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Original Research Article

Deep inspirational breast hold (DIBH) for right breast irradiation: Improved sparing of liver and lung tissue

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ABSTRACT

Objective: To reduce liver and lung dose during right breast irradiation while maintaining optimal dose to the target volume. This dose reduction has the potential to decrease acute side effects and long-term toxicity.
Materials and Methods: 16 patients treated with radiation therapy for localized carcinoma of the right breast were included retrospectively. For the planning CT, each patient was immobilised on an indexed board with the arms placed above the head. CT scans were acquired in free-breathing (FB) as well as with deep inspiration breath hold (DIBH). Both scans were acquired with the same length. Planning target volumes (PTV's) were created with a 5 mm margin from the respective clinical target volumes (CTV's) on both CT datasets. The liver was outlined as scanned. Dose metrics evaluated were as follows: differences in PTV coverage, dose to the liver (max, mean, V90%, V50%, V30%), dose to lung (mean, V20Gy, relative electron density) and dose to heart (Dmax). The p-values were calculated using Wilcoxon signed-rank tests. A p-value was significant when <0.05.
Results: Differences in PTV coverage between plans using FB and DIBH were less than 2 %. Maximum liver dose was significantly less using DIBH: 17.5 Gy versus FB: 40.3 Gy ($p < 0.001$). The volume of the liver receiving 10 % of the dose was significantly less using DIBH with 1.88 cm^3 versus 72.2 cm^3 under FB ($p < 0.001$). The absolute volume receiving 20 Gy in the right lung was larger using DIBH: 291 cm^3 versus 230 cm^3 under FB ($p < 0.001$) and the relative volume of lung receiving dose greater than 20 Gy was smaller with DIBH: 11.5 % versus 14 % in FB ($p = 0.007$). The relative electron density of lung was significantly less with DIBH: 0.59 versus 0.62 with FB, ($p < 0.001$). This suggests that the lung receives less dose due to its lower density when using DIBH.
Conclusion: Radiation of the right breast using DIBH spares liver and lung tissue significantly and thus carries the potential of best practice for right sided breast cancer.

Introduction

Radiation therapy is a proven treatment method to reduce locoregional recurrence and improve survival rates in patients with breast cancer [1,2]. For patients diagnosed with early-stage breast cancer, adjuvant irradiation of the whole breast is the standard of care. However, this type of treatment can result in side effects linked to irradiation of organs at risk (OARs) [3–10]. Risks such as cardiac mortality and coronary events from dose to the heart, as well as lung cancer and radiation pneumonitis resulting from dose to lung, must be considered when delivering whole breast radiation treatment [4–11].

Calculation of dose in low-density tissue, such as the lung, can be a challenge for treatment planning system algorithms [12,13]. Uncertainties in the actual dose to the lung rise with the implementation of deep-inspiration-breath-hold (DIBH) radiotherapy including; accurate segmentation of lung volume and the irradiated mass of lung tissue. Various techniques are being used to reduce dose to these OARs without compromising coverage of target volumes. These methods primarily focus on sparing healthy heart and lung tissue. DIBH is one technique that is widely used today in left-sided breast irradiation [14–28]. Many

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studies have been conducted to prove the benefit of using DIBH to reduce dose to heart and heart structures, such as the left anterior descending coronary artery (LAD). Mean Dose (Dmean) reductions of 31–63 % to the heart were achieved when using DIBH versus traditional FB techniques [18–22,24,26–28]. Although absolute lung volume increases within a certain dose level (Vx) during DIBH, lung tissue is spared as the relative irradiated lung volume decreases. The Dmean to the ipsilateral lung was also seen to be reduced by 7–15 % [21,22,24,25,27].

While there is plenty of evidence on the benefits of implementing DIBH for left-sided breast treatment, little exists on the advantages for right-breast irradiation. The available studies look primarily into heart and lung sparing for patients receiving regional nodal irradiation (RNI) [14,15]. Though the liver is a prominent OAR in right-sided treatment, few studies have investigated the benefits of liver sparing [15,16]. Immunotherapeutic drugs can affect the function of various organs, including liver. With the growing use of immune therapy in cancer treatment, it becomes even more important to decrease doses and possible toxicity to OARs during radiotherapy, including the liver [29].

This study investigates potential benefits of using DIBH versus FB for right-sided whole breast radiation therapy in regard to sparing dose to liver, lung and heart. Dose metrics for these OARs, as well as target volumes, are reported.

Materials and methods

Patient population and study design

A general hospital-based informed consent was obtained for all patients.

Sixteen patients receiving radiation therapy for localized carcinoma of the right breast were included retrospectively (radiation to loco-regional lymphatic regions was excluded). The median age was 60 years (range, 39–83 years; mean: 59 years). All patients were treated using the DIBH technique.

For the planning computer tomography (CT), each patient was immobilised on an indexed board with the arms placed above the head. Patients unable to hold their breath for a minimum of 20 s were excluded from the DIBH technique and study. Breathing was tracked using the Real-time Position Management™ (RPM) system (Varian Medical Systems, Palo Alto, CA) with patients receiving live, visual feedback.

Two CT scans were acquired for each patient on a GE Optima CT580 wide bore CT scanner with a slice separation of 2.5 mm. One scan was done in free-breathing (FB) and one in DIBH. Both scans were acquired with the same length and same position, from the bottom of the chin to approximately the level of L3-spinebody. The Eclipse™ (Varian) planning system was used for volume delineation and treatment planning.

Target volume and organs-at-risk

Target volumes were delineated by one radiation oncologist and independently peer reviewed by a second radiation oncologist prior to treatment planning. The breast CTV was defined as the visible breast tissue on the CT images. The planning target volume (PTV) was a 5 mm isotropic expansion of the CTV which was subsequently cropped 3–5 mm from the skin surface. Contours for both lungs were generated using an automated segmentation tool and adjusted manually where necessary. Normal structures of patient body, contralateral breast, liver, heart, left lung and right lung were contoured manually.

Dose metrics for the PTV, liver, lungs, and heart were collected and compared. The main endpoints evaluated were: differences in PTV coverage, maximum point dose to liver, volumes of liver covered by the 90 %-, 50 %-, 10 %-isodose and the volume of liver covered by the 30 Gy-isodose. In addition, the maximum point dose to the heart, mean dose to lungs, the volume of lung covered by the 20 Gy-isodose (V20Gy) as well as the relative change in Hounsfield numbers and relative electron density for the right lung were recorded.

Data was collected for the amount of irradiated lung volume and its density with and without a DIBH technique. In order to provide more quantitative data on damage to lung tissue as a result of irradiation, Starkschall et al. [30] recommended incorporating a dose-mass histogram (DMH). As many treatment planning systems do not typically compute DMHs, mean density of the lung in question was calculated from the volume and the mean value of Hounsfield numbers of the voxels encompassed by the structure outline.

Treatment planning

Treatment planning was carried out in Eclipse™ v15.6 (Varian Medical Systems). The prescription dose was 40.05 Gy in 15 fractions or 42.72 Gy in 16 fractions depending on whether a boost was planned or not. Treatment plans were generated using a 6 MV photon beam energy tangential beam arrangement with a sliding window IMRT technique. Dose coverage was according to ICRU [31] and plans were normalized to have the prescribed dose to the mean of the PTV volume. The dose volume objective for the lungs was defined as the volume receiving 20 Gy (V_{20Gy}) to be less than 20 %. Mean dose to the heart was restricted to less than 2 Gy, with the maximum dose being kept as low as possible. For the contralateral breast, mean dose was less than 2 Gy. All tolerances followed QUANTEC guidelines [19]. Each plan was generated by the same dosimetrist to ensure consistency across all plans. Dose calculations were performed with the Eclipse™ Anisotropic Analytical Algorithm (Version 15.6.04).

Statistics

For all endpoints; FB, DIBH, the relative difference between DIBH and FB in % (calculated as 100*(DIBH-FB)/FB)) and the absolute difference between DIBH and FB (calculated as DIBH-FB) were summarized using median and range. FB and DIBH were compared using Wilcoxon signed-rank tests. No correction for multiple testing was applied, thus all analyses are considered exploratory and hypothesis generating. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R 4.0.3 (The R Foundation; https://www.r-project.org).

Results

PTV

Dose-volume metrics for target volumes (PTV) are summarised in Table 1. There was no difference in plan quality between DIBH and FB plans for all groups in terms of target coverage. All plans, under both breathing conditions, met the target coverage criteria. We found that there was a less than 0.4 % difference in PTV coverage when considering

Table 1
Dose-volume metrics for target volumes for FB and DIBH plans.

PTV Variable	FB	DIBH	Rel. Diff. (DIBH-FB) (%)	Abs. Diff (DIBH-FB)	p-value
V95% Coverage (%)	95.8 (75.9, 97.3)	95.5 (78, 96.7)	−0.36 (−2.06, 3.6)	−0.35 (−2, 3.3)	0.453
V90% Coverage (%)	97.1 (82.8, 98.05)	96.8 (84.9, 98)	−0.31 (−1.89, 2.5)	−0.3 (−1.85, 2.1)	0.285

Abbreviations: FB: free breathing; DIBH: deep inspiration breath hold; V: volume of

In all the tables median and range are reported for FB, DIBH, the relative difference between DIBH and FB in % (calculated as 100*(DIBH-FB)/FB) and the absolute difference between DIBH and FB (calculated as DIBH-FB). The p-values were calculated using Wilcoxon signed-rank tests.

the V95% and the V90%. No compromise on target volume coverage had to be made.

Lung dose

There was a significant increase in total lung volume for DIBH compared to FB, from 1376.2 cm^3 (1008.8–2032.6 cm^3) for FB to 2472.0 cm^3 (1725.2–2977.0 cm^3) for DIBH ($P < 0.001$), as well as in any total or ipsilateral lung dose-volume metric between FB and DIBH (Table 2). While the absolute volume of lung within the 20 Gy isodose line increased (with DIBH: 291 cm^3 versus FB: 230 cm^3), the percentage of lung irradiated decreased, with an average decrease of the V20Gy (%) by 2.5 % (from 14 % to 11.5 %; $p = 0.007$). The right lung exposure significantly reduced with the application of DIBH in terms of mean dose and dense lung tissue irradiated. The mean Hounsfield numbers, thus the mean relative electron density of lung volume V20Gy, was significantly reduced with DIBH (Table 2, Fig. 1). The relative electron density of the ipsilateral lung had a significant reduction in the DIBH group by −7.52 % ($p = 0.007$) (Table 2).

Liver dose

We identified statistically significant reductions in the irradiated liver volume when comparing DIBH with FB. Table 3 gives the relative and absolute difference in the liver Dmax (Gy), the liver V50% (cm^3) and the mean dose in the liver (Gy). Physical distance between PTV and liver is visualized in Fig. 2. Mean liver dose was significantly lower with DIBH (FB: 2.1 Gy (0.6–6.3 Gy); DIBH: 0.8 Gy (0.1–2.6 Gy); $p = 0.0009$. Maximum dose to the liver was significantly less using DIBH: 17.5 Gy versus FB 40.3 Gy ($p < 0.001$). The relative difference for Dmax in the liver decreased by 48 % when using DIBH instead of FB. The liver is not only being spared from higher doses, the V10% for the liver was also significantly decreased from 72 to 1.9 cm^3 ($p < 0.001$). Overall, using DIBH is beneficial for the liver in both high and low dose regions when treating the whole right breast.

Cardiac dose

The mean and maximum heart doses were comparable between FB and DIBH plans, but there was still a statistically significant difference in the Dmax of the heart in favor of DIBH (Table 4).

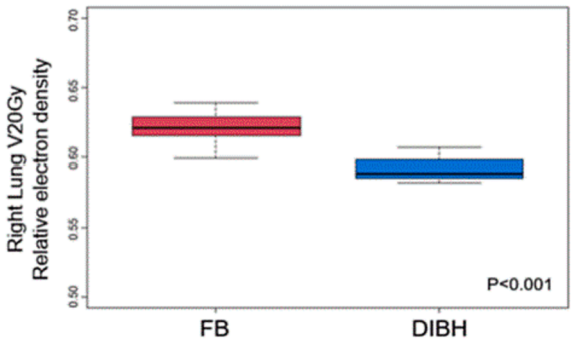

Fig. 1. Significant reduction in lung density for DIBH.

Discussion

This study supports the use of DIBH for right-sided patients with breast cancer without regional nodal irradiation, especially regarding the liver constraints which were significantly lower for all endpoints. Similarly, there was a significant difference in any total or ipsilateral lung dose-volume metric between FB and DIBH. When comparing our results to those found in previous studies, it is important to keep in mind the contrast between breast only and breast plus regional nodal irradiation. Many studies included the latter in their results, however our study focused solely on localized right breast cancer (RBC). Conway et al. did not investigate localized breast irradiation, Essers et al. found no significant decrease in mean lung dose [14,15]. Pandeli et al. observed that ipsilateral lung dose metrics decreased in terms of mean dose and percentage of lung receiving 20 Gy for whole breast only treatment [32]. Though these results are similar to our data, we observed an increase of 76.75 cm^3 in absolute volume of ipsilateral lung within the 20 Gy isodose region when using DIBH. At first glance, this may be interpreted as an increase in expected irradiated lung tissue, however, the percentage of involved lung must also be considered. While the total volume of lung increases, the percentage of ipsilateral lung tissue receiving 20 Gy decreases from 14.0 % to 11.5 % (p: 0.007) in FB and DIBH, respectively.

Also investigated was how the relative electron density of lung varied between FB and DIBH. DIBH reduces ipsilateral lung dose by expansion so that less tissue remains in the irradiated region. We observed a meaningful decrease in relative electron density in the V20Gy for ipsilateral lung. Oechsner et al. examined the differences between dose-volume histogram (DVH) and dose-mass histogram

Table 2
Dose-volume metrics for OAR lung.

Side	Lung Variable	FB	DIBH	Rel. Diff. (DIBH-FB) (%)	Abs. Diff (DIBH-FB)	p-value
Right	Volume (cm^3)	1376.2 (1008.8, 2032.6)	2472.0 (1725.2, 2977)	76.1 (40.9, 117.5)	1094.1 (716.4, 1320.7)	<0.001
	Average HU	−727.8 (−949, −678.5)	−823.3 (−844.3, −782.2)	13.5 (−13.7, 18.7)	−97.1 (−129.8, 130.2)	0.005
	Relative electron density	0.65 (0.54, 0.67)	0.6 (0.59, 0.62)	−7.52 (−9.83, 12.1)	−0.05 (−0.06, 0.06)	0.007
	V20Gy (cm^3)	230.5 (101.7, 329.5)	291.4 (191.4, 433.2)	34.6 (6.6, 103.9)	76.8 (11.9, 158.7)	<0.001
	V20Gy – Average HU	−782 (−826.3, −746.4)	−846.6 (−858.8, −810.3)	7.4 (3.9, 11)	−59 (−83.5, –32.4)	<0.001
	V20Gy - relative electron density	0.62 (0.6, 0.64)	0.59 (0.58, 0.61)	−4.87 (−6.7, −2.8)	−0.03 (−0.04, −0.02)	<0.001
	Mean dose (Gy)	6.66 (5.3, 9.2)	6.08 (4.8, 8.3)	−14.72 (−32.1, 4.9)	−0.99 (−2.9, 0.3)	<0.001
	V20Gy (%)	14.02 (8.6, 19.6)	11.5 (8.58, 17.7)	−15.8 (−37.42, 12.4)	−1.95 (−7.2, 1.9)	0.007
Left	Dmax (Gy)	0.63 (0.21, 3.21)	1.3 (0.04, 4.48)	98.34 (−89.74, 514.29)	0.73 (−0.35, 1.36)	<0.001

Abbreviations: FB: free breathing; DIBH: deep inspiration breath hold; Rt: right; Lt: left; HU: Hounsfield Units; HN: Hounsfield numbers: Gy: Gray; V: volume of.

Table 3
Dose-volume metrics for OAR liver.

Liver variable	FB	DIBH	Rel. Diff. (DIBH-FB) (%)	Abs. Diff (DIBH-FB)	p-value
Volume (cm^3)	1275.5 (1006.4, 2182.9)	1279.4 (986.9, 2837.4)	12.6 (−4.6, 89.56)	145.3 (−58.6, 1340.6)	0.007
Dmax (Gy)	40.3 (4.58, 48.6)	17.54 (1.9, 47.4)	−48.0 (−95.9, −0.1)	−19.3 (−43.9, −0.03)	<0.001
Mean dose (Gy)	2.1 (0.6, 6.3)	0.8 (0.1, 2.6)	−74.9 (−95.2, 150.6)	−1.6 (−4.9, 2)	0.009
V90% Isodose (%)	0.7 (0, 3.4)	0 (0, 1.5)	−100 (−100, 0)	−0.7 (−3.2, 0)	0.001
V10% Isodose (%)	6.9 (0, 42.0)	0.25 (0, 7.5)	−94.8 (−100, 0)	−5.8 (−42.0, 0)	0.001
V90% Isodose (cm^3)	8.1 (0, 43.6)	0 (0, 15.4)	−100 (−100, 0)	−8.1 (−43.6, 0)	0.001
V50% Isodose (cm^3)	36.8 (0, 118.7)	0 (0, 41)	−99.9 (−100, 0)	−29.4 (−106.7, 0)	0.001
V10% Isodose (cm^3)	72.2 (0.01, 202.5)	1.9 (0, 79.1)	−96.2 (−100, −40.9)	−54.7 (−163.3, 0)	<0.001
V30Gy Isodose (cm^3)	18.6 (0, 94.5)	0 (0, 14.5)	−100 (−100, 0)	−16.6 (−92.5, 0)	0.001
V30Gy Isodose (%)	1.3 (0, 7)	0 (0, 1.1)	−100 (−100, 5)	−1.2 (−6.8, 0.3)	0.001

Abbreviations: FB: free breathing; DIBH: deep inspiration breath hold; Gy: Gray: V: volume of.

(DMH) in respect to ipsilateral lung expansion during DIBH for left sided breast irradiation [33]. Their data suggest a potential mass related dose reduction to the left lung during DIBH. To quantify organ dose the DMH concept was reported to be superior to the calculation of DVHs [34]. As our commercial treatment planning system does not provide calculation of DMH, only relative electron densities for lung volumes, conclusion was reached as to whether a lower density tissue resulted in less dose.

Relative lung volume is predictive for irradiated lung tissue, but quantification requires the calculation of irradiated lung mass. Since lung density is not homogeneously distributed, with greatest density in the base which decreases toward the apex [8], there is a gradient in lung mass which has to be evaluated in future studies.

The relative reduction in ipsilateral lung V20Gy with DIBH in our study (−15.8 %; 14.02 % vs 11.5 %) was greater than previously reported for right sided patients with breast cancer receiving "breast only radiotherapy". For right sided breast treatment including RNI, the results from Conway et al. [15] and Essers et al. [14] showed a reduction in ipsilateral lung dose (V20Gy) of 7.8 % and 7.5 %, respectively. While our study reports an increase in absolute ipsilateral lung V20Gy, the absolute percentage of lung receiving 20 Gy decreased by 2.5 % with DIBH. Such differences in results are likely related to the irradiated geometry, the choice of treatment planning technique and the dose-volume metrics evaluated. For local breast radiotherapy, Essers et al. used a wide tangential treatment approach and reported small reductions in lung dose. This correlates with our results, as the absolute difference for ipsilateral lung V20Gy was 1.95 %, which is slight but significant [15]. With our tangential IMRT treatment approach, we achieve similar low-dose exposure as compared to conventional tangential breast irradiations techniques.

It is reported that DIBH for patients with RBC shows a benefit for

Table 4
Dose-volume metrics for OAR heart.

Heart variable	FB	DIBH	Rel. Diff. (DIBH-FB) (%)	Abs. Diff (DIBH-FB)	p-value
Dmax (Gy)	3.8 (2.2, 11.1)	3.1 (2.5, 6.7)	−8.8 (−39.1, 18.7)	−0.4 (−4.3, 0.5)	0.023

Abbreviations: FB: free breathing; DIBH: deep inspiration breath hold; Gy: Gray.

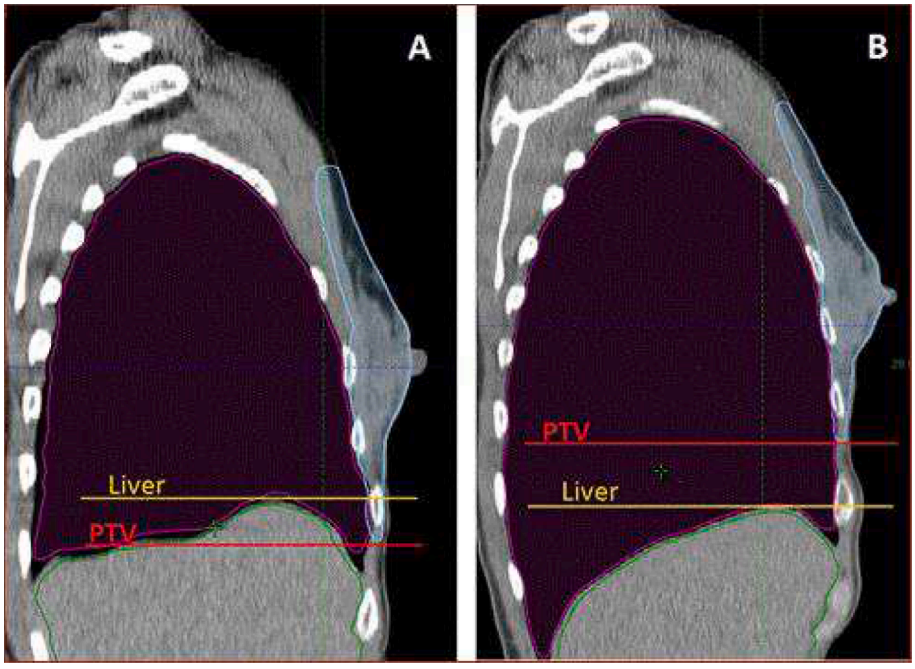

Fig. 2. Physical distance between PTV and liver is clearly visualized, naturally dependent on patient anatomy.

liver and heart dose [35,36]. They found that liver doses, although under accepted tolerances, did decrease with the addition of DIBH. While our study focused on patients undergoing treatment to intact breast, the results showed a similar decrease with maximum liver dose (Dmax) dropping by an average of 19.25 Gy from FB to DIBH. In fact, our study as well as that by Gunel Haji, et al., showed an improvement in every dose value that was evaluated [36]. This suggests that maximum dose and low dose levels can be decreased for RBC patients with or without intact breasts.

There are few studies that focus on the quantitative impact of reducing liver dose. Our study did not set acute toxicity as a specific endpoint; therefore, side effects such as nausea were not explicitly documented. On the contrary, Hormati et al. investigated a potential link between liver fibrosis after breast irradiation [37]. They concluded no significant impact of doses up to 40 Gy, using electrography as a measurement tool. What must also be considered is potential damage to the liver that may come from other sources. We believe that liver doses should be kept as low as possible to compensate for potential damage that may come from future irradiation, certain chemotherapy treatments, or even future hepatic tumours. Modern treatment techniques like VMAT would result in a wide low dose bath for a large part of the liver. Therefore, tangential IMRT would be more beneficial for the liver by preventing scattering.

With these unforeseeable future complications, it is important that we minimise dose to all organs at risk using the ALARA principle (as low as reasonably achievable), even when doses are otherwise below tolerance.

Although previous studies suggest there is a minimal difference in dose to the heart between FB and DIBH groups, it is still widely believed that any form of dose reduction should be applied in order to obtain long-term benefits [19]. While our study did not specifically investigate dose to LAD, we did see a clinically significant reduction in Dmax to the heart.

Another topic to be considered when introducing a new treatment technique is a cost-benefit analysis. We did not evaluate the cost effectiveness of this approach for patients undergoing radiotherapy to the right breast. However, there is at least one study which has shown that it is cost effective for left-sided treatment using “Field-in-Field” IMRT-irradiation-techniques [38]. Further studies need to be conducted in order to provide evidence that this method for RBC is also cost effective.

Conclusions

Radiation of the right breast using DIBH significantly spares liver and lung tissue and should therefore be considered as a potential new best practice for radiotherapy of right sided breast cancer. Based on these results we have implemented DIBH for right sided breast cancer as standard practice in our institute. Further we believe that patients who need irradiation to locoregional lymphatic regions would also benefit from DIBH. This should be investigated in future studies.

CRediT authorship contribution statement

Thomas Mader: Writing – original draft. **Rachel Pace:** Project administration. **Rui T. Boucas da Silva:** Formal analysis, Data curation, Writing – review & editing, Validation. **Lukas Erwin Johannes Adam:** Formal analysis, Resources, Investigation. **Gabriela Näf:** Formal analysis, Project administration, Investigation. **Christopher Charles Winter:** Resources, Supervision, Writing – review & editing. **Mania Maria Aspradakis:** Conceptualization, Methodology, Writing – review & editing. **Marco Radovic:** Writing – review & editing. **Aristotelis Spyridonidis:** Writing – review & editing. **Stefanie Hayoz:** Methodology, Formal analysis. **Brigitta Gertrud Baumert:** Conceptualization, Methodology, 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.

References

[1] Whelan TJ, Olivotto IA, Parulekar WR, et al. Regional nodal irradiation in early-stage breast cancer. N Engl J Med 2015;373(4):307–16. https://doi.org/10.1056/nejmoa1415340.

[2] Poortmans PM, Collette S, Kirkove C, et al. Internal mammary and medial supraclavicular irradiation in breast cancer. N Engl J Med 2015;373(4):317–27. https://doi.org/10.1056/nejmoa1415369.

[3] Darby SC, Ewertz M, McGale P, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 2013;368(11):987–98. https://doi.org/10.1056/nejmoa1209825.

[4] Swanson T, Grills IS, Ye H, et al. Six-year experience routinely using moderate deep inspiration breath-hold for the reduction of cardiac dose in left-sided breast irradiation for patients with early-stage or locally advanced breast cancer. Am J Clin Oncol: Cancer Clin Trials 2013;36(1):24–30. https://doi.org/10.1097/COC.0b013e31823fe481.

[5] Hjelstuen MHB, Mjaaland I, Vikström J, Dybvik KI. Radiation during deep inspiration allows loco-regional treatment of left breast and axillary-, supraclavicular- and internal mammary lymph nodes without compromising target coverage or dose restrictions to organs at risk. Acta Oncol (madr) 2012;51(3):333–44. https://doi.org/10.3109/0284186X.2011.618510.

[6] Hayden AJ, Rains M, Tiver K. Deep inspiration breath hold technique reduces heart dose from radiotherapy for left-sided breast cancer. J Med Imaging Radiat Oncol 2012;56(4):464–72. https://doi.org/10.1111/j.1754-9485.2012.02405.x.

[7] Schonecker S, Walter F, Freislederer P, et al. Treatment planning and evaluation of gated radiotherapy in left-sided breast cancer patients using the CatalystTM/SentinelTM system for deep inspiration breath-hold (DIBH). Radiat Oncol 2016;11(1). https://doi.org/10.1186/s13014-016-0716-5.

[8] Simonetto C, Eidemüller M, Gaasch A, et al. Does deep inspiration breath-hold prolong life? Individual risk estimates of ischaemic heart disease after breast cancer radiotherapy. Radiother Oncol 2019;131:202–7. https://doi.org/10.1016/j.radonc.2018.07.024.

[9] Dumane VA, Saksornchai K, Zhou Y, Hong L, Powell S, Ho AY. Reduction in low-dose to normal tissue with the addition of deep inspiration breath hold (DIBH) to volumetric modulated arc therapy (VMAT) in breast cancer patients with implant reconstruction receiving regional nodal irradiation. Radiat Oncol 2018;13(1). https://doi.org/10.1186/s13014-018-1132-9.

[10] McIntosh A, Shoushtari AN, Benedict SH, Read PW, Wijesooriya K. Quantifying the reproducibility of heart position during treatment and corresponding delivered heart dose in voluntary deep inhalation breath hold for left breast cancer patients treated with external beam radiotherapy. Int J Radiat Oncol Biol Phys 2011;81(4). https://doi.org/10.1016/j.ijrobp.2011.01.044.

[11] Betgen A, Alderliesten T, Sonke JJ, Van Vliet-Vroegindeweij C, Bartelink H, Remeijer P. Assessment of set-up variability during deep inspiration breath hold radiotherapy for breast cancer patients by 3D-surface imaging. Radiother Oncol 2013;106(2):225–30. https://doi.org/10.1016/j.radonc.2012.12.016.

[12] Ben-David MA, Sturtz DE, Griffith KA, et al. Long-term results of conservative surgery and radiotherapy for ductal carcinoma in situ using lung density correction: The university of Michigan experience. Breast J 2007;13(4):392–400. https://doi.org/10.1111/j.1524-4741.2007.00447.x.

[13] Pierce LJ, Griffith KA, Hayman JA, Douglas KR, Lichter AS. Conservative surgery and radiotherapy for stage I/II breast cancer using lung density correction: 10-year and 15-year results. Int J Radiat Oncol Biol Phys 2005;61(5):1317–27. https://doi.org/10.1016/j.ijrobp.2004.08.004.

[14] Essers M, Poortmans PM, Verschueren K, Hol S, Cobben DCP. Should breathing adapted radiotherapy also be applied for right-sided breast irradiation? Acta Oncol (madr) 2016;55(4):460–5. https://doi.org/10.3109/0284186X.2015.1102321.

[15] Conway JL, Conroy L, Harper L, et al. Deep inspiration breath-hold produces a clinically meaningful reduction in ipsilateral lung dose during locoregional radiation therapy for some women with right-sided breast cancer. Pract Radiat Oncol 2017;7(3):147–53. https://doi.org/10.1016/J.PRRO.2016.10.011.

[16] Rice L, Harris S, Green MML, Price PM. Deep inspiration breath-hold (DIBH) technique applied in right breast radiotherapy to minimize liver radiation. *BJR|Case Rep* 2015;1(2):20150038. https://doi.org/10.1259/bjrcr.20150038.

[17] Offersen BV, Boersma LJ, Kirkove C, et al. ESTRO consensus guideline on target volume delineation for elective radiation therapy of early stage breast cancer. Radiother Oncol 2015;114(1):3–10. https://doi.org/10.1016/j.radonc.2014.11.030.

[18] Feng M, Moran JM, Koelling T, et al. Development and validation of a heart atlas to study cardiac exposure to radiation following treatment for breast cancer. Int J Radiat Oncol Biol Phys 2011;79(1):10–8. https://doi.org/10.1016/j.ijrobp.2009.10.058.

[19] Marks LB, Yorke ED, Jackson A, et al. Use of normal tissue complication probability models in the clinic. Int J Radiat Oncol Biol Phys 2010;76(3 SUPPL.). https://doi.org/10.1016/j.ijrobp.2009.07.1754.

[20] Marks LB, Yu X, Vujaskovic Z, Small W, Folz R, Anscher MS. Radiation-induced lung injury. Semin Radiat Oncol 2003;13(3):333–45. https://doi.org/10.1016/S1053-4296(03)00034-1.

[21] Marks LB, Bentzen SM, Deasy JO, et al. Radiation dose-volume effects in the lung. Int J Radiat Oncol Biol Phys 2010;76(3 SUPPL.). https://doi.org/10.1016/j.ijrobp.2009.06.091.
[22] Rothwell RI, Kelly SA, Joslin CAF. Radiation pneumonitis in patients treated for breast cancer. Radiother Oncol 1985;4(1):9–14. https://doi.org/10.1016/S0167-8140(85)80056-6.
[23] Matzinger O, Heimsoth I, Poortmans P, et al. Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage i to III breast cancer (EORTC trial 22922/10925). Acta Oncol (madr) 2010;49(1):24–34. https://doi.org/10.3109/02841860903352959.
[24] Choi J, Kim YB, Shin KH, et al. Radiation pneumonitis in association with internal mammary node irradiation in breast cancer patients: An ancillary result from the KROG 08–06 study. J Breast Cancer 2016;19(3):275–82. https://doi.org/10.4048/jbc.2016.19.3.275.
[25] Hedin E, Bäck A, Chakarova R. Impact of lung density on the lung dose estimation for radiotherapy of breast cancer. Phys Imaging Radiat Oncol 2017;3:5–10. https://doi.org/10.1016/j.phro.2017.07.001.
[26] Rosenzweig KE, Hanley J, Mah D, et al. The deep inspiration breath-hold technique in the treatment of inoperable non-small-cell lung cancer. Int J Radiat Oncol Biol Phys 2000;48(1):81–7. https://doi.org/10.1016/s0360-3016(00)00583-6.
[27] Osman SOS, Hol S, Poortmans PM, Essers M. Volumetric modulated arc therapy and breath-hold in image-guided locoregional left-sided breast irradiation. Radiother Oncol 2014;112(1):17–22. https://doi.org/10.1016/j.radonc.2014.04.004.
[28] Grantzau T, Overgaard J. Risk of second non-breast cancer after radiotherapy for breast cancer: A systematic review and meta-analysis of 762,468 patients. Radiother Oncol 2015;114(1):56–65. https://doi.org/10.1016/j.radonc.2014.10.004.
[29] Hofmann L, Forschner A, Loquai C, et al. Cutaneous, gastrointestinal, hepatic, endocrine, and renal side-effects of anti-PD-1 therapy. Eur J Cancer 2016;60:190–209. https://doi.org/10.1016/j.ejca.2016.02.025.
[30] Starkschall G, Butler L. The dose mass histogram: a tool for evaluating thoracic treatment plans. Med Phys 2001;28:1228–9.
[31] International Commission on Radiation Units and Measurements. *Prescribing, Recording, and Reporting Photon Beam Therapy*. International Commission on Radiation Units and Measurements; 1999.
[32] Pandeli C, Smyth LML, David S, See AW. Dose reduction to organs at risk with deep-inspiration breath-hold during right breast radiotherapy: A treatment planning study. Radiat Oncol 2019;14(1). https://doi.org/10.1186/s13014-019-1430-x.
[33] Oechsner M, Düsberg M, Borm KJ, Combs SE, Wilkens JJ, Duma MN. Deep inspiration breath-hold for left-sided breast irradiation: Analysis of dose-mass histograms and the impact of lung expansion. Radiat Oncol 2019;14(1). https://doi.org/10.1186/s13014-019-1293-1.
[34] Mavroidis P, Plataniotis GA, Górka MA, Lind BK. Comments on "Reconsidering the definition of a dose-volume histogram" - Dose-mass histogram (DMH) versus dose-volume histogram (DVH) for predicting radiation-induced pneumonitis. Phys Med Biol 2006;51(24). https://doi.org/10.1088/0031-9155/51/24/L01.
[35] Borgonovo G, Paulicelli E, Daniele D, Presilla S, Richetti A, Valli M. Deep inspiration breath hold in post-operative radiotherapy for right breast cancer: a retrospective analysis. Rep Pract Oncol Radiother 2022;27(4):717–23. https://doi.org/10.5603/rpor.a2022.0085.
[36] Haji G, Nabizade U, Kazimov K, Guliyeva N, Isayev I. Liver dose reduction by deep inspiration breath hold technique in right-sided breast irradiation. Radiat Oncol J 2019;37(4):254–8. https://doi.org/10.3857/roj.2019.00206.
[37] Hormati A. Evaluation of breast cancer radiotherapy induced liver fibrosis by elastography. J. Gastroenterol. Hepatol. Res. 2014:2224–3992. https://doi.org/10.6051/j.issn.2224-3992.2014.03.446.
[38] Xie Y, Guo B, Zhang R. Cost-effectiveness analysis of radiotherapy techniques for whole breast irradiation. *PLoS One* 2021;16(3 March). https://doi.org/10.1371/journal.pone.0248220.