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DEGRO practical guidelines: radiotherapy of breast cancer III—radiotherapy of the lymphatic pathways

Postoperative regional nodal irradiation (RNI) has been an issue of controversy over the last decades as the awareness of late side effects increased. While RNI was part of the treatment in almost all studies investigating postmastectomy radiotherapy (PMRT) [9], only a minority of patients received RNI after breast-conserving surgery (BCS) [11]. Moreover, the term RNI is not uniformly defined. Older studies generally included radiotherapy of the supraclavicular (SCN-RT), axillary (ALN-RT), and internal mammary nodes (IMN-RT). More recently, the use of IMN-RT has substantially declined as it was suspected to enhance cardiac toxicity and morbidity [12]. Likewise, dedicated ALN-RT of levels I–III has been considered obsolete for node-negative patients after axillary lymph node dissection (ALND) or sentinel node (SN) biopsy and even for selected SN-positive patients, for whom implications for radiotherapy will be discussed below.

Final assessment of survival in breast cancer requires a follow-up of 10–15 years, a time period that inevitably implies substantial changes in treatment planning and technique. Therefore, it is difficult to extrapolate results achieved in the past to those achievable in the present or future using modern techniques. This dilemma is exemplarily illustrated regarding literature about RNI: Before the advent of 3D planning as a routine tool and the use of individual contouring of the different lymphatic pathways, inadvertent inclusion of parts of the axillary and mammary nodes in the tangential fields was common but remained unrecognized as no dosimetric evaluation was performed [17, 18]. On the other hand, for intentionally irradiated lymph node areas, the target definition on the basis of anatomical landmarks alone (such as bony structures), may result in an underdosage, undetected for the same reasons [31]. Even in the recent randomized trials, 2D planning was mostly used and the dose to nodal areas accordingly prescribed. As a consequence, exact discrimination of the effect yielded by RNI in comparison to whole breast/chest wall irradiation (WBI/CWI) alone, may be difficult. These limitations also apply for the recent studies that provided new evidence for the benefit of RNI [22, 40, 58]. Two opposite speculations are conceivable: *either* the benefit of RNI might be more pronounced with high tech three-dimensional (3D) planning, as it ensures adequate dose coverage of the target; *or* the results may even be inferior, assuming that inadvertent irradiation of the lymph nodes may have contributed to tumor eradication with older techniques.

The aim of the present paper is to provide an overview on recent literature and to discuss the different aspects concerning indications for RNI in light of new data on the basis of a comprehensive literature search. Moreover, the problem of nodal coverage with different techniques will be illustrated by reproducing field arrangements in the different studies and superimposing them on CT slices with individually contoured node areas.

Finally, practical guidelines for targeting and technique of radiotherapy of the lymphatic pathways after surgery for breast cancer will be outlined. The present recommendations are complement-

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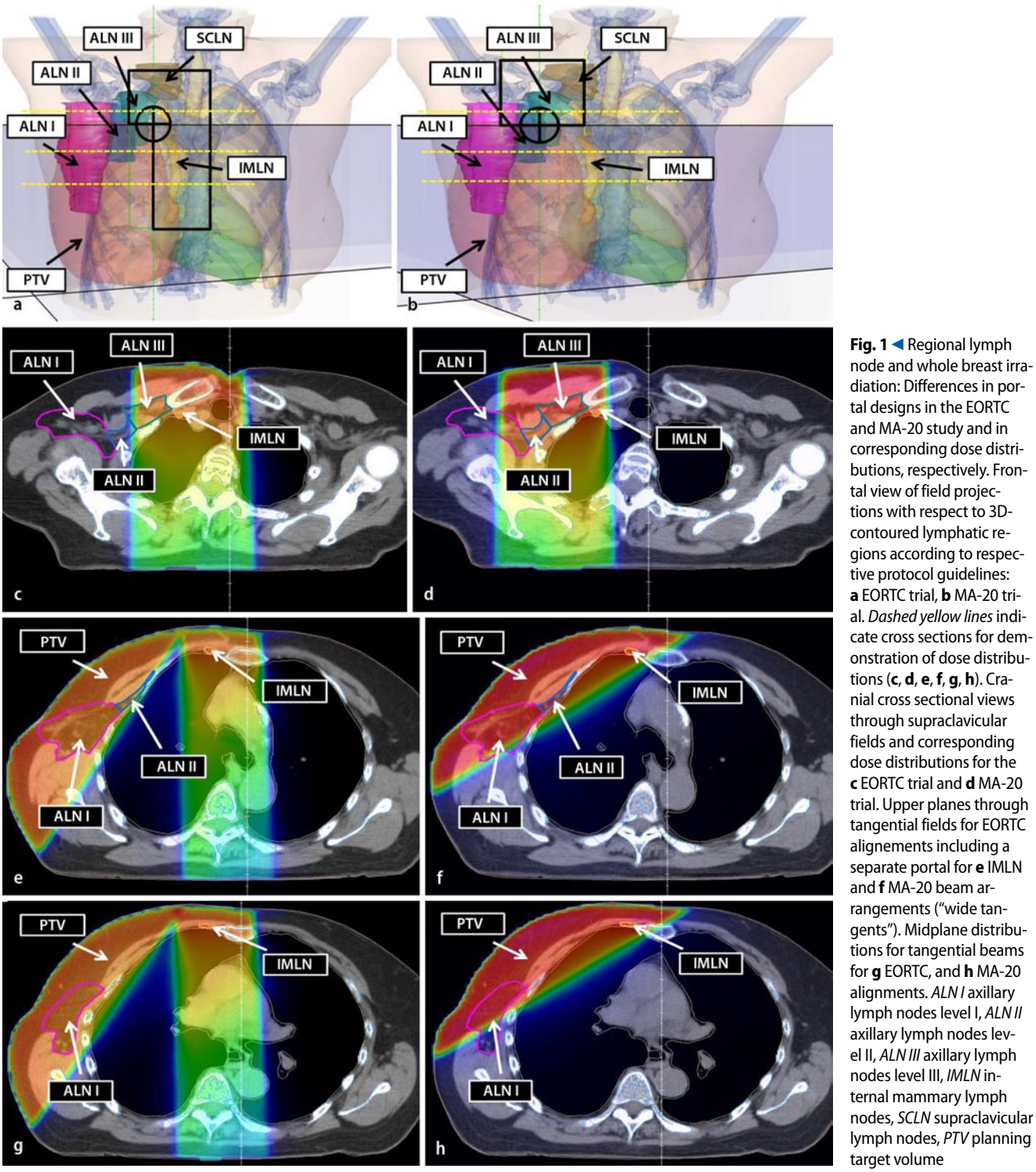

Fig. 1 ◀ Regional lymph node and whole breast irradiation: Differences in portal designs in the EORTC and MA-20 study and in corresponding dose distributions, respectively. Frontal view of field projections with respect to 3D-contoured lymphatic regions according to respective protocol guidelines: **a** EORTC trial, **b** MA-20 trial. *Dashed yellow lines* indicate cross sections for demonstration of dose distributions (**c**, **d**, **e**, **f**, **g**, **h**). Cranial cross sectional views through supraclavicular fields and corresponding dose distributions for the **c** EORTC trial and **d** MA-20 trial. Upper planes through tangential fields for EORTC alignements including a separate portal for **e** IMLN and **f** MA-20 beam arrangements ("wide tangents"). Midplane distributions for tangential beams for **g** EORTC, and **h** MA-20 alignments. *ALN I* axillary lymph nodes level I, *ALN II* axillary lymph nodes level II, *ALN III* axillary lymph nodes level III, *IMLN* internal mammary lymph nodes, *SCLN* supraclavicular lymph nodes, *PTV* planning target volume

ing and critically reviewing the interdisciplinary S3 guidelines provided by the German Cancer Society (DKG) published in July 2012 [48] and updating the practical guidelines published in 2008 by the breast cancer expert panel of the German Society of Radiation Oncology (DEGRO) [49].

General indications for regional nodal irradiation

In case of 4 positive axillary nodes, the indication for RNI is undisputed. For patients with 1–3 positive nodes (pN1), data concerning the effectiveness of RNI are less unequivocal [9, 19, 56, 62]. This incertitude is reflected by the heterogeneity of recommendations in different international guidelines. Indirect evidence for the benefit of RNI for patients with 1–3 positive axillary nodes was derived from subgroup analyses of the Danish Breast Cancer Group study and the British Columbia trial. Both randomized studies yield-

Abstract · Zusammenfassung

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DEGRO practical guidelines: radiotherapy of breast cancer III – radiotherapy of the lymphatic pathways

Abstract

Aim. The purpose of this work is to update the practical guidelines for adjuvant radiotherapy of the regional lymphatics of breast cancer published in 2008 by the breast cancer expert panel of the German Society of Radiation Oncology (DEGRO).

Methods. A comprehensive survey of the literature concerning regional nodal irradiation (RNI) was performed using the following search terms: "breast cancer", "radiotherapy", "regional node irradiation". Recent randomized trials were analyzed for outcome as well as for differences in target definition. Field arrangements in the different studies were reproduced and superimposed on CT slices with individually contoured node areas. Moreover, data from recently published meta-analyses and guidelines of international breast cancer societies, yielding new aspects compared to 2008, provided the basis for defining recommendations according to the criteria of evidence-based medicine. In addition to the more general statements of the German interdisciplinary S3 guidelines updated in 2012, this paper addresses indications, targeting, and techniques of radiotherapy of the lymphatic pathways after surgery for breast cancer.

Results. International guidelines reveal substantial differences regarding indications for RNI. Patients with 1–3 positive nodes seem to profit from RNI compared to whole breast (WBI) or chest wall irradiation alone, both with regard to locoregional control and disease-free survival. Irradiation of the regional lymphatics including axillary, supraclavicular, and internal mammary nodes provided a small but significant survival benefit in recent randomized trials and one meta-analysis. Lymph node irradiation yields comparable tumor control in comparison to axillary lymph node dissection (ALND), while reducing the rate of lymph edema. Data concerning the impact of 1–2 macroscopically affected sentinel node (SN) or microscopic metastases on prognosis are conflicting.

Conclusion. Recent data suggest that the current restrictive use of RNI should be scrutinized because the risk–benefit relationship appears to shift towards an improvement of outcome.

Keywords

Breast neoplasms · Radiotherapy, adjuvant · Regional nodal irradiation · Practice guidelines

DEGRO-Leitlinien für die Strahlentherapie des Mammakarzinoms III – Strahlentherapie der Lymphabflusswege

Zusammenfassung

Ziel. Aktualisierung der DEGRO-Leitlinie von 2008 zur adjuvanten Strahlentherapie des regionalen Lymphabflusses bei Mammakarzinom und Ergänzung der allgemeinen Empfehlungen der interdisziplinären S3-Leitlinie der Deutschen Krebsgesellschaft von 2012 durch spezifisch radioonkologische Leitlinien zur Indikation, Zielvolumendefinition und Technik der postoperativen Radiotherapie.

Methoden. Die DEGRO-Expertengruppe Mammakarzinom führte eine systematische Literaturrecherche nach randomisierten Studien, Metaanalysen sowie internationalen Leitlinien durch, die nach 2008 publiziert wurden und sich an den Kriterien evidenzbasierter Medizin orientierten. Suchbegriffe waren „breast cancer", „radiotherapy" und „regional node irradiation". Die Studien wurden sowohl auf ihre Ergebnisse als auch hinsichtlich der Unterschiede in den Zielvolumina analysiert und auf 3-D-Planungsschnittbilder mit CT-konturierten Lymphabflussgebieten projiziert.

Ergebnisse. Die Indikation zur regionalen Lymphabflussbestrahlung (RNI) wird in internationalen Leitlinien unterschiedlich gestellt. Bei Patientinnen mit 1–3 befallenen axillären Lymphknoten wurden nach RNI im Vergleich zur alleinigen Bestrahlung der Brust oder Brustwand Verbesserungen der lokoregionalen Kontrolle und des Überlebens beobachtet. Mehrere randomisierte Studien und eine Metaanalyse zeigten nach RNI (mit unterschiedlichen Zielvolumina) eine zwar geringe, jedoch signifikante Verbesserung des Überlebens. Bei positivem Sentinel-Lymphknoten (SN) ist die Lymphabflussbestrahlung einer axillären Lymphonodektomie (ALND) gleichwertig in der lokalen Tumorkontrolle, geht aber mit einer deutlich geringeren Lymphödemrate einher. Zur Frage, ob ein solch limitierter Lymphknotenbefall und selbst eine Mikrometastasierung langfristig einen Einfluss auf die Prognose haben, ist die Datenlage widersprüchlich.

Schlussfolgerung. Die restriktive Indikationsstellung zur Lymphabflussbestrahlung muss angesichts neuer Daten aus randomisierten Studien kritisch überdacht werden.

Schlüsselwörter

Brustneoplasien · Adjuvante Strahlentherapie · Regionale Lymphknotenbestrahlung · Leitlinien

ed an improvement of survival if postmastectomy radiation (PMRT) including the complete lymphatic pathways was used. Comparison of outcome according to the number of metastatic nodes revealed that patients with 1–3 and those with ≥4 positive nodes had a similar absolute overall survival (OAS) advantage of roughly 10% [38, 42]. As no comparison was made to chest wall irradiation alone, uncertainty remained how to quantify the contribution of RNI.

Patients allocated for primary systemic treatment (PST) should preferentially receive sentinel node biopsy (SNB) prior to treatment [28]. For patients with pathologically negative nodes after PST, who had initially presented with clinical lymphadenopathy, the decision for RNI should comply to the pretreatment stage, irrespective of the response to chemotherapy [1, 5, 35, 48]. This recommendation is not based on a high level of evidence as no randomized studies have been performed to assess the potential benefit of RNI in this situation. Data from retrospective studies are conflicting [13, 60]. In-

Tab. 1 Meta-analysis of survival data from two randomized trials

	MA-20 [58]	EORTC [40]	Meta-analysis [6]
Design	WBI + IM + MS + Ax level III vs. WBI alone	WBI/CWI + IM + MS vs. WBI/ CWI alone	
n	1832	4004	Total 5836
OAS	HR 0.76 (95% CI 0.75–0.96) p=0.07	HR 0.87 (95% CI 0.76–1.00) p=0.056	**HR 0.85** (95% CI 0.75–0.96) **p=0.011**
DFS	HR 0.67 (95% CI 0.52–0.87) p=0.003	HR 0.89 (95% CI 0.80–1.00) p=0.044	**HR 0.85** (95% CI 0.77–0.94) **p=0.002**
MFS	HR 0.64 (95% CI 0.47–0.85) p=0.02	HR 0.86 (95% CI 0.73–0.92) p=0.02	**HR 0.82** (95% CI 0.73–0.92) **p=0.001**

WBI whole breast irradiation, *IM* internal mammary nodes, *MS* medial/supraclavicular nodes, *Ax* axillary nodes, *CWI* chest wall irradiation, *OAS* absolute overall survival, *HR* hazards ratio, *CI* confidence interval, *DFS* disease-free survival, *MFS* metastasis-free survival.

terestingly, in one series, the largest benefit of PMRT (including RNI) was observed for the subgroup of patients with a complete remission after PST (33% vs.77% p=0.0016) [33]. Especially with regard to the emerging role of PST, a prospective controlled trial is highly warranted.

New evidence from randomized trials

Canadian trial (NCIC-CTG MA.20)

Beyond retrospective data, the first randomized study providing evidence for the benefit of RNI especially in patients with 1–3 lymph nodes (LN), was the NCIC-CTG MA.20 trial, presented at the ASCO 2011, not yet published as full paper [58]. The study comprised 1832 women with mostly 1–3 positive axillary nodes (85%) and a minority of women (10%) with negative nodes in the presence of high-risk factors (G3, lymphatic vessel invasion, T3 tumors, T2 tumors with <10 axillary lymph nodes removed and HR-negative). Patients were randomized after breast-conserving surgery and ALND to either whole breast irradiation (WBI) or WBI and additional RNI. The target volume in the RNI group included levels I–III of the axillary nodes, supraclavicular and internal mammary nodes (**Fig. 1b**). The 5-year locoregional recurrence-free survival was 96.8% with and 95.5% without RNI (p=0.02). The 5-year disease-free survival (DFS) was significantly improved in the RNI group: 89.7% vs. only 84% patients with WBI alone (p=0.003). This difference is twice as high as the absolute benefit in terms of local control, and therefore hypothetically attributable to the significant positive impact on distant metastases-free survival (DMFS) with an absolute 5.4% reduction at 5 years in the RNI arm (p=0.002). There was a trend towards improved OAS (92.3% vs. 90.7%), however, just below statistical significance (p=0.07). The rate of lymph edema (any grade) was 4% without vs. 7% with RNI (p=0.004) which is in accordance to recent literature [51]. The rate of pneumonitis was slightly increased after RNI (1.3%vs.0.2%) but altogether low. Data concerning cardiovascular toxicity were not yet provided. The authors concluded that RNI reduces the risk of locoregional and distant recurrence and improves DFS with a trend in improved OAS [58].

European study EORTC 22922-10925

The European study EORTC 22922-10925 [40] (not yet published as full paper either) included 4004 women stage I–III with mostly pT1–2 tumors (95%) and either involved axillary LN (55.6%) and/or a medially located primary tumor (44.5%). Patients were randomized after BCS (76.1%) or mastectomy (23%) to receive WBI/PMRT either with or without inclusion of the IMN and medial SCN (MSCN) (**Fig. 1a**) with 50 Gy in 25 fractions. After mastectomy, chest wall irradiation was applied to 73.2% of patients in both arms. Dose specifications for WBI/CWI were not required, presumably, relevant parts of the axilla were included in these fields. Nearly all LN-positive (99.0%) and 66.3% of the LN-negative patients received adjuvant systemic treatment. After adjustment for stratification factors, IM-MS RT significantly improved outcome at 10 years: OAS: 82.3 vs. 80.7%, p=0.049; DFS: 72.1 vs. 69.1%, p=0.044; metastases-free survival (MFS) 78.0 vs. 75.0%, p=0.020. The treatment effect on OAS was similar for pN1 vs pN2 patients but interestingly, most pronounced for node-negative patients (HR 0.79, 95% CI 0.61–1.02). In case of >10 positive nodes, no advantage was observed; however, the number of patients (about 2%) was small. The highest benefit was observed in patients receiving chemo- as well as endocrine therapy (HR 0.72, 95%CI 0.55–0.94). While the local recurrence rate was similar (5.3 vs. 5.6%), regional lymph node recurrence was 2.7% with RNI vs. 4.2% without. In contrast to the findings in the Canadian study, the rates of any-grade lymph edema at 3 years were identical in both groups [32]. No increase in lethal complications was observed so far. Therefore, the authors conclude that radiotherapy of the IMN and medial SCN should be recommended for patients with involved axillary LN and/or medially located primary tumor.

French study

In the French trial [22], 1334 patients with mostly T1–2 tumors (85%) and either positive axillary nodes (75%) or central/medial tumors irrespective of nodal status (25%) were included. All patients were treated with PMRT to the chest wall, including SCN (plus axillary apex, in node-positive cases) and were randomized to receive additional IMN-RT or not. IMN included the first 5 intercostal spaces. Roughly 60% received chemotherapy, about 50% endocrine systemic treatment. Overall, 10-year OAS was 62.57% with IMN-RT and 59.3% (p=0.8) without. Node-negative patients (25%) showed a trend towards a worse outcome with IMN-RT (n.s.), whereas node-positive patients seemed to profit from IMN-RT (n.s.). In patients with lateral tumors, who were treated with chemotherapy, the 10-year OAS was 67% vs. 64% (n.s.) in favor of IMN-RT, without chemotherapy 55% vs. 50.5% (ns) respectively. Node-

positive patients with medial/central tumors had a worse outcome compared to lateral ones, for whom 10-year OAS after chemotherapy was 57% vs. 49.8% and 54% vs. 47.5% without chemotherapy both in favor of IMN-RT, but also without statistical significance. The authors concede that the study may have been underpowered to prove a significant survival benefit for IMN-RT. No increase in cardiac toxicity was observed in the IMN-RT group but may have been incompletely reported; the authors admit that their data do not permit a definite conclusion regarding toxicity and conclude that they cannot reliably recommend for or against IMN-RT [22].

Meta-analysis of these trials

A meta-analysis of these data [6] revealed a more distinct benefit of RNI on OAS with a hazard ratio of 0.82 (p=0.011) (**Tab. 1**). The largest gain was observed for DMFS, possibly supporting the hypothesis of Hellman [21] that radiotherapy is "stopping metastases at their source".

Comments and conclusions of the DEGRO panel

- **Data from the MA-20 and EORTC studies suggest that *all* node-positive patients profit from comprehensive RNI including SCN and IMN.**
- **The respective contribution of RNI by site (SCN vs. IMN) on improved outcome cannot be distinguished, axillary nodes of level I and II were partly included in the control arms using WBI/CWI.**
- **Full publication of the MA-20 and the EORTC studies is pending; several important details or subgroup analyses are not yet available.**
- **No increase in cardiovascular toxicity by RNI was reported. However, follow-up of the MA- 20 study is too short to assess long-term toxicity; in the French study, exclusion of toxicity was not possible according to the authors. In the EORTC study, no increase of lethal complications was observed, however, without providing details how cardiac toxicity was assessed. Moreover, 10 years of follow-up may still be too short for final conclusions.**
- **Two of the studies permit comparison between the effect on locoregional and distant recurrence. In both trials the impact on MFS is greater than the difference in locoregional control, strongly suggesting that RNI prevents distant spread.**

Is RNI still obsolete for pN0 patients?

Statement of the German S3 Guidelines 2012 [48]

Statement RT 5a

RNI should not be performed in pathologically node-negative (pN0) patients (LoE 3b, GR A)

Generally, RNI is not recommended for patients with pathologically negative axillary nodes (pN0) assessed by adequate ALND or SNB. Already in 2009, a meta-analysis by Rowell et al. [44] revealed an improved survival of 14% for node-negative breast cancer patients after PMRT (including RNI) in the presence of one or more risk factors such as young age, high grade tumors, size >2 cm, or lymphovascular invasion. Again, the effect of RNI is not quantifiable, as in most of the studies evaluated in the meta-analysis, PMRT had been randomized vs. mastectomy alone. The above mentioned recent randomized trials included a varying percentage of node-negative patients (10–44%) with a medial/central tumor location; results are conflicting [22, 40, 58]. In the French study [22], pN0 patients did not profit from IMN-RT. In the Canadian trial, 182 node-negative patients with risk factors were included; however, no subgroup analysis has yet been presented [58]. Positive evidence was only provided in the EORTC study: a subgroup analysis according to nodal status showed a more pronounced effect of RNI on OAS (HR 0.79 95%CI 0.61–1.02) for node-negative patients compared to pN1 disease (HR 0.89, 95% CI 0.93–1.09) [40]. Details of the studies are discussed above.

Comments and conclusions of the DEGRO panel

- **RNI seems to yield a benefit for selected patients with pN0 stage and specific risk constellations or medial/central tumor location but current data are conflicting.**
- **In presence of additional risk factors, RNI should be individually discussed. From the available body of evidence, the panel cannot derive standardized recommendations for RNI in node-negative women.**

Regional nodal irradiation by site

As separate irradiation of the different nodal areas has hardly ever been investigated in a randomized setting, it is impossible to quantify the contribution to improved tumor control achieved by RT of the distinct sites. In most studies, RNI comprised either all or at least two sites.

Radiotherapy of the internal mammary nodes

Risk factors for metastatic spread to the internal mammary nodes (IMN) have been elaborated in a large series of 1679 Chinese women who underwent extended mastectomy including dissection of the mammaria interna nodes. Patients with following conditions had high risk of IMNS metastasis: 4 or more positive ALNs, medial tumor and positive ALNs, T3 tumors, and age less than 35 years. The incidence of IMN metastases for those patients was more than 20%. Positive IMN in accordance to the number of positive ALN with respect to index tumor location: 1–3 LN medial: 23% and central 32%; for those with 4–6 LN: medial 47%, central 22%. This is in contrast to the small number of patients diagnosed with clinically manifest IMN recurrence which is assumed to be only about 1% [17]. A possible explanation for this discrepancy is the lack of routine imaging of this area as part of the follow-up program. Moreover, parts of the IMN may be inadvertently included in tangential field arrangements (**Fig. 1a, b**). Another hypothesis is that micrometastasis in the IM-LN may

represent a source for metastatic spread without growing to clinically detectable size before distant metastases have been diagnosed [6].

Statement of the German S3 Guidelines 2012 [48]

Statement RT 5d

Radiotherapy of the internal mammary nodes should not be performed (GCP)

The statement of the German S3 guidelines was published before the data of the EORTC 22922-10925 trial [40] and the full paper of the French study [22] were available. It refers to NICE 2009 and NZGG 2009 [36, 37] and is more restrictive than other international guidelines. The NCCN [35] states that RT to the IMN should be "strongly considered" for node-positive patients, regardless of the number of affected nodes and irrespective of preceding surgery, i.e., breast-conserving treatment or mastectomy and even for pN0 patients with tumors >5 cm or close margins after mastectomy. The French guideline recommends "The supra/infraclavicular and the IMN nodes should be systematically irradiated. IMN-RT is particularly indicated in patients with internal-central tumors, node positive patients and those with ≥4 positive nodes" [5].

The restrictive use of IMN-RT accounts for the apprehension of enhanced cardiac toxicity [8, 12]. Indeed, an increase of cardiovascular-related mortality was observed in older studies [9]. The main reasons were a substantially larger target volume comprising the first 5 intercostal spaces and the bilateral lymph node chain. Moreover, anterior cobalt fields were used with direct dose exposition of major parts of the heart. Undisputedly, IMN-RT increases the dose to the heart, even with sophisticated 3D planning or IMRT, however, much less than formerly achieved [17, 46]. IMN-RT was not associated with an excess of cardiac death in the two aforementioned trials with a median follow-up of >10 years [22, 40], suggesting that even with the former outdated radiation techniques, cardiac toxicity will probably remain low, expectably even more seldom with modern techniques as nowadays used.

IMN-RT was part of the treatment in most PMRT studies [9, 38, 42] and the two aforementioned randomized trials investigating RNI [40, 58]. However, only one randomized trial specifically addressed the contribution of IMN-RT as part of PMRT in comparison to chest wall irradiation plus RNI without inclusion of the IMN [22]. Details are discussed above. Even though a nonsignificant benefit was observed for node-positive patients, the study was underpowered to demonstrate a clear advantage in contrast to RNI limited to the SCN and axillary nodes.

In contrast, a potential benefit of IMN-RT even for node-negative patients with medial/central tumors was observed in a recent retrospective French cohort study [10] comprising 1630 patients with negative ALND or SNB, treated between 1975 and 2008, of whom 489 received IMN-RT. Of 621 patients with medial/central tumor location, 46.5% received IMN-RT—in contrast to only 14% of those with outer quadrant tumors. For the entire group, no significant difference in survival was observed. However, a subgroup analysis according to tumor location revealed a significant benefit of IMN-RT for patients with medial/central tumors: 10- and 20-year OAS was 92.5 and 80.2% with IMN-RT vs. only 87 and 63% without (p=0.0052).

Comments and conclusions of the DEGRO panel

- **The perception that IMN-RT should not be performed (as stated in the German S3 guidelines) has to be scrutinized in light of new evidence from recent randomized trials and several population-based studies.**
- **The contribution of IMN-RT to improved outcome cannot be distinguished; parts of the IMN may have been included in the control arms using WBI/CWI.**
- **Medial tumor location should regain relevance among decision criteria for IMN-RT as part of RNI.**
- **No increased cardiovascular disease or lethal complications was observed after a median follow-up period of 10 years but the limitations discussed above do not yet permit final exclusion of late cardiac toxicity. Therefore, the panel does not yet derive standardized recommendations for IMN-RT from the currently available body of evidence. Further follow-up and subgroup analyses have to be awaited.**

Radiotherapy of the supra/infraclavicular nodes

Risk factors for a regional recurrence in the supra- and infraclavicular fossa are as described in several cohort studies. Yates et al. [61] analyzed outcome of 1065 consecutive patients with 1–3 positive axillary nodes without RNI. The 10-year rate of SCN recurrence was 0.8% in G1 vs. 10% in G3 tumors, for patients with one affected node 7.2% vs. 17.6% when three nodes were positive. As expected, patients with SCN recurrence had a significantly reduced 10-year OAS (18% vs. 65%, p<0.001). A similar observation was made by Yu et al. [62] who reported a 5-year SCN failure rate of 8.7% in 448 pN1-patients without SCN-RT, also associated with a significant deterioration of OAS. Main risk factors were extracapsular extension, lymphovascular invasion, and involvement of level II and III nodes.

The terms "apical axillary nodes" or "infraclavicular nodes" are synonyms for level III axillary nodes [2].

Statement of the German S3 Guidelines 2012 [48]

Statement 5e

Radiotherapy of the supra/infraclavicular nodes is indicated

- in case of >3 positive axillary nodes (LoE 1b, GR B)
- positive nodes in level III of the axilla (LoE 1b, GR B)
- when RT of the axillary nodes is performed (LoE 3b, GR B)

The German S3 guidelines are more restrictive with regard to the indication for SCN-RT than other national and international recommendations. In contrast, the recommendations of the Breast Commit-

tee of the Arbeitsgemeinschaft Gynäkologische Onkologie (AGO) [1] do permit SCN-RT for patients with 1–3 positive nodes, referring to the American NCCN guidelines [35], where SCN-RT is not only recommended for patients with 4 or more positive lymph nodes but should also be "strongly considered" in those with 1–3 positive lymph nodes. These recommendations are not evidence-based in a strict sense as RT of the SCN as an isolated mode of nodal irradiation has not been investigated in randomized studies. Therefore, the contribution of SCN-RT to improved outcome after RNI in the reported trials cannot be distinguished from the potential effect of IMN-RT. However, in terms of locoregional failure, SCN is the most frequently affected lymph node area [24, 53]. Thus, SCN-RT appears as a plausible compromise between reducing the locoregional recurrence risk on the one hand and accounting for the fear of toxicity by IMN-RT on the other. The practice of using SCN without IMN-RT has been widely adopted especially in Northern America [8, 17]; for instance, in Canada, the use of SCN-RT after BCS for patients with 1–3 positive nodes increased from 23% prior to 1997 to 57% thereafter [56] as a result of the publication of the late results of the PMRT trial [42] that had shown a benefit of PMRT including comprehensive RNI for pN1 patients. In a large retrospective analysis of the British Columbian database, where 2768 pN1 patients after BCS were evaluated, comparing outcome of WBI vs. WBI plus RNI, the 10-year locoregional control was improved by RNI (89% vs. 93%, p=0.006); however, OAS and breast cancer-specific survival were not significantly influenced [56].

Comments and conclusions of the DEGRO panel

- **For patients with >3 positive axillary nodes, SCN-RT as part of RNI is mandatory, on the basis of recent data it should also be strongly considered in case of with 1–3 nodes.**
- **As isolated SCN-RT has not been investigated in randomized studies, its benefit as part of RNI cannot be discriminated on a high level of evidence.**
- **Retrospective data indicate a benefit of SCN even without IMN-RT, while toxicity is minimal with modern techniques.**

Radiotherapy of the axilla

Risk factors for axillary *spread* in clinically node-negative patients were analyzed in a population-based study from the Eindhoven Cancer Registry. Of the 5125 patients with cN0, ALND revealed 1748 (34%) positive lymph nodes at pathological examination. After multivariate analysis, histologic type, tumor size, tumor site, and the number of lymph nodes in the axillary specimen remained as independent predictors of the risk of nodal involvement (p<0.001) [55]. The rate of clinically apparent ALN *recurrence* is much lower: In a cohort study of the International Breast Cancer Study Group, including 8106 patients after mastectomy who received chemotherapy without PMRT, only 5% ALN recurrences were observed [24].

Statement of the German S3 Guidelines 2012 [48]

Statement RT 5b [48]

Indication for radiotherapy of the axilla is restricted to patients with residual disease (LoE 2b, GR A) or if axillary nodes are clinically involved and no axillary dissection was performed. LoE 2b, GR A

The term "axillary RT" has not yet been consistently defined. Level I nodes are usually (at least partly) included into tangential field arrangements (in supine position) for whole breast or chest wall irradiation (**Fig. 1e, f, g, h**). Historically, "axillary RT" indicated a separate beam arrangement to cover levels II and III, in addition to the respective dose contributions from anterior SCN fields (**Fig. 1c, d**).

The S3 guidelines restrict the indication for ALN-RT to manifest tumor in the axilla, even extracapsular spread is not regarded as an indication for RNI.

The question whether ALN-RT might be a less toxic alternative to ALND had already been addressed in the 1990s and a randomized study was published in 2004 [29]. The 15-year outcome of ALND compared to axillary RT was evaluated in 658 patients with T1/T2 tumors and clinically uninvolved axillary lymph nodes. In all cases, wide excision of the tumor and WBI were performed. Of the patients in the ALND group, 21% turned out to be node-positive and received radiation to the SCN and IMN but not (intentionally) to the axilla. The 15-year survival rate was identical in the two groups, however, the axillary recurrence rate in the ALND group was 1% vs. 3% in irradiated patients (p=0.04) [29].

Recently, more extensive data were provided by the EORTC 10981-22023 AMAROS study [47] with a similar design. The effectiveness of ALN-RT (including SCN) was investigated in comparison to ALND. Overall, 4806 patients who had clinically negative nodes received SNB. Patients with negative SNB did not undergo any axillary treatment (except WBI) and the 5-year rate of axillary recurrence was 0.8%. SNB was pathologically positive in 1425 patients, who were randomized for either ALN-RT or ALND. Of the latter, 60% showed macrometastases (<2 mm). In the ALND group, 67% had no further positive nodes, 1–3 affected nodes were found in 25% and >4 nodes in 7.8%; subgroup analyses of these were not presented. The 5-year axillary recurrence rate was not significantly different: 0.43% after ALND and 1.19% after ALN-RT. The planned noninferiority test was underpowered because of the unexpectedly low number of events. No significant differences in OAS (93.2% vs. 92.5%, p=0.33) and DFS (86.9% vs. 82.6%, p=0.17) were observed. Lymph edema was found significantly more often after ALND: 5-year rate 28% compared to ALN-RT 14% (p=0.0001). Considering that the pattern of spread was equally distributed in both groups, it can be assumed that in the ALN-RT group roughly one third had remnant axillary metastases after SNB. The low recurrence rate of 1.19% strongly indicates the comparable effectiveness of ALN-RT as a less invasive procedure than ALND. Noteworthy, patients after BCS received WBI, including parts of the axilla. The outcome of patients who received mastectomy and

no irradiation may provide insights concerning the consequences of truly refraining from any local treatment of the axilla, but no such subgroup analysis has yet been presented. The authors conclude that ALN-RT can be "considered standard" in SN-positive patients [47].

Positive sentinel node—no axillary dissection—implications for radiotherapy

Statement of the German S3 Guidelines 2012 [48]

Statement 4.4.5. (operative-6)

Omission of ALND may be considered for patients with pT1–2 cN0 tumors who have 1–2 positive SN after BCS provided they receive whole breast irradiation. (GCP)

A new challenge for the radiation oncologist emerged with a change of practice in axillary surgery [18]. Based on data of a randomized study of the American College of Surgeons Oncology Group [16], several guidelines [35, 48] even permit omission of ALND in selected patients with one or two pathologically positive nodes after breast-conserving surgery, provided they receive adjuvant WBI. The ACOSOG-Z0011 study is a randomized noninferiority trial, including women with stage I or stage IIA breast cancer with clinically negative axilla who underwent SNB, revealing 1–2 pathologically affected nodes. Tumor characteristics were pT1 (70%) or pT2 invasive carcinomas, mostly ER+, well-differentiated tumors. Overall, 891 patients were randomized to either axillary dissection (n=445) or no further local treatment (n=446). All patients received adjuvant WBI. After a median follow-up of 6.3 years, no difference in OAS and DFS was observed, 5-year locoregional recurrence-free survival rate was 96.7% after SNB alone and 95.7% in patients with ALND. The authors conclude that ALND may no longer be justified in T1–2 tumors. However, the applicability of this conclusion as a "practice changing" implication on clinical routine has been doubted, especially for older women [7]. Moreover, the quality of evidence provided by the study has been questioned due to several serious methodological drawbacks [34].

A compromise accounting for a potentially increased risk of locoregional recurrence of SN-positive patients was proposed by Haffty et al. [18] who suggested the use of "high tangents", with the rationale of including the nodal area presumed to be at highest risk. This approach was based on several studies investigating the dose delivered to the axillary nodes by conventional tangential fields, and the exploration of techniques yielding an improved coverage of level I by minor field extensions in the cranial direction [3, 43, 50]. To facilitate identification of the region of interest, the SN resection site can be visualized by a clip placed at the hilum of the SN before its removal [41]. This technique is also recommended in the new textbook of *Radiation Oncology* edited by Perez and Brady [17].

Statement of the German S3 Guidelines 2012 [48]

Statement RT 5c

The benefit of RNI in case of isolated tumor cells or micrometastases in regional lymph nodes (pNmic) is not validated; therefore RNI is not recommended (LoE 3b, GR A)

In the German S3 guidelines, it is emphasized that less radical surgery should not lead to a more radical radiotherapy technique; therefore, inclusion of the axilla into the target volume is explicitly discouraged in case of microscopic involvement of the SN. However, the assumption that occult SN metastases have no impact on prognosis is not ascertained as elucidated by a subgroup analysis of the NSABP-B 32 trial. The study was originally designed to evaluate whether SNB alone was equivalent to complete axillary dissection in primarily SN-negative women [27]. Paraffin-embedded tissue blocks of sentinel lymph nodes obtained from 3887 patients randomized for either SNB alone or ALND with pathologically negative SN were centrally re-evaluated. Occult metastases were detected in 15.9%. Follow-up showed a small but significantly worse outcome of those patients with occult metastases compared to those who remained negative. The difference in 5-year OAS was 1.2% (94.6% vs. 95.8%, p=0.03), DFS even 2.8% (86.4% vs. 89.2%, p=0.02) [57]. Several large retrospective cohort studies show a similar trend for microscopically positive nodes [30, 39], whereas isolated tumor cells or clusters <0.2 mm do not seem to have an impact on prognosis [23]. As survival differences tend to become apparent after more than 10 years [11], long-term outcome will be of great relevance for future clinical practice. If the trend for deteriorated survival of these patients increases over time, it should be investigated whether the use of RNI could compensate the inferior outcome.

Comments and conclusions of the DEGRO panel

- **Data do not yet permit ultimate conclusions whether any local treatment of the axilla can be safely omitted in selected patients with 1–2 involved lymph nodes or in case of micrometastases.**
- **In case of macroscopic SN metastases, ALN-RT (as part of RNI) should be discussed as an alternative to ALND in light of the equivalent effectiveness and concurrent reduction of lymph edema. Of note, information of the patient and explanation of the different options should precede surgery.**

Targeting, technique, and dose for RNI

Three-dimensional treatment planning is mandatory; several anatomically-based instruction guidelines have been published to define individual contouring of the different lymph node regions [14, 25, 26, 45]. Substantial variations may be caused by patient positioning; especially the abduction of the arm plays an important role [26].

Internal mammary nodes

The target volume should be restricted to the ipsilateral side and not exceed below intercostal space 3–4 ([14], **Fig. 1a, b**). Contouring of the heart is mandatory, detailed instructions are provided by the atlas of Feng et al. [22]. Delineation of the

whole heart should start directly inferior to the left pulmonary artery. The left anterior descending artery (LAD) is one of the clinically most relevant structures for late toxicity, as it is the major coronary vessel in the closest vicinity to left-sided IMN. The LAD originates from the left coronary artery and runs in the interventricular groove between the right and left ventricle. Contouring and dose documentation in a dose–volume histogram may be helpful for quality control.

Supra/infraclavicular nodes

The term SCN is synonymous with inferior deep cervical LN. The medial part corresponds to the level IV neck nodes, while the lateral part corresponds to level Vb according to the AJCC classification of head and neck area [2].

The medial SC LNs consist of the inferior jugular nodal chain and the medial part of the transverse cervical nodal chain. When the target volume is restricted to this area (as in the EORTC 22922-10925 trial), the lateral field border extends to the mid clavicle. The lateral SC LNs consist of the lateral part of the transverse cervical nodal chain, which is the inferior part of the posterior triangle of the neck; in this case, the field extends to the coracoid process [14]. The term infraclavicular nodes is synonymous with apical or level III of the axillary nodes and are mostly included when SCN-RT is described (**Fig. 1c, d**).

Axillary nodes

The ALN are divided into level I (low axilla) which extends laterally from the pectoralis minor muscle and level II (mid axilla) between the medial and lateral borders of the pectoralis minor muscle and the interpectoral LN (Rotter). Level III (apical axilla) corresponds to infraclavicular LN (**Fig. 1a, b**). When ALN -RT is intended, the SCN are included and the lateral field border is extended according to the individual anatomy.

Dose and fractionation

Statement of the German S3 Guidelines 2012 [48]

Statement RT 5

The total dose for RNI should be around 50 Gy using conventional fractionation (5×1.8–2.0 Gy/week). For RT of the supra/infraclavicular nodes, single doses of 1.8 Gy are preferable (GCP).

The recommendation is in accordance with international guidelines [5, 35, 52]. Hypofractionation (HF) is currently not recommended for patients who receive RNI as larger doses per fraction may increase the risk of long-term effects like cardiac toxicity or plexopathy [4, 15, 54]. In the randomized studies investigating hypofractionation, 79% of the patients were node negative and only a minority of patients were treated with RNI (Canadian study: none, START A: 13%, START B: 7%) [20, 59]. The same applies for hypofractionation after chemotherapy [52] as the majority of HF patients had not received such treatment [20, 59] and most patients considered for RNI are nowadays intended to receive chemotherapy.

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Compliance with ethical guidelines

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References

1. AGO (2013) Diagnostik und Therapie primärer und metastasierter Mammakarzinome. Adjuvante Strahlentherapie. (Version 2013.1.D). http://www.ago-online.de. Accessed 28 Jan 2014
2. AJCC (2010) Cancer staging manual, 7th edn. by American Joint Committee on Cancer
3. Alço G, Iğdem S, Ercan T et al (2010) Coverage of axillary lymph nodes with high tangential fields in breast radiotherapy. Br J Radiol 83:1072–1076
4. Andratschke N, Maurer J, Molls M et al (2011) Late radiation-induced heart disease after radiotherapy. Clinical importance, radiobiological mechanisms and strategies of prevention. Radiother Oncol 100:160–166
5. Belkacémi Y, Fourquet A, Cutuli B et al (2011) Radiotherapy for invasive breast cancer: guidelines for clinical practice from the French expert review board of Nice/Saint-Paul de Vence. Crit Rev Oncol Hematol 79:91–102
6. Budach W, Kammers K, Boelke E et al (2013) Adjuvant radio-therapy of regional lymph nodes in breast cancer—a meta-analysis of randomized trials. Radiat Oncol 8:267
7. Caretta-Weyer H, Greenberg CG, Wilke LG et al (2013) Impact of the American College of Surgeons Oncology Group (ACOSOG) Z0011 trial on clinical management of the axilla in older breast cancer patients: a SEER-medicare analysis. Ann Surg Oncol 20:4145–4152
8. Ceilley E, Jagsi R, Goldberg S et al (2005) Radiotherapy for invasive breast cancer in North America and Europe: results of a survey. Int J Radiat Oncol Biol Phys 61:365–373
9. Clarke M, Collins R, Darby S et al (2005) Effects of radiotherapy and of differences in the extent of surgery for early breast cancer on local recurrence and 15-year survival: an overview of the randomised trials. Lancet 366:2087–2106
10. Courdi A, Chamorey E, Ferrero J-M et al (2013) Influence of internal mammary node irradiation on long-term outcome and contralateral breast cancer incidence in node-negative breast cancer patients. Radiother Oncol 108:259–265
11. Darby S, McGale P, Correa C et al (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10,801 women in 17 randomised trials. Lancet 378:1707–1716
12. Darby SC, Ewertz M, McGale P et al (2013) Risk of ischemic heart disease in women after radiotherapy for breast cancer. N Engl J Med 368:987–998
13. Daveau C, Savignoni A, Abrous-Anane S et al (2011) Is radiotherapy an option for early breast cancers with complete clinical response after neoadjuvant chemotherapy? Int J Radiat Oncol Biol Phys 79:1452–1459
14. Dijkema IM, Hofman P, Raaijmakers CPJ et al (2004) Loco-regional conformal radiotherapy of the breast: delineation of the regional lymph node clinical target volumes in treatment position. Radiother Oncol 71:287–295
15. Galecki J, Hicer-Grzenkowicz J, Grudzien-Kowalska M et al (2006) Radiation-induced brachial plexopathy and hypofractionated regimens in adjuvant irradiation of patients with breast cancer—a review. Acta Oncol 45:280–284
16. Giuliano AE, Hunt KK, Ballman KV et al (2011) Axillary dissection vs no axillary dissection in women with invasive breast cancer and sentinel node metastasis: a randomized clinical trial. JAMA 305:569–575

17. Goyal S, Buchholz T, Haffty B (2013) Breast cancer: early stage. In: Perez and Brady's radiation oncology, 6th edn.
18. Haffty BG, Hunt KK, Harris JR et al (2011) Positive sentinel nodes without axillary dissection: implications for the radiation oncologist. J Clin Oncol 29:4479–4481
19. Hallman MA, Keller L, Anderson P et al (2012) Impact of regional nodal irradiation on outcomes of breast cancer patients with 1–3 positive axillary nodes. Int J Radiat Oncol Biol Phys 84:S252–S253
20. Haviland JS, Owen JR, Dewar JA et al (2013) The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials. Lancet Oncol 14:1086–1094
21. Hellman S (1997) Stopping metastases at their source. N Engl J Med 337:996–997
22. Hennequin C, Bossard N, Servagi-Vernat S et al (2013) Ten-year survival results of a randomized trial of irradiation of internal mammary nodes after mastectomy. Int J Radiat Oncol Biol Phys 86:860–866
23. Karam I, Lesperance MF, Berrang T et al (2013) pN0(i+) breast cancer: treatment patterns, locoregional recurrence, and survival outcomes. Int J Radiat Oncol Biol Phys 87:731–737
24. Karlsson P, Cole BF, Chua BH et al (2012) Patterns and risk factors for locoregional failures after mastectomy for breast cancer: an International Breast Cancer Study Group report. Ann Oncol 23:2852–2858
25. Kiricuta IC, Gotz U, Schwab F et al (2000) Target volume definition and target conformal irradiation technique for breast cancer patients. Acta Oncol 39:429–436
26. Kirova YM, Castro Pena P, Dendale R et al (2010) Simplified rules for everyday delineation of lymph node areas for breast cancer radiotherapy. Br J Radiol 83:683–686
27. Krag DN, Anderson SJ, Julian TB et al (2010) Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol 11:927–933
28. Kuehn T, Bauerfeind I, Fehm T et al (2013) Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 14:609–618
29. Louis-Sylvestre C, Clough K, Asselain B et al (2004) Axillary treatment in conservative management of operable breast cancer: dissection or radiotherapy? Results of a randomized study with 15 years of follow-up. J Clin Oncol 22:97–101
30. Lupe K, Truong PT, Alexander C et al (2011) Ten-year locoregional recurrence risks in women with nodal micrometastatic breast cancer staged with axillary dissection. Int J Radiat Oncol Biol Phys 81:e681–e688
31. Madu CN, Quint DJ, Normolle DP et al (2001) Definition of the supraclavicular and infraclavicular nodes: implications for three-dimensional CT-based conformal radiation therapy. Radiology 221:333–339
32. Matzinger O, Heimsoth I, Poortmans P et al (2010) Toxicity at three years with and without irradiation of the internal mammary and medial supraclavicular lymph node chain in stage I to III breast cancer (EORTC trial 22922/10925). Acta Oncol 49:24–34
33. McGuire SE, Gonzalez-Angulo AM, Huang EH et al (2007) Postmastectomy radiation improves the outcome of patients with locally advanced breast cancer who achieve a pathologic complete response to neoadjuvant chemotherapy. Int J Radiat Oncol Biol Phys 68:1004–1009
34. Murthy V, Ballehaninna UK, Chamberlain RS (2012) Unanswered questions about the role of axillary dissection in women with invasive breast cancer and sentinel node metastasis. Clin Breast Cancer 12:305–307
35. NCCN (2013) Clinical practice guidelines in oncology: breast cancer, version 3.2013. National Comprehensive Cancer Network. http://www.nccn.org/professionals/physician_gls/f_guidelines.asp#site. Accessed 28 Jan 2014
36. NICE (2009) Early and locally advanced breast cancer: diagnosis and treatment. National Institute for Clinical Excellence (NICE)
37. NZGG (2009) New Zealand Guidelines Group. Management of early breast cancer—evidence-based best practice guidelines. New Zealand Guidelines Group, Wellington
38. Overgaard M, Nielsen HM, Overgaard J (2007) Is the benefit of postmastectomy irradiation limited to patients with four or more positive nodes, as recommended in international consensus reports? A subgroup analysis of the DBCG 82 b&c randomized trials. Radiother Oncol 82:247–253
39. Pepels MJ, Boer M de, Bult P et al (2012) Regional recurrence in breast cancer patients with sentinel node micrometastases and isolated tumor cells. Ann Surg 255:116–121
40. Poortmans P, Kirkove C, Budach V et al (2013) Irradiation of the internal mammary and medial supraclavicular lymph nodes in stage I to III breast cancer: 10 years results of the EORTC Radiation Oncology and Breast Cancer Groups phase III trial 22922/10925. EJC 47(Suppl 2)
41. Rabinovitch R, Ballonoff A, Newman F et al (2008) Evaluation of Breast Sentinel Lymph Node Coverage by Standard Radiation Therapy Fields. Int J Radiat Oncol Biol Phys 70:1468–1471
42. Ragaz J, Olivotto IA, Spinelli JJ et al (2005) Locoregional radiation therapy in patients with high-risk breast cancer receiving adjuvant chemotherapy: 20-year results of the British Columbia randomized trial. J Natl Cancer Inst 97:116–126
43. Reznik J, Cicchetti MG, Degaspe B et al (2005) Analysis of axillary coverage during tangential radiation therapy to the breast. Int J Radiat Oncol Biol Phys 61:163–168
44. Rowell NP (2009) Radiotherapy to the chest wall following mastectomy for node-negative breast cancer: a systematic review. Radiother Oncol 91:23–32
45. RTOG: breast cancer atlas for radiation therapy planning: consensus definitions. http://www.rtog.org/CoreLab/ContouringAtlases/BreastCancerAtlas.aspx. Accessed 28 Jan 2014
46. Rudat V, Alaradi AA, Mohamed A et al (2011) Tangential beam IMRT versus tangential beam 3D-CRT of the chest wall in postmastectomy breast cancer patients: a dosimetric comparison. Radiat Oncol 6:26
47. Rutgers EJ, Donker M, Straver ME et al (2013) Radiotherapy or surgery of the axilla after a positive sentinel node in breast cancer patients: final analysis of the EORTC AMAROS trial (10981/22023). J Clin Oncol 31 (Abstract LBA1001)
48. o A (2012) S3. Interdisziplinäre S3-Leitlinie für die Diagnostik, Therapie und Nachsorge des Mammakarzinoms, Langversion 3.0, Aktualisierung 2012, AWMF-Register-Nummer: 032-045OL
49. Sautter-Bihl M-L, Souchon R, Budach W et al (2008) DEGRO practical guidelines for radiotherapy of breast cancer II. Strahlenther Onkol 184:347–353
50. Schlembach PJ, Buchholz TA, Ross MI et al (2001) Relationship of sentinel and axillary level I–II lymph nodes to tangential fields used in breast irradiation. Int J Radiat Oncol Biol Phys 51:671–678
51. Shah C, Wilkinson JB, Baschnagel A et al (2012) Factors associated with the development of breast cancer-related lymphedema after whole-breast irradiation. Int J Radiat Oncol Biol Phys 83:1095–1100
52. Smith BD, Bentzen SM, Correa CR et al (2011) Fractionation for Whole Breast Irradiation: an American Society for Radiation Oncology (ASTRO) Evidence-Based Guideline. Int J Radiat Oncol Biol Phys 81:59–68
53. Strom EA, Woodward WA, Katz A et al (2005) Clinical investigation: regional nodal failure patterns in breast cancer patients treated with mastectomy without radiotherapy. Int J Radiat Oncol Biol Phys 63:1508–1513
54. Tjessem KH, Johansen S, Malinen E et al (2013) Long-term cardiac mortality after hypofractionated radiation therapy in breast cancer. Int J Radiat Oncol Biol Phys 87:337–343
55. Voogd AC, Coebergh JW, Repelaer van Driel OJ et al (2000) The risk of nodal metastases in breast cancer patients with clinically negative lymph nodes: a population-based analysis. Breast Cancer Res Treat 62:63–69
56. Wai ES, Lesperance M, Speers CH et al (2010) Increased use of regional radiotherapy is associated with improved outcome in a population-based cohort of women with breast cancer with 1–3 positive nodes. Radiother Oncol 97:301–306
57. Weaver DL, Ashikaga T, Krag DN et al (2011) Effect of occult metastases on survival in node-negative breast cancer. N Engl J Med 364:412–421
58. Whelan T, Olivotto I, Ackerman I et al (2011) NCIC-CTG MA. 20: an intergroup trial of regional nodal irradiation in early breast cancer. J Clin Oncol 29(Suppl); abstract LBA 1003
59. Whelan TJ, Pignol J-P, Levine MN et al (2010) Long-term results of hypofractionated radiation therapy for breast cancer. N Engl J Med 362:513–520
60. Wright JL, Takita C, Reis IM et al (2013) Predictors of locoregional outcome in patients receiving neoadjuvant therapy and postmastectomy radiation. Cancer 119:16–25
61. Yates L, Kirby A, Crichton S et al (2012) Risk factors for regional nodal relapse in breast cancer patients with one to three positive axillary nodes. Int J Radiat Oncol Biol Phys 82:2093–2103
62. Yu JI, Park W, Huh SJ et al (2010) Determining which patients require irradiation of the supraclavicular nodal area after surgery for N1 breast cancer. Int J Radiat Oncol Biol Phys 78:1135–1141