Title

The effect of deep inspiration breath hold (DIBH) Intensity-Modulated Radiation Therapy (IMRT) on sparing healthy tissues in the treatment of lymphoma involving the mediastinum

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Abstract

Survivors of Hodgkin's lymphoma have an increased risk of developing secondary malignancies and cardiovascular disease. This risk is directly correlated to the amount of radiation exposure and is significant even with the use of modern radiation therapy modalities. Deep inspiration breath hold (DIBH) techniques have been shown to lead to the delivery of lower amounts of radiation to organs at risk (OARs) during the treatment of breast cancer and Hodgkin's lymphoma. In this study, we evaluated the ability to DIBH techniques to decrease the amount of radiation exposure of OAR in 16 consecutive patients presenting to our cancer center for treatment of early stage mediastinal lymphoma. We determined that the amount of radiation delivered to the heart was significantly lower with DIBH techniques compared to conventional free breathing. In addition, the coronary arteries and aortic valve received less than half of the radiation when DIBH was used. Smaller lung volumes were exposed to low dose radiation (V5) with breath holding compared to free breathing as well. These findings are consistent with previous reports and suggest that utilizing DIBH could greatly decrease the radiation exposure of OAR and decrease the long-term complications young cancer survivors face.

Introduction

Currently combined chemo and radiation therapy is the standard of care in patients with early stage Hodgkin's disease achieving 10-year survival rates of 90% and disease free survival of over 40 years after initial remission [1-3]. The long disease free survival and the relatively young age of the patient population with Hodgkin's and non-Hodgkin's lymphoma make it imperative to consider the long terms sequelae of treatment and ways to reduce its associated morbidity.

Radiation therapy in particular is associated with long term complications such as secondary neoplasms in addition to cardiac toxicity [4,5]. Historically, the 25 year risk of developing a secondary malignancy following lymphoma treatment has been estimated at over 20%, with certain cancers, such as lung, thyroid, breast directly attributable to radiation treatment [4,6,7]. Cardiac toxicity after chest radiation therapy is also common, affecting the myocardium, pericardium, valves, and coronary vasculature [5]. Of these, radiation therapy induced coronary artery disease is the most notable, leading to increased risk of death due to ischemic heart disease [8]. The detrimental effects on surrounding tissues have been directly correlated to the dose of radiation received, so decreasing the radiation delivered to surrounding structures will diminish the incidence and the gravity of these morbidities [9-11]

Deep inspiration breath hold techniques have been utilized in the treatment of breast cancer and have been reported to significantly lower the radiation dose delivered to the lungs and heart [12,13]. Recent reports demonstrated that the DIBH approach could also be useful in the treatment of Hodgkin's disease, delivering lower doses to the lungs and the heart [14,15]. Our study aims to examine DIBH-based treatment plans in our cancer center population and evaluate the potential sparing of cardiac and lung tissue. We will further calculate the exposure of critical cardiac structure such as the coronary arteries and heart valves, which likely correlates with the long term cardiovascular risk of this patient population.

Material and Methods

Patients:

16 consecutive patients with early stage mediastinal lymphoma who presented to our Radiation Oncology department were included in this study. Patients were previously diagnosed with either Hodgkin's lymphoma or diffuse large B-cell lymphoma (DLBCL) and had undergone disease appropriate chemotherapy treatment. All patients were referred for consolidation radiation therapy.

Simulation and Treatment Procedures:

Prone CT simulation scans were obtained on TrueBeam (Varian) after contrast infusion in (5mm) slices. Two simulation scans were obtained for each patient, one scan while the patient was breathing freely and one with deep inspiration breath hold (DIBH). Patients were instructed to take a deep breath and hold the position for as long as they could. During treatment patients were similarly instructed. Their breathing pattern was monitored with visionRT technology (Varian) and treatment was stopped if the patient exhaled. Treatment was continued when deep inspiration was achieved again.

Delineation of the target and organs at risk:

Contouring was performed according to Radiation Therapy Oncology Group guidelines utilizing a involved node radiation therapy concept [16]. In short, gross tumor volumes (GTV) were defined as the length of the tumor pre-chemotherapy treatment with the width conformed to healthy tissues, but including all involved lymph node beds. PET scans were used when available to further delineate the GTV. Clinical target volumes (CTV) for the FB-CT simulation scans included all of the GTV with 15mm cranio-caudal margins added, unless abutting the heart when the margins were decreased to 5mm. CTV for DIBH-CT simulations included GTV with no additional cranio-caudal margins, due to the precision of the on-treatment monitoring and lack of breathing motion artefacts. All CTVs were conformed to existing anatomy and body contours. The planning target volume (PTVs) were obtained by adding 3mm margin to to CTV in both FB and DIBH scans for image modulated radiation therapy (IMRT) planning and 5mm for 3D radiation therapy planning. All PTVs were conformed to body contours.

Contoured organs at risk (OARs) included the lungs and heart. All organs were contoured according to RTOG 1106 OAR atlases [17]. Coronary anatomy was contoured according to previously validated heart atlas guidelines [18]. Coronary vessels, including the left anterior descending artery (LAD), left circumflex (LCx), and right coronary artery (RCA) were contoured jointly and were followed distally as much as contrast enhancement allowed. Care was taken to ensure that DIBH and FB coronary vessels were contoured to comparable caudal levels.

Treatment planning:

Treatment plans were generated using Eclipse Treatment Planning system (Varian) for TrueBeam Linear Accelerator (Varian). The prescription dose varied from 20Gy to 45Gy. Two Rapid Arc plans (IMRT) and two Anterior Posterior plans (APPA) were calculated for each patient: one for FB and one for DIBH. In the design of the IMRT treatment plans, four to six equidistant coplanar beams were used with the normalization based on the volume of the PTV.

For the APPA plans, parallel opposed static fields were used with a 1cm MLC block margin assigned to the PTV APPA. Dose constraints were assigned to the PTV, cord, esophagus, and the heart. The goal was to deliver >95% of the prescribed dose to >90-95% of the PTV. The PTV under-coverage, defined as the percentage of the PTV not encompassed by the 95% isodose line, was <5%. The maximum tolerated dose was 115% of the prescribed dose. The dose constraints for the OARs included a mean lung dose <14 Gy, the lung V20 <35%, and a mean heart dose <20 Gy. Normalization was done at the isocenter of the fields, which was the center of the PTV with the weighting adjusted to provide more anterior coverage to the PTV.

Data analysis:
Dose-volume histograms for each patient were obtained from Eclipse (Varian) and the four plans (DIBH-IMRT, DIBH-APPA, FB-IMRT, FB-APPA) were compared. For the heart, mean heart dose (Dmean), and V5Gy, V50Gy we calculated. For the lungs, V5Gy, V20Gy, and Dmean were determined. For the coronary arteries and the aortic valve, Dmean was calculated. Statistical analysis was performed using Excel (Microsoft Office) and Prism (GraphPad).

Results

Patient Characteristics	
Average Age (years)	**28.5**
Median Age (years)	**26.5**
Women (%)	**62.5**
Men (%)	**37.5**
Stage I (%)	**12.5**
Stage II (%)	**87.5**
Hodgkin's Lymphoma (%)	**81.25**
Diffuse large B-cell Lymphoma (%)	**18.75**
Bulky disease (%)	**68.75**
3 or more lymph node basins involved (%)	**81.25**
Non-favorable (%)	**81.25**

Table 1: Patient characteristics

The patients in our study were predominantly female with average age of 28.5 years (Table 1). The majority of the patients had bulky (69%), unfavorable disease (81%), involving at least three nodal basins (81%) (Table 1). 67% of patients achieved complete or near complete remission after 4 cycles of chemotherapy and with the exception of four patients were treated with 3060cGy in 17 fractions. One of the four patients who did not undergo standard therapy, one was only treated to 20Gy, after achieving complete remission after 2 cycles of chemotherapy. One patient was treated to 30Gy in 15 fractions prior to homologous stem cell transplant. The third patient received 36Gy in 24 fractions for unfavorable bulky disease. The last patient received the standard 3060cGy in 17 fractions followed by 1440cGy in 8 fractions for residual disease.

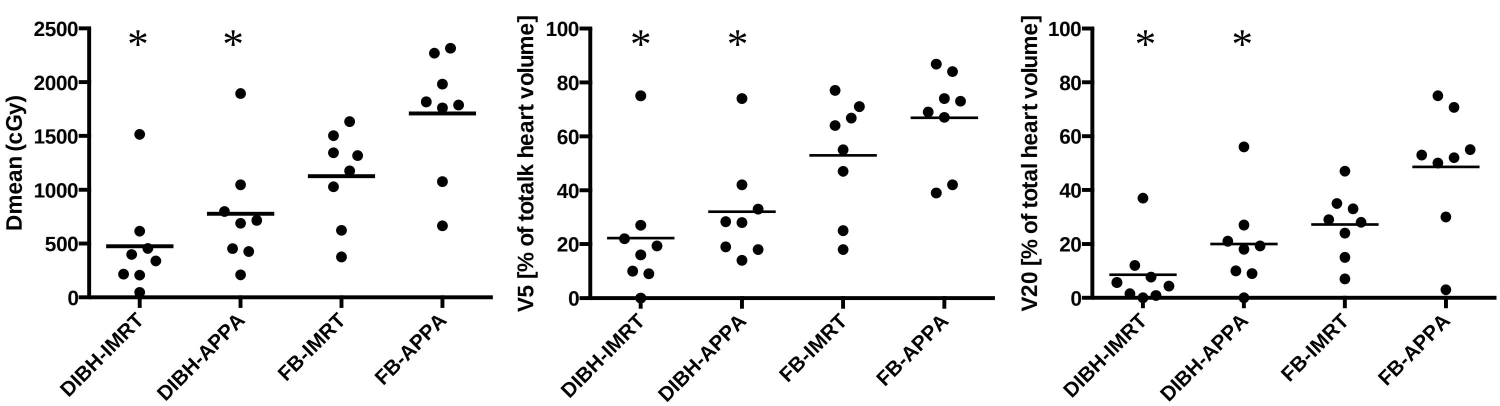

Figure 1. Heart radiation exposure utilizing different breathing techniques and planning modalities. ***A.*** Mean dose delivered to lung tissue ***B.*** Lung volume exposed to 5Gy of radiation (V5). ***C.*** Lung volume exposed to 20Gy of radiation (V20). DIBH-IMRT and DIBH-APPA plans were compared to FB-IMRT plans using paired t-tests, * represents p<0.05.

For each patient four different plans were calculated – two utilizing deep inspiration breath hold technique and two with free breathing with IMRT and APPA plans created for both breathing modalities. DIBH plans delivered significantly decreased mean doses to the heart with Dmean of 474.5cGy (DIBH-IMRT) and 779.0cGy (DIBH-APPA), compared to the free breathing plans with 1125.6cGy (FB-IMRT) and 1709.3cGy (FB-APPA) (Fig. 1A). In addition, the volume of cardiac tissue exposed to low dose radiation was also significantly diminished (Fig. 1B). DIBH-IMRT plans delivered 500cGy to about 22% of the total heart volume whereas FB-IMRT plans delivered 500cGy to 53% of the cardiac tissue (Fig. 1B). The volume of myocardium receiving 2000cGy of radiation was also decreased in the DIBH plans with less than 9% on average of the myocardium exposed to 2000cGy of radiation in the DIBH-IMRT plans compared to an average of 27% in the FB-IMRT plans.

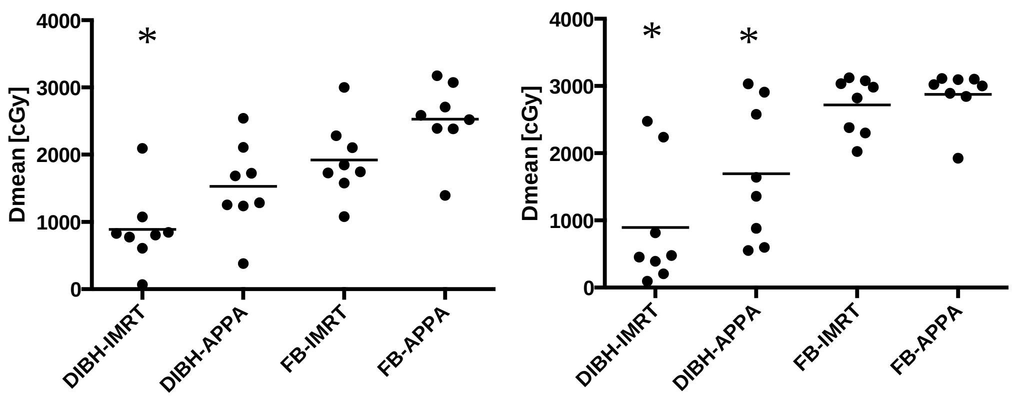

Figure 2. Mean radiation dose (Dmean) to organs at risk using different breathing techniques and planning modalities. *A.* Mean radiation dose to the coronary arteries ***B.*** Mean radiation dose to the aortic valve. DIBH-IMRT and DIBH-APPA plans were compared to FB-IMRT plans using paired t-tests, * represents $p<0.05$.

In addition, specific cardiac substructures such as the coronary arteries and the aortic valve also received reduced mean doses of radiation (Fig. 2). The coronary arteries in DIBH-IMRT plans received on average Dmean of 888cGy, DIBH-APPA plans -1528Gy, FB-IMRT 1921cGy and DIBH-APPA – 2529cGy (Fig 2A). Similar trend is present within the average dose delivered to the aortic valve with average Dmean for DIBH-IMRT plans of only 894cGy, compared to average Dmean of 1694cGy for DIBH-APPA plans, 2718cGy for FB-IMRT plans, and 2874cGy for FB-APPA plans.

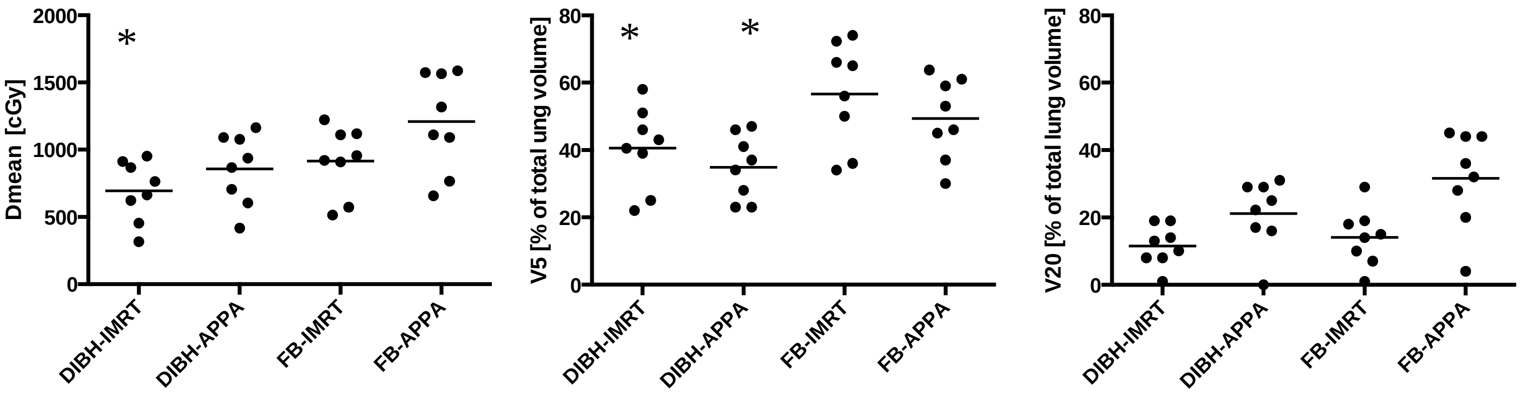

Figure 3. Lung radiation exposure utilizing different breathing techniques and planning modalities. ***A.*** Mean dose delivered to lung tissue ***B***. Lung volume exposed to 500cGy of radiation (V5). ***C***. Lung volume exposed to 2000Gy of radiation (V20). DIBH-IMRT and DIBH-APPA plans were compared to FB-IMRT plans using paired t-tests, * represents p<0.05.

Mean dose of lung exposure for DIBH-IMRT plans is also significantly lower than FB-IMRT plans (p=0.003) (Fig.3A). The volume of lung tissue receiving low dose radiation is significantly decreased in the DIBH-IMRT plan compered to the FB-IMRT plan (Fig. 3B), however the volume receiving 2000cGy is comparable between the DIBH and FB plans (Fig. 3C).

Discussion:

Late toxicities following radiation therapy are of significant concern especially in younger patients [4, 5]. In addition to secondary malignancies, heart disease has been a major focus with risk of cardiovascular disease, which starts to increase as soon as treatment is completed and continues to rise continuously over time [19]. Given the increase in risk factors for coronary artery and valvular disease in the general population, it is increasingly important to diminish radiation exposure of the myocardium.

Historically lymphoma treatment guidelines have changed to reflect the decreased size of treatment fields and dosing, with certain early stage lymphomas requiring chemotherapy alone [20]. However, when shrinking of the field and dose is no longer plausible, DIBH techniques may allow further sparing of organs at risk. In this report we demonstrate that coupling of DIBH with IMRT delivers significantly reduced dose to the heart and lungs. The benefit of DIBH is two fold – tumor immobilization and OAR displacement. Tumor immobilization allows greater targeting precision and smaller planning margins exposing less healthy tissue to unnecessary radiation regardless of tumor position or morphology. In addition, the heart is displaced inferiorly allowing patients with upper mediastinal tumors to benefit even further from DIBH based treatment plans. These benefits are well reflected in our results with some patients deriving great benefit from DIBH plans and some with only minimal improvement, however no patient doing worse when DIBH techniques are utilized. In addition, the DIBH simulations scans were easily obtained with no significant difficulties for patients to maintain deep inspiration during simulation or treatment. No significant additional time was required during daily treatment.

Multiple late cardiac toxicities are present in cancer survivors with congestive heart failure (CHF) being one of the most common due to the combined effects of chemotherapy and radiation [19]. Nevertheless, coronary artery disease is also prevalent [19]. Since the latent effects of radiation increase with time and patients accumulate more cardiovascular risk factors with age, coronary artery sparing is essential. Our study demonstrated that all patients received lower Dmean when DIBH plans were used (Fig.2A). Exposure of the aortic valve was used as a marker for all heart valves and was more dependent on tumor location with DIBH plans either comparable or significantly lower than FB plans (Fig. 2B). This is due to the very small volume of the valve and its central location.

In conclusion, our study is consistent with prior work and demonstrates the ability of DIBH plans to provide significant sparing of OAR even in a population with predominantly bulky, unfavorable disease. Utilization of DIBH disease in early stage mediastinal lymphoma coupled with excellent in treatment monitoring would allow us to diminish unnecessary radiation exposure and potentially improve cancer survivors long term outcomes.

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