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Original Research Article

Incidental dose distribution to contralateral internal mammary nodes in breast cancer patients undergoing adjuvant radiotherapy

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ABSTRACT

Background and purpose: In a relevant number of primary breast cancer patients, lymphatic drainage to the contralateral internal mammary nodes (cIMN) is being observed. Nevertheless, so far lymphatic drainage pathway to the cIMN is largely neglected during adjuvant radiotherapy.

Materials and methods: This study evaluated the incidental dose to the cIMN for 120 volumetric modulated arc therapy (VMAT) treatment plans for node positive breast in dependence of internal mammary node irradiation (IMNI) and deep inspiration breath hold (DIBH). Additionally, incidental dose distribution to the cIMN based on the field design in the MA20, EORTC22922/10925 and AMAROS trials was assessed.

Results: The incidental dose (Dmean ± SD) to the cIMN-CTV was 13.0 (±4.7) Gy with a maximum dose of < 30 Gy in 113/120 cases. If IMNI was included (n = 80), the Dmean to the cIMN-CTV was significantly higher compared to no IMNI, but still comparably low (n = 40; 14.3 Gy vs. 9.6 Gy; p = 0.0001). Furthermore, the dose in the cIMN during free breathing (n = 80) was higher compared to DIBH (n = 40; 13.9 Gy vs. 11.2 Gy; p = 0.002).

Simulated treatment plans based on the randomized RNI trials revealed neglectable dose coverage of the cIMN (Dmean 1.0–1.8 Gy) for all protocols.

Conclusion: Neither in the randomized RNI trials nor during contemporary treatment techniques clinically relevant dose distribution to the cIMN was observed. Further studies are warranted to assess the potential impact of intended irradiation of cIMN in high-risk patients.

Introduction

Regional nodal irradiation (RNI) has been demonstrated to enhance oncological outcomes for patients with early-stage breast cancer: The EORTC 22922 randomized trial revealed that disease-free survival, distant disease-free survival and breast cancer mortality rates improved following irradiation of the internal mammary nodes (IMN) and supraclavicular lymph nodes (SCN) [1]. Similarly, the MA20 trial reported a significant reduction in breast cancer recurrence rates after including IMN and SCN in the RNI treatment [2]. Additionally, studies conducted by the Danish Breast Cancer Cooperative Group and a separate Korean randomized trial highlighted the benefits of targeting the IMN during RNI, showing improvements in overall survival (OS) and progression-free survival (PFS) for patients at high risk [3,4].

Although contralateral IMN is generally not considered part of the locoregional lymphatic drainage system of the breast, well-founded evidence indicates that a significant number of patients exhibit physiological lymphatic drainage to the contralateral IMN. An anatomical study from 1932 described a lymphatic connection between the two internal mammary chains in 9–17 % of healthy subjects [5]. Furthermore, lymphoscintigraphic studies revealed that up to one third of patients with ipsilateral IMN metastasis have also contralateral IMN involvement [6–11]. This may be of particular interest because it is known that these patients have a worse prognosis and a higher risk of

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distant metastases [6–8].

Even though the contralateral IMN is usually not part of the target volume during RNI, incidental dose coverage to a certain extent needs to be expected due to the proximity to the contralateral breast and chest wall. Nevertheless, the incidental dose to the contralateral IMN has not yet been quantified despite evidence from previous trials (e.g. Z0011) showing that incidental dose to other parts of the lymphatic drainage system can impact oncologic outcomes [12,13].

Material & methods

Study population

40 patients with left-sided, node positive breast cancer undergoing adjuvant radiotherapy of the left breast or chest wall at the Department of Radiation Oncology, Technical University Munich between November 2015 and October 2019 were included into this study.

The study was approved by the local ethics board (2024–217-S-SB).

Evaluation of incidental IMN dose during contemporary treatment techniques

Treatment planning CT was performed on a Siemens Somatom Emotion 16 device (Siemens Healthineers, Erlangen, Germany) and target volume delineation was done in Varian Eclipse Software (Version 13.0, Medical Systems, Palo Alto, CA, USA). 20 patients received treatment planning CT both in free breathing (FB) and deep inspiration breath hold (DIBH) while another 20 patients received treatment planning CT only in FB.

For the first 20 patients, we created treatment plans (n = 80) with and without irradiation of IMN (IMNI) both in FB and DIBH. For another 20 patients, treatment plans (n = 40) with standard clinical to planning target volume (CTV-PTV) margin for the ipsilateral IMN region (n = 20) and with reduced PTV margins by excluding any lung tissue (n = 20) were calculated.

The prescription dose for all plans was a median dose of 50.4 Gy in 28 fractions to the breast or chest wall. Planning requirements for target and organs at risk (OAR) were individually determined depending on the clinical scenario and according to international guidelines [14–16]. In general, it was aimed to cover > 95 % of the PTV eval (PTV – lung volume and 5 mm skin) with > 95 % of the prescribed dose and to keep the maximum dose lower than 107–110 %. For the OARs, we aimed to keep the mean dose to the heart and left anterior descending coronary artery < 5 Gy and < 8 Gy, respectively. The mean dose to the contralateral breast was aimed to be lower than <3–5 Gy and the V20Gy of the ipsilateral lung lower than 20 %. The mean doses to the total lung, the esophagus, the thyroid, the liver and the bowel were kept as low as reasonably achievable.

All treatment plans utilized 6X photon beams of a Varian Clinac DHX linear accelerator in volume modulated arc therapy (VMAT) technique (Varian Medical Systems, Palo Alto, CA). For the dosimetric evaluation, contralateral IMN (1-4th intercostal space (ICS)) and SCN clinical target volumes (CTVs) were delineated according to ESTRO consensus guideline [17]. In addition, each ICS (1-5th) was contoured separately. Contralateral IMN (1-4th ICS) and SCN planning target volumes (PTVs) were generated with a symmetrical 5 mm margin (Fig. 1).

Evaluation of incidental IMN dose in RNI randomized trials

In a second step, treatment plans were calculated using the field design according to the study protocols of the AMAROS, EORTC 22922 and MA20 trials [1,2,13,18]. For each of the trials, three plans were created for either a regular (763 cm^3 breast volume), an obese (1201 cm^3 breast volume) and a lean (329 cm^3 breast volume) patient on three different planning CTs. Accordingly, contralateral IMN (1-4th ICS) and SCN CTVs were delineated and PTVs were generated with a symmetrical 5 mm margin.

Statistical analysis

For each structure we evaluated the mean (Dmean) and maximum dose (Dmax) as well as V30Gy of the contralateral IMN CTV and PTV. All values are reported as the mean of the measured dose with the standard deviation (±SD), to provide an indication of the variability around the

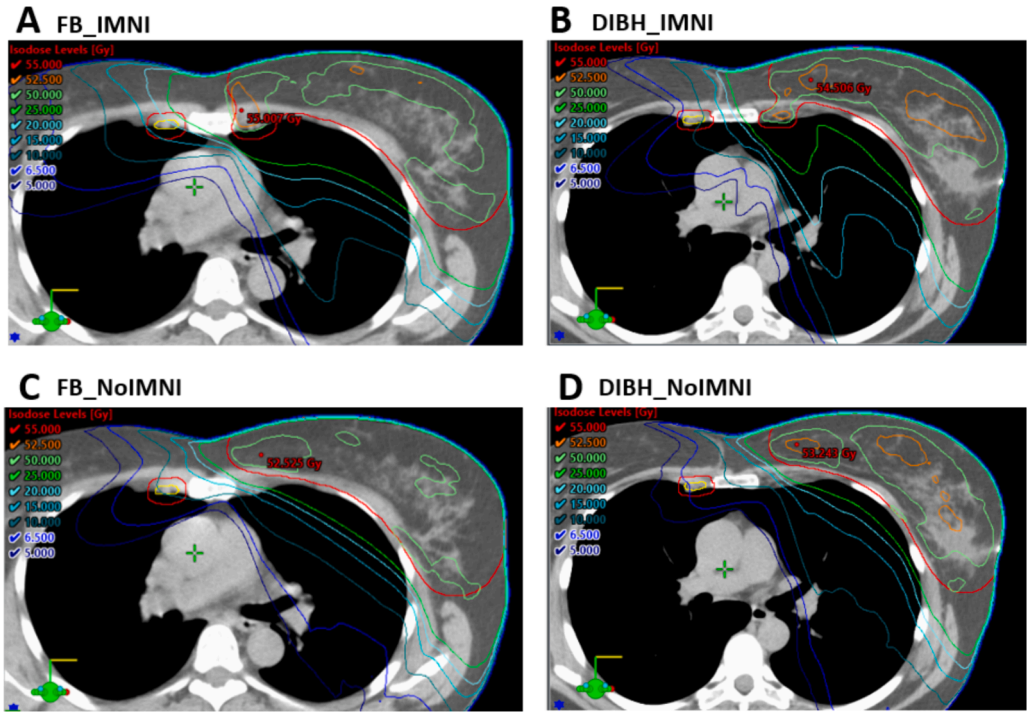

Fig. 1. Treatment plan (VMAT) of the left breast in FB (A/C) or DIBH (B/D) with (A/B) or without (C/D) IMNI.

mean dose. Dose-volume-histograms (DVH) were analyzed using an R package web application for DVH metrics [19] and SPSS version 26.0 (IBM SPSS Statistics, Armonk, NY, USA). For statistical significance we used the two tailed *t*-test. To test correlation between parameters we used the Pearson coefficient. The level of significance was defined as $p < 0.05$.

Results

Evaluation of incidental IMN dose during contemporary treatment techniques

The mean of all mean incidental doses of all treatment plans (n = 120) was 13.0 (±4.7) Gy to the contralateral IMN CTV and 13.2 (±4.6) Gy to the contralateral IMN PTV. The mean doses to the first to the fifth contralateral intercostal spaces were 14.5 Gy, 12.8 Gy, 13.1 Gy, 12.5 and 8.0 Gy respectively (Fig. 2). Dmean of the contralateral SCN CTV and PTV were both 14.1 (±3.2/2.9) Gy.

In only 7 of 120 treatment plans, the maximum dose to the contralateral IMN exceeded 30 Gy with a mean V30 of 0.2 (±0.9) cm^3. The majority of those (n = 6) were treatment plans with inclusion of IMN. The mean Dmax in the contralateral IMN CTV was 20.4 (±6.7) Gy.

The mean doses to the heart and both lungs were 4.3 (±1.4) Gy and 8.2 (±1.4) Gy, respectively.

The IMN CTV received the highest doses in treatment plans with inclusion of ipsilateral IMN in FB (n = 60; mean Dmean 15.4 (±4.0) Gy and the lowest doses in those without IMNI in FB (n = 20; 9.7 (±3.9) Gy; Fig. 3).

The mean dose to the contralateral IMN CTV correlated moderately with the mean dose of ipsilateral IMN CTV ($r = 0.55p < 0.0001$). The contralateral IMN CTV received significantly higher doses in treatment plans with inclusion of ipsilateral IMN compared to treatment plans without inclusion of ipsilateral IMN (14.3 Gy vs. 9.6 Gy; $p < 0.001$).

In comparison to treatment plans in DIBH (n = 40), the Dmean to the contralateral IMN CTV was significantly higher in FB (n = 80; 13.9 Gy (2.2 Gy to 25.6 Gy) vs. 11.2 Gy (3.5 Gy to 24.1 Gy); $p = 0.002$). The mean volume of the breast was 693.3 cm^3 (117.9 – 1622.1). There was no significant correlation of breast volume with the dose to either ipsilateral or contralateral IMN CTV.

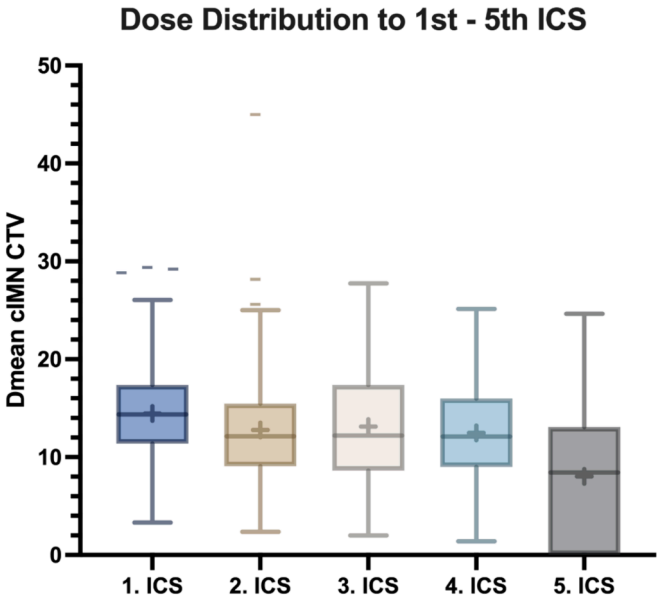

Fig. 2. Dose distribution of contralateral IMN CTV in the first to the fifth intercostal space (ICS) in all groups.

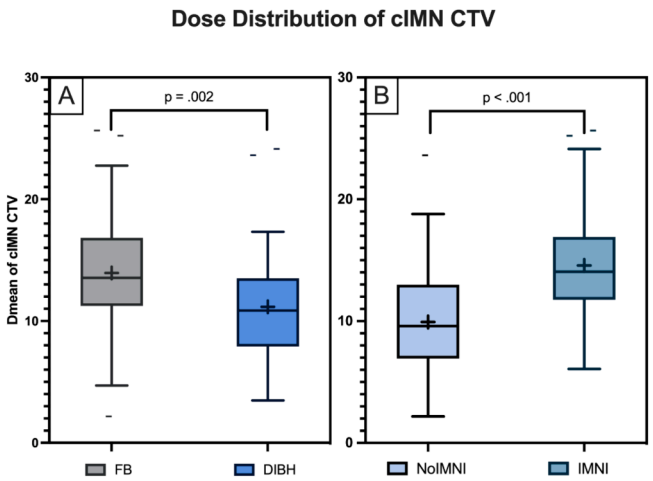

Fig. 3. Dose distribution of contralateral IMN CTV (1-4th ICS) for treatment plans in A – FB (left) or DIBH (right); B – without (left) or with (right) inclusion of IMNI.

Evaluation of incidental IMN dose in the RNI randomized trials

Mean doses of ipsilateral and contralateral IMN CTVs of reconstructed RNI trials are visualized in Fig. 4. Mean dose to the ipsilateral IMN CTV was 37.8 (±16.2) Gy for the MA20 field design, 28.1 (±20.4) Gy in the AMAROS and 41.8 (±6.3) Gy in the EORTC trial for the three patients (regular, obese, lean). Mean dose to the contralateral IMN CTV was 1.8 (±0.4) Gy in the MA20, 1.0 (±0.1) Gy in the AMAROS and 1.5 (±0.7) Gy in the EORTC trial plans. However, mean doses to the contralateral IMN CTV did not exceed 3 Gy in any of the calculated plans.

Discussion

Previous studies indicate that the ipsilateral IMN region receives substantial incidental dose values even if the irradiation of the IMN is not being intended. However, the reported dose coverage in the studies varies largely based on the irradiation technique and the target volume. In the OPTIMAL trial, in which the clinical effect on intentional vs. incidental RNI was investigated, the ipsilateral IMN received a dose of

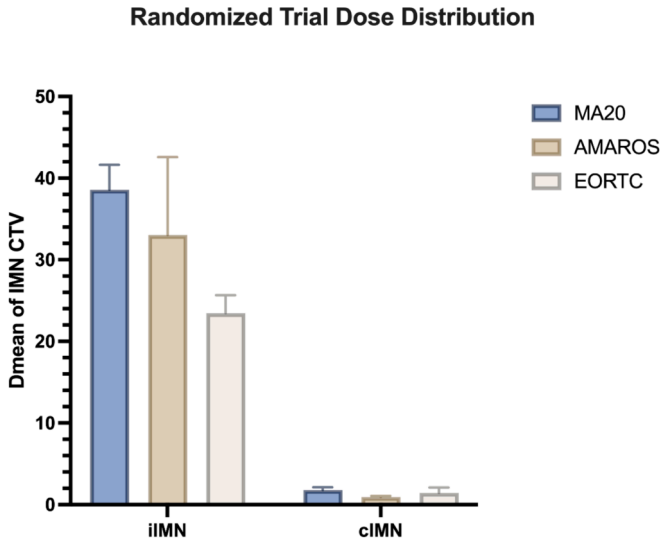

Fig. 4. Dose distribution of ipsilateral IMN (iIMN) and contralateral IMN (cIMN) CTV (1-4th ICS) in the reconstructed plans of MA20, AMAROS and EORTC 22922 trials.

19.8 – 24.3 Gy depending on whether axillary-clavicular lymph node areas were irradiated or not [20]. Other studies found mean incidental doses of up to 39 Gy in the ipsilateral IMN [13].

The current study, to our knowledge, presents the first analysis of the incidental dose to the contralateral IMN during adjuvant radiotherapy in breast cancer. 120 treatment plans with and without inclusion of the ipsilateral IMN in FB or DIBH showed low incidental irradiation of the cIMN in the first to the fourth ICS with mean values of 13 Gy ranging from 2.2 Gy to 25.6 Gy in the IMN CTV.

Our results reveal two different insights:

First, it is unlikely that incidental irradiation of the cIMN contributed to the oncologic benefit shown in the MA20 and EORTC 22922 randomized trials [1,2]. Therefore, it is not necessary to consider the dose coverage to the cIMN to achieve the oncologic benefit shown in these trials.

The DBCG IMN1/2 trials were not included in the current analysis, because they were non-randomized trials, and the field design and target volumes were not clearly defined by a study protocol. Thus, simulating a dose distribution is challenging. Furthermore, for many patients in the DBCG IMN2 trials the 3D-dose distribution is available and actual evaluation of the contralateral IMN could be performed [21]. However, given the low dose in the contralateral IMN irrespective of treatment technique, we would expect similar results for the DBCG cohort.

Even though the AMAROS trial did not intend to treat the IMN region the supraclavicular field in the AMAROS trial protocol partially overlapped with the cranial ipsilateral ESTRO-IMN-CTV [13]. Nevertheless, similar to the EORTC 22922 and MA20 trial no relevant doses were found in the contralateral IMN.

Secondly, our results show that also for contemporary treatment techniques the incidental dose to the cIMN is low with mean values below < 25 Gy. Notably, some Tumor-Control-Probability (TCP) models suggest a reasonable tumor response using doses of even < 30 Gy irradiation dose for subclinical disease in breast cancer patients [22,23]. For example, a TCP model by Chen et al. estimated that 25 Gy can improve the tumor control rates by approximately 15 %. Nevertheless, the doses observed in our study were mostly lower than 25 Gy, which indicates that an oncological effect of incidental irradiation to cIMN is unlikely for contemporary treatment techniques.

So far, there is a lack of evidence regarding the effect of irradiation of the cIMN region. Even more, there is barely any evidence regarding any treatment of this part of the lymphatic drainage system. This is remarkable given the fact that previous studies indicate abnormal contralateral lymphoscintigraphies in approximately 15 % of all patients and 1/3 of patients with abnormal ipsilateral lymphoscintigraphies [8,24]. Also, there is evidence that the proportion of patients with lymphatic drainage to the cIMN, which is observed to be 17 % in healthy patients, can increase after locoregional surgery [5,25,26]. In a recent study, we showed that the existence of gross cIMN metastasis correlates in 100 % of cases with the existence of abnormal crossing internal mammary perforator vessels to the contralateral side [27].

Recurrences in the cIMN are, similar to the ipsilateral IMN, reported to be low: Zhang et. al. found isolated cIMN recurrence in 5 of 96 patients (5.2 %) after chemotherapy, surgery and radiotherapy [28]. However, it can be hypothesized that eradicating microscopic disease in the cIMN could improve distant metastases free survival similar to irradiation of the ipsilateral IMN region. Previous studies indicate that patients with contralateral lymph node metastases have a better outcome compared to patients with clearly hematogenous distant metastases [29]. This raises the question if these patients, particular when ipsilateral IMN metastases are present, require elective bilateral IMNI.

Currently, the concept of elective irradiation of the cIMN is hypothetical, and clinical data supporting its efficacy is lacking with only a few case reports available.

Some studies suggest that patients with cIMN metastasis might benefit from locoregional treatment approaches instead of systemic treatment only and cIMN metastasis should not necessarily be rated as M1 [30]. A case report from China described a patient with lymphoscintigraphically diagnosed and histologically confirmed bilateral IMN metastases, who did not have distant metastasis. This patient underwent bilateral IMN dissection and subsequent adjuvant radiotherapy to the ipsilateral chest wall, ipsilateral SCN and bilateral IMN regions [10]. However, as major limitation of this case report, the clinical outcome of this patient is not reported.

The results of the current study enhance our understanding of RNI and underscore the importance of investigating the effects of contralateral IMNI in high-risk patients, such as those with gross metastases in the ipsilateral IMN. This is particularly important as RNI is becoming increasingly more personalized: While there is evidence to suggest that omission of RNI may be justified in T1-3, cN1 patients with nodal complete response following neoadjuvant chemotherapy, there is a consensus that patients with locally advanced breast cancer such as cN3, require individualized target volumes during adjuvant radiotherapy [31]. It is up to future studies to investigate the role of contralateral IMNI in this context.

Conclusion

The incidental dose distribution to the cIMN is negligible for the field design of the randomized trials investigating the effect of RNI. Even though for contemporary treatment techniques the incidental dose needs to be expected higher (with mean values of approximately 13 Gy), a clinically relevant effect is unlikely for the vast majority of cases.

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CRediT authorship contribution statement

Sophie T. Behzadi: Conceptualization, Methodology, Formal analysis, Investigation, Visualization. **Mathias Duesberg:** Methodology, Validation. **Rebecca Moser:** Validation. **Marciana-Nona Duma:** Validation. **Markus Oechsner:** Validation. **Sophia Kiesl:** Validation. **Jana Nano:** Validation. **Stephanie E. Combs:** Validation, Project administration. **Kai J. Borm:** Conceptualization, Methodology, Validation, Formal analysis, Visualization, Supervision.

Declaration of competing interest

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