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Cancer Related Fibrosis: Prevention or Treatment? A Descriptive Review

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Abstract

Cancer and its therapies including surgeries, radiation therapy, and chemotherapy, have a significant influence on the body of the patient. Tissue fibrosis is one of the most significant adverse effects noticed in cancer patients. Fibrosis caused by any tissue damage or various intracellular mechanisms can result in physical and functional impairments such as trismus, neuro-musculoskeletal dysfunction syndromes, fibrosis, speech and swallowing dysfunctions, upper limb and lower limb impairments, and sexual dysfunctions, all of which have a negative impact on patients' quality of life. Using manual therapy and therapeutic modalities, speech and swallowing therapy, and vocational rehabilitation are some of the important approaches to treating post-cancer treatment problems. As a result, when to begin rehabilitation to enhance and maintain functional and physical performance becomes critical.

Keywords: Cancer; Cancer related fibrosis; Physical therapy; Rehabilitation; Pathophysiology; Quality of life

Introduction

Cancer, as defined by the National Cancer Institute, is the uncontrollable proliferation of normal cells in the body with the potential to spread to other regions of the body. According to GLOBOCAN 2020 statistics, cancer is the largest cause of death and disability, as well as a barrier to life expectancy globally. An anticipated 19.3 million new cases and 10 million cancer deaths worldwide, with Asia accounting for 49.3 percent of cases and a mortality rate of 58.3 percent is a great cause of concern since the deaths are due to secondary morbidities. Cancers of the breast (female), lung, prostate, non melanoma of the skin, and Gastrointestinal (GI) cancer top the list in terms of new cases [1]. According to the expected incidence of cancer data in India for 2020, a total of 1,392,179 cases have been documented, with GI cancer being the most common, followed by malignancies of the oral cavity and throat [2].

Tissue fibrosis in cancer patients can result in significant morbidity and death globally, that may be caused by the disease or its therapies. Tissue damage and fibrosis are caused by different medical procedures such as radiotherapy, chemotherapy, and surgery. Not only do tumor cells interact with the surrounding cells, stromal cells and extracellular matrix, immune cells, and soluble signaling molecules in order to survive and thrive, but they also interact and form a microenvironment for the tumor. With increased mechanical stress, fibrosis can raise the risk of malignancy, which commonly manifests as substantial extracellular matrix buildup. Fibrosis can manifest as inflammation, excessive extracellular matrix deposition, linearization, and cross-linking [3,4]. The present review has attempted to describe the pathophysiology of cancer-related fibrosis due to cancer treatments and physical therapy.

Pathophysiology

Fibrosis is characterized by the accumulation of excess connective tissue, which results in stromal hardness and scar formation as well as poor epithelial healing. The extracellular matrix is remodeled via fibroblast deposition and matrix metalloproteinase secretion. Fibroblasts are the cells that are primarily responsible for fibrosis in both normal and pathologic environments. Fibrocytes, the progenitors of fibroblasts, and myeloid-derived suppressor cells, which promote tumor-associated fibrosis, are repressed in cancer. Other cells, such as mesenchymal stem cells, which aid in wound healing, and stellate cells, which influence immune responses to decrease inflammation and aid in tissue repair via differentiation, play a significant part in cancer related fibrosis. Because cancer produces persistent inflammation and damage, it can result in fibrosis as

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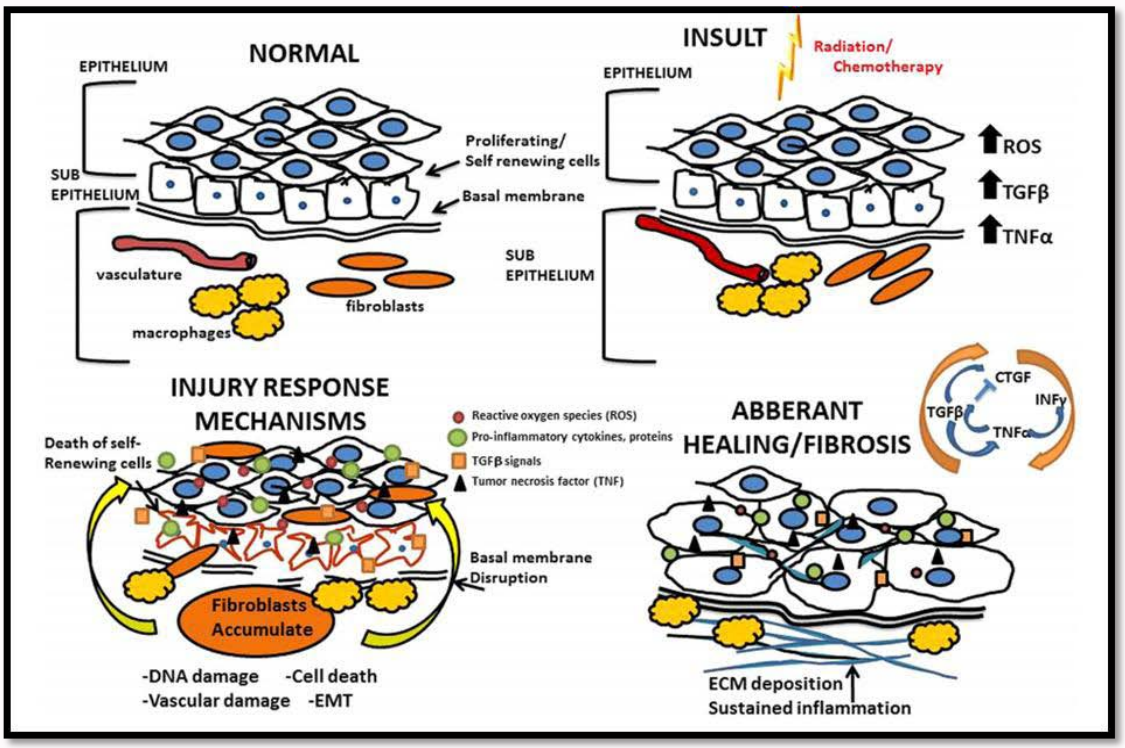

Figure 1: Tissue response to injury resulting in fibrosis [64].

part of the tissue remodeling and healing process. Instead of a typical, healthy reformed tissue, the tissue undergoes a continual fibrotic transformation. Cancer-associated fibrosis is said to be caused by this non-healing pattern of damage (Figure 1) [5-10].

Cancer treatment options including surgeries, radiation therapy, chemotherapy, immunotherapy and other innovative targeted medicines are also said to have a role in inducing cancer-related fibrosis leading to tissue damage as a reaction to repair by either one of two mechanisms: Radiolytic hydrolysis or activation of the innate immune response [11,12].

Radiation Therapy and its Role in Cancer-Related Fibrosis

During radiotherapy, the treated area is subjected to ionizing radiation causing free radicals to be released, resulting in biological consequences such as DNA damage. The release of free radicals promotes the development of fibrotic diseases such as idiopathic pulmonary fibrosis, liver fibrosis, and kidney fibrosis by increasing oxidative stress, which is the imbalance between the production of Reactive Oxygen Species (ROS) and the cell's ability to elicit an effective antioxidant response [12,13]. For example, individuals with head and neck cancer who undergo Radiation Therapy (RT) may experience side effects from the treatment harming the healthy tissue. This can result in secretion thickening, increased infection risk, discomfort and sensory abnormalities, tissue fibrosis, and salivary gland dysfunction. Oral mucositis is an acute reaction to RT that appears in the first 2 to 3 weeks and escalates to ulceration and pseudo-membranes as the RT continue. This is connected to the radiation dosage distribution, and non-keratinized oral tissue causing dermatitis [14]. Oropharyngeal candidiasis is notably prevalent in individuals with head and neck cancer that may spread to the esophagus, causing mucosal discomfort, taste changes, and dysphagia. There may be no burning sensitivity or pain, and leading to a coating feeling in their mouth, odynophagia, dysgeusia, and the odor of yeast infection [15]. Such alterations can result in fibrosis of the mucosal membrane in the oral cavity, known as oral submucosal fibrosis. As the disease and/or therapy develop, this might result in leukoplakia, scarring, and trismus. It is postulated that the Transforming Growth Factor (TGF) signal transduction pathway, which attribute significantly to collagen synthesis and inhibits collagen degradation by inducing the activity of Tissue Inhibitor of Matrix Metalloproteinase gene (TIMPs), causes over-synthesis of collagen by increased levels of Connective Tissue Growth Factor (CTGF). This is said to result in the development of fibrosis [16-19]. Post-treatment complications for patients with lung cancer, breast cancer, and lymphomas include radiation pneumonitis, pulmonary fibrosis, emphysema, respiratory difficulties, cardiac fibrosis, scar tissue development, and persistent arm lymphedema as a result of radiation therapy, chemotherapy, or surgery [20]. Radiation to the thorax puts the lungs and heart at more danger. More than 50 Grays (Gy) of RT has the potential to cause lung tissue damage, resulting in pneumonitis or fibrosis. 10% to 20% of irradiated patients get moderate to severe radiation induced pneumonitis, which is thought to be caused by alveolar destruction triggering an inflammatory reaction in the lungs' interstitial space. Because of the increased vascular permeability, this creates edema. Within 12 weeks of radiotherapy, 1% to 16% of patients get symptomatic with shortness of breath. Radiation with a higher dosage per fraction of 2.5 Gy to 2.75 Gy may result in this type of symptomatic pneumonitis. Pneumonitis is said to cause pulmonary fibrosis later in life. When paired with chemotherapy, radiation may have a combined severe adverse effect. The lung anomaly appears four to eight months after breast radiation treatment [20-22].

Significant morphological vaginal alterations with increasing dosage are seen to occur in cervical cancer survivors. Mucosal atrophy

Figure 2: Demonstration of measurement of Incisional mouth opening pre (a) and post (b) physiotherapy treatment and (c) Demonstration of myofascial release technique for trismus.

was seen in 91 percent of the survivors, as was pelvic fibrosis in 97 percent. High-density collagen was found in the connective tissue of individuals who had received external radiation [23]. Similarly, 10% to 30% of the gynecological cancer survivors have shown radiation-induced symptoms such as urgency syndrome, leakage syndrome, excessive gas discharge, excessive mucus discharge, and blood discharge [24]. The underlying mechanism is considered to be prolonged enhanced TGF signaling, which also causes latent fibrosis, and larger dosage per fraction may account for these higher rates [25]. TGFβ combined with tumor necrosis factor-α cause inflammatory injury which leads to increase in immune response and proliferation of fibroblasts at the site, leading additional tissue damage and fibrosis [26]. Tissue fibrosis, a degenerative condition defined by enhanced mesenchymal cell proliferation into the interstitial space resulting in organ failure, promotes cancer growth and metastasis. The unregulated wound healing process, as well as the inflammatory response and tissue remodeling, are thought to be fibrosis initiating factors. Genes that promote disease progression, such as CDKN2A, TP53, and SMAD4, are also implicated in tissue fibrosis because they contribute to the formation of the tumor microenvironment [27-29]. Stromal cells, fibroblasts and immune cells have a function in the tumor microenvironment. Fibroblast growth factor is secreted by stromal cells, which promotes cell proliferation and fibrosis. Cancer cachexia is a typical side effect of therapy, and the disease itself has a significant influence on the skeletal muscles. As a result of muscle regeneration, skeletal muscle injury can result in collagen and calcium depositions. Excessive calcium deposition may cause additional skeletal tissue injury [30-33]. The ADMA17/Notch signaling pathway, which are transmembrane receptors that govern fibroblast proliferation, is influenced by oxidative stress, resulting in dysregulation and profibrotic and inflammatory disorders [34].

Chemotherapy and its Role in Cancer-Related Fibrosis

Chemotherapy is ineffective in differentiating healthy cells from malignant cells. This can cause tissue toxicity and tissue damage, resulting in fatigue, cognitive impairment, and gastrointestinal symptoms such as cachexia and chemotherapy-induced diarrhea [35]. Fibrosis is another typical adverse effect of cancer therapy, which usually comes in three stages. Cytokines are produced during the inflammatory phase, which attracts fibroblasts and other immune cells to the site of damage. This results in a proliferative phase in which fibronectin matrix is generated together with deposits of collagen type III, establishing a new barrier. The remodeling phase is characterized by the accumulation of extracellular matrix from local fibroblasts over a period of many weeks [36]. As a result, when the wound healing mechanism is interrupted, re-epithelialization is impeded, resulting in continual extracellular matrix enlargement and fibrosis [37,38]. TGFβ levels are considerably higher in individuals receiving chemotherapy after bone marrow transplant. Chemotherapeutic drugs like bleomycin, doxorubicin, cyclophosphamide and other platinum-based drugs are known to be associated with chemotherapy related fibrosis [39]. An animal study has found abnormalities in the left ventricular function and myocardial fibrosis after inducing doxorubicin indicating its role in promoting collagen formation and cardiac fibroblasts via the neurokinin-1 receptor, resulting in cardiac muscle fibrosis independent of cardiomyocyte damage [40,41].

Surgery and its Role in Cancer-Related Fibrosis

Aspects such as age over 50, intraoperative high oxygen concentration, and surgical stress can all contribute to rapid respiratory impairment following surgery. Patients taking treatment for tumors such as lymphomas and soft tissue sarcoma are observed to develop left ventricular dysfunction and heart failure. There is an increase in collagen deposition as well as a considerable rise in cardiomyocyte apoptosis. Idiopathic pulmonary fibrosis, an abrupt respiratory impairment after anti-cancer treatment linked with interstitial pneumonia, affects 4% to 7.5% of lung cancer patients [42,43]. According to a 2010 research, interstitial pulmonary fibrosis is seen in 16% of individuals who have had surgery. Chemotherapy and other adjuvant treatments raise the risk of developing idiopathic fibrosis [44].

Role of Physical Therapy Rehabilitation

Cancer rehabilitation research has accelerated in the last decade, and treatment sequela such as trismus, neuro-musculoskeletal dysfunction syndromes, fibrosis, speech and swallowing dysfunctions, upper limb and lower limb impairments, and sexual dysfunctions are of concern because they impact patients' quality of life. As a

result, rehabilitation is necessary to enhance and preserve functional and physical abilities. Manual therapy and therapeutic modalities, speech and swallowing therapy and vocational rehabilitation are all approaches to treating post-cancer treatment problems.

Common consequences in head and neck cancers include trismus and shoulder dysfunction caused by spinal accessory nerve paralysis and radiation-induced fibrosis. Neck muscle fibrosis, trismus, neuropathy, physical deconditioning, myofascial restriction, frozen shoulder, and postural dysfunction must all be treated [45,46]. Radiation-induced trismus is widespread in clinical settings, but no standard approach has been established due to a lack of research. Active range of motion exercises, manual stretching, and contract-relax antagonist-contract approaches have been demonstrated to improve incisional mouth opening in the short and long term [47]. Therapeutic massage is also said to increase blood flow and relax the masticatory muscles, as well as exercises to break down myofascial adhesions and fibrosis, as well as jaw-mobilizing devices, can result in significant improvement in patients with radiation-induced trismus, particularly in the first 6 weeks (Figures 2a-2c) [48-50]. Temporomandibular joint mobilization and myofascial release to the neck muscles have demonstrated to be beneficial [51]. For oral sub mucous fibrosis, techniques such as therapeutic ultrasound in conjunction with topical *Aloe-vera* and turmeric gel administration and in combination with both are used. According to the literature, such therapies have no negative effects and have demonstrated benefits in mouth opening, tongue motions, mucosal flexibility, and changed oral sensation [52]. Myofascial release, a manual therapy technique, has shown to enhance head and neck posture and have an influence on postural alignments [53]. For axillary web syndrome which is commonly seen in breast cancer patients, moderate level of circular mobilization of the chest wall musculature including longitudinal tissue stretch of the cords is seen to help patients achieve an additional 10% to 15% of abduction range of motion, thoracic mobility, and decreased shoulder girdle pain and stiffness [54]. Fibrosis of the vocal cords and discomfort can also cause speech and swallowing problems, as well as physical dysfunction, with up to 75% of cancer patients experiencing dysphagia after therapy [55]. Radiation-induced adverse effects have been improved by myofascial release, physiotherapy exercises, external low-level laser and speech and swallowing therapy [56].

Post-treatment fibrosis is also noted in gynecological cancer patients. Dyspareunia is common which might have a psychosexual influence on the patient. Such individuals may exhibit sexual difficulty, body image concerns, pain, anxiety, sadness, and a variety of other medical and psychological symptoms. A physiotherapeutic strategy involving pelvic floor muscle exercises, biofeedback, manual therapy, home exercises, and counseling has been found to reduce sexual discomfort as well as physical and psychological symptoms in gynecological cancer survivors [57,58]. Urinary incontinence is present in more than 80% of endometrial cancer patients with no past bouts of incontinence due to weak pelvic floor muscles caused by surgery and radiation [59,60]. As a result, pre-rehabilitation is practical and crucial, and has demonstrated to avoid incontinence and preserve strength even one month after radiation. A 30-min intervention of eight maximal voluntary low contractions of six seconds with ten seconds rest, followed by eight one-second maximal voluntary contractions followed by relaxation, and voluntary precontraction of the pelvic floor muscles to increase intra-abdominal pressure before activities is highly recommended [61].

In gastrointestinal cancers, patients may undergo extensive surgeries which may result in aforementioned post-treatment complications. There is evidence to suggest that such complications may be managed through pre-operative physical therapy. In a multicenter trial, patients scheduled for major open abdominal surgery received a physical therapy intervention consisting of an information booklet, a 30-min physiotherapy education session, and a breathing exercise training session, as well as post-operatively early ambulation with no additional respiratory physiotherapy, all of who were followed for a year that concluded preoperative education and training to be beneficial to patients [62]. Another analysis recommended pre-operative exercise treatment for gastrointestinal cancer patients, using treatments such as walking and aerobic training, as well as resistance training from pre-rehabilitation to 8 weeks post-operative period. Nutritional counseling and relaxation techniques are also key components of recovery. Such therapies have been demonstrated to improve patients' quality of life, functional ability, and physical well-being [63].

Conclusion

Cancer and its therapies can have a detrimental impact on the body of the sufferer. As a result of the numerous physical and functional limitations, this might result in a lower quality of life. Pre- and post-rehabilitation can thus aid in the prevention, management, and treatment of these adverse effects. An early intervention in form of physical therapy has shown to prove beneficial to most of the patients. However, delay in the referrals or ignorance by the patient or patient party may increase secondary comorbidities leading to impairment, disability and decreased quality of life. As said, “Better Late than Never” physiotherapy either pre, early, or post- cancer treatment shall always prove beneficial to this vulnerable population.

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