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Phase III randomised trial

Reduced dose radiotherapy for local control in non-Hodgkin lymphoma: A randomised phase III trial ☆,☆☆

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ABSTRACT

Purpose: This multicentre, prospective, randomised-controlled trial compared efficacy and toxicity of differing radiotherapy doses in non-Hodgkin lymphoma (NHL).

Patients and methods: Patients with any histological subtype of NHL, requiring radiotherapy for local disease control, whether radical, consolidative or palliative, were included. Three hundred and sixty one sites of indolent NHL (predominantly follicular NHL and marginal zone lymphoma) were randomised to receive 40–45 Gy in 20–23 fractions or 24 Gy in 12 fractions. Six hundred and forty sites of aggressive NHL (predominantly diffuse large B cell lymphoma as part of combined-modality therapy) were randomised to receive 40–45 Gy in 20–23 fractions or 30 Gy in 15 fractions. Patients with all stages of disease, having first-line and subsequent therapies were included; first presentations of early-stage disease predominated.

Results: There was no difference in overall response rate (ORR) between standard and lower-dose arms. In the indolent group, ORR was 93% and 92%, respectively, ($p = 0.72$); in the aggressive group, ORR was 91% in both arms ($p = 0.87$). With a median follow-up of 5.6 years, there was no significant difference detected in the rate of within-radiation field progression (HR = 1.09, 95%CI = 0.76–1.56, $p = 0.64$ in the indolent group; HR = 0.98, 95%CI = 0.68–1.4, $p = 0.89$ in the aggressive group). There was also no significant difference detected in the progression free or overall survival. There was a trend for reduced toxicities in the low-dose arms; only the reduction in reported erythema reached significance.

Conclusion: In a large, randomised trial, there was no loss of efficacy associated with radiotherapy doses of 24 Gy in indolent NHL and 30 Gy in aggressive NHL, compared with previous standard doses of 40–45 Gy.

Radiotherapy is well-established in the management of non-Hodgkin lymphoma (NHL), used across histological and clinical sub-types. In indolent NHL, radiotherapy may cure early stage disease [1,2], and has a valuable palliative role in more advanced diseases [3–7]. In aggressive NHL, radiotherapy is used with curative intent in stage I disease after short course chemotherapy [8,9] and may also be given to consolidate chemotherapy response in sites of disease perceived to be high risk by nature of bulk or extra-nodal location [10,11]. Radiotherapy has a major palliative role for aggressive lymphoma causing local symptoms in patients intolerant to chemotherapy or with chemo-resistant disease. A recent study has defined the optimal utilisation rate for palliative radiotherapy in lymphoma at 6% of all newly diagnosed cases of which 88% will receive treatment to nodes and 12% to a primary extranodal site [12].

NHLs are known to be radiosensitive tumours requiring lower doses of radiation than epithelial malignancies. However, uncertainty remains regarding the optimal radiation dose required. Several studies have indicated a difference in sensitivity between indolent and aggressive lymphomas [1,8,13–15]. In aggressive NHL (histologically high-grade) no dose–response across a range 20–50 Gy was seen in a series from Stanford (1960–1970), with a recurrence rate of 30% [1]. In a British National Lymphoma Investigation (BNLI) series of 82 patients with stage I/II disease, treated with radiotherapy alone (1974–1981), the response was dependent on the radiotherapy dose, reaching 100% for doses of 45 Gy

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or more [16]. EORTC radiotherapy data from 1970–1980 showed a 30% local relapse rate in 94 patients who received <45 Gy radiotherapy, compared to 13% in 81 patients who received ⩾45 Gy [8]. In a series of 496 patients from Toronto (1967–1978), no dose–response was seen above 30 Gy [13].

The EORTC data supported the contention that indolent lymphomas (histologically low-grade) require lower radiotherapy doses than aggressive lymphomas, with no improvement in control of follicular lymphoma (FL) seen above 25 Gy [8]. In the Toronto series, dose–response reached a plateau at 20 Gy for indolent NHL [13].

These studies were mainly retrospective series of heterogeneous populations. Radiation fields and techniques varied within and across studies, and most patients in older studies did not receive chemotherapy, unlike the current situation where most radiotherapy for aggressive lymphoma is part of combined-modality therapy. The difficulties in comparison between studies and application of results from older studies to current practice are compounded by the use of many different histological classification systems for NHL over the past 50 years.

A general therapeutic principle is that the correct dose of a treatment is the lowest dose compatible with achieving optimal efficacy. Achieving this dose level is particularly important when administering cytotoxic treatments. In general, both acute and late radiation effects will be dose-dependent across the therapeutic range, acute reactions being primarily related to dose and dose rate. Late toxicities depend not only on total dose but are tissue dependent and influenced by the dose of each radiation fraction, with larger fraction size leading to increased risk of late effects. A retrospective study of patients treated for aggressive NHL on EORTC trials (1980–1999) looked at cardiovascular morbidity [17]. Protocols advised consolidation radiotherapy to sites of initial bulk disease, delivering a dose of 30 Gy for those in complete remission (CR) following first-line chemotherapy, and 40 Gy for those with partial remission (PR). Subgroup analysis suggested the risk of stroke and myocardial infarction was only substantially increased in the group who actually received ⩾40 Gy. Recent retrospective studies in Hodgkin lymphoma survivors have also demonstrated dose relationships with the risks of secondary breast cancer and thyroid abnormalities significantly increasing at >30 Gy [18,19] and >35 Gy exposure [20], respectively.

There are also pragmatic and health service advantages to minimising radiotherapy dose delivery since lower doses of radiotherapy will require fewer attendances for the patient. Ongoing critical evaluation of dose and fractionation schedules may have resource implications as well as clinical importance [21]. Furthermore, Ionising Radiation (Medical Exposure) Regulations 2000 (IRMER) support the need for all prescribers of radiation to critically appraise and justify each radiation exposure [22].

In the mid-1990s, standard radiotherapy practice in NHL throughout the United Kingdom and in the international published literature was to deliver doses of 35–40 Gy, with no distinction between different histological types. Based on the data above, a randomised trial was designed comparing a standard dose of 40 Gy to reduced doses of 24 Gy in indolent and 30 Gy in aggressive lymphomas.

Patients and methods

Study design

This prospective, randomised study was initiated and supported by the BNLI and subsequently the National Cancer Research Institute (NCRI) Lymphoma and Radiotherapy Clinical Studies Groups. Appropriate ethical approval was obtained, in accordance with the Declaration of Helsinki. Trial execution was overseen by an independent data monitoring committee. The data analysis, preparation of the manuscript, and interpretation were performed independently from the funders.

Eligibility

Consenting patients aged 18 years or over with a histological diagnosis of NHL (any subtype) were eligible. All indications for radiotherapy were included, whether radical for early stage disease, consolidative after chemotherapy or palliative. Diagnostic material was requested for central histological review. Initially, this was according to the BNLI classification alone [23]. In the latter part of the trial, following publication of the World Health Organisation (WHO) lymphoma classification [24], this diagnosis was also recorded.

Randomisation and treatment

Patients were randomised via telephone at the CR UK & UCL Cancer Trials Centre. Randomisation was stratified by centre and histological grade (indolent vs aggressive). The distinction between indolent and aggressive lymphomas was based on the BNLI histological grading of that time [23]; BNLI grade I histologies were "low-grade" or indolent (mainly FL and marginal zone lymphoma (MZL)) whilst BNLI grade II were aggressive, histologically "high-grade" lymphomas (mainly diffuse large B cell lymphomas (DLBCL)). Patients were randomised to receive either 40–45 Gy in 20–23 fractions (control arm) or an experimental low dose arm of 24 Gy in 12 fractions (indolent) or 30 Gy in 15 fractions (aggressive). It was permitted to randomise more than once for different disease sites but in fact this applied to only three patients. The prescription point was to an applied dose for single beams, a midplane dose for opposed beams or a tumour intersection dose for planned volumes. Treatment techniques were those routinely used in each department in accordance with the United Kingdom national cancer standards.

Assessment of response

Patients were assessed one month following completion of radiotherapy, then 6 monthly for the first 5 years, and annually thereafter. Tumour status within the irradiated field was assessed clinically or radiologically, as appropriate, and classified as CR (absence of detectable disease in the irradiated field), PR (⩾50% reduction in disease within field), stable disease (SD), progression or patient death. Information on distant relapse/progression was also collected.

Statistical considerations

Outcome measures

The primary outcome measure was overall response rate (ORR), defined as CR or PR within the radiotherapy field, one month after treatment. Secondary end points were freedom from local progression (FFLP), acute toxicity, late morbidity and overall survival (OS). FFLP was calculated from the date of randomisation to the date of within-field progression, patients dead without in-field progression being censored at the date of death. Progression free survival (PFS) was calculated from the date of randomisation to the date of any relapse or progression, or death from any cause. OS was calculated from the date of randomisation to the date of death from any cause. Acute toxicity within the irradiated field was assessed one month after treatment. Late morbidity was defined as symptoms arising within the irradiated volume more than 6 months after the completion of radiotherapy. Investigators were not blinded to the treatment received when making these assessments.

Sample size

The sample size calculation was based on the expected ORR of 85% and 60% for indolent and aggressive NHL, respectively, using standard radiotherapy doses (40–45 Gy). The trial was designed to detect a 15% difference in ORR with 90% power and 5% significance level (2-sided), requiring 340 sites of indolent NHL and 460 sites of aggressive disease.

Statistical Analyses

Analyses were performed on an intention-to-treat basis except for ORR at one month and acute toxicity. Patients who received at least one fraction of radiotherapy were included in the analysis of ORR; patients who received at least one fraction of radiotherapy and were alive at the time of the one-month assessment were included in the assessment of acute toxicity. All patients were included in the analysis of PFS and OS on an intention-to-treat basis, using the first randomisation for patients with more than one site randomised. The standard chi-squared test was used in the comparisons of ORR and acute toxicity. The log-rank test was applied to compare the Kaplan–Meier curves for FFLP, PFS and OS.

Results

Between April 1997 and January 2005, 1001(361 indolent, 640 aggressive) randomised treatment allocations were made from 40 treatment centres (998 patients; 3 had 2 separate randomisations) as shown in Consort diagram (Fig. 1). The baseline characteristics were well balanced between arms (Table 1). 83% of patients were to receive radiotherapy as, or as part of, first-line therapy, with the remainder being for relapsed or resistant disease. Of note, the patient population had predominantly early-stage disease. In those with indolent disease, the indication for therapy was radical (attempted cure without chemotherapy in early-stage disease) in 69%, whereas in those with aggressive disease, 80% had consolidation radiotherapy as part of combined-modality therapy.

Specimens for central review were received from 853 patients (85%), of which 816 were suitable for central review and have results available. In 82 cases in which only the BNLI classification was used, there was disagreement in 2 cases; both were randomised as aggressive but considered indolent on central review. 765 patients had a WHO diagnosis available of which 734 were from central review (Table 2). There was discordance with the local diagnosis in 53 cases (7%) with 20 indolent cases centrally classified as DLBCL, 6 felt to be high-grade transformation of FL, 1 case reclassified as Hodgkin lymphoma (HL), and 1 case diagnosed locally as MZL felt to be reactive. In the aggressive group, 11 were centrally classified as FL grade 1/2, 4 MZL, 8 HL, 1 myeloma and 1 acute myeloid leukaemia.

Compliance with trial treatment was excellent with over 95% of patients who received radiotherapy having the correct total dose and fraction number as stated in the protocol. In the control groups, the vast majority received 40 Gy in 20 fractions, with only 1 patient with indolent NHL and 3 with aggressive NHL receiving 41–45 Gy.

The one month response assessment showed excellent tumour control (Table 3). In the indolent group, ORR was 93% in the 40–45 Gy arm and 92% in the 24 Gy arm ($p = 0.72$; a difference of 1%, 95% CI of difference = −5% to 6%) with CR rates of 79% and 82%,

Table 2
WHO diagnosis, available for 765 patients (77%). 734 of these 765 (96%) had central review of histology, with discordance in 53 (7%). In these cases, the final diagnosis following central review is displayed here (see text). Central review was not possible in 31 (4%) of these 765 patients; in these cases, the local diagnosis is included in the above table. FL = follicular lymphoma; MZL = marginal zone lymphoma; MALT = mucosa-associated lymphoid tissue; CLL = chronic lymphocytic leukaemia; SLL = small lymphocytic lymphoma; LPL = lymphoplasmocytic lymphoma; MCL = mantle cell lymphoma; DLBCL = diffuse large B cell lymphoma; HG = high-grade; T-NHL = T-cell non-Hodgkin lymphoma.

	Indolent ($n = 289$)	Aggressive ($n = 476$)
FL Grade 1/2	171 (59%)	11 (2%)
Grade 3	14 (5%)	11 (2%)
MZL including MALT lymphoma	56 (19%)	4 (1%)
CLL/SLL	10 (3%)	0
LPL	2 (1%)	
MCL	8 (3%)	7 (2%)
DLBCL	20 (7%)	391 (82%)
HG transformation of FL	6 (2%)	15 (3%)
Burkitt's	0	3 (1%)
T-NHL	1 (<1%)	24 (5%)
Other	1 (<1%)	10 (2%)

Table 1
Baseline characteristics and indications for therapy.

	Indolent		Aggressive		Total
	24 Gy $N = 180$	40–45 Gy $N = 181$	30 Gy $N = 319$	40–45 Gy $N = 321$	
Age median (range)	62 (29–85)	64 (30–89)	65 (18–91)	65 (23–92)	64 (18–92)
Male gender N (%)	84 (47)	97 (54)	179 (56)	168 (52)	528 (53)
First-line treatment: stage N (%)					
I	69 (40)	72 (41)	77 (24)	68 (21)	286 (29)
IE	38 (22)	47 (27)	55 (17)	56 (18)	196 (20)
II/IIE	11 (6)	13 (7)	79 (25)	93 (30)	216 (20)
III/IV	6 (3)	12 (7)	45 (14)	45 (14)	108 (11)
Relapsed/refractory; any stage N (%)	50 (29)	30 (17)	44 (14)	41 (13)	165 (17)
Not known N	6	7	19	18	50
B symptoms N (%)	13 (8)	4 (2)	43 (15)	40 (15)	100 (11)
Time from diagnosis to randomisation; median months (range)	3.1 (0.2–220)	2.8 (0–179)	4.6 (0–352*)	4.5 (0–164)	4.1 (0–352)
Indication for RT radical	119 (66)	130 (72)	36 (12)	35 (12)	320 (32)
Palliation	56 (31	46 (25)	25 (8)	29 (9)	156 (16)
Consolidation	5 (3)	5 (3)	257 (81)	255 (79)	522 (52)
Previous/contemporaneous chemotherapy N (%)	46 (26)	36 (20)	256 (80)	252 (79)	590 (59)
Previous radiotherapy N (%)	15 (8)	24 (13)	32 (10)	29 (9)	100 (10)
Previous rituximab exposure N (%)	2 (1)	2 (1)	34 (11)	33 (10)	71 (7)
Karnofsky scale N (%)					
60–80	16 (12)	16 (11)	67 (30))	61 (30)	160 (23)
90	44 (34)	34 (24)	66 (29)	67 (32)	211 (30)
100	70 (53)	90 (64)	92 (41)	80 (38)	332 (47)
Not known	50	41	94	113	298

* The single patient 352 months from original diagnosis represented a recent aggressive transformation of indolent lymphoma.

Table 3
Response assessment at one month for all randomised sites of disease. CR = complete response; PR = partial response; SD = stable disease.

Response	Indolent		Aggressive		Total
	24 Gy	40–45 Gy	30 Gy	40–45 Gy	
CR	145 (82%)	138 (79%)	249 (82%	251 (83%)	783 (82%)
PR	18 (10%)	24 (14%)	29 (9%)	24 (8%)	95 (10%)
SD/ progression	14 (8%)	12 (7%)	25 (8%)	24 (8%	75 (8%)
Death	0 (0%)	0 (0%)	1 (<1%)	3 (1%)	4 (<1%)
Not assessable	2	2	0	3	7
No RT received	1	1	5	3	10
Missing	0	4	10	13	27
Total	180	181	319	321	1001

respectively ($p = 0.54$; a difference of -3%, 95% CI of difference = −8% to 6%). In the aggressive group, there was again no difference in ORR (91% in both arms; $p = 0.87$; a difference of 0, 95% CI of difference = −4.5% to 4.5%) or CR rate (83% and 82% in the standard and low-dose arms, respectively; $p = 0.62$; a difference of 1.5%, 95% CI = −6% to 8%).

The moderate or severe acute and late toxicities were modest (Table 4). Compared to the standard arms, there was a trend for lower rates of acute toxicity and late morbidity in the lower-dose arms especially for erythema (29% vs. 41%, $p < 0.001$).

With a median follow-up of 5.6 years, in the indolent group there were a total of 80 (38 high dose, 42 low dose) local progressions and 191 (100 high dose, 91 low dose) local and/or systemic progression; in the aggressive group, there were a total of 100 (48 high dose, 52 low dose) local progressions and 264 (129 high dose, 135 low dose) local and/or systemic progressions.

Comparison of Kaplan–Meier curves for FFLP gave a p-value of log-rank test 0.59 (hazard ratio (HR, HR > 1 in favour of high dose) 1.13; 95% CI = 0.73–1.75) in the indolent group; a p-value of 0.68 (HR = 1.09; 95% CI = 0.73–1.61) in the aggressive group (Fig. 2a). In the indolent group, 5-year FFLP was 78.9% for high-dose and 75.6% for low-dose, a difference of 3.3%, and 95% CI of the difference = −5.2% to 12.8%. In the aggressive group, 5-year FFLP was 83.5% for high-dose and 82.2% for low-dose, a difference of 1.3%, and 95% CI of the difference = −4.2% to 8.7%. Comparison of Kaplan–Meier curves for PFS gave a p-value of 0.37 (HR = 0.88; 95% CI = 0.66–1.17) in the indolent group; a p-value of 0.66 (HR = 1.06; 95% CI = 0.83–1.34) in the aggressive group. Overall PFS was 55% in the indolent group and 54% in the aggressive group (Fig. 2b).

There was no significant difference detected in OS (Fig. 2c) between arms. In the indolent group, a total of 107 (55 high dose, 52 low dose) deaths were observed; comparison of Kaplan–Meier curves gave a p-value of 0.84 (HR = 0.96, 95%CI = 0.66–1.41); the 5-year OS was 73% and 74% in the high and low dose arms, respectively, a difference of 1% and 95% CI of the difference = −9% to 8%. In the aggressive group, a total of 217 (102 high dose, 115 low dose) deaths were observed; comparison of Kaplan–Meier curves gave a p-value of 0.29 (HR = 1.15, 95% CI = 0.88–1.51); 5-year OS was 68% in the 40–45 Gy arm and 64% in the 30 Gy arm, a difference of 4% and 95% CI of the difference = −3% to 12%.

Further subgroup analyses were performed in an exploratory manner and should be interpreted with caution. In the indolent group, 248 patients received radical radiotherapy as the first-line therapy. There was no difference in PFS by dose allocation (HR(95%CI)=0.74(0.50–1.10); $p = 0.13$) for this group, with 54% in the control arm and 64% in the low-dose arm remaining alive without lymphoma recurrence at any site. Further exploratory sub-set

Table 4
Acute and chronic toxicities reported in all grades of lymphoma, by treatment arm. Of the 361 randomised patients with indolent NHL, 180 in the 40–45 Gy arm and 179 in the 24 Gy arm received at least one fraction of radiotherapy (RT) and were alive at the time of the one month assessment. Of the 640 randomised patients with aggressive NHL, 315 in the 40–45 Gy arm and 313 in the 30 Gy arm received at least one fraction of RT and were alive at the one-month assessment. Toxicities were graded as mild (1), moderate (2) or severe (3).

		Indolent NHL			Aggressive NHL		
		24 Gy (%)	40–45 Gy (%)	p Value	30 Gy (%)	40–45 Gy (%)	p Value
Acute toxicities recorded at one-month assessment							
Erythema	All grades	348	47 20	0.004	26	37	<0.001
	Grades 2/3	8	20		5	11	
Mucsitis	All grades	25	25	0.69	19	24	0.54
	Grades 2/3	11	9		6	8	
Dry desquamation	All grades	13	19	0.002	12	15	0.13
	Grades 2/3	1	9		3	5	
Moist desquamation	All grades	1	8	0.02	3	6	0.018
	Grades 2/3	0	4		2	3	
Nausea/vomiting	All grades	11	13	0.56	7	7	0.57
	Grades 2/3	4	3		2	1	
Diarrhoea	All grades /3	9	13	0.56	7	7	0.57
	Grades 2/3	1	3		2	1	
Late toxicities recorded in							
Skin fibrosis	All grades	17	18	0.92	16	15	0.32
	Grades 2/3	2	3		1	3	
Skin telengiectasia	All grades	8	13	0.40	11	10	0.58
	Grades 2/3						
Alopecia	All grades	16	16	0.21	9	15	0.29
	Grades 2/3	3	6		3	7	
Dry mouth	All grades	23	22	0.84	20	23	0.07
	Grades 2/3	8	9		5	7	
Mucosa	All grades	9	9	0.52	11	13	0.64
	Grades 2/3	4	2		3	4	
	Grades 2/3						
Bowel	All grades	4	3	0.91	3	7	0.05
	Grades 2/3	2	2		1	1	
Bladder	All grades	2	2	0.50	2	3	0.22
	Grades 2/3	1	1		0	1	

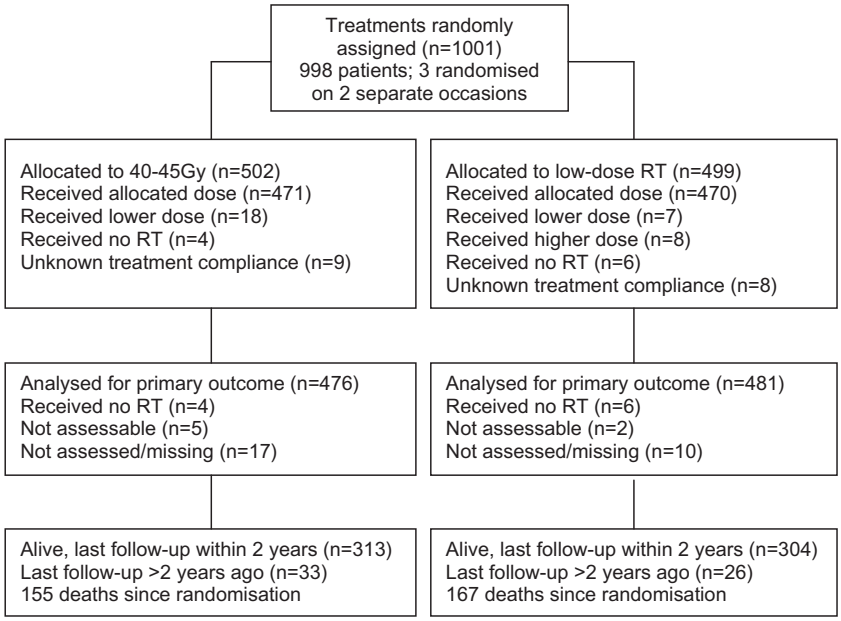

Fig. 1. Consort Diagram.

analyses showed PFS of 57% in the 126 known FL patients and 68% in the 41 MZL patients; no differences in PFS were detected between high and low dose levels.

469 patients in the aggressive group received consolidation radiotherapy as part of first-line therapy. At the time of analysis, 67% in the control arm and 64% in the low-dose arm were alive without progression and no difference was detected ($p = 0.43$). In the 64 patients who received rituximab as part of first-line combined-modality therapy for aggressive NHL, PFS was 80% with a median follow-up of 3.6 years. 71 patients received radical radiotherapy (without chemotherapy) for aggressive NHL and 48% are alive with no reported progression; again, there was no obvious difference between the low-dose and control arms.

Discussion

This large, randomised trial found no difference in local control of NHL comparing low-dose (24 Gy in indolent NHL; 30 Gy aggressive NHL) with conventional dose (40–45 Gy) radiotherapy. Furthermore, there was no significant difference detected in the in-field progression-free interval, PFS or OS in the low and high dose levels. Importantly the rates of local control were excellent for all radiotherapy doses, with ORR of 93% for indolent lymphoma and 91% for aggressive disease. This is higher than expected, probably due to the predominance of early stage disease, and for aggressive NHL, the use of combined-modality therapy.

The trial has answered the primary outcome of radiation dose response in ''low grade'' and ''high grade'' non Hodgkin lymphomas, but has some limitations. The trial was designed and began recruitment in the pre-WHO classification era, and it is not possible to accurately translate all of the histological classification at the time of trial entry into WHO terminology. However, a WHO diagnosis is available for more than three quarters of the patients in the study, most of which have also been subject to the rigours of central histological review. A further 8% of diagnoses were reviewed centrally according to the BNLI classification system, confirming their eligibility for study. 82% of WHO diagnoses in the aggressive group were of DLBC NHL, with a further 3% classified as high-grade transformation of FL. In the indolent group, 64% had follicular lymphoma and 19% had MZL or MALT, and it is likely that these figures are representative of the trial population as a whole. Exploratory subset analyses did not find any evidence of reduced treatment efficacy with lower-dose radiotherapy for any of the larger subsets of histological subtype.

It is recognised that the choice of local disease control at one month as primary end-point is rather arbitrary and whilst reflecting local response has less clinical relevance for those treated with curative intent. However, secondary end-points of time to local progression and overall survival provided important additional information, and, crucially, information on marginal relapses and distant recurrences were collected in a systematic way, allowing reliable comparisons of PFS to be made, and excluding any significant reduction in PFS with the lower doses of radiotherapy.

The trial population was heterogeneous in terms of histological diagnosis, indication for radiotherapy, and other treatment received. This could raise concerns about the application of the trial findings to all clinical settings where radiotherapy is given. However, two large groups of patients predominated – those with early stage, indolent lymphoma having first-line treatment with radical radiotherapy (248 patients) and those with aggressive NHL receiving consolidation radiotherapy as part of the first-line combined-modality therapy (469 patients). Although the study was not originally powered for this purpose, significant differences in treatment failure (which for these groups would be any recurrence or death from lymphoma) can be reliably excluded. The fact that there is no difference in FFLP supports the use of the lower dose in the palliative setting for indolent lymphomas. In addition, there was no significant difference in cure rates for patients having single-modality radiotherapy for aggressive NHL, although the numbers were smaller with only 71 such patients.

This trial reflects predominantly the experience of patients treated in the ''pre-rituximab era'', with only 12% of the first-line combined-modality regimens including rituximab. However, whilst long-term outcomes are likely to have improved with the widespread use of rituximab, the authors do not consider it likely that there would be any effect on radiotherapy dose–response.

As expected, lower doses of radiation were associated with some reduction in reported acute and late toxicities, particularly acute erythema. The study was not powered to detect significant

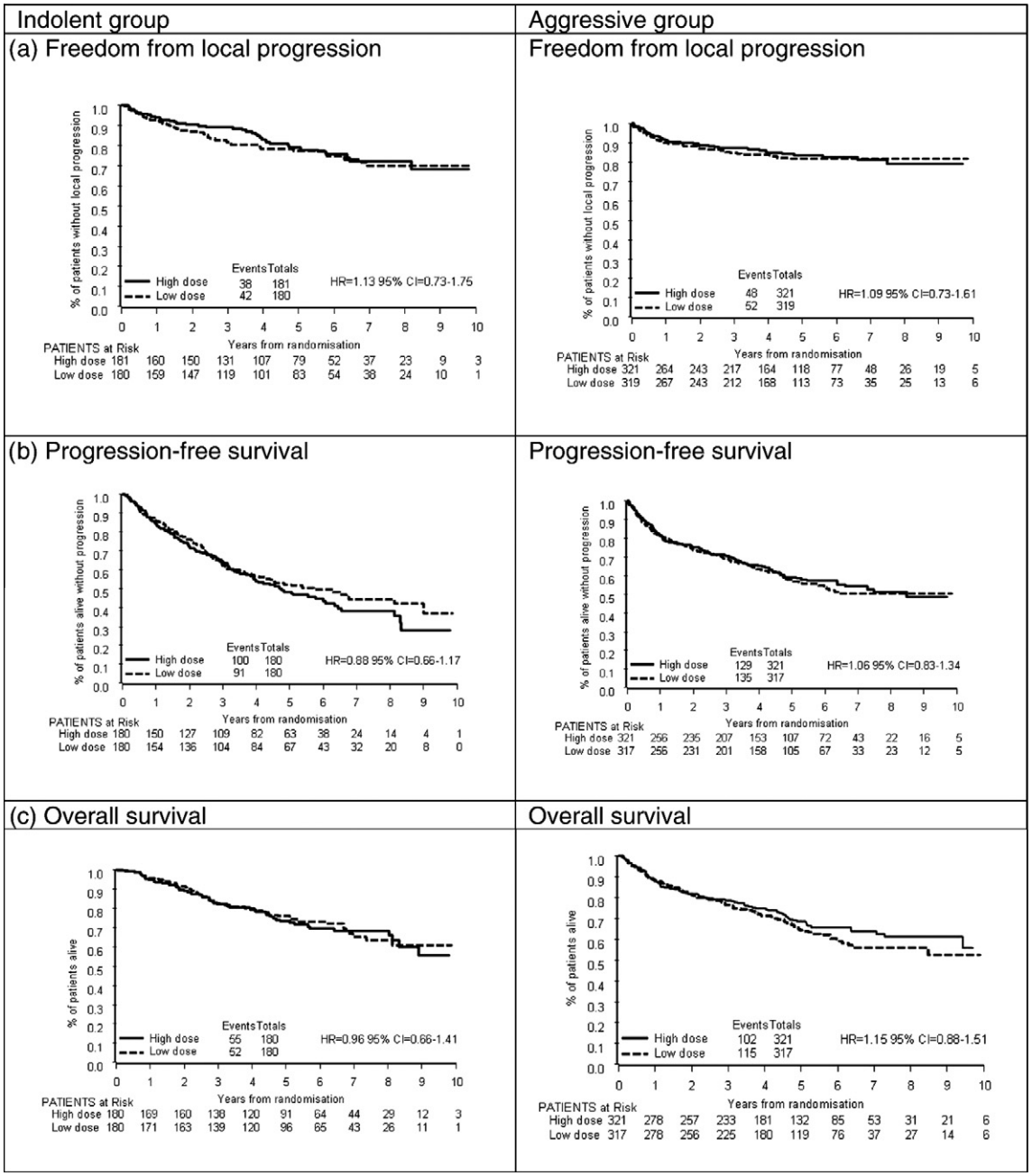

Fig. 2. Freedom from local progression, progression-free survival and overall survival for indolent and aggressive groups, by treatment arm. Freedom from local progression - patients with no progression/relapse within field were censored at the date of last follow-up or date of death. Progression-free survival (PFS) – duration from date of randomisation to date of any progression/relapse or date of death, whatever occurs first. Overall survival (PFS) – date of randomisation to date of death from any cause. PFS and OS calculated on an intention-to-treat basis, using the first randomisation for patients with more than one site randomised.

differences between treatment arms. In addition to minimising clinical side-effects, the use of lower doses of radiation results in fewer hospital attendances for the patient, and a reduction in the use of radiotherapy resources. Another approach to reduce toxicity from radiotherapy is to reduce the volume treated. Patients in this study received conventional involved field treatment; many current protocols follow the involved node (INRT) concept proposed by the EORTC in which the original sites of node involvement as defined on PET are the basis of the Clinical Target Volume [25,26].

In conclusion, this large, randomised trial shows that doses of radiotherapy can safely be reduced to 24 Gy in indolent lymphoma and 30 Gy in more aggressive histological subtypes, without compromising local tumour control in the short- or long-term. These radiation doses should become the new standard of care for patients receiving radiotherapy for NHL. Even lower doses of radiotherapy may be as efficacious in some settings, but this has yet to be confirmed in the setting of large, randomised trials. In follicular lymphoma doses of 4 Gy in two fractions have been shown to achieve effective local control [3–7]. We are currently recruiting patients into a randomised, phase III trial of 24 Gy vs. 4 Gy palliative or radical radiotherapy in patients with FL or MZL.

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References

[1] Fuks Z, Kaplan HS. Recurrence rates following radiation therapy of nodular and diffuse malignant lymphomas. Radiology 1973;108:675–84.
[2] Vaughan Hudson B, Vaughan Hudson G, MacLennan KA, et al. Clinical stage 1 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;69:1093–9.
[3] Ganem G, Lambin P, Socie G, et al. Potential role for low dose limited field radiation therapy in advanced low grade non-Hodgkin's lymphoma. Hematol Oncol 1994;12:1–8.
[4] Sawyer EJ, Timothy AR. Low dose palliative radiotherapy in low grade non-Hodgkin's lymphoma. Radiother Oncol 1997;42:49–51.
[5] Luthy SK, Ng AK, Silver B, et al.: Response to low-dose involved-field radiotherapy in patients with non-Hodgkin's lymphoma. Ann Oncol advance access published online July 22, 2008.
[6] Haas RLM, Poortmans P, De Jong D, et al. High response rates and lasting remissions after low-dose involved field radiotherapy in indolent lymphomas. J Clin Onc 2003;21:2474–80.
[7] Murthy V, Thomas K, Foo K, et al. Efficacy of palliative low-dose involved-field radiation therapy in advanced lymphoma: a phase II study. Clin Lymphoma & Myeloma 2008;8:241–5.
[8] Tubiana M, Carde P, Burgers J, et al. Prognostic factors in non-Hodgkin's lymphoma. Int J Radiat Oncol Biol Phys 1986;12:503–14.
[9] Miller TP, Dahlberg S, Cassady R, et al. Chemotherapy alone compared with chemotherapy plus radiotherapy for localized intermediate- and high-grade non-Hodgkin's lymphoma. N Eng J Med 1998;339:21–6.
[10] Ferreri AJM, Dell'Oro S, Reni M, et al. Consolidation radiotherapy to bulky or semibulky lesions in the management of stage III-IV diffuse large B cell lymphomas. Oncology 2000;58:219–26.
[11] Rube C, Nguyen TP, Klőss M, et al. Consolidation radiotherapy to bulky disease in aggressive NHL First results of the NHL B-94 trial of the DSHNHL. Ann Hematol 2001;80:B84–5.
[12] Jacob S, Wong K, Delaney GP, Adams P, Barton MR. Estimation of an optimal utilisation rate for palliative radiotherapy in newly diagnosed cancer patients. Clin Oncol 2010;22:56–64.
[13] Sutcliffe SB, Gospodarowicz M, Bush RS, et al. Role of radiation therapy in localised non-Hodgkin's lymphoma. Radiother Oncol 1985;4:211–23.
[14] Seydel HG, Bloedorn FG, Wizenberg M, et al. Time-dose relationships in radiation therapy of lymphosarcoma and giant follicle lymphoma. Radiology 1971;98:411–8.
[15] Cox JD, Koehl RH, Turner WM, et al. Irradiation in the local control of malignant lymphoreticular tumours. Radiology 1974;112:179–85.
[16] Lamb DS, Hudson GV, Easterling MJ, et al. Localised grade 2 non-Hodgkin's lymphoma: results of treatment with radiotherapy (BNLI report No. 24). Clin Radiol 1984;35:253–60.
[17] Mosser EC, Noordijk EM, van Leeuwen FE, et al. Long-term risk of cardiovascular disease after treatment for aggressive non-Hodgkin lymphoma. Blood 2006;107:2912–9.
[18] van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiation dose, chemotherapy, and hormonal factors in breast cancer following Hodgkin's disease. J Natl Cancer Inst 2003;95:971–80.
[19] Travis LB, Hill DA, Dores GM, et al. Breast cancer following radiotherapy and chemotherapy among young women with Hodgkin disease. JAMA 2003;290:465–75.
[20] Sklar C, Whitton J, Mertens A, et al. Abnormalities of the thyroid in survivors of Hodgkin's disease: data from the Childhood Cancer Survivor Study. J Clin Endo Metab 2000;85:3227–32.
[21] Williams MV, Summers ET, Drinkwater K, et al. Radiotherapy Dose Fractionation, Access and Waiting Times in the Countries of the UK in 2005. Clin Oncol 2007;19:273–86.
[22] Ionising Radiation (Medical Exposure) Regulations 2000. <http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4007957> [accessed 20 Aug 2008].
[23] Bennett MH, Farrer-Brown G, Henry K, et al. Classification of non-Hodgkin's lymphomas. Lancet 1974;304:405–8.
[24] Swerdlow SH, Campo E, Harris NL, et al. (eds): WHO Classification of Tumours of Haematopoietic and Lymphoid Tissue, 4th edition. World Health organisation, 2008.
[25] Girinsky T, van der Maazen R, Specht L, Aleman B, Poortmans P, Lievens Y, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 2006 Jun;79:270–7.
[26] Ganem G, Cartron G, Girinsky T, Haas RL, Cosset JM, Solal-Celigny P, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: concepts and guidelines. Radiother Oncol 2006 Jun;79:270–7.