localizations of extranodal NHL within the head and neck region, only the involved area should be irradiated as the sites of relapse according to the present experiences are unpredictable. If the treatment fields were sufficient to cover the involved volume, local recurrence was seldom observed after doses ranging from 30 to 50 Gy. Furthermore, no relationship seemed to exist between the total dose, the treatment period, and the treatment result. A sufficient total dose which is relatively independent of the treatment time or number of fractions seems to be necessary for the control of malignant lymphoid tumors (COX et coll. 1974).

In patients with clinically localized diffuse lymphomas, no differences in results were noted between extended field and involved field irradiation (JONES et coll. 1973). The histopathologic subtype had a definite role in predicting the prognosis (KIM et coll.) with a worse prognosis for histiocytic lymphoma than for lymphocytic lymphoma. In the present series diffuse lymphoma occurred in 94 per cent (63 of 67 patients). Most of the diffuse histiocytic lymphomas (23/26) and only about half of the diffuse lymphocytic, poorly differentiated type (9/17) were localized. However, the number of patients was too small for an analysis of the prognosis in the different subtypes. In a recent report concerning 551 NHL patients collected from 14 institutions in Japan, including the present ones, diffuse lymphoma ac-

counted for 82.9 per cent (YAMASHITA et coll.). As for the extranodal sites and Waldeyer's ring, the diffuse type accounted for 87.3 per cent; patients with diffuse lymphocytic, poorly differentiated types were also found in the advanced stage, while those with diffuse large lymphoid lesions were most frequent in Waldeyer's ring. The survival rate depended upon the origin of the lesions. The highest survival rate was found in Waldeyer's ring lymphomas and the lowest in nodal lymphoma.

The value of combined treatment of localized NHL cannot be discussed, as the present series did not contain a group of stage I and II patients treated with irradiation and chemotherapy. However, as improved survival has been reported after such combined treatment of localized extranodal NHL of diffuse histopathologic type (MONFARDINI et coll. 1980), a similar treatment regime has been applied at this hospital since 1980.

SUMMARY

A retrospective analysis was performed of localized extranodal non-Hodgkin's lymphomas in the head and neck region treated with irradiation. Histopathologic re-evaluation revealed 94 per cent with a diffuse type. The lesions were as a rule locally cured with doses ranging from 30 to 50 Gy. Relapses in localized stage I and II patients were, however, not seldom observed in distant extranodal sites. Gastrointestinal relapse in cases with lesions originally located in Waldeyer's ring was thus frequently observed, and the probability of multiple or systemic involvement should be considered also when the disease is located in the oral cavity or sinus region. The value of systemic examination for staging purposes is discussed.

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