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Original Article

Radiotherapy dose and fractionation regimens prescribed for Non-Hodgkin's Lymphoma (a local study)

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Abstract

Background: Non-Hodgkin's Lymphomas (NHL) are considered to be a highly radiosensitive group of diseases with radiotherapy playing a major role in their treatment. It is recognised that the different grades and stages of NHL require different treatment approaches with current recommendations including combined chemotherapy and radiotherapy, chemotherapy alone or radiotherapy alone. Despite these recommendations there still remains a variation in the radiotherapy dose and fractionation regimens prescribed for NHL and this could be attributed to a lack of written treatment protocols for these patients. This paper gives an overview of the literature and reports on a small local study.

Method: A retrospective study recorded the treatment details of 35 patients treated with radiotherapy for NHL between April and September 1996 in a major radiotherapy centre. An analysis of the various radiotherapy dose and fractionation regimens identified was carried out and an attempt to identify the rationale behind the variations was made by correlating them to the grade of disease, the age of the patients, the prescribing consultants and whether chemotherapy was part of the treatment regimen.

Results: Thirteen consultants were identified as prescribing treatment for NHL. Forty-nine percent of patients presented as low, 11% intermediate and 31% high grade NHL. Of the 60% of patients who underwent chemotherapy the majority (62%) were prescribed Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine) and Prednisolone (the CHOP regimen). Nineteen different radiotherapy dose and fractionation regimens were identified, 20 Gy in 5 fractions being the most common. No correlation was found between the age of the patients and the radiotherapy dose delivered. A strong positive relationship ($r = 0.95$) was identified between the radiotherapy dose and the number of fractions. There was no effect on the radiotherapy dose delivered between the different grades of disease or whether chemotherapy was administered .

Conclusions: It is considered that the implementation of a NHL treatment protocol is important and in an attempt to initiate this, specific NHL teams should be formed.

Keywords:

Non-Hodgkin's Lymphomas; treatment; radiotherapy dose

INTRODUCTION

Non-Hodgkin's Lymphomas (NHL) comprise a heterogeneous group of malignancies that can range from being virtually benign to highly aggressive in nature.[1–4] Due to this diversity in natural history there occurs a variation in sensitivity to currently available treatments such as chemotherapy and radiotherapy[1] and this leads to controversy over what is the optimal treatment technique.[5,6]

Whilst the aetiology of NHL is unknown a number of factors have been found to increase the risk of NHL,[7,8] including infective agents such as

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Epstein Barr Virus, immunodeficiency disorders such as ataxia telangiectasia and irradiation. A number of classification systems are in use worldwide which has led to some confusion and difficulty when data comparisons are carried out from different centres.[9] The Working Formulation is one of the most widely used classification systems and classifies NHL as low-, intermediate-, and high-grade based on the natural course of the disease and known responsiveness to treatments.[10,11] For staging purposes, the Ann Arbor staging system used for Hodgkin's Disease has been adopted with the addition of a suffix 'E' where the lymphoma is detected in an extranodal site.[8] However, following the recommendation by the Cotswold Conference the Anne Arbour staging classification can be applicable only for nodal lymphoma.[12]

It is widely accepted that there are a number of prognostic factors which are identified as affecting the choice of treatment and eventual clinical outcome, these include age, stage of disease, serum lactate dehydrogenase level, performance status and extent of tumour burden.[1–3]

It is well established that NHL is a generally radiosensitive disease and radiotherapy has traditionally made an important contribution to its treatment, indeed until approximately 15 years ago radiotherapy alone was the treatment of choice for localised NHL.[13] The advent of successful chemotherapy regimens altered the pattern of treatment and now a multidisciplinary approach is taken in the treatment of NHL.

TREATMENT

Low Grade NHL

Low grade lymphomas are not considered to be curative mainly due to the majority of patients presenting with advanced disease and only a small proportion of patients (15–20%) present with localised disease. In a review of NHL literature, Gustafsson[1] suggests that involved field radiotherapy should be the treatment of choice for Stage I low grade NHL. This is shown to result in long term survival in approximately 50% of cases with relapse free survival being reported in 47–80% of patients. It has been found that the survival curves for this relatively small proportion of patients plateau after 5–7 years indicating a potential cure.[1,14,15] Relapse has however been reported to occur after 15 years[11] and local recurrence rates after radiotherapy have been reported to range from 2–5%.[1] Historically, radiotherapy was the treatment of choice for Stage II low grade NHL,[13,14] however it was reported that the "cure" rates varied between 25–75% with a mean of less than 50%[9] and due to this high risk of relapse, radiotherapy alone is not recommended.[1]

The advent of combination chemotherapy has enabled an increase in the progression free survival rates of these patients and the current treatment recommendations are combination chemotherapy with or without involved field radiotherapy.[9] However, the actual role of the radiotherapy is uncertain. Villikka[16] reported that if radiotherapy is given then the number of chemotherapy cycles can be reduced from 6–8 to 3 or 4. This can then help reduce the side effects and minimise the disruption of the patient's life.

Low grade NHL generally present as disseminated Stage III and IV disease.[13] There have been numerous attempts to achieve an optimal treatment plan for these patients however there still remains some controversy.[17,18] This may be due to the natural history of this advanced disease varying from being very aggressive to very indolent.[5] The two most common treatment approaches include:

1. No initial treatment until symptoms require palliative single drug chemotherapy or involved field radiotherapy.
2. Second line treatment including extensive radiotherapy, aggressive chemotherapy or a combination of both.[17]

In the absence of a curative chemotherapy regimen, complicated extensive radiotherapy techniques have been attempted with two studies reporting greatly prolonged remission.[19,20] Unfortunately, only a small proportion of patients are able to undergo such extensive treatment due to older age and general health.[1]

Another attractive form of treatment for Stage III and IV NHL patients has been low dose Total Body Irradiation (TBI), however despite the theory and excellent survival rates that have been observed, there still lacks evidence of cure.[21] Due to a curative treatment for these patients being unavailable at present, it is considered to be appropriate in some instances to adopt a watch and wait policy.[3] This involves observing patients until B symptoms, haematopoietic impairment, bulky disease or progression occurs, indicating the requirement of treatment. This strategy is supported by the observation that in asympto-

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matic patients there is no disadvantage in survival when treatment is deferred and this is particularly important for elderly and other selected patients.[11]

High Grade NHL

High grade NHL accounts for approximately 40% of all NHL[9] and are generally treated with curative intent.[3] As with low grade NHL, Stage I and II disease is reported to obtain a better prognosis than Stage III and IV.[1,2] The clinical course of high grade NHL is much more rapid than that of low grade and has a median survival of approximately one year. Overall survival depends on the initial response to initial treatment in high grade NHL patients and for those who do not have a remission, or relapse after complete response, prognosis is poor regardless of any further treatment.[10]

Until the advent of chemotherapy, radiotherapy was the treatment of choice, especially for localised Stage I disease and this was reported to obtain complete response in 60–70% of patients gaining long term survival.[2] The use of chemotherapy became more widespread and long term survival of these patients was increased to over 80% with or without adjuvant radiotherapy. As with low grade lymphomas a variety of treatment options are observed for high grade NHL with the commonest approaches being combined chemotherapy and radiotherapy, chemotherapy alone or radiotherapy alone, each appearing to obtain similar rates of long term survival.[22]

Lee and Levitt,[23] recommend for Stage I disease, combination chemotherapy followed by radiotherapy to obtain a complete response of 96–100%. For Stage II disease they observed a 50–90% complete response with chemotherapy alone and a 95–97% complete response following Cyclophosphamide, Hydroxydaunorubicin, Oncovin (Vincristine) and Prednisolone (CHOP) and radiotherapy.

Since the frequency of relapse in Stage II disease is much higher, chemotherapy is unanimously recommended. However, the value of adjuvant radiotherapy is yet to be proven in randomised clinical trials with the results from retrospective comparisons showing no difference in response rates between combined chemotherapy and radiotherapy and chemotherapy alone.[1] Rosenberg[6] stated that the risk of relapse after 10 years is low therefore in the long term patients are cured with the initial treatment and survive longer.

Gustafsson[1] recommends that Stage III and IV disease be treated with chemotherapy alone as adjuvant radiotherapy has been shown to be of no value although consolidation radiotherapy may increase the number of complete responses. Neal and Hoskin[8] reported on the aggressive, often rapidly fatal nature of high grade immunoblastic and lymphoblastic lymphomas and although they observed a 70–80% complete response to chemotherapy the long term survival at 5 years was shown to be below 50%. All patients with bone marrow involvement, disease in the testes, facial sinuses or lymphoblastic lymphoma are at risk of Central Nervous System (CNS) involvement. Prophylactic methotrexate and/or CNS radiotherapy, usually 24 Gy, is recommended in these situations.

In a number of cases, treatment of NHL may be directed towards palliation.[3] Radiotherapy is considered to be a valuable option for relapsed or incurable disease such as symptomatic lymph node masses or extra nodal disease[24] and also where chemoresistance occurs.[13] Sutcliffe[25] recommends that a radiotherapy dose of 20 Gy is sufficient for low grade NHL and 30–35 Gy is required to obtain optimal control of relapsed high grade disease, while other studies suggest doses over 40 Gy are necessary especially for sites of bulky disease[1] with a dose response relationship of 100% local control being observed by Lamb[26] after 45 Gy or more for high grade NHL.

Sawyer and Timothy[13] reported that 'radical doses' are not required for TBI, with 4 Gy over two fractions being sufficient to achieve an 89% response rate, 37% complete response and 52% partial response while noting that this low dose radiotherapy also helps avoid toxicity, is well tolerated and is convenient for the patient.

AIM

Despite the recognition of the role of radiotherapy in the treatment of NHL there is a remaining disagreement as to the optimal dose of radiation required to control the disease.

The British National Lymphoma Investigation (BNLI) group proposed a randomised trial of radiation dose in NHL designed to determine the optimal treatment regimen because of the recognised disparity in practice.[24] It will be a number of years before the preliminary and long term results

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of this trial are available so with respect to this an individual, one centre investigation was proposed to obtain an indication of the situation at a local level.

The purpose of this small local study is to identify the variations in radiotherapy dose and fractionation regimens prescribed for NHL in a major radiotherapy centre treating in excess of 6000 new cancer patients per year. Once a variation is identified it is proposed to identify its rationale by correlating it with the grade and stage of disease, the age of the patient and whether chemotherapy was part of the treatment regimen.

METHOD

A total of 130 patients were treated with radiotherapy for NHL in the centre during 1996 from which a sample of 60 patient casenotes were identified at random to collect information. Twenty five of these casenotes were unobtainable leaving a total of 35 patients, the details of which are shown in Table 1.

A list of patients treated with radiotherapy between April and September 1996 was accessed from the database and this enabled a study to be carried out retrospectively. Since all patients had completed treatment in 1996 it also enabled the current status of the patients to be recorded.

The following clinical information for each patient was abstracted from the casenotes and recorded on a standardised data collection form:

- Patient ID number
- Consultant
- Gender
- Age
- Grade of NHL
- Stage of disease
- Chemotherapy regimen (if applicable).

Radiotherapy details including:

- Dose (Gy)
- Number of fractions
- Dates of treatment
- Area treated
- Any additional comments including the current status of the patient.

If previous radiotherapy had been administered this was recorded along with the patient status following the treatment.

Hospital approval was requested and granted before data collection commenced.

Table 1. Profile of patients

		n	%
Sex	Male	14	40
	Female	21	60
Age	Median	65	
	Range	28–92	
	<40	3	8
	40–59	10	29
	>60	22	63
Grade	Low	17	49
	Intermediate	4	11
	High	11	31
	N.A.	3	9
Chemotherapy	Yes	21	60
	No	14	40
Regimen	CHOP	13	62
	VAPEC-B	5	24
	Other	3	14

ANALYSIS

Descriptive statistics were carried out on all data. Spearman rank correlation was applied to establish the existance of the relationship between the radiotherapy dose (Gy) and the age of the patient, the number of fractions and the number of chemotherapy doses. The effect of the grade of NHL, whether chemotherapy was administered and the particular chemotherapy regimens on the radiotherapy dose (Gy) was determined using the Mann-Whitney U Test.

Statistical significance was adjudged to have been achieved when the significance level was $p < 0.05$.

RESULTS

The details of the patients included in this study is shown in Table 1. Twenty one patients were female (60%) and 14 were male (40%). The median age was 65 years (range 28–92), with only 8% of patients below 40 years of age and the majority (63%) were 60 years or over. In total, 13 consultants were identified as prescribing radiotherapy for NHL patients. The number of patients per consultant ranged from 1 to 6 (Fig. 1). Out of the 35 patients only 11 had the stage of disease recorded in the casenotes. This figure increases to 25 patients when the grades of NHL recorded is

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examined with 49% presenting as low-, 11% as intermediate-, and 31% as high-grade NHL.

Of the 21 patients who received chemotherapy the majority (62%) underwent CHOP, usually consisting of 6 doses. All patients received radiotherapy, the majority of which (80%) was for the first time in 1996. The radiotherapy dose ranged from 5 Gy to 50 Gy with a median of 35 Gy and the most common dose delivered being 20 Gy. Figure 2 shows that of the 35 patients studied, 19 different radiotherapy dose and fractionation regimens were identified. The number of fractions ranged from 1 to 23 with 5 fractions being the most common. All patients were treated for localised disease with the majority being treated with a single field.

The median dose prescribed for low grade NHL was 36 Gy with a range of 20–45 Gy (Fig. 3a) whilst the median dose prescribed for high grade NHL was 30 Gy with a range of 5 Gy-50 Gy (Fig. 3b)

Forty percent of patients had died following the radiotherapy treatment with 30% undergoing remission and 7 patients experiencing recurrence of their disease. Six of these patients had been treated previously and were undergoing further radiotherapy in 1996.

There was no statistically significant correlation between the age of the patient and the radiotherapy dose delivered with the coefficient of determination indicating that only 20% of variation in the radiotherapy dose delivered was due to a variation in age of the patients. Again there was no relationship detected between the radiotherapy dose and the number of chemotherapy doses administered with the coefficient of determination indicating only 4% of variation in radiotherapy dose was due to that in the number of chemotherapy doses.

The correlation coefficient between the radiotherapy dose and the number of fractions was high ($r = 0.95$) and indicates that there is a strong positive relationship between the two. The coefficient of determination indicates that the majority of variation (87%) in the radiotherapy dose delivered is due to the variation in the number of fractions.

Finally, it was determined that no statistically significant effect was detected on the radiotherapy dose delivered between different grades of disease, whether chemotherapy was administered and between the different chemotherapy regimens delivered.

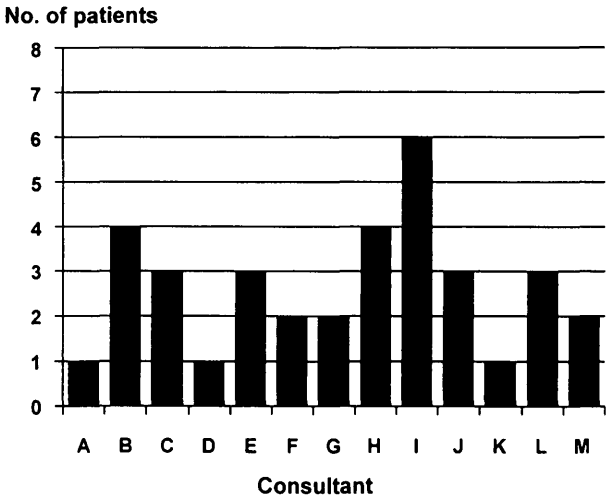

Figure 1. Number of patients treated per consultant

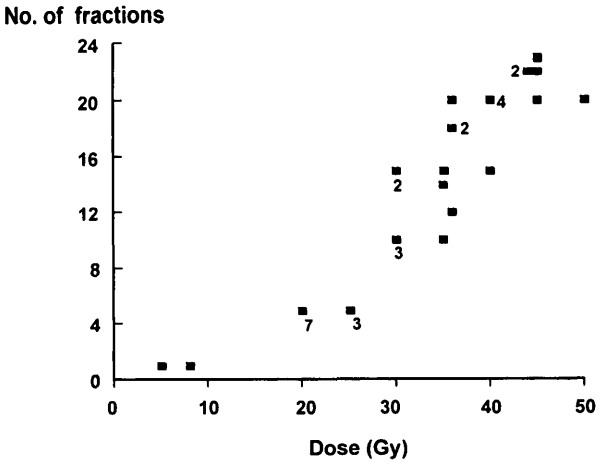

Figure 2. Distribution of radiotherapy dose and fractionation regimens

DISCUSSION

The importance of the identification of lymphomas, especially low grade, when they are still localised is one of the major challenges in the management of the disease and clarifies the need for standardised, accurate classification and staging systems.[9,21] Therefore, the lack of recording of the stage of disease and in 26% of cases the grade of NHL in casenotes is an important issue and because of the insufficient recording it is unfortunate that the stage of disease could not be included in the data analysis. There are a number of reports[3,10,11,27,28] which indicate that the stage of disease is one of the major determining factors of

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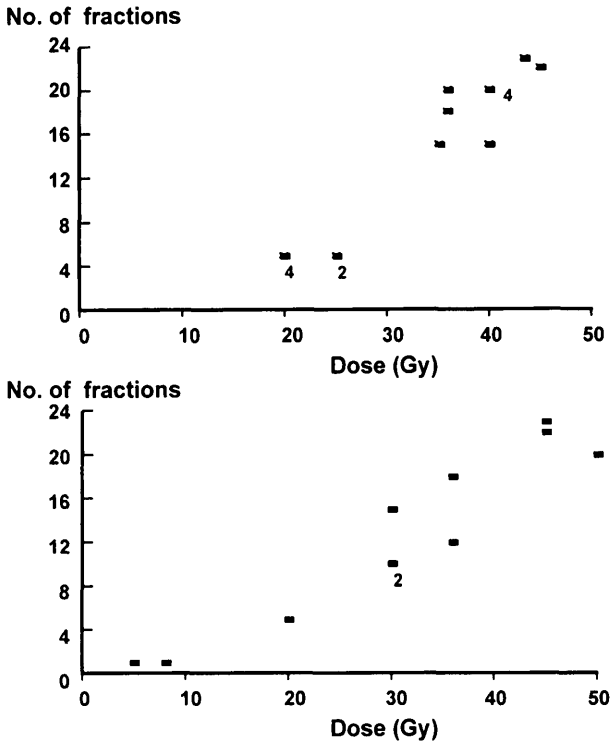

Figure 3. (a) (upper panel) Distribution of radiotherapy dose and fractionation regimens for low grade NHL; (b) (lower panel) Distribution of radiotherapy dose and fractionation regimens for high grade NHL

treatment choice and patient outcome so it should be thoroughly determined and recorded.

There does not appear to be any evidence of a relationship between the radiotherapy dose delivered and whether chemotherapy was part of the treatment regimen. This indicates that in a number of cases radiotherapy was delivered as an adjuvant therapy, the value of which is yet to be proven as a means of local control to prevent recurrence of disease. It was observed that CHOP was the most commonly administered chemotherapy regimen, adopting recommendations from a number of sources.[17,22,23,29]

The strong correlation between the radiotherapy dose delivered and the number of fractions was encouraging and confirmed the awareness and application of the biological effects and principles of radiotherapy. However the number of consultants involved indicated that the treatment of NHL was seen as something that most could be involved in rather than the domain of a specialised team.

The median dose for low grade NHL observed was 36 Gy (range 20–45 Gy) (Fig. 3a), which accords with Vaughan Hudson[30] who recommends 35 Gy to obtain local control of low grade NHL. A minimum of 40 Gy for local control of high grade disease is further advised by Hudson while Tubiana[28] reported a 30% incidence of local recurrence following doses < 45 Gy and only 13% incidence following doses > 45 Gy. In the local study being reported the median dose for high grade disease was 30 Gy with a range of 5 Gy to 50 Gy (Fig. 3b), although 50% of those were between 30 Gy and 40 Gy. In respect of this type of current practice the BNLI are randomising four different dose and fractionation regimens in the proposed trial to determine the optimal radiotherapy dose for NHL. These regimens include 24 Gy in 12 fractions or 40 Gy in 20 fractions for low grade NHL and 30 Gy in 15 fractions or 40 Gy in 20 fractions for intermediate and high grade NHL.

The most common dose, fractionation regimen of 20 Gy over 5 fractions, indicates the palliative intention of the treatment and suggests that control of recurrence sites as they occur is common practice. This relates to the usually advanced presenting stages of the disease and suggests that a watch and wait policy may be in place for a number of cases. Armitage[10] reports of a substantial number of untreated low grade NHL patients who undergo spontaneous remission. However, Horning[11] suggests that if an improvement in the understanding and management of low grade NHL is to be achieved then patients should be encouraged to participate in clinical investigations.

The NHL Classification Project[22] observed that although elderly patients were considered to have a poorer outcome compared to that of younger patients, age alone could not be a determining factor of poor outcome. This therefore suggests that in the majority of cases, age alone will not affect the treatment choice unless high dose chemotherapy or extensive radiotherapy techniques are being considered. This study also found that the percentage of patients treated with CHOP or other high dose chemotherapy regimens decreased with age. It is considered that this is predominantly due to the natural tendency of physicians to decrease the intensity of treatment for older patients due to poor performance status or associated disease. However, there appears to be no correlation between the radiotherapy dose delivered and the age of the patient.

An advantage of radiotherapy is that it is associated with relatively low toxicity rates.[14] Pendlebury

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et al[15] recommend 35 Gy in 20 fractions over 4 weeks for low grade lymphomas and comment on the lack of dose response data that is available over 30 Gy, suggesting that doses as high as 40 Gy may not be necessary. Similarly, Sawyer and Timothy[13] recommend 25–40 Gy in 1.8–2 Gy fractions for a radically intended treatment and the EORTC claim that 25–30 Gy is what is required to gain satisfactory local control.[28]

O'Reilly and Connors[9] conclude that until the controversy over the optimal treatment regimen is solved, consultants should select the approach with which they have the most confidence and use it in the maximally tolerated doses. It could be suggested that this is what is occurring in the study and although in this instance there appears to be no extreme doses being delivered there is a need for a NHL treatment protocol to be implemented. In an attempt to achieve this situation it may be necessary to form specific NHL teams which could ensure that patients are receiving the best available treatment regimens with the most recent treatment techniques and recommendations being applied where appropriate. This small local study provides a snapshot of current practice. Evidence upon which to base recommendations for best practice will become available when the BNLI study is reported.

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