Long-Term Outcome and Prognostic Factors in Early-Stage Nodal Low-Grade Non-Hodgkin's Lymphomas Treated with Radiation Therapy*

Hans Theodor Eich[1], Martina Heimann[1], Hartmut Stützer[2], Jan Kriz[1], Marcel Reiser[3], Rolf-Peter Müller[1]

Purpose: Retrospective analysis of therapy results in patients with stage I–II and limited stage III nodal low-grade non-Hodgkin's lymphoma (NHL).

Patients and Methods: The present retrospective study covers 65 patients treated between 1988 and 2006 at the Department of Radiation Oncology, University of Cologne, Germany. 50 patients were treated with radiotherapy alone (EF [extended field]: n = 35, IF/REG [involved field/regional field]: n = 9, TNI/TLI [total nodal/total lymphatic]: n = 6), 15 patients additionally received chemotherapy. Median age was 58 years. 58 patients presented with centroblastic-centrocytic or follicular lymphomas, seven patients had centrocytic lymphomas. Apart from overall and relapse-free survival, relapse patterns were examined and the impacts of patient characteristics and therapy modalities were analyzed.

Results: After a median follow-up of 9.1 years, overall 5-year and 10-year survival was 86% and 55%, relapse-free survival was 55% and 37%, respectively. Relapses occurred in 28 patients during the observation period. Overall survival was favorably influenced by low patient age (p = 0.037), centroblastic-centrocytic/follicular histology (p = 0.006), and early disease stage (p = 0.045). Favorable prognostic factors for relapse-free survival were low patient age (p = 0.035) and centroblastic-centrocytic/follicular histology (p = 0.001).

Conclusion: Radiotherapy of early-stage low-grade NHL is a curative therapy option, particularly in younger patients and patients with follicular histology. Relapse analysis confirmed the benefits of total nodal or total lymphatic irradiation, although the small number of patients needs to be considered.

Key Words: Non-Hodgkin's lymphoma · Low-grade · Radiotherapy

Strahlenther Onkol 2009;185:288–95
DOI 10.1007/s00066-009-1937-4

Behandlungsergebnisse und prognostische Faktoren nach Radiotherapie niedrigmaligner nodaler Non-Hodgkin-Lymphome in frühen Stadien

Ziel: Retrospektive Auswertung der Behandlungsergebnisse bei Patienten mit niedrigmalignen nodalen Non-Hodgkin-Lymphomen (NHL) im Stadium I–II und im limitierten Stadium III.

Patienten und Methodik: Die vorliegende retrospektive Studie umfasst 65 Patienten, die zwischen 1988 und 2006 in der Klinik und Poliklinik für Strahlentherapie der Universität zu Köln behandelt wurden. 50 Patienten erhielten eine alleinige Radiotherapie (EF [„extended field"]: n = 35, IF/REG [„involved field"]: n = 9, TNI/TLI [„total nodal/total lymphatic"]: n = 6), 15 Patienten zusätzlich eine Chemotherapie. Das mediane Alter betrug 58 Jahre. Bei 58 Patienten handelte es sich um ein zentroblastisch-zentrozytisches bzw. follikuläres Lymphom, bei sieben Patienten um ein zentrozytisches Lymphom. Neben Gesamtüberleben und rezidivfreiem Überleben wurden das Rezidivmuster untersucht und der prognostische Einfluss von Patientencharakteristika und Therapiemodalitäten analysiert.

Ergebnisse: Bei einer medianen Nachbeobachtungszeit von 9,1 Jahren betrug das 5- bzw. 10-Jahres-Gesamtüberleben aller Patienten 86% und 55%, das rezidivfreie Überleben 55% und 37%. Bei 28 Patienten kam es im Verlauf zum Auftreten eines Rezidivs. Prognostisch günstigen Einfluss auf das Gesamtüberleben hatten niedriges Patientenalter (p = 0,037), zentroblastisch-zentrozytische/follikuläre Histologie (p = 0,006) und frühes Erkrankungsstadium (p = 0,045). Für das rezidivfreie Überleben zeigten sich ebenfalls das jüngere Alter (p = 0,035) und die zentroblastisch-zentrozytische/follikuläre Histologie (p = 0,001) als günstige Prognosefaktoren.

Schlussfolgerung: Die Radiotherapie niedrigmaligner NHL in frühen Stadien ist eine kurative Therapieoption, insbesondere bei jüngeren Patienten und follikulärer Histologie. In der Rezidivanalyse erwies sich die totale nodale bzw. totale lymphatische Bestrahlung als vorteilhaft, zu berücksichtigen ist jedoch die geringe Patientenzahl.

Schlüsselwörter: Non-Hodgkin-Lymphome · Niedrigmaligne · Strahlentherapie

*Presented at the 14th Annual Meeting of the German Society for Therapeutic Radiology and Oncology (DEGRO), Vienna, May 1–4, 2008.

[1]Department of Radiation Oncology, University of Cologne, Germany,
[2]Institute of Medical Statistics, Informatics, and Epidemiology, University of Cologne, Germany,
[3]Clinic I for Internal Medicine, University of Cologne, Germany.

Received: July 28, 2008; accepted: February 12, 2009

Introduction

Non-Hodgkin's lymphomas (NHLs) are malignant lymphoproliferative disorders characterized by marked biological heterogeneity with differing patterns of behavior and response to treatment. Follicular lymphomas are the second most frequent type of nodal lymphomas, slowly progressive with frequent relapses and often diagnosed in an advanced stage only. However, approximately 20% of patients are diagnosed in the early Ann Arbor stages I and II [3]. About 5–10% of NHLs are mantle cell lymphomas. They tend to grow rapidly, with locally limited stages being established in 10–15%.

In early stages, radiotherapy is a curative option. While a consensus largely exists today as regards the required radiation dose, the extension of the optimum radiation volume remains unclear. Data on the efficiency of additional chemotherapy are likewise heterogeneous. In the present analysis, we report on our long-term data of 65 consecutive patients treated at the Department of Radiation Oncology, University of Cologne, Germany.

Patients and Methods

This study comprises a retrospective review of 65 patients treated at the Department of Radiation Oncology, University of Cologne, Germany, between 1988 and 2006. Patient and tumor characteristics are displayed in Table 1. 40 patients (62%) presented in Ann Arbor stage I, 17 (26%) and eight (12%) were diagnosed in stage II and limited stage III, respectively. 39 (60%) had CBCC (centroblastic-centrocytic) lymphomas, 18 (28%) were follicular grade I–II, and seven (11%) were CC (centrocytic) lymphoma cases. One follicular lymphoma which eluded grading was included. 50 patients (77%) were treated with radiotherapy alone (involved field [IF]: n = 2, regional field [REG]: n = 7, extended field [EF]: n = 35, total nodal [TNI]: n = 1, and total lymphatic [TLI]: n = 5 [10]). 15 patients (23%) received additional chemotherapy. The maximum dose ranged between 26 Gy and 46 Gy (median: 40 Gy).

Statistical Analysis

The endpoints of this study were overall survival (OS), relapse-free survival (RFS), and associated prognostic factors. OS was defined as the interval between the date of diagnosis and the date of death or of the last follow-up, RFS as the interval from the end of radiotherapy to the date of relapse diagnosis or of death. Survival curves were estimated according to the Kaplan-Meier method [17]. The prognostic factors for OS and RFS were evaluated by log-rank test and Cox regression analysis [5]. Results were accounted exploratively significant if associated p-values were < 0.05.

Results

Survival

The median follow-up was 9.1 years (range: 0.7–18.3 years). The OS rates at 5 and 10 years were 86% and 55%, with a median survival time of 10.6 years. The RFS rates at 5 and 10

Table 1. Patient and tumor characteristics. CC: centrocytic; CBCC: centroblastic-centrocytic; LDH: lactate dehydrogenase.

Tabelle 1. Patienten- und Tumorcharakteristika. CC: zentrozytisch; CBCC: zentroblastisch-zentrozytisch; LDH: Lactatdehydrogenase.

Characteristic	Patients n (%)
Gender	
• Female	27 (42)
• Male	38 (58)
Age	
• ≤ 50 years	19 (29)
• > 50 years	46 (71)
B-symptoms	
• Yes	4 (6)
• No	60 (92)
• Unknown	1 (2)
Ann Arbor stage	
• I	40 (62)
• II	17 (26)
• III	8 (12)
Histology	
• CBCC	39 (60)
• Follicular grade I	15 (23)
• Follicular grade II	3 (5)
• CC	7 (11)
• Follicular without grading	1 (2)
Number of involved regions	
• 1–2	51 (78)
• ≥ 3	14 (22)
Bulk > 7.5 cm	
• Yes	9 (14)
• No	50 (77)
• Unknown	6 (9)
Chemotherapy	
• Yes	15 (23)
• No	50 (77)
Target volume	
• Involved field	2 (3)
• Regional field	7 (11)
• Extended field	35 (54)
• Total nodal	1 (2)
• Total lymphatic	5 (8)
• Consolidating	15 (23)
Radiotherapy dose	
• ≤ 37 Gy	20 (31)
• > 37 Gy	45 (69)
LDH	
• Normal	44 (68)
• Pathologically elevated	9 (14)
• Unknown	12 (18)

years were 55% and 37%. The median RFS time was 5.3 years. Kaplan-Meier curves are shown in Figures 1 and 2.

Prognostic Factors for Overall Survival

Univariate analysis showed a significant prognostic impact of age (≤ 50 years vs. > 50 years; p = 0.005) and histology (CBCC/follicular vs. CC; p < 0.0005). In the group of patients aged up to 50 years, the 5- and 10-year survival rates were 95% and 86%. For patients > 50 years, the rates were 83% and 42%, respectively. Patients with CBCC/follicular lymphoma had a 5-year survival rate of 90% and a 10-year survival rate of 62%. For the CC lymphoma only a 5-year survival rate of 57% could be established (Figures 3 and 4).

Multivariate analysis of the covariates age, histology, stage, lactate dehydrogenase (LDH) and irradiation volume revealed advanced patient age (p = 0.037; hazard ratio [HR] 5.9, 95% confidence interval [CI] 1.1–31.3) and CC histology (p = 0.006; HR 6.2, 95% CI 1.7–22.9) as unfavorable prognostic factors of statistical significance. Another factor found to be statistically significant in the multivariate tests was the stage (p = 0.045). A summary of the prognostic factors reviewed is given in Table 2.

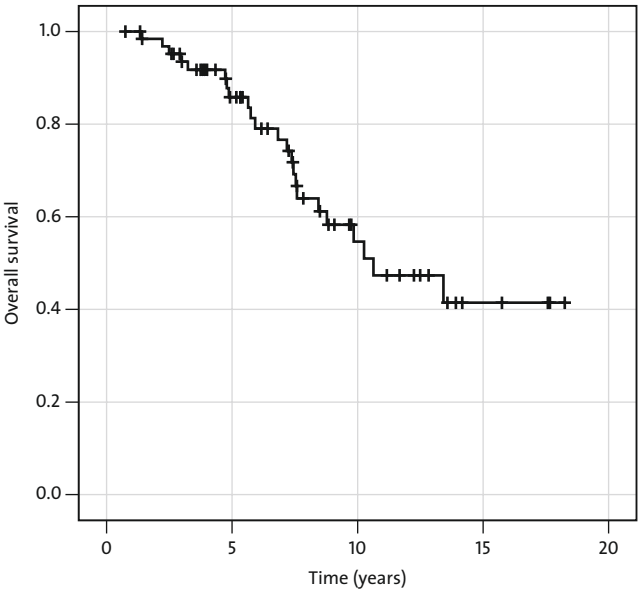

Figure 1. Kaplan-Meier curve for overall survival.

Abbildung 1. Überlebenskurve nach Kaplan-Meier für das Gesamtüberleben.

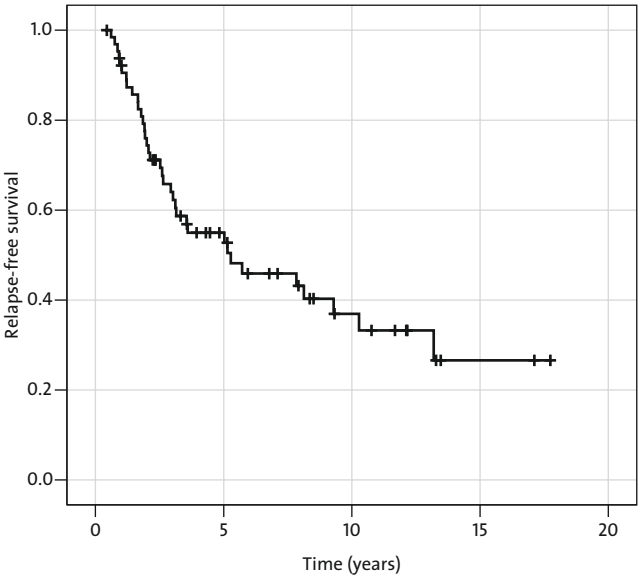

Figure 2. Kaplan-Meier curve for relapse-free survival.

Abbildung 2. Überlebenskurve nach Kaplan-Meier für das rezidivfreie Überleben.

Prognostic Factors for Relapse-Free Survival

In the univariate analysis, age (p = 0.005) and histology (p = 0.002) emerged as statistically significant factors for RFS. For patients aged ≤ 50 years, the probability of surviving without relapse for 5 or 10 years was 78% and 61%. The corresponding values for the patient group > 50 years were 45% and 25%. Patients with CBCC/follicular lymphoma had 5-year and 10-year RFS rates of 58% and 43%, respectively. The 5-year RFS among CC lymphoma patients, at 29%, was markedly lower.

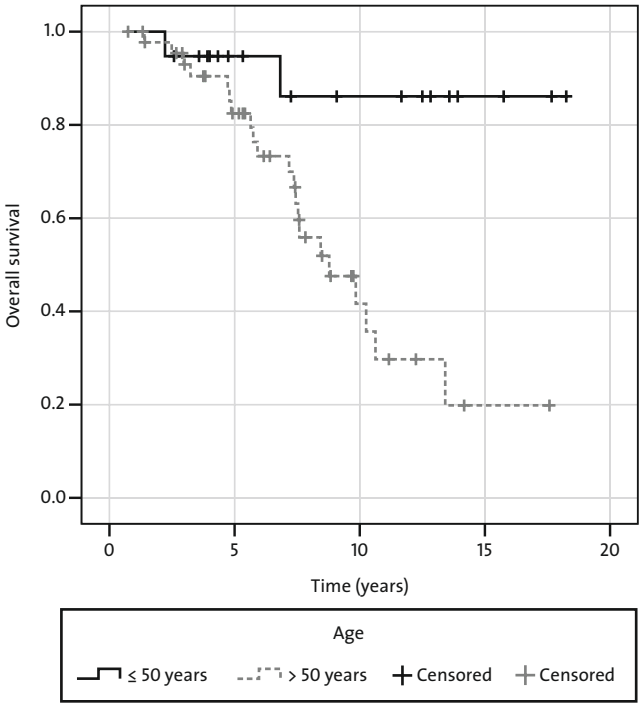

Figure 3. Kaplan-Meier curve for overall survival by age.

Abbildung 3. Überlebenskurve nach Kaplan-Meier für das Gesamtüberleben in Abhängigkeit vom Alter.

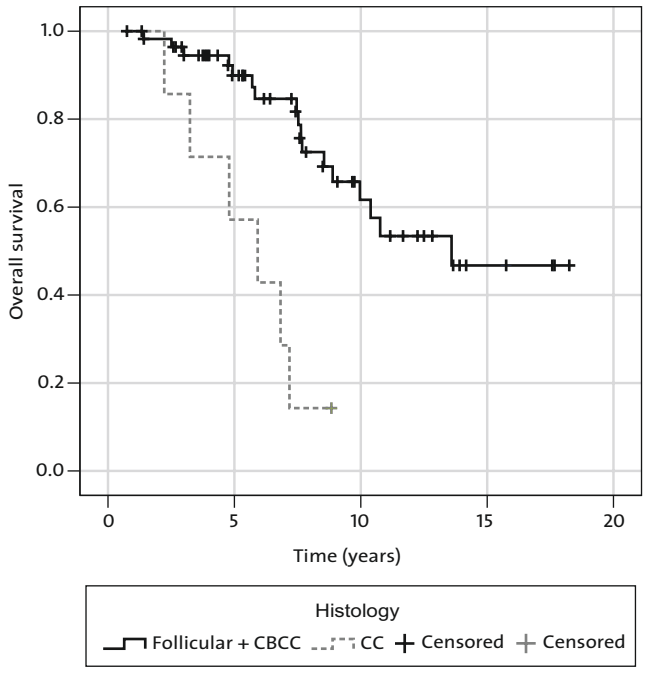

Figure 4. Kaplan-Meier curve for overall survival by histology.

Abbildung 4. Überlebenskurve nach Kaplan-Meier für das Gesamtüberleben in Abhängigkeit von der Histologie.

In a multivariate analysis examining the covariates age, histology, bulk tumor and irradiation volume or chemotherapy, advanced patient age (p = 0.035; HR 3.5, 95% CI 1.1–10.9) and CC histology (p = 0.001; HR 6, 95% CI 2.1–17.2) emerged as unfavorable influencing factors of statistical significance. Radiation volume was found to be of borderline statistical impact at p = 0.068 (univariate) and p = 0.052 (multivariate). The localized treatment volume showed an HR of 2.6 (IF/REG) and 5 (EF), respectively, vs. the TNI/TLI reference. The statistical significance of chemotherapy was marginal at p = 0.053 including all patients but no impact on prognosis was detectable (p = 0.143) if only CBCC/follicular lymphomas were considered. A summary of the prognostic factors examined is given in Table 3.

Acute and Long-Term Toxicity

Acute side effects > CTC grade 2 (Common Toxicity Criteria) occurred in 35% (23/65) of the patients. Hematotoxicity at 17% (11/65) and mucositis/dysphagia at 12% (8/65) were the most frequent forms [9]. The patients who suffered a hematotoxicity grade 3/4 were treated with rather larger portals (TLI: n = 5, TNI: n = 1, EF: n = 3, infradiaphragmatic irradiation after chemotherapy: n = 2), the patients with a mucositis/dysphagia grade 3/4 received a radiation volume (TLI: n = 1, EF:n = 4, REG: n = 2, supradiaphragmatic irradiation after chemotherapy: n = 1) including the throat and/or the esophagus.

Late toxicity including pneumonitis (n = 1), pericarditis (n = 1) and lung fibrosis (n = 1) was observed. Five second malignancies were recorded: rectal carcinoma (n = 2) in the radiation field; breast cancer (n = 1) out-field; lung cancer (n = 1) out-field; myelodysplastic syndrome (n = 1).

Analysis and Therapy of the First Relapse

Over the median follow-up of 9.1 years, 28 patients suffered a relapse. In 21 patients (75%) the relapse site was transdiaphragmal. The relapse was strictly in-field in two patients (7%), in-field and out-field in three (11%), and marginal-field in another three (11%). An out-field relapse occurred in 20 patients (71%).

Of the 28 relapsed patients, 21 had received radiotherapy alone (IF/REG: n = 3, EF: n = 18) and seven combined therapy beforehand. Of the patients initially treated with total nodal or total lymphatic irradiation, none (0/6) suffered a relapse.

23/28 relapsed patients were retreated. Complete remission was achieved in 16 patients. Details are given in Table 4.

Discussion

After a median follow-up of 9.1 years, OS rates for all 65 patients were 86% and 55% at 5 and 10 years after therapy. Among the group of patients with CBCC or follicular lymphomas in stage I and II, the 5- and 10-year survival rates were 89% and 63%. Although the patient collective presented here includes stage III and CC lymphomas, the 5-year survival rate of 86% is consistent with the literature [1, 11, 13, 19, 21, 31–33, 36, 40], where a 5-year survival between 81% and 93% was described.

The 10-year survival of stage I and II patients with a CBCC or follicular lymphoma was found to be 63% in this study, consistent with other authors [11, 21, 32, 34], who report 10-year survival rates of 62–68%.

RFS in the investigated group was 55% and 37% after 5 and 10 years. If only the patients with a CBCC/follicular lymphoma are considered, the rates are 58% and 43%. These findings correlate with literature data reporting 5-year RFS rates of 59–49% [6, 21, 33, 34] and 10-year RFS rates of 40–49% [6, 13, 19, 27, 40, 42].

Table 5 compares survival rates found in the literature to our own results. In interpreting these data, the use of different classification systems, different irradiation techniques, therapy forms (radiotherapy alone/combined modality) and definitions need to be taken into account.

Cox regression analysis identified younger patient age as a prognostic factor. This finding is consistent with the results of other authors, who likewise emphasized lower age as a favorable factor for OS [13, 19, 27, 31, 36] and/or RFS [19, 21, 31, 42].

OS and RFS were markedly more favorable in patients with CBCC/follicular lymphoma than in CC lymphoma patients. This finding is not easily comparable with other authors' results, which are often based on different lymphoma

Table 2. Uni- and multivariate analyses for overall survival. CC: centrocytic; CBCC: centroblastic-centrocytic; LDH: lactate dehydrogenase.

Tabelle 2. Uni- und multivariate Analysen hinsichtlich des Gesamtüberlebens. CC: zentrozytisch; CBCC: zentroblastisch-zentrozytisch; LDH: Lactatdehydrogenase.

Prognostic factors	2-year (%)	5-year (%)	10-year(%)	p (univariate)	p (multivariate)
Age				**0.005**	**0.037**
• ≤ 50 years	100	95	86		
• > 50 years	98	83	42		
Histology				**< 0.0005**	**0.006**
• CBCC/follicular		90	62		
• CC		57			
Ann Arbor stage				0.798	
• Stage I		86	63		**0.045 I, II, III**
• Stage II		86	45		**0.042 II vs. I**
• Stage III		88	33		0.084 III vs. I
Bulk > 7.5 cm				0.453	
• Yes		100	67		
• No		86	53		
Target volume				0.567	0.61
(1) Involved field/regional field		78	39	vs. 3	0.186
(2) Extended field		83	58	vs. 3	0.389
(3) Total nodal/ total lymphatic		100	67		
(4) Consolidating		93	58	vs. 3	0.378
Radiation dose				0.561	
• ≤ 37 Gy		85	63		
• > 37 Gy		86	50		
Chemotherapy				0.87	0.785
• Yes		93	58		
• No		98	55		
LDH				0.096	0.595
• Normal		87	57		
• Pathologically elevated			100	40	

classifications (Rappaport, Working formulation) whereas CC lymphoma does not constitute a separate entity. On a general level, CC lymphomas are accorded a much less favorable prognosis [10]. Leitch et al., after retrospective analysis of 26 patients with localized-stage CC lymphomas, reported 5- and 6-year survival rates of 68% and 48%, respectively, and a 5-year progression-free survival of 13% [20]. In our investigation, 5-year OS and RFS of the seven patients with CC lymphoma were 57% and 29%. The outcome of a large prospective observation study addressing CC lymphomas will be of utmost interest in this context [41].

In the patient group investigated here, stage could be identified as a prognostic factor for OS by multivariate analysis. A more favorable OS for stage I versus stage II patients is likewise reported by other authors [27, 32].

The optimal treatment volume remains a subject of controversy. While some authors describe higher RFS rates after total lymphatic irradiation, improved OS has not been demonstrated [21, 32]. However, some authors believe in the benefits of large-volume irradiation because of the elevated frequency of nodal out-field relapses [12, 31, 36]. In the present analysis, treatment volume as a prognostic factor for RFS was of marginal statistical significance, with patients given total nodal or total lymphatic treatment having a better survival chance. However, improved OS could not be established here.

The data on the efficiency of initial chemotherapy are likewise contradictory. While most studies in the literature reject the idea of extended OS as a result of chemotherapy [2, 13, 18, 27], the assessments of its value on RFS are inconsistent. Guadagnolo et al. and other authors noted no increase in RFS [13, 18, 25, 26, 39], yet two other studies [1, 23] did find extended RFS after combined-modality therapy. Yahalom et al. reported increased RFS after combination therapy in a patient group with intermediate-grade NHLs, but no such improvement could be shown for low-grade NHL patients [43]. Monfardini et al. and Nissen et al. described a significant impact on RFS in the subgroup with diffuse histology [25, 30]. In the present study, the statistical significance of combination treatment was marginal ($p = 0.053$) in terms of RFS. Among the CBCC/follicular lymphoma patients alone, no statistical significance was found at all ($p = 0.143$).

Over the median follow-up of 9.1 years, 28 patients (43%) suffered a relapse with 27 occurring during the first 6 years after primary therapy. Other authors report similar relapse rates of between 38% and 48% [1, 13, 27, 31, 36] and a higher relapse frequency for the first 5 years after initial treatment [16, 39].

Table 3. Uni- and multivariate analyses for relapse-free survival. CC: centrocytic; CBCC: centroblastic-centrocytic; LDH: lactate dehydrogenase.

Tabelle 3. Uni- und multivariate Analysen hinsichtlich des rezidivfreien Überlebens. CC: zentrozytisch; CBCC: zentroblastisch-zentrozytisch; LDH: Lactatdehydrogenase.

Prognostic factors	2-year (%)	5-year (%)	10-year (%)		p (univariate)	p (multivariate)
Age					**0.005**	**0.035**
• ≤ 50 years	95	78	61			
• > 50 years	68	45	25			
Histology					**0.002**	**0.001**
• CBCC/follicular		58	43			
• CC		29				
Ann Arbor stage					0.474	
• Stage I		53	39			
• Stage II		45	31			
• Stage III		88	33			
Bulk > 7.5 cm					0.773	0.124
• Yes		51	38			
• No		54	36			
Target volume					*0.068*	*0.052*
(1) Involved field/regional field		56	30	vs. 3	*0.054*	0.426
(2) Extended field		39	33	vs. 3	0.022	0.142
(3) Total nodal/total lymphatic		100	67	vs. 4	0.135	
(4) Consolidating		71	44	vs. 3		0.923
Radiation dose					0.696	
• ≤ 37 Gy		65	35			
• > 37 Gy		50	38			
Chemotherapy					0.33	0.053
• Yes		71	44			
• No		50	36			
LDH					0.792	
• Normal		52	39			
• Pathologically elevated		80	40			

Table 4. Therapy response to first relapse treatment. AK: antibody; CR: complete remission; CT: chemotherapy; PD: progressive disease, PR: partial remission; RT: radiotherapy.

Tabelle 4. Therapieansprechen nach erster Rezidivtherapie. AK: Antikörper; CR: komplette Remission; CT: Chemotherapie; PD: Krankheitsprogression, PR: partielle Remission; RT: Radiotherapie.

	Patients n (%)	RT	CT	RT/CT	CT/AK	RT/CT/AK
∑	23 (100)	11 (48)	7 (30)	2 (9)	2 (9)	1 (4)
CR	16 (70)	9 (39)	4 (17)	1 (4)	1 (4)	1 (4)
PR	1 (4)		1 (4)			
PD	5 (22)	2 (9)	2 (9)	1 (4)		
Not evaluable	1 (4)				1 (4)	

In the patients analyzed here, relapses tended to occur outside the irradiation field. This supports the findings of other authors who were able to demonstrate that the relapse risk is higher in nonirradiated regions than in areas subjected to adjuvant radiotherapy [1, 16, 21, 28, 31, 33]. Studies comparing different radiation volumes are scarce in the literature. While MacManus & Hoppe and Paryani et al. [21, 32] report an increased RFS after total lymphatic radiotherapy, other authors tend to see a risk of increasingly therapy-related side effects in a more extended irradiation [22, 35, 38]. It will be necessary to await the results of a large prospective German study comparing extended-field and total lymphatic irradiation [8, 41].

23 patients received salvage therapy after relapse. Complete remission could be restituted in 16 of these cases. Of the latter, nine had received radiotherapy alone. The feasibility and success of salvage radiotherapy are also emphasized by other authors [15, 27, 36, 37, 40].

Table 5. Literature overview on survival rates and own results. CBCC: centroblastic-centrocytic; CT: chemotherapy; OS: overall survival; RFS: relapse-free survival; RT: radiotherapy.

Tabelle 5. Überlebensraten in der Literatur und eigene Ergebnisse. CBCC: zentroblastisch-zentrozytisch; CT: Chemotherapie; OS: Gesamtüberleben; RFS: rezidivfreies Überleben; RT: Radiotherapie.

Study	Patients (n)	Stage	OS (%) 5-year	10-year	RFS (%) 5-year	10-year
Paryani et al. 1983[c] [32]	124	I–II	84	68	62	54
McLaughlin et al. 1986 [23]	76	I–II	67		48	
Lawrence et al. 1988 [19]	38	I–II	84	70	60	48
Taylor et al. 1988 [40]	64	I–II	81	78		I: 49
						II: 38
Epelbaum et al. 1992 [11]	48	I–II	83	68	71	57
Yahalom et al. 1993 [43]	44	I	RT	66[a]	47[a] (64)[a]	
		I	RT/CT	88[a]	83[a] (83)[a]	
Vaughan Hudson et al. 1994 [42]	208	I		71		47
Besa et al. 1995[c] [1]	144	I–II	81	69	66	56
Pendlebury et al. 1995 [33]	58	I–II	93	79	59	43
Denham et al. 1996 [6]	55	I–II	70	50	49	40
MacManus & Hoppe 1996[c] [21]	177	I–II	82	64	55	44
Sack et al. 1998 [36]	117	I–III	86[b]		70	60[b]
Kamath et al. 1999[c] [16]	72	I–II	73	46	62	59
Neumann et al. 2003 [27]	116	I–II	76	51	62	48
Ott et al. 2003 [31]	58	I–III	86	69	74	64
Petersen et al. 2004 [34]	460	I–II	79	62	56	41
Guadagnolo et al. 2006[c] [13]	106	I–II	93	75	72	46
Results of the present study	65	I–III	86	55	55	37
Results of the present study[c]	65	I–III			59	49
Results of the present study (only follicular and CBCC)	52 58	I–II I–III	89	63	 58	 43

[a]after 7 years (low grade)

[b]after 8 years

[c]FFTF (freedom from treatment failure), FFR (freedom from relapse)

New findings on the biology and pathology of malignant lymphomas have resulted in the development of new drugs in recent years. Rituximab is a monoclonal anti-CD20 antibody against indolent and aggressive B cell NHLs [14]. It has been used primarily in relapsed follicular lymphomas, showing response rates of approximately 50% [4]. A German multicentric phase II study is currently investigating the combination of rituximab and involved-field radiotherapy (MIR study) [24].

Another approach consists in radioimmunotherapy, which couples monoclonal antibodies with various radioisotopes (iodine-131 and yttrium-90) [29]. Lymphoma-specific (anti-idiotypic) vaccination is another promising approach [7].

Conclusion

The following results emerge from this study: radiotherapy constitutes a curative therapy option for low-grade NHLs in localized stages. The extension of the target volume still remains unclear. The present analysis, although based on a low number of patients, revealed an advantage in terms of RFS for total nodal or total lymphatic irradiation. The merits of additional chemotherapy are likewise unclear. Patient age and histology were found to be significant for OS and RFS. Progress was much less favorable in patients > 50 years or suffering from CC lymphoma. In the multivariate analysis, stage emerged as a significant prognostic factor for OS. A combination of systemic antibody therapy and local radiotherapy appears promising. This approach is currently being validated (MIR study).

References

1. Besa PC, McLaughlin PW, Cox JD, et al. Long term assessment of patterns of treatment failure and survival in patients with stage I or II follicular lymphoma. Cancer 1995;75:2361–7.
2. Bischof M, Karagiozidis M, Krempien R, et al. Radiotherapy for orbital lymphoma. Outcome and late effects. Strahlenther Onkol 2007;183:17–22.
3. Carbone PP, Kaplan HS, Musshoff K, et al. Report of the Committee on Hodgkin's Disease staging classification. Cancer Res 1971;31:1860–1.
4. Chapuy B, Borchmann P, Engert A, et al. Targeted-Therapie. Neue Zielstrukturen und Substanzen in der Behandlung maligner Lymphome. Onkologe 2006;12:651–8.

5. Cox DR. Regression models and life tables (with discussion). J R Stat Soc 1972;B34:187–202.
6. Denham JW, Denham E, Dear KB, et al. The follicular non-Hodgkin's lymphomas – I. The possibility of cure. Eur J Cancer 1996;32A:470–9.
7. Dreyling M, Schmidberger H, Hiddemann W. Aktuelle Therapieoptionen des indolenten Lymphoms. Onkologe 2006;12:612–8.
8. Engelhard M, Allgäuer M, Amela-Neuschwander S, et al. Follicular lymphoma, immunocytoma, and mantle cell lymphoma: randomized evaluation of curative radiotherapy in limited stage nodal disease. Strahlenther Onkol 2007;183:Special Issue 1:129.
9. Engelhard M, Allgäuer M, Bamberg M, et al. Follicular lymphoma, immunocytoma, and mantle cell lymphoma: prospective evaluation of curative radiotherapy in limited stage nodal disease. Strahlenther Onkol 2006;182: Special Issue 1:17.
10. Engelhard M, Stuschke M. Non-Hodgkin-Lymphome. In: Bamberg M, Molls M, Sack H, Hrsg. Radioonkologie 2. Klinik. München–Wien–NewYork: Zuckschwerdt, 2004:1052–97.
11. Epelbaum R, Kuten A, Coachman NM, et al. Stage I–II low grade non-Hodgkin's lymphoma: prognostic factors and treatment results. Strahlenther Onkol 1992;162:66–72.
12. Frank C, Zierhut D, Schulz-Ertner D, et al. Centroblastic-centrocytic non-Hodgkin's lymphoma stage I–III: patterns of failure following radiotherapy. Strahlenther Onkol 2001;177:597–603.
13. Guadagnolo BA, Li S, Neuberg D, et al. Long-term outcome and mortality trends in early-stage, grade 1–2 follicular lymphoma treated with radiation therapy. Int J Radiat Oncol Biol Phys 2006;64:928–34.
14. Haidenberger A, Popper BA, Ginestet A, et al. Kombinierte Radio/Immuntherapie mit MabThera (Rituximab) bei Non-Hodgkin-Lymphomen – Pilotstudie. Strahlenther Onkol 2006;182:Sondernr 1:17.
15. Heinzelmann F, Lang PJ, Ottinger H, et al. TLI (total lymphoid irradiation/ total lymphatische Bestrahlung) basierte Rekonditionierung ermöglicht engraftment und Langzeitüberleben nach Transplantatversagen bei Patienten mit hämatologischen Systemerkrankungen. Strahlenther Onkol 2007;183: Sondernr 1:130.
16. Kamath SS, Marcus RB, Lynch JW, et al. The impact of radiotherapy dose and other treatment-related and clinical factors on in-field control in stage I and II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1999;44: 563–8.
17. Kaplan EL, Meier P. Nonparametric estimations from incomplete observations. J Am Stat Assoc 1958;53:457–81.
18. Kelsey SM, Newland AC, Vaughan Hudson G, et al. A British National Lymphoma Investigation randomized trial of single agent chlorambucil plus radiotherapy versus radiotherapy alone in low grade, localised non-Hodgkin's lymphoma. Med Oncol 1994;11:19–25.
19. Lawrence TS, Urba WJ, Steinberg SM, et al. Retrospective analysis of stage I and II indolent lymphomas at the National Cancer Institute. Int J Radiat Oncol Biol Phys 1988;14:417–24.
20. Leitch HA, Gascoyne RD, Chhanabhai M, et al. Limited stage mantle cell lymphoma: clinical outcome in patients from British Columbia. Blood 2001;98:342a.abstract 1443.
21. MacManus MP, Hoppe RT. Is radiotherapy curative for stage I and II low-grade follicular lymphoma? Results of a long-term follow-up study of patients treated at Stanford University. J Clin Oncol 1996;14:1282–90.
22. Mauch P. Follicular non-Hodgkin's lymphoma: the role of radiation therapie. Ann Hematol 2001;80:6–65.
23. McLaughlin P, Fuller LM, Velasquez WS, et al. Stage I–II follicular lymphoma. Cancer 1986;58:1596–602.
24. MIR-Studie (MabThera und Involved-field Radiotherapie). Therapie des nodalen follikulären Non-Hodgkin-Lymphoms (WHO Grad I/II) im klinischen Stadium I/II mittels involved-field Bestrahlung in Kombination mit Rituximab. ARO 2007-2.
25. Monfardini S, Banfi A, Bonadonna G, et al. Improved five year survival after combined radiotherapy-chemotherapy for stage I–II non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1980;6:125–34.
26. Murtha AD, Knox SJ, Hoppe RT, et al. Long-term follow-up of patients with stage III follicular lymphoma treated with primary radiotherapy at Stanford University. Int J Radiat Oncol Biol Phys 2001;49:3–15.
27. Neumann H, Blanck H, Koch R, et al. Behandlungsergebnisse beim follikulären Keimzentrumslymphom Stadium I und II. Strahlenther Onkol 2003;179:840–6.
28. Nevinny-Stickel M, Poljanc K, Forthuber BC, et al. Optimized conformal paraaortic lymph node irradiation is not associated with enhanced renal toxicity. Strahlenther Onkol 2007;183:385–91.
29. Nickening C, Dreyling M, Nerl C, et al. Follikuläre und andere indolente Lymphome. Manual Maligne Lymphome. München: Tumorzentrum, Zuckschwerdt, 2004:97–107.
30. Nissen NN, Ersboll J, Hansen HS, et al. A randomized study of radiotherapy versus radiotherapy plus chemotherapy in stage I–II non-Hodgkin's lymphomas. Cancer 1983;52:1–7.
31. Ott OJ, Rödel C, Gramatzki M, et al. Radiotherapy for stage I–III nodal low grade non-Hodgkin's lymphoma. Strahlenther Onkol 2003;179:694–701.
32. Paryani SB, Hoppe RT, Cox RS, et al. Analysis of non-Hodgkin's lymphomas with nodular and favorable histologies, stages I and II. Cancer 1983;52:2300–7.
33. Pendlebury S, El Awadi M, Ashley S, et al. Radiotherapy results in early stage low grade nodal non-Hodgkin's lymphoma. Radiother Oncol 1995;36:167–71.
34. Petersen PM, Gospodarowicz M, Tsang R, et al. Long-term outcome in stage I and II follicular lymphoma following treatment with involved field radiation therapy alone. J Clin Oncol 2004;22:Suppl:563s.abstract.
35. Roth J, Martinez AE. Determination of organ doses and effective doses in radiooncology. Strahlenther Onkol 2007;183:392–7.
36. Sack H, Hoederath A, Stuschke M, et al. Strahlenbehandlung von follikulären Keimzentrumslymphomen. Ergebnisse einer deutschen multizentrischen und prospektiven Studie. Strahlenther Onkol 1998;174:178–85.
37. Schneider RA, Schultze J, Jensen JM, et al. 20 years of experience in static intensity-modulated total-body irradiation and lung toxicity. Results in 257 consecutive patients. Strahlenther Onkol 2007;183:545–51.
38. Schneider U, Lomax A, Pemler P, et al. The impact of IMRT and proton radiotherapy on secondary cancer incidence. Strahlenther Onkol 2006;182: 647–52.
39. Soubeyran P, Eghbali H, Bonichon F, et al. Localized follicular lymphomas: prognosis and survival of stages I and II in a retrospective series of 103 patients. Radiother Oncol 1988;13:91–8.
40. Taylor RE, Allan SG, McIntyre MA, et al. Low grade stage I and II non-Hodgkin's lymphoma: results of treatment and relapse pattern following therapy. Clin Radiol 1988;39:287–90.
41. Therapie der niedrigmalignen nodalen Non-Hodgkin Lymphome in frühen Stadien mit alleiniger Radiotherapie, ARO Reg. Nr. 1/98 Deutsche Krebshilfe 70-2317-Sa 13, 2. Aufl.
42. Vaughan Hudson B, Vaughan Hudson G, Maclennan KA, et al. Clinical stage I non-Hodgkin's lymphoma: long-term follow-up of patients treated by the British National Lymphoma Investigation with radiotherapy alone as initial therapy. Br J Cancer 1994;69:1088–93.
43. Yahalom J, Varsos G, Fuks Z, et al. Adjuvant cyclophosphamide, doxorubicin, vincristine and prednisone chemotherapy after radiation therapy in stage I low-grade and intermediate-grade non-Hodgkin lymphoma. Cancer 1993;71:2342–50.

Address for Correspondence
PD Dr. Hans Theodor Eich
Department of Radiation Oncology,
University of Cologne
Kerpener Straße 62
50937 Köln
Germany
Phone (+49/221) 478-5449, Fax -6158
e-mail: hans.eich@uk-koeln.de