Postoperative Irradiation of Left-Sided Breast Cancer Patients and Cardiac Toxicity

Does Deep Inspiration Breath-Hold (DIBH) Technique Protect the Heart?*

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Purpose: To evaluate the impact of deep inspiration breath-hold (DIBH) technique during postoperative left-sided tangential breast irradiation on minimizing irradiated heart amount compared to normal breathing.

Patients and Methods: In 22 patients with left-sided breast cancer, postoperative CT scanning was performed in different respiratory phases using the Varian Real-time Position Management System™ for monitoring of respiratory chest wall motion. Each patient underwent two CT scans: during normal breathing and DIBH. For each scan, an optimized plan was designed with tangential photon fields encompassing the clinical target volume after breast-conserving surgery or modified radical mastectomy. The resulting dose-volume histograms were compared between both breathing techniques for irradiated volume and dose to the heart.

Results: The mean patient age was 51 years (range: 34–77 years). The DIBH-gated technique was well accepted by all patients. The significant reduction in dose to the irradiated heart volume for the DIBH technique compared to the normal breathing was 56% (mean heart dose: 2.3 Gy vs. 1.3 Gy; p = 0.01).

Conclusion: This study demonstrates that irradiated cardiac volumes can significantly be reduced in left-sided breast cancer patients using DIBH technique for postoperative tangential radiotherapy. Moreover, the technique is safe and feasible in daily routine.

Key Words: Left-sided breast carcinoma · Deep inspiration breath-hold technique · Cardiac toxicity · Postoperative radiotherapy

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Postoperative Strahlenbehandlung bei Patientinnen mit linksseitigem Mammakarzinom und kardiale Toxizität. Kann eine atemgesteuerte Strahlenbehandlung in tiefer Inspiration das Herz schonen?

Ziel: Untersuchung des Stellenwerts einer atemgesteuerten postoperativen Strahlenbehandlung in tiefer Inspiration (DIBH) bei Patientinnen mit linksseitigem Mammakarzinom im Hinblick auf die Belastung des Risikoorgans Herz und Vergleich mit der Normalatemtechnik.

Patienten und Methodik: Bei 22 Patientinnen mit linksseitigem Mammakarzinom wurde postoperativ eine lokale Strahlenbehandlung durchgeführt. Um den Einfluss der Atmung auf die Thoraxbewegung nachzuweisen, wurden zwei Planungs-CTs durchgeführt: unter Bedingungen der Normalatmung und mit dem Varian Real-time Position Management System™ in tiefer Inspiration (Abbildung 1). Ein optimierter Bestrahlungsplan mit tangentialen Bestrahlungsfeldern unter Berücksichtigung des Zielvolumens wurde in beiden Planungs-CTs erstellt. Die jeweiligen Dosis-Volumen-Histogramme für das Herz wurden zwischen beiden Bestrahlungstechniken verglichen.

Ergebnisse: Der Mittelwert des Alters lag bei 51 Jahren (Range: 34–77 Jahre). Die DIBH-Bestrahlung wurde von allen Patientinnen gut toleriert. Die Dosisbelastung am Herzen (Tabelle 1) konnte im Rahmen der DIBH-Technik signifikant gesenkt werden (mittlere Herzdosis: 2,3 Gy vs. 1,3 Gy; p = 0,01).

Schlussfolgerung: Diese Studie demonstriert, dass der Einsatz einer DIBH-Technik die Strahlenbelastung am Herzen bei Patientinnen mit linksseitigem Mammakarzinom signifikant reduziert. Die Anwendung dieser Bestrahlungstechnik ist sicher und in der täglichen Routine einsetzbar.

Schlüsselwörter: Linksseitiges Mammakarzinom · Atemtriggerung · Kardiale Toxizität · Postoperative Strahlenbehandlung

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Introduction

Based on the results of several trials, postoperative breast cancer radiotherapy was considered mandatory and is a well- established management now, even in case of a noninvasive breast carcinoma [8, 9, 13, 17, 20, 21]. In order to reduce local relapse and improve survival, adjuvant irradiation has been established [1, 11, 16]. Convincing evidence exists of cardiac morbidity and mortality in particularly left-sided breast cancer patients if a substantial volume of the heart was exposed to radiation [3, 22]. Moreover, the cardiotoxic effects of radiation may be aggravated by the use of potentially cardiotoxic chemotherapeutic agents, which themselves may cause an irreversible effect on heart tissue [15, 18]. While modern treatments have reduced radiation exposure to the heart, they have not eliminated it. A promising attempt to minimize the volume of heart included in the treatment fields is increasing the distance between the target and the heart due to deep inspiration.

The intention of our prospective study was to evaluate the significance of deep inspiration breath-hold (DIBH) radiotherapy in breast cancer patients and compare this technique to conventional nongated irradiation with regard to cardiac involvement. Another purpose was to find a feasible technique for clinical routine without compromising the dose to the target or increasing the dose to the contralateral organs.

Patients and Methods

26 breast cancer patients received postoperative breathing-adapted radiotherapy. 22 of these patients with a left-sided carcinoma of the breast constitute our study population and were treated after written informed consent in accordance with a protocol approved by the ethics committee of the Medical School of Graz (EK 17-242). We explain our first experience for sparing heart tissue from radiation damage by respiratory-controlled irradiation. The Real-time Position Management (RPM) System™ (Varian Medical Systems, Palo Alto, CA, USA) permits breathing-synchronized CT scanning and radiotherapy during certain time intervals on the linear accelerator. In detail, radiation delivery is only achievable when patients hold their breath in deep inspiration. The present study started in October 2006 and focuses on left-sided breast cancer patients only. Patients underwent either breast-conserving therapy (n = 19) or modified radical mastectomy (n = 3). Chemotherapy was initiated in ten patients (45%) prior to the start of radiotherapy, mostly consisting of an epirubicin- and cyclophosphamide-containing schedule.

Real-Time Positioning Monitoring System™ and CT Scanning

After patient immobilization a lightweight box with two vertical reflective markers is placed horizontal on a bony structure of the chest wall, close to the xiphoid process. To avoid skin reactions, we position the box outside the treatment fields, ideally in the region of maximal anterior-posterior respiratory-induced movements. An infrared camera records the vertical movements of the reflective markers on the box and the information is projected real-time on a computer screen. Before the scanning procedure starts, the audio-coached patients are instructed to perform deep inspiration and to hold their breath for periods of 9–12 s. After setting the individually adapted gating threshold levels for DIBH, both CT scans are done with a slice thickness of 5 mm. The first scan is acquired for radiotherapy during controlled breathing and is followed by a scan for conventional treatment during free breathing without synchronization with the respiratory cycle. For planning-gated treatment, scanning is manually set up once the determined inspiratory plateau is reached. Scanning during DIBH mode is assigned for actual treatments, scanning during free breathing without respiratory control for experimental assessment and if the patient refuses treatment with DIBH radiotherapy for any reason. Both procedures, to train the patient to breathe in a deep inspiratory pattern and scanning processes are lasting about 45 min.

Treatment Planning and Radiotherapy

For consistency, the same physician performed all the delineation procedures and the same physicist the treatment-planning procedures. A three-dimensional conformal planning encompassing the clinical target volume-breast was individually optimized for each CT scan. Avoiding wide tangents, the fields were shaped with multileaf collimators if required and beam-modifying wedges when appropriate for dose homogenization. The patients were treated with external-beam irradiation (6-MV photons) using two opposing tangential fields, up to a dose of 50 Gy in 2-Gy daily fractions. An additional external boost with electrons (2 Gy/10–14 Gy) to the tumor bed was administered in 18 patients. The critical doses were evaluated for the ipsi- and contralateral breast, ipsi- and contralateral lungs, and the heart. Calculated dose-volume histograms were compared between both techniques for each of the aforementioned volumes. To compensate the additional time efforts using the DIBH technique, the daily dose rate was increased to 600 MU/min. The RPM System™ allows automatic on and off triggering of the linear accelerator during daily session, which guarantees delivery of irradiation only in the inspiration plateau phase.

Paired t-tests were used to estimate statistical significance of differences.

Results

For radiotherapy, we used the DIBH technique exclusively. The mean patient age was 51 years (range: 34–77 years). Neither the contralateral breast dosage nor the dose to the contralateral lung was increased when using DIBH. Irradiated liver volume was negligible in all 22 patients. All but one patient completed their course with respiratory-gated radiation. Treatment was discontinued at her own request, after a delivery of 32 Gy. She also refused to continue radiotherapy without respiratory control.

Table 1. Relative and absolute heart dose results (minimum, maximum, and mean) for all 22 patients. D: dose.

Tabelle 1. Relative und absolute Herzbelastung (Minimum, Maximum, Mittelwert) bei allen 22 Patienten. D: Dosis.

	Cardiac volume irradiated $\geq$ 20 Gy					$\geq$ 30 Gy				
	Normal breathing		Breath-hold		p-value	Normal breathing		Breath-hold		p-value
	cm^3	%	cm^3	%		cm^3	%	cm^3	%	
					p = 0.002					p = 0.01
D_{min}	0	0	0	0		0	0	0	0	
D_{max}	39.8	6.3	13.8	1.7		32.4	5.1	11.4	1.4	
D_{mean}	7.6	1.2	1.4	0.2		5.9	0.9	1	0.2	

Respiration Data

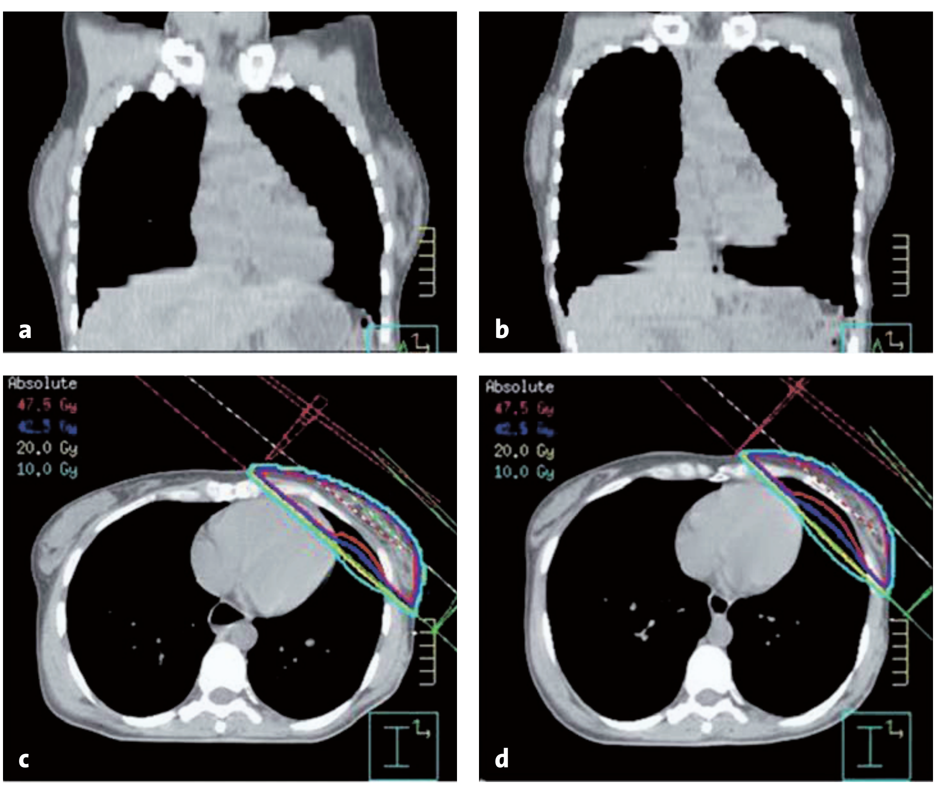
The mean anteroposterior chest wall motion at the position of the xiphoid process was 3.4 mm (range: 2.2–7.4 mm) during normal breathing and 25.1 mm (range: 15.4–37.2 mm) during DIBH scanning, respectively. Gated intervals were clearly defined, and the mean excursions within the gating window during respiratory- controlled therapy were 4 mm (range: 2–6.7 mm). Daily irradiation only took place in deep inspiration mode, as soon as the amplitude reached a certain threshold level. For patients treated with DIBH, the ipsilateral lung volume increased by a factor of 1.7 relative to normal breathing. The evaluated mean central lung distance was 1.8 cm for normal breathing and 2.1 cm for gated radiotherapy.

Cardiac Doses

As shown in Table 1, the relative and the absolute amount of cardiac volume within the radiation fields were significantly influenced by the respiratory mode. As a result of deep inspiration breath-hold, the left-sided breast and the heart were separated during radiation treatment, thus excluding substantial heart volumes from the high-dose area (Figure 1). These results were consistent for all patients, except patient # 7. This 77-year-old woman did not benefit from respiratory gating. However, we want to point out that the applied dose to the heart still was low (Table 1). The conclusive explanation for the cardiac dose excess was determined in her scans, which showed an adhesion of the anterior ventricle wall to the chest wall (Figure 2). These patients definitely are ineligible for breast irradiation in a deep inspiration mode.

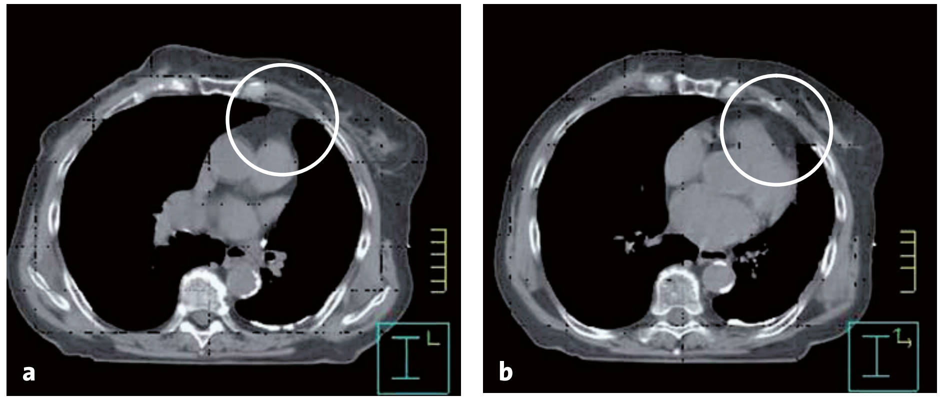
The mean dose to the entire heart was 2.3 Gy (range: 0.6–6.5 Gy) without and 1.3 Gy (0.5–2.4 Gy) with DIBH technique (p = 0.01), respectively. The median maximal dose to the heart was 40.9 Gy (range: 1.2–53.5 Gy) without and 27 Gy (range: 3.7–51.7 Gy) with DIBH (p = 0.01), respectively.

After the individual, but standardized respiratory training session, which did not last > 15 min, patients were able to constantly proceed in accordance with breathing commands without further training sessions. The DIBH mode acquired active participation and cooperation of the patient. The intense contact between physician, physicist and patient satisfies the individual patient demands and was appreciated by all patients.



Figures 1a to 1d. Scan during normal breathing (a) and DIBH (b). Axial CT image and dose illustration at normal breathing (c) and DIBH (d), taken at the same anatomic heart position. The images illustrate the impact of deep inspiration on patient anatomy.

Abbildungen 1a bis 1d. CT während Normalatmung (a) und DIBH (b). Gleiche axiale CT-Schicht durch das Herz mit Isodosenverläufen bei Normalatmung (c) und DIBH (d). Die Bilder zeigen den Einfluss der tiefen Inspiration auf die Patientenanatomie.



Figures 2a and 2b. Axial CT image from patient # 7 at normal breathing (a) and DIBH (b). The adhesive region of the heart is indicated by a white circle.

Abbildungen 2a und 2b. Axiale CT-Schicht der Patientin # 7 bei Normalatmung (a) und DIBH (b). Der weiße Kreis zeigt die Adhäsionen des Herzens an die Thoraxwand.

Discussion

As compared to the literature, the gated inspiration technique proved to be superior in regard to cardiac exposure of breast cancer patients to usually applied radiotherapy without breathing control [4]. The correlation of increased cardiac mortality and irradiation of left-sided breast cancer patients has been examined in earlier series [2]. Referring to the findings of Gyenes et al., who investigated on 100 left-sided breast cancer patients treated with standard irradiation, 5.7% of the entire heart received doses of ≥ 25 Gy [2]. Their final results point out that the amount of cardiac volume involved in the treatment fields are linked to long-term cardiac mortality and were recently discussed by Kuhnt [5]. In our study, we found a significant heart dose reduction using the inspiratory-controlled radiotherapy. Our results demonstrated that 1.4% of the heart received a dose of ≥ 20 Gy and 1.2% a dose of ≥ 30 Gy for normal breathing. In case of respiratory-controlled radiotherapy the dose was only 0.3% for the volume receiving ≥ 20 Gy and 0.2% for the volume receiving ≥ 30 Gy. Even during normal breathing the cardiac exposure is quantitatively small; we agree with others that every attempt should be made to reduce incidental radiotherapy of the heart as much as possible [12]. With the increasing chance of success in radiooncology, unavoidable radiation dose outside the target must be taken into account [14].

Pedersen et al. compared gated radiotherapy with the approach of intensity-modulated radiotherapy for breast tissue. Unfortunately, the advantages of dose homogenization and dose reduction to organs at risk are counterbalanced due to the higher dose to the contralateral breast [10]. Our findings clearly show, that if patients were treated with a DIBH technique, the dose to the contralateral breast tissue was not increased.

The potential risk of radiation-induced lung damage was discussed earlier and the authors postulate that the chance of experiencing a radiation pneumonitis is strongly dependent on the part of irradiated lung [6]. It is obvious that deep inhalation dilutes lung tissue and relatively increases the lung volume within the treatment fields. While lung volume may increase with deep inspiration, the lung density may decrease resulting in irradiation of a reduced fraction of normal lung mass [19].

We want to point out general advantages of using DIBH in breast cancer patients. Applying a procedure of breath-hold decreases the chance of respiratory motion artifacts on the CT scan. Thereby, the accuracy of the target volume and organ at risk dimensions could be improved. Consequently, the calculated dose distribution is more exact and quality of radiation treatment enhanced. Lung inflation significantly increases the distance between the target and the heart and prevents substantial heart volume to be included in the treatment fields. As a result, the dose to the heart, in particular to the anterior wall, is significantly reduced. Our findings given above are in accordance with others, postulated by Sixel et al. [19]. Moreover, with a mean chest wall excursion of 4 mm in the deep inspiratory phase there is nearly no motion for the duration of the treatment interval. To decrease respiratory-induced target movements during irradiation, a number of techniques have been reported with more or less patient comfort [4, 7, 10, 23].

We would like to acknowledge a limitation of the study. Without using intravenous contrast material the unambiguous identification of substructures of the heart would probably be imprecise, even though we made attempts to reach precision and the slice thickness was only 5 mm. Therefore, we are not distinguishing between different heart volumes in the final analysis, which particularly may be of interest.

To our knowledge, this is the largest report involving only left-sided breast cancer patients treated by deep inspiratory gating to advocate practice in daily routine. In the future we will not limit respiratory-controlled irradiation to left-sided cancer patients only. Every single patient will be eligible if heart dose calculation requires it. However, we want to point out that long-time surveillance with a large number of treated patients is necessary to prove if gated radiation, with the beam triggered to be on only during a predetermined phase of the respiratory cycle, is favorable to the outcome of breast cancer patients.

Conclusion

This study demonstrates that irradiated cardiac volumes can significantly be reduced in left-sided breast cancers using

DIBH technique for curative tangential radiotherapy. The method is safe and feasible with appropriate patient selection and instruction; for that reason it can be successfully implemented into clinical routine.

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