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# Quantitative Assessment of Irradiated Lung Volume and Lung Mass in Breast Cancer Patients Treated with Tangential Fields in Combination with Deep Inspiration Breath Hold (DIBH)

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**Purpose:** Comparison of the amount of irradiated lung tissue volume and mass in patients with breast cancer treated with an optimized tangential-field technique with and without a deep inspiration breath-hold (DIBH) technique and its impact on the normal-tissue complication probability (NTCP).

**Material and Methods:** Computed tomography datasets of 60 patients in normal breathing (NB) and subsequently in DIBH were compared. With a Real-Time Position Management Respiratory Gating System (RPM), anteroposterior movement of the chest wall was monitored and a lower and upper threshold were defined. Ipsilateral lung and a restricted tangential region of the lung were delineated and the mean and maximum doses calculated. Irradiated lung tissue mass was computed based on density values. NTCP for lung was calculated using a modified Lyman-Kutcher-Burman (LKB) model.

**Results:** Mean dose to the ipsilateral lung in DIBH versus NB was significantly reduced by 15%. Mean lung mass calculation in the restricted area receiving $\leq$ 20 Gy ($M_{20}$) was reduced by 17% in DIBH but associated with an increase in volume. NTCP showed an improvement in DIBH of 20%. The correlation of individual breathing amplitude with NTCP proved to be independent.

**Conclusion:** The delineation of a restricted area provides the lung mass calculation in patients treated with tangential fields. DIBH reduces ipsilateral lung dose by inflation so that less tissue remains in the irradiated region and its efficiency is supported by a decrease of NTCP.

**Key Words:** Breast cancer · Lung dose · Deep inspiration breath-hold technique · NTCP

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## Quantitative Bestimmung von Lungenvolumen und -masse von BrustkrebspatientInnen bei einer Bestrahlung mit tangentialen Feldern unter Einsatz einer Luftanhaltetechnik in tiefer Inspiration (DIBH)

**Ziel:** Vergleichende Bestimmung von bestrahltem Lungenvolumen und bestrahlter Lungenmasse in Normalatmung (NB) und tiefer Inspiration (DIBH) bei PatientInnen mit Brustkrebs, die mit tangentialen Feldern bestrahlt wurden, und ihrem Einfluss auf die Normalgewebskomplikationswahrscheinlichkeit (NTCP).

**Material und Methodik:** Computertomographiedatensätze von 60 PatientInnen wurden in NB und DIBH miteinander verglichen. Mit einem „Real-Time Position Management Respiratory Gating System" (RPM) wurden die anteroposteriore Thoraxbewegung aufgezeichnet und untere und obere Schwellenwerte definiert. Die ipsilaterale Lunge sowie eine beschränkte tangentiale Lungenregion wurden konturiert und die mittlere und maximale Dosis berechnet. Die bestrahlte Lungenmasse wurde mittels Dichteberechnung bestimmt. Die NTCP für die Lunge wurde mit einem modifizierten Lyman-Kutcher-Burman-(LKB-)Modell errechnet.

**Ergebnisse:** Die mittlere ipsilaterale Lungendosis war in DIBH gegenüber NB signifikant um 15% reduziert. Die mittlere Lungenmasse (errechnet nach Tabelle 1), die $\leq$ 20 Gy ($M_{20}$) erhielt, war in DIBH um 17% reduziert, während das Lungenvolumen deutlich vergrößert war (Tabelle 2). NTCP zeigte in tiefer Inspiration eine Verbesserung von 20% (Abbildung 1). Der Zusammenhang der individuellen Atmungsamplitudenzunahme zwischen NB und DIBH mit dem vergrößerten Lungenvolumen konnte dargestellt werden (Abbildung 2), während keine Korrelation zwischen der individuell erreichten Atmungsamplitude mit der NTCP aufgezeigt werden konnte (Abbildung 3).

**Schlussfolgerung:** Die Konturierung eines beschränkten Teils der ipsilateralen Lunge ermöglicht die Bestimmung der bestrahlten Lungenmasse bei Bestrahlung mit tangentialen Feldern. Bei tiefer Inspiration verbleibt ein geringerer Anteil an Lungengewebe im Feld und führt zu einer Reduktion der ipsilateralen Lungendosis, unterstützt durch eine Abnahme der NTCP.

**Schlüsselwörter:** Brustkrebs · Lungendosis · Atemtriggerung · NTCP

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## Introduction

In patients with left-sided breast cancer treated with tangential fields in combination with a deep inspiration breath-hold (DIBH) technique, a decrease of the dose to the heart by increasing the distance from the chest wall has been shown [12]. A reduction of absolute volume and dose may translate into a reduction of late effects of radiation and radiation in combination with neoadjuvant, concomitant, or adjuvant cardiotoxic systemic agents (e.g., chemotherapy, biologicals) [11, 27, 28].

The probability of pulmonary side effects is linked to lung dose, fraction dose and volume [13, 17], but its clinical significance has been shown to correlate with lung mass. It has to be kept in mind, however, that a DIBH technique increases the volume of lung receiving varying doses, which may "drain the gain", if one postulates that volume/dose is the dominant risk factor for lung tissue damage.

Lung dose calculation in low-density tissue proved to be a challenge for treatment-planning systems, which was discussed in studies implementing lung density corrections [2, 23] along with its impact on the prescribed target dose. Additional uncertainties, however, arise with the implementation of DIBH radiotherapy. These include the segmentation of lung volume, the dose calculation of the particular treatment-planning system and the irradiated lung tissue mass. When lung is voluntarily expanded, its density decreases and not volume but irradiated lung tissue mass becomes the predominant parameter to assess the radiation dose applied, irrespective of technique.

The purpose of our study was to analyze the amount of irradiated lung mass in a DIBH versus normal breathing (NB) mode and to quantify the applied doses with the tools a commercial treatment-planning system provides.

To the best of our knowledge, this is the first study to also consider the efficiency of DIBH by analyzing the correlation between breathing amplitude and normal tissue complication probability (NTCP).

## Material and Methods

### Patients

Between October 2006 and June 2008, 60 patients with breast cancer who were referred for postoperative irradiation took part in a study approved by the scientific ethics committee of the Medical University of Graz, Austria. 56 patients (including one male) had left- and four right-sided breast cancer; the median age was 49 years (range: 30–77 years). 57 patients received 50 Gy (2 Gy/day, 5 days/week); in three patients the daily dose was reduced to 1.8 Gy due to a large breast volume.

### Gating System

The Real-Time Position Management Respiratory Gating System (RPM, Varian Medical Systems, Inc., Palo Alto, CA, USA) uses a fiducial marker block placed on the thorax and an infrared camera, which monitors the anteroposterior movement of the chest wall in real time [33]. The definition of a gate – a small range in the breathing cycle – permits radiation only if the breathing amplitude is within a predefined upper and lower threshold.

All patients were audio-coached [10] in a DIBH technique [12] to reach their individual maximum of vertical chest wall movement. Individual gating thresholds were set in the RPM according to the patient's maximum and reproducible breathing amplitude.

Computed tomography (CT) data were acquired in a spiral mode with a slice thickness of 5 mm, with the first scan performed in a conventional breathing mode to allow for a change in treatment if necessary (e.g., lack of compliance or technical unavailability), followed by a manually triggered scan on the predefined individual gate.

### Treatment Planning

Both CT scans were transferred to our planning system (Pinnacle, Philips Medical Systems (Cleveland) Inc., Medical Imaging Equipment, Cleveland, OH, USA. Optimization of the tangential fields was achieved by adapting the radiation field size, weighting of fields, multileaf collimator shaping and, if required, wedges.

The absorbed dose was calculated for the target, the ipsilateral lung and the heart. Standard dose-volume histograms (DVHs) of the two breathing modes were compared. Although DVHs are useful to compare treatment plans, the change of lung volume due to deep inspiration leads to an overestimation of irradiated volume.

To quantify the changing lung density within breathing patterns, Butler et al. [4] recommended the calculation of a dose-mass histogram (DMH), which is likely to provide a better estimation of the actual number of lung cells damaged by radiation than lung volume. Since conventional planning systems do not normally offer DMHs, the mean density of the ipsilateral lung was calculated from CT voxels.

In addition, a smaller "restricted" region of the lung enclosed by the 10% isodose was delineated, excluding one voxel thickness in the peripheral region to avoid systematic errors from segmentation algorithm and artifacts [29].

### Data Analysis

Ipsilateral mean lung mass and mean density, as well as mean mass and density in the restricted area of the tangential region were tested for NB and DIBH. Masses were calculated as a product of volume and volume-based density. The Lyman-Kutcher-Burman (LKB) model [3, 15, 20], widely used to calculate the probability of lung damage, was adopted for NTCP calculation:

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \qquad (1),$$

with

$$t = \frac{MD - TD_{50}}{m \cdot TD_{50}} \qquad (2).$$

The modified clinical model [16] defines MD as mean lung dose, $TD_{50}$ = 37.6 Gy (95% confidence interval [CI], 34.6–41.4) for radiation-induced pneumonitis in the ipsilateral lung and m = 0.35 (95% CI, 0.29–0.43) [24]. Daily fractions with 1.8 Gy were converted with the linear-quadratic model with $\alpha/\beta = 3$ Gy.

For statistical analysis the two-sample single-tailed t-test was used. A probability level of $< 0.05$ was considered statistically significant.

### Results

The mean chest wall movement during DIBH was 24.9 mm (range: 13–38 mm). The amplitude during NB (mean: 3.5 mm; range: 1–8.3 mm) limited the range of the predefined gate during DIBH (mean: 4 mm; range: 2–8 mm) to keep the uncertainty due to NB thoracic movement equal.

The mean field size adaption from DIBH-gated isodose plans versus NB was 0.01 cm in longitudinal direction (range: 0–2 cm) for five patients and 0.15 cm (range: –0.5 to 2.5 cm) in vertical aperture for 42 patients. For 27 patients vertical field sizes were enlarged, whereas 15 patients required a field reduction.

Mean dose to the ipsilateral lung in DIBH was 5.03 Gy (range: 2.8–7.2 Gy), whereas mean lung dose (MLD) in NB was 5.8 Gy (range: 2.1–9.2 Gy; p = 0.005). The difference of the maximum dose to the ipsilateral lung in DIBH with 50.8 Gy (range: 44.2–54.4 Gy) versus the dose in NB with 50.9 Gy (range: 44.5–54.8 Gy) was not statistically significant.

Mean density of the ipsilateral lung was 0.19 g/$cm^3$ (range: 0.14–0.34 g/$cm^3$) in DIBH and 0.32 g/$cm^3$ (range: 0.21–0.45 g/$cm^3$) in NB mode (Table 1). Mass calculation differed ~ 6% in comparison. Considering only the tangential part of the left lung, mean density changed from mean 0.19 g/$cm^3$ to 0.16 g/$cm^3$ in DIBH, whereas in NB a density reduction to 0.25 g/$cm^3$ was observed. With an additional voxel-size exclusion in the restricted region, as defined above, mean density was reduced to 0.11 g/$cm^3$ (range: 0.05–0.25 g/$cm^3$) in DIBH and 0.19 g/$cm^3$ (range: 0.11–0.31 g/$cm^3$) in NB, respectively. Mass variations in both breathing modes were only 2%.

Mean lung mass receiving 20 Gy ($M_{20}$) was calculated with the volume receiving ≥ 20 Gy ($V_{20}$) with $M_{20} = V_{20} * \rho_{\text{restricted region}}$ (g) Gy (see Table 2). Considering volume in both breathing modes alone led to an explicit increase in DIBH, whereas the percental volume showed the opposite trend. The estimation of mean mass was associated with a statistically significant reduction of irradiated lung mass in DIBH.

The calculated NTCP for both breathing modes is shown in Figure 1. Mean NTCP in DIBH was 0.613% (range: 0.384–0.896%) versus NB with 0.727% (range: 0.331–1.29%; p = 0.001).

**Table 1.** Density and mass calculation of the ipsilateral lung and the restricted tangential part for all patients. DIBH: deep inspiration breath hold; NB: normal breathing.

**Tabelle 1.** Dichte- und Massenberechnung der ipsilateralen Lunge und des eingeschränkten tangentialen Anteils für alle PatientInnen. DIBH: Luftanhaltetechnik in tiefer Inspiration; NB: Normalatmung.

| | NB | DIBH |
|---|---|---|
| Mean total ipsilateral lung volume ($cm^3$) | 1,404.90 | 2,453.00 |
| Mean total ipsilateral lung density (g/$cm^3$) | 0.32 | 0.19 |
| Mean total ipsilateral lung mass (g) | 435.00 | 464.80 |
| Mean restricted lung volume ($cm^3$) | 279.60 | 460.00 |
| Mean restricted lung density (g/$cm^3$) | 0.19 | 0.11 |
| Mean restricted lung mass (g) | 49.50 | 48.90 |

**Table 2.** Comparison of $V_{20}$ and $M_{20}$ in deep inspiration breath hold (DIBH) and norma breathing (NB). $M_{20}$ was calculated with the mean density of the restricted region for each patient.

**Tabelle 2.** Vergleich von $V_{20}$ und $M_{20}$ in Atemanhaltetechnik in tiefer Inspiration (DIBH) und Normalatumung (NB). $M_{20}$ wurde mit der mittleren Dichte der eingeschränkten Region für jede Patientin/jeden Patienten einberechnet.

| Ipsilateral lung | $V_{20}$ Gy | | | | $M_{20}$ Gy | | | |
|---|---|---|---|---|---|---|---|---|
| | DIBH | | NB | | DIBH | | NB | |
| | $cm^3$ | % | $cm^3$ | % | g | % | g | % |
| Minimum | 27.5 | 1.5 | 10.3 | 0.9 | 4.0 | 1.3 | 2.1 | 0.6 |
| Maximum | 464.0 | 14.6 | 391.6 | 20.2 | 46.9 | 12.7 | 51.5 | 13.5 |
| Mean | 207.8 | 8.4 | 147.3 | 10.3 | 22.3 | 6.5 | 26.0 | 7.3 |
| | | | | | | | p = 0.005 | |

DIBH expands lung volume $\Delta V = V_{DIBH} - V_{NB}$ with a mean volume of 1,048 $cm^3$ (range: 379–1,707 $cm^3$). The dependence of $\Delta V$ and the increase of the breathing amplitude measured by the breathing cycle in the RPM system is demonstrated in Figure 2. The regression line shows the relationship between increased lung volume and breathing amplitude. In DIBH, increased lung volume is subjected to individually increased amplitude.

Patients were audio-coached to reach their maximum reproducible breathing amplitude, and in correlation with NTCP (Figure 3) there was no universally valid amplitude height suggesting a lower NTCP.

### Discussion

60 breast cancer patients were included in a study using an RPM gating system which enables dose delivery according to patients individual breathing gate defined in DIBH mode. While a dose/volume reduction of the heart has been demonstrated [11, 27, 28], the consequences of simultaneously increasing the irradiated lung volume are yet insufficiently investigated and hampered by the complexity of lung dose calculations, which include the following:

First, lung contains different structures with density changes in lung tissues ranging from –960 HU to –190 HU, which leads to artifacts and additional uncertainties concerning the estimation of HUs. Furthermore, CT scan measurements are affected by radiation dose in very-low-density lung

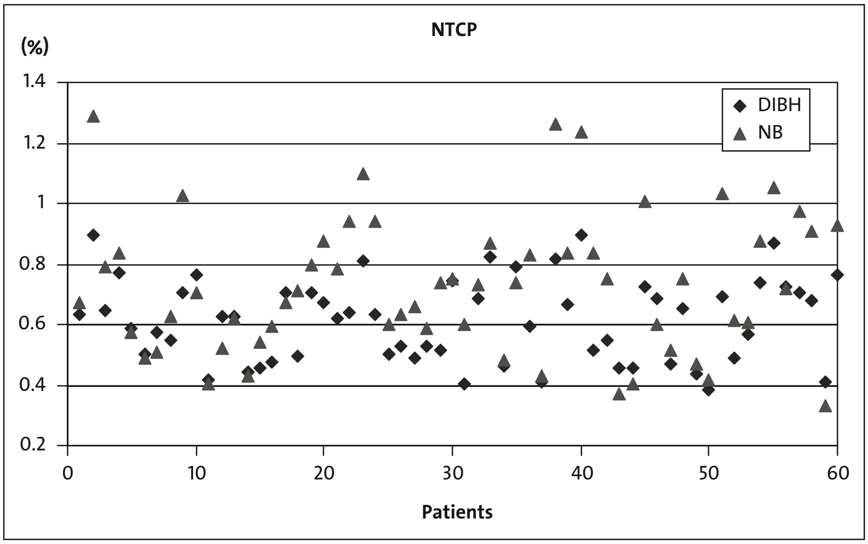

**Figure 1.** NTCP calculation (%) of all patients in DIBH versus NB mode.

**Abbildung 1.** Gegenüberstellung der NTCP-Berechnung (%) aller PatientInnen für DIBH und NB.

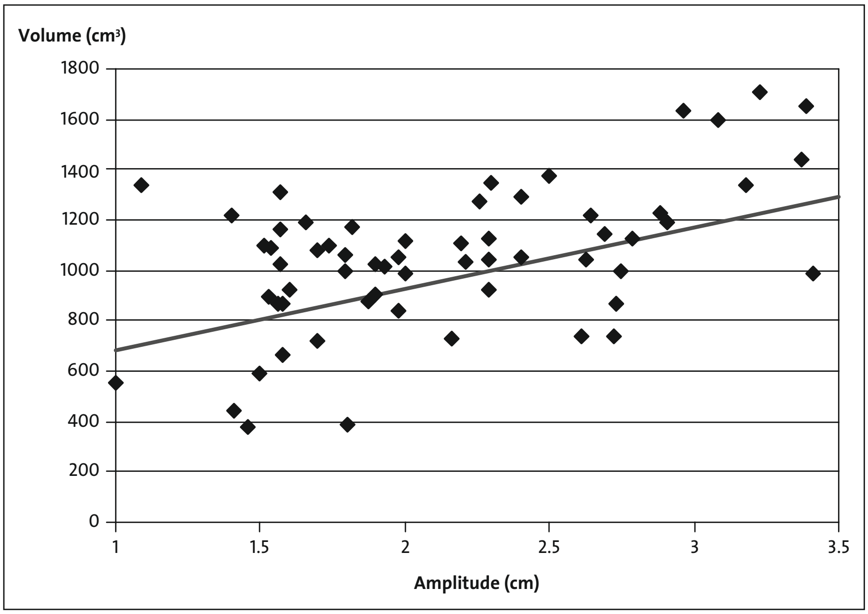

**Figure 2.** Correlation of each patient's increase ΔV of the ipsilateral lung volume to the increase of the measured breathing amplitude in DIBH.

**Abbildung 2.** Korrelation der individuellen ipsilateralen Lungenvolumenvergrößerung ΔV und der Vergrößerung der gemessenen Atmungsamplitude in DIBH.

structures [35], whereas lung volume is relatively insensitive to it. To minimize these influences, a side-specific CT conversion table was created with the same scan protocol as used for patients. There still remains an impact of HU variation on the treatment-planning system, which was discussed by Cozzi et al. [5] and Thomas [30], and is verified for low-density materials in a small deviation of MUs.

To quantify organ dose, Mavroidis et al. [21] proved the DMH concept to be superior to the calculation of DVHs. Our commercial treatment-planning system does not provide calculation of a DMH, but solely region-dependent density values with consecutive calculation of mass.

Since lung density is not homogeneously distributed, with greatest density in the base which decreases toward the apex [8], we chose to define the tangential part of the lung within the 10% isodose as region of interest. Such an approach seems supported by Vågane et al. [32], who recently analyzed density changes after breast cancer radiotherapy due to reduced air content dominated by the cranial-ipsilateral response. Further uncertainty factors, which influence mean density, are mismatch and registration errors in the segmentation process. The exclusion of lung tissue toward the chest wall of one voxel, as recommended by Theuws et al. [29], resulted in a difference of mean density of the whole lung versus tangential part in NB of about 42%, whereas in DIBH the difference added up to 43% (Table 1).

It should be taken into account that dose calculation in low-density tissues is strongly dependent on dose algorithms of the applied treatment-planning system. Fogliata et al. [7] studied the calculation of lung dose in different breathing patterns and demonstrated the calculation with pencil-beam algorithm to be strongly defective. The collapsed-cone algorithm as used by the Pinnacle planning system was considered to deliver adequate dose computation.

The incidence of pneumonitis has been shown to correlate with the increase of the MLD to the ipsilateral lung [34]. In DIBH, MLD with 5.03 Gy (range: 2.8–7.2 Gy) was significantly improved up to 15% versus NB with 5.8 Gy (range: 2.1–9.2 Gy; p = 0.005). With tangential treatment technique, MLD in both breathing modes is still less than in a multisequented conformal radiotherapy trial by Gulybán et al. [9], who reported a MLD of about 10 Gy. Generally, lung dose depends on technique [1, 19], but for tangential beams DIBH is favorable.

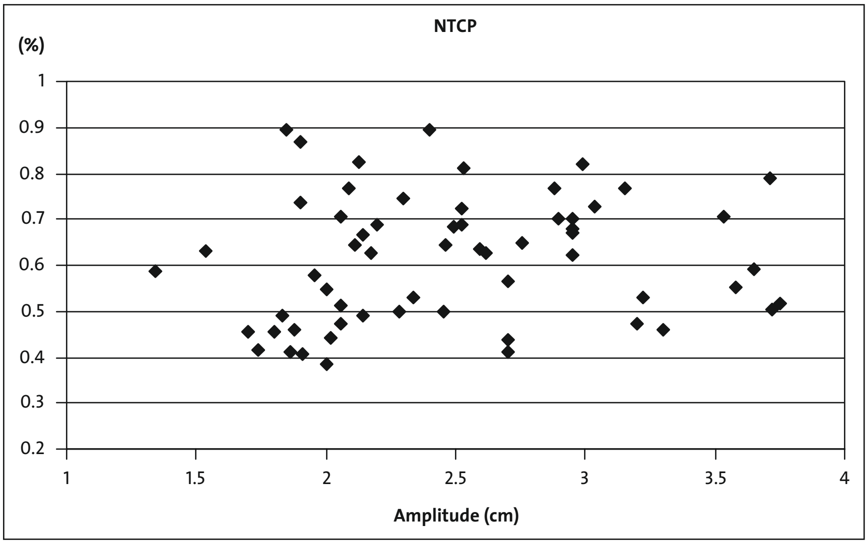

**Figure 3.** NTCP calculation subject to DIBH amplitude.

**Abbildung 3.** NTCP-Berechnung in Abhängigkeit von der Atmungsamplitude in DIBH.

Lind et al. [18] found $V_{20}$ to be an important variable for the occurrence of radiation-induced pulmonary toxicity in patients with breast cancer. In Table 2, the difference of lung volume $V_{20}$ versus irradiated lung mass for 20 Gy is presented. The mean $M_{20}$ value of DIBH shows a lower irradiated lung mass than in NB. The mean reduction was 17% which is supported by Butler et al. [4], who calculated, in a cohort of ten patients, a reduction by 19%. $V_{20}$ was increased in DIBH by 29%, whereas the percentage of $V_{20}$ was reduced in DIBH by 22%. Relative lung volume is predictive for irradiated lung tissue, but quantification requires the calculation of irradiated lung mass. Maximum mass in $M_{20}$, averaged for all patients, was reduced in DIBH by about 10%. In 16 of 60 patients, the $M_{20}$ with DIBH was higher than with NB showing a maximum value of 10 g. Examining this aspect, we found no correlation with the adaption of field margins. Furthermore, we could not identify pre-CT scan predictors, indicating which patients would have a higher irradiated lung mass in a gated treatment. Generally, irradiated lung mass was reduced in 73% of the patients; therefore, the individual potential benefit should be carefully assessed.

Another aim of the current study was the quantification of biological lung complication including different breathing patterns. Initially empirical NTCP calculation is based on observed complication. Considering the different NTCP models, most of the data concerning the calculation parameters were acquired with different planning algorithms [24, 31]. Figure 1 shows that for the irradiated ipsilateral lung NTCP is statistically significantly lower in deep inspiration with an overall benefit of about 20%. The NTCP value of 0.613% in our study is lower than in a large study of Minor et al. [22], who reported an overall rate of radiation pneumonitis of 1.2%. With changing dose/fraction schedules delivering a lower total dose with larger fractional dose [25, 26], DIBH may favorably influence potential late normal-tissue effects.

Korreman et al. [11] postulated a median of the relative reduction by 84% from NB to DIBH. Considering the volume delineation, pencil-beam calculation and the NTCP model adaption to nonuniform doses by DVH, their values show the benefit of gating, but their given percentage seems to be overestimated. Moreover, we think that the parameters in the NTCP model regarding extreme breathing situations need to be addressed in future. These parameters were limiting factors in our trial.

Some studies [6, 10, 11, 14] discussed different methods of breathing coaching and irradiation methods to deliver the dose in a gated state. At our clinic, we use an audio-coaching technique to support patients in reaching their individual maximum level of inspiration. The level was affected by comfort and reproducibility.

To our knowledge, this is the first trial to investigate if our breathing training and our definition of an individual amplitude correlates with NTCP. Figure 2 shows increased lung volume $\Delta V$ to be connected to the breathing amplitude, whereas no direct connection between chest wall amplitude and NTCP can be shown (Figure 3). Therefore, we conclude that the individual range patients reach in DIBH with our audio-coaching training technique changes NTCP (Figure 1) favorably.

## Conclusion

The delineation of a restricted lung area supports mean density calculation, which allows a good estimation of irradiated lung mass. Analysis of 60 patient data, treated with tangential breast irradiation, shows that DIBH significantly reduces mean ipsilateral lung mass in the vast majority of patients and its efficiency is supported by a decrease of NTCP.

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