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Late Toxicity of Radiotherapy: A Problem or a Challenge for the Radiation Oncologist?

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Keywords
Breast cancer · Late effects · Radiotherapy

Summary
Background: Large randomized clinical trials have established radiotherapy in conjunction with adjuvant systemic treatment as standard treatment in breast cancer after both mastectomy and lumpectomy. Although standard radiation therapy is well tolerated by the majority of patients, some patients might suffer from late normal tissue effects. **Methods:** The literature on radiotherapy following surgery of breast cancer was reviewed with regard to late toxicity. **Results:** Radiotherapy may, to some degree, cause persistent pain in the breast, arm and shoulder in up to 30–50% of patients after 3–5 years, lymphedema in 15–25%, and restriction of arm and shoulder movement in 35%. Awareness of cardiotoxicity is needed since anthracyclines, trastuzumab, and radiotherapy may cause damage to the heart. However, using modern radiotherapy techniques, the available evidence does not suggest a higher incidence of cardiac mortality. **Conclusions:** This review updates the database on toxicity from radiation in breast cancer. Advances in research of radiation-induced late effects may lead to improved treatment choices for breast cancer patients including radiotherapy and may improve quality of life after surviving breast cancer.

Schlüsselwörter
Brustkrebs · Spätfolgen · Strahlentherapie

Zusammenfassung
Hintergrund: Große, randomisierte Studien belegen die Bedeutung der Strahlentherapie in Kombination mit systemischer Therapie in der standardisierten Behandlung des Mammakarzinoms sowohl nach Mastektomie als auch nach brusterhaltender Therapie. Auch wenn die Mehrheit der Patientinnen die Behandlung gut toleriert, existieren Spätfolgen, die die Gesundheit der behandelten Patientinnen nachhaltig beeinflussen können. **Methoden:** Die vorliegende Literatur zur postoperativen Bestrahlung des Mammakarzinoms wurde hinsichtlich radiogener Spätfolgen gesichtet. **Ergebnisse:** Die Strahlentherapie als lokale Behandlungsform kann in einer Größenordnung von 30–50% der Patientinnen 3–5 Jahre nach Therapie bleibende Schmerzen im Brustareal, Arm- und Schulterbereich verursachen, ein Lymphödem in 15–25% der Patientinnen, und eine Einschränkung der Schulterbeweglichkeit in bis zu 35%. Eine potentielle Kardiotoxizität im Rahmen der Strahlentherapie muss Berücksichtigung finden, da auch medikamentöse Substanzen wie Anthracycline und Trastuzumab die kardiale Funktion beeinträchtigen können. Allerdings zeigen Daten zu modernen Bestrahlungstechniken keine erhöhte Inzidenz bezüglich der kardialen Mortalität. **Schlussfolgerungen:** Die vorliegende Übersichtsarbeit aktualisiert die Datenbasis zur Spättoxizität nach Strahlentherapie bei Brustkrebs. Fortschritte in der Erforschung radiogener Spätfolgen lassen erwarten, dass sich die Behandlungsentscheidungen für Brustkrebspatienten unter Einschluss der Strahlentherapie auch zukünftig verbessern und damit zu einer Verbesserung der Lebensqualität beitragen.

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Introduction

Large randomized clinical trials have established radiotherapy in conjunction with adjuvant systemic treatment as standard treatment in breast cancer after both lumpectomy and mastectomy [1–6]. Studies of breast-conserving therapy show a relatively low recurrence rate, with limited long-term morbidity and a high level of patient satisfaction concerning cosmetic outcome. However, late normal tissue toxicity might develop either as persistent breast edema, hyperpigmentation, and fibrosis or in a low percentage of patients as pneumonitis, brachial plexopathy, cardiac morbidity, or secondary malignancy. The probability of late side effects depends mainly on the dose per fraction, the interfraction time interval, total dose, and volume irradiated, as well as individual patient factors. Here, we discuss the main radiation-induced normal tissue effects of breast cancer treatment.

Specific Sequelae of Irradiation in Breast Cancer

Breast Appearance and Cosmetic Outcome

The rate of poor or fair cosmetic outcome in most series is 15–20% or less [7]. Surgical factors as the extent of breast tissue removed and scar orientation impact mostly on breast appearance and cosmetic outcome [8–10]. The use of chemotherapy and patient factors such as breast size, older age and race have also been associated with more frequent cosmetic failures. However, several radiation treatment factors are associated with poorer cosmetic outcomes as well. The effect of the radiation technique on the cosmetic result was demonstrated by de la Rochefordiere et al. [8]. They found that the use of > 2 fields, a boost given with interstitial brachytherapy, a boost dose > 18 Gy, and a breast dose > 50 Gy were associated with poorer cosmetic outcomes. The cosmetic results were significantly better with newer, contemporary irradiation techniques.

The effect of the boost on the cosmetic result was evaluated in the randomized European Organisation for Research and Treatment of Cancer (EORTC) 22881/10882 trial [11]. In 5569 early-stage breast cancer patients who received breast-conserving surgery and adjuvant radiotherapy, all patients received 50 Gy in 25 fractions over 5 weeks followed by either no further radiation treatment or a boost dose of 16 Gy in 2-Gy fractions. Cosmetic outcome in each arm was assessed at 3 years either by a 5-physician panel evaluating photographs in a sample of 713 patients or by the percentage of breast retraction assessment (BRA) relative to a reference length in a sample of 1141 patients. Postoperatively, there was no significant difference in cosmetic assessment between the two arms, but at 3 years, patients in the boost arm had a significantly lower rate of excellent/good cosmetic outcome (13% vs. 25.8%). Very few patients in either arm had a poor result after either time period.

In contrast, radiation did not have a deleterious effect on the cosmetic outcome in a subset of 101 women accrued to the Milan III trial, which randomised women with breast cancers equal or less than 2 cm in size to quadrantectomy (QUAD) or quadrantectomy plus breast irradiation (QUART) [12]. The absence of a negative effect from radiation in this trial may be due to the lower total dose to the boost area of 60 Gy versus 66 Gy in the EORTC trial.

In summary, cosmetic outcome in most series depends on the use of a boost dose, more than 2 fields (i.e. addition of the supraclavicular, axillary, or internal mammary field), the total dose, and dose heterogeneity in the breast fields. Contemporary techniques such as 3-dimensional (3D) conformal therapy or intensity-modulated radiation therapy might minimize morbidity [13].

Chronic Pain

Breast cancer patients can experience pain in the irradiated breast, nodal regions or chest wall for years after treatment. Pain after breast cancer surgery can result from injury to muscle and ligaments and is more likely to be transient as compared to persistent neuropathic pain due to damage to the nerve tissue [14, 15]. In a review of 32 studies published prior to 2006, the prevalence of pain in the arm and shoulder varied between 9 and 68% and in the breast area from 15 to 72%, 5–56 months after surgery [16]. The symptoms tended to diminish with time after surgery, but persisted in about 20% of the patients for 3 years after surgery. This estimate corresponds well with results from a survey of 127 breast cancer survivors revealing chronic pain in up to 28% of patients for, on average, 3 years post treatment [17]. In a large randomized trial of the Princess Margaret Hospital comparing tamoxifen alone with tamoxifen and breast radiotherapy after lumpectomy, no increased rates of breast pain up to 12 months after treatment were observed [18]. Another quality-of-life study that accompanied a randomized trial of observation versus breast radiotherapy after lumpectomy demonstrated that patients had increased breast pain during the treatment but not 2 years after [19].

Fibrosis

Skin thickening or fibrosis of the breast or chest wall is observed in about 1/3 of patients [15]. However, moderate or severe fibrosis are found in less than 5% of patients [20].

The influence of total dose and fraction size on the development of subsequent breast fibrosis is demonstrated by a study from the University of Hamburg that evaluated long-term radiation sequelae using Late Effects of Normal Tissue-Subjective, Objective, Management, and Analytic (LENT-SOMA) criteria [21] in 3 groups of women who had undergone breast-conserving therapy with a minimum of 6 years of follow-up: Group 1 received 60 Gy total breast dose with 2.5 Gy per fraction (1983–1987, n = 45), group 2 received 55 Gy total dose with 2.5 Gy per fraction (1988–1993,

n = 345); and group 3 received 55 Gy total dose in 2 Gy conventional dose per fraction (1993–1995, n = 200). Grades 2–3 breast fibrosis developed in 58, 51, and 20% of patients in groups 1–3, respectively [22]. The effect of hypofractionation and the latency for developing subcutaneous fibrosis were studied by Bentzen et al. [23]. The incidence of moderate to severe fibrosis was 96% in the hypofractionated arm (3.05 Gy/fraction twice weekly) vs. 45% in the standard arm of 50 Gy in 2.04 Gy per fraction over 5 weeks. The incidence of fibrosis increased with time during the first 4 years of follow-up. By 3.2 years, 90% of the fibrosis had been expressed. A longer latency was demonstrated for the most severe fibrosis at 4.4 years.

However, if the total dose is decreased from 50 Gy to about 40–42 Gy, hypofractionation with doses per fraction of 2.5–2.7 Gy is safe and might even inflict less late normal tissue damage as demonstrated in 2 very large randomized phase II trials [24, 25].

Lymphedema, Shoulder Immobility and Brachial Plexopathy

The prevalence of lymphedema following local therapies is observed in 15–25% 1–5 years after diagnosis, depending on the method of assessment. The primary treatment factors contributing to arm edema are the extent of axillary node dissection and nodal irradiation. Until recently, axillary node dissection was a standard part of the surgical management of invasive breast cancer, regardless of tumor size and nodal involvement. The incidence of subsequent lymphedema in different studies after surgery alone averages about 13% [26–30]. Sentinel lymph node biopsy has resulted in significantly less morbidity, with estimates of subsequent lymphedema of < 1–3%. The addition of supraclavicular and/or axillary radiation fields following dissection results in a higher incidence of lymphedema ranging from 9 to 58% (table 1). Breast irradiation alone after lumpectomy and axillary node dissection has a negligible effect on the incidence of lymphedema.

The prevalence of impaired arm and shoulder mobility varies from less than 10% to almost 70%, depending on the method of assessment (measured or self-reported), time since treatment, and type of surgery, with greater impairment for mastectomy than lumpectomy and radiotherapy versus no radiotherapy [14, 16]. A systematic review on the magnitude of late effects of breast cancer treatments on shoulder function was reported by Levangie and Drouin [31].

Brachial plexopathy with paresthesia, pain, and weakness of the arm after radiation therapy is uncommon and typically seen only when regional node irradiation has been delivered. The onset of symptoms can be seen within 6 months of completing radiation. While some studies document that most patients develop symptoms within 3 years, others have demonstrated that the risk is progressive with time. For an overview, see White and Joiner [15]. The mechanism of radiation-induced brachial plexopathy is not completely understood. Briefly, it is suspected that fibrosis of tissue around peripheral nerves occurs with injury to small vessels that leads to ischemia [32]. The incidence of radiation-induced brachial plexus sequelae is reported in less than 2% of patients [33–35]. Treatment techniques, total dose and concomitant chemotherapy are risk factors.

In an older post-mastectomy series, the incidence of plexopathy was reported to be associated with increasing fraction size and total dose, similar to what is seen for late fibrosis [36–38]. In the series from the University of Hamburg [38], the dose to the brachial plexus was 52 Gy in 2.6 Gy per fraction. Progressive damage was found with increasing time after radiotherapy, resulting in ≥ 3 plexopathy in 2% after 5 years, 5.5% after 10 years, 11.8% after 15 years, and 19.1% after 19 years, respectively [38].

Lung Sequelae

Symptomatic radiation pneumonitis is uncommon after adjuvant breast irradiation. The typical onset is 2–3 months after completing treatment, with a clinical syndrome of cough, fever, shortness of breath, and radiologic changes confined to the radiation therapy field [15, 39]. Symptoms can persist for several weeks and, in general, are self-limiting. Pulmonary fibrosis typically follows in the affected portion of the lung. Lingos et al. [40] reported on radiation pneumonitis in a retrospective review of 1624 patients treated with conservation surgery and irradiation. Overall, pneumonitis developed in 1% of patients. The incidence increased to 3% when nodal irradiation was added and 8.8% when nodal irradiation and chemotherapy was delivered. None of the patients had late or persisting pulmonary symptoms. In this study, the volume of lung irradiated did not correlate with the risk for development of radiation pneumonitis. The incidence of pneumonitis based on irradiated lung volumes from different radiation therapy techniques used to treat breast cancer patients has been

Table 1. Incidence of arm lymphedema after axillary dissection and nodal irradiation

Authors	Year	N	Surgery	Measure	AD, %	AD + RT, %
Segerstrom et al. [56]	1991	136	mastectomy	volume displacement > 150 cc	21	58
Bijker et al. [57]	1998	691	mastectomy	none given	6	28
Hojris et al. [58]	2000	84	mastectomy	limb volume > 200 cc	3	14
Meric et al. [20]	2002	294	BCS	arm circumference > 3 cm	10	18
Coen et al. [59]	2003	727	BCS	arm circumference > 2 cm	1.8	8.9

BCS = Breast-conserving surgery, AD = axillary dissection, RT = radiotherapy.

studied by Lind et al. [41]. A positive correlation was found between the incidence of pulmonary complications and increasing ipsilateral lung volumes receiving > 20 Gy [42]. The incidence of moderate symptomatic post-treatment pneumonitis requiring steroid treatment varied between 0.5% for small irradiated volumes and 11.5% for large treated lung volumes (i.e. in post-mastectomy treatments including supraclavicular fossae and internal mammary lymph node areas).

Cardiac Toxicity

The potential for excess cardiac morbidity associated with the use of radiation therapy in breast cancer has been extensively evaluated in randomized trials and meta-analyses.

Radiation for left-sided breast cancer has been associated with increased morbidity and mortality from ischemic heart disease [43–46].

The impact of the radiotherapy technique on cardiac morbidity has been studied extensively in the Stockholm trial [45–47]. This trial included 960 breast cancer patients enrolled between 1971 and 1976 who were randomly allocated to preoperative radiotherapy, postoperative radiotherapy, or to mastectomy alone. The different radiation techniques used in the trial were classified into 3 groups of low, intermediate, and high cardiac dose-volumes. Mortality due to ischemic heart disease was significantly higher in the 'high'-dose-volume subgroup when compared to surgical control. In the low- or intermediate-dose-volume subgroups, mortality due to ischemic heart disease was similar to patients treated with surgery alone.

Paszat et al. [48] conducted a study of 25,570 cases of invasive female breast cancer that were linked to radiation therapy records from Ontario cancer centers. Post-lumpectomy radiation therapy was administerd to 1555 patients on the left side and to 1451 on the right side. 2% of the women with left-sided radiation therapy had a fatal myocardial infarction compared with 1% of the women with right-sided radiation therapy (relative risk 2.1). Two other population-based studies, one from Sweden for patients treated during 1970–1985 and the other from Surveillance Epidemiology and End Results (SEER) for patients treated in the USA in 1973–1992, have reported a relationship between left-sided breast cancer treatment and subsequent late cardiac events and mortality [48, 49]. In addition, the meta-analysis of 40 randomized trials of radiotherapy involving 20,000 breast cancer patients by the Early Breast Cancer Trialists' Collaborative Group demonstrated that the addition of radiotherapy decreased cancer specific mortality, but that non-cancer mortality increased [50].

Three series from single institutions applying modern radiotherapy techniques did not find an increase in myocardial infarction [51] or cardiac-related mortality after 9–12 years of follow-up [52, 53]. Nevertheless, radiotherapy causes volume-dependent perfusion defects of the heart in up to 40% of patients within 2 years of treatment, leading to wall motion abnormalities [54]. Whether these changes are associated with clinically relevant functional deficits is unknown.

An analysis of the large randomized phase III Danish trials, with more than 10 years of follow-up, showed no excess cardiac mortality with the use of post-mastectomy radiation [55].

Summary

Moderate to severe late normal tissue damage inflicting considerable suffering on patients after breast-conserving surgery or mastectomy and adjuvant radiotherapy is observed in less than 5% of breast cancer patients. Modern radiation techniques such as 3D conformal and intensity-modulated radiotherapy and either standard fractionation with 50 Gy in 2 Gy per fraction or hypofractionation with 2.5 Gy to < 3 Gy per fraction and lower total doses are safe and well-tolerated treatments. Future studies are necessary to further reduce normal tissue toxicity, especially in combined-modality approaches with aggressive chemo- and immunotherapies.

Disclosure Statement

The authors declare no conflicts of interest.

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