A case report evaluating combined effect of intensity-modulated radiotherapy and deep inspiratory breath-hold for mediastinal lymphoma: A dosimetric analysis

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ABSTRACT

Excellent survival has been reported after combined modality treatment in bulky mediastinal Hodgkin's lymphoma. Late effects such as cardiac morbidity and secondary cancers have been reported after radiotherapy (RT), especially in young adults. Advanced RT techniques such as deep inspiratory breath-hold (DIBH), intensity-modulated RT (IMRT), and volumetric arc therapy have been used recently to reduce these late effects with encouraging results. We hereby present a case report evaluating combined effect of DIBH and IMRT in a young adult with mediastinal lymphoma.

KEY WORDS: Deep inspiratory breath-hold, intensity-modulated radiotherapy, mediastinal lymphoma, radiotherapy

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INTRODUCTION

Patients with early-stage Hodgkin lymphomas (HLs) have excellent survival (10-year overall survival: >80%) following combined modality treatment (CMT). Mediastinal involvement is common in young patients with HL.[1] Conventionally, extended field radiotherapy (EFRT)-like mantle field was used for mediastinal disease. However, patients who survived lymphoma presented with late side effects such as cardiac morbidity and secondary cancers.[2-4] This risk is a concern, particularly for young patients with longer life expectancy after treatment. This fact has increased emphasis on reducing long-term complications of radiotherapy (RT).

Attempts have been made to minimize normal tissue exposure during RT using various approaches, including reduction of RT dose and field size.[1,5-8] Advanced RT techniques such as deep inspiratory breath-hold (DIBH), intensity-modulated RT (IMRT), and volumetric arc therapy (VMAT) may further reduce organ at risk (OAR) doses in patients with HL. These novel approaches have been applied in the setting of mediastinal lymphoma, with encouraging results.[9]

We hereby present a case report highlighting the effectiveness of using DIBH with IMRT/VMAT technique in terms of protection of OARs in a young patient with bulky mediastinal HL.

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CASE REPORT

A 27-year-old male was evaluated for the complaints of cough, chest pain, and weight loss outside and was diagnosed with a case of Classical HL Stage IIAX. Chest X-ray demonstrated a large mediastinal mass. Computed tomography (CT) of the neck, chest, and abdomen (prechemo) showed a large anterior mediastinal mass, 18.5 cm × 6.5 cm × 4 cm, extending from a suprasternal notch above into anterior mediastinum with a large component extending inferiorly on the left side of mediastinum to the level of left ventricle, compressing left innominate vein. Enlarged right paratracheal and left deep cervical nodes were present. Biopsy from cervical lymph was suggestive of classical HL, nodular sclerosis type (CD30+, CD20+ [variable], and background population comprised CD3-positive small lymphocytes). No marrow involvement was observed on bone marrow biopsy. The patient received two cycles of ABVD (adriamycin, bleomycin, vinblastine, and dacarbazine)-based chemotherapy. Interim positron-emission tomography-CT (PET-CT) (post 2 cycles chemotherapy) showed a large well-defined nonfluorodeoxyglucose-avid mass with lobulated margin and internal septae in the anterior mediastinum, extending from the level of sternal notch up to the left ventricle. It was abutting innominate vein, arch of aorta, left pulmonary artery with indistinct margin, 15 cm × 11.4 cm × 6.2 cm, Deauville Score 2.

The patient received four more cycles of ABVD-based chemotherapy. Re-evaluation after six cycles chemotherapy with PET-CT showed metabolically inactive residual anterior mediastinal mass (Deauville 2), 9.4 cm × 6.1 cm, abutting brachiocephalic vein, aortic arch and pulmonary trunk and extending inferiorly to the left ventricle with subcentimetric supraclavicular lymph nodes. He was referred to RT department for consolidative irradiation to the mediastinal mass. Baseline echocardiography as well as pulmonary function tests was done to benchmark baseline functions which were required for assessing the feasibility of current treatment as well as long-term follow-up.

The patient was simulated supine with arms raised above head and immobilized with a Vacloc. Three simulation CT scans with 2-mm slice thickness from chin to L1 vertebrae were done for the patient: One using free-breathing (FB), second using DIBH, and third one was a four-dimensional CT (4DCT) scan. Breath-hold assessment was made during an initial training phase utilizing the real-time position management system (Varian Medical Systems, Palo Alto, CA, USA). As per our institutional protocol, patients who are able to hold their breath for a minimum of 20–25 s with reproducible amplitude are deemed eligible DIBH-gated RT delivery.

Targets were delineated on the FB, DIBH, and 4DCT scans by a single radiation oncologist and reviewed by the supervising treating consultant. A clinical target volume (CTV) was generated after the rigid registration of prechemotherapy CT and postchemotherapy PET-CT with each simulation CT dataset. Prechemotherapy scans were used to determine the craniocaudal extent of the CTV, and transverse diameter of CTV was defined by the postchemotherapy residual mediastinal disease. Planning target volume (PTV) was created as 1-cm isotropic expansion around CTV. Maximum intensity projection (MIP), end-inspiration and end-expiration data were used for target delineation in the 4DCT scan. Internal target volume (ITV) was determined for the 4DCT. For those scans with ITV generation, only a setup margin of 5 mm was used to generate PTV as per institutional policy. The heart was contoured from just below the pulmonary trunk and down to apex as per the published guidelines.[10] Other OARs, including ipsilateral lung, contralateral lung, common lung, spinal cord, left anterior descending (LAD) artery, ventricles, and esophagus, were contoured on all scans.

A dose of 36 Gy in 18 fractions over 3½ weeks was prescribed to PTV. RT planning was done on all three scans with IMRT and VMAT technique using the Eclipse Treatment Planning System (version 11, Varian Medical Systems) using the analytical anisotropic algorithm. IMRT plan was generated using a “butterfly” technique to minimize the low-dose bath.[11] Six plans were created as follows: FB-IMRT, DIBH-IMRT, FB-VMAT, DIBH-VMAT, 4DCT-IMRT, and 4DCT-VMAT.

Plans were evaluated using color wash and dose-volume histogram (DVH). Comparison between plans was made for target volume coverage and OAR dose. Criteria for target coverage were that ≥95% PTV received ≥95% of the prescribed dose. In addition, the volume of PTV receiving ≥107% dose should be <5%. OAR constraints used included as follows: (a) Heart – Mean dose <26 Gy, V30 Gy <46%, (b) common lung V20 Gy <30%, and (c) cord < Dmax < ALARA. Treatment was implemented using DIBH-IMRT plan on TrueBeam linear accelerator (6MV flattened beam). Setup verification was done before each fraction during DIBH using 2D or 3D kV imaging.

Target volume doses for all the six plans are shown in Table 1. All plans satisfied the treatment planning goals with sufficient coverage. Comparative DVH curves and color washes for all plans are shown in Figures 1-4. Results were compared with respect to DIBH-IMRT plan, which was considered as the standard plan.

DIBH, when compared with FB using either IMRT or VMAT, resulted in a reduction in all cardiac doses [Table 1 and Figure 3]. Similarly, IMRT, when compared with VMAT in either FB or DIBH phase, reduced most cardiac parameters. Compared with the FB-IMRT, DIBH-IMRT provided a significant reduction in the mean heart dose (5.54 Gy [29%]) and V30 Gy (7.2 Gy, 36.21%). In comparison, the difference was less significant between IMRT and VMAT technique.

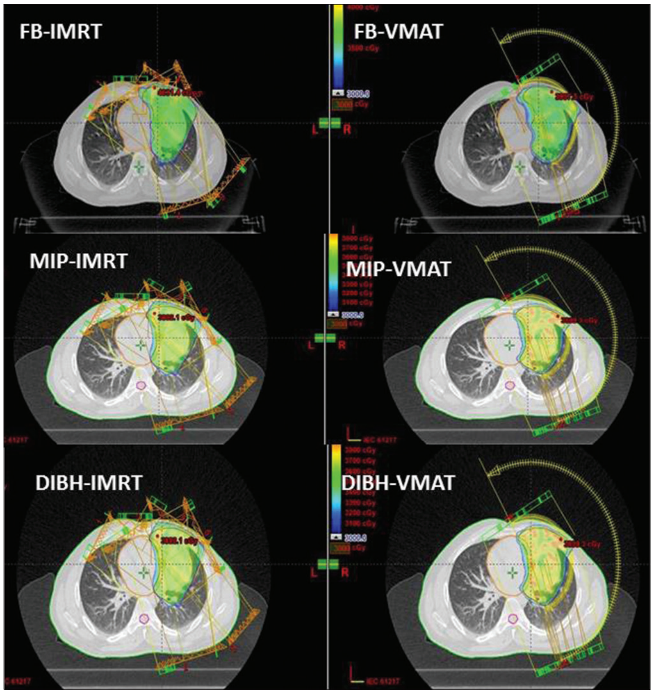

Figure 1: Dose color wash comparison for IMRT and VMAT plans in FB, DIBH, and 4DCT-MIP phase. IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric arc therapy, FB: Free breathing, DIBH: Deep inspiratory breath-hold, 4DCT: Four-dimensional computed tomography, MIP: Maximum intensity projection

Table 1: Dosimetric comparison between radiotherapy plans (IMRT vs VMAT) for Mediastinal Lymphoma in Free breathing (FB), deep inspiratory breath hold (DIBH) and 4DCT-Maximum Intensity Projection (4DCT-MIP) phase

Dosimetric Parameters	Free Breathing		Deep Inspiratory Breathhold		4DCT-MIP	
	IMRT	VMAT	IMRT	VMAT	IMRT	VMAT
Planning Target Volume						
D98% (Gy)	34.15	34.78	34.82	34.44	34.87	35.10
D95% (Gy)	35.34	35.53	35.53	35.27	35.69	35.68
D50% (Gy)	37.52	37.89	37.86	37.18	37.42	37.24
D2% (Gy)	38.84	39.25	38.45	38.33	38.37	38.39
V107% (%)	04.91	12.43	1.036	1.08	1.03	0.87
V95% (%)	97.96	99.14	98.02	98.56	98.70	99.79
Heart						
Volume (cc)	668.7	668.7	506.5	506.5	586.6	586.6
Mean (Gy)	19.10	19.50	13.56	14.42	15.76	15.88
V5Gy (%)	91.17	94.52	60.66	68.65	92.36	92.36
V10Gy (%)	74.44	64.56	41.22	42.72	57.93	58.19
V20Gy (%)	38.12	42.45	27.30	29.55	29.09	29.12
V25Gy (%)	32.33	34.87	23.26	25.39	22.31	22.32
V30Gy (%)	27.08	28.84	19.88	21.23	16.67	16.63
LAD						
Mean (Gy)	26.18	27.42	23.78	26.52	25.04	26.87
Left Ventricle						
Mean (Gy)	21.34	22.19	15.89	17.29	17.77	17.89
Right Ventricle						
Mean (Gy)	17.73	18.35	11.17	12.33	10.29	9.94
Left Lung						
Volume (cc)	1019.1	1019.1	2353.6	2353.6	1013.9	1013.9
Mean (Gy)	21.98	22.52	12.72	14.01	20.00	19.89
V5Gy (%)	98.05	97.66	69.34	71.75	96.69	96.07
V10Gy (%)	88.72	88.52	53.10	63.55	88.05	85.19
V20Gy (%)	53.78	60.39	23.48	26.10	45.86	46.48
V30Gy (%)	23.27	24.72	8.05	8.51	14.65	15.75
Right Lung						
Volume (cc)	1459.2	1459.2	2676.7	2676.7	1425.7	1425.7
Mean (Gy)	9.69	10.63	6.62	8.16	8.88	9.56
V5Gy (%)	62.69	76.13	47.48	55.16	56.95	70.70
V10Gy (%)	37.82	41.60	22.72	38.40	35.91	34.40
V20Gy (%)	10.89	10.23	4.61	5.72	08.05	08.36
V30Gy (%)	3.31	3.69	1.30	1.48	02.29	02.47
Common Lung						
Volume (cc)	2478.3	2478.3	5030.3	5030.3	2439.6	2439.6
Mean (Gy)	14.75	15.52	9.48	10.91	13.55	13.90
V5Gy (%)	77.15	85.09	57.74	62.97	73.71	81.40
V10Gy (%)	58.75	60.91	36.92	50.32	57.69	55.67
V20Gy (%)	28.58	31.01	13.49	15.31	23.70	24.28
V30Gy (%)	11.52	12.34	4.44	4.74	07.62	08.21
Cord						
Dmax	21.29	18.83	22.61	22.39	15.34	11.80
Monitor Units	1820	555	1434	951	1189	566
Body-PTV						
Mean dose (Gy)	5.57	5.80	4.90	5.75	5.23	5.42
V1Gy (%)	57.03	61.20	55.21	59.96	55.80	59.46
V2Gy (%)	47.72	52.29	45.27	50.41	46.34	50.41
V3Gy (%)	42.68	47.18	40.05	46.22	40.99	45.09
V4Gy (%)	38.10	42.47	34.85	42.73	36.13	39.86
V5Gy (%)	33.87	37.93	30.28	39.87	31.68	34.94

Comparative mean doses, V5%, V10%, V20%, and V30% for all six plans for ipsilateral, contralateral, and common lung are shown in Table 1 and Figure 4. DIBH led to an increase in the volume of common lung by 2552 ml (102.97%). DIBH, when compared with FB using either IMRT or VMAT, resulted in reduction in all lung dosimetric parameters. IMRT, when compared with VMAT also reduced mean lung doses; however, this difference was minimal.

Mean dose estimates for all OARs were lowered with DIBH when compared to FB. Interestingly, there was no significant difference in the estimated doses to the heart and lungs with IMRT versus VMAT (DIBH-IMRT vs. DIBH-VMAT). Although higher monitor units (MUs) were required to deliver IMRT plans in comparison to the VMAT plans; integral dose was lower with IMRT.

DISCUSSION

Documentation of serious late-effects with EFRT and effectiveness of present-day chemotherapy regimens have led to reconsideration of the role of RT in mediastinal HL. Reducing late toxicity of treatment is prime importance when managing young patients with mediastinal lymphoma.

RT is delivered as a consolidative treatment to macroscopic residual disease after chemotherapy. Lower RT doses, reduction in target volumes, and improvement in treatment delivery techniques have emerged as strategies to reduce risk of RT-induced toxicities and diminish normal tissue exposure. Another innovative RT technique being investigated in mediastinal lymphoma is DIBH. As with the IMRT technique, DIBH focuses on decreasing RT dose to

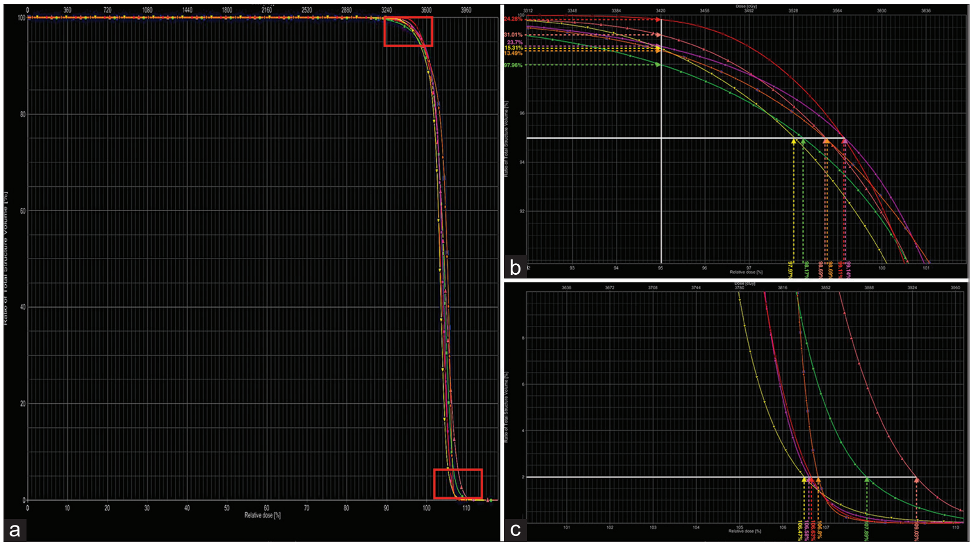

Figure 2: (a) Dose-volume histogram variations for planning target volume between IMRT and VMAT plans in FB, DIBH, and 4DCT-MIP phase with an inner enlarged panel showing D95% (b) and D2% (c) (Orange – DIBH-IMRT, Yellow – DIBH-VMAT, Magenta – 4DCT-IMRT, Red – 4DCT-VMAT, Green – FB-IMRT, Pink-FB-VMAT). IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric arc therapy, FB: Free breathing, DIBH: Deep inspiratory breath-hold, 4DCT: Four-dimensional computed tomography, MIP: Maximum intensity projection

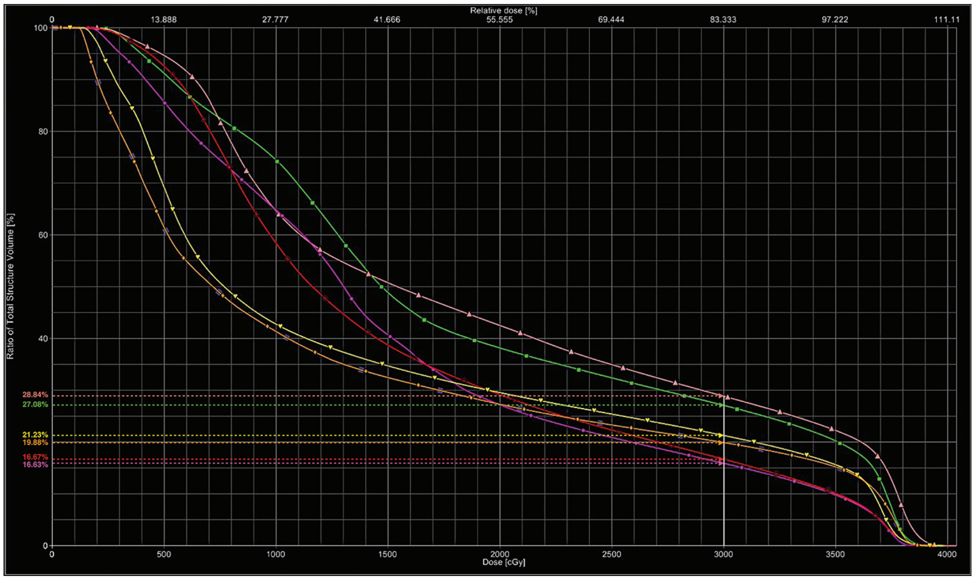

Figure 3: Dose-volume histogram variation for heart between IMRT and VMAT plans in FB, DIBH, and 4DCT-MIP phase (Orange – DIBH-IMRT, Yellow – DIBH-VMAT, Magenta – 4DCT-IMRT, Red – 4DCT-VMAT, Green – FB-IMRT, Pink-FB-VMAT). IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric arc therapy, FB: Free breathing, DIBH: Deep inspiratory breathhold, 4DCT: Four-dimensional computed tomography, MIP: Maximum intensity projection

OARs, especially heart by increasing the distance between heart and target volume. DIBH has been used to a limited extent for mediastinal lymphomas; however, data are fast evolving from lymphoma units.[11-13] As observed in our case, DIBH reduces heart and lung dosimetric parameters. DIBH results in elongation of the heart, resulting in greater separation from the target and an increase in lung volume.

Combination of both techniques (IMRT/VMAT and DIBH) is feasible and could be valuable for a patient subgroup, depending on the disease extent and location. The literature suggests less evident effect of DIBH on heart dose for tumors with extension inferiorly into the mediastinum and recommends IMRT in such a situation.[9,14] Our results are contrary to the above reports with benefit seen with DIBH even with bulky disease.

Paumier *et al*. evaluated the effect of DIBH in 28 patients of mediastinal lymphoma treated with IMRT and reported benefit of DIBH on the mean heart (15%–20% decrease) and lung dose (28% decrease in V20 Gy) for all patients.[14,15] Benefit was most evident for tumors localized to the upper mediastinum. Similar to our results, Voong *et al*.[11] estimated

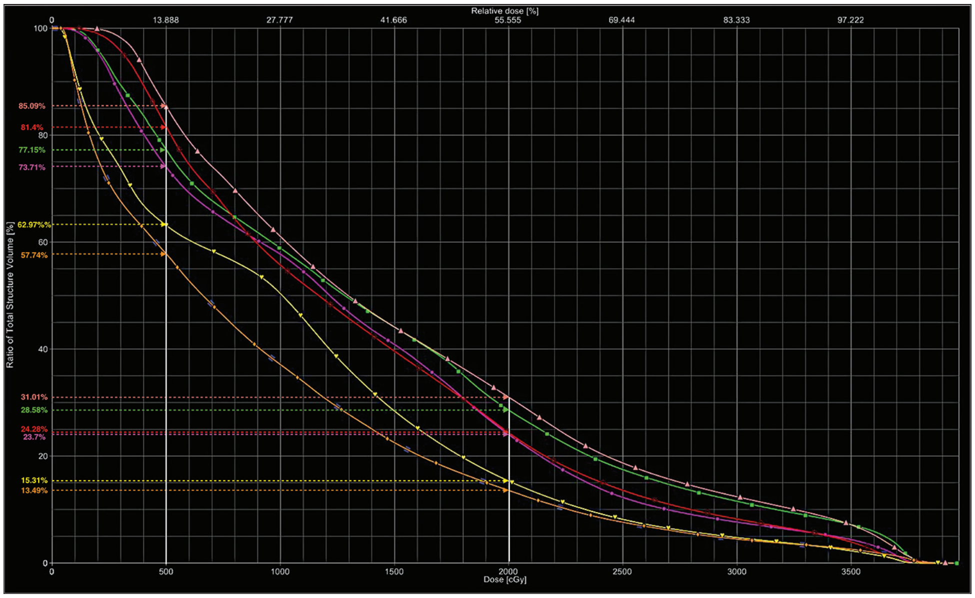

Figure 4: Dose-volume histogram variation for common lung between IMRT and VMAT plans in FB, DIBH, and 4DCT-MIP phase (Orange – DIBH-IMRT, Yellow – DIBH-VMAT, Magenta – 4DCT-IMRT, Red – 4DCT-VMAT, Green – FB-IMRT, Pink – FB-VMAT). IMRT: Intensity-modulated radiotherapy, VMAT: Volumetric arc therapy, FB: Free breathing, DIBH: Deep inspiratory breathhold, 4DCT: Four-dimensional computed tomography, MIP: Maximum intensity projection

and compared dose to heart, LAD artery and lung with IMRT and 3D conformal RT (3D-CRT) technique for nine patients with mediastinal HL during the breath-hold phase. Final analysis revealed lower doses with IMRT than 3D-CRT during breath-hold with combination noted to be extremely beneficial in large mediastinal tumors. Mulrooney *et al*. reported an increase in the incidence of myocardial ischemia with higher radiation doses (hazard ratio >12 for patients treated with mediastinal radiation during childhood). These results underline the importance of cardiac dose reduction, as was achieved with DIBH in our study.[16] V30 Gy for heart is often used as a predictor of pericardial effusion (risk 13% vs. 73% with V30 Gy <46% as cutoff) and was lowered with DIBH in comparison to FB and MIP in our study.[17]

Risk of radiation pneumonitis (RP) increases due to irradiation of partial lung volume after mediastinal irradiation. Fox *et al*.[18] reported 10% incidence of RP in their experience of patients with HL receiving CMT. Similar results were obtained by Hua *et al*.;[19] the mean lung dose was higher in pneumonitis patient population in comparison to asymptomatic control (14.4 Gy vs. 11.9 Gy). Breath-hold implementation led to a reduction in the mean lung dose (9.48 Gy) with combination of DIBH and IMRT technique in this study. Stromberg *et al*.[20] studied the use of breath-hold in five patients treated with mantle fields and reported 12% reduction in irradiated lung volume with DIBH in comparison to FB.

Risk of secondary malignancy also leads to significant apprehension following mediastinal RT. Gilbert *et al*.[21] estimated excess risk of 0.15/Gy implying the importance of keeping OAR dose as low as reasonably achievable. Valagussa and Bonadonna reported an incidence 10%–13% at 15 years of secondary malignancy with risk increasing every additional year.[22]

IMRT has been associated with increased exposure of normal tissue to low doses. Therefore, with IMRT, in contrast to DIBH, a compromise has to be made between predicted reduction in long-term side effects and potential increase in risk of secondary malignancy.[23] Centers round the world have started utilizing techniques with limited beam direction for IMRT or VMAT to account for above dilemma.[11,24] Some would debate that with similar dosimetric benefit in term of OAR doses and reduced MUs being used, VMAT may be an equally good treatment alternative to IMRT. However, as noted in our study, an integral dose exposure to nontumor tissue was lower with IMRT in comparison to VMAT, thereby leading to lower chance of secondary malignancies. Thus, a combination of DIBH and IMRT seems beneficial in sparing OARs for a patient with mediastinal lymphoma.

The main limitation of our study is that the perceived benefit seen was primarily dosimetric, with longer follow-up and larger number of patients required for us to draw clinical inferences. The dosimetric improvement achieved was mainly due to the favorable anatomical displacement achieved with DIBH. Furthermore, a reduction in PTV margin along with DIBH and IMRT cannot be justified at this time and further research on this aspect is required.

We have described a case of a young male with early-stage bulky mediastinal HL, receiving RT as a component of CMT. Using broadly accessible RT techniques (DIBH and

IMRT), we were able to achieve reduction in cardiac and lung doses while maintaining optimal target coverage. To the best of our knowledge, this is the first report in India describing the combined use of DIBH and IMRT/VMAT for mediastinal lymphoma.

To conclude, DIBH is a simple, well-tolerated, and feasible approach, in a relatively young and fit patient with mediastinal HL. In our study, we demonstrated a significant reduction in OAR doses with DIBH compared to FB in combination with IMRT technique. Possibility of broader use of DIBH in clinical practice is currently under evaluation, and further studies are required for the same.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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