HHS Public Access

Author manuscript

Expert Rev Qual Life Cancer Care. Author manuscript; available in PMC 2018 April 10.

Published in final edited form as:

Expert Rev Qual Life Cancer Care. 2016 ; 1(4): 323–328. doi:10.1080/23809000.2016.1191948.

The Etiology and management of radiotherapy-induced fatigue

Chao-Pin Hsiao[a], **Barbara Daly**[a], and **Leorey N. Saligan**[b]

[a]Frances Payne Bolton School of Nursing, Case Western Reserve University, Cleveland, OH, USA

[b]Division of Intramural Research, National Institute of Nursing Research, National Institutes of Health, Bethesda, MD, USA

Abstract

Fatigue is one of the most common side-effects accompanying radiotherapy, but arguably the least understood. Radiotherapy-induced fatigue (RIF) is a clinical subtype of cancer treatment-related fatigue. It is described as a pervasive, subjective sense of tiredness persisting over time, interferes with activities of daily living, and is not relieved by adequate rest or sleep. RIF is one of the early side-effects and long-lasting for cancer patients treated with localized radiation. Although the underlying mechanisms of fatigue have been studied in several disease conditions, the etiology, mechanisms, and risk factors of RIF remain elusive, and this symptom remains poorly managed. The purpose of this paper is to review and discuss recent articles that defined, proposed biologic underpinnings and mechanisms to explain the pathobiology of RIF, as well as articles that proposed interventions to manage RIF. Understanding the mechanisms of RIF can describe promising pathways to identify at-risk individuals and identify potential therapeutic targets to alleviate and prevent RIF using a multimodal, multidisciplinary approach.

Keywords

Fatigue; radiotherapy-induced fatigue; cancer-related fatigue; cancer treatment-related fatigue; radiation therapy; Cancer

Introduction

Radiotherapy (RT) is one of the major treatment modalities for a wide range of malignant tumors [1]. Localized or total body RT is used as a primary, neo-adjuvant or adjuvant combination modality with surgery, chemotherapy, hormone therapy, or immunotherapy across different stages of cancer [2]. While external beam intensity modulated RT successfully increases disease-free survival rates and life expectancy, ionizing radiation leads to increased treatment-related adverse effects. RT-related side effects include fatigue, dermatologic effects, and site-specific issues such as gastrointestinal symptoms [3], which

CONTACT Chao-Pin Hsiao, cxh416@case.edu, Frances Payne Bolton School of Nursing, Case Western Reserve University, 2120 Cornell Road, Cleveland OH44106, USA.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript.

may influence the compliance and efficiency of cancer treatment, as well as decrease the health-related quality of life (HRQoL) of patients [4,5].

Ionized radiation destroys both cancer cells and normal tissues in the irradiated area, but also in surrounding organs [6]. With the improvement of techniques (e.g. three-dimensional conformal RT, intensity-modulated RT, image-guided RT), the delivery of RT have minimized the side effects by efficiently sparing the surrounding normal tissue [7]. Radiation-related toxicities are experienced by individuals in varying degrees, so it is difficult to predict how these toxicities are manifested clinically. Therefore, preventing these toxicities such as fatigue is imperative.

Aim and method of review

This review aimed to provide an overview of the etiology and management of radiotherapy-induced fatigue (RIF). Specifically, this paper reviews the definition, proposed pathobiology and management of RIF. The National Comprehensive Cancer Network (NCCN) has categorized RIF as a clinical subtype of cancer-related fatigue (CRF) [8]. A search through PubMed, MEDLINE, and CINAHL using key phrases/words: radiation-induced fatigue, radiation-associated fatigue, cancer treatment-related fatigue, CRF as well as radiation therapy and fatigue yield 72 articles that were included in this narrative review. More, exhaustive systematic reviews on CRF were previously conducted [5,9–13]; however, this review focused on articles published within at least 10 years that defined, proposed mechanisms and interventions for RIF.

RIF

Fatigue is one of the early and long-lasting side effects of localized RT [5,6]. RIF is one of the debilitating symptoms most often reported by cancer patients receiving RT, often negatively impacting their HRQoL [5,14,15]. As a subtype of cancer treatment-related fatigue, RIF is described as a pervasive, subjective sense of tiredness persisting over time, interferes with activities of daily living and is not relieved by rest or sleep [4,5,8]. RIF often leads to depression, impaired cognitive function, sleep disturbance, decreased physical activity, and decreased HRQoL [14,16,17]. The prevalence and severity of fatigue is slightly different in cancer patients receiving varying treatments [18]. RIF has been noted to increase slightly beginning at week 3 of treatment, then worsen significantly in severity by week 6 of RT, remaining elevated following the completion of treatment [14,19–21]. RIF is a distressing and highly prevalent symptom experienced by cancer patients during RT. Unfortunately, the etiology of RIF remains elusive. This may be related to the lack of a widely accepted RIF phenotype that can drive the RIF biomarker discovery forward. This gap may be related to the lack of consensus on the standardized measure of RIF that can define its phenotype.

Proposed mechanisms of RIF

Recent evidence suggests that RIF may be related to mitochondrial dysfunction [19,22]. Downregulation of mitochondrial markers involved in cell death that are responsible for maintaining mitochondrial membrane integrity and regulating apoptosis (e.g. *BCL2,*

AIFM2) may influence the worsening of fatigue symptoms during RT [19]. Further evidence also suggests that genes that are related to regulation of the production of reactive oxygen species (ROS) and release of cytochrome *c* may be involved in the worsening of fatigue symptoms during RT [22]. It is specifically proposed that RIF could be due to attenuated physiological and cellular energy caused by a reduction in the capacity of mitochondria to utilize oxygen and synthesize adenosine triphosphate (ATP) [23]. These self-preservation physiological processes, such as apoptosis and autophagy, are activated in response to RT and may play significant roles in the worsening of fatigue symptoms during RIF. Other experts believe that impairment in these physiological processes to counter the toxic effects of RT, as well as bystander tissue damage from RT, may lead to the persistence and chronicity of symptoms through an altered immune response [24].

Other factors have been proposed in the literature to cause RIF including genetic factors, anemia, pro-inflammatory cytokine production, hypothalamic–pituitary–adrenal axis dysfunction, and neuromuscular abnormality [25,26]. We will discuss three of these major mechanisms.

Inflammation and immune response

The individual's inflammatory response is a main mechanism that is proposed to contribute to the experience of RIF. An increased serum level of IL-6sR was significantly associated with fatigue symptoms in women with stage 0-IIA breast cancer receiving 40 Gy of RT for 15 sessions [27]. Increased serum concentrations of IL6 were significantly associated with fatigue symptoms in individuals with unresectable non-small-cell lung cancer receiving curative conventional external beam RT with concurrent chemotherapy [28]. RIF was significantly associated with serum sTNF-R1and IL-6 levels after controlling for numerous covariates in locally advanced colorectal and esophageal cancer receiving concurrent chemoradiation therapy [29]. Homozygous (AA) alleles of IL-6 were associated with higher levels of evening and morning fatigue symptoms among cancer patients before, during, and those actively receiving RT [30].

Microglial and glial cells in the central nervous system (CNS) also produce cytokines especially in response to stressful conditions caused by RT [31]. The inflammatory cytokines (e.g. IL-1, IL-6, TNF-α) from these cells are thought to communicate with CNS structures causing fatigue by altering neurotransmission in the CNS through the afferent vagus nerve root [32]. For example, the neurons of the preoptic nucleus that synthesize IL-1β have processes that have ramifications for other CNS structures, including the limbic system and the brainstem causing modulation of the neural response leading to significant fatigue [31].

We recently proposed the biological underpinnings of RIF, based on the biomarkers and biological pathways we observed from our investigations, which indicated that cancer and cancer treatment induce a cascade of biological changes causing RIF [33–37]. These biomarkers and biological pathways include alpha-synuclein [34], neurotrophic factors (*BDNF, GDNF*, and *SNAPIN*) [35], para-inflammatory bystander markers (the interferon alpha-inducible protein 27, *IFI27*) [36], and immunespecific response markers (e.g. *MS4A1*) [37], mitochondrial associated genes (*BCL2L1, FIS2, BCS1L*, and *SCL25A37*) as well as

RIF-associated biological pathways (glutathione biosynthesis, γ-glutamyl cycle, and antigen presentation pathways) [37].

Anemia and radiation-induced fatigue

The pathological process of radiation injury begins immediately after radiation exposure, but the clinical features may not present for weeks, months, or even years after treatment completion [2,6]. Fatigue induced by RT may be the body's response to a toxic insult [38]. Several studies have indicated that RIF is associated with anemia and functional iron deficiency [39–44]. Heme levels (red blood cells, hemoglobin, hematocrit) are found to be correlated with fatigue severity at completion of external beam radiation therapy (EBRT) suggesting that stabilizing heme levels may prevent worsening of fatigue symptoms during EBRT [41]. A longitudinal study observed that the most predictive biologic factor for RIF is red blood cell count, after controlling for covariates [41,43]. Anemia, caused by cancer or cancer treatment, leads to decrease oxygen delivery to tissue and eventually a negative energy balance [40], causing fatigue in cancer patients.

Mitochondria bioenergetics and radiation-induced fatigue

In addition to the evidence that inflammation, immune, and anemia-modulated processes contribute to RIF, it is likely that mitochondrial energetics also play a role in the pathobiology of RIF. There is evidence that an increase in ROS formation from RT will cause cellular damage resulting in dysfunction to the mitochondria [45]. ROS are considered one of the major direct causes of ionizing radiation-induced damage [46], resulting in a number of adverse effects (e.g. fatigue, nausea, vomiting, diarrhea, peripheral neuropathy, and cognitive function impairment) that reduce the efficacy of treatment [47]. It is known that radiation-induced damage alters mitochondrial metabolism, inhibits the mitochondrial respiratory chain, and forms highly reactive peroxynitrite (ONO_2^-) [48]. Once mitochondrial proteins are damaged, the affinity of substrates or enzymes is decreased resulting in mitochondrial dysfunction [45].

The mitochondrial respiratory chain is essential to produce and to maintain effective cell content of ATP [45,49]. Our previous study has shown that changes in mitochondrial-related gene expression (e.g. downregulation of *BCS1L* and upregulation of *SLC25A37*) in lymphocytes were associated with fatigue symptoms experienced by men with nonmetastatic prostate cancer during RT [19,22]. Decreased *BCS1L* protein has been shown to lead to decreased incorporation of the Rieske iron–sulfur protein into complex III and decreased activity of complex III [50]. A defect in complex III will impair ATP production through a decrease in oxidative phosphorylation [51,52]. Additionally, decreased complex III activity is associated with increased superoxide (O_2^-) production and dismutation to hydrogen peroxide (H_2O_2) [53,54]. Furthermore, upregulation of *SLC25A37* increases the mitochondrial inner membrane mitoferrin-1 protein [19,22]. Increased mitoferrin-1 protein leads to increased iron uptake into mitochondria and promotes heme synthesis [55], and this increased matrix-free iron potentially can increase hydroxyl radical formation from H_2O_2. A physiological model of RIF proposes that radiation causes genetic instability and cellular damage, triggers a defect in mitochondrial oxidative phosphorylation, causes ATP depletion and ROS production, thus results in debilitating fatigue [56]. The proposed physiological

mechanism of RIF is linked to ATP depletion and impairment of mitochondrial bioenergetics, triggered by radiation-induced genetic instability and cellular damage. These hypotheses-testing and translational researches will provide pharmacologic therapy and potential nutraceutical strategies related to molecular-genetic targets, for example, coenzyme Q and ascorbate to bypass the complex III or energy-enhanced diet to increase ATP level.

Current treatment of RIF

There is no optimal pharmacologic therapy for RIF. NCCN Practice Guidelines in Oncology currently recommend five non-pharmacological interventions to manage fatigue related to cancer and/or cancer therapy, which include activity enhancement, psychosocial improvement, attention-restoring therapy, nutrition, and sleep [57]. For pharmacologic interventions, the NCCN guidelines recommend that after ruling out other causes of fatigue, the use of psychostimulants should be considered. Methylphenidate has been recommended, but available literature reports conflicting results in methylphenidate's ability to improve fatigue in two small, randomized clinical trials [57,58]. Recent studies have shown that another psychostimulant, modafinil, does not significantly improve fatigue or HRQoL of glioma patients undergoing RT [59,60].

A broad range of non-pharmacological interventions to alleviate fatigue have been evaluated. These include psychosocial interventions (e.g. mindfulness-based stress reduction [61], cognitive-behavioral therapy [62], and relaxation [63]), complementary and alternative therapies (e.g. acupuncture [64], acupressure [65,66], Chinese medicine [67], energy conservation [68]), physical exercise interventions (e.g. aerobics, resistance, and home-based exercise [69–75], and nutraceutical supplements (e.g. lipid replacement therapy [76,77], molecular replacement therapy [47], and L-carnitine and coenzyme Q10 [78]). However, even if non-pharmacological interventions reduced RIF, the mechanism behind the effect of these interventions on CRF remains unclear and the effect sizes of these treatments on CRF are small.

Of all these interventions suggested to manage RIF, only aerobic exercise has been shown to consistently reduce RIF [79]. There is growing body of evidence that increasing physical activity during and following RT can reduce RIF [80]. The NCCN guidelines recommend a combination of endurance and resistance exercises to manage RIF [57]. Most of these exercises to manage RIF are at least twice weekly and involves range of motion/flexibility, muscle strength, aerobic training, and mind/body fitness [79]. Early non-randomized trials of nutraceutical supplements such as levocarnitine or vitamins offer an intriguing possible avenue [81]. Nevertheless, there remains a critical need to develop a better understanding of the biologic mechanisms of RIF to identify therapeutic targets to develop precise interventions.

Expert commentary

In order to understand the etiology of RIF, it is critical that we start by addressing the challenges that is limiting our biomarker discovery investigations. First, we need to come to a consensus for a case definition of RIF. Second, we need a standardized assessment tool and

scoring criteria to define the RIF phenotype [82]. These gaps are needed to be addressed before we can move the discovery of RIF biomarker forward. Once those challenges are addressed, translational investigations can provide opportunities to gain new insights into the etiology of RIF.

This is not a systematic review, but a narrative of updated findings of studies that used molecular–genetic approaches to propose the biologic underpinnings of RIF. We also reviewed evidence to proposed interventions to manage RIF. The key issues are listed chronologically, based on the definition, trajectory, proposed etiology, and management of RIF.

Five-year view

Recent efforts are directed at predicting individuals who are at risk to develop RT-related side effects [35,41,83]. One study proposed specific gene signatures to classify and identify individuals who are at risk to develop severe adverse effects from RT [43]. These efforts not only allow identification of at-risk individuals, but also provide relevant information to understand the biologic underpinnings of RT-related side effects and can identify potential markers to reduce these toxicities.

A multimodal, multidisciplinary approach may be necessary to manage RIF including physical exercise, psychosocial intervention, and medications to address the contributing factors of RIF (e.g. anemia, inflammation). Other interventional modalities, such as such as mind–body medicine intervention, the use of cognitive behavioral therapy [84], or complementary therapies such as relaxation [65] can provide the greatest possibility of success to treat and prevent the development and intensification of RIF. Capturing the interplay of peripheral and central domains of RIF is essential in understanding its etiology and optimizing its management.

Acknowledgments

This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

1. Zagar TM, Willett CG, Czito BG. Intensity-modulated radiation therapy for anal cancer: toxicity versus outcomes. Oncology (Williston Park). 2010; 24(9):815–23. 828. [PubMed: 20923035]
2. Khan HA, Alhomida AS. A review of the logistic role of L-carnitine in the management of radiation toxicity and radiotherapy side effects. J Appl Toxicol. 2011; 31(8):707–713. DOI: 10.1002/jat.1716 [PubMed: 21818761]
3. Damber J-E, Aus G. Prostate cancer. Lancet. 2008; 371(9625):1710–1721. DOI: 10.1016/S0140-6736(08)60729-1 [PubMed: 18486743]

4••. Berger AM, Mooney K, Alvarez-Perez A, et al. Cancer-related fatigue, version 2.2015. J Natl Compr Cancer Netw. 2015; 13(8):1012–1039. Concisely and updated review on cancer-related fatigue from clinical practice guidelines in oncology.

5. Bower JE. Cancer-related fatigue–mechanisms, risk factors, and treatments. Nat Rev Clin Oncol. 2014; 11(10):597–609. DOI: 10.1038/nrclinonc.2014.127 [PubMed: 25113839]

6. Stone HB, Coleman CN, Anscher MS, et al. Effects of radiation on normal tissue: consequences and mechanisms. Lancet Oncol. 2003; 4(9):529–536. [PubMed: 12965273]

7. Bucci MK, Bevan A, Roach M 3rd, et al. Advances in radiation therapy: conventional to 3D, to IMRT, to 4D, and beyond. CA Cancer J Clin. 2005; 55(2):117–134. [PubMed: 15761080]

8. Piper BF, Cella D. Cancer-related fatigue: definitions and clinical subtypes. J Natl Compr Canc Netw. 2010; 8(8):958–966. [PubMed: 20870639]

9. Barsevick A, Frost M, Zwinderman A, et al. I'm so tired: biological and genetic mechanisms of cancer-related fatigue. Qual Life Res. 2010; 19(10):1419–1427. DOI: 10.1007/s11136-010-9757-7 [PubMed: 20953908]

10. Weis J. Cancer-related fatigue: prevalence, assessment and treatment strategies. Expert Rev Pharmacoecon Outcomes Res. 2011; 11(4):441–446. DOI: 10.1586/erp.11.44 [PubMed: 21831025]

11. Oh HS, Seo WS. Systematic review and meta-analysis of the correlates of cancer-related fatigue. Worldviews Evid Based Nurs. 2011; 8(4):191–201. DOI: 10.1111/j.1741-6787.2011.00214.x [PubMed: 21342434]

12. Campos MP, Hassan BJ, Riechelmann R, et al. Cancer-related fatigue: a practical review. Ann Oncol. 2011; 22(6):1273–1279. DOI: 10.1093/annonc/mdq458 [PubMed: 21325448]

13. Mitchell SA. Cancer-related fatigue: state of the science. PM&R. 2010; 2(5):364–383. DOI: 10.1016/j.pmrj.2010.03.024 [PubMed: 20656618]

14. Holliday EB, Dieckmann NF, McDonald TL, et al. Relationship between fatigue, sleep quality and inflammatory cytokines during external beam radiation therapy for prostate cancer: a prospective study. Radiother Oncol. 2016; 118(1):105–111. DOI: 10.1016/j.radonc.2015.12.015 [PubMed: 26743832]

15. Hickok JT, Morrow GR, Roscoe JA, et al. Occurrence, severity, and longitudinal course of twelve common symptoms in 1129 consecutive patients during radiotherapy for cancer. J Pain Symptom Manage. 2005; 30(5):433–442. DOI: 10.1016/j.jpainsymman.2005.04.012 [PubMed: 16310617]

16. Berger AM, Mitchell SA. Modifying cancer-related fatigue by optimizing sleep quality. J Natl Compr Canc Netw. 2008; 6(1):3–13. [PubMed: 18267055]

17. Pinto BM, Dunsiger S, Waldemore M. Physical activity and psychosocial benefits among breast cancer patients. Psycho-Oncol. 2013; 22(10):2193–2199.

18. Langston B, Armes J, Levy A, et al. The prevalence and severity of fatigue in men with prostate cancer: a systematic review of the literature. Supportive Care in Cancer. 2013; 21(6):1761–1771. [PubMed: 23455492]

19. Hsiao C-P, Wang D, Kaushal A, et al. Mitochondria-related gene expression changes are associated with fatigue in patients with nonmetastatic prostate cancer receiving external beam radiation therapy. Cancer Nurs. 2013; 36(3):189–197. DOI: 10.1097/NCC.0b013e318263f514 [PubMed: 23047795]

20. Danjoux C, Gardner S, Fitch M. Prospective evaluation of fatigue during a course of curative radiotherapy for localised prostate cancer. Support Care Cancer. 2007; 15(10):1169–1176. DOI: 10.1007/s00520-007-0229-8 [PubMed: 17333296]

21. Dhruva AMD, Dodd M, Paul SM, et al. Trajectories of fatigue in patients with breast cancer before, during, and after radiation therapy. Cancer Nursing May/June. 2010; 33(3):201–212. DOI: 10.1097/NCC.0b013e3181c75f2a

22. Hsiao C-P, Wang D, Kaushal A, et al. Differential expression of genes related to mitochondrial biogenesis and bioenergetics in fatigued prostate cancer men receiving external beam radiation therapy. J Pain Symptom Manage. 2014; 48(6):1080–1090. DOI: 10.1016/j.jpainsymman.2014.03.010 [PubMed: 24786901]

23. Eghbal MA, Pennefather PS, O'Brien PJ. H2S cytotoxicity mechanism involves reactive oxygen species formation and mitochondrial depolarisation. Toxicology. 2004; 203(1–3):69–76. DOI: 10.1016/j.tox.2004.05.020 [PubMed: 15363583]
24. Schaue D, McBride WH. T lymphocytes and normal tissue responses to radiation. Front Oncol. 2012; 2:119.doi: 10.3389/fonc.2012.00119 [PubMed: 23050243]
25. Bower JE, Ganz PA, Tao ML, et al. Inflammatory biomarkers and fatigue during radiation therapy for breast and prostate cancer. Clin Cancer Res. 2009; 15(17):5534–5540. DOI: 10.1158/1078-0432.CCR-08-2584 [PubMed: 19706826]
26. Ryan JL, Carroll JK, Ryan EP, et al. Mechanisms of cancer-related fatigue. Oncologist. 2007; 12(Suppl 1):22–34. (suppl_1). DOI: 10.1634/theoncologist.12-S1-22
27. Courtier N, Gambling T, Enright S, et al. Psychological and immunological characteristics of fatigued women undergoing radiotherapy for early-stage breast cancer. Support Care Cancer. 2013; 21(1):173–181. DOI: 10.1007/s00520-012-1508-6 [PubMed: 22644262]
28. Wang XS, Shi Q, Williams LA, et al. Inflammatory cytokines are associated with the development of symptom burden in patients with NSCLC undergoing concurrent chemoradiation therapy. Brain Behav Immun. 2010; 24(6):968–974. DOI: 10.1016/j.bbi.2010.03.009 [PubMed: 20353817]
29. Wang XS, Williams LA, Krishnan S, et al. Serum sTNF-R1, IL-6, and the development of fatigue in patients with gastrointestinal cancer undergoing chemoradiation therapy. Brain Behav Immun. 2012; 26(5):699–705. DOI: 10.1016/j.bbi.2011.12.007 [PubMed: 22251605]
30. Miaskowski C, Dodd M, Lee K, et al. Preliminary evidence of an association between a functional interleukin-6 polymorphism and fatigue and sleep disturbance in oncology patients and their family caregivers. J Pain Symptom Manage. 2010; 40(4):531–544. DOI: 10.1016/j.jpainsymman.2009.12.006 [PubMed: 20570482]
31. Watkins LR, Maier SF, Goehler LE. Cytokine-to-brain communication: a review & analysis of alternative mechanisms. Life Sci. 1995; 57(11):1011–1026. [PubMed: 7658909]
32. Dantzer R, Bluthé RM, Layé S, et al. Cytokines and sickness behavior. Ann N Y Acad Sci. 1998; 840:586–590. [PubMed: 9629285]
33•. Saligan LN, Olson K, Filler K, et al. The biology of cancer-related fatigue: a review of the literature. Support Care Cancer. 2015; 23(8):2461–2478. Comprehensive review on biological underpinnings of cancer-related fatigue. DOI: 10.1007/s00520-015-2763-0 [PubMed: 25975676]
34. Saligan LN, Hsiao CP, Wang D, et al. Upregulation of alpha-synuclein during localized radiation therapy signals the association of cancer-related fatigue with the activation of inflammatory and neuroprotective pathways. Brain Behav Immun. 2013; 27(1):63–70. DOI: 10.1016/j.bbi.2012.09.009 [PubMed: 23022913]
35. Saligan LN, Lukkahatai N, Holder G, et al. Lower brain-derived neurotrophic factor levels associated with worsening fatigue in prostate cancer patients during repeated stress from radiation therapy. World J Biol Psychiatry. 2015; :1–7. DOI: 10.3109/15622975.2015.1012227
36. Hsiao C-P, Araneta M, Wang XM, et al. The association of IFI27 expression and fatigue intensification during localized radiation therapy: implication of a para-inflammatory bystander response. Int J Mol Sci. 2013; 14(8):16943–16957. DOI: 10.3390/ijms140816943 [PubMed: 23959120]
37. Hsiao C-P, Reddy SY, Chen M-K, et al. Genomic profile of fatigued men receiving localized radiation therapy. Biol Res Nurs. 2016; 18(3):281–289. DOI: 10.1177/1099800415618786 [PubMed: 26620220]
38. Pettet AG, Flinton DM. Radiotherapy related fatigue: strategies and knowledge of the UK radiographer and nurse. Radiography. 2002; 8:149–158. DOI: 10.1053/radi.2002.0371
39. Grellier, N., Deray, G., Yousfi, A., et al. Bull Cancer. Vol. 102. French: 2015. [Functional iron deficiency, inflammation and fatigue after radiotherapy]; p. 780-785.
40. Mock V, Olsen M. Current management of fatigue and anemia in patients with cancer. Semin Oncol Nurs. 2003; 19(4 Suppl 2):36–41. [PubMed: 14702919]
41. Feng L, Chen M-K, Lukkahatai N, et al. Clinical predictors of fatigue in men with non-metastatic prostate cancer receiving external beam radiation therapy. Clin J Oncol Nurs. 2015; 19(6):744–750. DOI: 10.1188/15.CJON.744-750 [PubMed: 26583638]

42. Hoskin PJ, Robinson M, Slevin N, et al. Effect of epoetin alfa on survival and cancer treatment–related anemia and fatigue in patients receiving radical radiotherapy with curative intent for head and neck cancer. J Clin Oncol. 2009; 27(34):5751–5756. DOI: 10.1200/JCO.2009.22.3693 [PubMed: 19884550]
43. Wratten C, Kilmurray J, Nash S, et al. Fatigue during breast radiotherapy and its relationship to biological factors. Int J Radiat Oncol Biol Phys. 2004; 59(1):160–167. DOI: 10.1016/j.ijrobp.2003.10.008 [PubMed: 15093912]
44. Lind M, Vernon C, Cruickshank D, et al. The level of haemoglobin in anaemic cancer patients correlates positively with quality of life. Br J Cancer. 2002; 86(8):1243–1249. DOI: 10.1038/sj.bjc.6600247 [PubMed: 11953880]
45. Pieczenik SR, Neustadt J. Mitochondrial dysfunction and molecular pathways of disease. Exp Mol Pathol. 2007; 83(1):84–92. DOI: 10.1016/j.yexmp.2006.09.008 [PubMed: 17239370]
46. Zhao W, Robbins ME. Inflammation and chronic oxidative stress in radiation-induced late normal tissue injury: therapeutic implications. Curr Med Chem. 2009; 16(2):130–143. [PubMed: 19149566]
47. Nicolson GL, Conklin KA. Reversing mitochondrial dysfunction, fatigue and the adverse effects of chemotherapy of metastatic disease by molecular replacement therapy. Clin Exp Metastasis. 2008; 25(2):161–169. DOI: 10.1007/s10585-007-9129-z [PubMed: 18058028]
48. Zabbarova I, Kanai A. Targeted delivery of radioprotective agents to mitochondria. Mol Interv. 2008; 8(6):294–302. DOI: 10.1124/mi.8.6.7 [PubMed: 19144902]
49. Mandelker L. Introduction to oxidative stress and mitochondrial dysfunction. Vet Clin North Am Small Anim Pract. 2008; 38(1):1–30. DOI: 10.1016/j.cvsm.2007.10.005 [PubMed: 18249243]
50. Borisov VB, Liebl U, Rappaport F, et al. Interactions between heme d and heme b595 in quinol oxidase bd from Escherichia coli: a photoselection study using femtosecond spectroscopy. Biochemistry. 2002; 41(5):1654–1662. [PubMed: 11814360]
51. Hinson JT, Fantin VR, Schönberger J, et al. Missense mutations in the BCS1L gene as a cause of the Björnstad syndrome. New England J Med. 2007; 356(8):809–819. DOI: 10.1056/NEJMoa055262 [PubMed: 17314340]
52. Lesnefsky EJ, Hoppel CL. Oxidative phosphorylation and aging. Ageing Res Rev. 2006; 5(4):402–433. DOI: 10.1016/j.arr.2006.04.001 [PubMed: 16831573]
53. Kotarsky H, Keller M, Davoudi M, et al. Metabolite profiles reveal energy failure and impaired beta-oxidation in liver of mice with complex III deficiency due to a BCS1L mutation. PLoS One. 2012; 7(7):e41156.doi: 10.1371/journal.pone.0041156 [PubMed: 22829922]
54. Morán M, Marín-Buera L, Gil-Borlado MC, et al. Cellular pathophysiological consequences of BCS1L mutations in mitochondrial complex III enzyme deficiency. Hum Mutat. 2010; 31(8):930–941. DOI: 10.1002/humu.21294 [PubMed: 20518024]
55. Lill R, Diekert K, Kaut A, et al. The essential role of mitochondria in the biogenesis of cellular iron-sulfur proteins. Biol Chem. 1999; 380(10):1157–1166. [PubMed: 10595578]
56. Hsiao CP, Daly B, Hoppel C. Association between mitochondrial bioenergetics and radiation-related fatigue: a possible mechanism and novel target iMedPub journals. Arch Cancer Res. 2015; 3(4):1–9.
57••. National Comprehensive Cancer Network. Cancer-related fatigue. Natl Compr Cancer Netw Pract Guidel Oncol. 2016; 1:1–56. Current and comprehensive guideline for Cancer-related fatigue including radiotherapy-induced fatigue.
58. Bruera E, Valero V, Driver L, et al. Patient-controlled methylphenidate for cancer fatigue: a double-blind, randomized, placebo-controlled trial. J Clin Oncol. 2006; 24(13):2073–2078. DOI: 10.1200/JCO.2005.02.8506 [PubMed: 16648508]
59. Page BR, Shaw EG, Lu L, et al. Phase II double-blind placebo-controlled randomized study of armodafinil for brain radiation-induced fatigue. Neuro Oncol. 2015; 17(10):1393–1401. DOI: 10.1093/neuonc/nov084 [PubMed: 25972454]
60. Lee EQ, Muzikansky A, Drappatz J, et al. A randomized, placebo-controlled pilot trial of armodafinil for fatigue in patients with gliomas undergoing radiotherapy. Neuro Oncol. 2016; 18(6):849–854. DOI: 10.1093/neuonc/now007 [PubMed: 26902850]

61. Rahmani S, Talepasand S. The effect of group mindfulness - based stress reduction program and conscious yoga on the fatigue severity and global and specific life quality in women with breast cancer. Med J Islam Repub Iran. 2015; 29:175–175. [PubMed: 26034728]
62. Armes J, Chalder T, Addington-Hall J, et al. A randomized controlled trial to evaluate the effectiveness of a brief, behaviorally oriented intervention for cancer-related fatigue. Cancer. 2007; 110(6):1385–1395. DOI: 10.1002/cncr.22923 [PubMed: 17661342]
63. Potthoff K, Schmidt ME, Wiskemann J, et al. Randomized controlled trial to evaluate the effects of progressive resistance training compared to progressive muscle relaxation in breast cancer patients undergoing adjuvant radiotherapy: the BEST study. BMC Cancer. 2013; 13(1):162.doi: 10.1186/1471-2407-13-162 [PubMed: 23537231]
64. Bardy J, Finnegan-John J, Molassiotis A, et al. Providing acupuncture in a breast cancer and fatigue trial: the therapists' experience. Complement Ther Clin Pract. 2015; 21(4):217–222. DOI: 10.1016/j.ctcp.2015.08.003 [PubMed: 26573446]
65. Zick SM, Alrawi S, Merel G, et al. Relaxation acupressure reduces persistent cancer-related fatigue. Evid Based Complement Alternat Med. 2011; doi: 10.1155/2011/142913
66. Zick SM, Wyatt G, Murphy S, et al. Acupressure for persistent cancer-related fatigue in breast cancer survivors (AcuCrft): a study protocol for a randomized controlled trial. BMC Complement Altern Med. 2012; 12:132.doi: 10.1186/1472-6882-12-132 [PubMed: 22909076]
67. Yang L, Li TT, Chu Y-T, et al. Traditional Chinese medical comprehensive therapy for cancer-related fatigue. Chin J Integr Med. 2015; 22(1):67–72. DOI: 10.1007/s11655-015-2105-6 [PubMed: 26108523]
68. Barsevick AM, Dudley W, Beck S, et al. A randomized clinical trial of energy conservation for patients with cancer-related fatigue. Cancer. 2004; 100(6):1302–1310. DOI: 10.1002/cncr.20111 [PubMed: 15022300]
69. Schmidt ME, Meynköhn A, Habermann N, et al. Resistance exercise and inflammation in breast cancer patients undergoing adjuvant radiation therapy: mediation analysis from a randomized, controlled intervention trial. Int J Radiat Oncol Biol Phys. 2016; 94(2):329–337. DOI: 10.1016/j.ijrobp.2015.10.058 [PubMed: 26853341]
70. Al-Majid S, Wilson LD, Rakovski C, et al. Effects of exercise on biobehavioral outcomes of fatigue during cancer treatment: results of a feasibility study. Biol Res Nurs. 2015; 17(1):40–48. DOI: 10.1177/1099800414523489 [PubMed: 25504949]
71. Rogers LQ, Anton PM, Fogleman A, et al. Pilot, randomized trial of resistance exercise during radiation therapy for head and neck cancer. Head Neck. 2013; 35(8):1178–1188. DOI: 10.1002/hed.23118 [PubMed: 22847995]
72. Rogers LQ, Fogleman A, Trammell R, et al. Effects of a physical activity behavior change intervention on inflammation and related health outcomes in breast cancer survivors: pilot randomized trial. Integr Cancer Ther. 2013; 12(4):323–335. DOI: 10.1177/1534735412449687 [PubMed: 22831916]
73. Capozzi LC, McNeely ML, Lau HY, et al. Patient-reported outcomes, body composition, and nutrition status in patients with head and neck cancer: results from an exploratory randomized controlled exercise trial. Cancer. 2016; doi: 10.1002/cncr.v122.8
74. Grabenbauer A, Grabenbauer AJ, Lengenfelder R, et al. Feasibility of a 12-month-exercise intervention during and after radiation and chemotherapy in cancer patients: impact on quality of life, peak oxygen consumption, and body composition. Radiat Oncol. 2016; 11(1):42.doi: 10.1186/s13014-016-0619-5 [PubMed: 26984513]
75. Reis D, Walsh ME, Young-McCaughan S, et al. Effects of Nia exercise in women receiving radiation therapy for breast cancer. Oncol Nurs Forum. 2013; 40(5):E374–E381. DOI: 10.1188/13.ONF.E374-E381 [PubMed: 23989030]
76. Nicolson GL, Ash ME. Lipid replacement therapy: a natural medicine approach to replacing damaged lipids in cellular membranes and organelles and restoring function. Biochim Biophys Acta. 2014; 1838(6):1657–1679. DOI: 10.1016/j.bbamem.2013.11.010 [PubMed: 24269541]
77. Nicolson GL. Lipid replacement therapy: a nutraceutical approach for reducing cancer-associated fatigue and the adverse effects of cancer therapy while restoring mitochondrial function. Cancer Metastasis Rev. 2010; 29(3):543–552. DOI: 10.1007/s10555-010-9245-0 [PubMed: 20717704]

78. Iwase S, Kawaguchi T, Yotsumoto D, et al. Efficacy and safety of an amino acid jelly containing coenzyme Q10 and L-carnitine in controlling fatigue in breast cancer patients receiving chemotherapy: a multi-institutional, randomized, exploratory trial (JORTC-CAM01). Support Care Cancer. 2016; 24(2):637–646. DOI: 10.1007/s00520-015-2824-4 [PubMed: 26105516]

79. Stubbe CE, Valero M. Complementary strategies for the management of radiation therapy side effects. J Adv Pract Oncol. 2013; 4(4):219–231. [PubMed: 25032003]

80. Mustian KM, Morrow GR, Carroll JK, et al. Integrative nonpharmacologic behavioral interventions for the management of cancer-related fatigue. Oncologist. 2007; 12(Suppl 1):52–67. DOI: 10.1634/theoncologist.12-S1-52 [PubMed: 17573456]

81. Graziano F, Bisonni R, Catalano V, et al. Potential role of levocarnitine supplementation for the treatment of chemotherapy-induced fatigue in non-anaemic cancer patients. Br J Cancer. 2002; 86(12):1854–1857. DOI: 10.1038/sj.bjc.6600413 [PubMed: 12085175]

82. Filler K, Saligan LN. Defining cancer-related fatigue for biomarker discovery. Supportive Care in Cancer. 2015; 24(1):5–7. DOI: 10.1007/s00520-015-2965-5 [PubMed: 26438143]

83. O'Gorman C, Sasiadek W, Denieffe S, et al. Predicting radiotherapy-related Clinical toxicities in cancer: a literature review. Clin J Oncol Nurs. 2014; 18(3):E37–44. [PubMed: 24867122]

84. Appling SE, Scarvalone S, MacDonald R, et al. Fatigue in breast cancer survivors: the impact of a mind-body medicine intervention. Oncol Nurs Forum. 2012; 39(3):278–286. DOI: 10.1188/12.ONF.278-286 [PubMed: 22543386]

Key issues

- Fatigue is one of the debilitating symptoms most often reported by cancer patients receiving radiation therapy.
- RIF is a pervasive, subjective sense of tiredness persisting over time, interferes with activities of daily living, and is not relieved by rest or sleep.
- RIF increase significantly in severity during the course of radiation therapy, remaining elevated following the completion of treatment.
- The interactions of several mechanisms have been proposed to influence the individual's RIF experience, including genetic factors, energy expenditure, metabolism, aerobic capacity, and the patients' immune response to inflammation.
- No optimal pharmacologic therapy for RIF; however, the NCCN guidelines recommend that after ruling out other causes of fatigue, the use of psychostimulants should be considered.
- A multimodal, multidisciplinary approach may be necessary to manage and further prevent RIF, including physical exercise, psychosocial intervention, and medications to address the contributing factors of RIF.