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Review

Opportunities for rehabilitation of patients with radiation fibrosis syndrome

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ABSTRACT

This review discusses the pathophysiology, evaluation, and treatment of neuromuscular, musculoskeletal, and functional disorders that can result as late effects of radiation treatment.

Although radiation therapy is often an effective method of killing cancer cells, it can also damage nearby blood vessels that nourish the skin, ligaments, tendons, muscles, nerves, bones and lungs. This can result in a progressive condition called radiation fibrosis syndrome (RFS). It is generally a late complication of radiotherapy which may manifest clinically years after treatment. Radiation-induced damage can include "myelo-radiculo-plexo-neuromyopathy," causing muscle weakness and dysfunction and contributing to neuromuscular injury.

RFS is a serious and lifelong disorder which, nevertheless, may often be decremented when identified and rehabilitated early enough. This medical treatment should be a complex procedure consisting of education, physical therapy, occupational therapy, orthotics as well as medications.

1. Background

The status of cancer patient results not only from the direct and indirect effects of the disease but also from treatments such as surgery, radiotherapy, and chemotherapy.[1,2] These treatments may result in musculoskeletal and neuromuscular complications as well as dysfunction of any visceral organ, including the heart, lungs, gastrointestinal tract, and genitourinary tract.[1,3] Radiation-induced toxicity may be a result of acute radiation or a long-term disability following cancer treatment during radiation fibrosis syndrome (RFS).[4,5] RFS can affect any tissue type, including the skin, ligament, tendon, muscles, viscera, nerve, as well as lungs, the gastrointestinal and genitourinary tracts, bone, or other organs, depending upon the treatment site.[6–8] It is generally a late complication of radiotherapy which may not manifest clinically for years after treatment.[9] RFS may cause both functional

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and cosmetic impairment, which can lead to death or a significant deterioration in the quality of life (QoL).

2. Aim

The objective of the study was to review articles about physiopathology, and clinical evaluation of opportunities for rehabilitation in RFS patients.

3. The physiopathology of RFS

RFS is similar to inflammation, wound healing, and fibrosis of any origin. Typical histologic features include the presence of inflammatory infiltrates, particularly macrophages in the earlier stages of fibrosis, differentiation of fibroblasts into postmitotic fibrocytes, and changes in the vascular connective tissue with excessive production and deposition of extracellular matrix proteins and collagen. Among the secreted factors driving fibrosis, is the transforming growth factor beta 1 (TGF-β1) produced by a wide range of inflammatory, mesenchymal and epithelial cells which converts fibroblasts and other cell types into matrix-producing myofibroblasts. After myofibroblast activation, collagen production can be perpetuated independently of TGF-β1 by autocrine induction of a cytokine called connective tissue growth factor.[10] Although TGF-β1 is certainly a key cytokine, the fibrotic process cannot be explained by a single factor. TGF-β1 regulates epidermal growth factor (EGF), fibroblast growth factor (FGF), tumor necrosis factor (TNF α), and IL-1 by stimulating or inhibiting their production in various cell types, including fibroblasts, endothelial cells, and smooth muscle cells.[11] It involves a complex network of interacting cytokines and growth factors, which include radiation fibrosis IL-1, insulin-like growth factor-1 (IGF-1), and TNF α. Three histopathological phases of radiation fibrosis have been described,[10] including: (1) a prefibrotic phase characterized by chronic inflammation in which endothelial cells are thought to play an important role; (2) an organized fibrosis phase with patchy areas of active fibrosis containing a high density of myofibroblasts in an unorganized matrix adjacent to poorly cellularized fibrotic areas of senescent fibrocytes in a dense sclerotic matrix; and (3) a late fibroatrophic phase, characterized by retractile fibrosis and gradual loss of parenchymal cells. The mechanisms linking radiation to chronic vascular dysfunction and subsequent tissue sclerosis, fibrosis, and atrophy are complex and not completely understood. In one theory, Hauer-Jensen et al.[12] postulates that the predominant mechanism by which radiation causes tissue injury in tumors and normal tissues is the induction of apoptosis via free radical-mediated DNA damage. In normal tissues, radiation toxicity occurs in response to a sequence of overlapping events that are attributable to direct radiation-induced changes in cell function as well as indirect responses to tissue injury, causing activation of the coagulation system, inflammation, epithelial regeneration, and tissue remodeling, which is precipitated by molecular signals including cytokines, chemokines, and growth factors. Injury to the vascular endothelium probably plays a role in the response of most normal tissues to ionizing radiation. The abnormal accumulation of fibrin in the intravascular, perivascular, and extravascular compartments may be responsible for the progressive tissue fibrosis and sclerosis that characterizes RFS.[13]

The possible factors that may determine a patient's risk of developing clinical manifestations of RFS include age, medical and degenerative disorders, cancer status, particularly degenerative spine disease, exposure to neurotoxic, cardiotoxic, and other chemotherapy types.[5,14] Another factor in the development of radiogenic lung fibrosis is concomitant tamoxifen therapy as well as location, size of field, and type of radiation.[5,15]

4. Radiation and RFS

Factors associated with a greater risk of RFS include combining other treatment modalities with radiotherapy (i.e. surgery and/or chemotherapy, endocrine therapy), large-volume radiotherapy plans, high total radiotherapy dose, unusually high dose per fraction regimens, coincident infection or operative complications (e.g. wound drainage, and extensive hematoma), and inhomogeneity of dose delivery. The effects of radiation are cumulative, and patients radiated more than once at the same location for recurrent disease can be expected to develop worse radiation fibrosis. Patients given higher than normal doses of radiation are more likely to develop complications. Although subcutaneous radiation fibrosis is probably the most common manifestation of radiation injury, the exact depth in the skin most responsible for the fibrotic process is unclear. Bentzen et al.[16] proposed a range of 3.3–5.5 mm as acceptable reference point for subcutaneous fibrosis in the breast, with the best estimate at the depth of 4.1 mm. They also suggested that the best estimate for the alpha/beta ratio is 1.8 for the fibrosis endpoint. The reason why this may be important is that contemporary 3-dimensional radiotherapy planning systems do not model this dose satisfactorily because it exists in the steep dose gradient build up zone. For subcutaneous fibrosis in the neck tissues, Hirota et al.[16] specified the skin-absorbed dose at the depth of 4.1 mm (*d*4.1-mm depth) in the field center according to the recommendations of Bentzen et al.[16] They found that the *d*4.1-mm depth was affected by the number of fields used and the application of certain techniques such as electron boosts compared with photons. They showed a time dependence in the onset of radiation fibrosis and that patients undergoing prior surgery (neck dissection) have a higher incidence of subcutaneous fibrosis than those without surgery, confirming that the effects of multimodality treatment in addition to the accuracy of dose calculation must be taken into account in estimating late tissue effects. The influence of other factors including total dose as the biologically equivalent dose (BED) at *d*4.1-mm depth, fractionation, and systemic agents are also evident.[17] Dose sculpting techniques include intensity-modulated radiotherapy (IMRT) and image-guided radiotherapy[18] which allows a non uniform coverage of the radiation field to minimize exposure to normal tissues while maximizing the dose to the tumor by shaping the beam to closely approximate its shape in 3 dimensions. The radiation can be controlled to such a degree