Field and Nodal Irradiation in Early Stage Hodgkin's Lymphoma: A Single Institution Study

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Abstract:

Background: With the introduction of Hodgkin lymphoma patients receiving combined modality therapy, extended field radiation techniques were replaced by involved field radiotherapy (IFRT). Recent research has demonstrated the safety of further field site reductions. By using the idea of involved node radiotherapy (INRT), the risk of radiation-induced toxicity can be decreased without compromising the effectiveness of treatment. The foundation of INRT is treating only the lymph nodes that were initially involved and omitting any adjacent uninvolved nodal areas.

Patients and methods: 66 patients with early-stage Hodgkin's lymphoma were collected within the previous five years in SECI and were classified into two arms either IFRT or INRT after receiving chemotherapy according to disease stage. Out of those patients thirty eight received (IF) and twenty eight received (IN). Radiotherapy dose used for all patients was 20- 30 Gy. Patients were assessed for treatment toxicity and local recurrence.

Results: Median follow up time of all patients was about 40 months. It was found that involved INRT was not inferior to IFRT. No difference in efficacy between both arms and also with comparable toxicity. Both groups had comparable characteristics, laboratory data, and response to chemotherapy. Relapse occurred in four patients (10.5%) in IFRT group and two patients (7.1%) in INRT group. Also, both groups had insignificant difference as regard overall survival 56.78 ± 2.40 vs. 56.78 ± 2.19 (months), of (IF) and (IN) respectively with p- value of 0.30. Both groups had comparable early toxicity and its grades, response and late toxicity ($p > 0.05$). Late complications as hypothyroidism developed in three patients of IFRT group and two patients of INRT group. Pulmonary fibrosis developed only in four (10.5%) patients of IFRT group.

Conclusion: The main finding in this study is that (IN) is not inferior to (IF) as regards efficacy and at least same toxicity therefore (IN) radiotherapy can replace (IF).

Key words: Hodgkin's Lymphoma, Nodal Irradiation, Field irradiation.

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Introduction:

Hodgkin lymphoma (HL) is a rare B-cell-derived cancer. Most patients get diagnosed between the ages of 15 and 30, with another surge occurring in people over the age of 55. [1] Classic Hodgkin lymphoma (CHL) and nodular lymphocyte-predominant Hodgkin lymphoma (NLPHL) are the two main types of Hodgkin lymphoma (HL) according to the World Health Organization's (WHO) classification. Of all HL in Western countries, CHL accounts for 95% while NLPHL accounts for 5%. [2] In order to reach a final diagnosis, Reed-Sternberg cells in the biopsy samples need to be identified. Reactive lymphocytes, eosinophils, and histiocytes make up the rich cellular environment in which these cells are frequently observed. Hodgkin lymphoma has been classified into two separate disease entities: nodular lymphocyte-predominant Hodgkin lymphoma, which is uncommon,

and classical Hodgkin lymphoma, which is detected more frequently. [3] The Ann Arbor staging technique serves as the foundation for HL staging. Each stage is divided into subcategories A and B by the system; the latter is for the presence of B symptoms. "B" is given to patients who have unexplained fevers higher than 38°C, intense night sweats, or unexplained weight loss of more than 10% of their body weight within six months of diagnosis. "A" denotes the absence of systemic symptoms.[4,5] FDG-PET imaging, especially integrated FDG-PET and CT (FDGPET/CT), has proven as a crucial tool for initial staging and response evaluation at the end of treatment..[6,7] When used to stage and restage patients with lymphoma, FDG-PET scans shown good positivity and specificity in a meta-analysis..[8,9] Patients with both early-stage and advanced-stage disease have demonstrated to be significantly at risk for serious side effects when FDG-PET positive is present at the conclusion of treatment.[9-11] Chemotherapy or combination modality therapy (CMT; chemotherapy plus radiation therapy (RT) is the initial treatment for CHL. After chemotherapy is finished, patients are staged again to evaluate the effectiveness of the treatment. Evaluation of the first treatment's reaction is important since it determines if further treatment is required. [12] With accurate radiation delivery to the initially affected volume and minimal radiation dose to normal tissues, it is now feasible to modify radiotherapy for each patient. Extended field radiation techniques gave way to involved field radiotherapy (IFRT) with the introduction of combined modality treatment. [13, 14] Recent research has demonstrated the safety of further field site reductions. The concept of involved node radiotherapy (INRT) is to treat only the lymph nodes that were initially involved, leaving out any nearby uninvolved nodal areas, in an effort to lower the risk of radiotherapy-induced toxicity. [15,16] In this study we are going to compare retrospectively between radiation therapy, using involved field radiotherapy and involved node radiotherapy, and see the follow up of the patient to detect early and late toxicities and if there is any difference in using any of them in long term follow up.

Patients and Methods:

Patients:

66 patients retrospectively collected from SECI with clinically stage I–II supradiaphragmatic HL who were older than 18 and received either INRT or IFRT between 2018 and 2022. Women who were being pregnant or breastfeeding, as well as individuals with Nodular lymphocyte predominant Hodgkin lymphoma (NLPHL), patients who had previously had radiation therapy to the neck or thoracic region, were excluded.

Through national registries, we collected treatment data, follow-up information, and the current state of every patient (i.e., alive, dead, hospitalized). Utilizing The Radiation Therapy Oncology Group (RTOG) Terminology Criteria for Adverse Events, toxicity was evaluated retrospectively from patient charts.

Work up

The Ann Arbor staging classification was used to stage the patients. A physical examination, a medical history, and computed tomography (CT) scans of the pelvis, abdomen, and chest were all standard staging procedures. Serum chemistry, erythrocyte sedimentation rate (ESR), lactate dehydrogenase (LDH), complete blood counts (CBC), and bone marrow biopsy (for unfavorable conditions). Evaluation of the histopathology of the lymph nodes, echocardiography, Positron Emission Tomography (PET/CT) scan is performed before and after treatment for staging and follow-up, if feasible.

Treatment Protocol

Adriamycin, bleomycin, vinblastine, and dacarbazine (ABVD) chemotherapy was administered to the majority of patients; the number of cycles was determined by risk factors: Unfavorable: 4 cycles of ABVD; favorable 2 cycles of ABVD. Some patients in our PET protocol were assessed using FDG-PET/CT to enable therapy modification; in this case, patients received an additional 2 cycles of ABVD prior to RT in the event that they were not in either complete or partial remission. The remission status after chemotherapy had been determined for each initially involved lymph node exclusively using CT scans. Complete remission (CR) is defined as the complete disappearance of clinically and/or radiologically detectable disease. partial response (PR) is at least a 50% decrease in tumor size. Failure is less than a 50% decrease or any increase in tumor size.

Radiation Therapy:

After completing chemotherapy, patients were divided into two arms: either INRT, which is intended to treat the initial involved node only or IFRT, which covers the initially involved lymph node as well as contiguous nodal groups (involved nodal region) based on the location of the individual lymph node. Three to four weeks after the final cycle of chemotherapy ended, radiotherapy was started. CT scans were the only method used to verify whether each initially affected lymph node was in remission following chemotherapy.

Radiation dose and energy of the machine:

- Patients with favorable risk early stage disease who met the entry criteria for the German Hodgkin Study Group protocol received 20 Gy (2 Gy/fraction × 10 fractions).
- Patients who do not fulfill the criteria for the GHSG procedure (unfavourable) were given an additional boost of 10 GY with a total dose of 30GY (1.8–2 Gy/fraction), using the LINAC machine's 6MV photon energy.

Assessment of Response

Two months following Radiotherapy, patients received clinical and radiologic response evaluation using FDG-PET/CT scanning, if feasible. If PET-CT was not available, full body CT scanning was performed on the patients. Following that, patients were seen in the clinic every three months for the first year,

every six months for the second and third years, and then once a year for the fifth year. For the first two years, imaging with CT scanning or, if deemed required, FDG-PET/CT scanning was done as needed or once every twelve months. Freedom from treatment failure is defined as the time from the start of radiotherapy to the first of one of the following: Progressive disease (defined as appearance of new lesions or B symptoms, or an increase in any lesion of 25% in the largest diameter under treatment or within 3 months after the end of treatment). Relapsing disease (defined as appearance of new lesions or as reappearance of initial lesions or B symptoms after a period of at least 3 months of complete remission).

Overall survival is the time from starting treatment. While disease free survival is time after the treatment ended that the patient survived without any signs or symptoms of that cancer.

Toxicity:

The common toxicity criteria of the Radiation Therapy Oncology Group (RTOG) were used to evaluate the toxicity of the patients in both arms. Acute radiation toxicities are side effects that occurred on treatment or in the immediate post-treatment period. Onset may be 2–3 weeks after starting the radiation therapy as Skin changes, dysphagia, mucositis, laryngeal toxicity, and pulmonary symptoms suggestive of radiation pneumonitis were the most common toxicities. Late radiation toxicity is the toxicity that developed later than 90 days following completion of radiation therapy as hypothyroidism and pulmonary fibrosis.

Statistical Analysis:

IBM SPSS Statistics version 20 was used for the statistical analysis (SPSS Inc., Chicago, IL, USA). Frequencies and percentages were utilized to show categorical data, and the Chi-square test was employed to compare groups. The means ± standard deviations were employed to report continuous data, and the students' T-test was utilized to compare groups. The Kaplan-Mayar survival curve and log-rank test were used to compare progression-free survival. P-values less than 0.05 were deemed statistically significant in all statistical tests.

Results:

The current study had 66 patients in total—38 patients from the IFRT and 28 patients from the INRT.

Patients and tumor characteristics are shown in Table 1. Both groups had insignificant difference as regard mean age (35.05 ± 13.41 vs. 33.82 ± 11.93 (years); p= 0.70). Also, majority of both groups (57.9% of IFRT group and 64.3% of INRT group) were males with no significant difference (p= 0.39). B-symptoms were reported in thirteen (34.2%) and eleven (39.3%) patients of IFRT and INRT groups, respectively. In majority (81.6%) of IFRT and (85.7%) of INRT of both groups, patients underwent excisional biopsy. Sites of LNs were axillary, cervical and mediastinal LNs in four (10.5%), thirty-five (92.1%) and nine (23.7%) patients of IFRT group and were two (7.1%), twenty-seven (96.4%) and five (17.9%) patients of INRT group, respectively. Mixed cellularity was the most common histopathological subtype in both groups.

Table 2 shows radiotherapy (RTH) response and toxicity in the studied groups. Regarding radiotherapy; all patients started radiotherapy within 3-4 weeks following the end of chemotherapy cycles and after chemotherapy assessment. The majority of both groups received RTH in form of 2000 cGy, the unfavorable risk patients of both groups received 3000 cGy. Both groups had comparable early toxicity and its grades, response and late toxicity (p> 0.05). Majority of patients in both groups developed grade-I toxicity (55.2% of IFRT group and 64.3% of INRT group) and complete response (89.5% of IFRT group and 96.4% of INRT group). Skin change, dysphagia and pneumonitis occurred in nineteen (50%), fourteen (36.8%) and six (15.8%) patients of IFRT group, respectively and fifteen (53.6%), thirteen (46.4%) and one (3.6%) patient of INRT group, respectively. Majority of both groups developed no late toxicity. Late complications as hypothyroidism developed in three patients of IFRT group and two patients of INRT group. Pulmonary fibrosis developed in four (10.5%) patients of IFRT group. Table (3) shows that relapse occurred in (10.7%) patients in IFRT group and 2 (7.1%) patients in INRT group with mean disease-free survival (DFS) was (38.92 ± 2.44 vs. 41.57 ± 2.71 (months); p= 0.49). Also, both groups had insignificant difference as regard overall survival 56.78 ± 2.40 vs. 56.78 ± 2.19 (months), respectively with p=0.30. Table (4) demonstrates the difference in mean dosimetric parameters between the INRT and IFRT methods. The volume of included organs at risk decreases as a result of the PTV being reduced from IFRT to INRT.

Figure (1) show disease free survival among the studied groups with mean disease free survival (DFS) was (38.92 ± 2.44 vs. 41.57 ± 2.71 (months) in IFRT vs INRT respectively.

Figure (2) show overall survival among studied groups with 56.78 ± 2.40 vs. 56.78 ± 2.19 (months) in IFRT vs INRT respectively.

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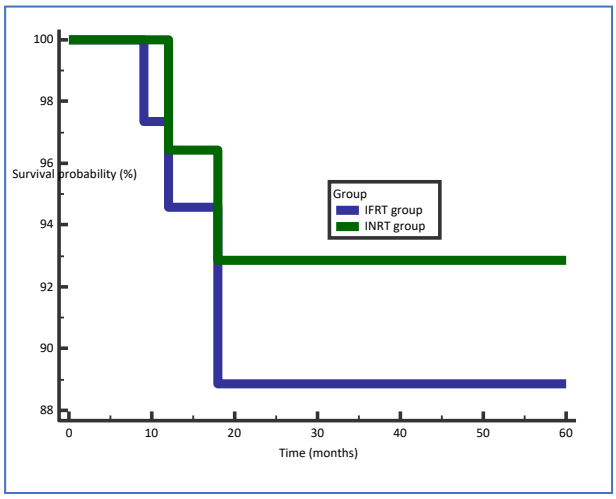

Fig. (1): Disease free survival among the studied groups. IFRT: involved field irradiation; INRT: involved nodal irradiation

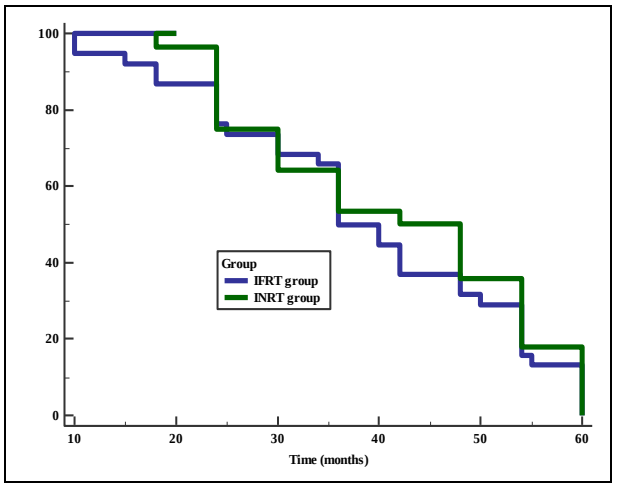

Fig. (2): Overall survival among the studied groups. IFRT: involved field irradiation; INRT: involved nodal irradiation

Table (1): Baseline data of the studied groups:

	IFRT group (n= 38)	INRT group (n= 28)	*P* value
Age (years)	35.05 ± 13.41	33.82 ± 11.93	0.70
Sex			
Male	22 (57.9%)	18 (64.3%)	0.39
Female	16 (42.1%)	10 (35.7%)	
Performance status			
PS-0	29 (76.3%)	24 (85.7%)	0.41
PS-1	7 (18.4%)	2 (7.1%)	
PS-2	2 (5.3%)	2 (7.1%)	
Family history of HL	3 (7.9%)	2 (7.1%)	0.64
B-symptoms	13 (34.2%)	11 (39.3%)	0.43
Size of LNs	3.82 ± 1.16	3.98 ± 1.47	0.62
Groups of LNs			
One	8 (21.1%)	8 (28.6%)	
Two	20 (52.6%)	14 (50%)	0.52
Three	10 (26.3%)	5 (17.9%)	
Four	0	1 (3.6%)	
Type of biopsy			
Core biopsy	7 (18.4%)	4 (14.3%)	0.46
Excisional biopsy	31 (81.6%)	24 (85.7%)	
Histopathology			
Mixed cellularity	22 (57.9%)	16 (57.1%)	0.57
Nodular sclerosis	16 (42.1%)	12 (42.9%)	
Sites of LNs			
Axillary LNs	4 (10.5%)	2 (7.1%)	0.49
Cervical LNs	35 (92.1%)	27 (96.4%)	0.43
Mediastinal LNs	9 (23.7%)	5 (17.9%)	0.39
Stage of disease			
Stage-I	10 (26.3%)	8 (28.6%)	0.52
Stage-II	28 (73.7%)	20 (71.4%)	
Favorable disease	22 (57.9%)	17 (60.7%)	0.51

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. IFRT: involved field irradiation; INRT: involved nodal irradiation; HLL Hodgkin lymphoma; PS: performance status

Table (2): Radiotherapy response and toxicity in the studied groups:

	IFRT group (n= 38)	INRT group (n= 28)	*P* value
RTH dose (cGy)			
2000	22 (57.9%)	17 (60.7%)	0.34
3000	16 (42.1%)	11 (39.3%)	
Response			
CR	34 (89.5%)	27 (96.4%)	0.27
PR	4 (10.5%)	1 (3.6%)	
Toxicity			
Skin change			
Grade-1	12 (31.6%)	11 (39.3%)	0.23
Grade-2	7 (18.4%)	4 (14.3%)	
Dysphagia			
Grade-1	7 (18.4%)	6 (21.4%)	0.50
Grade-2	7 (18.4%)	7 (25%)	
Pneumonitis			
Grade-1	2 (5.3%)	1 (3.6%)	0.42
Grade-2	4 (10.5%)	0	
Grade of toxicity			
Grade-I	21 (55.2%)	18 (64.3%)	0.28
Grade-II	18 (47.4%)	11 (39.3%)	
Late toxicity			
None	31 (81.6%)	26 (92.9%)	0.20
Hypothyroidism	3 (7.9%)	2 (7.1%)	
Pulmonary fibrosis	4 (10.5%)	0	

Data expressed as frequency (percentage), mean (SD). *P* value was significant if < 0.05. IFRT: involved field irradiation; INRT: involved nodal irradiation; CR: complete response; PR: partial response

Table (3): Disease Free Survival (DFS) and Overall Survival in the studied groups:

	IFRT group (n= 38)	INRT group (n= 28)	*P* value
Relapse	4 (10.5%)	2 (7.1%)	0.49
Disease free survival (m)	38.92 ± 2.44	41.57 ± 2.71	0.49
Overall survival (m)	56.78 ± 2.40	56.78 ± 2.19	0.30

Table (4): Comparing the various dosimetric parameters for each group:

	IFRT group (n= 38)	INRT group (n= 28)	*P* value
PTV mean (cm3)	1806±323	981±191	0.000
Lung			
-mean dose (GY)	10.45±5.19	7.41±4.30	0.309
-V5 (%)	49.92±16.86	29.00±14.66	0.050
-V20 (%)	28.57±5.82	17.16±11.51	0.046
Heart			
-mean dose (GY)	17.22±5.54	9.30±5.42	0.033
-V30 (%)	28.95±13.09	14.28±11.61	0.073
Breast mean dose (GY)			
-RT Breast	3.40±1.39	1.75±1.32	0.087
-LT Breast	3.25±1.55	1.90±1.27	0.174
Thyroid mean dose (GY)	16.47±7.66	7.14±5.67	0.001

Discussion:

When treating patients with early-stage classical Hodgkin lymphoma (ESHL), combined modality treatment (CMT) with short-term chemotherapy and radiation therapy (RT) ensures high cure rates and maintains local control. RT for ESHL has changed over time to lower the risk of severe treatment side effects. The use of highly conformal RT techniques and advanced imaging has made it possible to significantly minimize the irradiated tissue volume. [17, 18]. The current study evaluated the possibility of reducing the irradiation field by comparing INRT with IFRT. In our study, the results showed non inferiority for INRT technique in comparison with IFRT technique. No difference in efficacy was noted between both arms where relapse occurred in four (10.5%) patients in IFRT group and two (7.1%) patients in INRT group with insignificant difference P- value=0.3. In line with our study Nielsen et al. addressed the outcomes of a 10-year unselected cohort of ESHL patients treated with CMT, including INRT, in accordance with modern guidelines, with long-term monitoring and full outcome data. In their investigation, they discovered excellent and long-lasting disease control with a crude relapse rate of 6.6%. [19] Median disease-free survival (DFS) was (38.92 ± 2.44 vs. 41.57 ± 2.71 (months); in IFRT and INRT retrospectively with P- value = 0.49 In another trial enrolled a total of 325 patients with ESHL the three radiation therapy groups had the following case distributions: EFRT (39%), IFRT (30%), and INRT (31%). For those still alive, the median follow-up was 80 months. It took 37 months median time for a relapse. Twelve relapses occurred: four after extended filed RT (EFRT, 4%); five after IFRT (5%); and three after INRT (3%). Following INRT, there were no marginal recurrences. Progress-free survival (PFS) was 97% and overall survival (OS) was 95% at five years. [20]. As regarding safety and side effects of RT in the studied patients; skin change, dysphagia and pneumonitis occurred in 19 (50%), 14 (36.8%) and 6 (15.8%) patients of IFRT group, respectively and 15 (53%), 13 (46.4%) and 1 (3.6%) patient of INRT group, respectively. Majority of both groups developed no late toxicity. Late complications as hypothyroidism developed in three patients of IFRT group and two patients of INRT group. Pulmonary fibrosis developed in 4 (10.5%) patients of IFRT group. Similarly, a previous study by Zwam et al, was done there were sixteen patients in the INRT arm and nineteen in the IFRT arm. According to the authors, following four cycles of ABVD chemotherapy, reducing the volume size of radiotherapy from IFRT to INRT provides results that are similar to those of IFRT in terms of response and toxicity. [21] The latter study reported that both groups had comparable patients' characteristics and other data concerned with the disease. CR was achieved in 87.5% in INRT group and 78.9% in IFRT group. Skin changes, dysphagia, mucositis, laryngeal toxicity, and pulmonary symptoms suggestive of radiation pneumonitis were the most common toxicities, with no statistically significant difference seen. [21] The main conclusion of our study is that INRT in Hodgkin lymphoma patients in the early stages of the disease had excellent outcomes with an acceptable degree of toxicity. It had comparable outcome as IFRT as regard response, safety, disease free survival and overall survival. Yet, there are some limitations in our study as it included relatively small sample size and being conducted in single center.

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Conflicts of Interest of each author/ contributor: None

Availability of data and material: On reasonable request, the corresponding author will make the data used and/or analyzed during the current work available.

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