The impact of involved node radiotherapy on organs at risk on treatment of limited stage Hodgkin lymphoma

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Abstract

Background:

Radiotherapy is an important component of the combined modality treatment of limited stage Hodgkin lymphoma. Using such combination resulted in high cure rates exceeding 90%. Unfortunately, long-term survivors are at increased risk of critical long-term morbidities including second malignancy, lung, and cardiac toxicities. Radiation induced toxicity is related to dose and field size. The concept of involved node radiotherapy (INRT) is to minimize the irradiated volume to cover only the primarily involved nodes, while maintaining high local control rates.

Objectives: The aim of this study is to analyze to what extent reducing the target volume using INRT compared with involved field radiotherapy IFRT, can minimize doses to adjacent normal tissues.

Patients and methods: 20 patients diagnosed with limited stage HL who received 2-4 cycles of ABVD were planned to receive consolidation radiotherapy. For each patient, two plans were generated: IFRT and INRT. The radiotherapy dose used was 20-30 Gy. Organs at risk OARs including lungs, heart, breasts, and thyroid gland were delineated and different dosimetric parameters of both plans were compared.

Results: compared to IFRT, INRT showed significant reduction in mean doses and dose-volume metrics of contoured OARs. Mean dose to the heart (17.47/8.98 Gy), to lung (11.5/7.3 Gy), to breasts (left 3.1/1.8 Gy, and right 3.3/1.6 Gy) and to thyroid (17.5/7.1Gy).

Conclusion: reducing the treatment volume from IFRT to INRT is associated with decrease in radiation exposure of OARs with subsequent reduction in late complications.

Keywords: Hodgkin lymphoma, involved field, involved node.

Introduction:

Hodgkin lymphoma (HL) is a rare B-cell lymphoid malignancy that affects about 8480 new cases in the United States each year **(Siegel et al., 2020)**. It constitutes 0.6% of all the cancers diagnosed worldwide and 10% of all lymphomas **(Siegel et al., 2016).**

Its incidence has two peaks, the first is in young adults (15- 30 years), and the second is in patients aged 55 years and older. The exact etiology for developing HL stills unknown. HL is a complex of related conditions that are mediated by infectious diseases, immune deficiency, and genetic susceptibilities. There is little evidence to suggest any other environmental factors to be involved in the etiology. **(Cartwright RA et al.,2004).**

The recommended treatment guidelines for limited stage Hodgkin lymphoma (HL) patients are multi-agent combination chemotherapy followed by consolidative radiotherapy **(Herbst et al. 2010)**, achieving 10-years survival rates approximately of 90% **(Campbell et al., 2008).**

As a result, increased concern on long-term morbidities of HL treatment had emerged. Radiotherapy related complications include but not limited to cardiovascular diseases, lung toxicity, endocrinopathy, and secondary malignancies **(Oeffinger et al., 2006).**

In an attempt to decrease radiation related toxicity to adjacent normal tissues, further field reduction from IFRT to INRT including only the initially involved nodes in the target volume has been advocated **(Campbell et al., 2012).**

The aim of this study is to compare OARs dose-metric outcomes with INRT vs IFRT in treatment of limited-stage HL, using conventional radiotherapy techniques.

Patients and methods

Twenty patients with limited stage, supradiaphragmatic, pathologically confirmed HL after receiving combination chemotherapy (2 – 4 cycles of ABVD), were planned to receive consolidation radiotherapy. For each patient two plans were generated IFRT and INRT. The radiotherapy dose used was 20 Gy over 10 fractions (2 Gy per fraction) + 10 Gy boost over 5 fractions (2 Gy per fraction) for unfavorable cases and/or residual disease. OARs including lungs, heart, breasts, and thyroid gland were delineated and different dosimetric parameters of both plans were compared.

Inclusion criteria

Patients with histopathologically proved Hodgkin lymphoma (excluding nodular lymphocyte predominant subtype) (NLPHL), clinically stage I-II, only supra-diaphragmatic nodes (both favorable and unfavorable prognostic subsets), aged between 18 and 75 years.

Exclusion Criteria

Patients with advanced or infra-diaphragmatic Hodgkin's disease, patients diagnosed with nodular lymphocyte predominant subtype) (NLPHL), Patients with previous neck and chest irradiation and Pregnant or lactating women.

Study design

All patients were classified based on the classic EORTC clinical prognostic factors into favorable and unfavorable diseases. Unfavorable disease includes patients with: Clinically stage II with ≥ 4 nodal regions or patients aged≥50 years or mediastinal lymph nodes occupying>one third of the chest width or an ESR ≥ 50 (without B-symptoms) or ESR ≥ 30 (with B symptoms). Favorable disease includes patients without any of the above-mentioned criteria of unfavorable disease. The prescribed dose was 20 Gy with10 Gyboostto unfavorable and residual disease.

- IFRT plan was defined to include the initially involved nodal regions, covering the pre-chemotherapy involved lymph nodes plus contiguous nodal groups.
- INRT plan was defined to include only the initially involved lymph nodes.

Radiotherapy technique

CT simulation with slice thickness 2.5 mm or less with intravenous contrast, immobilization devices were used for proper implementation of involved node radiotherapy. CT scans and pre-chemotherapy PET-CT were performed more or less in the same treatment position. 3D-conformal radiotherapy based two plans were generated for every patient using IFRT and INRT techniques following the GHSG guidelines **(Eich et al., 2008)**.

For **INRT,Gross Tumor Volume (GTV):** is the residual lymph node(s). **Clinical Target Volume (CTV):** is the primarily involved volume of lymph node(s) prior to chemotherapy, incorporating the initial location and extent of the disease. **Planning Target Volume (PTV):** equal CTV plus a margin to consider organ movement and set-up errors. 0.5 -1 cm safety margin was considered adequate. For **IFRT, GTV:**is the residual lymph node(s).**CTV:** Is the initial volume of the lymph nodes plus contiguous nodal groups according to the site of the individualized lymph nodes. **PTV:**equalCTV plus a margin to consider organ movement and set-up errors. 0.5 -1 cm safety margin was considered adequate.

Organs at Risk Delineation

The heart, Lungs, breasts, and thyroid gland were contoured as organs at risk (OARs). The heart delineation started from the branching of

the pulmonary trunk, including all cardiac chambers. The thyroid gland was contoured based on the extent of the glandular tissue. Breasts were delineated from head of the clavicle superiorly, to the xiphoid process inferiorly, and from the sternal-rib junction medially to anterior border of latissimus dorsi laterally, and from skin anteriorly to pectoralis muscle posteriorly. **(Weber et al., 2009).**

Plan assessment

The target volume (PTV volume) in each plan was calculated. OARs mean doses and dose-volume metrics were calculated for each delineated OAR. The calculated dose-volume parameters in this study are based on many previous studies **(Reymen et al., 2010; Campbell et al., 2012; and Cella et al., 2013) were:**

- Combined lungs: mean dose, V5, V10 and V20.
- Heart: mean dose, V30.
- Right and left breasts: mean dose, V5, V20.
- Thyroid gland: mean dose, V5, V20

For eachplan, the mean doses and dose-volume metrics were calculated and compared to estimate the differences in radiation exposure for each OAR by IFRT and INRT plans.

The current study has been approved by the Ethics Committee of South Egypt Cancer Institute, Assiut University, Assiut, Egypt.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics version 20 (SPSS Inc., Chicago, IL, USA). Categorical data were presented as frequencies and percentages, while Chi-square test was used for comparisons between groups. Continuous data were reported as means ± standard deviations and students' T-test was used for comparisons between groups. For comparison between progression free survival (PFS), Kaplan-Mayer survival curve and log-rank test were performed. In all statistical tests p-value <0.05 was considered statistically significant.

Results

Table (1) shows patients and treatment characteristics. The median age was 29 years with age ranged from 19 to 56 years. 55% of patients were males and 45% were females. Performance status of patients ranged between 0-2 with 85% of patients had PS=0.

60% of patients presented with mixed cellularity subtype and 40% nodular sclerosis HL. Only 20% had B symptoms. 30% diagnosed with stage I and 70% had stage II. 45% of patients had unfavorable disease.

Table 1. Baseline and treatment characteristics:

Characteristic		**n**	**%**
No. of patients		20	
Age range		19-56	
Median age		29 years	
Sex	Male	11	55
	Female	9	45
Performance	0	17	85
	1	2	10
	2	1	5
Histopathology	Mixed Cellularity	12	60
	Nodular Sclerosis	8	40
B symptoms	**Yes**	4	20
	No	16	80
No. of LN groups	**1**	5	25
	2	11	55
	3	4	20
	4	0	0
Stage	I	6	30

	II	14	70
Favorability	**Favorable**	11	55
	Unfavorable	9	45

Doses to organs at risk

Table (2) shows that reduction of the irradiated volume from IFRT to INRT was associated with significant reduction in the mean doses and dose-volume metrics received by lungs, breasts, thyroid and heart.

Regarding lungs, mean doses were 11.5/7.3 GY (P=0.038), V5 54.8/38.1 % (P=0.006), V10 46.6/41.5 % (P=0.008), and V20 28.5/16.5 % (P=0.003), for IFRT/INRT, respectively.

Regarding heart, mean doses were17.5/8.9 GY (P=0.001), and V30 was 29.5/14.3 % (P=0.002), for IFRT/INRT, respectively.

Regarding right breast,mean doses were 2.3/1.6 GY (P=0.005), V5 11.4/8.1 % (P=0.251), and V20 was 3.5/2.3 % (P=0.155), for IFRT/INRT, respectively.

Regarding left breast, mean doses were 3.2/1.9 GY (P=0.036), V5 11.4/7.8 % (P=0.208), and V20 was3.6/2.3 % (P=0.070), for IFRT/INRT, respectively.

Regarding thyroid gland mean doses were 17.5/7.1 GY (P=0.001), V5 95.9/63.8 % (P=0.017), and V20 was 81/43.5 % (P=0.001) for IFRT/INRT, respectively.

Table 2. Comparison of different dosimetricparameters:

		IFRT	INRT	P VALUE
PTV mean (cm^3)		1641± 418	1051± 196	< 0.001
LUNG N (11)	**mean dose (GY)**	11.48± 5.37	7.32± 2.86	0.038
	V5 (%)	54.81± 13.79	38.08± 13.57	0.006
	V10 (%)	46.61± 12.15	31.49± 11.72	0.008
	V20 (%)	28.52± 5.09	16.55± 10.49	0.003
HEART N (11)	**mean dose (GY)**	17.47± 4.88	8.98±4 .96	0.001
	V30 (%)	29.50± 11.29	14.33± 8.89	0.002
RT. breast N (9)	**mean dose (GY)**	3.30±1 .23	1.60±0 .93	0.005
	V5 (%)	11.42± 6.23	8.11±5 .52	0.251
	V20 (%)	3.52±1 .42	2.35±1 .86	0.155
LT. breast N (9)	**mean dose (GY)**	3.16±1 .36	1.87±0 .98	0.036
	V5 (%)	11.44± 6.19	7.82±5 .5	0.208
	V20 (%)	3.61±1 .24	2.30±1 .60	0.070
thyroid N (12)	**mean dose (GY)**	17.55± 8.07	7.15±5 .65	0.001
	V5 (%)	95.90± 13.26	63.83± 38.71	0.017
	V20 (%)	81.00± 22.59	43.58± 26.31	0.001

Discussion

Studies observed that recurrences of limited stage HL after treatment with chemotherapy alone typically occurred in the initially involved nodes **(Shahidi et al., 2006)**. This observation was the basis for development of the INRT approach in 2006, by Girinsky et al. The rationale for INRT is reduction of radiation therapy induced morbidities in limited stage HL patients treated with combined chemotherapy and radiotherapy without jeopardizing the

excellent disease outcome achieved by IFRT **(Campbell et al., 2008).**

The EORTC H10 trial confirmed the efficacy of INRT after 3 cycles of adriamycin, bleomycin, vinblastine, dacarbazine (ABVD) for favorable ESHL, with results comparable to those seen with the use of IFRT in the RAPID and EORTC H7 trials **(Ferme et al., 2007; Radford et al., 2015; Andre et al., 2017**).

In 2009, Weber et al. compared radiotherapy target field reduction from IFRT to INRT using intensity modulated radiotherapy IMRT and volumetric modulated arc therapy VMAT for ten females diagnosed with mediastinal HL and showed a significant reduction in mean doses of OARs with INRT instead of IFRT **(Weber et al.,2009**). This study showed marked decrease in mean doses and dose-volume metrics to OARs that are comparable to those of weber et al.

Since the use of IMRT for mediastinal irradiation is not standard due to several causes, koeck et al. compared IFRT and INRT using both IMRT and conventional 3-dimensional radiotherapy 3DRT. It reported decrease in OARs doses from 20% to 50%, with marked decrease of high doses to the heart. INRT using either IMRT or 3DRT showed better dose-metricsfor OARs. Therefore, they confirmed that reducing the irradiated volume most effectively protects OARs from excess radiation exposure, regardless of the used radiation technique. The mean volumes of PTV for IFRT and INRT were 1705 cm^3 and 1015 cm^3, respectively**(koeck et al., 2012**). This result is comparable to ours, 1641 cm^3, 1051 $cm^3$for IFRT and INRT, respectively.

Campbell et al. published a study with 10 females diagnosed with stage I-II, supradiaphragmatic HL. Three radiotherapy plans were generated for each patient (IFRT, INRT, and INRT using VMAT) to a dose of 30.6 Gy in 1.8 Gy fractions. Results showed marked reduction in OARs mean doses for INRT rather than IFRT. Mean dose to the heart (10.5/6.9 Gy), whereas mean dose to lungs (10.3/7.3 Gy), breasts (2.4/1.6 Gy), and mean dose to thyroid (29.7/13.5) for IFRT and INRT, respectively **(Campbell et al., 2012).** These results are comparable to those of our study in which, mean dose to the heart (17.47/8.98 Gy), whereas mean doses to lung (11.5/7.3 Gy), breasts (left 3.1/1.8 Gy, and right 3.3/1.6 Gy) and mean dose to thyroid (17.5/7.1).

Maraldo et al. conducted a study with 29 patients diagnosed with supradiaphragmatic, clinical Stage I-II HL, treated with chemotherapy and INRT to a dose 30-36 Gy and simulated a mantle field (MF) plan for each patient to a dose of 36 Gy. It showed a significant decrease in mean doses to the heart, coronary arteries and the four heart valves, for INRT instead of MF technique With INRT the mean doses for the heart were 7.7 Gy (SD 7.4).**(Maraldo et al., 2012).**This result is comparable to our results with mean heart dose 8.9 GY in INRT plan.

Murray et al, generated 4 radiotherapy plans (IFRT, ISRT, INRT and residual post-chemotherapy volume) for 15 patients already treated with mediastinal irradiation. Rates of relative and absolute second malignancies were calculated with the use of the organ equivalent dose. Results showed significant increased doses to OARs including heart, lungs, breasts and thyroid in IFRT arm compared to those with IFRT arm **(Murray et al., 2015).** These results are in line with our results.

It was found that the risk of developing heart disease increased linearly with increasing the mean heart dose with a 2.5-fold increase in the risk of cardiac events in patients receiving a mean heart dose of 20 Gy **(Swerdlow et al., 2007**). In this study the mean heart dose significantly decreased from 17.47 GY in IFRT to 8.98 GY in INRT.

Reducing the irradiated volume from IFRT to INRT across different trials represented reduction in radiation induced acute and late toxicities. In our study, all OARs contoured showed a statistically significant decrease in received doses with the use of INRT plan.

Conclusion

Reducing the irradiated volume from IFRT to INRT can significantly reduce the unnecessary

radiation exposure of adjacent normal tissues. This is associated with decreasing serious late complications of radiotherapy including cardiac toxicity, second malignancy, endocrinopathy and pulmonary morbidities.

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