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ORIGINAL ARTICLE

Dose variability in different lymph node levels during locoregional breast cancer irradiation: the impact of deep-inspiration breath hold

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Abstract

Purpose Aim of the present analysis was to evaluate the movement and dose variability of the different lymph node levels of node-positive breast cancer patients during adjuvant radiotherapy (RT) with regional nodal irradiation (RNI) in deep-inspiration breath hold (DIBH).

Methods Thirty-five consecutive node-positive breast cancer patients treated from October 2016 to February 2018 receiving postoperative RT of the breast or chest wall including RNI of the supra-/infraclavicular lymph node levels (corresponding to levels IV, III, Rotter LN (interpectoral), and some parts of level II) were analyzed. To evaluate the lymph node level movement, a center of volume (COV) was obtained for each lymph node level for free-breathing (FB) and DIBH plans. Geometric shifts and dose differences between FB and DIBH were analyzed.

Results A significant movement of the COV in anterior (y) and cranial (z) dimensions was observed for lymph node levels I–II and Rotter lymph nodes ($p < 0.001$) due to DIBH. Only minor changes in the lateral dimension (x axis) were observed, without reaching significance for levels III, IV, and internal mammary. There was a significant difference in the mean dose of level I (DIBH vs. FB: 38.2 Gy/41.3 Gy, $p < 0.001$) and level II (DIBH vs. FB: 45.9 Gy/47.2 Gy, $p < 0.001$), while there was no significant difference in level III ($p = 0.298$), level IV ($p = 0.476$), or internal mammary nodes ($p = 0.471$).

Conclusion A significant movement of the axillary lymph node levels was observed during DIBH in anterior and cranial directions for node-positive breast cancer patients in comparison to FB. The movement leads to a significant dose reduction in level I and level II.

Keywords Breast cancer · Deep-inspiration breath hold · Lymphatic pathways · Radiotherapy · Lymph node movement

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Dosisvariabilität verschiedener Lymphknotenstationen während der lokoregionalen Bestrahlung bei Mammakarzinom: Einfluss des Luftanhaltens in tiefer Inspiration

Zusammenfassung

Fragestellung Ziel der vorliegenden Analyse war es, die Bewegungs- und Dosisvariabilität der verschiedenen Lymphknotenstationen nodalpositiver Brustkrebspatientinnen während der adjuvanten Bestrahlung inklusive regionaler Lymphabflussbestrahlung (RNI) in tiefer Inspiration („deep inspiration breath hold“, DIBH) zu bewerten.

Methoden Von Oktober 2016 bis Februar 2018 wurden 35 nodalpositive Brustkrebspatientinnen mit postoperativer RT der Brust oder Brustwand einschließlich RNI der supra-/infraklavikulären Lymphknotenregionen (entsprechend Level IV, III, Rotter-Lymphknoten interpektoral und Anteile von Level II) untersucht. Zur Beurteilung der Bewegung der Lymphknotenstationen wurde für jedes Lymphknotenlevel der geometrische Volumenmittelpunkt („center of volume“, COV) in freier Atmung („free breathing“, FB) und DIBH ermittelt. Die räumlichen Bewegungen und Dosisunterschiede zwischen FB und DIBH wurden analysiert.

Ergebnisse Eine signifikante Bewegung des COV in anteriorer (y) und kranialer (z) Richtung wurde für die Lymphknotenlevel I–II sowie für die Rotter-Lymphknoten ($p<0{,}001$) in DIBH beobachtet. Es wurden nur geringe Veränderungen im Bereich der lateralen Dimension (x-Achse) beobachtet, welche für die Level III, IV und die Mammaria-interna-Lymphknoten nicht signifikant waren. Es zeigten sich außerdem signifikante Dosisunterschiede für das Lymphknotenlevel I (DIBH vs. FB: 38,2 Gy/41,3 Gy; $p<0{,}001$) und II (DIBH vs. FB: 45,9 Gy/47,2 Gy; $p<0{,}001$), während es keinen signifikanten Unterschied für das Level III ($p=0{,}298$), IV ($p=0{,}476$) und Mammaria interna ($p=0{,}471$) gab.

Schlussfolgerungen Eine signifikante Bewegung der axillären Lymphknotenstationen während DIBH wurde vorwiegend in anteriorer und kranialer Richtung im Vergleich zu FB beobachtet. Die Bewegung führte zu einer signifikanten Dosisreduktion innerhalb der Lymphknotenlevel I und II.

Schlüsselwörter Brustkrebs · Luftanhalten in tiefer Inspiration · Lymphabflusswege · Strahlentherapie · Lymphknotenbewegung

Introduction

Adjuvant radiotherapy (RT) after breast-conserving surgery (BCS) or mastectomy significantly reduces locoregional recurrences and breast cancer (BC)-specific mortality [1–3]. In recent years, the indication for regional nodal irradiation (RNI) in addition to whole-breast or chest wall irradiation has been revised. Two large studies and a meta-analysis recently showed improved local control and overall survival (OS) by additional irradiation of regional lymph nodes (LN) including the internal mammary nodes (IMN), supraclavicular (SCV, corresponding to ESTRO guidelines level IV [4]), infraclavicular (ICV, corresponding to ESTRO guidelines level III [4]), Rotter lymph-nodes (interpectoral, and some parts of level II), and, in one of the studies, also the axillary lymph node levels I and II in node-positive or “high-risk” node-negative breast cancer patients [5–8]. Most patients in these trials received additional systemic chemotherapy or endocrine treatment according to the standard recommendations at time of patient recruitment [6, 7]. However, these protocols are considered outdated compared to current standards, as they used old radiation techniques.

At the same time, several studies investigated the side effects of breast RT on organs at risk (OARs) and showed an increase in coronary events and cardiac death, especially in patients irradiated for left-sided breast cancer [9–12]. However, in the latter studies, old-fashioned radiotherapy techniques were used, including 2-dimensional RT, in which the heart dose was only estimated and not calculated [9–12]. In fact, the analysis conducted by Darby et al. estimated a linear correlation between the mean heart dose and coronary events [12]. For this reason, several cardiac dose-sparing and avoidance techniques are nowadays utilized to optimize left-sided breast RT such as, for example, the deep-inspiration breath hold (DIBH) technique [13–18]. DIBH is considered a safe and reproducible technique for heart sparing, while ensuring good planning target volume (PTV) coverage [19–21]. When RNI is performed with the DIBH technique, several considerations should be made regarding anatomical changes of the mammary gland and significant movements of the axillary lymph node levels in anterior and cranial directions [22]. A warning about a possible RT dose reduction in axillary lymph node level I during DIBH compared to free breathing (FB) has been recently published [22]. The impact of this dose variation in the accidental irradiation of level I lymph nodes in node-negative early breast cancer patients remains unknown and a longer follow-up must be awaited to evaluate its potential influence on oncologic outcome [22]. On the other hand, in node-positive patients, it can be hypothesized that the effect of this dose difference may be even greater, also because axillary lymph node dissection (ALND) currently plays a decreasing role in the treatment of breast cancer patients. The potential advantages and disadvantages of ALND over sentinel lymph node biopsy (SLNB) have been widely debated in recent years, especially in cases of complete remission after neoadjuvant chemotherapy [23–25].

With this background, the aim of the present analysis was to evaluate the movement and dose variability of the different lymph node levels of node-positive breast cancer patients during adjuvant irradiation with RNI in DIBH.

Materials and methods

All patients were treated in the prospective SAVE-HEART study, which was performed in accordance with the Declaration of Helsinki, approved by the ethical committee of the LMU medical faculty (13.09.2016, no. 355-16) and registered in the German Clinical Trials Register (DRKS-ID: DRKS00011213). Inclusion criteria were patients aged over 18 years, left-sided breast cancer or carcinoma in-situ with an indication for adjuvant RT, and patient compliance for DIBH (ability of breath hold for 20 seconds). A specific informed consent was obtained for each patient. For the present analysis, all node-positive BC patients receiving postoperative RT of the breast or chest wall including a regional irradiation of the supra-/infraclavicular lymph node levels (corresponding to level IV, III, interpectoral Rotter LN, and some parts of level II according to the ESTRO-guidelines [4]) were included.

Every patient received two planning CT scans, one in FB and one in DIBH, with an axial slice thickness of 3 mm and without contrast enhancement. The patients were immobilized in a supine position on a positioning device (WingSTEP®, IT-V, Innsbruck, Austria), with both arms elevated above the head. The DIBH maneuver was performed during CT simulation and treatment delivery using the surface-based Catalyst/Sentinel™ system (C-RAD, Uppsala, Sweden) as described elsewhere [13].

A clinical target volume ($CTV_{breast/chestwall}$) encompassing the chest wall or the glandular breast parenchyma and a planning target volume ($PTV_{breast/chestwall}$) achieved by adding a 5 mm margin to $CTV_{breast/chestwall,}$ were first contoured in the FB-CT then transferred to the DIBH-CT and adapted to the changed anatomy. In cases where a boost was applied, CTV_{boost} included the tumor bed, visible surgical clips, and anatomical distortion. The PTV_{boost} was generated using a 5 mm isotropic expansion on CTV_{boost}. The supra-/infraaclavicular lymph node levels (corresponding to level IV, III, Rotter LN, and some parts of level II according to the ESTRO guidelines [4]) were contoured separately ($PTV_{LN\ SCV/ICV}$) and added to the $PTV_{breast/chestwall}$. The part of the level II which was intentionally included in the $PTV_{LN\ SCV/ICV}$ was a small region dorsal to the minor pectoral muscle. The different OARs, including contra- and ipsilateral lung, contra-lateral breast gland, as well humerus and heart were outlined in both FB- and DIBH-CT according to RTOG Atlas [26].

Treatment planning was performed on the FB- and DIBH-CT for each patient with 3-dimensional conformal radiation therapy (3D-CRT) using the Oncentra Masterplan treatment planning system version 4.5.2 (Elekta AB, Stockholm, Sweden). All plans consisted of two opposing tangential beams for the breast/chest wall with the addition of some subfields to increase dose homogeneity, as well as anterior/posterior fields for the infra-/supraclavicular lymph node levels. A total dose of 50 Gy in 25 fractions was prescribed to the $PTV_{breast/chestwall + LN\ SCV/ICV.}$ A total dose of 10–16 Gy in 2 Gy single fractions was applied to the PTV_{boost}.

To evaluate lymph node movement of the individual lymph node levels, each level was retrospectively contoured in both CTs according to the EORTC consensus guideline (axilla level I, level II, Rotter LN, level III, level IV, and internal mammary) [4]. A center of volume (COV) was obtained for each lymph node level for FB and DIBH plans, as described elsewhere [22]. COV-FB and COV-DIBH coordinates along the three spatial axes lateral (x), anterior-posterior (y), and craniocaudal (z) were compared to evaluate the position change due to the DIBH maneuver. The length (d) of the three-dimensional shift was calculated by $d = \sqrt{(\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2}$ where $\Delta x, y, z$ is the difference between x_{FB} and x_{DIBH}. For evaluation of dose changes, the mean doses of each single lymph node level were calculated and compared to each other. To evaluate the geometric shifts and the dose differences between FB and DIBH, a Wilcoxon signed-rank test was performed for statistical analysis using SPSS version 24.0 (IBM, Armonk, NY, US). The threshold for statistical significance was $P < 0.05$.

Results

Thirty-five consecutive node-positive breast cancer patients treated from October 2016 to February 2018 in the prospective "SAVE-HEART" study with a median age of 53 years (range: 32–77 years) were evaluated for the present study. Patient characteristics are summarized in Table 1. Overall, 48.6% of patients received neoadjuvant chemotherapy (NAC), 12 patients before breast-conserving surgery (BCS) and 5 patients before mastectomy. The indication for postoperative RT in this setting was taken after consideration of the clinical stage at the time of diagnosis and the pathologic response to NAC according to the national German

Table 1 Cohort characteristics of 35 node-positive patients. All ypTis/ypT0 or ypN0 patients received neoadjuvant chemotherapy and were clinically node positive at time of diagnosis

		35 patients	
		n	(%)
Age at diagnosis (years)	<40	6	(17.1)
	40–49	9	(25.7)
	50–59	8	(22.9)
	60–69	7	(20.0)
	≥70	5	(14.3)
	Median age (years)	53.3	–
Tumor histology	NST	31	(88.6)
	Invasive lobular	4	(11.4)
Tumor status	ypTis	2	(5.7)
	ypT0	9	(25.7)
	pT1	9	(25.7)
	pT2	11	(31.4)
	pT3	4	(11.4)
Nodal status	ypN0	10	(28.6)
	pN1	20	(57.1)
	pN2	2	(5.7)
	pN3	3	(8.6)
Grade	G1	3	(8.6)
	G2	20	(57.1)
	G3	12	(34.3)
Estrogen receptor	Positive	28	(80.0)
	Negative	7	(20.0)
Progesterone receptor	Positive	23	(65.7)
	Negative	12	(34.3)
Her2/neu	Positive	4	(11.4)
	Negative	31	(88.6)
Ki-67	<15%	8	(22.9)
	15–30%	16	(45.7)
	>30%	11	(31.4)
Surgery	Breast conserving surgery	23	(65.7)
	Mastectomy	12	(34.3)
Axillary surgery	Axillary dissection	21	(60.0)
	Sentinel node biopsy	14	(40.0)
Chemotherapy	Yes	31	(88.6)
	-Neoadjuvant	17	(48.6)
	-Adjuvant	14	(40.0)
	No	4	(11.4)
Targeted therapy	Yes	4	(11.4)
	No	31	(88.6)
Endocrine therapy	Yes	24	(68.6)
	No	11	(31.4)

NST invasive carcinoma of no special type

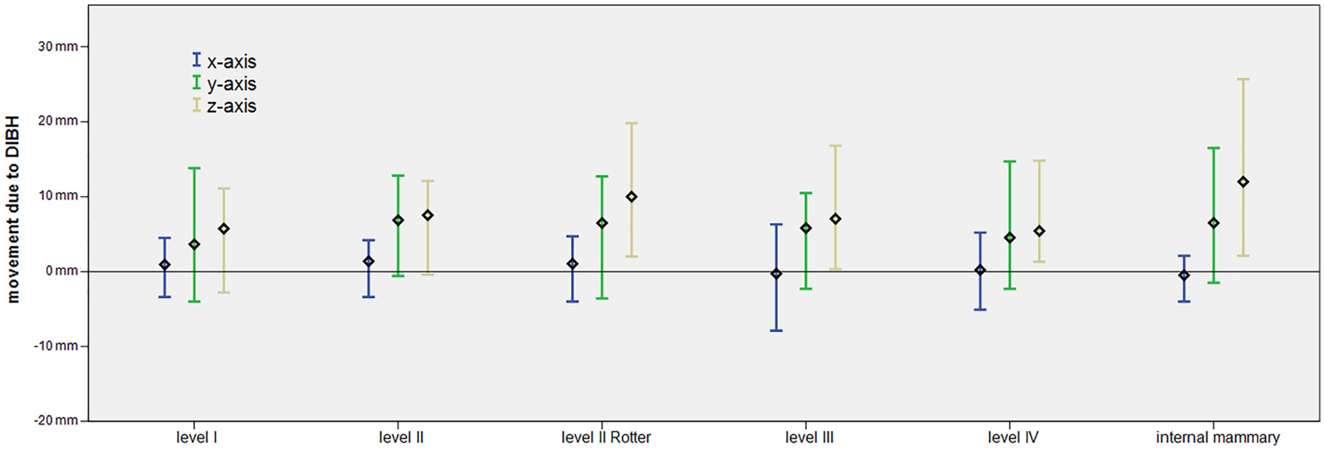

Fig. 1 Visualization of the three-dimensional movement of each lymph node level due to DIBH. For exact values and significance see Table 2. *x* lateral, *y* anterior-posterior, *z* cranio-caudal

Table 2 Geometric shifts of the single lymph node levels between free breathing (*FB*) and deep-inspiration breath hold (*DIBH*)

Axis	Level I mean (range)	Level II	Rotter LN	Level III	Level IV	Internal mammary
x	0.09 (–0.34–0.45)*	0.14 (–0.34–0.42)*	0.10 (–0.40–0.47)*	–0.03 (–0.79–0.63)	0.02 (–0.51–0.52)	–0.05 (–0.40–0.21)
y	0.36 (–0.40–1.38)*	0.68 (–0.06–1.28)*	0.65 (–0.36–1.27)*	0.58 (–0.23–1.05)*	0.45 (–0.23–1.47)*	0.65 (–0.15–1.65)*
z	0.57 (–0.28–1.11)*	0.75 (–0.04–1.21)*	1.00 (0.20–1.98)*	0.70 (0.03–1.68)*	0.54 (0.13–1.48)*	1.20 (0.21–2.57)*
$\overrightarrow{3D}$	0.79 (0.26–1.61)	1.08 (0.06–1.59)	1.26 (0.42–2.13)	1.01 (0.37–2.13)	0.82 (0.17–1.57)	1.44 (0.27–2.76)

The changes were calculated using the coordinates of the center of volume (*COV*) obtained for each lymph node level in FB and DIBH along the three spatial axes lateral (*x*), anterior-posterior (*y*), and craniocaudal (*z*) in centimeters. The three-dimensional vector was calculated by $d = \sqrt{(\Delta x)^2 + (\Delta y)^2 + (\Delta z)^2}$, where $\Delta x, y, z$ is the difference between x_{FB} and x_{DIBH}
*Significant movement ($P \leq 0.05$)

guidelines [27]. A complete axillary lymph node dissection (ALND) was carried out in 13% of patients receiving BCS and in 91.6% of patients undergoing mastectomy.

A significant movement of the COV in anterior (y) and cranial (z) dimensions was observed for lymph node levels I–II and Rotter lymph nodes ($p < 0.001$) due to DIBH. Only minor changes in the lateral dimension (x axis) were observed, without reaching significance for levels III, IV, and internal mammary. The shifts in the x, y, and z directions for each lymph node level are depicted in Fig. 1.

The overall averaged movement in the x, y, and z directions for all lymph node levels was 0.05 cm (range: –0.05–0.14 cm), 0.56 cm (range: 0.36–0.68 cm), and 0.80 cm (range: 0.54–1.2 cm), respectively. The $\overrightarrow{\text{shifts}}$ for every single axis and the respective 3D vector (3D) for each lymph node level are shown in Table 2.

The average dose variations for the different lymph node levels in FB and DIBH are shown in Fig. 2. There was a significant difference in the mean dose for the level I (DIBH vs. FB: 38.2 Gy vs. 41.3 Gy, $p < 0.001$), level II (DIBH vs. FB: 45.9 Gy vs. 47.2 Gy, $p < 0.001$), and Rotter LN (DIBH vs. FB: 49.7 Gy vs. 50.1 Gy, $p = 0.008$), while there was no significant difference in level III (DIBH vs. FB: 49.7 Gy vs. 49.9 Gy, $p = 0.298$), level IV (DIBH vs. FB: 48.9 Gy vs. 48.9 Gy, $p = 0.476$), or internal mammary nodes (DIBH vs. FB: 21.2 Gy vs. 20.0 Gy, $p = 0.471$).

Discussion

During whole-breast or chest wall RT, the unintended irradiation of axillary lymph node levels could probably have an impact on the effectiveness of the local treatment. In fact, the ACOSOG Z0011 trial hypothesized that a therapeutic effect of tangential breast RT could occur through sterilization of residual tumor cells in the level I of the axilla [28]. Nevertheless, it should be noted that although the ACOSOG Z0011 protocol required standard whole-breast irradiation by tangential fields without any RNI, detailed information on RT volumes published in 2014 by Jagsi et al. [28] found that 50% of patients had received “high tangents” (cranial tangent border ≤2 cm from humeral head)

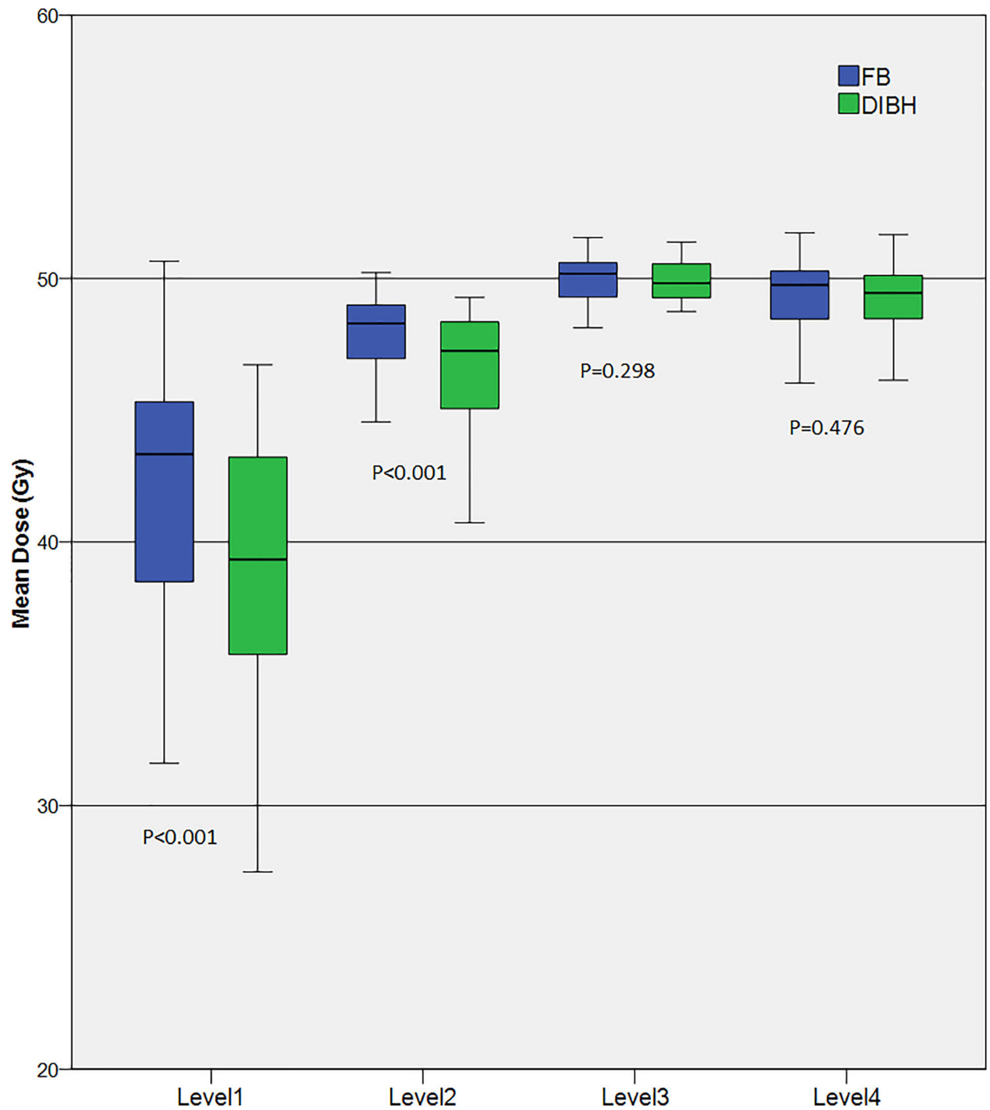

Fig. 2 Mean dose changes and *p*-value for the different lymph node levels in free breathing (*FB*) and deep-inspiration breath-hold (*DIBH*)

and 18% received an additional RNI to the supraclavicular region.

Several studies showed that conventional tangential 3D-CRT or intensity-modulated RT (IMRT) in FB for whole breast irradiation does not reliably encompass level I–II lymph nodes [29–32]. Among these experiences, Reed et al. [31] reported that only 55% of the lymph node levels I and II received 95% of the prescribed dose in 50 patients treated with tangential fields using 3D-CRT. Regarding IMRT plans, Zhang et al. [33] retrospectively evaluated the incidental radiation doses to lymph node levels I–III and observed inadequate dose coverage to all axillary levels (levels I, II, and III were 29 Gy, 10.9 Gy, and 2.8 Gy, respectively) in node-negative patients.

To date, the unintended irradiation of lymph nodes during DIBH has not been sufficiently addressed. Borm et al. published the first and only study available, reporting the differences regarding unintended regional nodal irradiation during tangential field RT of node-negative breast cancer patients during DIBH [22]. The study analyzed patients who received whole breast RT without irradiation of the lymphatic pathways. The findings showed a significant dose reduction in level I through the DIBH procedure (33.9 Gy vs. 30.8 Gy, $p < 0.001$), while only minor changes in dose distribution were found for levels II and III. The authors concluded that DIBH seems to have an impact on unintended regional nodal irradiation as compared with FB [22].

Based on this background, the objective of the present analysis was to evaluate movements and dose changes of lymph node levels for irradiation of node-positive BC patients receiving whole-breast-/chest wall RT including the infra-/supraclavicular lymphatic pathways during DIBH. To our knowledge, this is the first experience in the literature on this specific issue. In terms of lymph node level movements, a significant movement in the anterior (y) and cranial (z) dimensions was observed for all lymph node levels

(Table 2), without reaching significance for levels III, IV, and internal mammary. The latter results were similar to those published by Borm et al. [15]. In terms of dose variability, the present analysis showed a significant mean dose reduction of –3.09 Gy in level I ($p<0.001$), –1.28 Gy in level II ($p<0.001$), and –0.36 Gy in Rotter LN ($p=0.008$), while there was no significant difference in levels III–IV or internal mammary. Despite differences in terms of dose/volumes, the present data are similar to those reported by Borm et al. [22]. In fact, considering that the surgical axillary dissection includes only levels I–II, RT dose to the lymph node level III should be carefully evaluated. Level I showed a mean dose reduction during DIBH of 3 Gy. This result could have a detrimental effect on local control rates, especially in patients undergoing a sentinel lymph node biopsy (SLNB) without a complete axillary dissection [28, 34].

From the randomized AMAROS trial, which compared radiotherapy or surgery of the axilla (ALND) after a positive sentinel node (SLNB), we know that there are no significant differences in disease-free survival or overall survival between the two procedures [35]. In this context, node-positive breast cancer patients with a significant positive response after neoadjuvant chemotherapy are nowadays often treated with SLNB instead of a complete axillary dissection (>10 LN). This treatment strategy has been applied to over 48% of patients of the present analysis and resulted in 28.6% node-negative histology following NAC.

To give an order of magnitude, a mathematical model proposed by Okunieff et al. [36] in the mid-1990s calculated that a dose reduction of around 3 Gy of lymph node level I could lead to a reduction in tumor control probability of about ~10%. However, this model cannot be applied to current modern multimodal approaches, including modern systemic therapies, and the real impact on locoregional control rates of unintended regional nodal irradiation remains unknown.

Conclusion

A significant movement of the axillary lymph node levels was observed during DIBH in anterior and cranial directions for node-positive breast cancer patients in comparison to FB. The movement leads to a significant dose reduction in levels I and II. Considering the potential relevance of unintended regional nodal irradiation of lymph node in the era of deescalated axillary dissection or following neoadjuvant chemotherapy regimens, it remains difficult to estimate the real impact on local control rates. Further clinical trials are needed to establish the most effective treatment strategy in this patient population.

Conflict of interest M. Pazos, A. Fiorentino, A. Gaasch, S. Schönecker, D. Reitz, C. Heinz, M. Niyazi, M.-N. Duma, F. Alongi, C. Belka, and S. Corradini declare that they have no competing interests.

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