

# Radiotherapy of the lymphatic drainage pathways in breast carcinoma: time for a reassessment

## Radiotherapie der Lymphabflusswege bei Mammakarzinom: Zeit für eine Neubewertung



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### ABSTRACT

**Background** The treatment administered for regional lymph nodes has altered dramatically in recent years. The state of the evidence on radiotherapy has also substantially improved and a reassessment is required.

**Materials and results** Randomized studies are available on axillary surgery versus radiotherapy (AMAROS); on refraining from axillary dissection after a positive sentinel node (SN) when radiotherapy is planned (ACOSOG Z0011); and on adjuvant radiotherapy of the regional lymph nodes (LNs). ACOSOG Z0011 shows that refraining from axillary dissection is possible even when there are one or two positive SNs. The meta-analysis of the studies on adjuvant radiotherapy for the regional LNs (EORTC, Canadian, and French studies) shows a significant survival benefit with radiotherapy, and a Danish cohort study has confirmed this result. The reduction in breast cancer-specific mortality in these studies was partly based on a “systemic” effect of regional radiotherapy, with a reduction in the rate of distant metastases.

**Conclusions** The principle applying in surgical treatment of the axilla is “less is not worse.” By contrast, the principle applying in radiotherapy of the regional lymph nodes is “more may be better in some circumstances.” There is as yet no clear explanation for the discrepancy between these two

findings. An immunological effect (through immunogenic cell death due to irradiation) has been discussed. Further research is needed on which patients are today capable of benefiting from regional radiotherapy.

## ZUSAMMENFASSUNG

**Hintergrund** Die Therapie der regionalen Lymphknoten hat sich in den letzten Jahren dramatisch gewandelt. Auch bezüglich der Strahlentherapie hat sich die Evidenzlage wesentlich verbessert, und eine Neubewertung ist erforderlich.

**Material und Ergebnisse** Randomisierte Studien existieren zur Frage einer Axilla-OP versus Strahlentherapie (AMAROS), Verzicht auf Axilladisektion nach positivem SN bei geplanter Strahlentherapie (ACOSOG Z0011) sowie zur adjuvanten Radiotherapie der regionalen LK. ACOSOG Z0011 zeigt, dass ein Verzicht auf die Axilladisektion auch bei 1–2 positiven Sentinel-Lymphknoten möglich ist. Die Studien zur adjuvanten

Radiotherapie der regionalen LK (EORTC-Studie, kanadische Studie, französische Studie) zeigen in der Metaanalyse einen signifikanten Überlebensvorteil durch die Strahlentherapie; eine dänische Kohortenstudie bestätigt dieses Ergebnis. Die Reduktion der brustkrebspezifischen Mortalität beruhte in diesen Studien zum Teil auf einem „systemischen“ Effekt der regionalen Radiotherapie mit einer Reduktion der Rate an Fernmetastasen.

**Schlussfolgerungen** Für die operative Therapie der Axilla gilt: „Weniger ist nicht schlechter.“ Für die Strahlentherapie der regionalen Lymphknoten gilt dagegen: „Mehr kann unter Umständen vorteilhaft sein.“ Eine eindeutige Erklärung für die Diskrepanz dieser Befunde gibt es noch nicht. Ein immunologischer Effekt (durch immunogenen Zelltod nach Bestrahlung) wird diskutiert. Welche Patientinnen heutzutage von einer regionalen Bestrahlung profitieren, muss noch besser erforscht werden.

## Introduction

Radiotherapy of the regional lymphatic drainage pathways (regional nodal irradiation, RNI) in patients with breast carcinoma has been a subject of controversy in recent decades. In nearly all studies on post-mastectomy radiotherapy (PMRT), the entire regional lymphatic drainage routes – i. e., the supraclavicular nodes (SCNs), axillary lymph nodes (ALNs), and internal mammary nodes (IMNs) – have been irradiated. By contrast, adjuvant radiotherapy after breast-conserving surgery (BCS) has often been restricted to whole-breast irradiation (WBI) and RNI has not been routinely included. Most studies have carried out randomized comparisons of adjuvant radiotherapy versus refraining from any radiotherapy, but not using or refraining from additional RNI [1, 2]. It has therefore not been possible to quantitatively analyze the effect of RNI on survival. This gap has been closed to some extent by a few recent randomized studies, and the published results may have led to a change of direction.

The introduction of sentinel node biopsy (SNB) created a paradigm shift in the radicality of axillary surgery. For radio-oncology, it also raised fresh challenges – e. g., the question of whether and with what risk patterns axillary node radiotherapy (ALN-RT) might represent an alternative to axillary lymph-node dissection (ALND). Newly published randomized data [3] are suggesting a potential for future individualization of the treatment approaches here.

The aim of the present study is to provide an overview of the current data and their implications for the indication for regional nodal irradiation.

## RNI with one to three positive axillary lymph nodes

While the indication for RNI when there are four or more positive axillary lymph nodes remained undisputed, it became a matter of controversy in patients with one to three positive lymph nodes

(pN1) or with pT3 pN0 tumors [4–6]. This question was first explicitly investigated in the Canadian study (NCIC-CTG MA20, recruiting period 2000–2007) [7]. A total of 1832 patients were included, most of whom had one to three positive axillary lymph nodes (85 %), while 10 % had negative lymph nodes and a high-risk pattern. After breast-conserving surgery and axillary lymph-node dissection, the patients were randomly assigned either to WBI alone or WBI with additional RNI. The RNI in the study consisted of irradiation of the supraclavicular nodes and internal mammary nodes. Around 8 % of the women in both arms of the study also received axillary radiotherapy. After 10 years, locoregional control was 95.2 % with RNI and 92.2 % without it ( $P=0.009$ ), and the rate of in-breast recurrences was comparable in the two groups, as expected (4.3 % vs. 3.6 %). By contrast, lymph-node recurrences were five times less frequent after RNI (2.5 % vs. 0.5 %). Overall, the recurrence-free survival after RNI was 82 %, in comparison with only 77.4 % in the control arm ( $P=0.01$ ), and similarly the metastasis-free survival (MFS) was 86.3 % versus 82.4 % ( $P=0.03$ ). These differences go beyond the improvement in locoregional tumor control. Avoiding lymph-node recurrences thus appears to prevent distant metastases. Improvement in the probability of survival with additional RNI was only observed in estrogen receptor-negative patients ( $n=465$ ; 10-year overall survival 81.3 % vs. 73.9 %), while in the group as a whole the overall survival rates with and without RNI were approximately 81.8 % versus 82.8 %.

The European study (EORTC 22922–10925, recruiting period 1996–2004) [8] included 4004 patients mainly with pT1–2 tumors (95 %) and either positive axillary lymph nodes (55.6 %) and/or a medial tumor location (44.5 %). After BCS (76 %) or mastectomy (23 %), they were randomly assigned either to WBI/PMRT alone or additional RNI. Nearly all of the patients received adjuvant systemic treatment. After 10 years, a significant improvement in the disease-free survival (DFS) was noted in the RNI group (72 % vs. 69 %;  $P=0.04$ ) and also in the MFS (78 % vs. 75 %;  $P=0.02$ ). The overall survival also showed a trend in favor

► **Table 1** Summary of the results of studies on regional radiotherapy.

	without RT of regional LNs	with RT of regional LNs	P
Canadian study, NCIC-CTG MA20; n = 1832, 10-y data [7]			
▪ locoregional tumor control	92.2 %	95.2 %	0.009
▪ metastasis-free survival	82.4 %	86.3 %	0.03
▪ disease-free survival	77.4 %	82.0 %	0.01
▪ overall survival	81.8 %	82.8 %	n.s.
European study, EORTC 22 922 – 10 925; n = 4004, 10-y data [8]			
▪ regional recurrences	4.2 %	2.7 %	–
▪ metastasis-free survival	75 %	78 %	0.02
▪ disease-free survival	69 %	72 %	0.04
▪ overall survival	80.7 %	82.3 %	0.06
French study, n = 1334, 10-y data [18]			
▪ overall survival	59.3 %	62.5 %	n.s.
Danish cohort study; n = 3089, 8-y data [19]			
▪ overall survival	72.2 %	75.9 %	0.005

► **Table 2** Meta-analysis of randomized studies on prophylactic regional radiotherapy [9].

end point	hazard ratio	P
metastasis-free survival	0.84 (95 % CI, 0.75 to 0.95)	0.002
disease-free survival	0.86 (95 % CI, 0.78 to 0.95)	0.002
overall survival	0.88 (95 % CI, 0.78 to 0.99)	0.034

of RNI (82.3 % vs. 80.7 %;  $P = 0.06$ ). The rate of lymph-node recurrences was in favor of RNI, at 2.7 % versus 4.2 %. Lymph-node tumor control thus appears to have an influence on metastasization here as well. The results are summed up in ► **Table 1**.

A meta-analysis of these data [9] found that all of the survival advantages were significant (► **Table 2**). The hazard ratio (HR) for the overall survival (OS) was 0.88 (95 % CI, 0.78 to 0.99;  $P = 0.034$ ) and the HR for the DFS was 0.86 (95 % CI, 0.78 to 0.95). The greatest effect was seen in the MFS (HR 0.84; 95 % CI, 0.75 to 0.94;  $P = 0.002$ ), and this may support Hellman's hypothesis that radiotherapy "stops metastases at their source" [10].

## Radiotherapy of the internal mammary nodes (IMNs)

Data from extensive surgical groups showed in the 1960s that there is a high rate of IMN metastases when the tumor is in a medial location and there is axillary involvement [11]. A Chinese study published in 2008 confirmed similar findings in a group of 1679 patients in whom dissection of the IMNs was carried out in addition to extended mastectomy, and IMN metastases were confirmed at histopathology in more than 20 % of the cases

when risk factors were present (medial location, four or more positive axillary lymph nodes, T3, age <35y) [12]. In contrast to what might be expected following these data, however, clinically manifest IMN recurrences are actually only observed rarely in patients with breast carcinomas (only in approx. 1 %) [13]. A hypothetical explanation for this discrepancy might be unintentional simultaneous irradiation of the IMNs when the intention is to carry out radiotherapy of the breast or chest wall "alone," using the "tangential fields" that were formerly customary. Since in addition systematic imaging of the IMNs does not form part of routine follow-up, metastases in this area sometimes remain clinically unrecognized, particularly when a distant metastases has in the meantime become the focus of clinical symptoms [14]. It is therefore not surprising that the indication for IMN radiotherapy has been severely restricted during the last decade, particularly since increased cardiovascular toxicity was reported in older studies [15, 16]. This can be largely avoided with modern techniques, however, as the dosage to the heart can be minimized [17].

Only two prospective studies have explicitly investigated the effect of IMN radiotherapy. The only randomized study, conducted in France [18], included 1334 patients who after mastectomy were found to have either positive axillary LNs (75 %) or a central/medial tumor location (25 %). The PMRT always included the

supraclavicular nodes. The target of randomization was additional IMN radiotherapy. After 10 years, no survival advantage was seen (62.5 % vs. 59.3 %) with IMN radiotherapy, and in lymph node-negative patients there was even a trend towards a reduced probability of survival. By contrast, lymph node-positive patients had a nonsignificant survival advantage. The authors admit that the study may not have been sufficiently powered to demonstrate significant effects. No increased cardiotoxicity was observed.

In contrast to those findings, a more recent prospective study in Denmark reported a significant benefit with additional IMN radiotherapy [19]. This population-based cohort study included 3089 patients with positive lymph nodes (2003 – 2007), among whom 1492 women with right-sided tumors received simultaneous irradiation of the IMNs while 1597 women with left-sided tumors underwent radiotherapy without the IMNs (to avoid potential cardiotoxicity). ALND and adjuvant systemic therapy were carried out in all cases. The tumor characteristics and risk factors were similar in the two groups. The 8-year OS was 75.9 % with IMN radiotherapy versus 72.2 % without it, and thus improved by 3.7 % ( $P = 0.005$ ). Mortality rates due to ischemic cardiac diseases were similar in the two groups. The positive effect of IMN radiotherapy was clearest when there was a high risk of IMN metastases. A subgroup analysis of patients with a medial/central location and/or four or more involved lymph nodes thus showed an 8-year OS that was 7.4 % better (72.2 % vs. 64.8 %;  $P = 0.001$ ). Although the study was not randomized, it has a prospective design, homogeneous patient groups, and a short period of 4 years in which all patients with breast carcinoma were treated in a standardized way in the national tumor centers.

According to current studies, in addition to modern techniques the extent of the target volume should be limited craniocaudally to the first to third intercostal spaces, in order to avoid the increased cardiac toxicity that used to be seen in earlier studies when the IMNs were irradiated simultaneously [7, 8].

## Assessment of the state of research

It should be pointed out when discussing these studies that systemic therapy was the standard practice at the time; adjuvant chemotherapy followed in all studies, with anthracycline- and taxane-containing regimens, and adjuvant endocrine therapy was mainly with tamoxifen. Aromatase inhibitors and trastuzumab had not yet been approved during the recruitment period in most cases; aromatase inhibitors were used in the Danish cohort study starting in 2004. The possibility can therefore not be excluded that the results might have been fundamentally different with intensified “modern” systemic therapy; but on the other hand this is unlikely. In general, the relative effect of radiotherapy is greater the more effective the systemic therapy is.

It is particularly noteworthy that significant cardiac toxicity was excluded by regional irradiation in the two current studies, with median follow-up periods of 10.9 years in the EORTC study and 9.5 years in the MA20 study. As a disadvantageous effect of radiotherapy was already evident even after a relatively short follow-up period in the last meta-analysis of the earlier studies,

relevant cardiac toxicity during the subsequent course is very unlikely [15].

The most important finding in these research studies is surely the fact that the effect of regional irradiation on the metastasis-free survival was at least as large or even larger than the effect on the locoregional recurrence rate. This type of “systemic effect of radiotherapy” has not previously been observed with breast carcinoma, but it has recently come to be regarded as quite plausible. Radiotherapy can produce immunogenic cell death, so that it can trigger “off-scope” effects (remissions outside of the target volume of the radiotherapy). This is currently being investigated in clinical studies. If such an immunological effect does indeed exist, it will probably mainly be found in patients with a low “residual risk” – i. e., after (optimal) systemic therapy.

## Procedure with positive sentinel lymph nodes: nothing, or X-rays instead of scalpels?

Sentinel node biopsies (SNBs) have become an established standard and have reduced the role of ALND when there are clinically negative findings. On the basis of data from a randomized study by the American College of Surgeons Oncology Group (ACOSOG), various guidelines also allow avoidance of ALND and also ALN radiotherapy in patients with a favorable risk profile, even when there are one or two involved lymph nodes [4 – 6].

In the ACOSOG’s 2011 study [20], 891 patients with T1 (70 %) to T2 (30 %) tumors and positive hormone receptor status underwent randomization after SNBs had histologically demonstrated involved axillary LNs (one or two involved LNs in approx. 90 % of cases, micrometastases in 45 %). No ALND was carried out in the experimental arm, but it was done in the traditional way in the control arm. In accordance with the protocol, all of the women were to undergo whole-breast irradiation. After 5 years, no differences were seen in the DFS, OS, or local recurrence rate. The authors concluded that in patients with “limited SLN metastatic breast cancer with breast conservation and systemic therapy,” ALND does not improve the prognosis – i. e., has no therapeutic effect. However, the study has substantial methodological weaknesses: recruitment was interrupted prematurely, and a total of 103 patients could not be analyzed. In violation of the explicit protocol requirements, additional RNI was carried out in around 15 % of them [21, 22].

With regard to the prognosis when there is sentinel node involvement, a countertrend emerged in a subgroup analysis in the NSABP-B-32 study [23]. Fifteen percent of the lymph nodes initially evaluated as histopathologically negative were found to have occult LN metastases at an additional histological examination. After 5 years, these patients had slightly but significantly reduced DFS (2.8 %) and OS (1.2 %) rates.

The effectiveness of ALN radiotherapy in comparison with ALND was investigated in the randomized and prospective AMAROS study (EORTC 10981 – 22023) [3]. A total of 1425 patients with positive SNs underwent randomization (ALND,  $n = 744$ ; ALN radiotherapy,  $n = 681$ ). The axillary 5-year recurrence

rate was unexpectedly low in both arms, at 0.43 % after ALND and 1.19 % after ALN radiotherapy (n.s.). The planned noninferiority test was therefore not sufficiently powered. With comparable axillary tumor spread in the two groups, it can be assumed that additional metastases were present in the axilla after the SNB in around one-third of the patients who underwent axillary radiotherapy. However, as the axillary recurrence rate after 5 years was only 1.19 %, it can be concluded that these were effectively eliminated by the RT. Nor were any differences seen in the DFS and OS. By contrast, lymphedema was reported significantly more often after ALND, at 28 % after 5 years in comparison with 14 % after ALN radiotherapy ( $P < 0.0001$ ).

The question of whether patients with a clinically unremarkable axilla (cN0) require axillary therapy, and if so which, can therefore hardly be answered at present. The studies cited above show that supplementary ALND with one or two positive SNs does not offer any therapeutic advantage. This has been confirmed by Li et al. recently in a meta-analysis of 12 studies including a total of 130 575 patients [24]. In comparison with SNB alone, supplementary ALND showed no therapeutic benefit. However, the authors limit their conclusions to patients with one to three positive SNs, due to insufficient data for patients with more positive SNs and patients who did not meet the ACOSOG 20011 criteria.

### Procedure with at least three positive SNs

Bonneau et al. investigated the question of whether supplementary ALND can also be dispensed with when there are three or more positive LNs. Data were extracted from the SEER database for a total of 9521 patients who were treated between 2003 and 2008 and whose prognostic characteristics matched the inclusion criteria for the ACOSOG-20011 study. The analysis showed that no prognostic benefit is achieved with supplementary ALND even with at least three involved SNs [25].

The number of involved lymph nodes was for decades the most important parameter for deciding on whether to administer adjuvant systemic therapy. In recent years, this parameter has increasingly been replaced by assessment of intrinsic molecular biomarkers and the use of multigene assays, however, so that in this respect as well, complete ALND for diagnostic purposes has become dispensable [26–28].

In individual cases, and also only indirectly, nomograms may be helpful for assessing the risk of additional LN metastases following positive sentinel nodes. The model presented by Katz et al. [29], which calculates the probability of finding four or more positive LNs after supplementary axillary dissection in patients with positive SNs, takes numerous established risk factors into account (including the number of positive SNs, tumor size, extranodal involvement, size of the positive SN, and histology).

### The clinically negative axilla

As the data presented show, refraining from axillary dissection presupposes that the axilla is clinically negative. According to the criteria in the ACOSOG 20011 study, negative palpation findings were sufficient to establish a clinically negative axilla. Ultrasonography of the axilla has in the meantime become established,

and in a meta-analysis of 16 studies it was found to have moderate and widely varying sensitivity (49–87 %), but higher specificity (56–97 %) [30]. It is expected that the INSEMA study that is currently in progress will clarify the diagnostic and therapeutic procedure in patients with cN0. Two additional prospective studies (NCT 02 466 737 and NCT 02 167 490) are also investigating whether it might even be possible to dispense with SNB when the axilla is negative on ultrasound [31, 32].

### Complete inclusion of the axilla with extensive LN involvement

According to the present state of the data, extending RNI to the complete axilla does not appear to be justified after complete axillary dissection, even when there is evidence of more extensive involvement (pN3), except in cases of residual tumor [5, 6, 33].

## Planning and technique of radiotherapy in RNI

CT-based three-dimensional planning of radiotherapy is the standard [33–35]. Contouring guides for the breast or breast wall and for the individual LN stations [36–38] are helpful for defining the irradiation volume. Contouring of the at-risk organs (particularly the heart, and ideally with partial volumes such as the left coronary artery, lungs, and plexus) and documentation of the radiation dosage to each of these structures are important. More recent techniques such as intensity-modulated radiotherapy (IMRT) and volume-modulated radiotherapy (VMRT) can be used to optimize the dose distribution and can markedly reduce the radiation burden on healthy organs [17, 39]. When the tumor is left-sided, respiration-triggered radiotherapy or breath gating techniques [40] and special positioning aids [41] can increase the distance between the target volume and the heart and thus reduce the dosage.

The radiation dosage is usually 50.0–50.4 Gy in individual doses of 1.8–2.0 Gy. Accelerated hypofractionation (HF; 40.0–42.5 Gy in individual doses of 2.60–2.66 Gy over a treatment period of around 3 weeks) is not currently recommended as the fractionation method of choice for patients receiving RNI, since higher individual doses may increase the risk of late sequelae such as cardiac toxicity or plexopathy [42, 43] and there are as yet insufficient data on this from randomized HF studies [44, 45]. In particular, the risk of lymphedema after hypofractionation is unclear and is currently being investigated in a study in Denmark.

## Implications for everyday practice

The studies published in recent years have for the first time investigated the value of lymph-node irradiation as an individual measure; previously there had only been indirect comparisons between studies with local radiotherapy (breast, breast wall) and studies with local plus regional radiotherapy. The most important finding of the current research on lymph-node irradiation is: “more radiotherapy may be beneficial in some circumstances.” There is thus a clear discrepancy from surgical treatment of the

axillary lymph nodes, for which a survival advantage resulting from “more surgery” has never been demonstrated. An immunological effect (via immunogenic cell death after radiotherapy) is under discussion as a possible explanation for this. However, it is difficult to transfer these results into everyday practice. It is very likely that regional radiotherapy is still advantageous for specific groups of patients even today. The issue of which patients who are receiving modern systemic treatments may be able to benefit from regional radiotherapy still requires better research. By contrast, it is very unlikely that lymph-node irradiation is disadvantageous.

## Conflict of Interest

The authors declare that they have no conflict of interest.

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