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Effective palliation by low dose local radiotherapy for recurrent and/or chemotherapy refractory non-follicular lymphoma patients

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Abstract

In this work, we have studied the response rates and duration of response after low-dose (4 Gy) involved field radiotherapy (LD-IF-RT) in relapsed or chemotherapy refractory indolent and aggressive lymphoma patients. 71 patients (177 symptomatic sites) received LD-IF-RT consisting of 39 males and 32 females with a median age of 69 years (range 43–93). Patients included were those with small lymphocytic lymphoma/chronic lymphocytic leukaemia ($n = 23$), marginal zone lymphoma, nodal type ($n = 18$), mantle cell lymphoma ($n = 17$), and diffuse large B-cell lymphoma ($n = 13$). Bulky disease ($\geqslant 5$ cm) was present in 73% of all patients. A median of two prior chemotherapy regimens (range 0–10) preceded LD-IF-RT. Median time since diagnosis was 31 months (range 1–216 months). Time to (local) progression was calculated according to the Kaplan–Meier method. Differences in response rates were compared using the χ^2-test. The results showed that overall response rate was 87%; complete remission (CR) was reached in 34 patients (48%) and a partial remission (PR) in 28 patients (39%). Stable disease (SD) was maintained in nine patients (13%). The median time to progression (TP) was 12 months and the median time to local progression (TLP) was 22 months. The 34 CR patients showed a median TP of 16 months and a median TLP of 23 months. None of the factors studied (age, sex, lymphoma subtype, radiotherapy regimen, number of prior regimens or time since diagnosis, number of positive sites or largest lymphoma diameter) were found to relate to response. At time of death 70% of patients were without in-field progression after LD-IF-RT. It appears that LD-IF-RT is a valuable asset in the management of relapsed disease in both indolent and aggressive lymphoma and should be considered to palliate symptoms in patients with recurrent and/or chemotherapy refractory disease.

Keywords: Radiotherapy; Indolent lymphomas; Aggressive lymphomas; Palliation

1. Introduction

Several studies have shown the value of low dose involved field radiotherapy (LD-IF-RT) up to 4 Gy in recurrent follicular lymphoma (FL) patients [1–5]. In our experience [5], the overall response rate (RR) was 92%, with complete remission (CR) in 67 patients (61%), partial remission (PR) in 34 patients (31%), stable disease (SD) in six patients (6%) and progressive disease (PD) in two (2%). The median time to progression (TP) was 14 months and the median time to local

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progression (TLP) was 25 months. In view of the clinical characteristics of advanced stage FL with its indolent course, multiple relapses, incurable nature and its high radiation sensitivity, this radiotherapy schedule is highly attractive as a palliative treatment for this disease. However, many other malignant lymphomas, both indolent and aggressive, also relapse after prior treatment. Whether LD-IF-RT could be applied to palliate symptoms for those patients was unknown. To further investigate the role of LD-IF-RT, patients with the indolent small lymphocytic lymphoma/chronic lymphocytic leukaemia (BCLL) and marginal zone lymphoma, nodal type (MZL), and the more aggressive diffuse large B-cell lymphoma (DLCL) and mantle cell lymphoma (MCL) were studied, according to the World Health Organization Classification System [6]. These lymphomas, both at presentation and at relapse, are usually treated by various chemotherapy and immunotherapy schedules that are tailored to their specific characteristics. These regimens have proven to be effective in providing both cure and palliation to these patients. However, relapses after a previous response or chemotherapy refractory disease is also seen. Seldom these end-stage patients are offered radiation to palliate local symptoms.

In this study, we have evaluated the response rates, response duration, pattern of relapse and toxicity of LD-IF-RT to explore its value in a palliative setting in various types of indolent and aggressive NHL.

2. Patients and methods

2.1. Patient characteristics

In a prospective study, between March 1998 and November 2004, 71 patients were included. Eligibility criteria were: patients with symptomatic recurrent B-cell lymphomas; patients with chemotherapy refractory B-cell lymphomas; and elderly patients with localised symptomatic B-cell lymphomas for whom systemic treatment was thought to be too toxic. This study was approved by the local Ethics Committee. In this study, data were available for analysis from 71 patients (39 males and 32 females, median age 69 years (range 43–93), 30 patients $\geqslant$71 years). Pathology subtypes were; 23 BCLL patients, 18 MZL patients (these two subtypes together were designated as indolent types), 17 MCL patients and 13 DLCL patients (designated as aggressive lymphomas). Of these 71 patients, 36 were treated in the Netherlands Cancer Institute and 35 in the Bernard Verbeeten Institute. Patient characteristics, as described in Table 1, were evenly distributed over the two radiotherapy departments. Prior to and after irradiation, all patients were staged by physical examination, ultrasound of neck nodes and contrast enhanced CT scan of chest and abdomen. If the last pathological confirmation of the diagnosis was more than 1 year ago, fine needle aspiration cytology of the fastest growing or easiest accessible node was performed. Another six patients were irradiated, but they were not included in this analysis because of concurrent use of a corticosteroids or chemotherapy. For 56 patients data were available on the size of the pathological lymph nodes. In 41/56 patients (73%) bulky disease was present, defined as nodes $\geqslant$5 cm and 29% of the patients had nodes $\geqslant$10 cm. In most cases (42 patients) only one lymph node area was symptomatic, range 1–11. The total number of irradiated sites was 177 (average 2.5 sites per patient). Patient characteristics are summarised in Table 1.

Table 1
Patient characteristics ($n = 71$)

	n	%
Sex		
Male	39	55
Female	32	45
Age (median 69 years)		
$\leqslant$50 years	3	4
51–70 years	38	54
$\geqslant$71 years	30	42
Pathology		
Chronic lymphocytic leukaemia (BCLL)	23	33
Marginal zone lymphoma (MZL)	18	25
Mantle cell lymphoma (MCL)	17	24
Diffuse large cell lymphoma (DLCL)	13	18
Radiotherapy dose		
2×2 Gy	36	51
1×4 Gy	35	49
Number of prior regimens (median = 2 regimens)		
0	12	17
1–2	37	52
3–5	18	25
6–10	4	6
Time since diagnosis (median = 31 months)		
$\leqslant$24 months	34	48
25–60 months	20	28
61–120 months	11	16
>120 months	6	8
Number of sites per patients (median = 1 site)		
1	42	59
2	14	20
3–10	9	13
Total nodal irradiation	6	8
Largest node/site per patient (median = 7 cm)		
$\leqslant$5 cm	15	27
6–10 cm	25	44
>10 cm	16	29
Unknown diameter	15	

2.2. Pre-irradiation treatments

In 59 of these 71 patients, a median of two types (range 1–11) of systemic treatment preceded LD-IF-RT. More than three prior regimens preceded LD-IF-RT

in 22 patients. For 12 patients LD-IF-RT was the first therapy they received. Median time since diagnosis was 31 months, range 1–216 months. In six patients (all BCLL) relapses of lymphoma had already been persisting for longer than 10 years.

2.3. Radiotherapy prescriptions

Patients received a dose of 4 Gy, specified according to the ICRU 62 guidelines, either as 2×2 Gy ($n = 36$), with an interval of 24 ($n = 16$) or 48 h ($n = 20$), or as a single fraction of 4 Gy ($n = 35$). The target area could be either the entire involved lymph node area or the affected lymph node with a 1.5 cm margin. The choice was left to the discretion of the individual radiation-oncologist. Megavoltage photon beams of 4–18 MV and/or electron beams of 6–14 MeV were used, according to the localisation of the individual lymphadenopathy. Radiotherapy was only applied to involved sites. A total of six patients were treated by total nodal irradiation because of extensive lymph node involvement.

2.4. Supportive care and additional treatment

All registered anti-emetic drugs were allowed to prevent nausea and vomiting for abdominal radiation fields, except corticosteroids. None of the analysed patients were irradiated concurrent with chemotherapy. As soon as a patient received chemotherapy or corticosteroids after LD-IF-RT either because of local failure or because of distant relapse, the patient was counted as (local or distant) failure at that time-point.

2.5. Endpoints and statistical methods

The primary endpoint 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. The definitions for the local response were according to the "Cheson Criteria" [7]. Patients with SD or PD were designated as non-responders. If patients were irradiated to more than one site and the response differed per site (*e.g.*, CR in 1 site and PR in another) the patient was assigned to the worst category. Response assessments were performed 4–6 weeks after irradiation and 3-monthly afterwards.

Time to (local) progression (TP and TLP) was calculated according to the Kaplan and Meier method. The statistical SPSS program version 10 was used for the calculations.

Starting point for (local) time to progression was the first day of LD-IF-RT. For TP, the endpoint was either in-field or out-field progression (event) or end of follow-up for other reasons (censoring). For TLP the endpoint was in-field recurrence, either alone or synchronous with new lymphoma localisations, chemotherapy or corticosteroid medication even for non-malignant indications (*e.g.*, exacerbation of chronic obstructive pulmonary disease; event) or end of follow-up for other reasons

Table 2
Response rates, median time to progression and median time to local progression

	n (at $t = 0$)	%	Duration (months)	Median TP (months)	Median TLP (months)
First low dose treatment	71			12	22
RR	62	87			
CR	34	48	1–42+	16	23
PR	28	39	1–30+	10	11
SD	9	13	1–9+	8	9
Indolent subgroup (BCLL + MZL)	41			14	23
RR	38	93			
CR	23	56	1–42+		
PR	15	37	2–30+		
SD	3	7	1–9+		
Aggressive subgroup (DLCL + MCL)	30			9	20
RR	24	80			
CR	11	37	1–21+		
PR	13	43	1–24+		
SD	6	20	1–9		
Retreatment	29			13	23
RR	29	100			
CR	21	72	1–18		
PR	8	28	3–22		
SD	0	0			

Abbreviations: n, number; TP, time to progression; TLP, time to local progression; RR, response rate; CR, complete remission; PR, partial remission; SD, stable disease; BCLL, chronic lymphocytic leukaemia; MZL, marginal zone lymphoma; DLCL, diffuse large cell lymphoma; MCL, mantle cell lymphoma.

(censoring). Median follow-up for patients still in remission was 9 months.

3. Results

3.1. Response rates

The overall response rate (RR) was 87%. A complete remission (CR) was seen in 34 patients (48%) lasting up to 42 months and ongoing at the time of analysis. A partial remission (PR) was achieved in 28 patients (39%) lasting up to 30 months and ongoing. stable disease (SD) was maintained in the remaining nine patients (13%). Progressive disease (PD) was not seen after LD-IF-RT in this population. A LD-IF-RT retreatment (after a prior response) was given to a subpopulation of 29 patients after a median interval of 15 months (range 1–35 months). RR was 100%, compared to 87% for the first LD-IF-RT and CR was achieved by 21 patients (72% *versus* 48%). Table 2 summarises the data and the progression-free (Fig. 1(a)) and local progression-free (Fig. 1(b)) curves are shown for the group of patients receiving first LD-IF-RT.

3.2. Time to progression (TP), time to local progression (TLP) and survival

The median TP (either in-field or out-field) was 12 months and the median TLP was 22 months. (Table 2 and Fig. 1). The 34 patients achieving CR showed a median TP of 16 months and a median TLP of 23

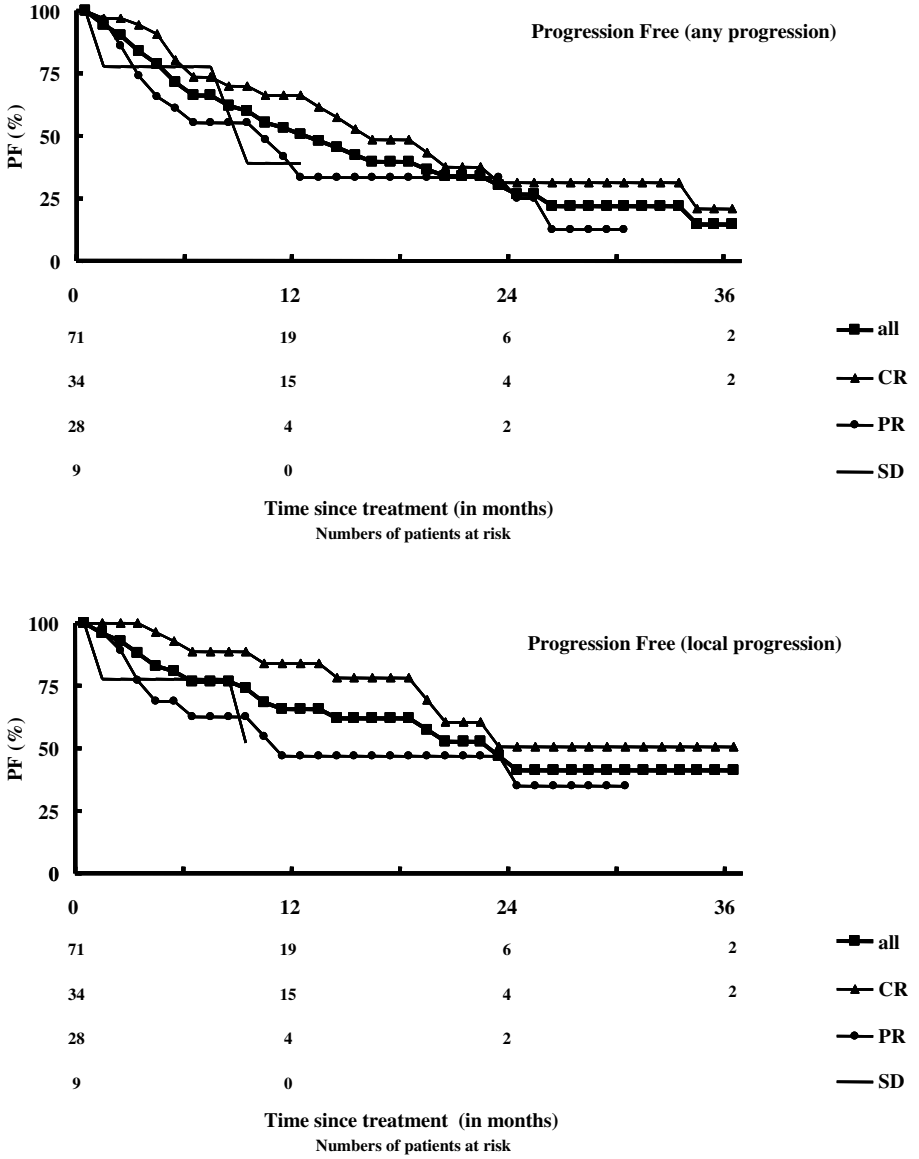

Fig. 1. Progression free and local progression free curves after LD-IF-RT, according to response. The numbers of patients at risk correspond to the category on the same line.

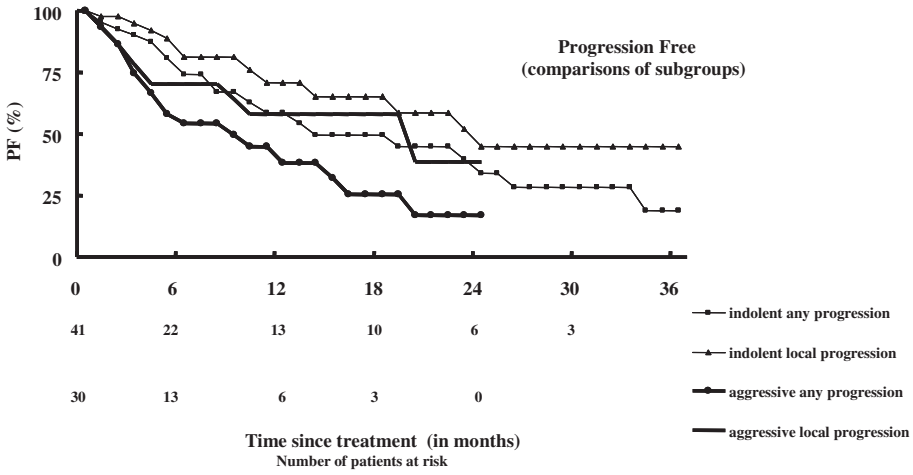

Fig. 2. Progression free and local progression free curves after LD-IF-RT; comparison of indolent *versus* aggressive lymphoma subtypes. The upper row of numbers of patients at risk correspond to the indolent lymphoma subtypes, the lower row corresponds to the aggressive lymphoma subtypes.

months. Since the first sign of progression in the 28 patients achieving PR was usually in-field, there was no difference between median TP and median TLP in this group; 10 months *versus* 11 months, respectively. The same pattern was seen in the patients maintaining SD.

Separate analyses of indolent lymphomas (BCLL and MZL; $n = 41$) and aggressive lymphomas (MCL and DLCL; $n = 30$) were performed. There was no statistically significant difference between the RR in patients with indolent or aggressive lymphomas: 93% *versus* 80%, $P = 0.12$. The same applied for the difference between the CR rate: 56% *versus* 37%, $P = 0.08$. For the indolent subgroup, the median TP was 14 months and the median TLP was 23 months. The aggressive subpopulation had shorter time periods until relapse: 9 and 20 months, respectively (Fig. 2).

The median overall survival was 36 months. For the 41 patients with indolent lymphoma subtypes (MZL and BCLL) the median OS was 67 months, which was, as expected, much longer than the median OS of 8 months for the 30 patients with aggressive lymphoma subtypes (MCL and DLCL). During follow-up 30 patients had died; in 21 patients death was caused by lymphoma progression only outside the irradiated fields (with ongoing local control) and nine patients (30%) due to lymphoma progression both in- and out-field.

3.3. Toxicity

Toxicity, as scored by the NCI-CTC Toxicity scale Version 2.0, was absent. Prophylactic non-corticosteroidal anti-emetic medication was prescribed in upper abdominal fields. Patients with bulky disease received antihyperuricaemic medication (allopurinol; dosage depending on creatinin-clearance) and no patients showed gout or tumourlysis syndrome.

3.4. Prognostic factors

Prognostic factors for response could not be distinguished in this group of patients. Tested parameters were age, sex, lymphoma subtype, radiotherapy regimen, number of prior regimens and time since diagnosis, number of positive sites and largest lymphoma diameter. *P*-values of borderline clinical significance were found for the difference in CR-rate between patients having $\leqslant 1$ prior regimen compared with those with more pretreatments ($P = 0.04$), as well as between patients with lymphoma size $\leqslant 7$ cm and patients with larger nodes ($P = 0.01$).

4. Discussion

This series on low-dose involved field radiotherapy (LD-IF-RT) of 4 Gy in 71 recurrent and/or chemotherapy refractory lymphoma patients showed a 87% rate of inducing remissions without any significant toxicity. We studied an elderly population (median age 69 years; 42% of patients $\geqslant 71$ years) after several types of systemic chemotherapy (median number of 2), often with bulky disease (defined as nodes $\geqslant 5$ cm) with a poor median overall survival. At time of death 70% of patients were without local progression after LD-IF-RT. Importantly, not only did indolent lymphomas respond to this treatment but also more aggressive entities like diffuse large cell lymphoma (DLCL) and mantle cell lymphoma (MCL). Therefore, we propose LD-IF-RT as an attractive approach in the palliative treatment of NHL patients.

The results in this analysis are in agreement to those in the highly radiosensitive follicular lymphoma (FL) population that was previously studied by our group [5]. The response rate (RR) in FL patients was 92%,

the chance of complete remission (CR) was 61%, the median time to progression wsa 14 months and the median time to local progression was 25 months. Since significant toxicity to this mild radiation regimen is absent, an immediate re-treatment could be considered if a patient only responded with partial remission and was still symptomatic. However, in this phase II trial it was not recommended to do so but to wait for the first signs of progression.

To the best of our knowledge, the only published data on low-dose irradiation in lymphomas concern low-dose total body irradiation (TBI) and a limited amount of data on localised disease. Leitch [8] described one non-responding MCL patient who refused further irradiation after 1 fraction of 2 Gy. A study from Denmark [4] presented the results of this regimen in 22 patients with indolent lymphomas, seven patients were treated for B-cell chronic lymphocytic leukaemia (BCLL) and they were irradiated to eight sites. A local CR was seen in two out of eight sites, a PR was reached in four out of eight sites (overall RR 75%).

Several studies have shown the efficacy of low-dose TBI to a dose of 1.5–2.5 Gy in 10–15 cGy fractions in BCLL [9–13] leading to a RR of 50–88% with a median response time of 14–51 months. However, low-dose TBI is seldom applied, neither in FL patients nor in BCLL, due to the risk of lasting thrombocytopenia and the induction of secondary acute myelogenous leukaemia/myelodysplastic syndrome. The chance of this secondary malignancy does not seem to be higher than after alkylating agents like chlorambucil or cyclophosphamide [14]. These possible disadvantages are not seen after LD-IF-RT.

Localised marginal zone lymphomas (MZL), both nodal and extranodal, can be controlled by radiotherapy only. In the last decade studies have shown that the historically applied doses of 40 Gy in 20 fractions of 2 Gy in 4 weeks can be significantly reduced. For MZL localisations in the orbit 25–30 Gy [15–20], for stomach 30 Gy [21,22], 25–33 Gy for the lacrimal gland [23,24], 30 Gy for the bladder [25], 25–30 Gy for salivary glands [19] and 30 Gy for thyroid [19] are currently advised. In the present series, one patient with rectal MZL showed a pathologically confirmed CR after LD-IF-RT for 42 months and in one patient with a bladder site, disease is locally controlled for 26 months.

There are no data available on low-dose radiotherapy in diffuse large B-cell lymphomas (DLCL) and mantle cell lymphomas (MCL). In stage I and II patients, radiation either as a single agent modality or after induction polychemotherapy, has been to shown to improve progression free survival and overall survival [8,26]. However, prescribed radiotherapy doses are significantly higher than in this study; 30–40 Gy in combined modality regimens and 36–45 Gy as monotherapy. Radiation-induced cell death after doses of 2 and 4 Gy in MCL cell lines *in vitro* has been studied by M'kacher *et al.* [27]. They found $SF_{2\,Gy}$-values (surviving fraction after 2 Gy) of 0.12–0.26. These values are significantly lower than the $SF_{2\,Gy}$-values for solid tumours with an average of 0.5, suggesting that MCL is a radiosensitive malignancy as well. In their experiments, radiation sensitivity, measured by the induction of chromosomal aberrations and levels of apoptotic cell death, differed significantly between studied cell lines. Furthermore, p53- and ATM gene mutations also separated the cell lines into relatively radiosensitive and radioresistant populations.

Lymphocyte predominance Hodgkin's lymphoma (LPHL) is the least common subtype of Hodgkin's lymphoma (HL). Only 2–3% of all HL patients are diagnosed with this subtype. This entity has many features in common with follicular lymphoma; both are B-cell neoplasms, both of germinal centre origin and both shows a protracted clinical course. Patients with recurrent disease have been offered LD-IF-RT also. Due to its rarity we have treated only six patients and their data have not been included in the results section. Three of them were treated by Prof. Dr. Th. Girinsky in the Institute Gustave Roussy in Villejuif, Paris. One of them has SD for 17 months, one patient had PR and progressed after 15 months with new lymphoma sites and was treated by chemotherapy. The other four patients showed CR that is ongoing for 9–36 months.

The mechanisms of low dose irradiation in haematology are poorly understood. Classical radiobiological calculations in the LQ-model [28] can not explain the results. Safwat [29] suggested that immune enhancement, rather than direct radiation cell killing, could be one of the mechanisms by which low-dose irradiation exerts its effect. We have shown, in a pathologically controlled study, that apoptosis plays a central role in FL patients in the response to LD-IF-RT and that this process can be visualised *in vivo* by ^{99m}Tc-Annexin-V-scintigraphy [30]. It is likely that apoptosis also contributes to the response in the lymphoma entities studied in this analysis, but needs experimental verification.

In conclusion, LD-IF-RT induces high response rates in recurrent and/or chemotherapy refractory indolent and aggressive B-cell lymphoma patients and can be administered without significant toxicity. The majority of patients are locally controlled after LD-IF-RT for the rest of their life span, especially in the subgroup of patients with aggressive lymphomas. Therefore, this radiotherapy regimen, as a local treatment for a systemic disease, is a valuable asset in the palliation of symptomatic lymphoma patients, especially if it concerns only a limited number of symptomatic lymphoma sites.

Conflict of interest statement

None declared.

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