

LOCALIZED EXTRANODAL LYMPHOMA OF THE HEAD AND NECK: RETROSPECTIVE ANALYSIS OF A SERIES OF 107 PATIENTS FROM A SINGLE INSTITUTION

Paolo Frata¹, Michela Buglione¹, Salvatore Grisanti², Bartolomea Bonetti¹, Elisabetta Vitali¹, Agostina De Stefani¹, Elena Magri¹, Andrea Peveri¹, Giovanni Marini², Giuseppe Rossi³, and Stefano M. Magrini¹

¹University Department of Radiation Oncology, Istituto del Radio "O. Alberti", Spedali Civili, Brescia; ²Medical Oncology Department, ³Hematology Department, Spedali Civili, Brescia, Italy

Purpose: To retrospectively analyze the outcome and patterns of relapse in localized extranodal non-Hodgkin's lymphoma of the head and neck (HN-NHL) after radiotherapy alone or combined modality treatment.

Patients and methods: A retrospective analysis of 107 patients with HN-NHL was performed. Relapse patterns, overall survival (OS) and relapse-free survival (RFS) were analyzed. Only stage I (n = 50) and stage II (n = 57) patients were included with either low-grade (n = 21) or high-grade (n = 86) lymphoma. Fifty-nine patients were treated with radiotherapy (RT) alone and 48 patients received combined-modality treatment (CMT) consisting of chemotherapy (CHOP or CHOP-like) followed by radiotherapy. The volumes of irradiation included local field (n = 24), involved field (n = 13) and extended field (n = 70). The median age at diagnosis was 63 years (range, 17-86 years).

Results: The overall response rates (CR+PR) in the radiotherapy group and the combined modality group were 100% and 96%, respectively. With a median follow-up of 49.4 months, 29 of 59 patients after RT alone (37%) and 30 of 48 patients after CMT (62%) were disease-free. In the whole series the projected five-year OS and RFS were 58.7% and 61.8%. At univariate analysis of clinical variables with potential impact on survival including age, stage, histology, IPI score, single or combined treatment and volumes of irradiation, only age and, to a limited

extent, type of treatment influenced OS (age ≤ 60 years 79%, >60 years 41%, $P < 0.001$; RT alone 54.9%, CMT 62.8%, $P = 0.0487$) and RFS (≤ 60 years 75%, >60 years 50%, $P < 0.001$; RT alone 54%, CMT 71%, $P = 0.039$). Better OS and RFS rates were obtained in patients with stage II and high-grade disease treated with CMT (five-year OS and RFS 63% and 69%, respectively; the corresponding values for RT alone were 38% and 34%). The final model of the multivariate analysis retained only age (≤ 60 years) as a significant prognostic factor for both RFS and OS ($P < 0.001$). In the whole series, the sites of relapse were mainly systemic (n = 32/40, 80%) and in-field relapses were rare (n = 3/40, 7.5%).

Conclusion: HN-NHL is characterized by a high risk of relapse, particularly at distant sites. Older patients have a significantly worse prognosis. Radiotherapy offers a very good local control rate although combined modality treatment possibly produces better RFS and OS, especially for stage II and high-grade disease. Better systemic approaches are warranted for a more consistent impact on survival in this particular subset of extranodal lymphoma. However, radiotherapy alone may offer a feasible and effective modality for patients who cannot tolerate more aggressive treatments. Extended-field radiotherapy and the treatment of a larger number of uninvolved lymph nodal regions does not confer a RFS or OS advantage, either after RT alone or after CMT.

Key words: combined modality treatment, extranodal lymphoma, head and neck, radiotherapy, relapse.

Introduction

Radiation therapy is an effective and commonly applied treatment for non-Hodgkin's lymphoma (NHL) either as single therapy or combined with chemotherapy. Both indolent and aggressive lymphomas may benefit from radiation therapy (RT). Indolent lymphomas such as follicular lymphoma with limited extension can be treated effectively with low-dose involved-field radiotherapy alone¹⁻⁶. The results of radiotherapy alone in limited, aggressive lymphomas have been less good, mainly because of distant relapses⁷. During the 1980s the therapeutic approach for aggressive NHL has evolved with the observation that the combination of short-course chemotherapy followed by involved-field radiotherapy was more effective than chemotherapy alone given for more cycles⁸. It was also demonstrated

that with combined-modality treatment (CMT), extended-field radiotherapy could be safely substituted with involved-field treatments, with lower toxicity. Thus, short-term chemotherapy followed by involved-field radiotherapy became the "gold standard" for limited stage, aggressive NHLs⁹.

Lymphomas arising in the head and neck area constitute the second most frequent extranodal site after the gastrointestinal tract¹⁰. In historical series, primary head and neck lymphomas with limited extension have been shown to remain localized and to display a favorable behavior after local treatments such as involved-field radiotherapy¹¹⁻¹⁴. However, after a good initial response, more than 50% of both indolent and aggressive lymphomas relapse outside the field of irradiation^{11,14,15}. Thus, involved-field radiotherapy alone may result in unsatisfactory disease control at regional and distant

Correspondence to: Prof. Stefano M. Magrini, Department of Radiation Oncology, Università degli Studi di Brescia, Piazzale degli Spedali Civili 1, 25123 Brescia, Italy. E-mail magrini@med.unibs.it

Received February 2, 2005; accepted July 5, 2005.

levels. The problem of systemic failure might assume even greater relevance for patients with poor performance status, advanced age or severe comorbidities, who are not eligible for systemic chemotherapy¹⁶.

To contribute to the information available on this issue, we here report the results of a retrospective analysis of a large series of patients with extranodal lymphomas of the head and neck. Our aim was to define the possible relationship between the radiation-treated volumes and the patterns of relapse. Overall survival (OS) and relapse-free survival (RFS) were also evaluated according to a number of clinical and therapeutic factors including stage, histology, bulky disease, age, International Prognostic Index (IPI) score, treatment modality (RT alone vs CMT), and RT-treated volumes.

Patients and methods

A retrospective analysis of a single-institution series was conducted. All patients were diagnosed, treated and prospectively followed up at the Radiation Oncology, Medical Oncology and Hematology Departments of the Spedali Civili Hospital of Brescia between 1985 and 2002. Selection criteria included a histologically proven diagnosis of stage I or II non-Hodgkin's lymphoma with a dominant extranodal presentation in any structure of the head and neck district. Primary central nervous system lymphoma was considered a separate entity and excluded. Histological diagnoses were classified according to the Working Formulation. Patients with lymphoblastic and Burkitt's lymphomas were excluded from the analysis. Patients were then divided into two groups: a "low grade" lymphomas group, corresponding to categories A-C of the Working Formulation, and an "intermediate-high grade" lymphomas group, corresponding to categories D-H.

All patients were staged according to the Ann-Arbor Conference staging system¹⁷. The staging workup varied along the period of observation but included a thorough clinical examination, both general and of the head and neck district, bone marrow biopsy, chest radiograph and chest-abdomen computed tomography scan. None of the patients underwent a staging laparotomy. In the absence of a clear definition of bulky disease for head and neck lymphomas, the category "bulky" disease was arbitrarily defined as any mass of 5 cm or more in greatest diameter, as described by Rujis *et al.*¹³ Patient performance status was retrospectively recorded according to the Eastern Cooperative Oncology Group (ECOG) criteria.

One hundred and seven patients were included in the study. The median age at diagnosis was 63 years (range, 17-86 years) and the male-female ratio was 1.5:1. The main patient and disease characteristics are summarized in Table 1. Waldeyer's ring was the most commonly involved structure, with the tonsils being the most frequent primary site (58%) followed by the nasopharynx (17%) and the base of the tongue (6.5%). Other less common sites were the nasal sinuses, paranasal sinuses,

Table 1 - Patient and disease characteristics

Feature	No. (%)
<i>Age</i>	
≤60y	46 (43)
>60y	61 (57)
<i>Sex</i>	
Male	64 (60)
Female	43 (40)
<i>Primary site</i>	
Waldeyer's ring	87 (81.5)
Tonsil	62 (58)
Nasopharynx	18 (17)
Base of the tongue	7 (6.5)
Nasal sinus	8 (7)
Paranasal sinuses	7 (6.5)
Ocular adnexa	3 (3)
Larynx	2 (2)
<i>Purely extranodal involvement</i>	53 (50)
1 extranodal site	47 (89)
2 extranodal sites	6 (11)
<i>Extranodal & nodal involvement</i>	54 (50)
1 nodal site	35 (65)
≥2 nodal sites	19 (35)
<i>Bulky disease (greatest diameter ≥5 cm)</i>	49 (46)
<i>Stage</i>	
I	50 (46)
II	57 (54)
<i>ECOG performance status</i>	
0	33 (32)
I	55 (50)
II	19 (18)
<i>Histology</i>	
Intermediate/high-grade lymphoma	86 (80)
Low-grade lymphoma	21 (20)

ocular adnexa and larynx. No thyroid lymphomas were found in the series. A purely extranodal presentation was seen in 53 (50%) patients and six (11%) of them had two involved extranodal sites. In 54 (50%) patients there was both nodal and extranodal involvement, with one involved nodal site in 35 patients and two involved nodal sites in 15 patients. Fifty and 57 (46% and 54%) patients had stage I and stage II disease, respectively. Bulky disease (>5 cm) was documented in 49 (46%) patients. Most signs and symptoms were related to the presence of a local mass: local pain, headache, nasal obstruction, rhinorrhea, epistaxis, dysphagia. None of the patients had B symptoms. The vast majority of patients (82%) had a good performance status (ECOG PS: 0-1) and none of them was assigned to ECOG categories 3-4. Eighty-six (80%) patients had intermediate-high grade lymphoma and 21 (20%) had low-grade lymphoma.

Treatment consisted of either radiotherapy alone or combined-modality treatment (chemotherapy followed by radiotherapy). RT alone was administered to 59 (55%) patients whereas 48 (45%) patients received CMT. The choice to use chemotherapy was based on several clinical factors including the patient's age, presence of comorbidity and lymphoma histology. In particular, RT alone was given to 33% (15/46) of patients aged 60 or less and to

72.5% (44/61) of those older than 60 years. With regard to histology, RT alone was given to 85% (18/21) of low-grade lymphomas and to 48% (41/86) of high-grade lymphomas, whereas CMT was given to 14% (3/21) of low-grade lymphomas and to 52% (45/86) of high-grade lymphomas. Patients with significant comorbidity were mainly treated with RT alone.

Chemotherapy consisted of a short-term (3-4 cycles) CHOP or CHOP-like regimen in the vast majority of patients (94%) treated with CMT; only three patients received a chemotherapy regimen not including anthracyclines.

Radiotherapy was delivered either with a cobalt teletherapy unit or with X-rays from a linear accelerator. A conventional fractionation was used and the median delivered dose was 43.2 Gy (range, 33.6-52 Gy) in the radiation alone group and 40 Gy (range, 27-56 Gy) in the CMT group. The radiation treatment volumes used in this study included local field, involved field and extended field. The local field encompassed only the clinically evident site of disease with an adequate margin. The involved field included the entire involved nodal region. The extended field included the adjacent uninvolved lymph nodal regions at high risk of subclinical disease. In the latter case, the number of irradiated uninvolved regions was calculated. Considering the entire group of patients, radiotherapy was delivered to extended fields in the majority of patients (65%), to involved fields in 13 patients (12%) and to local fields in 24 patients (23%). The percentage of cases treated with extended-field radiotherapy in the RT group and in the CMT group was 66% and 65%, respectively.

The number of uninvolved nodal regions treated with extended-field radiotherapy was greater than three in 23% of the patients treated with radiation alone and in 16% of the patients treated with chemotherapy and ex-

Table 2 - Description of treatments

	RT (n = 59) No. (%)	CMT (n = 48) No. (%)
Chemotherapy		
Anthracycline-containing		45 (93)
Non-anthracycline		3 (6)
Number of cycles		
2		3 (6)
4		14 (29)
6		13 (27)
other (3, 5, 8)		18 (37)
Radiotherapy fields		
Local fields	13 (22)	11 (23)
Involved fields	7 (12)	6 (12)
Extended fields	39 (66)	31 (65)
Number of irradiated uninvolved regions		
None	20 (34)	17 (35.5)
One	11 (19)	11 (23)
Two	15 (25)	12 (25)
Three	4 (7)	6 (12.5)
≥4	9 (15)	2 (4)
Radiotherapy dose (Gy)		
Median	43.2	40
Range	33.6-52	27-56

Table 3 - Volumes of radiotherapy and disease characteristics

Treatment	Disease characteristics	Radiotherapy fields - No. (%)			
		Local	Involved	Extended	
RT	Stage	I (n = 32)	12 (37.5)	0 (0)	20 (62.5)
		II (n = 27)	1 (4)	7 (26)	19 (70)
	Bulky	<5 (n = 39)	9 (23)	5 (13)	25 (64)
		≥5 (n = 20)	4 (20)	2 (10)	14 (70)
Histology	Low (n = 18)	3 (17)	1 (5)	14 (78)	
	High (n = 41)	10 (24)	6 (15)	25 (61)	
CMT	Stage	I (n = 18)	8 (44)	0 (0)	10 (56)
		II (n = 30)	3 (10)	6 (20)	21 (70)
	Bulky	<5 (n = 19)	7 (37)	3 (16)	9 (47)
		≥5 (n = 29)	4 (14)	3 (10)	22 (76)
	Histology	Low (n = 3)	1 (33)	0 (0)	2 (67)
		High (n = 45)	10 (22)	6 (13)	29 (65)

tended-field radiotherapy. A slightly higher proportion of patients with bulky disease and with stage II disease was submitted to extended-field radiotherapy, both in the RT alone and in the CMT groups. Treatment details are listed in Tables 2 and 3.

Responses were retrospectively classified according to the criteria published by Cheson *et al.*¹⁸ Toxicity from radiation therapy was evaluated according to the Radiation Therapy Oncology Group (RTOG) radiation morbidity scoring criteria. The primary endpoint of the study was to analyze the patterns of relapse in the whole series. Relapses were defined as "in field" (InFR) if they occurred inside the radiotherapy field, "regional" (RegR) if they occurred in adjacent regions, and "systemic" (SysR) if they occurred in non-adjacent lymphatic regions or in distant organs. Secondary endpoints were overall survival and relapse-free survival.

Survival curves were calculated according to the Kaplan-Meier method and the significance of the differences between the curves was estimated with the log-rank test¹⁹. P values of 0.05 or less were considered statistically significant. Statistical analysis was conducted using the SPSS 12.0 software package (©SPSS Inc., Chicago, IL). Multivariate analysis was applied, when needed, according to the Cox model²⁰, but the results should be interpreted with caution because of the small number of cases in each subgroup.

Results

Outcome

In the entire series (Table 4), the number of complete responses (CR), partial responses (PR) and no-change/progression (NC/PD) was 93 (87%), 12 (11%) and 2 (2%), respectively. Corresponding values for the RT alone and CMT groups were 86%, 14%, 0% and 88%, 8% and 4%, respectively.

After a median follow-up of 49.4 months (range, 3-219 months) in the whole series, 50% of patients were alive and disease-free, 4% were alive with evidence of disease and the remaining 46% were dead. Within the RT and CMT groups, 37% and 62%, respectively, remained disease-free. Eight of 40 relapses

Table 4 - Outcome

	Entire series	RT	CMT
All patients	107	59	48
Response, no (%)			
Complete	93 (87)	51 (86)	42 (88)
Partial	12 (11)	8 (14)	4 (8)
No change	1 (1)	0	1 (2)
Progression	1(1)	0	1 (2)
Relapse, no (%)			
Yes	40 (37)	27 (46)	13 (29)
No	67 (63)	32 (54)	35 (71)
Site of relapse, no (%)			
In field	3 (3)	1 (2)	2 (4)
Regional	5 (5)	4 (7)	1 (2)
Systemic	32 (29)	22 (37)	10 (21)
Overall survival			
Median	42.3 mos	40 mos	53 mos
Range	3-207 mos	6-190 mos	3-207 mos
Relapse-free survival			
Median	37 mos	29 mos	39 mos
Range	2-200 mos	0-188 mos	2.4-200 mos

(20%) were late relapses that occurred after five or more years of follow-up.

The projected actuarial five-year overall survival and relapse-free survival in the entire series were 59% and 62%, respectively (Figure 1). In the radiotherapy alone group OS and RFS were 55% and 56%, respectively, while in the combined treatment group these figures were 63% and 72%, respectively. The difference was more evident for patients with stage II disease (OS and RFS 38% and 34% after RT alone and 63% and 69% after CMT, $0.02 < P < 0.04$). The same trend was observed in patients with high-grade histology (OS and RFS 51%

and 49% after RT alone and 69% and 72% after CMT, $0.003 < P < 0.007$).

Univariate analysis was performed to identify clinical variables with potential impact on patient outcome including age, stage, histology, treatment modality and extent of radiotherapy fields. The only variable with a strong significant difference was age, with older patients showing worse OS and RFS values ($P \leq 0.001$). When patients were arbitrarily divided into two groups aged 60 years or less or older than that, the five-year RFS and OS rates were 75% vs 50% and 79% vs 41%, respectively ($P < 0.001$) (Table 5).

It should be noticed, however, that older patients were less often treated with CMT and that better OS and RFS rates were registered for patients treated with CMT (OS and RFS after RT alone 55% and 56%, respectively, as opposed to 63% and 72%, respectively, for CMT, $0.039 < P < 0.0487$) (Table 5).

Multivariate analysis (initial model including age, stage, histology, treatment modality and RT-treated volumes) retained only age in the final model ($P < 0.001$) for both RFS and OS; the same results were obtained by including in the initial model a smaller number of factors, to take into account the relatively small number of events observed in the whole series.

Analysis of relapse

No relapses were detected in central nervous system sites. Relapses occurred more frequently in high-grade than in low-grade lymphomas (43% and 33%, respectively), and in stage II than in stage I patients (59% and

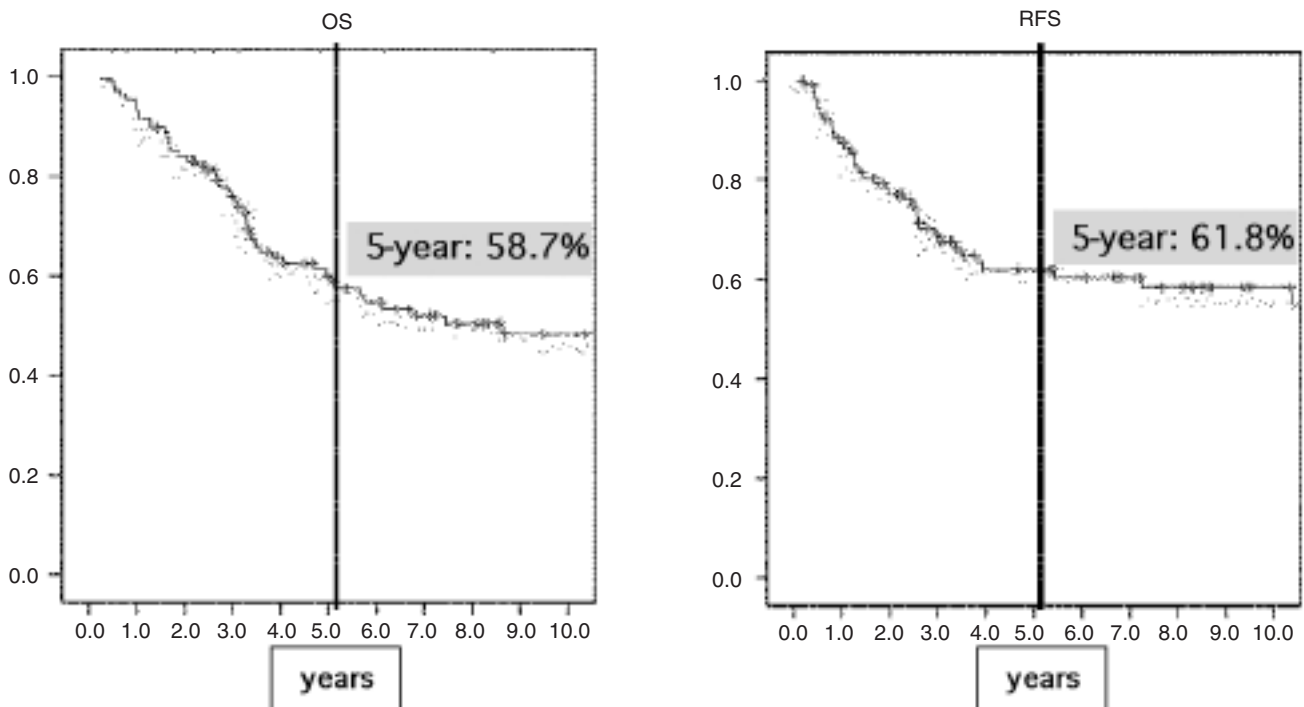


Figure 1 - Kaplan-Meier 10-year actuarial overall and relapse-free survival curves for the whole series.

Table 5 - Overall and relapse-free actuarial survival according to various potential prognostic factors

Prognostic factor		5-year OS			5-year RFS		
		No.	%	P	No.	%	P
Age	≤60 years	46	79	0.000	46	75	0.001
	>60 years	61	41		61	50	
Histology	high grade	86	57	0.21	86	61	0.32
	low grade	21	62		21	65	
Stage	I	50	68	0.39	50	71	0.35
	II	57	51		57	54	
Treatment	RT	59	55	0.048	59	56	0.039
	CMT	48	63		48	72	
Radiotherapy field	LF	24	71	0.97	24	71	0.4
	IF	13	50		13	47	
	EF	70	57		70	61	

OS, overall survival; RFS, relapse-free survival; RT, radiotherapy; CMT, combined-modality treatment; LF, local field; IF, involved field; EF, extended field.

34%). Relapses occurred in 27 patients treated with RT alone (46%) and in 14 patients treated with CMT (29%). In the RT alone arm there were 1 InFR (2%), 4 RegR (7%) and 22 SysR (37%), while in the CMT arm there were 2 InFR (4%), 1 RegR (2%) and 10 SysR (21%). Late recurrences, occurring later than five years, accounted for 2% of all relapses (8/40). The distribution of recurrences in relation to treatment modality, RT-treated volumes and other variables is shown in Tables 6a and 6b.

Toxicity

Both RT alone and CMT were generally well tolerated and no treatment-related deaths occurred. There were no acute side effects higher than grade 3. The most common acute side effect of radiotherapy was mucositis (76.3% of the patients, in 23% of them grade 3) and xer-

Table 6a - Distribution of relapses according to clinical and therapeutic features in the group treated with RT alone

Clinical/therapeutic features		Relapse - No. (%)			
		NoR	InFR	RegR	SysR
Total	59 pts	32 (54)	1 (2)	4 (7)	22 (37)
Age	≤60 (n = 15)	9 (60)	0	1 (7)	5 (33)
	>60 (n = 44)	23 (53)	1 (2)	3 (7)	17 (38)
Stage	I (n = 32)	21 (66)	0	1 (3)	10 (31)
	II (n = 27)	11 (41)	1 (4)	3 (11)	12 (44)
Bulky	<5 cm (n = 39)	22 (57)	0	4 (10)	13 (33)
	≥5 cm (n = 20)	10 (50)	1 (5)	0	9 (45)
Histology	Low (n = 18)	11 (61)	0	1 (6)	6 (33)
	High (n = 41)	21 (51)	1 (3)	3 (7)	16 (39)
Fields	Local (n = 13)	10 (77)	0	0	3 (23)
	Involved (n = 7)	2 (29)	1 (14)	0	4 (57)
	Extended (n = 39)	20 (51)	0	4 (10)	15 (39)

NoR, no relapse; InFR, in-field relapse; RegR, regional relapse; SysR, systemic relapse.

Table 6b - Distribution of relapses according to clinical and therapeutic features in the group treated with CMT

Clinical/therapeutic features		Relapse - No. (%)			
		NoR	InFR	RegR	SysR
Total	48 pts	35 (73)	2 (4)	1 (2)	10 (21)
Age	≤60 (n = 31)	21 (68)	1 (3)	1 (3)	8 (26)
	>60 (n = 17)	14 (82)	1 (6)	0	2 (12)
Stage	I (n = 18)	13 (72)	1 (6)	0	4 (22)
	II (n = 30)	22 (73)	1 (3)	1 (4)	6 (20)
Bulky	<5 cm (n = 19)	13 (68)	2 (11)	0	4 (21)
	≥5 cm (n = 29)	22 (76)	0	1 (3)	6 (21)
Histology	Low (n = 3)	1 (33)	0	0	2 (67)
	High (n = 45)	34 (75)	2 (5)	1 (2)	8 (18)
Fields	Local (n = 11)	7 (64)	1 (9)	0	3 (27)
	Involved (n = 6)	4 (67)	1 (16)	0	1 (17)
	Extended (n = 31)	24 (78)	0	1 (3)	6 (19)

NoR, no relapse; InFR, in-field relapse; RegR, regional relapse; SysR, systemic relapse.

ostomia was the most common late side effect (59% of the patients, in 1% of them grade 3). In the entire series, six patients (5.6%) developed second malignancies, two (4%) in the combined modality group and four (8%) in the radiotherapy alone group: colorectal (n = 1), gastric (n = 1), pancreatic (n = 1), endometrial (n = 1), prostatic (n = 1) and breast (n = 1) cancer. No relationship whatsoever was demonstrated with the extent of the RT-treated volumes.

Discussion

This paper presents the results of a retrospective analysis of a single-institution series of primary extranodal lymphomas of the head and neck observed over 15 years. The aim of this analysis was to determine the outcome and patterns of relapse of patients with a localized disease presentation after local treatment (radiotherapy alone) or a systemic approach (combined modality treatment).

In previously reported series of localized extranodal lymphomas of the head and neck, radiotherapy alone produced a very high complete remission rate but was followed by a high relapse rate^{11-14,21-28}.

The clinical characteristics of our series were similar to those published by others. In particular, the lymphomas showed predominant extranodal localization in the Waldeyer's ring with a nodal component in 50% of the cases. The most common histology was the diffuse large B-cell type and the performance status was good (ECOG 0-1) in over 80% of patients. Older age was surely the most important determinant of a worse survival (P [univariate] <0.001 for both RFS and OS), even though older patients were less often submitted to more aggressive treatments (i.e., with the addition of chemotherapy).

Treatment outcome was also similar to other reported data. Radiotherapy alone obtained a very good (100%) overall rate of response (CR+PR), but CMT was superi-

or to RT alone in terms of median OS (53 vs 40 months) and RFS (39 vs 29 months). The five-year RFS and OS rates were slightly influenced ($P = 0.039$ and 0.0487 , respectively) by the treatment modality, with an advantage for patients receiving CMT. This advantage was more evident for patients with stage II disease (OS: 38% vs 63%; RFS: 34% vs 69%) and high-grade histology (OS: 51% vs 69%; RFS: 49% vs 72%). RT alone was associated with a higher overall relapse rate than CMT (46% vs 29%). However, in both the RT alone group and the CMT group, most relapses occurred outside the irradiation fields and were "systemic" in nature.

In our series the extended-field treatment was most commonly utilized both in the RT alone and the CMT groups (66% and 65%, respectively). Nonetheless, the majority of systemic relapses occurred in patients treated with the extended-field technique in both groups. Accordingly, the use of different radiotherapy fields did not affect either OS or RFS in both groups. In particular, the use of extended-field radiotherapy including a greater number of uninvolved irradiated regions did not yield a better outcome.

The management of head and neck lymphomas remains controversial. On the whole, our data confirm the indications in the literature concerning the use of RT alone. The major unresolved problem remains the high rate of distant relapses as a consequence of the progres-

sion of untreated disease at sites undetectable during baseline staging, after both RT alone and CMT. In extranodal lymphomas, several papers confirmed the high frequency of multiple occult clusters of lymphoma cells at sites distant from the primary^{15,29}, raising the issue of more accurate staging of extranodal involvement in these lymphomas. In this regard the concept of what can really be considered limited disease should be reviewed not only for nodal but also for extranodal lymphomas³⁰.

At present, CMT seems to produce better, even if unsatisfactory, RFS and OS rates, and should probably be favored, especially in patients with high-grade histology and stage II disease; however, RT alone can be considered a good alternative for those patients who are not optimal candidates for systemic chemotherapy. An agreement on the most appropriate total dose to be used for low and high-grade disease and with RT alone as opposed to CMT has not been reached so far³¹; however, in the present series, the prevailing choice of slightly reducing the doses in patients treated also with chemotherapy appears to be confirmed.

Many of the questions raised in this paper can be answered only by accumulating a larger body of information on extranodal head and neck lymphomas. Well designed prospective trials are warranted to further investigate the role of external-beam radiotherapy and the use of new systemic agents for the cure of this disease.

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