

# DEGRO Practical Guidelines for Radiotherapy of Breast Cancer II

## Postmastectomy Radiotherapy, Irradiation of Regional Lymphatics, and Treatment of Locally Advanced Disease

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**Background and Purpose:** The aim of the present paper is to update the practical guidelines for radiotherapy of breast cancer published in 2006 by the breast cancer expert panel of the German Society for Radiooncology (DEGRO). These recommendations were complementing the S3 guidelines of the German Cancer Society (DKG) elaborated in 2004. The present DEGRO recommendations are based on a revision of the DKG guidelines provided by an interdisciplinary panel and published in February 2008.

**Methods:** The DEGRO expert panel (authors of the present manuscript) performed a comprehensive survey of the literature. Data from lately published meta-analyses, recent randomized trials and guidelines of international breast cancer societies, yielding new aspects compared to 2006, provided the basis for defining recommendations referring to the criteria of evidence-based medicine. In addition to the more general statements of the DKG, this paper emphasizes specific radiooncologic issues relating to radiotherapy after mastectomy (PMRT), locally advanced disease, irradiation of the lymphatic pathways, and sequencing of local and systemic treatment. Technique, targeting, and dose are described in detail.

**Results:** PMRT significantly reduces local recurrence rates in patients with T3/T4 tumors and/or positive axillary lymph nodes (12.9% with and 40.6% without PMRT in patients with four or more positive nodes). The more local control is improved, the more substantially it translates into increased survival. In node-positive women the absolute reduction in 15-year breast cancer mortality is 5.4%. Data referring to the benefit of lymphatic irradiation are conflicting. However, radiotherapy of the supraclavicular area is recommended when four or more nodes are positive and otherwise considered individually. Evidence concerning timing and sequencing of local and systemic treatment is sparse; therefore, treatment decisions should depend on the dominating risk of recurrence.

**Conclusion:** There is common consensus that PMRT is mandatory for patients with T3/T4 tumors and/or four or more positive axillary nodes and should be considered for patients with one to three involved nodes. Irradiation of the lymphatic pathways and the optimal time point for onset of radiotherapy are still under debate.

**Key Words:** Radiotherapy of breast cancer · Postmastectomy radiotherapy · Locally advanced disease · Lymph node irradiation · Sequencing of local and systemic treatment

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## DEGRO-Leitlinien für die Radiotherapie des Mammakarzinoms II. Indikationen nach Mastektomie, für die Bestrahlung der Lymphabflussgebiete und bei lokal fortgeschrittenen Situationen

**Hintergrund und Ziel:** Ziel der Arbeit ist eine Aktualisierung der 2006 publizierten Leitlinie der „Expertengruppe Mammakarzinom“ der Deutschen Gesellschaft für Radioonkologie (DEGRO). Diese war seinerzeit in Ergänzung zur interdisziplinären S3-Leitlinie der Deutschen Krebsgesellschaft (DKG) von 2004 verfasst worden. Zwischenzeitlich erfolgten eine Überarbeitung und Aktualisierung der S3-Leitlinie der DKG, die im Februar 2008 publiziert wurde.

**Methodik:** Die Expertengruppe (identisch mit den Autoren dieses Manuskripts) führte eine umfassende Literaturrecherche durch. Aktuelle Metaanalysen und randomisierte Studien, die neue Aspekte gegenüber 2006 ergaben, sowie Empfehlungen internationaler Fachgesellschaften wurden in die Bewertung von Therapieindikationen einbezogen. Diese orientieren sich an den Kriterien evidenzbasierter Medizin. In Ergänzung zu den eher allgemeinen Statements der DKG 2008 werden spezielle radiotherapeutische Fragestellungen behandelt, die eine Strahlentherapie nach Mastektomie (PMRT) und/oder bei fortgeschrittenen Tumoren, die Bestrahlung der Lymphabflusswege und die Sequenz von Radio- und Systemtherapie betreffen. Zielvolumendefinition und Dosierung werden im Detail beschrieben.

**Ergebnisse:** Die PMRT senkt die Lokalrezidivrate bei Patientinnen mit hohem Rückfallrisiko (T3/T4-Tumoren und/oder befallene axilläre Lymphknoten; 12,9% mit und 40,6% ohne PMRT). Je ausgeprägter die durch die Radiotherapie bewirkte lokale Tumorkontrolle ist, desto stärker wirkt sich dies auf die Überlebenswahrscheinlichkeit aus. Bei lymphonodal positiven Patientinnen ergab sich eine absolute Verminderung der tumorspezifischen Sterblichkeit um 5,4% nach 15 Jahren. Hinsichtlich des Nutzens einer Strahlentherapie der Lymphabflusswege ist die Datenlage widersprüchlich. Eine Bestrahlung der Supraklavikularregion ist jedoch bei vier oder mehr befallenen axillären Lymphknoten stets indiziert und sollte bei ein bis drei positiven Lymphknoten erwogen werden. Bezüglich der Sequenz von Radio- und Systemtherapie gibt es keine richtungweisenden Evidenzen zugunsten einer Therapiemodalität. Postoperativ sollte die Sequenz vom dominierenden Risiko abhängig gemacht werden.

**Schlussfolgerung:** Nach Mastektomie ist die PMRT bei T3/T4-Tumoren, Resttumor und/oder axillären Lymphknotenmetastasen obligat. Die Bestrahlung der regionalen Lymphabflusswege und die Sequenz von Radio- und Systemtherapie bleiben bei unzureichender Datenlage Gegenstand interdisziplinärer Diskussionen.

**Schlüsselwörter:** Strahlentherapie bei Mammakarzinom · Lokal fortgeschrittenes Mammakarzinom · Mastektomie · Strahlentherapie der Lymphabflusswege · Sequenz der Radio- und Systemtherapie

### Introduction

The present paper completes the first part of the practical guidelines for radiotherapy of breast cancer [39] of the German Society of Radiooncology (DEGRO) which was restricted to breast-conserving treatment. The following recommendations are an update of the guidelines for radiotherapy of breast cancer compiled by the breast cancer expert panel of the DEGRO; these were based on the revised interdisciplinary guidelines for breast cancer diagnosis, therapy and follow-up of the German Cancer Society, published in March 2008 [8]. The respective statements, the level of evidence (LOE), and the grade of recommendation (GR) are depicted at the beginning of each chapter. In addition to these more general statements, the present recommendations are further specified with regard to radiotherapeutic aspects, problems, and techniques. The aim of the paper was to give a summary of the most important issues of postmastectomy radiotherapy (PMRT), locally advanced disease, regional irradiation of the lymphatics, and sequencing of different treatment modalities. Therefore, a comprehensive survey of the literature was performed, comprising lately published meta-analyses, data from recent randomized controlled trials, and guidelines of international breast cancer societies.

### Postmastectomy Radiotherapy (PMRT) – Rationale and Indications

- **PMRT of the chest wall decreases the local recurrence rate (LOE 1a)**
- **In patients with a high risk of local recurrence, PMRT improves survival (LOE 1a)**
- **PMRT of the chest wall is indicated in patients with**
  - T3/T4 tumors (LOE 2a, GR A)
  - R1/R2 resection (LOE 2a, GR A)
  - pN+ (> 3) (LOE 1a, GR A)
- **Patients with 1–3 positive axillary nodes may profit from PMRT (LOE 1a, GR 0)**
- **After primary systemic treatment, the indication for PMRT should be based on the preoperative tumor stage (T- and N-status) irrespective of response to systemic treatment (LOE 2a, GR A)**

Statement RT-4 of the German Cancer Society

While there is common consensus regarding whole breast radiotherapy after breast-conserving surgery (BCS), some indications for PMRT continue to be an issue of debate.

Several meta-analyses and randomized controlled trials have provided clear evidence that PMRT substantially re-

duces the locoregional failure rate in all patients except those with small tumors and node-negative disease, indicating that the benefit is proportional to the stage-dependent risk of local relapse [6, 10, 32, 40, 50, 51, 56]. Consequently, the greater the reduction of local recurrence rates, the more it translates into increased survival [11, 56]. In the latest meta-analysis of the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) encompassing data from trials up to 2000 [6], patients with positive nodes had a benefit in cancer-specific survival of 5.4% and in overall survival of 4.4% after 15 years. The survival benefit was greatest (6.2%) in patients with four or more positive nodes whose 5-year local recurrence rate was reduced from 40.6% to 12.9%. Therefore, PMRT is internationally recommended for patients with a large tumor size (pT3–4), incomplete resection, and/or four or more positive axillary nodes [8, 26, 27, 42, 48].

#### PMRT for Patients with One to Three Positive Nodes

Recently, the benefit of PMRT has also been demonstrated for patients with one to three positive axillary lymph nodes. In the latest meta-analysis of the EBCTCG [6], patients with one to three positive axillary nodes experienced an absolute reduction of breast cancer mortality of 4.4% after 15 years. The local recurrence rate amounted to only 5.3% with radiotherapy versus 24.3% without. In a subgroup analysis of the Danish Breast Cancer Study Group, the survival gain after 15 years was 9% for patients with four or more positive nodes (21% vs. 12%). Interestingly, the subgroup with one to three affected nodes had the same absolute survival gain of 9% (57% vs. 48%), while the rate of overall survival was higher [31]. The 20-year analysis of the British Columbia trial provided similar results [34]. On the basis of these data, several guidelines recommend that PMRT should be considered for patients with one to three positive nodes as well [26, 27, 32, 48]. Results from the UK Medical Research Council/EORTC 22052-10051 SUPREMO trial to answer this question are still pending. However, in a recently published editorial, Marks et al. explicitly state that the distinction between one to three versus four or more positive nodes is arbitrary and that it is therefore “time to end the debate” [23].

#### Conclusion of the DEGRO Panel

- For patients with one to three positive axillary nodes bearing an intermediate risk for locoregional recurrence after mastectomy, PMRT should no longer be considered optional only, but an indication based on strong evidence (LOE 1).

As a consequence, in the next update of the German Cancer Society the respective recommendation should be modified accordingly.

#### PMRT and Age

For patients > 70 years there is limited level I evidence on the effects of PMRT. Therefore, its benefit is not ultimately proven as this group has, so far, been underrepresented in the published

meta-analyses and made up for only 3.5% of all patients [6, 9, 46]. In a recent retrospective evaluation of the SEER Medicare database, a survival benefit was described for patients whose risk of local recurrence was high (T3/4, N2/3) [44].

#### Conclusion of the DEGRO Panel

- Patients should not be precluded from PMRT on the basis of formal age criteria alone.
- When PMRT is indicated according to TMN stage [49], it should only be omitted in case of poor clinical condition or comorbidities substantially reducing life expectancy.

#### PMRT and Other Risk Factors

The significance of other risk factors such as age < 40 years, blood or lymphatic vessel invasion, infiltration of the pectoral fascia, or close resection margins < 1 mm has not been definitely assessed, therefore, the respective benefit of PMRT is not yet quantifiable on a high LOE [29]. As radiotherapy may prevent secondary distant spread by reducing local recurrence [15], the panel recommends to consider PMRT in these situations, especially in patients with several of the above-mentioned risk factors.

#### Radiotherapy of the Regional Lymph Node Areas

- **The benefit of postoperative irradiation of the lymphatic pathways has not been proven in prospective randomized trials, therefore, the decision has to be made individually (LOE 3b)**
  - **There is no indication for radiotherapy of the axilla, when sentinel node biopsy was tumor-negative (LOE 1b, GR A)**
  - **Radiotherapy of the axilla is indicated**
    - in presence of residual tumor in the axilla (LOE 2b, GR A)
    - in case of clinically apparent tumor spread to the axilla or in case of positive sentinel node biopsy without or after incomplete axillary dissection (LOE 3b, GR A)
  - **There are no sufficient data supporting irradiation of the axilla in case of extracapsular tumor spread**
  - **Radiotherapy of the supra-/infraclavicular nodes is recommended**
    - when more than three nodes are positive (LOE 2a, GR B)
    - in case of tumor spread to level III (LOE 3b, GR B)
    - when radiotherapy of the axilla is indicated (LOE 3b, GR B)
  - **Radiotherapy of the internal mammary nodes is generally no longer recommended except in clinical trials**
- Statement RT-5 of the German Cancer Society

The impact of radiotherapy of the regional lymph node areas on outcome in breast cancer has not been ultimately proven in prospective randomized studies; therefore, the indication for regional lymphatic irradiation remains an individual de-

cision [26–28, 35, 42, 48]. On the other hand, in those studies that showed improved survival in the irradiated patients, the regional lymphatic pathways were mostly included [6, 32]. However, the contribution of lymph node irradiation to the improvement of outcome cannot yet be quantified. The results of ongoing clinical trials clarifying the impact of adjuvant radiotherapy of regional lymphatics are still pending. It seems noteworthy that most of the data referring to radiotherapy with additional lymphatic irradiation were evaluated in PMRT patients, whereas lymph node irradiation was performed only in a minority of studies with BCS [6]. This may be explained by the restriction of BCS studies to patients with small tumors and favorable prognostic factors in whom additional lymphatic irradiation did not seem to be beneficial.

#### Radiotherapy of the Supraclavicular Fossa

Radiotherapy of the supraclavicular fossa is regarded as mandatory when more than three axillary nodes are positive [42]. The National Comprehensive Cancer Network (NCCN) recommends to consider radiotherapy of the supraclavicular fossa even for patients with one to three positive nodes, though with a lower GR [26, 27]. The Canadian guidelines recommend inclusion of the supra-/infraclavicular nodes in all patients who receive PMRT [48].

#### Conclusion of the DEGRO Panel

Supra-/infraclavicular irradiation is

- mandatory when four or more axillary nodes are positive,
- an individual decision in patients with one to three positive axillary nodes.

#### Radiotherapy of the Axilla

Radiotherapy of the axilla is only recommended for patients with residual tumor after axillary dissection or in case of clinical involvement and inadequate axillary clearance [26, 27, 42, 47, 48]. Positive sentinel node biopsy (SNB) without consecutive axillary dissection is another indication [22, 27, 42, 48], whereas radiotherapy should be omitted after negative SNB [52, 53]. Data supporting a benefit of irradiation of the axilla in case of extracapsular extension (ECE) are inconsistent. Therefore, ECE is not regarded as indication [12, 25, 45, 54, 55].

#### Conclusion of the DEGRO Panel

Radiotherapy of the axilla is performed only in patients

- without axillary dissection or with residual tumor thereafter,
- in case of clinical involvement and inadequate axillary clearance as defined in the guidelines of the German Cancer Society,
- with positive SNB without consecutive axillary dissection.

#### Radiotherapy of the Internal Mammary Chain

Radiotherapy of the internal mammary chain (IMC) is generally no more recommended as a routine treatment unless these nodes are clinically or pathologically positive. The Canadian

guidelines [48] refrain from giving a definite recommendation for IMC irradiation due to the inconsistency of data. The NCCN guidelines representatively demonstrate the controversial views taken by different scientists on the issue of IMC irradiation: “There is considerable disagreement, some panel members believe that irradiation of the internal mammary nodes is unnecessary and produces possible morbidity. Others believe IMC should be included as used in those studies that demonstrated an advantage of radiotherapy.” The panel’s compromise is reflected by the statement that “the treatment of the internal mammary nodes is left to the discretion of the treating radiooncologist”. Moreover, the NCCN does recommend consideration of IMC radiation (and supraclavicular fossa) even for patients with one to three positive nodes after mastectomy [27]. Clarification of the issue whether the benefit outweighs potential risks of IMC irradiation is expected from the EORTC 22922/10925 trial that is currently investigating the impact of IMC radiotherapy in patients with medial/central location and/or axillary lymph node involvement [33]. More than 4,000 patients have been randomized; results are expected in 2011.

#### Conclusion of the DEGRO Panel

- No routine use of IMC radiotherapy.
- However, IMC irradiation should not be regarded as obsolete for patients with four or more positive axillary nodes and large tumors, especially those with medial/central location. Any decision has to be made individually considering the patient’s specific risk pattern.

#### Radiotherapy of Locally Advanced Breast Cancer and Primarily Inoperable Tumors

- **For patients with tumors that are irresectable at diagnosis (stage IIIB) primary systemic treatment is recommended, followed by surgery and radiotherapy (LOE 1b, GR A)**
- **If primary systemic treatment fails to achieve operability, radiotherapy is recommended, possibly in combination with concomitant systemic treatment (GR B)**

Statement RT-6 of the German Cancer Society

Generally accepted criteria for the definition of locally advanced breast cancer (LABC) are tumors of a size > 5 cm in diameter or with either skin or chest wall involvement. Further criteria are fixed (matted) axillary lymph node masses or spread to the ipsilateral supraclavicular or IMC nodes. Inflammatory carcinomas are regarded as a subgroup of LABC [2, 7, 43].

LABC is currently treated with primary systemic therapy, i.e., chemo- or endocrine therapy with the aim of tumor shrinking and consecutive resectability (mastectomy or in a breast-conserving setting). Preoperative radiotherapy may increase the rate of breast conservation and seems to have no negative impact on cosmetic outcome. However, radiotherapy should

not replace consecutive resection [19, 36, 41, 48]. Treatment strategy and indication for radiotherapy should be discussed in an interdisciplinary setting prior to the start of primary systemic therapy and decisions based on pretreatment tumor stage irrespective of response to treatment [18]. Patients with LABC and operable tumors (stage IIIA) should receive chemotherapy either as primary treatment with consecutive surgery and irradiation or as postoperative treatment. Complete remission following primary systemic treatment is a favorable predictive parameter and especially these patients profit from PMRT [24]. For inoperable patients, in whom primary systemic treatment fails to achieve operability, concomitant radiochemotherapy may be indicated [21, 27, 41].

Inclusion of the axilla into the target volume depends on the extent of surgery and histopathologic findings and is recommended in case of residual tumor. The value of IMC irradiation is unclear [26, 27, 41].

### Timing and Sequencing of Radiotherapy

- **The most effective sequencing of radiotherapy and systemic treatment cannot be defined on the basis of current data. Postoperative sequencing should be determined according to the predominant risk of recurrence as the optimal time point for each treatment is unclear (LOE 1a, GR B)**
- **Consistent data referring to sequencing of radiotherapy and trastuzumab are not yet available**
- **Simultaneous application of trastuzumab and radiotherapy does not seem to enhance toxicity and is feasible, provided that no IMC irradiation is performed (LOE 3a). Antiestrogen treatment may be performed simultaneously with radiotherapy or sequentially (LOE 1a)**

Statement RT-7–9 of the German Cancer Society

As currently data do not permit to define an optimal sequence of surgery, systemic treatment and radiotherapy, the therapeutic strategy should be determined in an interdisciplinary approach, oriented on stage of the disease and individual risk factors.

Basically, sequencing and timing of chemo- and radiotherapy should be individually adapted to the predominant risk of recurrence [4, 16, 18, 20]. An early onset of radiotherapy is indicated when the risk of local relapse is prevailing (e.g. T4 tumors, gross residual disease, or close margins < 2 mm).

Radiotherapy should be started 4–6 weeks after surgery or after completion of the primary or adjuvant chemotherapy [30, 42]. Theoretically, it seems tempting to minimize the delay of local treatment by using concomitant radiochemotherapy, moreover, an additional radiosensitization of tumor cells might be expected. However, simultaneous radiochemotherapy yields higher toxicity.

Trastuzumab is established for adjuvant treatment of HER2-neu-positive tumors. In a prospective study with large

patient numbers, no increased toxicity was observed when trastuzumab was applied simultaneously with radiotherapy. IMC irradiation was not permitted in this setting [3, 13, 37]. There are no contraindications for simultaneous endocrine treatment and radiotherapy [1, 14, 17].

### Technique of Radiotherapy – Chest Wall

Usually, radiotherapy is performed in supine position with abducted arm ( $\geq 90^\circ$ ) using breast tilt boards with arm rest to maintain the patients' daily position. Immobilization devices may be used to facilitate daily reproducibility and minimize setup errors.

In order to achieve optimized dose distribution, three-dimensional CT planning is mandatory, followed by either conventional or virtual simulation with treatment verification of each field. The planning target volume (PTV) comprises the chest wall including the scar and a safety margin. The cranial and caudal field borders are adapted to the size and position of the contralateral breast with the inferior extension about 1.5 cm below the original submammary fold. The maximum depth of the irradiated lung should not exceed 2 cm. The dose is 50–50.4 Gy delivered in 1.8–2 Gy per fraction. In areas at high risk of local recurrence, a boost may be considered in case of close margins or R1 resection status [5, 27, 38, 41].

### Technique of Radiotherapy – Lymph Node Areas

For irradiation of the *supraclavicular lymph nodes*, three-dimensional planning is desirable but not mandatory. The PTV comprises the supraclavicular nodes and the axillary nodes of level III (apex axillae) with a safety margin of 1–2 cm. Reference points for supraclavicular nodes are usually chosen in a depth of about 3 cm and for level III nodes in about 5 cm, respectively, depending on the individual anatomy. Care has to be taken to match the field border of the tangential portal [5].

When additional irradiation of the *axilla* is indicated, this is usually performed by opposing techniques. The PTV comprises the supraclavicular fossa and the axillary lymph nodes in levels I–III with a safety margin of 1–2 cm. In case of including the supraclavicular nodes into opposing beam arrangements, the difference in anatomic diameter has to be taken into consideration in order to avoid an overdose in the supraclavicular area.

The dose in the reference point is 50/50.4 Gy. In case of increased risk for supraclavicular metastases, i.e., in the presence of massive axillary lymph node involvement, the dose may be increased up to 56 Gy. The tolerance dose (TD 5/5) using a daily fraction of 2 Gy is considered to be 56 Gy for the brachial plexus. The daily fraction size should therefore not exceed 1.8/2 Gy per day [27, 38, 41].

For radiotherapy of the *internal mammary nodes*, three-dimensional planning is mandatory. The PTV comprises the ipsilateral lymphatic pathway along the ipsilateral internal mammary vessels encompassing the first three or four intercostal spaces with a safety margin of 1 cm. Although there is



an anastomotic drainage to the contralateral side, irradiation of the contralateral lymph nodes is generally not recommended. For optimal protection of heart and lung, mostly a combination of electrons and photons is used. The dose to the heart should not exceed 30 Gy in 30% of the heart volume. After pretreatment with anthracyclines and other cardiotoxic agents, the dose should be limited to 20 Gy in 30% of the heart volume [38].

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