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 lymphomas 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 doses 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 (17–78) cm^2 to 15. (0.0–78) cm^2. 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. gastrointestinal 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...
Planning studies have shown that controlled radiotherapy of the stomach with treatment only in pre-specified phases of the respiratory cycle 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].

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 respiratory cycle 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 localised 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 to 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 completed all procedures in the study. Two patients did not want to participate and two were excluded because they were not able to follow the instruction.

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 planning target volume (PTV) was defined as the isodose line that is centered on the target volume (CTV) and has a 1 cm margin in all directions. The planning target volume (PTV) was defined as the isodose line that is centered on the target volume (CTV) and has a 1 cm margin in all directions.

PTV coverage, defined as % of PTV receiving at least 95% dose level (V95%), 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 (V20), ≥ 10 Gy (V10), and ≥ 5 Gy (V5) for the heart, kidneys, and lungs, and the absolute volume receiving ≥ 20 Gy (V20), ≥ 10 Gy (V10) and ≥ 5 Gy (V5) 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 crano-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 the primary endpoint to 95% dose level (V95%), 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 (V20), ≥ 10 Gy (V10), and ≥ 5 Gy (V5) for the heart, kidneys, and lungs, and the absolute volume receiving ≥ 20 Gy (V20), ≥ 10 Gy (V10) and ≥ 5 Gy (V5) 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 crano-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.

Table 1

| ID | Age | Histology | Stage | Pr Chemotherapy | Total Dose Gy | Gy/Fr | Radiotherapy technique | Preferred plan | Local relaps |
|----|-----|-----------|-------|----------------|--------------|------|------------------------|---------------|------------|
| 1  | 81  | MCL       | Stomach relaps | 8X R-CHOP | 24           | 2    | VMAT                  | DIBH          | Local relaps |
| 2* | 72  | DLBCL     | 1EA    | 6X 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    | 3X R-CHOP   | 30           | 2    | VMAT                  | DIBH          | CR         |
| 11 | 70  | DLBCL     | 1EA    | 6X R-CHOP   | 30           | 2    | VMAT                  | DIBH          | CR         |
| 12 | 71  | MZL       | 1EA    | Helicobact AB | 24           | 2    | VMAT                  | DIBH          | CR         |
| 13 | 60  | DLBCL     | 1EA    | 4X 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, vincristin and prednisone.
VMAT: Volumetric arc therapy.
DIBH: Deep inspiration breath-hold.
CR: Complete response, NED: no evidence of disease, NA: not applicable.
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

| Target coverage | FB_1 cm Median (range) | FB_1.5 cm Median (range) | DIBH Median (Range) | P (Wilcoxon signed rank test) |
|----------------|------------------------|--------------------------|---------------------|-----------------------------|
| PTV D95 (%)    | 96 (94–99)             | 97 (91–98)               | 96 (93–99)          | 0.49/0.45                   |
| Heart          | 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                 |

FB_1 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

≥ 20 Gy (V20), ≥ 10 Gy (V10) and ≥ 5 Gy (V5) 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 heart were provided in DIBH, compared to FB 1.0 cm, and the mean doses and absolute volumes of these organs receiving ≥20 Gy (V20), ≥10 Gy (V10) and ≥5 Gy (V5) 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 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-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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