

# The role of exercise and physical activity in osteosarcoma for patients and survivors

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## Abstract

Exercise has been found to improve function, mitigate disability, enhance the anticancer immune system response, and improve quality of life for patients with osteosarcoma and its survivors. Of late, exercise has additionally been implemented as an adjuvant to standard therapies. These products of exercise, along with the benefits of physical activity in pre- and postoperative rehabilitation, were summarized in the recently published book chapter *Exercise and Physical Activity in Patients with Osteosarcoma and Survivors*. This commentary is intended to share its findings, provide new information since its publication, give an example of how this work is being programmatically implemented, and provide an update to exercise guidelines for patients undergoing cancer treatment and cancer survivors.

**Keywords:** Exercise, Physical activity, Osteosarcoma, Bone sarcoma, Cancer treatment, Survivors

## Introduction

Exercise has been found to be not only feasible in patients with cancer but potentially tumor-reducing. The study of the benefits of exercise in the treatment of cancer and hindrance of tumor growth can be traced as far back as 1938 in animal models and later in human clinical trials starting in the 1980s [1]. Studies demonstrating benefits to quality of life and the immune system followed, and exercise as an adjuvant to cancer therapy began to gain acceptance. Patients undertake exercise regimens as part of their cancer therapy as a necessary means of rehabilitation but have also found them overall doable, satisfying, and a way to build endurance and fitness while improving their mental and social well-being. In *Exercise and Physical Activity in Patients with Osteosarcoma and Survivors* [2], the feasibility, benefits, and barriers to exercise and physical activity in patients and survivors of osteosarcoma are described (Table 1). This work will briefly share and comment on these findings, provide new information since its publication, give an example of how this work is being programmatically implemented, and provide an update to exercise guidelines for patients undergoing cancer treatment and cancer survivors.

## Exercise and Physical Activity

The words exercise and physical activity appear frequently throughout the chapter. Outside of the clinical setting these words are often used interchangeably; however, clinically and throughout the book chapter, they are used to define two different forms of movement. Physical activity requires energy and is movement performed by skeletal muscles. Exercise too requires energy, is movement carried out by skeletal muscle, and additionally, it is meant to define structured, repetitive, and intentional movement to improve or maintain physical fitness [3]. Physical activity contributes to health, well-being, and function, but exercise additionally improves fitness of body systems including but not limited to cardiorespiratory, immune, and musculoskeletal [3,4]. Both exercise and physical activity have been linked to decreasing risk of certain cancers [4].

## Exercise and Physical Activity During the Treatment of Osteosarcoma

Importantly, before exercise regimens can be prescribed to improve patient physical activity, quality of life, or as treatment, it must first be established that it is both feasible and safe. Exercise feasibility and safety for patients with osteosarcoma undergoing active treatment have been demonstrated by

qualitative measures, such as patient ability to complete assigned exercise and improvement in fatigue and strength without adverse effects, as well as patient compliance and overall satisfaction [5,6]. Physical activity levels of cancer patients is lower than that of non-cancer patients. Some of this can be attributed to tumor burden hindering activity and fitness. Patient physical activity levels improve as time following tumor resection or surgery increases during active therapy [7]. Even so, for physical gains to be maintained, patients should continue with their exercise programs beyond cancer therapy [8].

To further promote feasibility and compliance, exercise should not be limited to traditional aerobic activity, e.g. brisk walking and upper extremity ergometry or weight-based strength training. Benefits on function, endurance, and quality of life can also be gained from gentle yoga, qigong, or tai chi [9-11] at home or in community-based settings [7,12-15]. Additionally, the importance of a multidisciplinary team is highlighted for a successful incorporation of exercise into the treatment regimen of osteosarcoma patients [16-20]. Without full support of a patient's medical and psychosocial teams, this economical and physically and emotionally rewarding adjuvant therapy may be easily neglected [21-23]. The positive effects exercise has on quality of life, including improved physical fitness and emotional health, are well-accepted.

Furthermore, exercise as a true adjuvant and treatment intervention in cancer therapy is gaining more support, which is likely to increase the commitment of care providers to supporting exercise for patients. One of the most convincing reasons to exercise during cancer therapy may be its impact on treatment efficacy. Newly emerging evidence suggests that physical activity or exercise improves chemotherapy full-dose completion rates [24], while preclinical studies demonstrate decreased tumor burden in exercised subjects [25-27], both effectively translating to improved efficacy. Exercise-induced modulation of the immune system may be one way that exercise could inhibit tumor progression. Exercise is known to change immune cells in both innate and adaptive immunity in healthy individuals which may thus hinder further tumorigenesis in patients with cancer [28]. Preclinical studies for example have demonstrated an improved innate immunity through altering macrophage, neutrophil, and NK cell infiltration in tumors of mice with solid tumors [29-32]. Pre-clinical and patient models have also shown an alteration of adaptive cell immunity in exercised mice and patients with an increase in dendritic cells and intra-tumoral T-cell composition [33,34].

### **Exercise and Physical Activity of Survivors of Osteosarcoma**

Nearly 70% of children and adolescent young adult patients diagnosed with osteosarcoma will survive into adulthood [35]. Regrettably, these survivors are 5 times more likely than their siblings to report severe and chronic conditions, including ischemic heart disease, obesity, dyslipidemia, hypertension, and depression with 95.5% of survivors suffering from a serious or disabling chronic health condition by age 45 [36]. These conditions have fortunately been shown to be improved by exercise in the general population [37-39] and could be mitigated in the lives of survivors with similar application. The greatest obstacle may in fact be initiating a change in lifestyle as reportedly nearly 30% of childhood osteosarcoma survivors are completely sedentary and an additional 30% perform

less than 150 minutes of moderate physical activity per week [40]. Understandably, in survivors who suffer from treatment- or cancer-related disability, engaging in routine exercise or vigorous physical activity can be daunting [41]. Thus, specific and individualized guidance will be essential for compliance, comfort, and self-empowerment to exercise regularly. While safety and efficacy of exercise have been shown in sarcoma survivors who have undergone amputation and developed subclinical cardiomyopathy due to anthracycline exposure [42], an exercise prescription tailored to an individual survivor's needs would be optimal. Tapered supervision is necessary until survivors gain comfort and resolve. Subsequent regular check-ins in person and/or virtually with a physical therapist or trainer experienced in exercise for survivors of cancer would allow for continued intensity adjustment and strength gains as well as ensure safety and accountability.

### **Chronic Health Conditions in Survivors of Osteosarcoma and the Role of Exercise**

To further elucidate the impact that treatment of bone sarcomas has on long term health, the St. Jude's Lifetime Cohort Study recently reported on the cumulative burden of chronic health conditions in adult survivors of childhood osteosarcoma and Ewing sarcoma [43]. They found that survivors demonstrated an increased prevalence for cardiomyopathy and hypertension compared to controls and were impaired in their physical abilities including the 6-minute walk test, walking efficiency, mobility, strength, and endurance [43]. Not previously reported, they also found a deficit in survivor executive function and attention [43]. This study is shared here as there is potential for early exercise intervention to ameliorate the risk or detriment of these co-morbidities in osteosarcoma survivors. Exercise in cancer survivors has been found to improve blood pressure and cardiovascular health [44], as well as improve muscle strength and balance [45]. Emotional improvement of anxiety, depression, or stress in exercising survivors compared to non-exercising controls has also been reported [46]. More recently, the effect of exercise in patients with cancer has shown positive effect on cognitive function and brain measures [47].

### **Exercise in Practice for Patients and Survivors of Osteosarcoma**

Not mentioned in *Exercise and Physical Activity in Patients with Osteosarcoma and Survivors* is the American College of Sports Medicine's (ACSM) Moving Through Cancer initiative and mission "to assure that all people living with cancer and beyond are assessed, advised, and referred to and engaged in appropriate exercise and rehabilitation programming as standard of care" [48]. The ACSM believes that "exercise is medicine" and have developed an exercise program registry designed to assist patients, families, and providers find hospital- and community-based exercise programs [48]. The ACSM's Exercise is Medicine website (<https://www.exerciseismedicine.org/>) also provides resources for patients, families, and providers regarding exercise prescriptions and updated cancer exercise guidelines [48]. Following the writing of the chapter in discussion, guidelines updating exercise recommendations for cancer patients and survivors were updated. These were published in *Medicine & Science in Sports & Exercise and CA: A Cancer Journal for Clinicians* [49-51]. Prior to these updated publications, the only organized exercise guidelines available were primarily for cancer survivors, not including active patients, from the ACSM,

Benefit	Study population
Improved function	Sarcoma patients [16]
Improved fitness, strength, balance, endurance	Sarcoma patients [54,55] Multiple diagnoses [21]
Improved post-operative rehabilitation	Sarcoma patients after limb salvage surgery [6,16]
Enhanced immune system	Pre-clinical mouse models of multiple tumor models [28-34]
Reduced tumor burden/improved chemotherapy efficacy	Pre-clinical mouse and rat models of multiple tumor models [25-27]
Improved chemotherapy completion rate due to reduced side effects	Multiple diagnoses (systematic review) [24]
Improved fatigue	Solid tumor patients undergoing chemotherapy [14,23] Multiple diagnoses (systematic review) [56]
Improved cognition and memory	Breast cancer survivors [57] Pediatric leukemia & brain tumor survivors [58,59] Multiple diagnoses, patients over 80 [60]
Improved quality of life	Multiple diagnoses during cancer treatment (Meta-analysis) [61]
Reduced risk of co-morbidities	Sarcoma survivors [62,63]

**Table 1.** Benefits of Exercise in Osteosarcoma Patients and Survivors.

published in 2010, and the American Cancer Society, published in 2012 [52,53] Both the ACSM and American Cancer Society recommended 150 minutes of exercise per week for cancer survivors, similar to recommendations for the general public [52,53]. The new guidelines reflect recent evidence that both cancer survivors and patients receiving active treatment can derive benefits from exercise, and with less time than previously endorsed [1]. Based on current literature, the new guidelines recommend an exercise program that includes moderate-intensity aerobic training at least 3 times per week for 30 minutes per session and the addition of resistance training at least 2 times per week [49].

## Conclusion

Exercise is indeed an important component of a multidisciplinary approach to cancer treatment and survivorship. Osteosarcoma patients will benefit in all aspects of health-physical function, cognitive, psychosocial-when adhering regularly to its prescription. With time, clinical studies may further support the use of exercise as treatment based on preclinical findings of improvement in immune or chemotherapeutic efficacy.

## Conflicts of Interest

Authors have no conflicts of interest to declare.

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Osteosarcoma is rarely diagnosed in patients younger than 5 years (about 1% of cases). [8]. In children aged 5-9 years, the annual incidence is 2.6 cases for African Americans and 2.1 cases for Caucasians per million population. Finally, the role of the emerging field of oncolytic viruses for the treatment of osteosarcoma is currently being explored (ClinicalTrials.gov, NCT00503295 and NCT00931931). Morbidity/mortality. The overall 5-year survival rate for patients whose condition was diagnosed between 1974 and 1994 was 63% (59% for male patients, 70% for female patients). Complications. The following complications have been reported: Pilot study of vascular health in survivors of osteosarcoma. *Pediatr Blood Cancer*. 2013 Oct. Exercise has the potential to positively affect patients with osteosarcoma by improvement of function, mitigation of disability, and maintenance of independence and quality of life. Exercise may also directly impact cancer treatment efficacy. This chapter examines the feasibility and use of exercise or physical activity as therapy in the treatment of osteosarcoma and its survivors. This chapter will also discuss barriers to exercise and physical activity for patients with osteosarcoma and its survivors, emphasizing the need for a comprehensive and cohesive support system to promote its incorporation into patient treatment plans and ensure compliance. Keywords. Exercise: The miracle cure and the role of the doctor in promoting it. Two men sadly became widowers in the same week. Both were in their late 60s, and were retired. Physical activity improves cardiorespiratory health.<sup>21</sup> Furthermore, in COPD, exercise training reduces dyspnoea symptoms and increases ability for exertion.<sup>16</sup> Heart disease and/ or Heart failure and/or Angina. All studies show clear improvements in cardiovascular health with moderate exercise.<sup>30</sup> There are similar beneficial effects for sufferers of angina.<sup>27</sup> Overall, exercise reduces cardiac mortality by 31%.<sup>16</sup> For cancer survivors, physical activity is a means to not only promote health but also to ameliorate side effects (e.g., fatigue, pain) and promote cognitive functioning, sleep, and blood count recovery. Patients with cancer often ask their oncology nurses about physical activity during and after cancer treatment. Should they rest or be physically active? The purpose of this chapter is to introduce the concept of physical activity and review the roles of healthcare and fitness professionals who promote physical activity. Different ways to open the discussion with cancer survivors about the value of physical activity are also pre- 1. Applying existing resources for principles of physical activity and exercise science to oncology nursing practice.