DEGRO Practical Guidelines for Radiotherapy of Breast Cancer I

Breast-Conserving Therapy

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Background: The present paper is an update of the practical guidelines for radiotherapy of breast cancer published in 2006 by the breast cancer expert panel of the German Society of Radiation Oncology (DEGRO) [34]. These recommendations have been elaborated on the basis of the S3 guidelines of the German Cancer Society that were revised in March 2007 by an interdisciplinary panel [18].
Methods: The DEGRO expert panel performed a comprehensive survey of the literature, comprising lately published meta-analyses, data from recent randomized trials and guidelines of international breast cancer societies, referring to the criteria of evidence-based medicine [25]. In addition to the more general statements of the German Cancer Society, this paper emphasizes specific radiotherapeutic aspects. It is focused on radiotherapy after breast-conserving surgery. Technique, targeting, and dose are described in detail.
Results: Postoperative radiotherapy significantly reduces rates of local recurrence. The more pronounced the achieved reduction is, the more substantially it translates into improved survival. Four prevented local recurrences result in one avoided breast cancer death. This effect is independent of age. An additional boost provides a further absolute risk reduction for local recurrence irrespective of age. Women > 50 years have a hazard ratio of 0.59 in favor of the boost. For DCIS, local recurrence was 2.4% per patient year even in a subgroup with favorable prognostic factors leading to premature closure of the respective study due to ethical reasons. For partial-breast irradiation as a sole method of radiotherapy, results are not yet mature enough to allow definite conclusions.
Conclusion: After breast-conserving surgery, whole-breast irradiation remains the gold standard of treatment. The indication for boost irradiation should no longer be restricted to women $\leq$ 50 years. Partial-breast irradiation is still an experimental treatment and therefore discouraged outside controlled clinical trials. Omission of radiotherapy after breast-conserving surgery of DCIS should be restricted to individual exceptions.

Key Words: Radiotherapy breast cancer · Breast-conserving therapy · Boost irradiation · Partial-breast irradiation · DCIS

Strahlenther Onkol 2007;183:661–6
DOI 10.1007/s00066-007-1811-1

DEGRO-Leitlinien für die Radiotherapie des Mammakarzinoms I: Brusterhaltende Therapie

Hintergrund: Es handelt sich um ein Update der 2006 publizierten Leitlinien der Expertengruppe Mammakarzinom der Deutschen Gesellschaft für Radioonkologie (DEGRO) [34]. Diese waren in Ergänzung zur S3-Leitlinie der Deutschen Krebsgesellschaft verfasst worden, die durch ein interdisziplinäres Gremium im März 2007 überarbeitet worden war [18].
Methodik: Die Expertengruppe (identisch mit den Autoren dieses Manuskripts) führte eine Literaturrecherche durch, die sämtliche neuen Metaanalysen und randomisierte Studien, die neue Gesichtspunkte gegenüber 2006 erbrachten, sowie Empfehlungen

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Update: October 2007

internationaler Fachgesellschaften in die Bewertung von Therapieindikationen einbezog und sich an den Kriterien evidenzbasierter Medizin orientierte [25]. In Ergänzung zu den eher generellen Statements der Deutschen Krebsgesellschaft fanden spezielle radiotherapeutische Fragestellungen besondere Berücksichtigung. Die vorliegende Arbeit beschränkt sich auf die Strahlentherapie nach brusterhaltender Operation. Technik, Zielvolumendefinition und Dosierung werden im Detail beschrieben.

Ergebnisse: Die postoperative/adjuvante Bestrahlung senkt die Lokalrezidivrate. Je ausgeprägter diese Reduktion ist, umso mehr verbessert dies die Überlebensrate: Vier verhinderte Lokalrezidive vermeiden einen tumorbedingten Todesfall. Dieser Effekt ist altersunabhängig. Eine zusätzliche Boostbestrahlung senkt die Lokalrezidivrate signifikant, wobei dieser Effekt auch bei Frauen > 50 Jahre nachgewiesen wurde (Hazard-Ratio 0,59). Beim DCIS betrug die Lokalrezidivrate ohne Strahlentherapie auch bei Vorliegen günstiger Faktoren 2,4% pro Patientenjahr; eine entsprechende Studie wurde deshalb aus ethischen Gründen vorzeitig beendet. Für die Teilbrustbestrahlung liegen noch keine Langzeitergebnisse vor, die eine endgültige Bewertung erlauben.

Schlussfolgerung: Weiterhin ist nach brusterhaltender Operation eines invasiven Mammakarzinoms die postoperative/adjuvante Bestrahlung der gesamten Brust unverzichtbarer Bestandteil des multimodalen Therapiekonzepts. Die Indikation zur Boostbestrahlung sollte großzügiger gestellt werden und nicht mehr nur Patientinnen bis zum 50. Lebensjahr vorbehalten sein. Die alleinige Teilbrustbestrahlung stellt nach wie vor eine experimentelle Therapie dar und sollte nicht außerhalb kontrollierter klinischer Studien erfolgen. Beim DCIS sollte nach brusterhaltender Operation nur in begründeten Ausnahmefällen auf eine Strahlentherapie verzichtet werden.

Schlüsselwörter: Strahlentherapie bei Mammakarzinom · Brusterhaltende Therapie · Boostbestrahlung · Teilbrustbestrahlung · DCIS

Introduction

The present recommendations are an update of the guidelines for radiotherapy of breast cancer compiled by the breast cancer expert panel of the German Society of Radiation Oncology (DEGRO) [34]. They are based on the interdisciplinary guidelines for breast cancer therapy of the German Cancer Society [18] which have been revised in March 2007. The respective statements, the level of evidence (LoE), and the grade of recommendation (GR) – presented at the 27th Annual Meeting of the German Society of Senology in June 2007 – are depicted at the beginning of the different chapters. In addition to these more general statements, the present recommendations are further specified with regard to special radiotherapeutic aspects, problems, and techniques. The aim of the present paper is to give a summary of the most important issues of radiotherapy after breast conserving surgery.

Radiotherapy after Breast Conserving Surgery

- **For invasive carcinoma postoperative radiotherapy of the breast is indicated after breast conserving surgery (LoE 1A, GR A)**
- **External beam radiotherapy provides improved local control and increased survival (LoE 1A)**
  Statement 23 of the S3 guidelines of the German Cancer Society

For patients who receive breast-conserving surgery (BCS), percutaneous homogeneous irradiation of the whole breast including the adjacent chest wall (WBRT) is an obligatory part of the treatment concept. Even though it has been recognized for decades that radiotherapy reduces the risk of local recurrence [8, 9], only recently, several meta-analyses provided evidence that increased local control translates into improved survival [6, 42, 43]. Statistically, one breast cancer death is avoided by four local recurrences prevented [6, 26]. The impact on survival is correlated to the difference in local control: when radiotherapy reduces the 5-year recurrence rate by 10–20%, the 15-year absolute reduction of mortality is 4.5%, whereas > 20% reduction in 5-year local recurrence rate translates into an absolute survival gain of 6% after 15 years [6].

Radiotherapy and Age

The relative reduction of local and regional recurrence rate is independent of age [6]; however, young patients with a high risk of local relapse have the greatest absolute benefit [6, 7]. The absolute gain for patients of older age and with favorable risk factors is smaller [6, 26]. To quantify the benefit of WBRT for postmenopausal women, Fyles et al. performed a randomized study including 769 women > 50 years (the majority of whom was > 60 years) with small estrogen receptor-positive node-negative tumors who were assigned to tamoxifen alone versus tamoxifen plus WBRT. After 5 years, disease-free survival was significantly better in irradiated patients (91 vs. 84%; $p = 0.004$) [12].

As patients > 70 years are not routinely included in clinical studies, data are sparse and it is difficult to assess the impact of improved local control on survival in this group. This issue was addressed by one randomized study [17] including 636 women > 70 years with small tumors and negative nodes who received either tamoxifen only or an additional WBRT. Radiotherapy significantly increased freedom from local and regional recurrence but did not have an effect on overall survival. A similar result was found in a retrospective evaluation of the SEER Medicare database [39] analyzing 8,727 women

> 70 years with and without WBRT. Radiotherapy was associated with an absolute risk reduction for local relapse.

In summary, WBRT is internationally recommended [4, 23, 24, 37] for all patients receiving BCS with the possible exception of those women > 70 years with small node-negative and estrogen receptor-positive tumors. In case of primary systemic treatment and consecutive BCS, the panel regards postoperative WBRT as indicated, even though data do not yet provide sufficient evidence to quantify its effectiveness in this situation.

Whole-Breast Radiotherapy – Treatment Technique and Dose

Three-dimensional CT planning with verification of each portal are mandatory in order to achieve maximal homogeneity and optimization of dose distribution. The clinical target volume (CTV) comprises the whole breast (gland and chest wall). In order to compensate setup errors, a safety margin of 1–1.5 cm is used to generate the planning target volume (PTV). The maximum margin of lung included in the tangential field should not exceed 2 cm in depth. The patient is treated supine with elevated arm. In general, radiotherapy of the breast is performed by tangential beam arrangements with photons. The total dose is 50/50.4 Gy in single fractions of 2/1.8 Gy five times per week, as higher fraction sizes seem to yield inferior cosmetic results than lower single doses [10]. The dose is specified according to ICRU 50/62 Reports.

Boost to the Tumor Bed

- **A boost to the tumor bed reduces the rate of local recurrences in all age groups, an impact on survival has not yet been demonstrated (LoE 1B)**
- **Boost irradiation is generally indicated (LoE 1B, GR B)**
- **The recommended dose is (10–)16 Gy in conventional fractionation (LoE 1B, GR A)**
- **Benefit for postmenopausal women (> 60 years) with small tumors and a low risk of local recurrence is small, in this subgroup the boost may be omitted (LoE 2A, GR 0)**

Statement 24 of the S3 guidelines of the German Cancer Society

The rationale for a localized boost is the dose dependence of tumor control probability. Moreover, incidence and amount of subclinical residual disease are higher in the tumor bed than elsewhere [15]. Two prospective randomized trials [1–3, 32] provided evidence that the local recurrence rate is significantly decreased by a boost to the tumor bed, with the largest effect in younger women.

Boost Irradiation – Indications

On the basis of these data, until recently, the boost was recommended for patients ≤ 50 years and only optionally for patients > 50 years in the presence of additional risk factors. However, the latest update of the EORTC trial [1, 3] provided evidence that the relative beneficial effect of a boost on tumor control is independent of age, even though in younger patients the local failure rate was higher, and, therefore, the absolute reduction was greater. These data led to the recommendation to offer boost irradiation to all patients, with the possible exception of those with a low risk of local recurrence such as women > 60 years with small tumors [23, 24, 37].

Boost Irradiation – Treatment Technique and Dose

For the localization of the tumor bed, preoperative mammograms are mandatory, postoperative ultrasound and treatment-planning CT are helpful. An additional tool is intraoperative placement of titanium clips to the surgical margins [28]. After oncoplastic surgery, it is difficult to assess the tumor bed; therefore, a more generous PTV has to be delineated.

The boost treatment can be performed using external radiotherapy (photons/electrons), brachytherapy (HDR, PDR, LDR) [31], or intraoperative techniques, mostly electrons [30] or, lately, 50-kV X-rays [20]. In the EORTC trial 22881-10882, the dose was 16 Gy [1–3] by fractionated external-beam irradiation. The randomized study of Romestaing et al. [32], which demonstrated a benefit of the boost with only 10 Gy in 2001, has not been updated since. As the follow-up was only 3.3 years, long-term effectiveness of this regimen is not confirmed.

Using interstitial boost techniques with HDR, the dose is between 10 and 16 Gy; in PDR or LDR technique (dose rate 40–100 cGy/h), and after incomplete resection, doses up to 20 Gy should be delivered [14]. If PDR/LDR technique is not available, the dose of 20 Gy can be given in a fractionated schedule.

The EORTC published a subgroup analysis in 2004 and found no impact of the technique (electrons, photons, brachytherapy) on outcome. In their subgroup analysis, no difference between these modalities was found in terms of local control, toxicity, and cosmetic results [27]. Intraoperative techniques were not evaluated in this study.

Accelerated Partial-Breast Irradiation (APBI) instead of WBRT

- **Accelerated partial-breast irradiation as a sole intraoperative or postoperative radiotherapy instead of whole-breast radiotherapy is an experimental method and should not be performed except in studies (LoE 3, GR A)**

Statement 24a of the S3 guidelines of the German Cancer Society

APBI is recently propagated as an alternative to WBRT in patients with low risk of local recurrence – mostly women of older age and with favorable histological and prognostic factors. The main advantage of ABPI is a shortening of treatment

time, which is appealing especially when radiation resources are limited [35].

The following techniques are used: interstitial multicathether technique [40], 3-D conformal percutaneous radiotherapy [44], balloon catheter technique (Mammosite™) [5], and intraoperative radiotherapy with electrons (IOERT) [13, 21] or 50-kV X-rays (Intrabeam™) [41]. These techniques show marked differences in dose distribution [22].

So far, no subgroups have been unequivocally identified for whom risk-adapted use of ABPI can be regarded as a safe alternative to WBRT [35]. Neither the proper treatment volume nor the adequate total dose have been defined. Moreover, it remains unclear whether large single fractions as used in ABPI have biologically equivalent effectiveness compared to conventional fractionation. Concern has been expressed that doses delivered by APBI might be inadequate to ensure optimal in field-tumor control [33]. As recurrences of breast cancer can occur after a considerable time delay, final assessment of APBI will only be valid after sufficient follow-up from prospective randomized trials with large patient numbers. Until then, WBRT remains the gold standard for patients with BCS. There is international consensus that APBI instead of WBRT is still an experimental treatment and should exclusively be performed in prospective randomized clinical trials [23, 36, 45].

Ductal Carcinoma in Situ (DCIS)

- **Postoperative radiotherapy after breast-conserving surgery of DCIS reduces the risk of invasive and noninvasive recurrence (LoE 1A)**
- **Data suggest, that the effectiveness of radiotherapy depends on individual characteristics such as age of the patient, tumor size, grading, surgical technique, and margin status**

  Statement DCIS 3 of the S3 guidelines of the German Cancer Society

DCIS is a noninvasive lesion with malignant cells confined to the duct lumen without invasion of the adjacent breast tissue. Nonetheless, it is regarded as a premalignant condition as transformation into invasive disease occurs in 30–50%, if untreated. The practical relevance of DCIS is increasing as it is diagnosed more frequently with upcoming screening and makes up for 20–30% of all breast cancers. In case of recurrence, about 50% of the tumors are invasive [38].

Postoperative radiotherapy after breast-conserving radiotherapy reduces the risk for invasive and noninvasive in-breast recurrence (LoE 1A). The absolute benefit of radiotherapy depends on age, tumor size, grading, surgical procedure, and width of the margins.

Three randomized trials provided evidence that local recurrence of DCIS is reduced by 50–60% when radiotherapy is used [11, 16, 19]. Without radiotherapy, the rate of in-breast recurrence is about 30% after 10 years. Half of these patients have to undergo mastectomy.

Even though no patient subgroup has yet been identified in prospective trials that would not profit from radiotherapy, the indication has remained an issue of controversy especially in the presence of favorable prognostic factors. In the DEGRO guidelines published in 2006 [34], it was stated, that omission of radiotherapy might be considered in patients who fulfill all of the following conditions: tumors < 2 cm, low-grade differentiation, safety margin ≥ 10 mm, and age > 50 years. However, recent data suggest to scrutinize these factors as a reason to omit postoperative radiotherapy.

Wong et al. [46] performed a controlled prospective trial including women with alleged low risk: patients were > 50 years and had well or moderately differentiated (G1–2) DCIS, tumor size was ≤ 2.5 cm, and wide excision was performed with clear margins ≥ 1 cm. Patients with these favorable factors received no further treatment. The accrual goal was 200 patients; however, the study was closed prematurely at 158 patients because the number of recurrences met the predetermined stopping rules. The rate of in-breast recurrence was 2.4% per year corresponding to a 5-year rate of 12%. Nine patients (69%) experienced recurrence of DCIS and four (31%) had invasive carcinoma.

Complementary to scientific evidence, the psychological situation of patients with DCIS has to be taken into consideration as demonstrated by a study of Rakovitch et al. [29]: The investigation focused on how women with DCIS perceived their risks of recurrence and of dying from breast cancer. The psychological distress was compared to patients with early-stage invasive breast cancer. Participants who had either invasive cancer or DCIS answered a questionnaire; responses were scored and compared between the two groups. No significant difference was observed in perceptions of risk related to the likelihood of developing local recurrence or dying of breast cancer; both groups expressed similar levels of psychological distress and anxiety. The authors conclude that despite their excellent prognosis, women with DCIS express serious concerns and report similar psychological morbidity as women with invasive cancer. These data suggest, that patients with DCIS should not be exposed to an increased risk of recurrence with consecutive psychosocial distress by omitting radiotherapy – even if survival is not affected.

Technique and dose are as described in the chapter of invasive carcinoma. The PTV is restricted to the mammary gland without adjacent chest wall structures. The value of a boost is not defined but may be considered in case of close or positive margins.

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