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Original Research Article

A phase 2 trial of deep-inspiration breath hold in radiotherapy of gastric lymphomas

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ABSTRACT

Background and purpose: Radiotherapy (RT) is an important part in the treatment of gastric lymphomas and the prognosis after radiotherapy is very good with a good chance of long-term survival, so prevention of long-term adverse effects is important. In patients with gastric lymphomas cardiac late effects are of most concern. The aim of this study was to assess if the dose to the heart could be reduced with deep inspiration breath-hold (DIBH) without compromising the dose to the target or increasing the risk of other late effects.

Methods and patients: Fifteen patients with gastric lymphoma were included. RT plans were made using DIBH and Free breathing (FB) scans. Clinical target volume (CTV) was the stomach plus 1 cm margin. The heart and surrounding organs at risk (OAR) were contoured. Two sets of plan comparisons were made, one with 1 cm CTV to planning target volume (PTV) margin in both DIBH and FB and one set with an additional 5 mm CTV to PTV margin in cranio-caudal direction with FB. Datasets were analysed with Wilcoxon signed rank test for non-parametric paired data.

Results: All patients tolerated the procedures and were treated with volumetric arc therapy technique in DIBH. Target coverage was kept equal between FB and DIBH, while a statistically significant reduction of the estimated does to the heart was seen with DIBH. Median mean heart dose was reduced from 7.1 Gy (5.7–12) to a median of 3.2 Gy (1.2–7.0) and heart V20 from a median of 54 (17–106) cm^3 to 15. (0.0–78) cm^3. The estimated mean doses to the liver, duodenum, pancreas and spinal cord were at the same level.

Conclusion: This clinical trial of RT with DIBH for gastric lymphomas showed that the heart dose could be reduced without compromising PTV coverage. The doses to abdominal OARs were similar with FB and DIBH.

1. Introduction

Radiotherapy is an important part of the curative treatment of localized extranodal lymphomas in the stomach, either as the single treatment modality in indolent gastric lymphomas or as part of combined modality therapy of aggressive gastric lymphomas [1–3]. Prevention of long-term radiation side-effects after radiotherapy is important in these patients with an excellent outcome after radiotherapy with a very good chance of long overall survival. Most patients with gastric lymphomas are older than 60 years of age, so late effects as second cancers are of less concern than cardiac late effects [4].

Modern radiotherapy is usually executed using 3-D conformal or intensity modulated radiotherapy techniques (IMRT or volumetric modulated arc therapy (VMAT)). The treatment is planned and delivered with the patient fasting to keep the stomach as empty as possible in order to standardize positioning and to treat the smallest possible volume.

The respiration causes internal variations of the shape and position of the organs in the upper abdomen during the treatment fractions. The stomach, in particular, moves substantially, especially in the cranio-caudal direction [5,6]. Therefore, an extra margin must be added to the clinical target volume (CTV), which consists of the stomach and the perigastric lymph nodes, to ensure that the CTV is treated to the intended dose.

The extra margin to account for the internal movements will cause extra radiation dose to the surrounding organs in the upper abdomen and consequently increase the risk of side-effects e.g. gastro-intestinal toxicity due to increased bowel dose and late effects such as cardiovascular disease, diabetes and secondary cancer. Therefore, the dose to the surrounding structures must be reduced as much as possible.

One strategy to reduce internal movements is to use deep inspiration breath-hold (DIBH) during treatment. DIBH has been shown to reduce

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Table 1
Patient characteristics.

ID	Age	Histology	Stage	Pr Chemotherapy	Total Dose Gy	Gy/Fr	Radiotherapy technique	Prefered plan	Local relaps
1	81	MCL	Stomach relaps	8 X R-CHOP	24	2	VMAT	DIBH	Local relaps
2*	72	DLBCL	1EA	6 × R-CHOP	36	2	VMAT	DIBH	NED
3	63	MZL	1EA	Rituximab	24	2	VMAT	DIBH	CR
4	82	MZL	1EA	Helicobact AB	24	2	VMAT	DIBH	CR
5	62	MZL	1EA	0	24	2	VMAT	DIBH	Dead, NED
6	51	MZL	1EA	0	30	2	VMAT	DIBH	CR
7	54	MZL	1EA	0	24	2	VMAT	DIBH	CR
8	76	MZL	1EA	0	24	2	VMAT	DIBH	CR
9	61	MZL	1EA	Helicobact AB	24	2	VMAT	DIBH	CR
10	59	FL	1EA	3 × R-CHOP	30	2	VMAT	DIBH	CR
11	70	DLBCL	1EA	6 × R-CHOP	30	2	VMAT	DIBH	CR
12	71	MZL	1EA	Helicobact AB	24	2	VMAT	DIBH	CR
13	60	DLBCL	1EA	4 × R-CHOP	30	2	VMAT	DIBH	NA
14	73	MZL	1EA	Helicobact AB	24	2	VMAT	DIBH	CR
15	68	MZL	1EA	0	24	2	VMAT	DIBH	CR

*: patient cancelled radiotherapy after planning.
MCL: Mantle cell lymphoma, DLBCL: Diffuse large B-cell lymphoma, MZL: Marginal zone B cell lymphoma, FL: Follicular lymphoma.
Helicobact AB: helicobacter pylori eradication treatment.
R-CHOP: Chemotherapy with cyclophosphamide, Adriamycin, vincrestin and prednisone.
VMAT: Volumetrin arc therapy.
DIBH: Deep inspiration breath-hold.
CR: Complete response, NED: no evidence of disease, NA: not applicable.

doses to lungs and heart in mediastinal lymphomas and breast cancer [7,8], and it is now implemented in routine practice in these patients. Planning studies have shown that breathing controlled radiotherapy of the stomach with treatment only in pre-specified phases of the respiration reduces doses to the organs at risk (OARs) and one study showed that DIBH can reduce the doses to the liver, heart, lungs, and spinal cord without compromising the dose to the stomach and surrounding lymph nodes (CTV). [5,9].

Therefore, the aim of this clinical trial was to assess the possibility to reduce the dose to the heart without compromising the dose to the CTV or substantially increasing the risk of other late effects in a prospective study.

2. Methods and patients

2.1. Patients

Patients diagnosed with localized lymphoma in the stomach who were referred to our institution between 2015 and December 2019 were eligible for the study. The inclusion criteria were: Age ≥ 18, gastric radiotherapy expected to be a part of the treatment, patient able to comply with the procedures, and a signed consent.

19 patients were eligible for the study and 15 of these patients completed all procedures in the study. Two patients did not want to participate and two were excluded because they were not able give informed consent. The remaining 15 patients tolerated and complied with the breath-hold instructions during imaging. One patient cancelled radiotherapy after planning was done, the remaining 14 patients complied with breath-hold during treatment. In all 15 patients, VMAT technique in DIBH was the chosen technique for treatment. The study was approved by the regional ethics committee for Copenhagen (H-15015802).

2.2. Procedures

The inspiration level was monitored during the planning CT and treatment using the RPM® system (Varian Medical Systems, Palo Alto, USA), as described elsewhere [10,11]. A treatment planning scan was done in both free breathing (FB) and in DIBH when the patient was able to reproduce the level of DIBH.

The CTV encompassed the entire stomach with a 1 cm margin, modified to account for solid surrounding organs such as bone, liver diaphragm, spleen, but not for mobile structures such as bowel. The OARs were also contoured: heart, left and right lung, left and right kidney, bowel bag, pancreas, liver, duodenum, spleen. The whole heart, kidneys, pancreas, spleen and duodenum were contoured. The entire lungs were contoured if possible and bowel bag and spinal cord were contoured to at least the cranio-caudal level of CTV + 2 cm.

2.3. Radiation treatment planning and delivery

Plans were created for all patients in both DIBH and FB using VMAT with two 6 MV arcs (AcurosXB v13.6, 13.7, and 15.5, Eclipse, Varian Medical Systems (all plans for each patient were created with the same version)). A CTV-to-PTV margin of 1 cm in all directions was used for all plans. The plan that was determined to be the best in terms of target coverage (i.e. PTV) and sparing of the heart was chosen for treatment.

PTV coverage, defined as % of PTV receiving at least 95% dose level ($V_{95\%}$), and the mean doses to the heart, lungs, liver, kidney, duodenum, pancreas, and spinal cord were calculated for each patient in both DIBH and FB. Likewise, the relative volume receiving ≥20 Gy (V_{20}), ≥10 Gy (V_{10}), and ≥5 Gy (V_5) for the heart, kidneys, and lungs, and the absolute volume receiving ≥20 Gy (V_{20}), ≥10 Gy (V_{10}) and ≥ 5 Gy (V_5) for heart, lungs, liver, duodenum, pancreas, and spinal cord. Because different dose levels were used in for the different lymphoma types, we also compared the volumes of the heart receiving the following dose levels: ≥D80%, ≥D60% and ≥D40%. To investigate the dosimetric impact of a choice of a larger margin to account for respiratory motion for FB plans, additional plans were created with a CTV-to-PTV margin of 1.5 cm in the cranio-caudal direction and 1 cm in other directions. Position verification was performed before treatment using daily cone-beam CT (CBCT) imaging (25). If the treatment was delivered in DIBH, position verification was also performed in DIBH in order to verify the level of inspiration.

2.4. Statistical analyses

The study was designed as an exploratory study with reduction of heart dose as the primary endpoint, so no meaningful power calculation was possible. Wilcoxon signed rank test for non-parametric paired data was used to compare differences for the dependent variables in the FB and DIBH RT plans with a two-tailed significance level of 0.05. We tested the two sets of FB data with 1.0 cm (FB 1.0 cm) and 1.5 cm CTV-to-PTV margin cranio-caudally (FB 1.5 cm) with the DIBH data separately. All

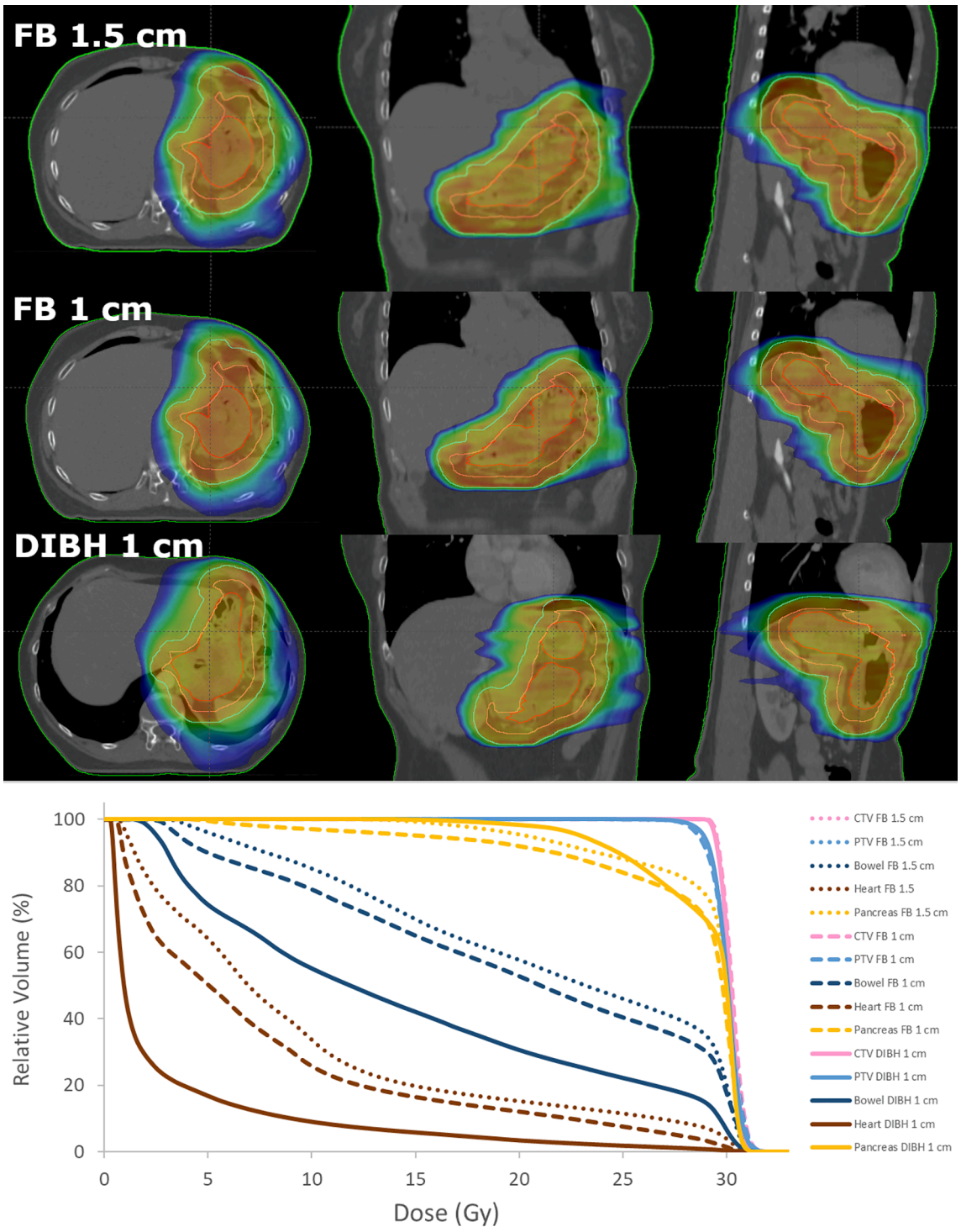

Fig. 1. Dose distribution for an example patient shown in the axial, coronal, and sagittal planes (with colour wash minimum set to 50% of prescription dose) for plans in free breathing (FB) with a PTV margin of 1.5 cm in the cranio-caudal direction and 1 cm in other directions (top), in FB with a PTV margin of 1 cm (middle), and in deep inspiration breath-hold (DIBH) with a PTV margins of 1 cm (bottom). Contours: red: stomach, pink: CTV, cyan: PTV. Dose volume histogram: Dotted line: FB with 1.5 cm margin in the cranio-caudal direction, Dashed line: FB with 1 cm margin, solid line: DIBH with 1 cm margin. Pink: CTV, blue: PTV, brown: heart, navy: bowel, yellow: pancreas. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

statistical analyses were performed with the SPSS statistical software v. 25.

3 Results.

The characteristics of the participating 15 patients are shown in Table 1. Fig. 1 illustrates the dose distribution and dose volume histogram for one example patient in FB and DIBH. The resulting dose estimates with FB and DIBH, respectively, are presented in Table 2. There was no statistically significant difference in either the sizes of CTV or PTV, or in estimated PTV coverage (V95%), between FB and DIBH.

Statistically significant reductions of the estimated mean doses to the

Table 2
Dose calculations for plans in free breathing and deep inspiration breath-hold.

	FB_1 cm Median (range)	FB_1.5 cm Median (range)	DIBH Median (Range)	P (Wilcoxons signed rank test)
Target coverage				FB_1/FB_1.5 vs DIBH
PTV D95 (%)	96 (94–99)	97(91–98)	96(93–99)	0.49/0.45
Heart				
Mean dose (Gy)	5.5(4.4–11)	7.1(5.7–12)	3.2 (1.2–7.0)	0.001/0.001
V20 (ccm)	54(17–106)	76(30–142)	15(0.0–78)	0.001/0.001
V10 (ccm)	124 (73–360)	163 (98–413)	46 (0.0–214)	0.001/0.001
V5 (ccm)	205 (123–537)	234 (165–595)	93 (1.8–316)	0.001/0.001
Liver				
Mean dose (Gy)	11.0 (5.2–12.9)	11.4 (5.9–14)	12(6.0–14)	0.04/0.75
Pancreas				
Mean dose (Gy)	21(11–34)	22(13–35)	22(14–34)	0.02/0.95
Duodenum				
Mean dose (Gy)	9.4(4.1–19)	9.4- (4.1–19)	11(4.6–23)	0.01/0.18
Right Kidney				
Mean dose (Gy)	4.3 (0.5–8.5)	4.8 (0.5–9.0)	3.8 (0.8–8.9)	0.22/0.04
Left Kidney				
Mean dose (Gy)	5.5(1.0–16)	7.2(1.4–15)	5.6(1.0–16)	0.50/0.01
Bowel Bag				
Mean dose (Gy)	12(3.9–20)	13(4.8–21)	14(4.6–18)	0.36/0.65
Spinal Cord				
Mean dose (Gy)	8.7(3.9–12)	9.7(4.3–14)	7.9(2.3–12)	0.02/0.001
Left Lung				
Mean dose (Gy)	2.6 (1.4–5.3)	3.3 (1.7–6.1)	3.0 (1.8–4.5)	0.02/0.004
Right Lung				
Mean dose (Gy)	1.2 (0.9–2.1)	1.6 (1.1–2.4)	1.5 (0.8–1.8)	0.04/0.22

FB_cm /FB_1.5 cm: Data obtained with 1 cm/ 1.5 cm CTV to PTV margin in free breathing. DIBH: Data obtained with 1 cm CTV to PTV margin in deep inspiration breath-hold.
PTV: planning target volume, V95: Relative volume receiving at least 95% of prescribed dose.
V20/V10/V5 ccm: Volume receiving 20 Gy/10 Gy/5 Gy.

heart and to the absolute and relative volumes of the heart receiving ≥20 Gy (V_{20}), ≥10 Gy (V_{10}) and ≥5 Gy (V_5) were demonstrated. The estimated absolute and relative volumes of the heart receiving the following dose levels: ≥D80%, ≥D60% and ≥D40% were also lower with DIBH than in FB 1.0 cm. The sparing of the heart was as expected more pronounced when DIBH was compared to FB 1.5 cm (Table 2).

The estimated mean doses to the liver, duodenum, and pancreas were increased in DIBH, compared to FB 1.0 cm, and the mean doses and absolute volumes of these organs receiving ≥20 Gy (V_{20}), ≥10 Gy (V_{10}) and ≥5 Gy (V_5) were statistically higher in DIBH than in FB 1.0 cm (Table 2). When FB 1.5 cm was compared to DIBH, no statistically significant differences were seen in the estimated mean doses to the liver, duodenum, and pancreas (Table 2). The estimated dose levels to the left kidney were similar with DIBH and FB 1.0 cm. With FB 1.5 cm the dose to the kidneys was statistically higher than in DIBH, but the dose differences were small (Table 2). The lung dose and dose to the spinal cord were very low in both FB and in DIBH (Table 2).

4. Discussion

In this prospective study we demonstrate that, with VMAT radiotherapy, a significant reduction of the estimated radiation doses to the heart is obtained with DIBH compared to FB without compromising the dose to the target.

This difference is due to the anatomical changes with DIBH, separating the stomach from the heart, and in addition to the reduction of the CTV-to-PTV margin in the cranio-caudal direction made possible by the DIBH reducing internal motion. It is worth noticing that DIBH is a simple and a well-tolerated approach for motion management even in this group of mostly elderly patients.

A limitation of this study is that we demonstrated reductions in dosimetric parameters and not in clinical effects. However, the clinical effects of interest have a significant latency of up to several decades, so the use of dosimetric surrogates is necessary and justified in such a rare disease. Furthermore, in a planning study like this, it is very important to investigate whether an estimated dose reduction to the heart in breath-hold is achieved at the expense of an increased dose to other organs. The study clearly showed that is the case when using the same CTV-to-PTV margins. Now that we are aware of these increases in dose to the abdominal OARs, it is possible that optimization objectives could be reprioritized in an attempt to mitigate some of the dose increases to other OARs, but the redistribution of dose might cause increases in dose in other areas that are undesirable. When FB plans using an increased margin in cranio-caudal direction to account for respiratory movements were compared to DIBH plans, the doses to organs at risk (other than then heart) were generally not statistically different. Hence, the present study demonstrates that it is possible to reduce the dose to the heart with DIBH without increasing the dose to other OARs. These findings are in concordance with a previous study [9]. Previous studies in both breast cancer and Hodgkin lymphoma have shown that the risk of cardiac disease after radiation is substantially increased in a dose dependent manner [12–14]. In one study the rate of major coronary events increased by 7 % for each increase of 1 Gy in the mean radiation dose delivered to the heart [15]. The dose to the heart in our study was localised to the left ventricle which has been suggested to lead to an increased risk of cardiac events. Hence, the significant reductions in estimated delivered doses to the heart with DIBH compared to FB are likely to be clinically relevant. One study in gastric MALT lymphomas showed that the treatment of large volumes was associated with a higher risk of death. A substantial part of the deaths was due to cardiac events [4]. We have substantial data on late effects due to RT with large fields in patients with Hodgkin Lymphoma (HL) and in seminoma. Based on these data, we have relatively reliable estimates of the benefit of a reduced radiation dose to the OARs in HL [16]. The dose–response relationship for cardiac long-term effects was shown to be approximately linear with no lower dose threshold (17). Hence, any reduction of the radiation dose to the heart should therefore be considered beneficial [13].

The significance of dose to other OARs is assumed to be of less concern as in a group of gastric lymphoma patients with a median age of 60 as the increased risk of a radiation induced second cancer must be modest. In the largest follow-up study of late effect, very few second cancers were seen [4].

Clinical testing of the DIBH strategy would require a very large phase 3 study with long follow-up. It is thus unlikely that the clinical benefit of the dose reduction to the lungs, heart, and cardiac substructures will be verified in a clinical study.

The present study demonstrates that RT in DIBH for gastric lymphoma makes it possible to reduce the radiation dose to the heart without compromising target coverage. The doses to abdominal OARs increased marginally if the PTV margin was the same in DIBH and FB but were similar if appropriate margins were used with FB. The DIBH technique is simple and most patients can comply with the procedure. Hence, the DIBH technique should be considered in patients requiring RT for gastric lymphoma.

CRediT authorship contribution statement

Peter Meidahl Petersen: Conceptualization, Methodology, Formal analysis, Investigation, Validation, Visualization, Data curation, Software, Writing – original draft, Writing – review & editing. **Laura Ann Rechner:** Conceptualization, Writing – review & editing. **Lena Specht:** Conceptualization, Funding acquisition, Project administration, Writing – review & editing.

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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References

[1] Illidge T, Specht L, Yahalom J, Aleman B, Berthelsen AK, Constine L, et al. Modern radiation therapy for nodal non-hodgkin lymphoma—target definition and dose guidelines from the international lymphoma radiation oncology group. Int J Radiat Oncol 2014;89:49–58. https://doi.org/10.1016/j.ijrobp.2014.01.006.

[2] Wirth A, Gospodarowicz M, Aleman BMP, Bressel M, Ng A, Chao M, et al. Long-term outcome for gastric marginal zone lymphoma treated with radiotherapy: a retrospective, multi-centre, International Extranodal Lymphoma Study Group study. Ann Oncol 2013;24:1344–51. https://doi.org/10.1093/annonc/mds623.

[3] Tsang RW, Gospodarowicz MK. Radiation therapy for localized low-grade non-Hodgkin's lymphomas. Hematol Oncol 2005;23:10–7. https://doi.org/10.1002/hon.743.

[4] Reinartz G, Pyra RP, Lenz G, Liersch R, Stüben G, Micke O, et al. Favorable radiation field decrease in gastric marginal zone lymphoma. Strahlentherapie Und Onkol 2019;195:544–57. https://doi.org/10.1007/s00066-019-01446-5.

[5] Matoba M, Oota K, Toyoda I, Kitadate M, Watanabe N, Tonami H. Usefulness of 4D-CT for radiation treatment planning of gastric MZBCL/MALT. J Radiat Res 2012;53:333–7. https://doi.org/10.1269/jrr.11127.

[6] Johnson ME, Pereira GC, El Naqa IM, Goddu SM, Al-Lozi R, Apte A, et al. Determination of planning target volume for whole stomach irradiation using daily megavoltage computed tomographic images. Pract Radiat Oncol 2012;2:e85–8. https://doi.org/10.1016/j.prro.2012.02.001.

[7] Petersen PM, Aznar MC, Berthelsen AK, Loft A, Schut DA, Maraldo M, et al. Prospective phase II trial of image-guided radiotherapy in Hodgkin lymphoma: benefit of deep inspiration breath-hold. Acta Oncol (Madr) 2015;54:60–6. https://doi.org/10.3109/0284186X.2014.932435.

[8] Pedersen AN, Korreman S, Nyström H, Specht L. Breathing adapted radiotherapy of breast cancer: reduction of cardiac and pulmonary doses using voluntary inspiration breath-hold. Radiother Oncol 2004;72:53–60. https://doi.org/10.1016/j.radonc.2004.03.012.

[9] Choi SH, Park SH, Lee JJB, Baek JG, Kim JS, Yoon HI. Combining deep-inspiration breath hold and intensity-modulated radiotherapy for gastric mucosa-associated lymphoid tissue lymphoma: Dosimetric evaluation using comprehensive plan quality indices. Radiat Oncol 2019;14:59. https://doi.org/10.1186/s13014-019-1263-7.

[10] Korreman SS, Pedersen AN, Nøttrup TJ, Specht L, Nyström H. Breathing adapted radiotherapy for breast cancer: comparison of free breathing gating with the breath-hold technique. Radiother Oncol 2005;76:311–8. https://doi.org/10.1016/j.radonc.2005.07.009.

[11] Damkjær SMS, Aznar MC, Pedersen AN, Vogelius IR, Bangsgaard JP, Josipovic M. Reduced lung dose and improved inspiration level reproducibility in visually guided DIBH compared to audio coached EIG radiotherapy for breast cancer patients. Acta Oncol (Madr) 2013;52:1458–63. https://doi.org/10.3109/0284186X.2013.813073.

[12] Aleman BMP, van den Belt-Dusebout AW, De Bruin ML, van 't Veer MB, Baaijens MHA, Boer JP De, et al. Late cardiotoxicity after treatment for Hodgkin lymphoma. Blood 2007;109:1878–86. doi:10.1182/blood-2006-07-034405.

[13] Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368:987–98. https://doi.org/10.1056/nejmoa1209825.

[14] Maraldo MV, Brodin NP, Vogelius IR, Aznar MC, Munck Af Rosenschöld P, Petersen PM, et al. Risk of developing cardiovascular disease after involved node radiotherapy versus mantle field for Hodgkin lymphoma. Int J Radiat Oncol Biol Phys 2012;83:1232–7. https://doi.org/10.1016/j.ijrobp.2011.09.020.

[15] Van Nimwegen FA, Schaapveld M, Cutter DJ, Janus CPM, Krol ADG, Hauptmann M, et al. Radiation dose-response relationship for risk of coronary heart disease in survivors of Hodgkin lymphoma. J Clin Oncol 2016;34:235–43. https://doi.org/10.1200/JCO.2015.63.4444.

[16] Maraldo MV, Brodin NP, Aznar MC, Vogelius IR, Munck af Rosenschöld P, Petersen PM, et al. Estimated risk of cardiovascular disease and secondary cancers with modern highly conformal radiotherapy for early-stage mediastinal Hodgkin lymphoma. Ann Oncol 2013;24:2113–8. doi:10.1093/annonc/mdt156.