Strahlentherapie
und Onkologie

Wide Tangential Fields Including the Internal Mammary Lymph Nodes in Patients with Left-Sided Breast Cancer

Influence of Respiratory-Controlled Radiotherapy (4D-CT) on Cardiac Exposure

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Purpose: To evaluate the impact of wide-tangent fields including the internal mammary chain during deep inspiration breath-hold (DIBH) radiotherapy in patients with left-sided breast cancer on cardiac exposure.

Patients and Methods: Eleven patients with left-sided breast cancer were irradiated postoperatively and underwent CT scans during free breathing and DIBH. For scientific interest only, treatment plans were calculated consisting of wide tangents including the ipsilateral mammary lymph nodes using both, the free breathing and respiratory-controlled CT scan. The resulting dose-volume histograms were compared for irradiated volumes and doses to organs at risk.

Results: The mean patient age was 51 years (range: 37–65 years). Radiotherapy using wide tangents with DIBH as compared to free breathing led to a significantly lower cardiac exposure. Mean irradiated heart volumes (≥ 20 Gy) were 14 cm^3 (range: 0–51.3 cm^3) versus 35 cm^3 (range: 2.1–78.7 cm^3; p = 0.01). For eight patients, DIBH reduced irradiated relative lung volume, while in three patients, the lung volume slightly increased.

Conclusion: Radiation exposure of organs at risk can significantly be reduced for breast cancer patients using the DIBH technique. If radiotherapy of the internal mammary lymph nodes is considered necessary, DIBH may be the preferable technique.

Key Words: Left-sided breast carcinoma · Deep inspiration breath-hold technique · Internal mammary chain · Organs at risk · Wide tangents

Strahlenther Onkol 2009;185:155–60
DOI 10.1007/s00066-009-1939-2

Bestrahlung mit flachen tangentialen Feldern und Einschluss der Lymphknoten entlang der A. mammaria interna bei Patientinnen mit linksseitigem Mammakarzinom. Einfluss der atemgetriggerten Bestrahlungstechnik (4D-CT) auf die Herzbelastung

Ziel: Untersuchung des Stellenwerts einer atemgesteuerten (DIBH) Strahlenbehandlung bei Verwendung flacher tangentialer Felder und Einschluss der Lymphknoten entlang der A. mammaria interna bei Patientinnen mit linksseitigem Mammakarzinom im Hinblick auf die Herzbelastung.

Patienten und Methodik: Bei elf Patientinnen mit linksseitigem Mammakarzinom wurde postoperativ eine lokale Strahlenbehandlung durchgeführt. Für diese CT-Studie wurden unter Bedingungen der Normalatmung und in tiefer Inspiration (Abbildung 1) ein Planungs-CT durchgeführt und jeweils ein optimierter Bestrahlungsplan mit zwei flachen tangentialen Bestrahlungsfeldern unter Berücksichtigung der ipsilateralen Lymphknoten entlang der A. mammaria interna erstellt. Die Dosis-Volumen-Histogramme für die Risikoorgane wurden zwischen beiden Atmungstechniken verglichen.

Ergebnisse: Der Mittelwert des Alters lag bei 51 Jahren (Range: 37–65 Jahre). Die Bestrahlung mit flachen Tangenten und DIBH erbrachte im Vergleich zur Normalatmung eine signifikant geringere Herzbelastung. Die mittlere Herzbelastung (≥ 20 Gy) ergab 14 cm^3 (Range: 0–51,3 cm^3) im Vergleich zu 35 cm^3 (Range: 2,1–78,7 cm^3; p = 0,01; Tabelle 1). Bei acht Patientinnen reduzierte die atemgetriggerte Bestrahlung auch das bestrahlte Lungenvolumen (%), wobei es bei drei Patientinnen geringfügig anstieg (Tabelle 2).

Schlussfolgerung: Die atemgetriggerte Bestrahlung in tiefer Inspiration reduziert signifikant die Strahlenbelastung an Risikoorganen. Bei Indikation des Einschlusses der Lymphknoten entlang der A. mammaria interna kann die Bestrahlung in DIBH von Vorteil sein.

Schlüsselwörter: Linksseitiges Mammakarzinom · Atemtriggerung · Lymphknoten entlang der A. mammaria interna · Risikoorgane · Flache Tangenten

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Received: July 16, 2008; accepted: November 7, 2008

Introduction

Based on the results of several meta-analyses, postoperative radiotherapy in patients with breast cancer is able to substantially improve local control and survival and is a well-established treatment now [2, 9, 10, 12, 18, 20]. The need for locoregional irradiation in patients with four or more positive axillary lymph nodes after an axillary dissection remains clear, but there is an ongoing debate for patients with less than four positive lymph nodes [9, 10, 12–14, 21]. In fact, radiation technique used within the convincing trials of the Danish Breast Cancer Cooperative Group and the British Columbia randomized trial consistently included the internal mammary nodes (IMN) in the treatment fields [9, 10, 12]. The value of including the IMN is presently uncertain and the issue was addressed in EORTC (European Organization for Research and Treatment of Cancer) randomized controlled studies. The majority of American radiooncologists do not advocate IMN radiotherapy because of awaited adverse effects [5]. At that point, we refer to the current treatment guidelines of the German Society of Radiation Oncology (DEGRO), recommending irradiation of the IMN in carefully selected patient subgroups [17].

However, convincing evidence exists of increased cardiac morbidity and cardiovascular deaths in left-sided breast cancer patients if a substantial amount of the heart was included in the treatment fields [8, 22, 23]. While modern treatment planning on the basis of computed tomography (CT) scans has effectively reduced radiation exposure to organs at risk, it remains to be a challenge. A promising attempt is increasing the distance between the target and the heart and diluting the lung tissue due to deep inspiration breath-hold (DIBH) radiotherapy.

The intention of our CT study was to assess the dose and the volume of organs at risk in normal breathing and in deep inspiration-gated radiotherapy in breast cancer patients using the Real-time Position Management (RPM) system™ (Varian Medical Systems, Palo Alto, CA, USA), while tangential field irradiation was targeting the IMN.

Patients and Methods

Eleven patients with left-sided breast cancer were treated postoperatively with breathing-adapted radiotherapy. Informed consent and an approval by the ethics committees of the Medical School of Graz (EK 17-242), Austria, were obtained. The patients underwent an individual training session with the RPM system™ which enabled assessment of breath-hold length, optimal breath-hold level, and patient comfort and compliance capability. Afterwards, for each patient, two sets of CT scans (slice thickness: 5 mm, pitch: 1) were performed, both when the patient held her breath after a deep inspiration and when the patient breathed normally. For the CT study only, the clinical target volume included the breast/chest wall and ipsilateral IMN, and contouring with a safety margin was performed manually by the same physician. Based on the assumption that IMN are adjacent to internal mammary vessels, localization of internal mammary vessels was used as surrogate for IMN.

Planning Procedure and Treatment

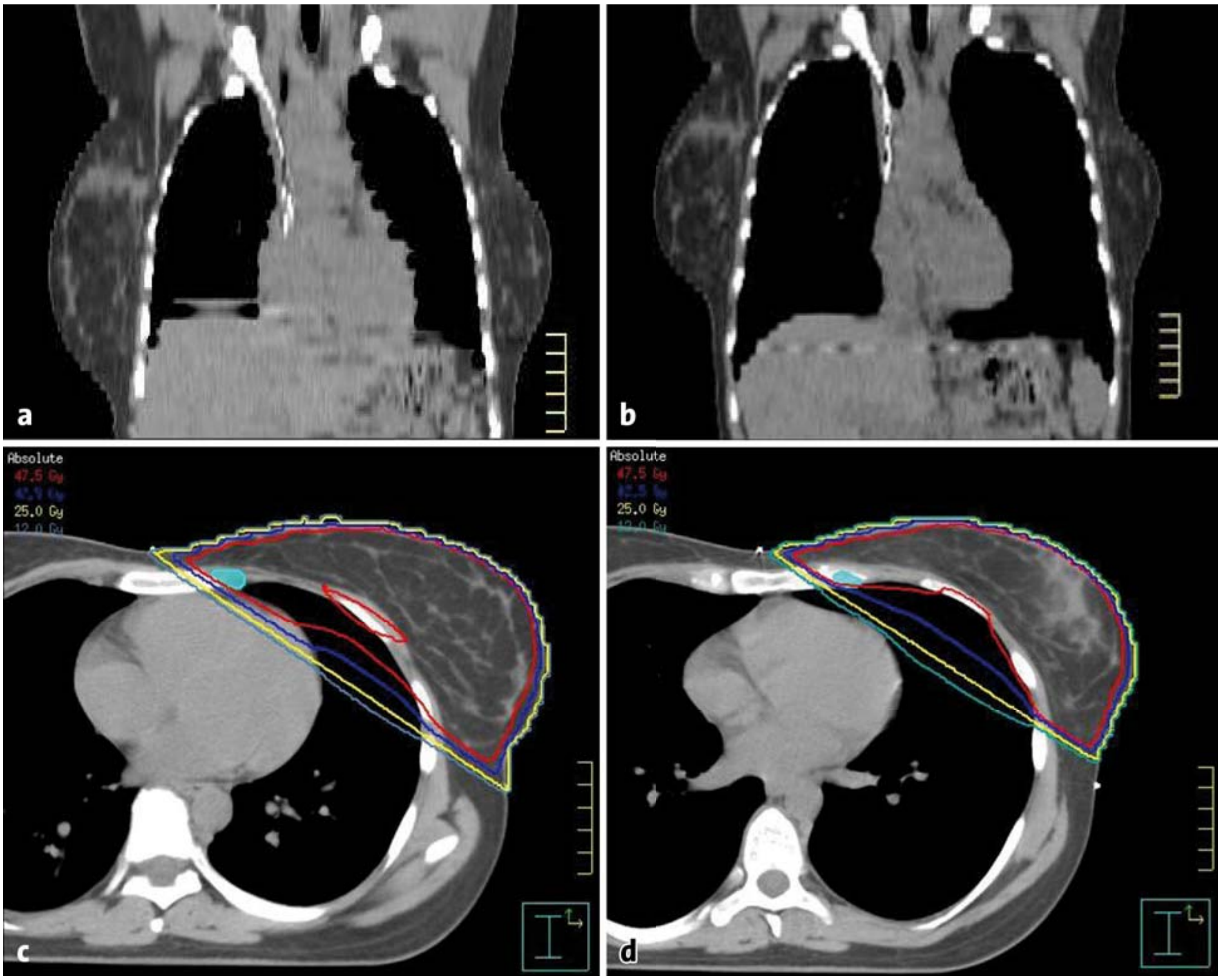
After patient immobilization, a box with two vertical reflective markers was placed on the chest wall in the region of maximal anteroposterior respiratory-induced movements. The gating system identified the vertical movements of the markers and the information was projected real time on a computer screen. In the breath-hold modus patients were audiocoached instructed to perform reproducible breath holds for periods of 9–12 s. The first scan was acquired for radiotherapy during respiratory-controlled breathing and was followed by a scan for conventional treatment during free breathing without synchronization with the respiratory cycle. Scanning during DIBH modus was assigned for actual treatments, scanning during free breathing without respiratory control for experimental evaluation. For constancy, the same physicist performed all planning procedures. A three-dimensional conformal planning encompassing the target volume (regular tangents for radiotherapy and wide tangents targeting the IMN for experimental use) was individually optimized for each CT scan. Patients received respiratory-gated radiation with regular tangents (6-MV photon). For experimental analyses only, treatment plans were divided into two groups based on the applied respiratory technique and matched as follows: group A: normal breathing and wide tangents targeting the IMN; group B: DIBH and wide tangents targeting the IMN. For each group the respective doses and volumes for the breast, lungs and the heart were evaluated and analyzed in dose-volume histograms. The RPM system™ assured daily irradiation of the patients only in the inspiration plateau phase.

All reported significance levels were based on two-sided tests and a p-value of ≤ 0.05 conferred statistical significance.

Results

The mean patient age was 51 years (range: 37–65 years). All patients were able to complete their entire course in accordance with breathing commands without changing to conventional treatment without respiratory control. Figure 1 demonstrates examples of patient CT images (acquired with and without DIBH) and illustrates the impact of deep inspiration on patient anatomy. The mean anteroposterior chest wall movement at the position of the xiphoid process was 4 mm (range: 2–9 mm) during normal breathing and 26 mm (range: 18–35 mm) during DIBH scanning, respectively. Individually gated intervals were defined, and the mean excursions observed within the gating window during respiratory-controlled therapy were 4 mm (range: 2–5 mm).

To ensure inclusion of the IMN in wide tangents, the medial field margin was moved to 2.2 cm (mean) with a range of 0.2–5 cm across midline for group A and to 2.4 cm (mean) with a range of 0.7–4.4 cm for group B, whereas other field borders remained identical. For patients treated with DIBH, the ipsilateral lung volume increased by 39% relative to normal breathing and, consequently, lung tissue density was lowered due to inflation. The measured central lung distance (mean) for group A was



Figures 1a to 1d. Scan during normal breathing (a) and DIBH (b). Axial CT sections showing dose distributions and contouring of the mammary chain at normal breathing with wide tangents (c) and at DIBH with wide tangents (d), taken at the same heart position.

Abbildungen 1a bis 1d. CT während Normalatmung (a) und während DIBH (b). Axiale CT-Schichten durch die gleiche Herzebene mit Isodosen und Darstellung der Lymphknotenregion entlang der A. mammaria interna, in Normalatmung mit flachen Tangenten (c) und in DIBH mit flachen Tangenten (d).

2.8 cm for normal breathing and 3.3 cm for gated radiotherapy (group B). In ten patients, the actual amount of irradiated lung (cm^3) increased with DIBH (Table 2). For eight patients, DIBH reduced irradiated relative ipsilateral lung volume (%), while in the remaining three patients the irradiated lung volume slightly increased. The absolute and relative amount of volumes ≥ 20 Gy for heart and lung tissue within the radiation fields using the different respiratory techniques is depicted in Tables 1 and 2 and was significantly influenced by the respiratory mode. Lung inflation increased the distance between the target and the heart and prevented substantial heart volume to be included in the treatment fields. The amount of heart varied noticeably among all patients, but the application of DIBH reduced heart exposure significantly (Table 1). The mean dose to the entire heart was 4 Gy (range: 1.2–8.5 Gy) for group A and 2.5 Gy (0.7–6.4 Gy) for group B ($p = 0.001$), respectively. The mean dose to the contralateral breast was 1.2 Gy for group A and 1.4 Gy for group B without statistical significance. Irradiated liver volume was negligible in all patients.

Discussion

As a consequence of advances in modern radiooncology, increasing numbers of patients are surviving their malignancies. Treatments leading to increased survivorship, however, may be associated with adverse effects. Therefore, unavoidable radiation dose outside the target should be kept to a minimum even though the applied dose was low [15]. Despite the fact that some have shown IMN involvement in patients with definite tumor characteristics like primary tumor localization in the central or inner portion of the breast and involved axil-

Table 1. Absolute and fractional cardiac results for all eleven patients. DIBH: deep inspiration breath-hold technique.

Tabelle 1. Absolute und relative Herzbelastung bei allen elf Patientinnen. DIBH: Atemtriggerung.

	Absolute and fractional volumes of ipsilateral heart irradiated ≥ 20 Gy (V20heart)				
	Normal breathing Wide tangents Group A		DIBH Wide tangents Group B		
Patient	cm³	%	cm³	%	
1	78.7	13.3	51.3	9.3	
2	68.7	12.1	18.0	4.5	
3	52.5	7.3	34.5	4.2	
4	62.0	7.6	15.0	1.8	
5	65.8	10.4	28.0	5.0	
6	2.1	0.5	0.0	0.0	
7	2.5	0.4	0.0	0.0	
8	4.1	0.8	4.6	1.1	
9	5.9	0.9	0.0	0.0	
10	28.0	4.9	2.4	0.4	
11	15.0	1.7	0.3	0.1	
					p-value
Mean	35.0		14		0.01

Table 2. Absolute and fractional lung results for all eleven patients. DIBH: deep inspiration breath-hold technique.

Tabelle 2. Absolute und relative Lungenbelastung bei allen elf Patientinnen. DIBH: Atemtriggerung.

	Absolute and fractional volumes of ipsilateral lung irradiated ≥ 20 Gy (V20lung)				
	Normal breathing Wide tangents Group A		DIBH Wide tangents Group B		
Patient	cm³	%	cm³	%	
1	343	19.0	578	20.7	
2	259	17.7	339	18.4	
3	253	18.2	279	13.6	
4	284	18.4	384	12.1	
5	147	13.6	338	17.3	
6	270	16.3	241	9.7	
7	322	19.9	495	18.0	
8	330	18.9	465	18.7	
9	144	15.2	241	12.2	
10	227	19.6	338	15.1	
11	372	18.8	403	12.4	
					p-value
Mean	268		373		0.002

lary lymph nodes, failure rates involving the IMN remain low [6, 7, 16]. Therefore, the widely accepted practice of not specifically including the IMN seems comprehensible. Otherwise, verified internal mammary nodal chain drainage is a prognostic indicator in axillary node-positive breast cancer patients and predicts a threefold increased mortality risk in node-positive patients [24]. The potential benefit of treating the area of the IMN is that microscopic involvement may theoretically represent a source of distant metastases and therefore this node group is assuming new importance [6, 12, 16].

The EORTC conducted a trial addressing the potential advantages and disadvantages of treating the internal mammary chain in patients with medially or centrally located tumors but definitive results will not be available before 2010. A recently published study proved that the quality assurance program in the context of the aforementioned trial was of great assistance and probably will increase the reliability of the final trial results [11].

Hare et al. found that when using standard tangential fields, 73% of patients had complete or at least partial incidental inclusion of the IMN [7]. This may in part explain the low IMN failure pattern. However, Fowble et al. were not able to find a beneficial effect for IMN irradiation, but while patients were designated as having irradiation restricted to the breast, radiation techniques may inadvertently include at least parts of the IMN as discussed before [4].

As the risk of cardiovascular and lung toxicity is related to applied radiation dose and volume, the intention of our investigation was to quantify the doses in organs at risk while targeting the breast or chest wall and IMN using deep tangents. Moreover, we compared the results between both respiration techniques.

As shown by Sautter-Bihl et al., the mean heart dose was 3.8 Gy (range: 2–17.4 Gy) using deep tangential field irradiation for left-sided breast cancer [19]. These results were consistent with our findings in patients treated with normal breathing technique. However, application of the DIBH technique proved to significantly lower irradiated heart dose. For three patients, the respiratory-gated radiotherapy moved the heart completely out of the radiation fields. In another four patients < 2% of the cardiac tissue was included in the target volume. The fact that patients benefited from the DIBH modus in terms of cardiac exposure indicates that the attempt to use this respiratory maneuver is comprehensible, but benefit needs to be established. Particularly for patients with a specific anatomy that aggravates difficulties in limiting the dose to the heart, respiratory-controlled irradiation might offer a practicable resolution.

The impact of respiratory-gated irradiation on lung tissue was also considered. There was a high variation of individual lung volume within the patients representing the diversities in body contours. Increasing the absolute amount of lung volume in the tangential field due to deep inspiration does not mean that the actual amount of lung volume was increased. The total lung volume increased due to deep inspiration and, therefore, lung density was reduced. By calculating dose-volume histograms for lung, we found out that in eight out of eleven patients the relative amount of irradiated lung volume decreased and only slightly increased in three patients, if the DIBH technique was used. Moreover, the mean fractional lung volume in the radiation field with DIBH was significantly lower compared to free breathing (Table 2). For that reason, we conclude that there is no increased risk for radiation-induced pneumonitis with DIBH compared to normal breathing.

A disadvantage of applying deep tangents is that depending on the body contour medial parts of the contralateral breast probably will receive higher radiation doses. For our patients, the mean dose to the contralateral breast was 1.2 Gy for group A (normal breathing) and 1.4 Gy for group B (DIBH). Compared to the literature where patients were equally treated with wide tangents, the evaluated dose to the contralateral breast was specified with 2.2 Gy [19]. Consequently, our results especially with the DIBH technique were excellent. It is plausible that the scattered dose to the opposite breast may have a carcinogenic effect and therefore normal tissue should be prevented from any dose excess as far as possible, though the benefit of radiotherapy outweighs the risk by far [3].

We would also like to acknowledge some limitations of the study, for example the small study group. Without using intravenous contrast medium, exact identification and contouring of substructures of the heart would probably be imprecise, even though we made attempts to solve this problem and the slice thickness was only 5 mm. Therefore, we are not differentiating between heart subvolumes in the final analysis, which particularly may be of interest. Besides that, most studies have reported only the mean dose to the whole breast.

Given the literature about treatment or exclusion of IMN, there may be clinical situations where the individual radiooncologist may decide to target the IMN. It is obvious, that care should be taken to decrease the amount of heart and lung in the treatment field, particularly in low-risk patients with a high life expectancy receiving cytotoxic systemic therapy [1].

Conclusion

This study demonstrates that radiation exposure to the heart and lung due to wide tangential radiotherapy can significantly be reduced for left-sided breast cancer patients using the DIBH technique. In the next years, we are awaiting conclusive recommendations deducted from results of large trials, but today, the question of treating the IMN remains unanswered. If radiotherapy of the IMN is required in carefully selected patients, DIBH may be a feasible technique for daily routine in respect of organs at risk.

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