

## Original Article

# Changing practice in the radiation treatment of non-Hodgkin's lymphoma

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## Abstract

**Background:** Radiotherapy is well established in the treatment of non-Hodgkin's lymphoma (NHL) but there is considerable variation in the radiotherapy regimens prescribed, even within one cancer centre. This paper compares the varying radiation schedules prescribed in the Beatson Oncology Centre, Glasgow, in a sample of patients treated in 1996 with a second sample treated in 1999 following the creation of a lymphoma team with defined treatment protocols.

**Method:** In 1997 a retrospective study within the Beatson Oncology Centre recorded the treatment details of 35 patients treated with radiotherapy for NHL in 1996. The various radiotherapy dose and fractionation regimens prescribed were analysed to identify the rationale behind the variations by correlating them to the grade of disease, the age of the patient, the prescribing consultant and use of cytotoxic chemotherapy. A further audit of 36 patients treated over a three-month period in 1999 re-examined the radiotherapy prescribed and was able to include intent of treatment and stage of disease in the analysis.

**Results:** The demographics of the 1996 and 1999 patients were similar. In the latter group all patients had grade of disease recorded and 83% had stage recorded compared to 91% had grade and only 31% had stage recorded in 1996. The range of doses prescribed was 20–45 Gy (Gray) (median 36) for LGNHL (low grade non-Hodgkin's lymphoma) in 1996 with a range of 5–50 Gy (median 30) for HGNHL (high grade NHL). In 1999 the LGNHL range was 20–45 Gy (median 30) with HGNHL 20–50 (median 40). The 1999 audit showed better recording of data and this allowed further analysis of radiotherapy regimens. The patients could be grouped into three categories of treatment intent: primary radical treatment with radiotherapy alone (36%), consolidation following chemotherapy (25%) and palliation (39%). The radical and consolidation groups received similarly high doses (median 40 Gy) which were significantly greater than the palliation group (median 20 Gy).

**Conclusions:** The creation of a lymphoma team has improved the recording of treatment data and reduced the variations in clinical practice. We would advocate that patients with NHL should be irradiated according to evidence based protocols and suitable patients should be considered for the current BNLI trial of radiation dose in NHL.

## Keywords

non-Hodgkin's lymphoma, radiotherapy, evidence-based protocols

## INTRODUCTION

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphomas with various options for treatment. The aim is to achieve cure with minimum toxicity.

There are two major prognostic groups documented within the Revised European-American Lymphoma (REAL) classification: indolent and aggressive.<sup>1</sup> This is the current pathological classification used in diagnosis of lymphoma and was introduced in the mid 1990's, prior to this the Working Formulation was used.<sup>2</sup> Ann Arbor Staging is used to separate patients into prognostic and treatment groups.

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Radiotherapy alone has been reported to be effective in long-term survival for stage I indolent NHL in up to 60% of patients.<sup>3-5</sup> In addition it has been found to be effective in treating early stage High Grade NHL, including elderly patients.<sup>5-8</sup> High Grade NHL is treated more effectively with combination chemotherapy and radiotherapy.<sup>9-11</sup>

Radiation dose is an important consideration in the treatment of NHL. Retrospective series have shown that the dose can range from 30–45 Gy (Gray) although further studies have shown that at least 40 Gy of radiation over 4 weeks is required for adequate control.<sup>5,8,9,12</sup> The dose of radiation depends on many factors, which include histological type, patient's stage, performance status, the goal of treatment (palliative or curative), the proximity of sensitive organs and whether in combination with chemotherapy.

An audit was carried out in the Beatson Oncology Centre, Glasgow, in 1996 to review the radiotherapy practice in non-Hodgkin's lymphoma.<sup>13</sup> A range of radiotherapy dose and fractionation schedules was being used and an analysis was performed to find out the rationale for the differences. Thereafter a site specialist team was created and a repeat audit was performed in the department in 1999 to determine the changes in radiation practice. We describe the results of the latter audit and compare the changes in practice.

## METHODS

In 1997 the details of all non-Hodgkin's lymphoma (NHL) patients treated with radiotherapy at the Beatson Oncology Centre, Glasgow, over a 6-month period in 1996 were collated. One hundred and thirty patients were treated and a random sample of sixty patients was selected of which thirty-five case notes were found and analysed. An analysis was carried out to identify the rationale behind the variations of radiotherapy dose and fractionation, by correlating them to the grade of disease, age of the patient, prescribing consultant and whether chemotherapy was used as part of the regimen. The details of the report have already been published.<sup>13</sup>

In the audit of 1999, patients treated over a 3-month period were collected. A total of 52 NHL patients were treated. Thirty-six patient case

records were retrieved and retrospectively studied. Information was collected as before on patient age, gender, prescribing consultant, as well as staging details using the Ann Arbour classification and grade of tumour was documented using the Working Formulation and REAL Classification.<sup>1,2</sup> Further details of treatment were able to be collected because of an improvement in data recording: treatment intent as radical, palliative or consolidation, radiotherapy doses and number of fractions used.

## Statistical analysis

Statistical analysis included descriptive statistics. Continuous data are given as median and range. Categorical data are displayed as actual numbers and percentages. Spearman rank correlation was used to analyse the 1996 data.<sup>13</sup> The 1999 data was similarly analysed but additional analyses were possible with the 1999 data. The relationship between factors (radiation dose, chemotherapy prescribed, grade and treatment intent) was analysed using the Mann-Whitney U test. Statistical significance was achieved when the significance level was  $p < 0.05$ .

The data collected in 1999 were analysed using MINITAB software (release 12).

## RESULTS

The audit carried out in 1999 assessed 36 patients with NHL who were treated with radiotherapy over a 3-month period.

Twenty patients were female and 16 were male. The age ranged from 20–89 years old, the median was 64 years old. Therefore the group included many elderly patients.

Details of stage, grade, previous radiotherapy, previous chemotherapy and intent of treatment are tabulated (Table 1). The data reported in the 1996 audit is tabulated for comparison (Table 1). Thirty-six patients were analysed in the 1999 audit, which is similar to the number studied in 1996. The male to female ratio and age range was similar. The number of patients diagnosed with high grade and low grade NHL in 1999 was 47% and 53% respectively. This was again similar to the audit in 1996. The Working Formulation was the grading

Table 1. Patient Characteristics from the 1996 and 1999 audit

Characteristics	No. of Patients		No. of Patients	
	1999	(%)	1996	(%)
<b>Gender</b>				
Male	16	(44%)	14	(40%)
Female	20	(56%)	21	(60%)
<b>Age</b>				
Range (years)	20–89		28–92	
Median	66		65	
<b>Grade</b>				
Low	17	(47%)	17	(49%)
Intermediate			4	(11%)
High	19	(53%)	11	(31%)
N/A			3	(9%)
<b>Stage</b>				
1	16	(44%)		
2	7	(19%)		
3	3	(8%)		
4	10	(28%)		
N/a				
<b>Chemotherapy</b>				
Yes	22	(61%)	21	(60%)
No	14	(39%)	14	(40%)
<b>Prev radiotherapy</b>				
Yes	4	(11%)	7	(20%)
No	32	(89%)	29	(80%)
<b>Treatment intent</b>				
Radical	13	(36%)	N/a	
Consolidation	9	(25%)	N/a	
Palliative	14	(39%)	N/a	
<b>Radiation dose (median) (Gy)</b>				
High grade	40		30	
Low grade	30		36	

classification favoured at the time of the first audit, now the REAL Classification is used to classify Non-Hodgkin's Lymphoma.

In the 1999 audit 61 per cent of patients had previously been treated with cytotoxic chemotherapy and only 11% had had previous radiotherapy to a different site. Radiotherapy was prescribed in 1999 using a variety of dose and fractionation schedules. The range of radical and consolidation radiotherapy dose regimens used was 44 Gy/22 #, 40 Gy/20 #, 35 Gy/15 #, 50 Gy/20 #, 45 Gy/10 #, 34 Gy/17 #, 40 Gy/15 #, and 30 Gy/10 #. The 1999 audit revealed that 11 consultants prescribed the treatment and used 12 different regimens with one consultant treating 13 patients and the others treating 3 or less. In comparison the 1996 audit noted 13 different consultants using 19 different radiation schedules with one consultant treating 6 patients and the others treating 4 or less.

Further data obtained from the case records in the 1999 audit included stage of lymphoma and treatment intent. The Ann Arbor stage for each patient in 1999 is tabulated in Table 1. The majority of patients (63%) were of Stages 1 and 2. In the 1996 audit only 11/35 patients had tumour stage documented and details in staging were therefore not included in the analysis. Differing radiotherapy schedules would be used if the treatment intent were palliative, consolidation or primary radical treatment. This data is tabulated in Table 1 for the 1999 audit and in Table 2 a comparison is shown between treatment intent and grade of lymphoma. There is a higher proportion of high grade lymphoma patients treated with consolidation radiotherapy and a smaller proportion treated with radical radiotherapy reflecting the role of combination treatment in high grade lymphoma ( $P=0.026$ , chi-square test). The prescribed dose did vary with intent of treatment. This was found to a significant relationship when the radiation

Table 2. Percentage and number of patients of high and low grade NHL according to treatment intent in the 1999 audit.

	Grade			
	High grade		Low grade	
Intent	%	No. patients	%	No patients
consolidation	42.1%	8	5.9%	1
palliative	36.8%	7	41.2%	7
radical	21.1%	4	52.9%	9

dose for palliative treatment was compared with the group of radical and consolidation treatment dose ( $p < 0.001$  Mann-Whitney U test). The radical and consolidation patients received a similarly high dose (median 40 Gy in 20 fractions) and the palliative radiotherapy patients received a lower dose (median 20 Gy in 5 fractions). This can be seen in Figure 1.

When comparing the radiation dose prescribed with grade of lymphoma there was a trend towards a higher dose with high grade tumours, though

this was not statistically significant,  $P < 0.16$  (Mann-Whitney U test). This can be seen on Figure 2. In contrast the 1996 audit revealed the trend to be higher for low grade: the range of doses prescribed was 20–45 Gy (median 36) for low grade and 5–50 Gy (median 30) for high grade, not statistically significant.<sup>13</sup>

### DISCUSSION

We have reviewed the radiotherapy regimens prescribed for NHL patients at the Beatson

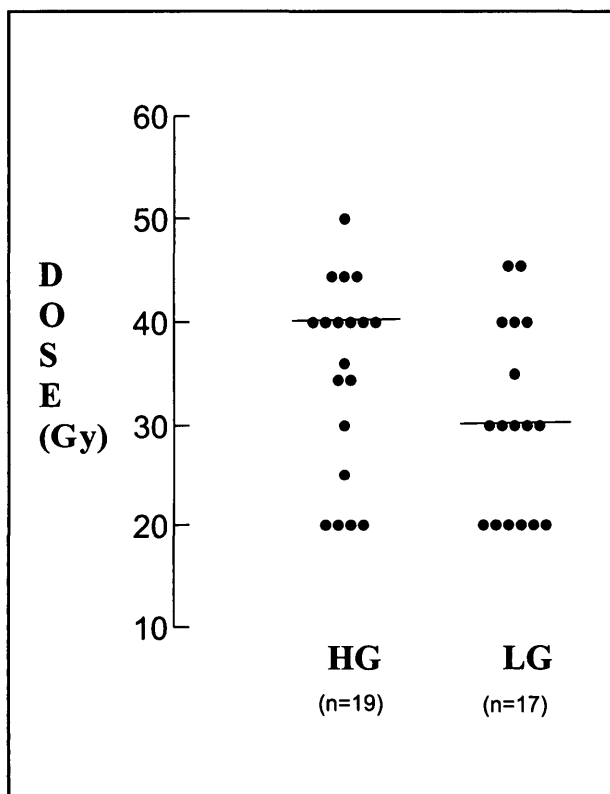


Figure 1. Radiation dose according to treatment intent. A dot plot depicting the radiation dose according to treatment intent. Each dot represents the dose of an individual patient. The line represents the median dose for each group. (1999 Audit)

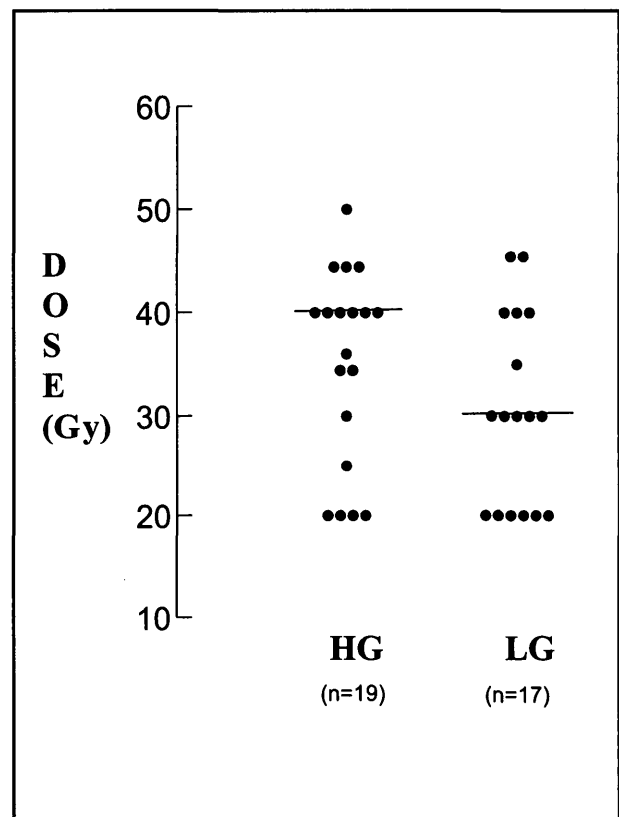


Figure 2. Radiation dose according to grade of NHL. A dot plot of radiation dose according to grade of NHL. Each dot is an individual patient and the line is the median dose. (1999 Audit)

Oncology Centre during a three month period in 1999, and in a previous audit in 1996.<sup>13</sup> The aim of the audit was to determine the changes in radiation practice. After the 1996 audit a site specialist Lymphoma team was formed whose aim was to develop the expertise in managing these patients and to concentrate on evidence based treatment. This team consists of a clinical oncologist, medical oncologist, and haematologist, as well as input from the referring haematologist. There are weekly clinical-pathological meetings whereby patients are presented and their management is discussed. In the audit of 1996 study there were a large number of consultants treating lymphoma patients, which reduced after the introduction of the lymphoma team. We can report that the number of radiation schedules reduced also. Data documentation improved after the first audit. Details of patient stage and treatment intent could now be extracted in the 1999 audit on all patients. Further analysis showed that radiation dose varied with treatment intent. Patients treated with palliative radiotherapy received a different radiation dose to those treated with radical and consolidation radiotherapy. Radiation dose was not shown to vary with chemotherapy treatment, age of patient or stage of NHL.

There is however still considerable variation in the range of radiation schedules that may reflect the lack of evidence for optimal radiation schedules in low-grade or high-grade NHL, or palliative, consolidation and radical treatments. Radiotherapy alone has been reported to be effective in the long-term survival in Stage 1 indolent NHL in up to 50% of patients.<sup>3-5</sup> Hudson et al., have reported a BNLI study of 451 patients who received radical radiotherapy as their definitive treatment. Their analysis revealed that disease free survival in low grade NHL was 47% and similar results have been reported in other studies.<sup>3-5,7,12</sup> The treatment of advanced indolent NHL is more varied because the likelihood of cure is less and the natural history tends to be prolonged. Symptomatic patients can be treated with local radiotherapy or chemotherapy.

No prospective trials have been reported to determine the optimal dose of radiotherapy. Most centres now use 35–40 Gy in 15–20 fractions based on the BNLI (British and National Lymphoma Investigation) NHL dose/fractionation study

which evolved from discussion with all radiotherapists in BNLI regarding commonly used regimes.<sup>17</sup> This BNLI study is recruiting patients to address the issue of optimal irradiation dose.<sup>17</sup> Patients are randomised to 2 different radiation schedules each, for low and high-grade lymphoma. This study will add to the previous evidence available for the radiation treatment of lymphoma patients.<sup>5,8,9,16</sup>

Aggressive NHL that is localised is optimally treated with combination chemotherapy and involved-field radiotherapy.<sup>10,11,14</sup> The irradiation dose has been shown to show a dose response and is recommended to be above 35 Gy.<sup>3,4,8</sup> Van der Maazen et al. reported a 3% infield recurrence rate when 40 Gy was prescribed.<sup>9</sup> However, the elderly patient and those unfit for chemotherapy are two groups of patients in whom it is desirable to use local radiotherapy as the only modality in high grade NHL. Wylie et al reported a retrospective audit of the patients treated in this way who obtained 5-year disease free survival in 31% of patients.<sup>6</sup> They reported that their most common radiotherapy schedule used was 25 Gy in 8 fractions. Radiotherapy has less of a role in the treatment of advanced aggressive NHL.<sup>15,16</sup>

There will continue to be some variation in radiation treatment due to the diverse range of NHL presentation and complications. Factors that need to be considered in the treatment of NHL include the stage of disease, the grade, performance-status of the patient, the intent of the treatment and the proximity of critical organs. Details of site of disease were not analysed in the 1996 audit and therefore this could not be compared with the 1999 audit. The site of disease tends to affect the overall treatment management.<sup>3,10,14,15</sup> In this study the radiation dose was affected by treatment intent. And analysis showed a trend towards the use of a higher dose of radiation in high-grade lymphoma rather than the reverse that was found in the 1996 audit (median dose 30 Gy and 40 Gy for low grade and high grade respectively).

## CONCLUSION

In conclusion from this study we have shown the improvement in data collection in the 1999 audit for lymphoma patients treated with radiotherapy. This will improve patient management and allow

outcome analysis whereas previously this was not possible. The introduction of a lymphoma team will ensure the patients are managed according to evidence based treatment protocols. It will also ensure patients are considered for current lymphoma studies, which are aimed to improve the management of these patients.

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