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TREATMENT OF NON-HODGKIN LYMPHOMAS IN THE NASAL CAVITIES AND PARANASAL SINUSES

A failure analysis

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Abstract

Twenty-five patients with sinonasal lymphoma were treated mainly with irradiation. All were non-Hodgkin lymphomas of diffuse type. Twenty patients had stage I A, 2 had stage I B, 1 stage II A, 1 stage III A, and 1 stage IV A disease. Relapse developed in 16 (64 %) of the 25 patients, with a failure rate of 64 per cent in the stage I patients (14/22). Most patients with failures had distant spread of the disease with or without local recurrence. Only one patient had local recurrence alone at the first relapse. Histologic classification according to the new working formulation seemed to be a reliable prognostic indicator for relapse: failure rates for low, intermediate, and high grade lymphomas were 0 per cent (0/2), 46 per cent (6/13), and 100 per cent (10/10), respectively. Computed tomography was valuable for planning of radiation therapy and for follow-up.

Key words: Lymphoma, non-Hodgkin, sinonasal, treatment.

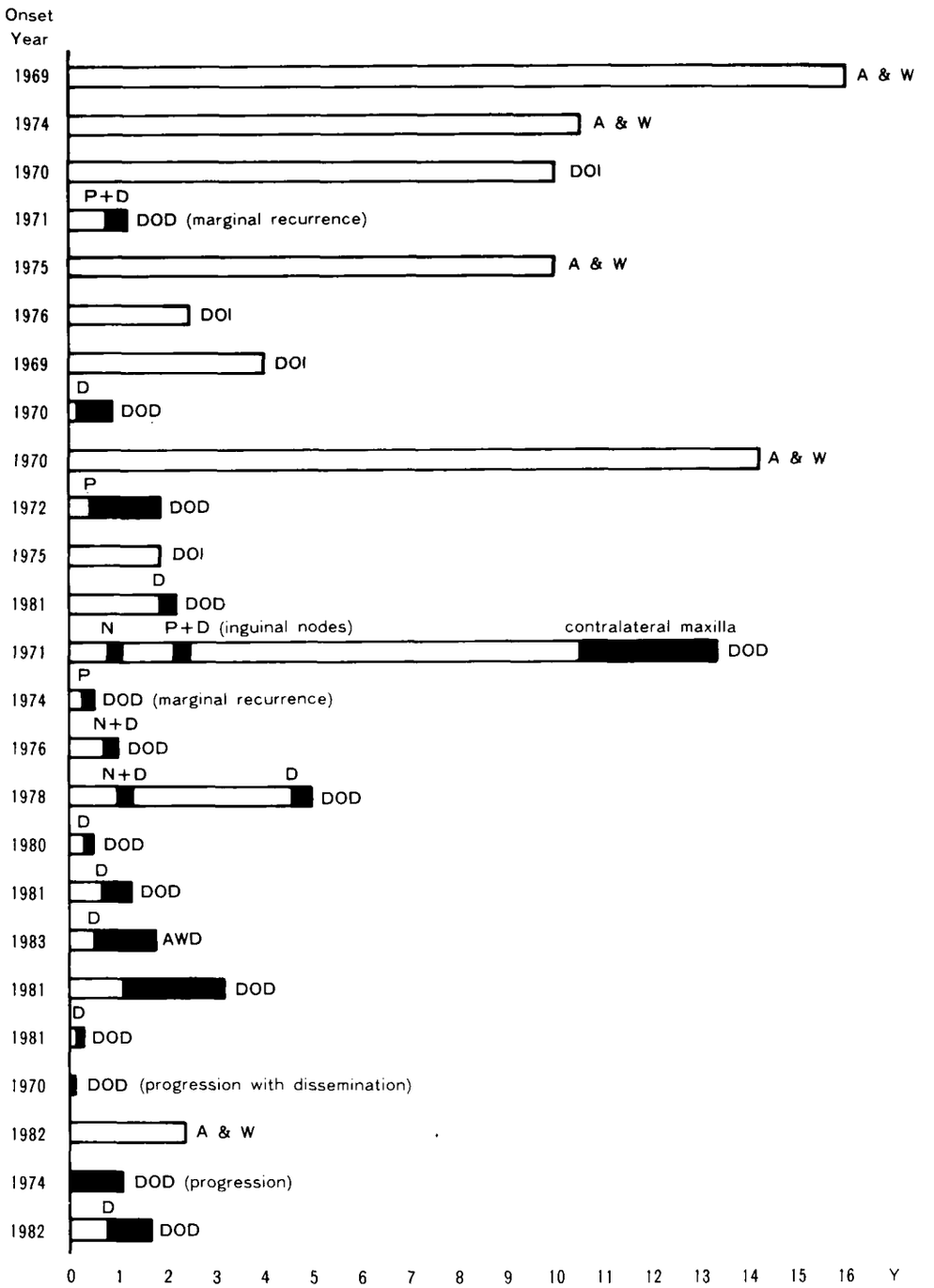
Radiation therapy has been the treatment of choice for malignant lymphomas of the nasal cavities and the paranasal sinuses. However, 20 to 67 per cent of reported patients with localized disease have had a relapse after irradiation (1, 3, 7, 8, 15, 22, 25, 26). Even for stage I patients, high relapse rates of 20 to 55 per cent have been reported (1, 7, 8, 25, 26). For several reasons, it is difficult, from the literature, to define the most suitable form of therapy for sinonasal lymphomas. First, the incidence rate of malignant tumors originating in the sinonasal cavities is low, and malignant lymphomas constitute only 5 to 8 per cent of these tumors (20, 22). In a large multiinstitutional study, only 9 of 1 064 well-documented cases of non-Hodgkin lymphoma had sinonasal involvement at the first presentation (23), and therefore, no single institution can collect a large number of cases in a short period. Secondly, prognostic factors have not been well defined. Treatment itself may be prognostically important but radiation techniques were old, or not well defined in some series (2, 3), which may be a reason for the reported relatively high local recurrence rates. Thirdly, the now obsolete GALL & MALLORY classification was used in many reports (1, 3, 5, 6, 14, 21, 22, 24). Since histology may be one of the most important prognostic factors, a histologic classification system must be uniform. Although the RAPPAPORT classification has been widely used because of its clinical relevance, it is now regarded as pathogenetically inadequate on the basis of cytologic and immunologic studies. There are at present at least six major classification systems for non-Hodgkin lymphomas elaborated by distinguished pathologists (23). A study group sponsored by the National Cancer Institute has therefore proposed a working formulation for histologic classification of non-Hodgkin lymphomas suitable for clinical usage (23), in order to allow translation between the major classification systems. Fourthly, to define the site of origin of the lesions is often difficult, and therefore sinonasal lesions are in several reports pooled with lesions in Waldeyer's ring or the oral cavity (2, 4, 7, 9, 24). Fifthly, since all reports as well as the present analysis include cases collected over rather long periods, uniform staging has not been performed. The mentioned factors, as well as inadequate follow-up in some series, makes a meaningful comparison between different reports difficult or impossible.

Accepted for publication 9 December 1985.

Case No.	Sex	Age	Histology			Staging procedures	Stage	Radiation dose(Gy)	Chemotherapy (total dose)
			Working	Formulation	Rappaport				
1	M	51	small	lymphocytic	WDL	–	I A	60	BLM 95mg 5-FU 30mg
2	M	18	small	lymphocytic	WDL	–	I A	24	–
3	M	59	small	cleaved	PDL	–	I A	30	BLM 300mg
4	M	17	small	cleaved	PDL	–	I A	30	BLM 300mg
5	M	32	small	cleaved	PDL	–	I A	36	CYC 3000mg BLM 75mg
6	F	84	small	cleaved	PDL	Ga	I A	36	–
7	M	87	mixed small & large		M	–	I A	40	–
8	F	65	mixed small & large		M	–	I A	16	5FU 4 g
9	M	63	mixed small & large		M	–	I A	40	–
10	M	52	mixed small & large		M	–	I A	30	BLM 300mg
11	M	50	large	cleaved	H	–	I A	48	BLM 105mg
12	M	70	large	noncleaved	H	Ga, CT	I A	60	–
13	M	52	large	immunoblastic	UD	–	I A	–*	–
14	M	46	large	immunoblastic	H	–	I A	46	5FU 5 g
15	F	82	large	immunoblastic	H	–	I A	30	BLM 30mg
16	M	63	large	immunoblastic	H	Ga, CT	I A	50	CYC 7000mg VCR 10mg
17	M	63	large	immunoblastic	H	Ga,LAG,CT BM	I A	40	CHOP of 30% doses × 2
18	M	65	large	immunoblastic	H	Ga,LAG,CT	I A	50	CYC 1500mg VCR 4mg PSL 120mg
19	F	79	large	immunoblastic	H	Ga, CT	I A	40	–
20	F	63	small	noncleaved	UD	Ga,LAG,CT BM	I A	50	–
21	M	38	large	cleaved	H	Ga,LAG,CT BM	I B	50	–
22	M	61	large	immunoblastic	H	–	I B	14	–
23	F	70	large	cleaved	H	Ga,LAG,CT BM	II A	40	CHOP × 6
24	F	22	small	cleaved	PDL	–	III A	20	CYC 700mg VCR 7mg BLM 210mg
25	F	56	large	immunoblastic	H	Ga,LAG,BM	IV A	–	CHOP × 6

* He had maxillectomy under the wrong diagnosis of cancer.

Fig. 1. Summary of data from 25 patients with sinonasal NHL. WDL: well differentiated, diffuse, lymphocytic. PDL: poorly differentiated, diffuse, lymphocytic. M: mixed lymphocytic-histiocytic. UD: undifferentiated. Ga: gallium scintigram. LAG: lymphangiography. BM: bone marrow examination. BLM: bleomycin. 5-FU: 5-fluorouracil. CYC: cyclophosphamide. VCR: vincristine. PSL: prednisolone. CHOP: cyclophosphamide-doxorubicin-vincristine-prednisolone. A & W: alive without signs of lymphoma. DOI: dead of intercurrent disease without signs of lymphoma. DOD: dead with lymphoma. N: cervical node relapse. D: distant relapse. P: local relapse of primary lesion.



Material and Methods

From 1969 through 1983, 25 patients (17 males and 8 females) with sinonasal non-Hodgkin lymphoma were seen at this institution or at affiliated hospitals. Ages ranged from 17 to 87 years (median 61 years). The staging procedure included physical examination, blood counts, peripheral blood chemistry, and roentgen examination of chest and sinuses, including sinus tomography. Bipedal lymphangiography (LAG), ^{67}Ga scanning, and bone marrow biopsy have more recently been introduced. LAG was performed in 6, ^{67}Ga scanning in 10, and bone marrow biopsy in 5 patients. Twenty-two patients had disease confined to the sinonasal region. Two patients had enlarged cervical node(s), and one patient had enlarged axil-

lary and inguinal nodes and splenomegaly. One patient (No. 20) had in addition to the nasal lesion a lymphoma lesion at the base of the tongue but was classified as stage I. All patients without cervical lymphadenopathy had negative findings at lymphangiography, ^{67}Ga scanning or bone marrow biopsy. Only one patient with enlarged cervical nodes was upstaged because of positive results from LAG, ^{67}Ga scanning, or bone marrow biopsy. Two patients had systemic symptoms. According to the Ann Arbor system 20 patients had stage I A, 2 stage I B, 1 stage II A, 1 stage III A, and 1 stage IV A disease. Computed tomography of the sinonasal region was performed in 9 patients before treatment. The histopathologic slides were reviewed by one of us (A. M.) and the tumors classified according to RAPPAPORT (19) and the working formulation of non-Hodgkin lymphomas for clinical usage (23). All showed diffuse histology. According to the Rappaport classification, 12 cases were diffuse histiocytic, 5 diffuse poorly differentiated lymphocytic, 4 diffuse mixed, 2 diffuse undifferentiated non-Burkitt, and 2 diffuse well-differentiated lymphocytic lymphomas. Distribution of the cases according to the working formulation is shown in Table 1; 2 cases were low grade, 13 intermediate grade, and 10 high grade lymphomas. Twenty-three patients received local radiation treatment without prophylactic irradiation of the neck. The total doses ranged from 14 to 60 Gy (median 40 Gy) fractionated with 2 Gy per day, 5 to 6 times per week. The treatment fields were adapted to the estimated extension of the tumor, which in recent years has been determined by CT. For unilateral lesions, a box field technique with a wedge pair was commonly used. For midline lesions, a single anterior port was used. One patient received total maxillectomy under the clinical diagnosis of maxillary carcinoma. Two patients received CHOP chemotherapy with the following doses, during 6 cycles repeated every 21 days: doxorubicin 50 mg/m^2 i.v., day 1; cyclophosphamide 750 mg/m^2 i.v., day 1; vincristine 1.4 mg/m^2 (maximum 2.0 mg) i.v., day 1; and prednisolone 50 mg/m^2 p.o., days 1–5. Fourteen patients received either single-agent or combination chemotherapy with doses that usually were lower than those at present recommended for advanced stage NHL. The basic data concerning the cases are given in Fig. 1.

Table 1

Incidence according to the working formulation

Cell type	No. of cases
Low grade	
Small lymphocytic	2
Follicular, small cleaved	0
Follicular, mixed, small and large	0
Intermediate grade	
Follicular, large	0
Diffuse, small cleaved	5
Diffuse, mixed, small and large	4
Diffuse, large, cleaved or non-cleaved	4
High grade	
Large, immunoblastic	9
Lymphoblastic	0
Small noncleaved	1

Table 2

Relapse versus histologic subtype

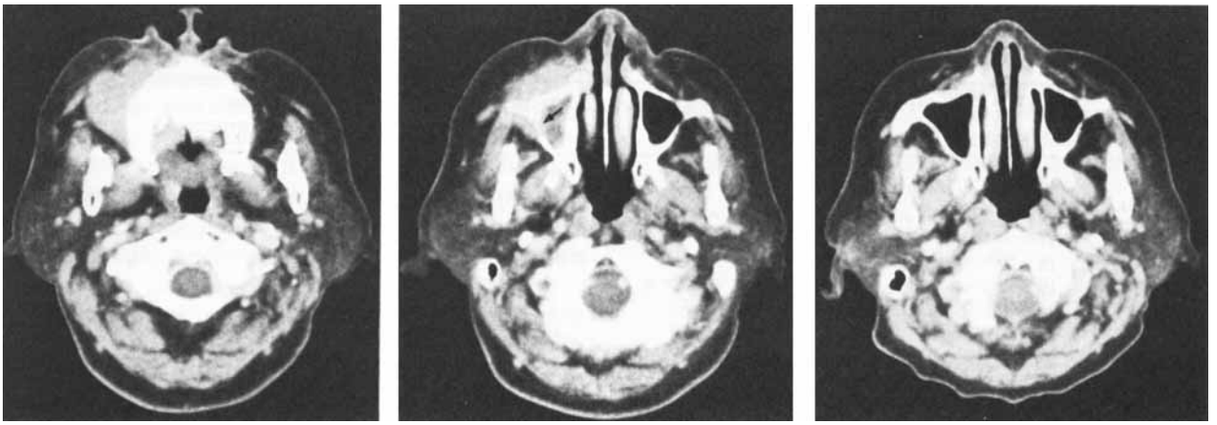
Histologic subtype	All cases*	Stage I A
Rappaport classification		
Diffuse well-differentiated lymphocytic	0/2	0/2
Diffuse poorly differentiated lymphocytic	2/5	1/4
Diffuse mixed	2/4	2/4
Diffuse histiocytic	10/12	7/8
Diffuse undifferentiated, non-Burkitt	2/2	2/2
Working formulation		
Low grade	0/2	0/2
Intermediate grade	6/13	4/10
High grade	10/10	8/8

* No. of relapse/No. at risk.

Results

A summary of the clinical courses is shown in Fig. 1. Relapse occurred in 16 (64%) of the 25 patients: in 14 of the 22 stage I patients and 2 of the 3 stage II–IV patients. Both patients with initial systemic symptoms relapsed. Relapse was observed in 10 of the 17 male patients and in 6 of the 8 female patients. The mean and median ages of the relapsing patients were 55.8 and 62 years, respectively, compared with 57.1 and 59 years for the non-relapsing patients. Relapse occurred in 9 of 13 patients with nasal location of the original lesion and in 7 (58%) of 12 patients with the original lesions in the paranasal sinuses. In 2 patients the disease progressed in spite of the primary treatment. The other 14 relapsing patients had disease-free intervals of 1 to 23 months before relapse. All but one relapsing patient died of the disease.

In 15 patients distant spread of the disease was observed at the time of the first relapse. Except for the 2 patients in whom primary radiation treatment was stopped because of progressive disease, only 2 patients had local recurrence after irradiation. These 2 recurrences were probably due to inadequate coverage of the tumors by the radiation fields, as suggested by re-examination of the roentgen films. Cervical nodal lesions alone as the first relapse were seen in only one patient. In all other cases with cervical lymphadenopathy at the time of the first relapse, this was accompanied with distant spread of the disease. Interestingly, the skin and the subcutaneous tissue was a frequent site of the first relapse: 8 of the 15 patients with dissemination had cutaneous or subcutaneous lesions either alone or as a component of the relapse. There was no obvious dose-response relation for local



a b c

Fig. 2. Case 23. Female aged 70, with sinonasal lesions, lesion in right gingivobuccal sulcus, and lymphadenopathy in right submandibular region. CT at presentation shows the extension of the tumor in the right cheek (a) and, in a different slice (b), abnormal soft tissue density in right cheek, maxillary sinus and infratemporal fossa. Subtle destruction of the right posterior maxillary wall is seen (→). At the completion of 6 cycles of CHOP chemotherapy all abnormal masses had disappeared and the right posterior maxillary wall had returned to normal (c). Courtesy of J. Comput. Assist. Tomogr. 8 (1984), 216.

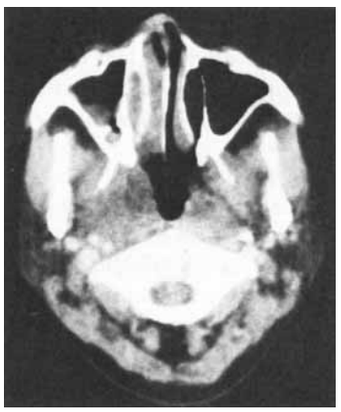


Fig. 3. A patient with stage IV disease not included in the analysis due to recent primary treatment. CT shows abnormal masses in the right nasal cavity and maxillary sinus without bone destruction. The right lateral wall of the nasopharynx is grossly involved. The left wall of the nasopharynx may also be involved, to judge from the appearance of the Rosenmüller fossa.

control. Excluding the 2 patients in whom the radiation treatment was interrupted and the 2 patients with possible marginal recurrences there were no true recurrences. Two patients receiving only 24 and 16 Gy remained locally free of recurrence.

Relapse developed in 11 of 16 patients who received chemotherapy and in 5 of 9 patients without chemotherapy. The two patients who received full-dose CHOP chemotherapy achieved complete remission. In one of these patients (stage II A) disappearence of the tumor mass was revealed by CT before booster irradiation (Fig. 2); this patient is alive and well at the time of writing. One patient (stage IV A) received full-dose CHOP chemotherapy alone and had a relapse outside the sinonasal region, but no local recurrence.

Table 2 shows relapse rates according to histology. The working formulation seemed to predict relapse better than the Rappaport classification, but the subgroups were too small for definite conclusions.

The CT findings at first presentation are shown in Table 3. Even with CT, estimation of the site of origin was difficult in some cases, due to involvement of multiple sites (Figs 2, 3). Abnormal soft tissue density in the sinonasal cavities was seen in all patients. In one patient, an abnormal mass was visible only in the unilateral nasal cavity. The other 8 patients had abnormal soft tissue density in two or more sites within the sinonasal region. Multiple biopsies from the different sites were done in 4 cases, and all showed lymphoma involvement. Definite bone destruction was evident in only 3 patients. In some cases equivocal findings of bone erosion were revealed by CT; however, follow-up CT after treatment usually showed disappearance of the abnormal masses, and intact bony walls.

Follow-up CT was performed in 7 patients. It showed in 6 cases complete disappearance of the abnormal masses. In one patients a residual, although reduced, mass was observed in the sphenoid sinus; however, no regrowth of this residuum was observed in several repeat CTs. In one patient, CT immediately after CHOP chemotherapy showed complete disappearance of the abnormal masses (Fig. 2). Later on, a soft tissue density was again observed in the irradiated maxillary sinus; this was considered to be due to inflammatory changes, as ^{67}Ga scanning was nega-

Table 3

Involved sites of lymphomas shown by computed tomography

Case No.	Nasal cavity	Maxilla	Ethmoid	Sphenoid	Naso-pharynx	Others	Bilateral	Bone destruction
12			+	+			+	
16	+	+						+
17		+	+			+		
18	+	+			+			+
19	+							
20	+						+	
21	+	+			+			
23		+				+		+

Table 4

Reported incidence according to the working formulation and relapse rates of stage I A

Subtype	Ref. 23	Ref. 25	Ref. 8	Present series
Low grade				
Small lymphocytic	–	7	–	2 (0/2)
Follicular, small cleaved	–	–	1	–
Follicular, mixed, small and large	–	–	1	–
Intermediate grade				
Follicular, large	–	–	–	–
Diffuse, small cleaved	1	4	4 (1/1)	5 (1/4)
Diffuse, mixed, small and large	2	5	2 (0/1)	4 (2/4)
Diffuse, large, cleaved or non-cleaved	3	18	9 (3/6)	4 (1/2)
High grade				
Large, immunoblastic	2	2	–	9 (7/7)
Lymphoblastic	1	–	–	–
Small non-cleaved	–	1	–	1 (1/1)
Total	9	37	17 (4/8)	25 (12/20)

In parentheses, No. of relapse/No. of stage I A.

tive while it had shown abnormal uptake in the maxillary sinus before treatment. The patient is alive and well at 28 months after diagnosis. In the patients for whom CT was used for planning of the radiation treatment no local recurrence has so far been observed.

Discussion

The present analysis suggests that the histology may be the single most important predicting factor for relapse, in patients with sinonasal lymphoma. The new working formulation of non-Hodgkin lymphomas for clinical usage (23) showed in this limited study impressively good correlation with the risk of relapse. In the literature, there is a wide range of relapse rates reported for sinonasal lymphomas, even in stage I patients. One reason may be differences in distribution of histologic subtypes. Unlike the present series, diffuse large immunoblastic lymphomas are rather rare in the other reported series (Table 4). Interestingly, the relapse rates for stage I patients with diffuse large follicular center cell type lymphoma were similar in the series of KAPADIA et coll. (8) and in the present investigation.

The prognostic significance of clinical stage cannot well be defined from the present analysis or from other reports. Most patients with sinonasal lymphoma present with stage I–II disease. A lack of thorough staging hampers a critical analysis of the literature (7–9, 15, 25). Also many of the present patients had undergone rather poor staging procedures, as they were collected over a long period. More thorough staging may upstage some patients, and patients with stage I, after aggressive staging, may have a good prognosis after radiation therapy alone. However, in the present study, no positive yield was obtained by LAG, ^{67}Ga scanning and bone marrow biopsy in the patients without palpable neck nodes. The prognosis, after radiation therapy, for stage I–II patients with head and neck non-Hodgkin lymphoma seems to be the same regardless of whether the patients are staged with LAG or not (26).

CT is useful for planning of radiation therapy, in order to assure inclusion of all lesions. Prophylactic irradiation of the neck seems to have no place in the treatment of stage I patients with sinonasal lymphomas (7, 22, 24, 26). Most patients who relapsed had distant spread of the disease. Patients with stage II disease should receive radiation therapy both against the primary lesion and the neck node region. Stage I–II patients with favorable histology could preferably receive radiation therapy alone and then be followed.

There are strong indications that chemotherapy should be added to radiation therapy for stage I–II patients with sinonasal lymphoma of high or intermediate grade. Aggressive combination chemotherapy such as CHOP or CHOP-Bleo (13, 16) seems more effective in adjuvant situations for localized non-Hodgkin lymphomas than less intensive combination regimens such as CVP (cyclophosphamide, vincristine, prednisolone) (12, 17, 18). In our experience, CHOP alone can produce complete remissions even in high grade lymphomas, and cure is possible. We therefore recommend aggressive chemotherapy combined with radiation therapy for localized sinonasal lymphomas of high or intermediate grade unless medically contraindicated. Since microdissemination is often present we recommend that chemotherapy be started before radiation therapy. In combination with chemotherapy the radiation doses in the sinonasal region may be reduced to 30 to 40 Gy.

Although CT clearly delineated the lesions, estimation of the site of origin within the sinonasal cavities, as well as differentiation of tumors of sinonasal origin from those of Waldeyer's ring or the oral cavity, may be difficult (Figs 2, 3). In sinonasal lymphomas, destructions of the bony wall are often subtle or absent (11), in contrast to sinonasal carcinoma (10). All nasal and paranasal cavities with abnormal soft tissue masses at CT should be considered at risk and included in the radiation fields.

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