

RESEARCH COMMUNICATION

Lymphoma Cases Referred to the Radiation Oncology Service of a Tertiary Referral University Hospital in Karachi, Pakistan: a Retrospective Study

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Abstract

Introduction: Radiation therapy is an important component of curative therapy for Lymphoma [Hodgkin's disease (HD) and non Hodgkin's Lymphoma (NHL)]. The current study was conducted to give us an overview of lymphoma patients presenting to a tertiary care hospital for complementary adjuvant RT. **Method:** Data of lymphoma patients who underwent radiotherapy during February 2006 till August 2009 at the department of radiation oncology, Aga Khan University, Hospital, Karachi was retrieved from the medical records and analyzed using SPSS (version 16.0). **Results:** A total of 1,678 cancer patients were registered, 75 (0.45%) were lymphoma patients (25.3% HD; 74.7% NHL). HD and NHL were both seen predominantly in males, with a male:female ratio of 2 and 3 respectively. Nodal HD comprised 94.7% and nodal NHL comprised 41.1%. Extranodal NHL (EN-NHL) comprised 53.6% whereas 5.4% cases had both nodal and EN-NHL; 6.7% of EN-NHL were primary CNS lymphomas. Stages of presentation for HD were IIA (52.6%), IA (21.1%), IIB (10.5%) and IB, IIIB and IVA collectively 15.9%. The ages of HD patients ranged from 11 to 54 years (median 23.5 years \pm 13.2 SD). Response to therapy for HD was 52.6% complete remission, 36.8% partial response, and 5.3% each with stable and progressive disease. Almost all patients (94.7%) received radical treatment with radiation doses (between 1950 cG to 5404 cGy) with a median of 40 Grays. Stages at presentation for NHL were II (23.2%), IV (21.4%) and IE (17.9%); I, IIE, and III were found to be 12.5%. NHL patients ranged from 15 to 88 years. It was more commonly observed amongst the elderly with 25% diagnosed in the fifth decade of life; 50% patients aged at or above 50 years, 41.1% belonged to the 25-49 years age group and 8.9% below 25 years of age. Majority of the cases were diffuse NHL (82.1%), follicular NHL (7.1%), 'Primary CNS unclassified type (8.9%), and unclassified other than CNS variety (1.8%). Response to chemotherapy for NHL was 51.8% complete remission, 25.9% progressive disease, 20.4% partial response. Forty (71.4%) with NHL received radical treatment with radiation doses between 2340 cG to 6600 cGy; 28.6% received palliative RT. **Conclusion:** Radiation therapy, though important for cure of lymphoma, is relatively underutilized in our population, despite encouraging outcomes.

Key Words: Lymphoma cases - Hodgkin's disease - non Hodgkin's lymphoma - stage - treatment

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Introduction

Lymphoma, the malignant transformation of normal lymphoid cells, is a wide spectrum of lymphoid tumors that range from indolent to the most malignant, with outcomes ranging from highly curable to incurable. Morphologically, lymphoma is divided into two major categories: Hodgkin's disease (HD) and non-Hodgkin's lymphoma (NHL).

The incidence of lymphoma varied from 2.8 per 100,000 between 2002-2006 in US for Hodgkin's Disease (HD) to 19.5 per 100,000 for non Hodgkin's Lymphoma (NHL) (Horner et al., 2008). Lymphoma is not uncommon in Karachi, our catchment population. The Karachi Cancer Registry (KCR) has reported NHL as the sixth most

common malignancy in both genders with an incidence of 9.6 per 100,000 in males and 7.2 per 100,000 in females (Bhurgri et al., 2006).

Currently the role of complimentary radiotherapy (RT) in the treatment of lymphoma is highly recommended. Historically the basic principles of modern radiotherapy for HD were developed by Henry Kaplan at Stanford University in the early 1960s (Kaplan, 1962; 1973). His studies revealed that lymph nodes adjacent to clinically involved sites were at high risk for subsequent involvement if left untreated. These findings were used for a better definition of radiation fields and still represent the current standard in modern RT. Meanwhile the role of RT has changed during the past three decades, from an effective single modality to a complementary adjuvant.

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This current study was conducted to give us an overview of lymphoma patients presenting to a tertiary care hospital for complementary adjuvant RT.

Materials and Methods

This study was conducted at the Radiation Oncology Department of the Aga Khan University Hospital (AKUH), Karachi, Pakistan which is equipped with the Eclipse treatment planning system, and the Varian Acuity Simulator. Majority of the radiotherapy treatment (RT) is planned on a three dimensional conformal technique (3-D CRT), on the Varian Eclipse Planning System, however, the two dimensional technique (2-D) is also in use.

Lymphoma patients, after receiving systemic chemotherapy from the treating hematologist attend the Radiation Oncology clinic after a post-chemotherapy CT scan, instead of a PET scan, which is not yet available in the country. The hematologist being the primary clinician also keeps them on the follow up along with the Radiation Oncologist.

A pre-coded questionnaire was developed for this study which included the patient’s demographic information; stage and histologic type of lymphoma, history of chemotherapy, and type of RT. Lymphoma were categorized using the WHO classification of hematologic malignancies, 2008 revision. All 75 histologically proven HD and NHL cases, who had undergone RT in the Radiation Oncology Department (AKUH) from February ’06 (date of establishment of the department) to August ’09, were included in our study.

The patient’s data were retrieved through the AKUH registration system and analyzed using SPSS version 16.0. Frequencies and percentages were computed for categorical variables including gender, sites according to disease distribution, variants of disease, chemotherapy followed by response to treatment and the Mean Standard Deviation was computed for numerical variables including age, dose and duration of radiation therapy. t-Test, was applied to all the numerical data and level of significance was taken at $p < 0.05$.

Results

A total of 1,678 cancer patients were registered at the Radiation Oncology department (AKUH) in the study period, amongst whom there were 75 (0.45%) lymphoma patients. Out of these 75 patients, 25.3% (n=19) were suffering from HD and the remaining 74.7% (n=56) had NHL (Figure 1 and Table 1).

HD was seen predominantly in males 68.4% (n=13) with a male:female ratio of 2. It primarily involved the lymph nodes (94.7%; n=18), with 5.3% (n=1) cases being extra nodal. Nodal regions involved in HD were cervical and mediastinal simultaneously 31.6% (n=6), or specifically cervical 26.3% (n=5). Those presenting with Stage IIA disease equated to 52.6% (n=10) cases, followed by 21.1% (n=4) with stage IA disease, and 10.5% (n=2) with stage IIB disease. The proportion of patients categorized under stage IB, IIIB and IVA were 15.9% only.

The ages of HD patients ranged from 11 to 54 years;

median 23.5 years 13.223 SD. Ten (52.6%) patients belonged to the below 25 years age group followed by 36.8% (n=7) between 25 to 49 years, and 10.5% (n=2) 50 years and above. On the basis of histology, majority of the cases of HD were of nodular sclerosis 42.1% (n=8), followed by mixed cellularity 31.6% (n= 6), and lymphocyte predominant type 15.8% (n=3). One (5.3%) case each belonged to the “diffuse and unclassified – other than primary CNS” variant.

Reporting the response to chemotherapy for HD, 52.6% (n=10) had complete remission, followed by 36.8% (n=7) with partial response, and 5.3% (n=1) each with stable and progressive disease. Almost all the patients 94.7% (n=18) with HD received radical treatment with radiation doses (between 2340 cG to 5404 cGy) with a median of 40 Grays. Amongst a total of 75 cases, 2 patients with NHL did not get chemotherapy (1 denied treatment and the other was given RT prior to chemotherapy for cord compression). 1 patient with HD was planned for treatment, but left against medical advice (LAMA).

NHL was seen in a greater proportion amongst males, equating to 73.2% (n=41) with a male:female ratio of 3. Twenty three (41.1%) NHL solely involved the nodes; 53.6% (n=30) cases were extra nodal and 5.4% (n=3) cases had both nodal and extra nodal involvement. Nodal regions involved were 34.8% (n=8) in the neck, and 26.1% (n=6) in the para-aortic region. Elaborating on extra-nodal NHL 26.7% (n=8) were primary CNS lymphomas.

Those presenting with Stage II disease equated to 23.2% (n=13) cases, followed by 21.4% (n=12) with stage IV disease, and 17.9 % (n=10) with stage IE disease. The incidence of stage I, IIE, and III were found to be 12.5 % (n=7), 1.8 % (n=1) and 8.9 % (n=5) for each respective stage.

The ages of NHL patients ranged from 15 to 88 years. NHL was more commonly observed amongst the elderly with 25% (n=14) patients diagnosed in the fifth decade of life. Overall, 50% (n=28) patients were aged at or above 50 years, followed by 41.1% (n=23) belonging to the 25-49 years age group and 8.9% (n=5) below 25 years of age. On basis of histology, majority of the cases were diffuse NHL 82.1% (n=46), followed by 7.1% (n=4) cases of follicular NHL, and 8.9% (n=5) belonging to the ‘Primary CNS un-classified type’, and 1.8 % (n=1)

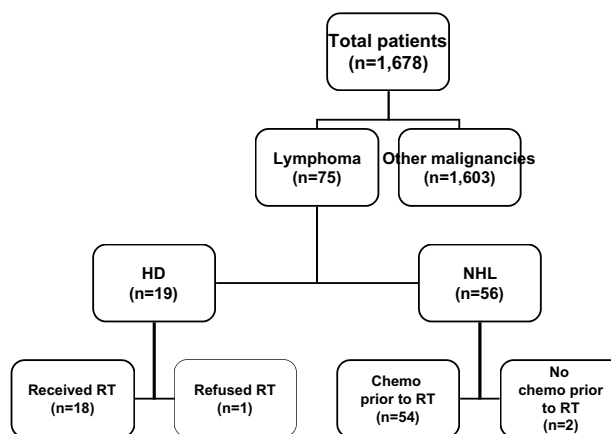


Figure 1. Patient Chart with Therapeutic Details for the Present Study of Lymphomas in Karachi, Pakistan

Table 1. Gender and Age-based Grouping of Lymphoma Patients

Sex		HD	NHL	Total
Male	<25 years	7	4	11
	25-49 years	5	17	22
	≥50 years	1	20	21
	Total	13	41	54
Female	<25 years	3	1	4
	25-49 years	2	6	8
	≥50 years	1	8	9
	Total	6	15	21

contributing to the “unclassified other than CNS variety”.

Reporting the response to chemotherapy for NHL, 51.8% (n=28) had a complete remission, followed by 25.9% (n=14) who exhibited a progressive disease, 20.4% (n=11) with partial response, and none (n=0) with stable disease. Forty (71.4%) patients with NHL received radical treatment with radiation doses between 2340 cG to 6600 cGy, whereas 28.6% (n=16) received palliative RT.

Discussion

Lymphoma is a common malignancy affecting all age groups. Considering the high curative response, its management requires attention by oncologists, public health planners and researchers, especially in the developing countries, where relevant literature is sparse, especially that related to RT aspect of management. Lymphoma comprises 7.0% and 3.5% of all malignancies in Karachi for males and females respectively (Bhurgri et al., 2005). Overall institutional data report a frequency of 6.1% for the city (Hanif et al., 2009), whereas a variation is apparently observed in the country, as lymphoma has been reported as the most common cancer in Northern Pakistani males probably a result of a combination of environmental, infectious and genetic factors (Ahmad et al., 1992; Aziz et al., 2004). In the present study the frequency of lymphoma was 0.45%, probably indicating under-usage of the RT facility for lymphoma management in comparison to other malignancies.

It is a global observation that the occurrence of NHL is higher amongst men than women (Muller et al 2005). This male predominance is more marked in the present data; the male, female ratio of 3 is higher than the KCR population-based reported ratio of 2 (Bhurgri et al, 2005).

On a population parameter, KCR reported in 2005 that a fourth of the NHL cases registered were extra-nodal, of which the largest group was of gastrointestinal origin (54.1% male, 38.5% female) and the gastric component was 21% in males and 25.6% in females. In the current data EN-NHL comprised approximately half (53.6%) the NHL cases reported, suggesting that RT was being utilized more for the management of EN-NHL as compared with the nodal. Moreover the most common EN-NHL site was the brain an unusual site on the population parameter. The histology however for the current data and the KCR data was identical. Both reported diffuse B cell NHL as the major morphological variant in more than 80% cases, indicating that histology was not one of the features or modalities on which the treatment protocols were based.

RT is an important component of curative therapy for HD and NHL (The NCCN, non-Hodgkin's lymphoma clinical practice guidelines, 2007), malignancies of hematopoietic origin being radiosensitive. Among normal tissues, one of the most radiosensitive is the bone marrow; tissues such as those in the liver, kidney, and lung are more radio-resistant (Gerald et al., 2008).

The results of the present data were comparable with international outcomes. The skill of the treating radiation oncologist is essential to the success of RT and the outcomes can depend on the experience and training of the entire Radiation Oncology team. Cure requires disease eradication, therefore achieving complete remission with the initial treatment plan is the key to success, and optimal systemic therapy is essential before embarking on to the option of RT. In patients who have recurrence of disease, no curative therapy is available. Palliative RT is an effective modality in providing symptomatic treatment for local control in certain cases. Due to the wide distribution of lymphoid tissues in the body, the RT planning for lymphomas are dependent on the location and extent of target volume. To ensure reproducibility, consistency and accuracy of RT delivery, quality assurance monitoring is done on a regular basis.

PET scanning is useful in assessing the completeness of response to the given treatment; however it cannot detect residual microscopic disease reliably. Presently, there is no evidence that in cases where standard therapy includes RT, a negative PET scan following chemotherapy implies that RT can be safely omitted. Studies are ongoing to evaluate the value of PET in patient selection for adjuvant RT (Gospodarowicz, 2008).

Randomized trials have continued to demonstrate that RT contributes to important endpoints, including overall survival and local disease control (Laskar et al., 2004 and Nachman et al., 2002). The technique of RT for HD and NHL has been amended accordingly, now supporting the use of involved-field radiation therapy (IFRT), rather than extended field radiation therapy (EFRT), thus reducing toxicity, and improving cure rates. The smallest volume commonly used is the involved-field (IF) volume in which all clinically involved lymph nodes of a given region are irradiated. The extended field (EF) includes the involved-field (IF) as well as all adjacent lymph node regions. When RT alone was given, a superior outcome was documented in prospectively randomized studies for those patients treated with the EF technique compared with the IF technique (Kaplan, 1973; Specht et al., 1998; Nachman et al., 2002; Laskar et al., 2004). Modern combination chemotherapy and RT have raised the long term survival of HD to more than 80% over the last decades (Eich et al., 2005). Most patients with localized NHL who receive RT are treated with the intent of achieving local control. Both RT and chemotherapy carry high risks of long-term adverse effects, including second malignancies and cardiopulmonary disease. The risk of adverse effects is related to the radiation dose and the size of irradiated volume; the goal is therefore to reduce doses and field sizes as much as possible, without reducing the chance of cure (Bolling et al., 2006; Dorr et al., 2006; and Trott et al., 2006).

In conclusion, radiation therapy though important for cure of lymphoma, is relatively underutilized in our population, despite encouraging outcomes.

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