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ORIGINAL ARTICLE

Variability in lymph node irradiation in patients with breast cancer—results from a multi-center survey in German-speaking countries

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Abstract

Purpose Lymph node irradiation in breast cancer has gained complexity due to recently published studies and technical innovations which then led to changes in international guidelines. We sought to determine real-time variability in lymph node irradiation in clinical practice in German-speaking countries.

Methods The Department of Radiation Oncology, Technical University of Munich (TUM), developed an online-based questionnaire focusing on the indication, target definition, and treatment technique of lymph node irradiation in patients with breast cancer. The invitation to participate in the survey was sent to members of the German Society of Radiation Oncology (DEGRO) by e-mail. The results of the survey were exported from the online platform into SPSS for a detailed analysis.

Results In total, 100 physicians completed the questionnaire between 05/2019 and 06/2019. Despite the existence of several treatment and contouring guidelines, we observed large variability of lymph node irradiation: The guideline recommendation for internal mammary irradiation is not consistently implemented in clinical practice and irradiation of the axilla after positive SLNB (sentinel lymph node biopsy) or ALND (axillary lymph node dissection) is handled very differently. Furthermore, in most clinics, the ESTRO (European Society for Therapeutic Radiology and Oncology) contouring consensus is not used, and PTV (planning target volume) definitions and margins vary considerably.

Conclusion Further clinical studies should be performed with a particular focus on radiotherapy for lymphatic drainage to support and amend the existing guidelines. These studies should establish a more standardized treatment of the lymph node regions in clinical practice. Quality assurance should enforce broad implementation of consensus recommendations.

Keywords Lymph node irradiation · Breast cancer · Variability · Patterns of care · Survey

Introduction

Lymph node irradiation is a crucial component in the adjuvant treatment of high-risk breast cancer patients. Its aim is the eradication of microscopic residual disease in the lymphatic drainage system after surgery and (neo)adjuvant systemic therapy. Evidence for lymph node irradiation (RNI) has emerged from large randomized trials (EORTC 22922/10925, MA.20, AMAROS). According to these studies, RNI (including the supra-/infraclavicular and the internal mammary region as well as parts of the axilla) leads to better regional control rates as well as better distant metastases-free survival and disease-specific survival in high-risk patients [1–3]. However, internal mammary irradiation (IMI) is associated with higher radiation doses to the heart, which potentially cause clinically relevant late toxicity [4]. Thus, before the publication of the EORTC 22922/10925 and MA.20 results, IMI was generally not recommended. This has changed over the past 5 years based on the excellent results of the two randomized studies and a prospective population cohort study from Denmark showing a survival benefit for IMI in addition to

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supra-/infraclavicular irradiation (SII) [1, 2, 5]. So far, it is unclear whether the recommendations to include the internal mammary region in RNI are implemented in clinical practice.

Another crucial point that has been altered in recent years in the guidelines is the treatment of the axilla. For many years, complete axillary lymph node dissection (ALND) was the standard therapy in node-positive patients. Nowadays, many patients receive sentinel lymph node biopsy only (SLNB). The 10-year data of the Z0011 confirm that complete ALND may be omitted in breast cancer patients in case of positive (≤2) sentinel lymph nodes without compromising locoregional control or survival [6]. The role of adjuvant radiotherapy (RT) in this setting is not fully understood. The current AGO (Arbeitsgemeinschaft Gynäkologische Onkologie) guideline (2019) is the first to recommend irradiation of the axilla up to the axillary veins, since a large number of patients in the Z0011 study received high tangential external beam irradiation [7].

Interpreting the existing data and translating the results into daily clinical practice is challenging. Most of the randomized studies were initiated in the 2D era, and technical improvements such as 3D-planning, intensity-modulated radiotherapy (IMRT), and image-guided radiotherapy (IGRT) have fundamentally changed treatment since then.

Comprehensive treatment guidelines and contouring atlases for breast cancer have been published [7–11]. However, these guidelines differ in relevant points and are not always used in clinical practice. Hence, relevant variability needs to be expected during RNI in daily practice. So far, no comprehensive study focusing on patterns of practice of RNI has been performed. We thus conducted an investigation amongst German-speaking radiation oncologists to gain information about real-life concepts regarding RNI in patients with breast cancer. The aim of the current study was to reveal aspects in RNI that need increased efforts in continuing medical education or clarification in future studies and scientific discussions.

Methods

A pattern-of-care questionnaire regarding RNI in breast cancer was developed at the department of radiation oncology at the Technical University of Munich (TUM). The questionnaire focused on (1) indication, (2) target volume definition, and (3) treatment technique of RNI. Additionally, (4) general information of the responders such as age and experience were assessed. The total number of questions was $n=25$. All questions regarding RNI ($n=20$) were designed as multi-choice questions allowing multiple answers as well as free responses in case of missing options. All authors reviewed the questions for understandability. The questionnaire was implemented in the online platform "survio.com" and the corresponding link was sent via e-mail to all members of the German Society of Radiation Oncology (DEGRO). The online survey was available from 13th of May 2019 to the 13th of June 2019. The data obtained on the online platform was exported to SPSS (IBM statistics, version 25, Armonk, NY, USA) and analyzed.

Results

In total, 100 questionnaires were completed at the online platform. The majority of participants (92.9%) were specialists in radiation oncology; the remaining participants (7.1%) were residents in radiation oncology. 48% of the participants worked in private practice and 52% in hospitals (24% university hospital, 28% non-university hospitals). 48% of the participants were male, 52% female. The current study represents at least 52 centers out of (approximately) 455 centers in Germany [12].

Indication for lymph node irradiation

When the participants were asked for their primary aim of RNI, the most frequent answer was to prevent regional lymph node recurrences ($n=84$), followed by improvement of overall and/or disease-specific survival ($n=75$) and reduction of distant metastases ($n=54$).

The questionnaire listed potential reasons for SII, and the participants were asked in which situation they would perform SII. The results are presented in Fig. 1a. The majority of participants perform SII in case of positive supra-/infraclavicular lymph nodes (85%), ≥4 positive lymph nodes (85%), or in case of 1–3 positive nodes and additional risk factors (75%).

For most radiation oncologists, RNI does not regularly comprise SII and irradiation of the internal mammary region (IMI). Instead, most radiation oncologists (75%) decide individually whether IMI should be performed (e.g., in high-risk patients). Only 10% agreed that the internal mammary region should always be treated when SII is performed and no contraindications for IM irradiation are present (Fig. 1b).

72% (9%) of the physicians stated that additional cardiac (pulmonary) toxicity is the most critical reason for not performing IMI. 39% based concerns regarding the IMI on inconclusive data and a lower level of evidence. Only 9% saw the technical requirements and the time effort as an obstacle for IMI.

Current guidelines (AGO 2019) advise against IMI in case of "cardiac risk" and "concomitant administration of trastuzumab." In our survey, only 46.2% agreed that the simultaneous application of trastuzumab is a contraindication for IMI. The following factors were chosen as

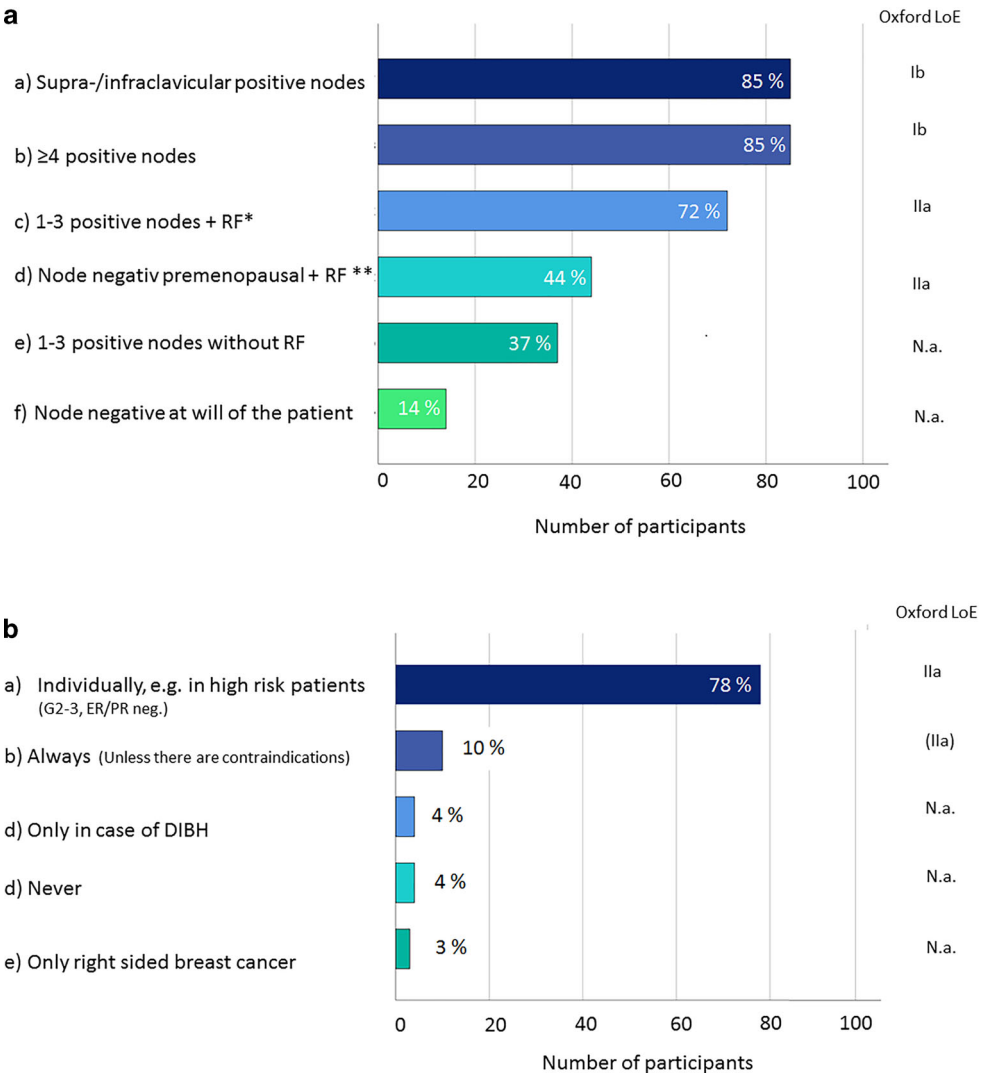

Fig. 1 Indications for irradiation of the supra-/infraclavicular region (**a**) and the internal mammary region (**b**). **a** *Asterisk* Central or median and G2–3 or ER/PgR negative, premenopausal, and G2–3 or ER/PgR negative. *Two asterisks* Premenopausal and central or medial and G2–3 and ER/PgR negative. **b** Additional comments: irradiation in case of medial tumor ($n = 13$) irradiation in case of positive internal mammary lymph nodes. *RF* risk factor, *DIBH* deep-inhalation breath-hold, *LoE* Level of Evidence, *ER* estrogen receptor, *PgR* progesteron receptor

further contraindications for IMI in our survey: history of acute cardiac ischemia (63.7%), coronary heart disease (48.4%), congestive heart disease (36.3%), an anthracycline-based chemotherapy regimen prior to RT (36.3%), old age (34.1%), vascular risk factors (e.g., smoking, diabetes 24.2%), and arrhythmia (25.3%). 25.3% choose free-text answers, mostly stating that the IMI decision should be based on the actual dosimetric data and careful risk/benefit assessment instead of absolute contraindications.

Fig. 2 presents the results of our survey regarding axillary irradiation after positive SLND or positive ALND.

Target definition

Most radiation oncologists use consensus guidelines for target delineation. The most commonly used contouring guideline is the RTOG (Radiation Therapy Oncology Group) consensus guideline (71%) followed by the ESTRO (European Society for Therapeutic Radiology and Oncology) consensus guideline (25%). 9% of the participants use both guidelines depending on the risk constellation (ESTRO low risk, RTOG high risk). 6% do not use any of the published guidelines. 86% agreed that the axillary level III should be included in the supra-/infraclavicular CTV (clinical target volume) and 31% include in addition to this also level II in the clinical target volume for SII.

Further results regarding the target delineation were:

1. the cranial border of the supra-/infraclavicular lymph node CTV is set at the cricoid cartilage in 56%
2. 75% connect the PTVs (planning target volume) of the breast and the lymph nodes to avoid gaps.
3. 39% crop lung tissue from the PTV
4. 62% crop skin from the PTV
5. The most common CTV to PTV margin is 5 mm (50%)

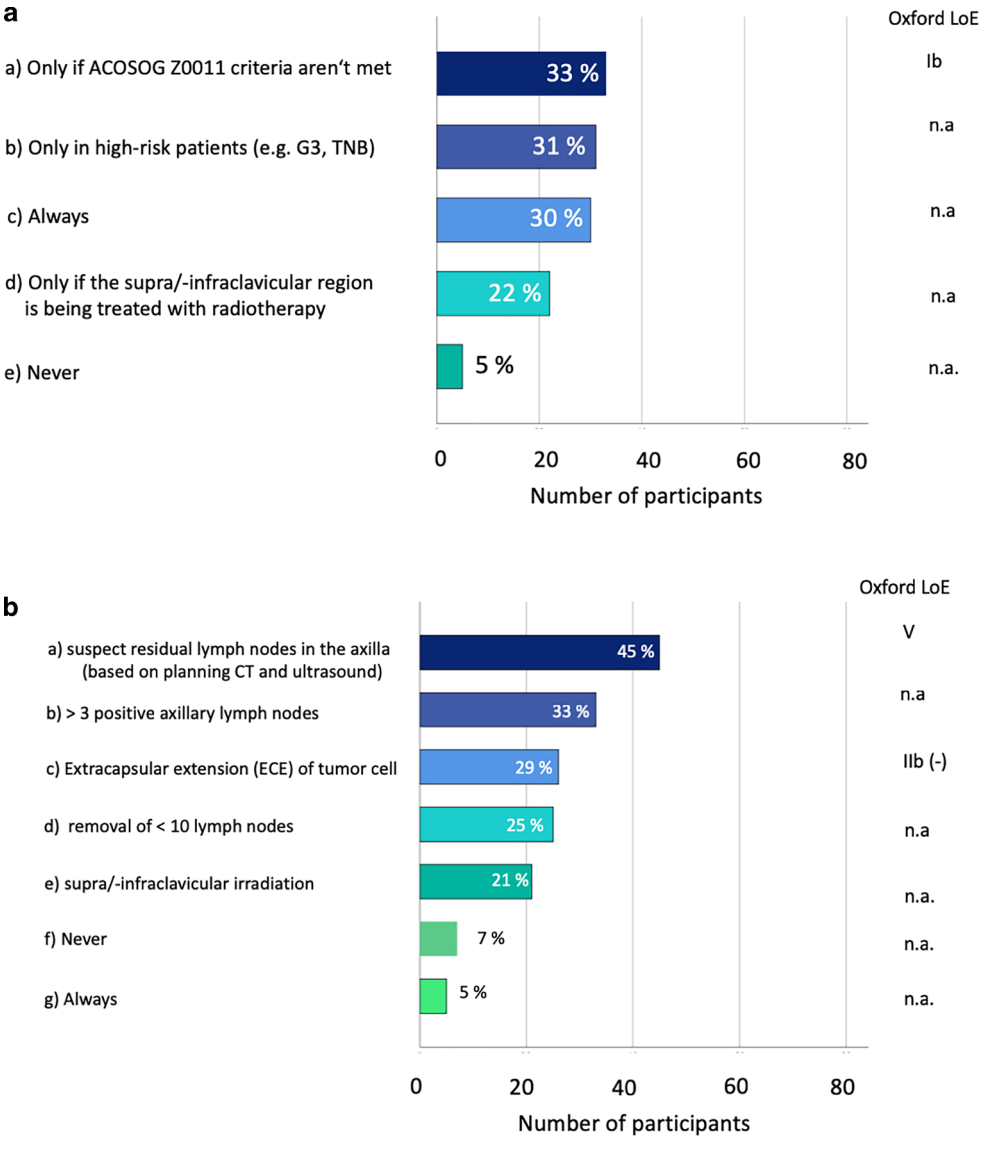

Fig. 2 Indications for irradiation of the axilla after positive SLND (**a**) and after ALND (**b**). *TNB* triple-negative breast cancer, *SLND* sentinel lymph node dissection, *ALND* axillary lymph node dissection, *LoE* Level of Evidence

Table 1 Irradiation techniques used for the internal mammary and the supra-/infraclavicular region

Technik	Internal mammary region (%)	Supra-/infraclavicular region (%)
Wide tangents	27	n.a.
Anterior electron field	3	0
Anterior photon field	18	45
3D-IMRT	65	57
VMAT	59	54
Helical IMRT	8	8

3D-IMRT 3D-Intensity modulated radiotherapy, *VMAT* volumetric modulated arc therapy, *Helical IMRT* Helical Intensity modulated radiotherapy

Irradiation technique

The most frequently used dose regimens for lymph node irradiation are 50.4 Gy in 28 fractions (85%) and 50 Gy in 25 fractions (25%). Only 12% of the participants use hypofractionated regimens (42.5 Gy in 16 fractions and 40.05 Gy in 15 fractions). Three out of these 12 participants use only hypofractionated regimens. The techniques used for IMI and SII are summarized in Table 1.

Image guidance for lymph node irradiation is performed with either 2D X-rays (44%), CBCTs (Conebeam Computed Tomography) (47%), MVCT (Megavoltage Computed Tomography) (9%), or surface scanners (9%). 2D

X-rays, CBCT, and MVCT are mostly performed once a week; surface scanners are often used daily (75%).

Discussion

We performed a survey among German-speaking radiation oncologists who are members of DEGRO regarding indications for RNI, target volume definition, and choice of technique in patients with breast cancer. Although several consented treatment and contouring guidelines exist, large heterogeneity regarding RNI in patients with breast cancer was shown. The guideline recommendations for IMI are not consistently implemented in clinical practice and irradiation of the axilla after positive SLNB or ALND is handled very differently. Furthermore, at most sites, the ESTRO contouring consensus is not applied, and PTV definitions and margins vary considerably.

The MA.20 and EORTC 22922/10925 studies assessed the effect of regional nodal irradiation to the internal mammary nodes and the upper axillary nodes, including the supraclavicular region, in addition to whole-breast irradiation or chest wall irradiation. In the MA.20 study, regional (2.7% vs. 0.7%) and distant recurrences (17.3% vs. 13.4%) were reduced, and the disease-specific survival was improved by 5% at 10 years in those who received nodal irradiation. In the EORTC study, regional radiation therapy reduced the incidence of regional recurrences from 4.2 to 2.7% and the incidence of distant metastases from 19.6 to 15.9% after a median follow-up of 10.9 years. Based on these results, the NCCN (National Comprehensive Cancer Network) guidelines recommend irradiation of infraclavicular and supraclavicular areas, internal mammary nodes, and any part of the axillary bed that may be suspicious in case of ≥4 positive nodes (category 1) and 1–3 positive nodes (category 2A). Irradiation of the regional nodal area is generally not recommended by the NCCN panel in case of node-negative patients. The German guidelines (S3, AGO, DEGRO practical guidelines) differ from the NCCN guidelines in several points regarding RNI [7, 10, 13, 14]. The most important difference is that separate treatment recommendations exist for each lymph node region and that more factors in addition to lymph node involvement are considered.

The highest approval rate for SII (Fig. 1a) among the participating radiation oncologists was achieved for more than 3 positive lymph nodes or positive supraclavicular nodes (85%) as well as 1–3 lymph positive lymph nodes with additional risk factors (72%). In these situations, all guidelines recommend RNI, and there is good evidence for an additional benefit. Thus, the omission of lymph drainage radiation should be limited to individual cases after careful consideration. The controversial opinions among the responders about SII in case of node-negative patients with risk factors and patients with 1–3 positive lymph nodes can be attributed to conflicting recommendations in the German and the NCCN guidelines.

The MA.20 as well as the EORTC study investigated the additional effect of RNI. Due to the design of these trials it is not possible to attribute the positive effect on subvolumes within the lymphatic drainage system (e.g., contribution of IMI). In a Danish population-based cohort study, additional IMI increased overall survival in patients with early-stage node-positive breast cancer [5]. A randomized French trial on the other hand failed to show a significant benefit for addition IMI during postmastectomy irradiation [15, 16].

The NCCN guidelines state that IMI should be strongly considered when delivering regional nodal irradiation. In accordance with this, in the latest German guideline (AGO 2019), the criteria for IMI and SII are almost the same. Nevertheless, as shown in our survey, only a few radiation oncologists consider the combination of SII and IMI as a standard treatment in RNI. Instead, most radiation oncologists decide individually (e.g., in the case of high-risk patients) whether the internal mammary region should be included or not. Hesitations regarding internal mammary irradiation in our study were mainly based on increased cardiac and pulmonary doses and toxicity. In addition to this, many physicians doubt an additional effect if IMI is performed. Since the rationale for RNI is mainly based on the results of the MA.20 and EORTC studies and modern treatment techniques (deep-inhalation breath-hold, wide tangents, IMRT) allow better sparing of organs at risk (OARs) compared to these randomized trials, the guideline recommendations to include the internal mammary region are comprehensible and omission of IMI should be limited to individual cases.

The German guidelines cite “cardiac risk” and concomitant trastuzumab as reasons against IMI. As shown in our results, the interpretation of cardiac risk factors in clinical practice is very different, and not all radiation oncologists agree that IMI plus concomitant trastuzumab should be avoided. Instead of using strict contraindications, it might be helpful to assess the actual dose distribution in the OARs resulting from IMI using the best available technique (e.g., deep inhalation breath hold [DIBH]). Based on these values in the OAR, an interdisciplinary decision regarding IMI should follow for high-risk patients. The German breast cancer group has published a detailed study on dose constraints of the heart in breast cancer patients [17]. Even if the authors state that exceeding these constraints may be unavoidable and justifiable in case of comprehensive regional irradiation, the values can help to define constraints for RNI.

In case of positive SLNB without ALND, 30% of radiation oncologists participating in the questionnaire would always treat the axilla and another 30% only if the Z0011

criteria are not met. Given the fact that most patients in the Z0011 received high doses in the (lower) axillary levels I–II, irradiation might be justified even if the Z0011 criteria are met [18]. The AGO guideline [7] is the first to recommend such an approach. According to the German guideline, irradiation of the axilla after ALND is only indicated in case of suspected residual tumor after axillary dissection [7, 9, 10]. Even though not recommended in the current German guidelines, one quarter of the participants treat the axilla in case of >3 LN or <10 dissected lymph nodes. In the MA.20 trial, an additional posterior field was used to cover the axillary levels I–II in case of >3 LN or <10 dissected lymph nodes [2]. This might have contributed to the excellent outcome of this trial. Thus, in individual cases (e.g., >3 positive LN), irradiation of the axilla can be justified. This is supported by the NCCN guidelines stating that irradiation of *"any part of the axillary bed at risk"* is recommended [9].

Target definition is a crucial step in 3D radiotherapy. Alteration of the CTV margins leads to a different dose distribution in the lymph node system and the OARs. This has an impact on the effectivity and the toxicity of the treatment. Differences regarding target volume definition among the randomized RNI trials impede interpretation of the study results [13, 19]. The vast majority of participants use either the RTOG or the ESTRO consensus for irradiation of the lymphatic drainage system. Substantial differences exist between the two guidelines (RTOG vs. ESTRO). The ESTRO contouring consensus [20] was published in 2015. It represents a vessel-based approach that results in smaller target volumes compared to the RTOG (2009) contouring guideline. The ESTRO guideline aimed to prevent that target volumes in the 3D era are larger compared to the 2D era, which might cause additional toxicity. Several studies assessed the RTOG and ESTRO guidelines for RNI by mapping lymph node metastases. In these studies, the ESTRO guidelines covered the relevant areas safely within the lymphatic drainage system [21, 22]. The ESTRO guideline is adapted to modern techniques and reduces potential side effects related to RNI. Nevertheless, only 25% of the participants use this contouring guideline in clinical practice.

Even if the CTVs are defined based on the same contouring guidelines, target volumes can vary due to different safety margins and definition of the lymph node areas (e.g., of the infraclavicular region). Despite the same intent of SII, dose distribution may vary due to the definition of the infraclavicular region (± level II). 50% of the participants use CTV to PTV of 5 mm for irradiation of the lymph node system. No recommendation regarding the PTV margins can be found in the guidelines. However, a PTV margin of 5 mm is also frequently used in previous and ongoing studies on lymph node irradiation [1, 2, 23]. If the lung is cropped from the PTV (as stated by 40%) very small posterior CTV to PTV margins may result. Considering that the intrafractional movement of the internal mammary region can be up to 5 mm, this may be critical, and careful image guidance should be performed to verify the patient position [24].

Daily imaging improves patient positioning but usually comes at the price of additional radiation (X-ray or CT imaging). Careful risk–benefit assessment is therefore necessary. A good option are surface scanners. These scanners can be used on a daily basis without further irradiation exposure [25]. However, this technique is only available in a few centers to date.

The vast majority of participants use normofractionated schemes for irradiation of the lymph node system. This represents the current consensus of the American and German guidelines [7, 9, 10]. Until now, late toxicity data in the lymphatics and the plexus are insufficient to recommend hypofractionated irradiation for all patients. However, evidence that hypofractionated schedules can safely be applied to the lymph node system is constantly improving. Last year, Wang et al. recently published a randomized trial showing that postmastectomy hypofractionated radiotherapy, including RNI, is non-inferior and had similar toxicities compared to conventionally fractionated radiotherapy [26].

For irradiation of the lymph node system, IMRT and VMAT (volumetric modulated arc therapy) are the most frequently used techniques in German-speaking countries. Still, 45% (18%) of the participants use also anterior photon fields for the supra-/infraclavicular (or the internal mammary) region. If anterior fields are used, careful evaluation of the dose in the heart and lung is essential. Ranger et al. [27] showed that simple wide-tangent radiotherapy delivered in DIBH achieves satisfactory coverage of the IMC (internal mammary chain) and acceptable doses in the heart and lung. Thus, it might be a good option for centers in which IMRT is not available for irradiation of the internal mammary region [27].

Conclusion

As consequence of numerous treatment and contouring guidelines for breast cancer treatment, we observed large variability in RNI. The current guideline recommendations (S3, AGO, NCCN) for IMI are not implemented adequately in clinical practice and irradiation of the axilla after positive SLNB or ALND remains controversial. The planning target volumes vary mainly due to the use of different contouring atlases and definitions, as well as PTV margins. Further clinical studies should be performed with a particular focus on RNI to support and amend the existing guidelines and to establish a more standardized treatment in clinical practice.

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Conflict of interest K. J. Borm, K. Kessel, M. Devecka, S. Muench, C. Straube, K. Schiller, L. Schüttrumpf, H. Dapper, B. Wöller, S. Pigorsch, and S. E. Combs declare that they have no competing interests.

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