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CASE STUDY

A case study evaluating deep inspiration breath-hold and intensity-modulated radiotherapy to minimise long-term toxicity in a young patient with bulky mediastinal Hodgkin lymphoma

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Abstract

Radiotherapy plays an important role in the treatment of early-stage Hodgkin lymphoma, but late toxicities such as cardiovascular disease and second malignancy are a major concern. Our aim was to evaluate the potential of deep inspiration breath-hold (DIBH) and intensity-modulated radiotherapy (IMRT) to reduce cardiac dose from mediastinal radiotherapy. A 24 year-old male with early-stage bulky mediastinal Hodgkin lymphoma received involved-site radiotherapy as part of a combined modality programme. Simulation was performed in free breathing (FB) and DIBH. The target and organs at risk were contoured on both datasets. Free breathing-3D conformal (FB-3DCRT), DIBH-3DCRT, FB-IMRT and DIBH-IMRT were compared with respect to target coverage and doses to organs at risk. A 'butterfly' IMRT technique was used to minimise the low-dose bath. In our patient, both DIBH (regardless of mode of delivery) and IMRT (in both FB and DIBH) achieved reductions in mean heart dose. DIBH improved all lung parameters. IMRT reduced high dose (V20), but increased low dose (V5) to lung. DIBH-IMRT was chosen for treatment delivery. Advanced radiotherapy techniques have the potential to further optimise the therapeutic ratio in patients with mediastinal lymphoma. Benefits should be assessed on an individualised basis.

Introduction

Radiotherapy remains an important component of combined modality therapy (CMT) in patients with early-stage Hodgkin lymphoma (HL). CMT results in cure rates in the order of 85–93%.[1,2] These excellent cancer control outcomes, along with the young median age of patients, has increased the focus on minimising the long-term complications of therapy. Substantial risks of late effects, in particular cardiac disease and second malignancy, have been documented in patients treated with historical extended-field, high-dose radiotherapy.[3] This has motivated efforts to reduce radiotherapy dose and field size while maintaining high cure rates. Emerging evidence suggests that this approach will ultimately reduce the risk of late toxicity in HL survivors.[4,5] Radiotherapy may be omitted for selected patients with early-stage HL, however this entails a higher risk of relapse requiring intensive salvage therapies, even when guided by a negative interim positron emission tomography (PET) scan.[6]

Along with a reduction in radiotherapy field size and dose, advanced radiotherapy techniques may further reduce normal tissue exposure in patients with HL.[7] Deep inspiration breath-hold (DIBH) and intensity-modulated radiotherapy (IMRT) have been recently applied in the context of mediastinal HL, with promising early results.[8]

In this article, we describe the case of a young male with bulky mediastinal Hodgkin lymphoma treated with a combination of DIBH and IMRT, in order to illustrate the potential benefits and limitations of these techniques.

Clinical Case

The described patient provided consent for publication of this case.

A previously well 24-year-old male was diagnosed with unfavourable bulky stage IIB classical HL involving mediastinal and right hilar nodes. He presented with 1 month of fatigue, cough, drenching night sweats and weight loss. Physical examination was unremarkable.

Chest X-ray demonstrated a large mediastinal mass. A computed tomography (CT) scan of the chest showed bulky mediastinal lymphadenopathy, consistent with lymphoma. Staging PET/CT demonstrated FDG-avid mediastinal, right hilar and right internal mammary nodes, with no additional nodal or extranodal disease. Incisional biopsy of the mediastinal mass confirmed lymphocyte-depleted HL.

The recommended treatment was combined modality therapy using the German Hodgkin Study Group HD14 regimen of two cycles of escalated BEACOPP and two cycles of ABVD, followed by 30 Gy involved-site radiotherapy (ISRT).[9]

Interim PET/CT after two cycles of chemotherapy showed a complete metabolic (and partial structural) response. The patient proceeded with two further cycles of chemotherapy followed by ISRT to a dose of 30.6 Gy in 17 fractions. This was delivered during DIBH with an IMRT technique. Post-treatment PET/CT confirmed an ongoing complete metabolic response and further reduction in size of the residual soft tissue mass.

Follow-up is ongoing. Counselling was provided with regards to minimising cardiovascular risk factors and the risk of second malignancies. Avoiding smoking and the importance of sun protection were emphasised. Thyroid function will be monitored on an annual basis.

Technical Description

Simulation

The patient was simulated supine with both arms raised, immobilised with a chest board (CIVCO Medical Solutions, Orange City, IA) and arm rests. CT scans were acquired with 2 mm slice thickness from the chin to T12, during free-breathing (FB) and DIBH. Four-dimensional CT (4DCT) was acquired during FB for assessment of respiratory motion. The 4DCT dataset was generated using a 64-slice CT scanner (SOMATOM Definition AS, Siemens Healthcare, Forchheim, Germany) coupled with the Real-Time Position Management (RPM) system (Varian Medical Systems, Palo Alto, CA). The 4DCT was captured in helical mode using 120 kVp, 2 mm slice thickness, 2 mm increment and 0.47 sec rotation time, and images were reconstructed at 3 mm slice thickness. The average intensity projection was exported for target and organ-at-risk delineation. The maximum intensity projection, end-inspiration and end-expiration datasets were exported to assist with target delineation. The RPM system was also used for respiratory monitoring during DIBH. Eligibility for DIBH required a minimum 15-sec breath-hold that was reproducible over multiple attempts. This was assessed during an initial coaching session, and a comfortable breath-hold level was defined using a 5 mm (i.e $\pm$2.5 mm) gating window. Video goggles were worn by the patient to assist in achieving the desired breath-hold level during simulation and treatment delivery.

Target and organ-at-risk delineation

Targets were delineated on both the FB (4DCT) and DIBH (three-dimensional CT) datasets by a single radiation oncologist. Clinical target volumes (CTVs) were defined according to the principles of ISRT,[10] with reference to the pre- and post-chemotherapy PET/CT scans. An internal target volume (ITV) was formed on the FB 4DCT using the MIP, end-expiration and end-inspiration datasets. On both datasets, planning target volumes (PTVs) were created as 1 cm isotropic expansions of the CTV/ITV. The heart was contoured by a single radiation therapist according to published guidelines,[11] then reviewed by a single radiation oncologist. The lungs were auto-segmented. The spinal cord (bony spinal canal) was contoured from T1 to T12.

Treatment planning

Radiotherapy plans were created using XiO version 4.7 (Elekta AB, Stockholm, Sweden) for three-dimensional conformal (3DCRT) planning, and Monaco version 4.3 (Elekta AB) for IMRT planning. The PTVs were treated to a dose of 30.6 Gy in 17 fractions. 3DCRT plans consisted of anterior and posterior parallel-opposed fields, with field-in-fields used to optimise homogeneity and conformity. IMRT plans were generated using a ‘butterfly’ technique as described by Voong et al.,[12] to minimise the low-dose bath (Fig. 1). A 5-field technique was chosen with beam angles of 330°, 0°, 30°, 150° and 210°. Four plans were created: FB-3DCRT, DIBH-3DCRT, FB-IMRT and DIBH-IMRT, all by a single radiation therapist.

The treatment planning goals for targets and organs-at-risk (OARs) are shown in Table 1, and were derived from

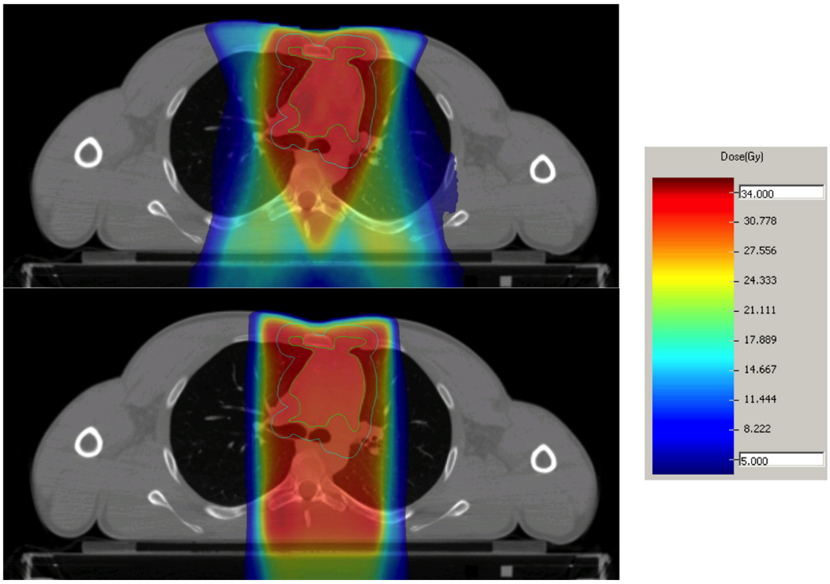


Figure 1. Axial dose wash comparing 'butterfly' intensity-modulated radiotherapy plan (top) and 3D conformal (anterior and posterior parallel-opposed) plan (bottom). Volume receiving 5 Gy or more is shown. Deep inspiration breath-hold datasets displayed, with clinical target volumes (green) and planning target volumes (cyan).

the relevant literature.[13–17] Plans were optimised aiming to keep the dose to all OARs as low as reasonably achievable while maintaining adequate target coverage. They were reviewed visually and with dose-volume histogram analysis in order to select the plan felt to offer the most favourable therapeutic ratio.

Treatment delivery and verification

The DIBH-IMRT plan was selected for treatment delivery, as described below. Treatment setup verification was performed prior to each fraction during DIBH, using orthogonal kilovoltage imaging. Image matching was based on bony anatomy (primarily vertebrae and sternum) and the carina, with a 5 mm tolerance. In addition, the RPM system was used to ensure that each breath-hold was maintained within the 5 mm gating window defined at simulation.

Results

Target doses for the four plans are shown in Table 2. All plans satisfied the prospectively defined goals for target coverage and dose homogeneity.

Comparative DVH curves and mean doses for all four plans for the heart are shown in Figure 2. Both FB plans exceeded the mean heart dose goal (<15 Gy). DIBH, when compared with FB using either IMRT or 3DCRT, resulted in a reduction in all cardiac dose parameters. Similarly IMRT, when compared with 3DCRT in either FB or DIBH, reduced most cardiac parameters (including

Table 1. Treatment planning goals.

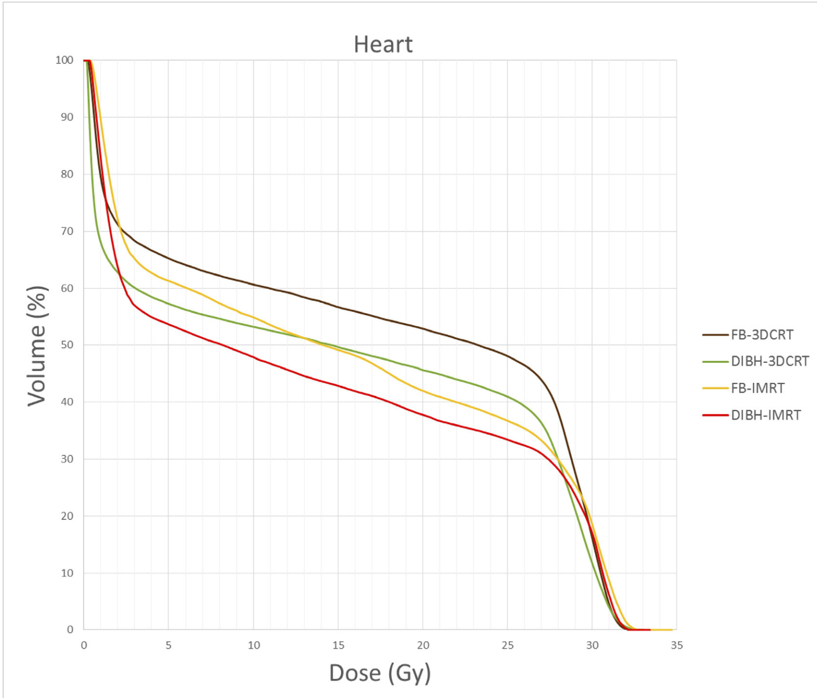
Structure	Goals
CTV/ITV	D100% > 95% (29.1 Gy)
PTV	D95% > 95% (29.1 Gy)
	D99% > 90% (27.5 Gy)
	D2% < 107% (32.7 Gy)
	Dmax < 115% (35.2 Gy)
Lungs (left plus right lung minus CTV/ITV)	V5 Gy < 55%
	V20 Gy < 30%
	Mean < 13.5 Gy
Heart	Mean < 15 Gy

CTV, clinical target volume; ITV, internal target volume; PTV, planning target volume.

Table 2. Target coverage parameters.

Technique	CTV/ITV D100% (Gy)	PTV D95% (Gy)	PTV D99% (Gy)	PTV D2% (Gy)	PTV Dmax (Gy)
FB-3DCRT	29.6	29.9	29.1	32.5	32.9
DIBH-3DCRT	29.7	29.5	28.1	32.5	33.1
FB-IMRT	29.6	30.1	29.5	32.5	34.6
DIBH-IMRT	29.8	29.9	29.1	32.4	33.2

FB, free breathing; DIBH, deep inspiration breath-hold; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy; CTV, clinical target volume; ITV, internal target volume; PTV, planning target volume.



Technique	Mean heart dose (Gy)
FB-3DCRT	17.0
DIBH-3DCRT	14.8
FB-IMRT	15.1
DIBH-IMRT	13.5

Figure 2. Dose-volume histograms and mean doses for heart. FB, free breathing; DIBH, deep inspiration breath-hold; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

mean dose) although the volume of heart exposed to very low doses (<~2.5 Gy) increased with IMRT. Compared with the 'standard' approach of FB-3DCRT, either DIBH or IMRT provided a similar reduction in mean heart dose (approximately 2 Gy, or 12%). A further approximate 1.5 Gy reduction in mean heart dose was achieved by combining DIBH and IMRT. Overall, the technique chosen for treatment delivery (DIBH-IMRT) achieved a 3.5 Gy (20.6%) reduction in mean heart dose compared with the FB-3DCRT technique.

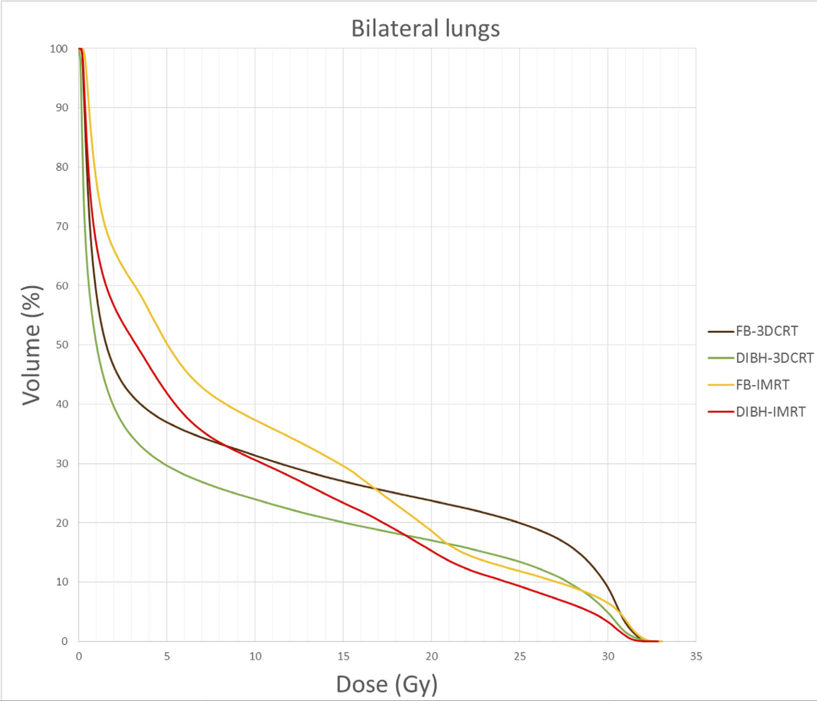
Comparative DVH curves, mean doses, V5 and V20 for all 4 plans for bilateral lungs are shown in Figure 3. All plans satisfied the treatment planning goals. DIBH, when compared with FB using either IMRT or 3DCRT, resulted in a reduction in all lung dose parameters. DIBH increased lung volume by 1950 mL (61%). IMRT, when compared with 3DCRT in either FB or DIBH, increased low doses (including V5) while reducing high doses (including V20) to lung. Mean lung dose was also higher (by 0.7–1.1 Gy) with IMRT. Compared with the 'standard' approach of FB-3DCRT, the combination of DIBH and IMRT reduced mean dose and intermediate/high dose to lung, while increasing the volume of lung exposed to low doses (<~8 Gy).

IMRT increased the total volume of tissue receiving 5 Gy or more by 819 mL (18%) and 1027 mL (22%) in FB and DIBH respectively.

Discussion

We have described a case of a young male with early-stage bulky mediastinal HL, receiving RT as a component of CMT. Using two widely available RT technologies (DIBH and IMRT), we were able to achieve a 20% reduction in mean heart dose, the dosimetric parameter best correlated with late cardiac toxicity, while maintaining optimal target coverage. To our knowledge, this is the first report in Australasia describing the combined use of DIBH and IMRT for mediastinal lymphoma, suggesting that these techniques may be underutilised in the region.

Historically, cardiovascular disease has been the predominant non-cancer cause of death in Hodgkin lymphoma survivors (relative risk (RR) 2.2–12.7), with



Technique	Mean lung dose (Gy)	Lung V5 (%)	Lung V20 (%)
FB-3DCRT	8.9	37	23.8
DIBH-3DCRT	6.8	29.7	17.1
FB-IMRT	9.6	50.3	18.7
DIBH-IMRT	7.9	41.9	15.3

Figure 3. Dose-volume histograms and selected doses for bilateral lungs. FB, free breathing; DIBH, deep inspiration breath-hold; 3DCRT, three-dimensional conformal radiotherapy; IMRT, intensity-modulated radiotherapy.

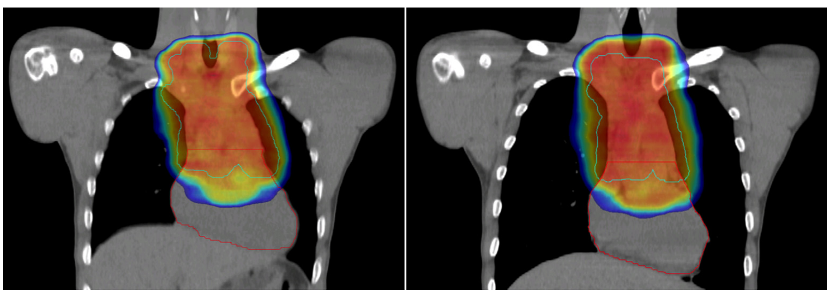


Figure 4. Coronal view of planning target volume (cyan) and heart (red) in free-breathing (left) and deep inspiration breath-hold (right). Volume receiving 15 Gy or more is shown. Intensity-modulated radiotherapy plan displayed.

mediastinal radiotherapy a major risk factor.[18] Coronary artery disease is the most common form of cardiac morbidity.[3] Although RT-related cardiac effects have been known to be dose-related for some time,[19] only recently have more detailed dose–response relationships been described.[5,20] There appears to be a linear relationship between mean heart dose and cardiovascular events without a threshold dose, similar to what has been observed in breast cancer patients.[21] According to one recent dose–response relationship, the 3.5 Gy mean heart dose reduction achieved through the use of DIBH and IMRT in our patient could be expected to reduce his risk of coronary heart disease by approximately 26%,[5] compared with a conventional FB-3DCRT technique.

Deep inspiration breath-hold is becoming a standard technique for cardiac sparing in patients with left-sided breast cancer.[22] The use of DIBH for mediastinal lymphoma has been more limited, but reports have recently emerged from a number of expert lymphoma units.[12,14,23,24] As observed in our case, DIBH reduces heart and lung doses, at all dose levels, in the majority of patients. This is achieved through elongation of the heart, resulting in greater separation from the target volume, and an increase in lung volume (Fig. 4). Some centres also apply smaller PTV margins in the context of DIBH, further accentuating the benefit. Intrafraction cardiac motion is reduced during DIBH, but its impact on cardiac dose is currently unknown and an area for future research.

The use of IMRT in mediastinal lymphoma has been described by several investigators.[7,25] As expected, IMRT improves dose conformality, while increasing the volume of tissue exposed to low doses, such as lung and breast (in females). Therefore with IMRT, unlike DIBH, a trade-off exists between an anticipated reduction in deterministic effects (e.g. cardiovascular disease, pneumonitis) and a potential increase in second malignancy risk.[26] For this reason, some centres have adopted techniques that limit the beam directions used for IMRT or volumetric-modulated arc therapy (VMAT).[12,13] We elected to use one such technique in our patient. A recent planning study suggested that IMRT may only provide additional cardiac-sparing benefit over DIBH alone in patients with large targets extending inferiorly in the mediastinum.[8] In our patient, the PTV extended anterior to the heart, and IMRT achieved a 1.3 Gy mean heart dose reduction in addition to the 2.2 Gy reduction achieved with DIBH.

Practical implementation of DIBH and IMRT in the setting of mediastinal lymphoma is relatively straightforward. These techniques are currently used in many radiotherapy departments. Patients with Hodgkin lymphoma are often young with good respiratory function, facilitating the use of DIBH. Deep-inspiration breath hold required approximately 10–20 min of coaching at simulation and prior to fraction one. It prolonged daily treatment by only a few minutes, and IMRT had minimal additional impact on treatment time. Patients with mediastinal lymphoma only account for a small proportion of departmental workload. Care needs to be taken when delineating target volumes during DIBH due to anatomical changes compared with pre-chemotherapy staging scans that are often acquired during FB. Pre-chemotherapy PET/CT scans during DIBH have been described,[24] but may not be feasible in many departments. Our treatment verification protocol relied on the RPM device and daily kilovoltage imaging. Cone beam CT during DIBH, acquired over multiple breath holds, is feasible[14] and can be considered for additional soft tissue verification.

In conclusion, the use of advanced radiotherapy technology (DIBH and IMRT) has the potential to reduce cardiac dose and thus long-term morbidity from RT in patients with mediastinal lymphoma. The available literature suggests that not all patients benefit, and some may be disadvantaged, by use of these techniques and an individualised approach is recommended.[7] When using IMRT, attention should be paid to the low-dose bath. In the future, decision-support tools may assist in quantifying risks and benefits of different dose distributions to further inform physician and patient decision making.[27]

Conflict of interest

The authors have no conflict of interest to declare.

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