



# Decreased heart dose with deep inspiration breath hold for the treatment of gastric lymphoma with IMRT

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## ABSTRACT

We hypothesized that deep inspiration breath-hold (DIBH) and computed-tomography image-guided radiotherapy (CT-IGRT) may be beneficial to decrease dose to organs at risk (OARs), when treating the stomach with radiotherapy for lymphoma. We compared dosimetric parameters of OARs from plans generated using free-breathing (FB) versus DIBH for 10 patients with non-Hodgkin lymphoma involving the stomach treated with involved site radiotherapy. All patients had 4DCT and DIBH scans. Planning was performed with intensity modulated radiotherapy (IMRT) to 30.6 Gy in 17 fractions. Differences in target volume and dosimetric parameters were assessed using a paired two-sided *t*-test. All heart and left ventricle parameters including mean dose, V30, V20, V10, and V5 were statistically significantly lower with DIBH. For IMRT-FB plans the average mean heart dose was 4.9 Gy compared to 2.6 Gy for the IMRT-DIBH group ( $p < 0.001$ ). There was a statistically significant decrease in right kidney dose with DIBH. For lymphoma patients treated to the stomach with IMRT, DIBH provides superior OAR sparing compared to FB-based planning, most notably reducing dose to the heart and left ventricle. This strategy could be considered when treating other gastric malignancies.

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## 1. Introduction

The gastrointestinal tract is a common location for extranodal involvement of Non-Hodgkin lymphoma (NHL) [1]. Radiotherapy (RT) is used for definitive management of low grade extranodal marginal zone lymphoma (MALT), or as consolidation after chemotherapy for high-grade NHL (i.e. diffuse large B-cell lymphoma [DLBCL]). Radiotherapy to the gastrointestinal tract can be challenging due to variations in target anatomy related to bowel filling and breathing motion that may necessitate larger margins with expanded target volumes [2]. This can lead to higher doses to organs at risk (OARs), increasing the toxicity risk.

The proximity of the stomach to the diaphragm leads to variable gastric motion with breathing [3–5]. With advanced RT techniques including respiratory management and daily CT image-guided radiotherapy (CT-IGRT), target volumes can be safely

reduced [6]. There is evidence that deep-inspiratory breath-hold techniques may permit reduced dose to OARS for gastric tumors [7,8]. In gastric lymphoma, the target is the intact stomach and we hypothesized that DIBH leads to reduced dose to OARs through improved spatial separation between the heart and stomach, while simultaneously allowing for reduced target volumes. We examined dosimetric parameters for target volumes and OARs comparing 4-dimension computed tomography (4DCT) planning technique to DIBH for gastric RT.

## 2. Methods

After Institutional Review Board approval, we identified patients  $\geq 18$  years old, with gastric NHL treated between 2011 and 2015 with 4DCT and DIBH scans available.

Our institutional practice is to treat gastric NHL patients using IMRT with DIBH. A series of 3 – 4 breath hold scans are acquired at time of simulation to ensure reproducibility and for internal target volume (ITV) gastric generation. Typically a 1 cm planning target volume (PTV) expansion on the DIBH ITV-stomach is utilized for planning when daily CT is performed for image guidance [9].

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IMRT plans with 5–7 6-MV photon beams were created with the Pinnacle Treatment Planning System (Philips Medical Systems, WI). For a typical treatment, 1–2 breath holds are required to deliver each field. To minimize inter-fractional variations in gastric filling, patients fast  $\geq 6$  h before therapy and ideally are treated in the morning after an overnight fast. Daily CT-IGRT is paramount to ensure target coverage while minimizing PTV margins [6].

In an effort to evaluate dosimetry to OARS reflective of modern RT, patients were planned per the above institutional standards. All plans were created with a prescription dose of 30.6 Gy in 17 fractions. Target volumes included: clinical target volume (CTV, defined as the entire stomach from the gastro-esophageal junction to the pylorus), ITV (CTV contoured on all phases of the 4DCT scan or multiple DIBH scans) and PTV (ITV + 1 cm uniform expansion). We utilize an ITV approach with multiple breath hold scans as there can be motion between repeated breath hold scans, which helps account for inter-fractional variation in day-to-day stomach position. This approach can also potentially account for intra-fractional motion since multiple breath holds are required to deliver one fraction of RT. We mandated 95% coverage of the PTV by 100% of the prescription dose. OARs included the heart, left ventricle (LV), left and right kidneys, and liver. Cardiac contours were based on an accepted atlas [10]. Priority was placed on PTV coverage and cardiac sparing. For IMRT treatment planning a minimum of 6 beam angles were used.

To compare dose and volume between regions of interest for each patient, paired *t*-tests were performed, with  $p < 0.05$  considered statistically significant. We examined multiple dosimetric parameters (i.e. V5 [volume of given organ receiving 5 Gy], V10, V20, V30, mean dose, and actual volume of the ITV-stomach, PTV, heart, LV and overlapping volume of the total heart and ITV stomach contour). Statistical analyses were performed with IBM SPSS Statistics, Version 24 (IBM, NY, USA).

### 3. Results

We identified 10 NHL patients (MALT,  $n = 5$ ; DLBCL,  $n = 5$ ) with 4DCT and DIBH scans available. The contoured volume of the LV,

heart, stomach, PTV, and overlap between the PTV and heart, were all significantly less with DIBH compared to 4DCT (Table 1). Overall, the ITVs for DIBH compared to 4DCT plans were smaller. Maximum differences (anterior/posterior, right/left and superior/inferior) for ITV generation for DIBH and 4DCT plans are compared in Supplementary Table 1. The median differences in any direction for multiple DIBH scans was  $\leq 7$  mm, while the median differences in any direction for 4DCT scans (compared to free breathing) was  $\geq 11.5$  mm. PTV coverage was similar between planning techniques (DIBH, 96.4%; 4DCT, 95.6%;  $p = 0.19$ ). Fig. 1 shows a coronal CT image of a patient with 4D-CT based planning compared to DIBH. DIBH technique allowed for a significant reduction in all heart and LV parameters measured, as well as a reduction in dose to the right kidney (Table 1). Mean heart dose (MHD) for the DIBH plans was 2.6 Gy (Range: 1.3–4.3 Gy), compared to 4.9 Gy for 4DCT plans (Range: 3.6–7.1 Gy). The range of reduction (dose with 4DCT – dose with DIBH) varied from 0.4–4.6 Gy for MHD, and 0.2–6.3 Gy for mean LV dose. There was no significant difference in dose to the liver or left kidney between techniques. Every patient had improvement in heart and LV dose on the DIBH plan compared to the 4D plan (Fig. 2). Average dosimetric parameters for the total heart and LV dose according to planning technique for all patients are shown in Fig. 3.

### 4. Discussion

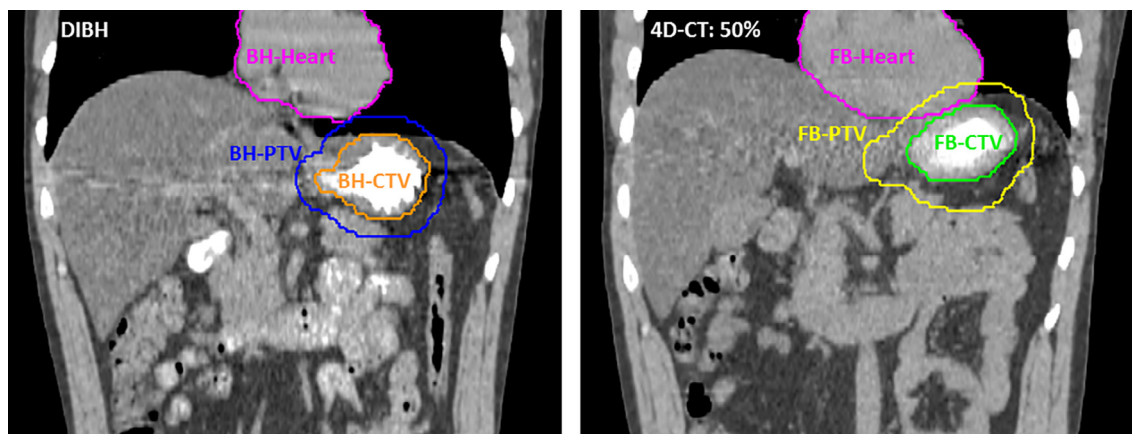
In the current study we evaluated the impact of DIBH on the dosimetry of OARs among patients receiving gastric RT for NHL. DIBH permitted dose reduction to the heart for all patients in addition to decreased doses to the right kidney. This data suggests DIBH should be used for RT to the stomach when maximal cardiac sparing is desired.

When targeting abdominal structures, oncologists may overlook the potential for RT dose to impact neighboring thoracic structures. Available literature on cardiac doses for gastric RT planning is lacking; comparable series have not reported volumetric parameters for the heart or substructures [8,11,12]. In a free breathing

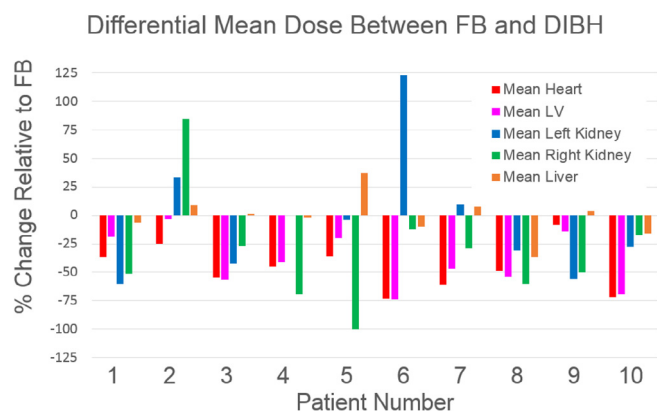
**Table 1**  
Dosimetric parameters based on planning technique.

Planning Parameter	4D (Mean $\pm$ SD)	DIBH (Mean $\pm$ SD)	Absolute Difference (4DCT – DIBH)	P value
<i>Heart</i>				
Mean Heart (Gy)	4.9 $\pm$ 1.1	2.6 $\pm$ 0.9	2.4	<0.001
V30 Heart (%)	2.7 $\pm$ 1.7	0.9 $\pm$ 1.1	1.8	0.007
V20 Heart (%)	7.6 $\pm$ 3.2	3 $\pm$ 1.94	4.6	0.001
V10 Heart (%)	15.3 $\pm$ 4.6	7 $\pm$ 4.	8.3	0.004
V5 Heart (%)	25.2 $\pm$ 5.6	11.8 $\pm$ 7.9	13.4	0.001
<i>Left Ventricle</i>				
Mean LV (Gy)	6.7 $\pm$ 2.0	3.9 $\pm$ 1.7	2.8	0.002
V30 LV (%)	3.9 $\pm$ 3.2	1.8 $\pm$ 2.2	2.1	0.045
V20 LV (%)	11.3 $\pm$ 5.7	5.3 $\pm$ 4.1	6	0.008
V10 LV (%)	20.5 $\pm$ 6.6	11 $\pm$ 7.2	9.5	0.008
V5 LV (%)	32.9 $\pm$ 10.3	16.4 $\pm$ 9.2	16.5	0.001
<i>Kidney</i>				
Left Kidney Mean (Gy)	4.3 $\pm$ 2.4	4.0 $\pm$ 3.2	0.3	0.735
Left Kidney V5 (%)	28.3 $\pm$ 13.1	28.1 $\pm$ 30.8	0.2	0.981
Right Kidney Mean (Gy)	3.2 $\pm$ 1.6	2.1 $\pm$ 1.3	1.3	0.015
Right Kidney V5 (%)	22.7 $\pm$ 15.3	10.7 $\pm$ 11.5	12	0.047
<i>Liver</i>				
Liver Mean (Gy)	9.4 $\pm$ 0.8	8.3 $\pm$ 3.5	1.1	0.340
Liver V30 (%)	6 $\pm$ 1.9	6.0 $\pm$ 2.7	–0.04	0.970
<i>Target Volume</i>				
Stomach (cc)	399 $\pm$ 151	309 $\pm$ 101	90	0.012
PTV (cc)	935 $\pm$ 267	770 $\pm$ 196	165	0.011
Heart (cc)	802 $\pm$ 187	734 $\pm$ 177	68	0.007
Left ventricle (cc)	248 $\pm$ 71	221 $\pm$ 63	27	0.045
Overlap* (cc)	26.5 $\pm$ 16.8	5.9 $\pm$ 7.6	20.5	0.002

Abbreviations: SD, standard deviation; V30, volume receiving 30 Gy; V20, volume receiving 20 Gy; V10, volume receiving 10 Gy; V5, volume receiving 5 Gy; LV, left ventricle; cc, cubic centimeter; PTV, planning target volume; overlap\*, overlap of the stomach ITV and total heart contours.



**Fig. 1.** Coronal image showing the difference in target volume and heart position for DIBH technique (left panel) compared to planning using a 4D-CT technique (right panel) for the same patient. For image clarity the stomach CTV was contoured on the 50% phase of the 4D-CT. Abbreviations: DIBH, deep inspiratory breath hold; 4DCT, 4-dimension computed tomography; PTV, planning target volume; CTV, clinical target volume.



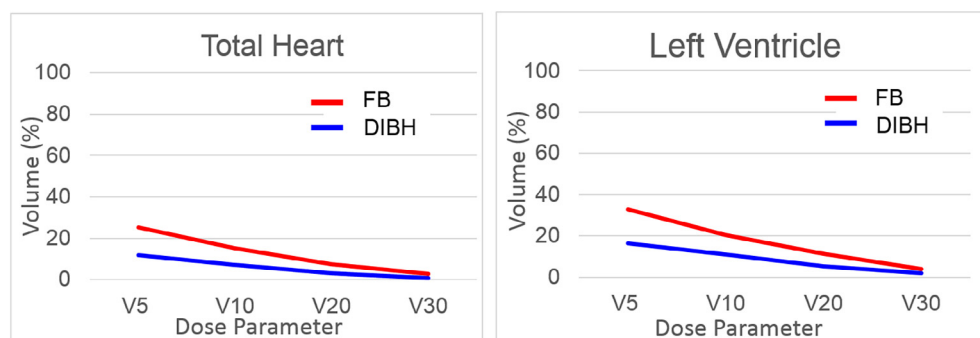
**Fig. 2.** Bar plots of percent differences in mean doses to the heart, LV, right kidney, left kidney, and liver for DIBH relative to FB. Negative values (downward bars) indicate a mean dose reduction (and improvement) for DIBH versus FB. Positive values (upward bars) indicate a mean dose increase (and worse) for DIBH versus FB. Abbreviations: 4DCT, 4 dimensional computed tomography; DIBH, deep-inspiratory breath hold; LV, left ventricle.

(FB) state, the LV abuts the fundus of the stomach; DIBH allows for physical separation between the base of the heart and the stomach. Ionizing radiation can cause late cardiac morbidity, which may be amplified in the presence of cardiotoxic systemic therapy [13–15]. Minimizing radiation heart exposure is critical to mitigate risks of late cardiac events for NHL patients treated with combined modality therapy. For patients with low grade histologies treated with RT alone, it remains equally important to reduce heart dose given the

excellent prognosis and expected long term survival. In the current study, using DIBH, IMRT and CT-IGRT resulted in an average MHD of 2.6 Gy, and mean LV dose of 3.9 Gy, which even by pediatric and Hodgkin lymphoma survivorship studies are considered low [16–18]. Indeed in a study by the International Extranodal Lymphoma Study Group (IELSG) of 102 gastric MALT lymphoma patients treated between 1981 and 2004 with involved field or whole abdominal RT, 8 patients died of cardiovascular causes [19]. In that study the influence of RT on the cardiovascular deaths is unclear, however it is essential to limit potential treatment related toxicity as much as possible.

A recent study has also demonstrated the dosimetric benefits of DIBH when coupled with modern RT targeting. Choi et al. compared the dosimetry of 3D, tomotherapy, IMRT and volumetric-modulated arc therapy (VMAT) planning for patients with gastric MALT, using FB and DIBH [8]. In their study the IMRT DIBH plans were superior to IMRT FB plans, with lower RT doses to the liver, heart and lung. The MHD was reduced by roughly half with a MHD of 3.6 Gy for the DIBH-IMRT plans compared to 7 Gy for the IMRT-FB plans. Taken together, this study and our current work underscore the ability of DIBH to reduce cardiac RT exposure compared to FB. Using techniques such as prolonged fasting period and high-quality daily imaging may allow for even further MHD, as shown in our study.

Determination of optimal PTV margins can be challenging in the treatment of the stomach with RT, however appropriate PTV expansions are essential for local control while minimizing OAR doses. A study examining PTV margins in gastric lymphoma patients determined that a uniform 2.2 cm margin was required



**Fig. 3.** Comparison of dose volume parameters for 4DCT (red) compared to DIBH (blue) for total heart and left ventricle. Abbreviations: 4DCT, 4 dimensional computed tomography; DIBH, deep-inspiratory breath hold; V5, volume receiving 5 Gray; V10, volume receiving 10 Gray; V20, volume receiving 20 Gray; V30, volume receiving 30 Gray. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

for patients treated in FB with imaging alignment to bony anatomy [4]. DIBH can help limit inter-fractional respiratory motion in the abdomen [7]. Daily CT imaging is also important to consider in PTV generation. Indeed among 12 patients treated to the stomach with DIBH and IMRT, PTV margins of 1 cm were adequate with daily CT image guidance. However, with bony x-ray based alignment, PTV coverage suffered when 1 cm margins were used [6]. In the current study we utilized diet modification, DIBH, daily CT imaging and a PTV margin of 1 cm. We also use the strategy of multiple DIBH scans to generate a sufficient stomach ITV, which ultimately allows for smaller isotropic PTV expansions. With this approach doses to organs at risk were low. This technique has been used at our institution and yields excellent local control rates [9]. It is important to recognize however that in the absence of extended fasting times and high-quality daily CT – IGRT, larger PTV margins are likely required.

DIBH may provide cardiac sparing for the treatment of other gastric cancers. As with NHL, cardiac dosimetric studies for adjuvant RT for gastric adenocarcinoma are lacking [7]. Patients with primary gastric adenocarcinoma may be treated with cardiotoxic systemic therapies, thus minimizing RT cardiac dose again seems intuitively beneficial [20,21]. While the prescription doses used for adenocarcinoma are  $\geq 50$  Gy, we suspect a similar trend could be observed (relative reduction in mean cardiac and left ventricle dose by 40–50%) when moving from 4DCT planning to DIBH with CT-IGRT.

Limitations of this study are inherent to any dosimetric study. Moreover, while OAR dose reduction with DIBH was demonstrated, we cannot confirm that the dosimetric benefits would result in reduced toxicity incidence. Additionally, planning techniques and PTV expansions are institution dependent, and these OAR doses may not be achievable without daily CT-based IGRT. Despite these limitations, this study shows benefit of utilizing DIBH for patients with gastric NHL and highlights the benefit of cardiac sparing.

## 5. Conclusions

This study confirms that DIBH allows for improved cardiac and renal sparing for patients undergoing radiation to the stomach, without compromising target coverage or increasing dose to other OARs. This technique can be safely used in patients with gastric NHL with daily CT-IGRT and may be beneficial when treating other gastric histologies as well.

## 6. Data sharing statement

Research data are stored in an institutional repository and will be shared after clearance by our institutional IRB and upon request to the corresponding author.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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