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Radiotherapy-Induced Fatigue in Breast Cancer Patients

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Abstract
Background: A large proportion of breast cancer patients who undergo adjuvant radiotherapy suffer from radiotherapy-induced fatigue. The possible causative factors of this specific side effect are diverse. ***Summary:*** Prevalence, duration, and severity of radiotherapy-induced fatigue are dependent on the type of radiotherapy, as well as on the irradiated volume, dose scheme, on the number of radiation fields, the combination with other treatments, diurnal rhythm, smoking, and time-to-hospitalization. Recommended treatments include non-pharmacologic interventions, such as physical and psychosocial interventions. Pharmacologic therapies include treatment with methylphenidate and modafinil. In addition to its early detection with standardized instruments, adequate education to breast cancer patients about risks and predisposing factors of radiotherapy-induced fatigue is essential. Multidimensional strategies help to maintain the patients' quality of life and therefore guarantee treatment adherence and efficacy. ***Key Messages:*** Radiotherapy-induced fatigue is an underreported, underdiagnosed, and undertreated side effect. This review provides an overview of radiotherapy-induced fatigue in breast cancer patients receiving adjuvant radiotherapy.

Introduction

Adjuvant radiotherapy (RT) is the standard treatment for more than 90% of breast cancer (BC) patients, aiming to decrease locoregional recurrence and improve overall survival [1, 2]. Despite its beneficial role, numerous side effects are associated with RT, and among the most common is RT-induced fatigue (RIF) [3]. In particular, up to 77% of BC patients who undergo RT suffer from RIF as a disorder, characterized by a state of generalized weakness with a pronounced inability to summon sufficient energy to accomplish daily activities [1, 4]. Despite the high incidence rate, the symptom lacks a clear definition. The National Comprehensive Cancer Network (NCCN) defined RIF as a clinical subtype of cancer-related fatigue (CRF) that either arises during RT (acute RIF) or continues afterwards (chronic RIF). RIF is a distressing, persistent, and subjective sense of physical, emotional, or cognitive tiredness or exhaustion, related to cancer or cancer treatment that is not proportional to recent activity, and interferes with normal functioning [5, 6]. Although RIF possibly compromises patients' treatment adherence [7], it is still underreported, underdiagnosed and undertreated [5, 8]. This narrative review provides a comprehensive overview of RIF in BC patients who are undergoing adjuvant RT.

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Pathophysiology

Multiple factors have been proposed to cause RIF. Some factors include genetics (e.g., DNA damage and telomere length), hypothalamic-pituitary-adrenal axis dysregulation, 5-hydroxytryptophan neurotransmitter dysregulation, and alterations in the adenosine-triphosphate (ATP) muscle metabolism. Other factors include endocrine disturbances (reduction in estrogen and testosterone), mitochondrial dysfunction, cytokine dysregulation, inflammation and immune response, anemia, circadian rhythm disruption, disruption in the blood-brain barrier, and psychological mechanisms [3, 9–15].

Regarding mitochondrial dysfunction as a potential cause of RIF, the following pathophysiological pathway is being proposed. During RT, the mitochondrial membrane integrity is disrupted, and radiation may lead to a reduction of mitochondrial capacity to utilize oxygen and synthesize (ATP) [16, 17]. Side effects arise when ionizing radiation produces reactive oxygen species (ROS) that cause oxidative damage in late responding healthy tissues. The initial burst of ROS can subsequently lead to point mutations in mitochondrial DNA and further propagate ROS production by the dysfunctional mitochondria. This results in the accumulation of oxidative stress and a prolonged inflammation state [12, 18]. Studies have also indicated that RIF is associated with anemia and functional iron deficiency [12, 15, 18, 19]. ROS produced during RT can cause membrane changes, including lipid peroxidation, phospholipid hydrolysis, and disulfide bridge formation. The cytoskeleton may be affected due to changes in the cell membrane. This process results in the hemolysis of red blood cells and hemoglobin leakage [20]. Red blood cell count, hemoglobin and hematocrit were found to correlate with the severity of fatigue during external beam radiation therapy (EBRT), suggesting that stabilizing these levels may prevent the worsening of fatigue symptoms during EBRT [19].

Severity and Assessment

In general, fatigue can be classified according to its severity by using grades from 1 to 3. Grade 1 would be "fatigue relieved by rest," "fatigue not relieved by rest, limiting instrumental activities of daily living" is grade 2, and "fatigue not relieved by rest, limiting self-care activities of daily living" is grade 3. Apart from this classification, objective measurement of fatigue remains a significant challenge. There is no fatigue-specific standardized assessment tool or scoring system to define the severity grade accurately [10, 21]. For both CRF and RIF, assessment by a single-item symptom checklist has led to a certain underestimation in several studies [3]. Currently, subjective questionnaires like the Multidimensional Fatigue Inventory, Revised Piper Fatigue Scale, Brief Fatigue Inventory, Lee Fatigue Scale, Functional Assessment of Chronic Illness Therapy, European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, or the Visual Analogue Scale are used to asses CRF [22–24].

Besides the diversified choice of questionnaire instruments used in the studies, the time point of fatigue evaluation differed strongly. The available studies included time points, such as during the appointment with the radiation oncologist, prior to starting RT, before starting RT, at the beginning of RT, during the first week of RT, or no specification of the starting time point given. Regarding the total number of fatigue assessments within the study, protocols vary from one to four different protocols used [15, 25–32]. The results emphasize that standardization of the timing of the fatigue evaluation and the fatigue assessment tool still needs to be established. An overview of the most prevalent scales to measure RIF is presented in Table 1 [15, 27, 33–39].

Impact of Irradiation

It is well known that the prevalence, duration, and severity of fatigue depend on the type of RT, the irradiated volume and dose scheme, and on the combination with other treatments, as patients receiving combined therapies (e.g., chemotherapy plus RT) showed the highest fatigue scores [2, 3, 9, 40–42]. For some years now, hypofractionation has been considered the standard treatment in whole breast irradiation for early-stage BC without lymph node involvement. The UK Trialists' Collaborative Group and Whelan et al. [43] were able to demonstrate equal oncological safety using 15–16 fractions of 2.66 Gy, compared to the standard fractionation scheme using 25–28 fractions of 2.0 Gy [43–45]. Although the single dose is higher, hypofractionated schemes are associated with fewer side effects, such as RIF, due to the reduced total dose and shorter treatment duration (3 instead of 5–6 weeks) [46].

Apart from the fractionation, treatment volumes to the region have an impact on the side effects of adjuvant RT [47]. Whole breast irradiation has been the standard of care after breast-conserving surgery for years. However, most of the local recurrences appear close to the tumor bed, so that efforts were made to reduce the treatment volume around the resected tumor. The hypothesis is that external beam accelerated partial breast irradiation (EB-APBI) with a safety margin of surrounding tissue might reduce side effects while maintaining the high rate of local control seen with whole breast radiation [48]. However, recently published data from two prospective

Table 1. Assessment tools to measure fatigue in BC patients

Instrument	Brief description	Patients, *n*	Year of publication	Ref. No.
Fatigue Symptom Inventory (FSI)	11-point scale: 0 (not present) to 10 (as bad as you can imagine); 4 items rate the severity of fatigue within the past week; 7 items assess the degree to which fatigue is judged to interfere with the general level of activity, ability to bathe and dress, normal work activity, ability to concentrate, relations with others, enjoyment of life, and mood in the past week; frequency is measured by the number of days with fatigue in the past week	1,129	2005	33
Lee Fatigue Scale (LFS)	18-item scale with 13 items assessing fatigue and 5 items assessing energy; each item is rated on a 0–10 numeric rating scale; total score is calculated as the mean of all items with higher scores indicating greater fatigue severity; validated cut-off scores for clinically meaningful levels of fatigue (≥3.2 for morning fatigue, ≥5.6 for evening fatigue) and energy (≥6.2 for morning energy, ≥3.5 for evening energy)	75	1991	34
Functional Assessment of Cancer Therapy: Fatigue (FACT-F)	13-item fatigue subscale, uses a 5-point Likert self-report scale ranging from 0 (not at all) to 4 (very much); total score (sum of all items) ranges from 0 (worst condition) to 52 (best condition); the score is calculated after re-parameterization of items 7 (I have energy) and 8 (I am able to do my usual activities) for which 0 is the worst condition and 4 the best condition owing to the inverse relationship to the other 11 subscale items	164	2018	35
Functional Assessment of Cancer Therapy: Fatigue-General (FACT-G)	27-item scale: 4 sub-scales assessing physical wellbeing (PWB, 0–28), functional wellbeing (FWB, 0–28), social/family well-being (SWB, 0–28), and emotional wellbeing (EWB, 0–24); with higher scores indicating better quality of life	164 141 116	2018 2011 2004	35 36 15
Visual Analogue Scale (VAS)	Single-item scale with 2 endpoints; no standardized stem questions and anchors (examples for stem questions: energy level, quality of life, ability to perform daily activities; examples for anchors: 0 = exhausted, 100 = have energy; 0 = very bad, 100 = very good); patients make a mark on the VAS line to describe the point between the 2 anchors that best reflects their fatigue status	42	2009	27
Functional Assessment of Chronic Illness Therapy (FACIT)	In total 13 items: originally developed as an addition to the Functional Assessment of Cancer Therapy (FACT) measurement system, forms the FACT-Fatigue (FACT-F) together with the FACT-G	42 58	2009 2019	27 37
Brief Fatigue Inventory Scale (BFI)	In total 9 items: 3 items focusing on fatigue severity (fatigue at present, usual level and worst level of fatigue within the past 24 h) and 6 items to assess the impact of fatigue on areas of daily functioning during the past 24 h (daily activity, mood, walking, work, enjoyment of life, and relations with others); each item scores between 0 and 10; global fatigue score is calculated by averaging all 9 BFI items; higher scores indicate worse fatigue and greater interference; global fatigue score cut-offs according to NCCN Clinical Practice Guidelines: ≥4: no-mild fatigue (0–3) and moderate-severe fatigue (4–10)	90	2010	38
PFS-12	In total 12 items: shortened version of the 22-item revised Piper Fatigue Scale (PFS-R) containing 4 subscales (behavior, affect, sensory and cognition)	799	2012	39

trials showed conflicting results regarding the equivalence to whole breast irradiation. Of note, side effects like RIF occurred less frequently [49, 50].

A study enrolled 30 early-stage BC patients receiving either partial breast RT, whole-breast RT, or MammoSite brachytherapy with a total dose of 34 Gy, or 3D conformal RT with a full dose of 50 Gy. The patients with partial breast RT showed lower rates of fatigue; women who received whole breast RT reported worsened fatigue over time [9]. In another study with 362 older women undergoing breast-conserving therapy for early-stage BC, two types of accelerated partial breast irradiation were compared: intraoperative electron RT and EB-APBI with 10 × 3.85 Gy [51]. The cross-sectional analysis showed significantly worse fatigue symptoms in intraoperative electron RT patients than in EB-APBI patients, which normalized after 3 months.

Risk Factors and Prevention

Pretreatment fatigue levels have been proposed as an essential risk factor for fatigue development during RT [25]. Diagnosing fatigue and recognizing it as a predictor for this condition during treatment within the first appointments seems to be of uttermost importance. Other factors influencing the grade of severity of RIF that have been described in the literature include the diurnal rhythm, where morning fatigue appears to be more affected by biologic factors and evening fatigue by behavioral factors. Another factor is smoking, with smokers experiencing considerably more fatigue than non-smokers. Time-to-hospitalization appears to influence the grade of severity of RIF, with significantly worse symptoms of fatigue in patients who had to travel 2 or more hours compared to patients who had to travel <2 h [22]. Factors such as stress, anxiety, depression, a weakened physical condition, diarrhea, malnourishment, and anemia possibly further deteriorate fatigue [22]. Geinitz et al. [52] observed a significant increase in pretreatment fatigue levels compared to posttreatment values. In women with depression and anxiety, fatigue levels were reported to persist for more than 2 years after the termination of RT. Contrary to that, disease staging and neoadjuvant chemotherapy did not impact the severity of fatigue in a study performed by Lavdaniti et al. [26].

Anticipation and early recognition of the individual risk for RIF could lead to possible preventive measures, such as prehabilitation instead of rehabilitation. A multimodal, multidisciplinary approach may be necessary to prevent RIF, including psychosocial intervention, physical exercise, and medications to address the contributing factors of RIF. As heme levels seem to have an impact on the incidence of RIF upon completion of EBRT, their stabilization is vital to prevent the worsening of fatigue symptoms during treatment [53]. Patients with increased age and high baseline fatigue levels are at risk of experiencing severe RIF [47]. In 2004, in a prospective study with 52 early BC patients undergoing adjuvant RT, Wratten et al. [15] reported that RIF appeared to plateau between week 4 of treatment and 2 weeks after treatment; fatigue was beginning to settle by 6 weeks after treatment. In their study, significant fatigue was predicted by a higher baseline fatigue score, red blood cell count, neutrophil count, and D-dimer level. Baseline fatigue correlated with higher body mass index and altered levels of C-reactive protein, soluble thrombomodulin, tissue plasminogen activator, von Willebrand factor antigen, interleukin-6, ICAM-1, hemoglobin, red blood cells, monocyte, and neutrophil counts. The most predictive factors for RIF in their study were a higher baseline fatigue level and more elevated baseline neutrophils and red blood cell counts. Results of a feasibility study presented in 2018, aiming to evaluate behavioral interventions in early BC patients with RIF, are awaited and they will undoubtedly be of interest in this context [54].

Chronic Fatigue

The impact of fatigue and debilitating tiredness is the loss of independence and impaired physical and mental function. In the mid-1990s an international working group developed a definition of the chronic fatigue syndrome. The description included requiring a person to experience 6 or more months of chronic fatigue of new or definite onset, that is not substantially alleviated by rest, not the result of ongoing exertion, and results in substantial reductions in occupational, social, and personal activities [55]. In most BC patients who undergo adjuvant RT, fatigue severity scores increase significantly from the beginning to half the duration of RT. They then remain elevated until the end of the treatment. After completion of RT, severity scores decreased to pretreatment scores within 4–8 weeks [22, 38, 52, 56].

In contrast, previous studies have reported that up to 40% of patients were still suffering from RIF 1 year after completing adjuvant RT [36], or even 5–10 years following the completion of adjuvant RT [57]. The chronification of fatigue appears to correlate with psychological distress; patients with pretreatment elevated fatigue, anxiety, or depression were shown to be at risk for the chronic state [3, 52]. Chronic fatigue can again lead to depression, impaired cognitive function, sleep disturbance, decreased physical activity, and the deterioration of the individual's quality of life [5, 10, 58]. Chronic fatigue may also influence the patient's compliance and, therefore, impact the efficiency of anticancer treatments [1, 9, 10, 36, 57, 58].

Different Treatment Approaches

Clinical practice guidelines are available to assist physicians in the management of RIF [59–63]. According to the NCCN, physical therapy and occupational therapy are recommended as the interventions of choice in patients with RIF [5]. The NCCN also recommends psychosocial interventions, such as cognitive-behavioral therapy, psycho-educational therapy, supportive-expressive therapy, nutritional guidance, hygiene, stimulus control, and sleep restriction [64]. Besides the non-pharmacologic treatment approaches, the NCCN advises the use of psychostimulants, such as methylphenidate and modafinil, after excluding other causes of fatigue like pain, anxiety, depression, anemia, sleep alteration, nutritional factors, and other comorbidities [64].

Non-pharmacologic treatment approaches include music therapy, yoga, and polarity therapy [27, 31, 32, 35]. During and after RT, patients are recommended to take 150 min of "moderate-intensity exercise" per week (e.g., walking 30 min 5 days per week). Most of these exercises involve range of motion/flexibility, muscle strength, aerobic training, and mind/body fitness [65]. A randomized controlled trial about yoga's impact on inflammation, mood, and fatigue in BC survivors showed that immediate posttreatment fatigue was lower in patients who practiced yoga 3 months after completing treatment. Vitality was also higher in the yoga group, even directly after treatment [66]. With regards to yoga, the NCCN advises being cautious in cases of bone metastasis, thrombocytopenia, anemia, fever, active infection, and secondary limitations due to metastasis or other diseases [64]. A large meta-analysis, including 738 BC patients, reported that exercise during RT was significantly more effective in reducing RIF than a control intervention (e.g., management of pain or nausea) [1]. Statistically significant benefits of supervised, combined aerobic resistance exercise regarding fatigue were shown.

Physical Medicine and Rehabilitation

In cancer pre- and rehabilitation, exercise is a very suitable means to reduce fatigue and improve the overall quality of life and participation [67–71]. Improvement of muscular strength, endurance capacity, sensorimotor functions, and flexibility seems to be of high clinical relevance concerning the overall quality of life, general health, survival, and return to work [67–71]. There are recent international recommendations for exercise in cancer patients, which serve as a guide for the fitness and health care professionals working with cancer survivors [71]. Cancer survivors can safely engage in exercise to restore physical functioning, enhance the quality of life, and mitigate CRF [71].

In some cases, cancer patients are not able to perform systematic and regular exercise due to different painful musculoskeletal conditions, such as plantar fasciitis or calcaneal spur, calcifying tendinopathy of the shoulder, tennis elbow, or Achilles tendinopathy [67, 68, 72]. In most cases, such painful musculoskeletal conditions prohibit active participation in exercise programs and therefore have to be treated before starting vigorous exercise [67, 68, 72].

Physical Medicine and Rehabilitation (PM&R) is a specialty with competencies in diagnostics and therapy, as well as coordination of the multi-professional and interdisciplinary rehabilitation teams [67, 68]. It is needed in all phases of medical care, from the prevention of diseases to palliative medicine, with the model of the International Classification of Functioning, Disability and Health as a basis [67]. Cancer pre- and rehabilitation includes many treatment approaches from PM&R, which have been shown to reduce musculoskeletal pain. They are prescribed depending on the individual needs, abilities, and objectives of each patient [67, 68]. Mechanical therapy is a modality that includes exercise, physiotherapy, water and immersion therapy, occupational therapy, massages, and special massages like lymphatic massage, ultrasound, extracorporeal shock-wave treatment, and extension. Another modality is electrical therapy, including low-frequency, middle-frequency, and high-frequency therapy, such as transcutaneous electrical nerve stimulation, galvanic baths, and short-wave diathermy. Thermotherapy includes the application of heat or cold, while phototherapy includes ultraviolet light, so-called cooled red light, and infrared light. Balneology and climate therapy include baths, mud, and different climatic conditions, which have been shown to be effective in muscular relaxation, pain reduction, and improvement in the flexibility of structures [67–70].

Table 2. Available treatment options for fatigue in BC patients

Non-pharmacologic interventions	Pharmacologic interventions
Physical interventions PM&R: e.g., physical therapy, occupational therapy, moderate-intensity physical exercises, stretching programs, yoga	*Psychostimulants* e.g., methylphenidate, modaphenyl
Psychosocial interventions e.g., cognitive-behavioural therapy associated with hypnosis, psycho-educational therapy, supportive-expressive therapy, nutritional guidance, hygiene, stimulus control, sleep restriction	

Several years ago, malignant tumors, metastasis, multiple myeloma, and lymphoma were considered contraindications for treatment by using physical modalities [68, 72]. However, these historical paradigms have changed in the past [68, 72]. Today, physical modalities are only contraindicated at the tumor site but should be used in cancer patients for pain relief and mobilization only by qualified personnel. Especially, extracorporeal shock-wave treatment seems to be a very effective, safe, and time- and cost-efficient conservative modality for the treatment of musculoskeletal disorders in cancer patients [72]. After pain reduction by using physical modalities, exercise programs to improve muscular strength, endurance capacity, and improvement of the quality of life can be started in almost all cancer patients [67, 68]. A general summary of the available treatment options for cancer patients with fatigue is summarized in Table 2.

Conclusion

In BC patients who undergo adjuvant RT, RIF is underreported, underdiagnosed and undertreated. RIF may become a chronic state with subsequent non-compliance, which further compromises treatment efficacy. It is essential to evaluate patients for their potential risk and to adequately inform them about predisposing factors and treatment options to prevent and treat fatigue. Standardization of the evaluation and assessment tools need to be established to ensure the full reliability of study results. Adequate management should involve an early start after cancer diagnosis and before commencing cancer treatment using a multimodal, multidisciplinary approach to prevent high severity and chronification.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

L.K., C.D., and A.F. reviewed the literature; L.K., C.D., R.C., S.K., and A.F. prepared the manuscript; C.F.S. provided clinical and scientifical support; all authors approved the final version of the manuscript.

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