Consolidation radiotherapy for Early-Stage Hodgkin's Lymphoma either with involved node radiotherapy or involved field radiotherapy.

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Abstract

Background: Radiation therapy still plays an important role in the treatment of patients with Hodgkin's lymphoma. The goal of treatment of early-stage, stage I or II, Hodgkin's lymphoma is to cure the disease together with minimizing the short and long-term complications. Complications related to radiation therapy depends on the radiation dose and the irradiated field size. Over the past four decades, the very large extended field RT had been replaced with the involved field RT using technological developments in imaging, treatment planning, and treatment machines. This allowed very significant reduction in radiation doses to normal tissues without reducing the coverage of the affected nodes. Our study is to evaluate the possibility of much reducing the radiation field size from involved field RT to involved node RT without affecting the efficacy of treatment.

Methods: All newly diagnosed early-stage supradiaphragmatic Hodgkin's lymphoma patients attending south Egypt cancer institute were enrolled into this study after receiving 2 – 4 cycles of ABVD and after a written consent. Patients were randomized to receive consolidation radiotherapy using either IFRT or INRT technique. Radiotherapy dose used for all patients was 20- 30 Gy. Patients were assessed for treatment toxicity and local recurrence.

Results: 49 patients were enrolled in our study: 19 patients in the INRT arm and 30 patients in the IFRT arm. The median follow-up was 14 months. The overall survival for all patients was 98% and freedom from treatment failure was 89.8% with no difference in survival rates between both arms. Also, post radiotherapy complete remission was 9(47.4%) versus 12(40%), relapse 2 (10.5%) versus 3 (10%), and death (0 versus 1) respectively the outcome was similar in both arms. Regarding acute and sub-acute toxicities no significant difference could be detected between both arms except that IFRT arm was associated with a higher incidence of radiation pneumonitis (4 versus 1 patient).

Conclusion: reducing the irradiated field size in treatment of early-stage Hodgkin's lymphoma from involved field RT to involved node RT can be used without affecting the efficacy of treatment and with less treatment toxicity.

Keyword: Hodgkin's Lymphoma; Nodal Radiotherapy; Field Radiotherapy

Introduction:

Hodgkin's lymphoma (HL), used to be called Hodgkin's disease, is a rare malignancy affecting the lymph nodes and the lymphatic system**.** Its incidence shows marked variability regarding age, sex, social class, race, geographic area, and histopathological subtype. [1]

Although Hodgkin's lymphoma can affect any age group, its incidence generally has an obvious bimodal distribution over most countries and studies. The first peak is in young adults (15-34 years); HL is the most commonly cancer that diagnosed in teens (15 to 19) years. The second peak is in old adults (> 55 years). [2] Its incidence is more in males than in females, particularly in the pediatric population, as 85% of cases occur in boys. [3] There are no clearly approved risk factors for the occurrence of this disease and the exact etiology of HL still unknown. Factors that could be associated with HL include familial factors, viral infections, and immune suppression. [4]

During the past few decades, there was significant progress in the management of HL patients, HL can be cured in at least 80% of patients. Patients with Early-stage Hodgkin's lymphoma (HL) treated with combination chemotherapy (usually 2-4 cycles of ABVD) and radiation therapy have an excellent clinical outcome, together with an overall survival of approximately 90%.[5]

Radiation therapy stills a key component in the combined modality treatment of early-stage HL.

However, its use has been questioned because of its related late complications, including cardiac problems, pulmonary toxicities, and secondary malignancies. Radiation toxicity depends on the delivered radiation dose and the irradiated field size. [6,7]

The concept of involved node radiation therapy (INRT) for early-stage Hodgkin's lymphoma (ESHL) was first introduced by the European Organization for Research and Treatment of Cancer (EORTC) since 2006, aiming to use the smallest effective treatment volume, that is individualized to the patient's disease, avoiding potentially unnecessary risks of normal tissues exposure and toxicity that are associated with the use of the standard involved field radiation therapy (IFRT). [8,9]

For early-stage HL, the initial disease sites present at diagnosis was considered the smallest effective volume assuming that chemotherapy is able to control the adjacent potential microscopic disease. The efficacy of involved node RT for early-stage HL was subsequently confirmed in many prospective randomized trials. [10]

Patients and Methods:

From May 2018 to July 2020, a prospective study was conducted on 49 patients with early-stage, supradiaphragmatic, pathologically confirmed HL after receiving combination chemotherapy (2 – 4 cycles of ABVD), 30 patients planned with IFRT technique and the other 19 patients had INRT plans. The median follow-up period was 14 months.

Inclusion criteria

Newly diagnosed patients with histologically proven Hodgkin's lymphoma (excluding the nodular lymphocyte predominant subtype) (NLPHL), Clinical stage I or II, Only supra-diaphragmatic nodes (both favorable and unfavorable prognostic subsets), aged between 18 and 75 years, with Good general condition (WHO performance status 0-2) and Free of concurrent disease.

Exclusion Criteria

Patients with impaired heart, lung, liver, or kidney function, Previous malignant diseases or HIV-positive status, Patients with advanced or infra-diaphragmatic Hodgkin's disease, patients diagnosed with nodular lymphocyte predominant subtype) (NLPHL), Patients with prior irradiation to the neck and thoracic region and Pregnant or lactating women.

Pretreatment evaluation

Patients were staged according to the Ann Arbor staging classification. Routine staging procedures included medical history; physical examination; computed tomography of the neck, chest, abdomen, and pelvis, Bone marrow biopsy (for unfavorable cases), CBC, serum chemistry, LDH, ESR, Echocardiography, Pre-chemotherapy, and post-chemotherapy PET/CT scan was done as possibly in the same treatment position and Consultation of dentist and ENT before start of Radiotherapy. 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. **Complete remission unconfirmed (Cru)** is defined as at least a 75% decrease in tumor size. **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.

Study design

Patients were classified in to 2 arms after finishing the chemotherapy:

- IFRT Arm was defined as radiation therapy fields that encompass the initially involved nodal regions to cover the initially involved lymph nodes plus contiguous nodal groups.
- INRT arm was defined as radiation therapy to treat the initially involved lymph nodes only.

Radiotherapy started within 3 - 4 weeks after the end of the last chemotherapy course. The prescribed dose for all patients in both treatment arms was 20 Gy over 10 fractions (2 Gy per fraction) with a boost of 10 Gy over 5 fractions to unfavorable disease and/or areas with residual disease.

All patients were stratified according to the classic EORTC clinical prognostic factors into the favorable and unfavorable diseases. **Unfavorable disease** includes patients with: Clinical stage II with 4 or more nodal areas or an age of 50 or more years or mediastinal lymphadenopathy more than a third of the chest width or an ESR $\geq$ 50 (without B-symptoms) or ESR $\geq$ 30 (with B symptoms). **Favorable disease** includes all other patients with criteria not applicable to the unfavorable disease.

Radiotherapy technique

CT simulation with slice thickness 2.5 mm or less, 3D-conformal radiotherapy, and immobilization devices were used for proper implementation of involved node radiotherapy. Pre-chemotherapy PET-CT and CT scans performed in the treatment position.

For **INRT, The Gross Tumor Volume (GTV):** Represents the lymph node remnant(s) and should be contoured first in such condition. **The Clinical Target Volume (CTV):** Is the initial volume of the lymph node(s) before chemotherapy. In case of limitations of baseline imaging or changes in patient position, more generous CTV was taken to avoid inadequate tumor coverage. In other words, the CTV incorporates the initial location and the extent of the disease and considers the displacement of normal structures. In case of a Cru with a visible lymph node remnant, the lymph node remnant was included. **The Planning Target Volume (PTV):** is the CTV with a margin to consider organ movement and set-up variations. In most situations, a 0.5 -1 cm safety margin is considered adequate. For **IFRT, The Gross Tumor Volume (GTV):** Represents the lymph node remnant(s) and should be contoured first in such condition. **The Clinical Target Volume (CTV):** Is the initial volume

of the lymph nodes plus contiguous nodal groups according to the site of the individualized lymph nodes. **The Planning Target Volume (PTV):** is the CTV with a margin to consider organ movement and set-up variations. In most situations, a 0.5 -1 cm safety margin is considered adequate.

Follow-Up

Physical examination, Full lab and LDH every 3 months were done, Computed tomography at 3 months intervals during the first year, every 6 months in the second year. **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).

Toxicity

Patients of both arms were assessed for toxicity according to the Radiation Therapy Oncology Group (RTOG) common toxicity criteria. The most frequently occurring toxicities included skin changes, dysphagia, mucositis, laryngeal toxicity, and pulmonary symptoms suggesting radiation pneumonitis.

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:

This study included 49 patients with early-stage supra-diaphragmatic Hodgkin's lymphoma, newly diagnosed at South Egypt Cancer Institute between May 2018 and July 2020, of which 30 patients treated with IFRT and 19 patients treated with INRT.

Patient's characteristics

Table (1) summarized our patients and disease characteristics.

Median age was 30 years ranged from 18 to 57 years in IFRT arm and was 29 years ranged from 19 to 56 years in INRT arm. Performance status was also determined for both treatment groups with no statistically significant difference between them (p = 0.913).

Treatment Outcome

All patients started radiotherapy within 3 - 4 weeks after the end of the last chemotherapy cycle and after chemotherapy CT assessment. Post chemotherapy assessment showed that 5 (16.7%) patients achieved complete remission CR, 19 patients (63.3%) achieved complete remission unconfirmed (Cru) and 6 patients (20%) had partial remission in IFRT arm. while in INRT arm, 4 (21.2%), 12 (63.2%) and 3 (15.8%) patients achieved CR, Cru and PR, respectively with no significant difference between both treatment arms.

Radiation therapy dose was determined depending on response and disease favorability. Patients in CR and Cru and those with favorable disease criteria received 20 Gy/10 over 2 weeks while patients with PR and those with unfavorable disease criteria received an additional boost of 10 Gy to residual disease. This approach was applied for either group.

After Radiation therapy, assessment was done one month later then at 3 months intervals during the first year, and every 6 months in the second year. In IFRT arm, CR, Cru and PR was achieved in 12(40%), 15 (50%) and 3 (10%) patients respectively, While in INRT arm, CR, Cru and PR was achieved in 9(47.4%), 9 (47.4%) and 1 (5.3%) patient, respectively with no significant difference between both treatment arms as shown in table (2).

After a median follow-up of 14 months relapses in both arms were a total of five cases, 2 cases in the INRT and 3 in the IFRT arm with no statistically significant difference between both arms as shown in table (2). Regarding relapsing cases all of them relapsed in the initially involved sites before starting treatment.

The 2 years progression free survival for the INRT group is 89.5% and for the IFRT group it is 90%, with no statistically significant difference between both groups as represented in Figure (1).

Radiation toxicity

Table (2) illustrate incidence and grades of radiation toxicity in both arms.

Patients of both arms were assessed for toxicity according to the Radiation Therapy Oncology Group (RTOG) common toxicity criteria. The most frequently occurred acute toxicities included skin changes, dysphagia, mucositis, and pulmonary symptoms suggesting radiation pneumonitis, with no statistically significant difference between both treatment arms. Late toxicity was reported in 2 patients of IFRT arm who had chronic pneumonitis G1. None of the toxicities reported in this study were higher than grade II toxicity.

Dose to Organs at Risk

Reducing the PTV volume from IFRT to INRT resulted in reduction of the volume of included organs at risk. Table (4) shows the comparison of the mean dosimetric parameters between IFRT and INRT techniques.

Table (1): Patient's characteristics

	IFRT (n=30)	INRT (n=19)	P-value*
Age in years			
Range	18-57	19-56	0.772
Median	30	29	
Sex			
- Male	17 (56.7%)	12 (63.2%)	0.652
- Female	13 (43.3%)	7 (36.8%)	
Performance			
- 0	25 (83.3%)	16 (84.2%)	0.903
- 1	4 (13.3%)	2 (10.5%)	
- 2	1 (3.3%)	1 (5.3%)	
Histopathology			
- Mixed cellularity	17 (56.7%)	11 (57.9%)	0.933
- Nodular sclerosis	13 (43.3%)	8 (42.1%)	
B symptoms			
- Yes	10 (33.3%)	7 (36.8%)	0.801
- No	20 (66.7%)	12 (63.2%)	
BM examination			
- Yes	13 (43.3%)	7 (36.8%)	0.652
- No	17 (56.7%)	12 (63.2%)	
No. of LN groups			
- 1	8 (26.7%)	6 (31.6%)	
- 2	16 (53.3%)	9 (47.4%)	0.600
- 3	6 (20.0%)	3 (15.8%)	
- 4	0 (0.0%)	1 (5.3%)	
LN sites			
- Cervical	20 (66.7%)	12 (63.2%)	0.951
- Mediastinal	7 (23.3%)	5 (26.3%)	
- Axillary	3 (10.0%)	2 (10.5%)	
Stage			
- I	8 (26.7%)	6 (31.6%)	0.711
- II	22 (73.3%)	13 (68.4%)	
Favorability			
- Favorable	17 (56.7%)	12 (63.2%)	0.652
- Unfavorable	13 (43.3%)	7 (36.8%)	

Table (2): Radiotherapy data of studied groups

	IFRT (n=30)	INRT (n=19)	P-value*
Radiotherapy dose			
- 3000 Gy	13 (43.3%)	7 (36.8%)	0.660
- 2000 Gy	17 (56.7%)	12 (63.1%)	
Response			
- Cr	12 (40.0%)	9 (47.4%)	0.785
- Cru	15 (50.0%)	9 (47.4%)	
- Pr	3 (10.0%)	1 (5.3%)	
Relapsed cases	3 (10.0%)	2 (10.5%)	0.953

Table (3): Radiation toxicity

	IFRT (n=30)	INRT (n=19)	P-value*
Acute toxicity			
- Skin changes	16 (53.3%)	10 (52.6%)	
- Mucositis	13 (43.3%)	7 (36.8%)	0.610
- Dysphagia	10 (33.3%)	8 (42.1%)	
- Pneumonitis	4 (13.3%)	1 (5.3%)	
Skin changes			
- G1	10 (62.5%)	7 (70.0%)	0.696
- G2	6 (37.5%)	3 (30.0%)	
Mucositis			
- G1	9 (69.2%)	5 (71.4%)	0.919
- G2	4 (30.8%)	2 (28.6%)	
Dysphagia			
- G1	8 (80.0%)	6 (75.0%)	0.800
- G2	2 (20.0%)	2 (25.0%)	
Pneumonitis			
- G1	3 (75.0%)	1 (100.0%)	0.576
- G2	1 (25.0%)	0 (0.0%)	

Table (4): Comparison of different dosimetric parameters for both groups

	IFRT (n=30)		INRT (n=19)		P-value*
	N	mean±SD	N	mean±SD	
PTV mean (cm^3)	30	1806±323	19	981±191	0.000
Lung					
- Mean dose (GY)	7	10.45±5.19	5	7.41±4.30	0.309
- V5 (%)	7	49.92±16.86	5	29.00±14.66	0.050
- V20 (%)	7	28.57±5.82	5	17.16±11.51	0.046
Heart					
- Mean dose (GY)	7	17.22±5.54	5	9.30±5.42	0.033
- V30 (%)	7	28.95±13.09	5	14.28±11.61	0.073
Breast mean dose (GY)					
- Rt breast	7	3.40±1.39	4	1.75±1.32	0.087
- Lt breast	7	3.25±1.55	4	1.90±1.27	0.174
Thyroid mean dose (GY)	20	16.47±7.66	12	7.14±5.67	0.001

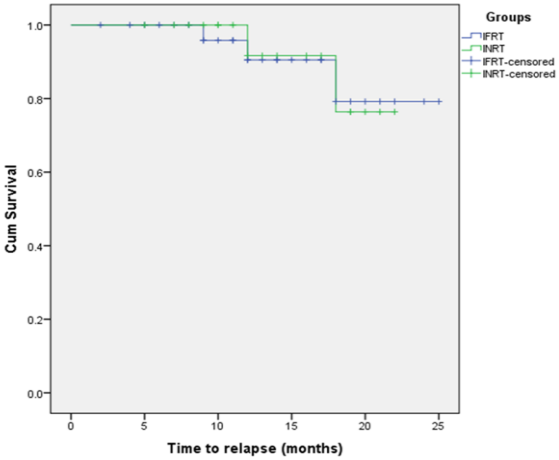

Figure (1): Progression free survival

Discussion:

Since early-stage Hodgkin's lymphoma is considered a curable disease in more than 90% of patients, the main goal of current and future studies is to reduce late complications together with achieving high cure rates. Various studies reported less risk for cardiac complications and/or breast cancer when total dose, irradiated volume, or the amount of mediastinum and/or breasts which exposed to radiation was reduced [11-13].

Although reducing the size of the irradiated volume would be expected to reduce toxicity, it could be associated with an increased risk of marginal and/or out-of-field failures. Recently, evidence is accumulating to support the effectiveness of INRT with no excess failures at the treatment margin. [14-16]

A retrospective cohort study of 97 patients with early-stage Hodgkin's lymphoma treated with chemotherapy and INRT, was reported by Maraldo et al. [17] who showed no marginal failures.

Also, INRT was used in the control arm of early-stage Hodgkin's lymphoma patients in EORTC/LYSA/FIL Intergroup H10 trial. The interim analysis of this trial showed similar disease progression rates to previous results with using IFRT technique. [16]

Campbell et al. [18] published a retrospective trial with 325 patients with early-stage Hodgkin's lymphoma receiving combined treatment modality and were studied in a single clinical trial performed at the British Colombia cancer center, to compare the efficacy of Extended field radiation therapy (EFRT), involved field radiation therapy (IFRT), and involved node radiation therapy (INRT). Median follow-up for living patients was 80 months. Median time to relapse was 37 months. Twelve relapses (12) occurred: four (4) after EFRT (3%); five (5) after IFRT (5%); and three (3) after INRT (3%). No marginal recurrences after INRT. At 5 years, the progression-free survival (PFS) was 97%, and the overall survival (OS) was 95%. These results are comparable to ours regarding relapse free survival at 2 years that was 90% in IFRT arm (95% CI: 20.6 – 25.1) and 89.5% in INRT arm, (95% CI: 18.7 – 22.4) without statistically significant difference between both arms (P=0.958).

As regards acute toxicity, in this study no statistically significant difference was found between the INRT arm and IFRT arm resulting from irradiation of oral cavity, upper airway or the pharynx. On the other hands, Incidence of radiation pneumonitis was higher in the IFRT arm for patients received mediastinal irradiation. In the INRT arm. Reducing the included lung volume leads to consequent reduction of lung toxicity.

HL is often presented in the cervical nodal chain, either alone or in combination with mediastinal nodes. Several studies reported the risk of thyroid complications, including hypothyroidism (HT), after radiotherapy for HL [19-21]. In Maraldo et al [17], hypothyroidism was the most frequently reported late effect, being observed in 10 patients. While in our study, no cases reported with hypothyroidism in either treatment arm. On the other hands, chronic pneumonitis was the only late toxicity reported, 4 patients (13.3%) in IFRT arm and only 1 patient (5.3%) in INRT arm, which could be attributed to the short follow up period in our study.

Amy M. et al. [22] reported 75 patients with newly diagnosed Hodgkin's lymphoma, who treated with IFRT to the mediastinum and 17 patients with refractory or relapsed Hodgkin's lymphoma also treated with IFRT to the mediastinum before or after transplant. 7 patients (10%) who received mediastinal irradiation as a part of initial treatment, developed Radiation pneumonitis. The predictor for radiation pneumonitis occurrence was a mean lung dose of 13.5 Gy or more ($p = 0.04$) and/or a 33.5% of lung volume receiving 20 Gy or more ($p = 0.009$). In our study, 4 patients (13.3%) in IFRT arm and only 1 patient (5.3%) in INRT arm developed radiation pneumonitis.

Weber et al. [23] compared IF-PTV to IN-PTV for intensity modulated radiotherapy (IMRT) and volumetric modulated arc therapy (VMAT) in 10 female patients diagnosed with mediastinal Hodgkin's lymphoma and showed a significant decrease in doses received to OAR with the use of IN-PTV instead of IF-PTV. In our study, target volumes are about twice the size for IF-PTV as for IN-PTV. Also, the reduction of mean doses to heart, lung, and breasts observed by Weber et al. with the use of IN-PTV is comparable to our results.

Koeck et al. [24] conducted a trial based on 20 computed tomography (CT) datasets of early unfavorable mediastinal HL patients and created treatment plans for 3D radiation therapy and IMRT for both the IFRT and INRT techniques according to the German Hodgkin Study Group (GHSG) guidelines. The mean volumes of IF-PTV and IN-PTV were 1705 cm^3 and 1015 cm^3, respectively. Mean doses for IFRT and INRT to the heart were (17.94/9.19 Gy for 3DRT and 13.76/7.42 Gy for IMRT), whereas mean doses to lung (10.62/8.57 Gy for 3DRT and 12.77/9.64 Gy for IMRT) and breasts (left 4.37/3.42 Gy for 3DRT and 6.04/4.59 Gy for IMRT, and right 2.30/1.63 Gy for 3DRT and 5.37/3.53 Gy for IMRT). These results are comparable to those of our study in which, the mean volumes of IF-PTV and IN-PTV are 1806 cm^3 and 981 cm^3, respectively. Mean doses for IFRT and INRT to the heart were (17.22/9.30 Gy), whereas mean doses to lung (10.45/7.41 Gy), and breasts (left 3.07/1.85 Gy, and right 3.40/1.75 Gy).

Cardiac toxicity and Second malignancy are considered the most serious radiation induced late complications, constituting the most common non-lymphoma mortality causes in long term Hodgkin's survivors [25].

Maraldo et al. [26] studied 29 patients with supradiaphragmatic, clinical Stage I-II HL, who were treated with chemotherapy and INRT to 30 to 36 Gy and simulated a mantle field plan for each patient to a dose of 36 Gy. Results showed significantly lower mean doses to heart, coronary arteries and the four heart valves, for INRT than for MF technique.

Large case-control studies analyzed the incidence of lung cancer for HL patients and found an increased risk secondary to prior irradiation, further enhanced by the simultaneous use of alkylating agents [27,28].

Our study reported that the use of INRT considerably reduces most of the evaluated OAR dose parameters compared to those of IFRT. Therefore, we could hypothesize that these lower doses could result in lower rates of secondary cancers.

Conclusion:

In order to reduce the unnecessary excess doses to normal tissues, modern imaging and modern RT techniques including INRT should be used. This will be associated with subsequent reduction of long-term complications associated with larger RT fields.

Conflict of Interests:

The authors declare that they have no conflict of interests.

References:

[1] Hoppe RT, Advani RH, Bierman PJ, et al. Hodgkin Lymphoma: Clinical Practice Guidelines in Oncology, Journal of the National Comprehensive Cancer Network, Vol. 4, No. 3, 2006, pp. 210-230.

[2] Lymphoma - Hodgkin: Statistics. Cancer.Net. Available at https://www.cancer.net/cancer-types/lymphoma-hodgkin/statistics.

[3] Howlader N, Noone AM, Krapcho M, et al. eds. SEER Cancer Statistics Review, 1975- 2014. Bethesda, MD: National Cancer Institute; 2017. seer.cancer.gov/csr/1975_ 2014/

[4] Glaser SL, Jarrett RF. The epidemiology of Hodgkin's disease. Baillieres Clin Haematol. 1996;9(3):401–416.

[5] Fermé C, Eghbali H, Meerwaldt JH, et al. EORTC-GELA H8 Trial: Chemotherapy plus involved-field radiation in early-stage Hodgkin's disease. N Engl J Med 2007, 357(19):1916–1927.

[6] Ng K. Late Complications after Treatment for Hodgkin Lymphoma, Curr Hematol Malig Rep. 2008 Jul;3(3):119-25.

[7] Ng K, Bernardo MP, Weller E, et al., Long-Term Survival and Competing Causes of Death in Patients with Early-Stage Hodgkin's Disease Treated at Age 50 or Younger. J Clin Oncol. 2002 Apr 15;20(8):2101-8.

[8] Girinsky T van der Maazen R, Specht L, et al. Involved-node radiotherapy (INRT) in patients with early Hodgkin lymphoma: Concepts and guidelines. Radiotherapy Onco l2006; 79:270-277.

[9] Yahalom J, Mauch P. The involved field is back: Issues in delineating the radiation field in Hodgkin's disease. Ann Onco l2002; 13:79-83.

[10] Andre MPE, Girinsky T, Federico M, et al. Early positron emission tomography response-adapted treatment in stage I and II Hodgkin lymphoma: Final results of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol 2017;35:1786-1794.

[11] Franklin J, Pluetschow A, Paus M, et al. Second malignancy risk associated with treatment of Hodgkin's lymphoma: Meta-analysis of the randomized trials. Ann Oncol 2006; 17:1749-1760.

[12] De Bruin ML, Sparidans J, van't Veer MB, et al. Breast cancer risk in female survivors of Hodgkin's lymphoma: Lower risk after smaller radiation volumes. J Clin Oncol 2009; 27:4239-4246.

[13] Hancock SL, Tucker MA, Hoppe RT. Factors affecting late mortality from heart disease after treatment of Hodgkin's disease. JAMA 1993; 270:1949-1955.

[14] Paumier A, Ghalibafan M, Beaudre A, et al. Involved-node radiotherapy, and modern radiation treatment techniques in patients with Hodgkin lymphoma. Int Radiat Oncol Biol Phys 2011;80(1):199-205.

[15] Filippi AR, Piva C, Giunta F, et al. Radiation therapy in primary mediastinal B-cell lymphoma with positron emission to myography positivity after rituximab chemotherapy. Int Radiat Oncol Biol Phys 2013;87(2):311-316.

[16] Raemaekers M, Andre MP, Federico M, et al. Omitting radiotherapy in early positron emission tomography-negative stage I/II Hodgkin lymphoma is associated with an increased risk of early relapse: clinical results of the preplanned interim analysis of the randomized EORTC/LYSA/FIL H10 trial. J Clin Oncol2014;32(12):1188-1194.

[17] Maraldo MV, Aznar MC, Vogelius IR, et al. Involved node radiation therapy: an effective alternative in early-stage Hodgkin lymphoma. Int Radiat Oncol Biol Phys 2013;85(4):1057-1065.

[18] Campbell BA, Voss N, Pickles T, et al., Involved Nodal Radiation Therapy as a Component of Combination Therapy for Limited-Stage Hodgkin's Lymphoma: A Question of Field Size," J Clin Oncol. 2008 Nov 10;26(32):5170-4.

[19] Bethge W, Guggenberger D, Bamberg M, et al. Thyroid toxicity of treatment for Hodgkin's disease. Ann Hematol 2000; 79:114–8.

[20] Constine LS, Donaldson SS, McDougall IR, et al. Thyroid dysfunction after radiotherapy in children with Hodgkin's disease. Cancer 1984; 53:878–83.

[21] Hancock SL, Cox RS, McDougall IR. Thyroid diseases after treatment of Hodgkin's disease. N Engl Med 1991; 325:599–605.

[22] Fox AM, Dosoretz AP, Mauch PM, et al. Predictive Factors for Radiation Pneumonitis in Hodgkin Lymphoma Patients Receiving Combined Modality Therapy. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):277-83.

[23] Weber DC, Peguret N, Dipasquale G, et al. Involved-node and involved-field volumetric modulated arc vs. fixed beam intensity modulated radiotherapy for female patients with early-stage supradiaphragmatic Hodgkin lymphoma: A comparative planning study. Int J Radiat Oncol Biol Phys 2009; 75:1578-1586.

[24] Koeck J, Abo-Madyan Y, Lohr F, et al. Radiotherapy for Early Mediastinal Hodgkin Lymphoma According to the German Hodgkin Study Group (GHSG): The Roles of Intensity-Modulated Radiotherapy and Involved-Node Radiotherapy. Int J Radiat Oncol Biol Phys. 2012 May 1;83(1):268-76.

[25] Aleman BA, van den Belt-Dusebout AW, Klokman WJ, et al. Long-Term Cause Specific Mortality of Patients Treated for Hodgkin's Disease. J Clin Oncol. 2003 Sep 15;21(18):3431-9.

[26] Maraldo MV, Brodin NP, Vogelius IR, et al. Risk of Developing Cardiovascular Disease After Involved Node Radiotherapy Versus Mantle Field for Hodgkin Lymphoma, Int J Radiat Oncol Biol Phys. 2012 Jul 15;83(4):1232-7.

[27] van Leeuwen FE, Klokman WJ, Stovall M, et al. Roles of radiotherapy and smoking in lung cancer following Hodgkin's disease. Natl Cancer Inst 1995; 87:1530–7.

[28] Travis LB, Gospodarowicz M, Curtis RE, et al. Lung cancer following chemotherapy and radiotherapy for Hodgkin's disease. Natl Cancer Inst 2002; 94:182–92.