High Response Rates and Lasting Remissions After Low-Dose Involved Field Radiotherapy in Indolent Lymphomas

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Purpose: **To study the response rates and duration of response after low-dose (4 Gy) involved field radiotherapy (LD-IF-RT) in patients with recurrent indolent lymphoma.**

Patients and Methods: **A total of 109 assessable patients (304 symptomatic sites) were irradiated (53 males and 56 females; median age, 62 years; range, 35 to 93), including 98 patients with follicular lymphoma (43 grade 1 and 55 grade 2), nine extranodal marginal zone lymphomas of mucosa-associated lymphoid tissue-type and two patients with lymphoplasmacytoid lymphoma. Bulky disease (≥5 cm) was present in 52% of all patients. A median of two prior regimens (range, 0 to 11) preceded LD-IF-RT. The median time since diagnosis was 41 months (range, 2 to 358 months). Time to (local) progression was calculated according to the Kaplan-Meier method. Differences in response rates between treatments within the same patient were compared using the McNemar test.**

Results: **The overall response rate was 92%; complete response was reached in 67 patients (61%), partial response in 34 patients (31%), stable disease in six patients (6%), and progressive disease in two patients (2%). The median time to progression was 14 months. The median time to local progression was 25 months. The 67 patients with complete response showed a median time to progression of 25 months and a median time to local progression of 42 months. None of the factors studied (age, sex, follicular lymphoma grade, radiotherapy regimen, number of previous regimens and previous history, number of positive sites or largest lymphoma diameter) were found to be related to response rate.**

Conclusion: **LD-IF-RT is a valuable asset in the management of patients with follicular lymphoma and should be considered in patients with recurrent disease.**

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OF ALL non-Hodgkin's lymphomas (NHLs), 20% are follicular lymphoma (FL), and 80% of these patients present in (advanced) Ann Arbor stage III to IV. The incidence rises with age, and the incidence rates are estimated to rise annually in about 5% of patients.[1]

The median survival time from the diagnosis of patients with advanced stage FL varies from 5 to 8 years. Over the past decades, overall survival time has not improved. Although FL is very sensitive to both chemotherapy and radiotherapy, no curative treatment is available.

The natural history of FL is characterized by multiple relapses and sometimes spontaneous remissions. The interval between subsequent relapses tends to shorten over time.[2-8]

There is no consensus as to which first-line treatment should be provided to patients with advanced stage FL, although in general, either cyclophosphamide, vincristine, prednisone (CVP) polychemotherapy or chlorambucil single-agent therapy[9-22] are advised. These regimens are applied in recurrent disease as well.

FL is considered to be one of the most radiosensitive tumors. In early-stage FL, prolonged remissions are seen after radiotherapy to a dose of 36 to 40 Gy only. In advanced-stage FL, low-dose total-body irradiation (1.5 to 2.5 Gy in 10 to 15 cGy fractions) produces durable remissions as well.[23-32] In recurrent FL, low-dose (2 × 2 Gy) involved field radiotherapy (LD-IF-RT) has been studied. Girinsky et al[33] reported their series with a median follow-up of 3.3 years in 48 patients and found a response rate of 89%. A complete remission (CR; defined as the complete disappearance of all lymphoma activity within the radiation portals) was seen in 37%.[33,34] Two smaller series (Sawyer and Timothy[35] and Johansson et al[36,37]) confirmed these results.

Chemotherapy (such as chlorambucil, CVP, cyclophosphamide, doxorubicin, vincristine, prednisone; and fludarabine) and immunotherapy (such as the anti-CD20 monoclonal antibody rituximab) for recurrent systemic disease has proven relatively effective in palliating symptoms. These regimens have several disadvantages, such as treatment duration (several months), side effects, and costs.

Until recently, patients referred for radiotherapy with recurrent disease were selected on the basis of having only one or at most a few active sites, after multiple relapses, with chemotherapy-refractory disease, or a combination of these. They were treated with fractionated regimens to a total dose of 20 to 36 Gy.

This article presents the results of LD-IF-RT (4 Gy) regimens tested in the Netherlands in the HORA-1 phase II study. We have treated 109 assessable patients with various types of recurrent indolent B-cell NHL. The main purpose was to evaluate the

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response rates, response duration, pattern of relapse, and toxicity of this regimen.

PATIENTS AND METHODS

Patient Characteristics

From November 1997 to March 2002, we treated 111 patients. Patients were included if they had symptomatic recurrent B-cell indolent lymphomas. Patients with proven histologic transformation or concurrent use of any corticosteroid drug or chemotherapy were excluded. Of these 111 patients, two were not assessable, because of refusal of an evaluation computed tomographic scan (n = 1) and because of the prescription of inhalation corticosteroid medication to palliate an exacerbation of chronic pulmonary obstructive disease (n = 1). Before and after irradiation, all patients were staged by physical examination, ultrasonography of neck nodes, and contrast-enhanced computed tomographic scans of the chest and abdomen. If the last pathologic confirmation of the diagnosis were more than a year before, fine-needle aspiration cytology of the fastest-growing or most easily accessible node was performed.

A total of 109 patients, 53 males and 56 females (median age, 62 years; range, 35 to 93) were assessable for analysis. Pathology subtypes were: 98 patients with FL (43 grade 1 and 55 grade 2), nine with extranodal marginal-zone lymphomas of mucosa-associated lymphoid tissue-type, and two with lymphoplasmacytoid lymphomas.

Lymphoma-size data were available for 92 patients. (Table 1) In 48 patients (52%) bulky disease was present, defined as nodes ≥ 5 cm; 13% had nodes ≥ 10 cm.

A median of two lymph node areas were positive for malignant lymphoma (divided into 11 nodal areas: left and right neck and axillae, mediastinum, paraaortic, spleen, left and right parailiac, and femoro-inguinal). The total number of irradiated sites was 304. (Patient characteristics are summarized in Table 1.)

Table 1. Patient Characteristics

Characteristics	Patients (N = 109) No.	%
Sex		
Male	53	49
Female	56	51
Age, median 62 years		
≤ 50 years	20	18
51-70 years	65	60
≥ 71 years	24	22
Pathology		
Follicular Lymphoma	98	90
Grade 1	43	39
Grade 2	55	50
Marginal zone NHL, MALT-type	9	8
Immunocytoma	2	2
Radiotherapy dose		
2 × 2 Gy	80	73
1 × 4 Gy	29	27
Number of prior regimens, median = 2 regimens		
0-2	71	65
3-5	29	27
6-11	9	8
Time since diagnosis, median = 44 months		
≤ 24 months	35	32
25-60 months	30	28
61-120 months	26	24
> 120 months	18	16
Number of sites per patients, median = 2 sites		
1-2	71	65
3-5	25	23
6-10	7	6
Total nodal irradiation	6	6
Largest node/site per patient, median = 6 cm		
≤ 5 cm	44	40
6-10 cm	36	33
> 10 cm	12	11
Unknown diameter	17	16

Abbreviations: NHL, non-Hodgkin's lymphoma; MALT, mucosa-associated lymphoid tissue.

Preirradiation Treatments

In 102 of these 109 patients, several lines of systemic treatment preceded LD-IF-RT. A median of two previous regimens (range, 1 to 11) were administered. More than six previous regimens preceded LD-IF-RT in nine patients. In seven patients, LD-IF-RT was offered as a first-line regimen for various reasons, usually older age. The median time since diagnosis was 41 months (range, 2 to 358). In 18 patients relapses of lymphoma had already persisted for longer than 10 years.

In 31 patients, radiotherapy was part of one or more previous regimens; total-body irradiation (2.5 Gy in 10 cGy) was administered to two of them. The median radiotherapy dose was 30 Gy (range, 2.5 to 40 Gy). The LD-IF-RT fields had been previously irradiated in four patients. In 18 of 102 patients, the last regimen was radiotherapy after a median interval of 34 months (range, 5 to 108 months). No patients received overlapping fields.

Radiotherapy Prescriptions

Patients received a dose of 4 Gy, either as 2 × 2 Gy, after an interval of 48 hours (n = 80), or as a single fraction of 4 Gy (n = 29). The target area could be either the entire lymph node area (eg, neck from mastoid to clavicles for a single node) or the node with a 1.5 cm margin. The choice was left to the discretion of the individual radiation oncologist. Megavoltage photon or electron beams (or both) of appropriate energy were used. Radiotherapy was only given to involved sites. A total of 13 patients were irradiated on six areas or more; six were treated by total nodal irradiation.

Supportive Care

To prevent nausea and vomiting when treating abdominal radiation fields, all registered antiemetic drugs were allowed except corticosteroids, such as dexamethasone. However, if in the best interest of the patient the radiation oncologist prescribed dexamethasone, either as a single agent or in combination with other antiemetics, this patient was taken off the study. The same rule was applied for the prescription of any corticosteroid medication for any other indication.

Additional Treatment

None of these patients were irradiated concurrently with chemotherapy. As soon as a patient received chemotherapy after low-dose irradiation, either because of local failure or because of distant relapse, the patient went off the study, and the treatment was counted as a (local) failure at that time point.

End Points

The main end point of the study was in-field lymphoma control. Therefore, in this study the definitions (complete remission [CR], partial remission [PR], stable disease [SD], and progressive disease [PD]) applied to the local lymphoma activity only. Patients were assigned to the best category found during follow-up. Nonresponders were patients with SD or PD. If patients were irradiated at more than one site and the response differed for each site (eg, CR in one site and PR in another) the disease was assigned to the worst category. Response assessment was performed 4 to 6 weeks after irradiation and then every 3 months.

Statistical Methods

Time to progression (TP) and time to local progression (TLP) were calculated according to the Kaplan-Meier method. The starting point for

Table 2. Response Rates Median Time to Progression and Median Time to Local Progression

	No. of Patients (baseline)	%	Duration (months)	Median TP (months)	Median TLP (months)
First low-dose treatment					
All	109	100		14	25
CR	67	61	1-77+	25	42
PR	34	31	1-28+	9	10
Nonresponders	8	8	1-29+	2	2
Retreatment					
All	41	100		14	25
CR	29	71	2-35+	15	25
PR	11	27	2-37+	8	NR (>37)
Nonresponders	1	2	—	—	—

NOTE. NR (> 37) = not reached but exceeds 37 months; however, the numbers are small.
Abbreviations: TP, time to progression; TLP, time to local progression; CR, complete remission; PR, partial remission; NR, not reached.

(local) time to progression was the first day of LD-IF-RT. For TP, the end point was either in-field or out-of-field progression (event) or end of follow-up for other reasons (censoring). For TLP the end point was in-field recurrence, either alone or synchronous with new lymphoma localizations; chemotherapy or corticosteroid medication, even for nonmalignant indications (eg, exacerbation of chronic obstructive pulmonary disease; event); or end of follow-up for other reasons (censoring). The median follow-up for patients still in remission was 7 months.

Differences in response rates between treatments within the same patient were compared using the McNemar test. Prognostic factors for response were tested for statistical significance by the χ^2 test. The progression-free interval after LD-IF-RT and previous chemotherapy regimens was calculated from the start of treatment to any relapse. The statistical SSPS program version 10 was used for the calculations.

Relapsed Disease Management After LD-IF-RT

Treatment of relapsed disease (either in-field progression or out-of-field progression with ongoing local control) depended on the response to the first LD-IF-RT and the extent of the relapse. Patients who responded to the LD-IF-RT regimen, had chemotherapy-refractory disease, or preferred a second low-dose treatment were offered one. The second series could be either a re-treatment of the prior field(s) or an irradiation of a new area.

RESULTS

Response Rates

The overall response rate (RR) was 92%. The first low-dose irradiation (in 109 patients) resulted in a CR in 67 patients (61%) and in a PR in 34 patients (31%). SD was maintained in six patients (6%), and two patients (2%) had PD, resulting in eight nonresponders. CR lasted up to 77 months and was ongoing at the time of analysis. For PR patients, the response lasted up to 28 months and was ongoing as well. Of 304 irradiated sites, 203 reached a CR (66%), 90 reached a PR (30%), nine remained stable (3%), and progressive disease was seen in two (1%). There are no differences between the response rates or the CR rates on a patient-based analysis compared with the results on a site-based analysis in FL patients. Therefore, all further analyses are patient-based.

The onset of the response was usually rapid. At the time of first follow-up and response assessment (four to six weeks after LD-IF-RT), the response had been reached in all but two patients. These two patients showed slowly regressing masses over six months. Frequently, patients noticed a response within 10 days.

An LD-IF-RT re-treatment was given to 41 patients. Of course, this is a favorable group a priori, because they were selected based on a good response to a first LD-IF-RT. RR was 98%, which is not significantly better than for the first LD-IF-RT. A CR was achieved by 29 patients (71%) and a PR by 11 patients (27%); one patient's disease progressed (Table 2). Fig 1 shows the progression-free and local progression-free curves for the group of patients receiving LD-IF-RT for the first time.

LD-IF-RT was the first regimen in only seven patients, who showed a 100% RR, 72% CR, and a median TP of 23 months.

Radiotherapy Protocol Compliance

All 109 patients fulfilled the protocol radiotherapy prescriptions. None received elective irradiation of uninvolved adjacent regions. As mentioned above, one patient was excluded from the analysis because of corticosteroid medication after irradiation but before response assessment.

Time to Progression

For a first low-dose treatment in 109 patients, the median TP (either in-field or out-of-field) was 14 months, and the median TLP was 25 months (Table 2 and Fig 1). The patients achieving a CR on a first treatment showed a median TP of 25 months and a median TLP of 42 months. Because the first sign of progression in patients achieving a PR was usually in-field, in this group there was no difference between median TP and median TLP (nine *v* 10 months, respectively). The same pattern was seen in the nonresponding patients, in whom the median TP and median TLP were both two months.

Toxicity

Toxicity was virtually absent. Successful prophylactic noncorticosteroidal antiemetic medication was prescribed for upper abdominal fields. Transient alopecia was seen in one FL patient with upper neck nodes, and transient hyperpigmentation was seen in one FL patient in an inguinal nodal field. Patients with bulky disease usually received antihyperuricemic medication

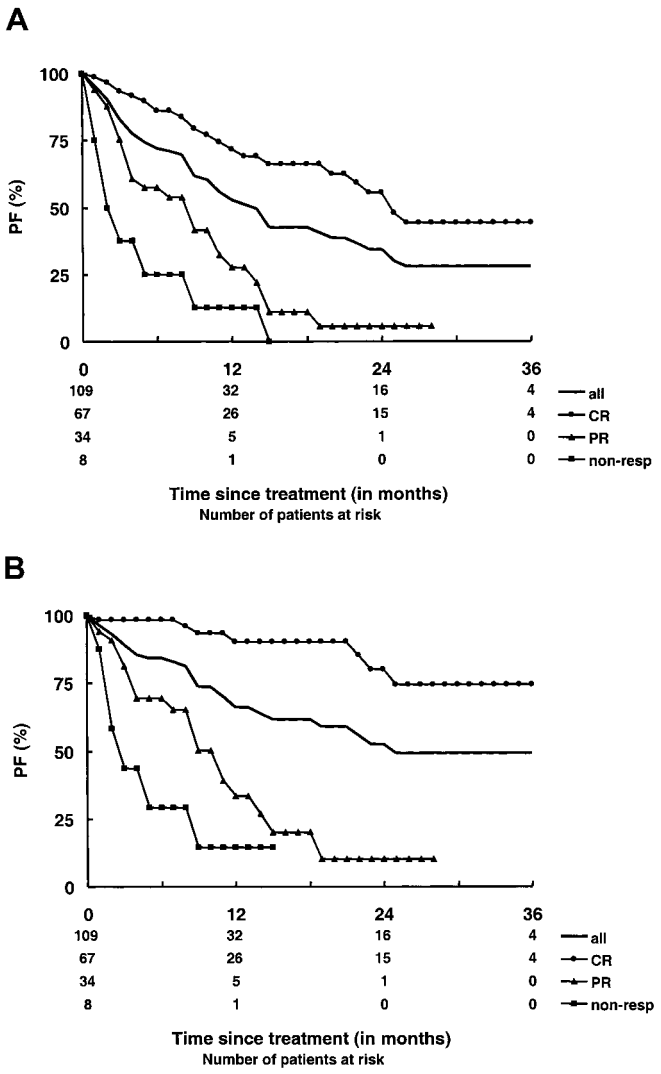

Fig 1. (A) Progression-free and (B) local progression-free curves after LD-IF-RT.

(allopurinol; dosage depending on renal function); no patients showed gout or tumor lysis syndrome.

Prognostic Factors

Prognostic factors for RR could not be distinguished in this group of patients. We tested for age, sex, FL grade, radiotherapy regimen, number and history of previous regimens, number of positive sites, and largest lymphoma diameter. Small *P* values were found for the difference in CR rate between patients having ≤two lymphoma sites and patients with more sites ($P = .01$), as well as between patients with lymphoma size ≤5 cm and patients with larger nodes ($P = .006$). However, in view of the large number of comparisons, the observed *P* values are still too large to allow definite conclusions. Other factors, such as serum levels of beta-2-microglobulin, lactate dehydrogenase, or the International Prognostic Index score were not found to be of prognostic value within this LD-IF-RT regimen, either for response or for CR. Beta-2-microglobulin was elevated above the upper limit of normal in four patients; lactate dehydrogenase was elevated in five patients.

Comparison of Low-Dose IF-RT to Previous Regimens

LD-IF-RT results were compared with the RR and response duration after each previous (usually chemotherapy) regimen in this same patient group. In Table 3, results are shown for all 109 patients. As stated above, for seven of these patients, LD-IF-RT was the first regimen; therefore, they had no other first or last previous regimen. For some patients the first treatment was also the last treatment—namely, those patients who were irradiated at first recurrence. The number of patients dropped to 17 patients receiving five previous regimens, the last subgroup to be analyzed. (Eight patients received six regimens, five patients received seven, two patients received eight, one patient received 10, and one patient received 11.)

The overall RR of LD-IF-RT is slightly better than the RR of the second ($P = .04$) and the last ($P = .03$) regimens. No difference was found between the RR after LD-IF-RT of the first ($P = .08$), the third ($P = .3$), the fourth ($P = .6$), and the fifth ($P = .7$) regimens. Of course, because of decreasing numbers, the power of the comparison drops progressively. In none of the previous regimens were observed RR rates higher than those of LD-IF-RT.

The probability of having no progression 1 year (about 50%), 2 years (about 33%), 3 years (about 25%), and 5 years (about 10%) after LD-IF-RT is comparable to that after the best, namely the first, previous treatment. The observed percentages of being disease-free at any time point studied for any pretreatment line is lower than for the LD-IF-RT regimen, except for the first pretreatment (Table 3 and Fig 2).

Fifty percent of all LD-IF-RT patients had disease that was refractory to the last regimen with which they were treated (defined as progressive disease on treatment or within six months after treatment completion). There were no differences between the chemorefractory and chemosensitive subgroups as far as RR, CR rate, and median TP are concerned.

Malignant Transformation to Diffuse Large-B-Cell Lymphoma During Follow-Up

During follow-up, a total of 10 patients were diagnosed with a transformation to a diffuse large-B-cell lymphoma. Analyzing these 10 patients separately shows six CR patients (60%), three PR patients, (30%) and one PD patient(10%). These response rates are similar to those of nontransforming patients. However, the median TP of these 10 patients was only 3 months.

DISCUSSION

This series of low-dose involved field radiotherapy (LD-IF-RT) with a dose of 4 Gy in 109 patients with recurrent indolent lymphoma shows a 92% rate of inducing rapid and often lasting remissions without significant toxicity. Patients selected for a second low-dose treatment of an in-field or out-of-field progression show similar high RR as compared with the first LD-IF-RT. This is an attractive feature, and it is in contrast to standard chemotherapy regimens, because patients treated by a previous regimen usually have inferior results.

Watchful waiting is a widely accepted approach, both at diagnosis and in recurrent and advanced-stage asymptomatic

Table 3. Response Rates and Response Duration of All Treatments Up to Five Regimens

	No. of Patients	% of Patients				Median TP (months)	% Progression-free			
		RR	CR	PR	SD/PD		1y	2y	3y	5y
LD-IF-RT	109	92	61	31	8	14	53	34	28	14
Regimen										
Last	102	72	44	28	28	10	44	26	15	6
1st	102	85	51	34	15	18	60	36	24	15
2nd	67	69	44	25	31	11	45	28	19	10
3rd	40	72	47	25	28	11	45	33	20	10
4th	26	77	46	31	23	9	35	27	27	15
5th	17	76	52	24	24	7	47	24	12	0

NOTE. Seven patients did not have a last or a first regimen since LD-IF-RT was their first line treatment.

Abbreviations: RR, response rate; CR, complete remission; PR, partial remission; SD, stable disease; PD, progressive disease; TP, time to progression; y, years; LD-IF-RT, low-dose involved field radiotherapy.

patients. In the case of symptomatic disease, however, a regimen should be chosen that provides high response rates with a rapid onset of response, is of short treatment duration, and leaves the patient with a minimum of toxicity. The obvious choice for this systemic disease would be either chemotherapy (eg, chlorambucil; CVP; cyclophosphamide, doxorubicin, vincristine, prednisone; or fludarabine) or immunotherapy (rituximab). A local treatment such as the LD-IF-RT regimen could be considered as well, and weighted against treatment side effects and costs.

The results of this study are in agreement with data published previously.[33-37] However, this study is based on a considerably larger number of patients, and it compares the results with those of previous regimens. There are many striking similarities between the results of our study and the series by Girinsky et al,[33] which represents the most extensively analyzed series published up to now. Girinsky's analysis is site-based (135 sites in 48 patients). Our findings in terms of RR, CR, two-year freedom from local progression and two-year freedom from local progression in CR patients and inferior results for bulky sites are in line with Girinsky et al's data. Not all results are confirmative, however. In the Paris patient group, the two-year freedom from local progression in PR patients seems better (46%) than that of ours (10%). The Paris investigators found a higher response on LD-IF-RT if patients had less then one previous regimen ($P < .01$) or were ≤ 65 years of age ($P = .003$). In our series, neither CR nor overall RR was found to be associated with the number of previous regimens or age. Perhaps the differences can be explained by the relatively large number (18 patients, 38%) of stage I and II patients. These patients were not enrolled in our study. However, these differences between the two studies may also be due to chance.

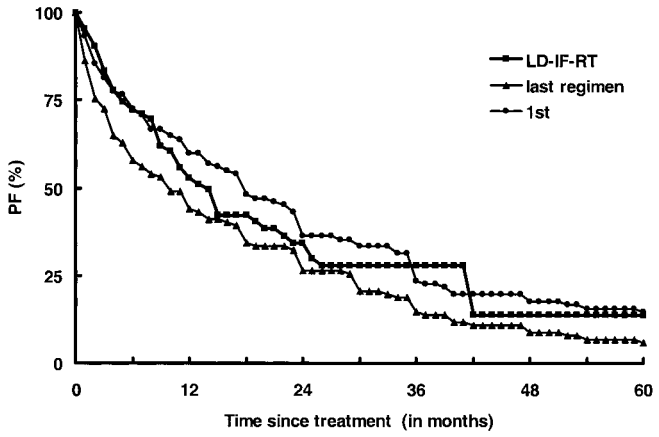

Fig 2. Comparison of the progression-free curves between the LD-IF-RT group, the first regimen, and the last regimen before LD-IF-RT.

We have seen transformation to diffuse large-B-cell lymphoma in 10 patients after LD-IF-RT. (This number is to be expected, given the number of patients and the duration of follow-up of this study[38]). In these patients, RR on LD-IF-RT before transformation had been similar to that in the other 99 nontransformed patients. In parallel to this phase II study, another group of 25 patients (12 mantle-cell lymphoma, nine de novo diffuse large-B-cell lymphoma patients and four FL grade 3 patients) were treated by LD-IF-RT because of high age, chemotherapy refractory, or recurrent disease outside the protocol for palliative reasons. These patients showed a RR of 76%, a CR rate of 36%, a median TP of five months and a median TLP of 22 months. A third and last group of 14 patients small lymphocytic lymphoma/chronic lymphatic leukemia (in the WHO classification this is recognized as an indolent lymphoma as well) also received LD-IF-RT to palliate symptoms. These patients showed an RR of 86%, a CR rate of 43%, a median TP of 10 months, and a median TLP of 14 months; again, these results are comparable to the 109 indolent lymphoma patients analyzed in this article.

In general, cancer patients experience many problems that have a negative influence on their quality of life. These problems can be caused both by the disease itself, but also by treatment side effects. There are few data on quality-of-life issues for FL patients. Cole et al[39] showed that interferon alfa-2b was able to prolong progression-free survival after chemotherapy in FL, but at the cost of significant toxicity. The protracted course of disease may have serious negative effects on quality of life. Webster and Cella[40] showed that 141 lymphoma patients had significantly lower physical, emotional, and functional well-being, as well as lower total quality-of-life scores after treatment, as compared with baseline values. As far as quality of life is concerned, they advise treating these patients with the least aggressive approach possible. The lack of toxicity and the

nonaggressive nature of this LD-IF-RT regimen may contribute to improve the quality of life of these patients.

Our present research on LD-IF-RT in these patients focuses on two issues. First, the high radiosensitivity in indolent lymphomas is poorly understood. It is known, however, that the lymphocyte is one of the most radiosensitive of all human cells. Basic biologic studies will be performed to explain these observations. Second, the high and often lasting RR in this and previous phase II studies has led to the design of a phase III trial: the HOVON 47/EORTC 20,013 Intergroup study (www.hovon.nl). This trial will compare 2 × 2 Gy IF-RT to chlorambucil chemotherapy in previously untreated FL patients. The main end points are progression-free survival and quality of life.

In conclusion, LD-IF-RT induces high RR in recurrent indolent lymphoma patients. RR was not found to be dependent on age, sex, histology, radiotherapy regimen, number of previous regimens, history, number of positive sites, and largest lymphoma diameter. LD-IF-RT can be administered without significant toxicity.

The results of LD-IF-RT at recurrent disease are comparable to the results of the first-line chemotherapy, especially in a time-without-treatment–based analysis. Low-dose re-treatment for a recurrence after a first LD-IF-RT regimen provides a similarly high RR. Therefore, this radiotherapy regimen, as a local treatment for a systemic disease, is a valuable asset in the management of FL patients and is an option for patients with recurrent disease.

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