Chapter 5
Exercise Oncology from Diagnosis to Treatment: An Overview of Outcomes and Considerations

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Introduction

Advances in cancer therapies have been instrumental in improving survival rates in a variety of cancer types and stages. Unfortunately, it is well established that individuals who are exposed to different cancer therapies experience wide-ranging acute and persistent toxicities [1, 2]. Musculoskeletal impairments, cardiovascular dysfunction and body composition alterations are among the commonly reported side effects of various cancer treatments that are compounded by aging and inactivity [3–7]. These physiological impairments put individuals at a heightened risk of treatment-related toxicities, reduced physical function, cardiovascular disease, metabolic syndrome and cancer-related and all-cause mortality [8–12]. Although recent advances in screening, detection and treatments have resulted in an increase in the 5-year survival rate in a variety of cancers, the result is an increased proportion of individuals burdened by the physical and psychosocial consequences of treatment [13]. Fortunately, there is mounting evidence, built over the last three decades, indicating that exercise can protect against many of these treatment-related toxicities. The early work by Winnigham et al. in the 1980s [14–16] and Dimeo in the 1990s [17–19] and the influential first randomized controlled trials published in the *Journal of Clinical Oncology* in 2001 and 2003 by Segal [20, 21] and Courneya [22], which led to an accompanying editorial from the journal [23], provided a critical platform for the area we now know as *exercise oncology* to expand substantially.

In this chapter, we [1] provide a brief overview of common cancer treatments and adverse effects, [2] describe examples from early studies undertaken during treatment leading to the development of the PEACE framework, [3] present examples of contemporary trials in exercise oncology including those from pretreatment to

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during treatment phases, [4] discuss different study endpoints and outcomes from trials and how these have evolved and progressed over the past four decades and finally [5] provide considerations and future opportunities in this well-established and yet continuing area of research growth in exercise oncology.

Common Treatment and Adverse Effects

The magnitude of impairments in physiological systems or psychosocial wellbeing will vary based on the cancer site, treatment dose, duration, sequence or combination [24, 25]. An overview of common impairments from various cancer treatments is provided in Table 5.1. Surgery to remove the tumour and/or surrounding tissue is associated with local impairments in form and function of the tissue or organ. The extent of limitations experienced from surgery will vary based on the location and type of tumour. It's possible that surrounding tissues/organs may be affected. For example, removal of soft tissue sarcoma may involve the removal of surrounding muscle tissue, resulting in impairments in function [26, 27]. Lymphedema, defined as a protein-rich swelling of the body, particularly in the extremities, is another concern especially in breast cancer [28].

Radiotherapy is used to damage genetic material of DNA, limiting the ability of cancer cells to divide and proliferate. Radiotherapy typically damages the tissue that is being irradiated, though surrounding organs and tissue may be affected as well. Fibrosis to cardiac or lung tissue can have long-term effects on cardiopulmonary function [29, 30].

Whilst surgery and radiation are typically used to treat cancer locally, chemotherapy acts systemically, working throughout the whole body to target and kill rapidly dividing cells. Due to the systemic nature of this treatment, it can impact healthy cells and has a variety of acute and persistent toxicities that vary according to the specific agent used, mechanism of action, dose and duration of administration. Nausea, fatigue, weakness and gastrointestinal distress are particularly evident during active therapy [31–34]. Importantly, chemotherapy is associated with many serious persistent side effects. Cognitive function and memory can be affected for many years following the cessation of treatment [35]. Cardiotoxicity is of chief concern, particularly in individuals receiving anthracycline chemotherapy [3, 9, 36, 37]. Chemotherapy-induced peripheral neuropathy (CIPN), resulting in numbness in the hands and feet along with balance impairments, is particularly evident with taxane-based chemotherapeutic agents, with evidence of symptoms of CIPN up to several years after treatment [38]. Weight changes are also common, though the direction and magnitude of change can differ based on the type of cancer, chemotherapeutic agent, administration of corticosteroids and concomitant therapy along with lifestyle factors [39, 40].

Hormone therapy is most commonly used in the treatment of breast and prostate cancer, using exogenous hormones or surgery to either block hormone receptors or interfere with hormone production. The magnitude of side effects experienced is

Table. 5.1 Overview of common impairments from various cancer treatments

	Fatigue	Pain	Cardiovascular dysfunction	Pulmonary changes	Peripheral neuropathy	Cognitive changes	Body composition changes	Bone Health	Immune system change	Lymphedema	Gastrointestinal Distress
Surgery	•	•		•		•	•			•	•
Radiotherapy	•	•	•	•		•	•		•	•	•
Chemotherapy	•	•	•	•	•	•	•	•	•		•
Hormonal therapy	•	•	•			•	•	•	•		•
Targeted therapies	•	•	•			•			•		•

Adapted from Schmitz et al. [112]

based on a variety of factors, including the type of therapy received, mechanism of action and treatment duration. Hormone therapy for breast cancer is associated with postmenopausal symptoms such as hot flashes, joint pain, fatigue, weight gain and dyslipidaemia [41, 42]. Androgen deprivation therapy for prostate cancer is consistently associated with a reduction in muscle mass and bone mineral density. This, coupled with a pronounced accumulation of body fat, dramatically increases the risk of further cardiometabolic damage and disease risk (i.e. obesity, hypertension, insulin resistance, dyslipidaemia) [43]. Additionally, it has been proposed that physiological and psychological impairments as a result of cancer treatment can accelerate functional decline and the trajectory towards a disability condition [1, 2].

Targeted therapies aim to stop the growth and spread of cancer by interfering with specific molecules, such as genes, proteins or the tissue environment contributing to cancer growth. Immunotherapy attempts to use elements of the immune system mostly to combat cancer. Due to the specific or "targeted" nature of these treatments, healthy cells are not as readily affected as other treatments, though most commonly reported side effects include dermatological, such as damages to the skin, hair and nails [44, 45]. Additionally, fatigue and muscle aches are also commonly reported side effects of targeted therapies and immunotherapy [46]. Clearly, the deleterious, often long-lasting effects of various cancer therapies identify a critical area of concern. Mounting evidence indicates that exercise may be useful in managing many of the side effects of common cancer therapies. The subsequent sections of this chapter will be focused on providing an overview of the extant literature on the role of exercise in the prevention and management of cancer treatment side effects from diagnosis through the end of treatment. A hypothetical trajectory of physiological systems affected by various cancer treatments with no exercise and various opportunities for exercise participation along the cancer continuum to mitigate cancer-related adverse effects and preserve/enhance physiological capacity is presented in Fig. 5.1.

From Early Studies to the PEACE Framework

In this section a brief perspective of the exercise oncology research is presented with the earliest research published in the mid-1980s. Cunningham et al. examined the effects of a resistance exercise in patients with acute leukaemia [47]. Participants were randomized to either 3 or 5 days per week of exercise or a non-exercising group for 5 weeks. Outcomes of interest were nitrogen balance, creatinine excretion, skinfold measures and arm circumference. There were no changes in anthropometric measures or nitrogen balance over the course of the intervention. However, the authors suggested that decreasing levels of creatinine excretion from pretest to posttest indicated a favourable response in both training groups. Winnigham et al. investigated a 10-week aerobic exercise program in breast cancer patients undergoing chemotherapy [15]. Participants were randomized to supervised aerobic exercise 3 days per week, a flexibility program 1 day per week or a non-exercising control.

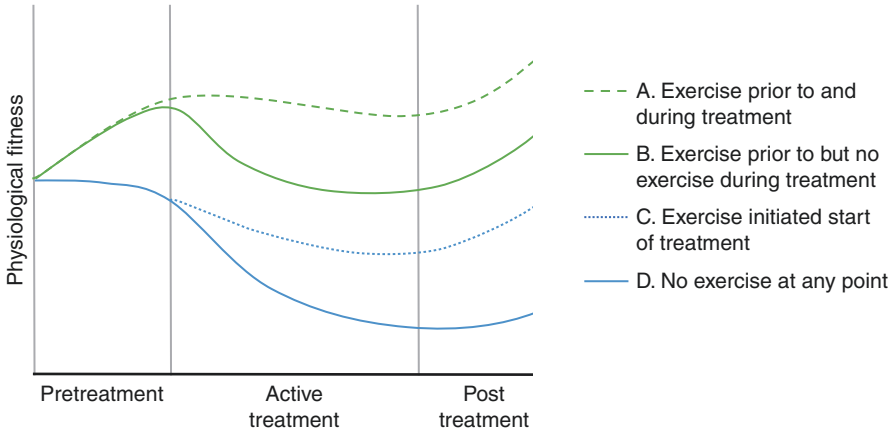

Fig. 5.1 Hypothetical trajectory of physiological systems in accordance with exercise participation along the cancer continuum. (**a**) Theoretical trajectory of physiological fitness of those who begin exercise at diagnosis and through treatment. It is hypothesized that prehabilitation and continued exercise during treatment would yield the most favourable results in buffering the side effects of treatment, providing the greatest likelihood of resuming normal activity and fitness levels after treatment. (**b**) Prehabilitation alone without exercise during treatment could result in some improvements in physiological fitness that would most likely be lost during treatment without activity, as documented by reports of the magnitude of treatment toxicities experienced by inactive individuals receiving treatment. (**c**) Individuals who do not participate in exercise prior to treatment but begin at the onset of treatment would likely experience a "buffering" effect of exercise, whereby reductions of physiological fitness are lessened or reversed compared to those who do not participate in exercise. (**d**) Those who are inactive throughout the entire treatment continuum are likely to experience the greatest reductions in physiological fitness, in addition to a blunted recovery of these systems following the cessation of treatment

The primary outcome of nausea was significantly improved in the exercise group compared to the flexibility and control groups. This early work was critical in highlighting the preliminary safety of participating in exercise during cancer treatment.

Dimeo et al. [18] followed this early work by expanding on the investigation of exercise during high-dose chemotherapy before autologous blood stem cell transplantation. The authors demonstrated that compared to non-exercising controls, hospital-based aerobic exercise was associated with attenuation of physical decline and a reduction in duration of thrombopenia and neutropenia and length of hospital stay [18]. An important landmark in the field of exercise oncology occurred with the publication of the results of a trial in the *Journal of Clinical Oncology* in 2001 by Segal et al. [20]. This trial investigated the effects of self-directed or supervised exercise in breast cancer patients receiving treatment (chemotherapy, hormonal therapy or radiotherapy) [20]. Results of the trial revealed that exercise was associated with improvements in physical function and a reduction in body weight. This publication in a prestigious cancer journal provided the field of exercise oncology with great exposure to the medical community and served to bolster the credibility of the line of research.

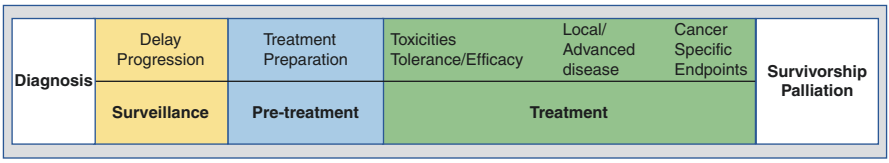

Fig. 5.2 Adapted PEACE framework to include surveillance, pretreatment and treatment

The first 10–15 years of research in the field of exercise oncology was critical in providing evidence contrary to the prevailing dogma that bedrest would be most beneficial for individuals receiving cancer treatment. The culmination of this work resulted in the PEACE framework, proposed by Courneya in 2001 [48]. This framework, which was modified in 2007 [49], has served as the reference point of exercise oncology research for almost two decades. The updated framework splits the cancer experience into six time points, two pre-diagnosis (prescreening and screening/diagnosis) and four post-diagnosis (pretreatment, treatment, survivorship and end of life). Accompanying the six time points are eight cancer control outcomes that are proposed to be responsive to physical activity interventions. These are prevention and detection during the pre-diagnosis phase and treatment preparation/coping, treatment effectiveness/coping, recovery/rehabilitation, disease prevention/health promotion, palliation and survival in the post-diagnosis phase. For the purpose of this chapter, we have adapted the PEACE framework (Fig. 5.2) to include [1] surveillance/pretreatment and [2] treatment phases with the latter divided into (I) treatment-related toxicities, (II) treatment tolerance/efficacy, (III) treatment in patients with advanced disease and (IV) cancer-specific endpoints.

Diagnosis

A diagnosis of cancer is often seen as a "teachable moment", where individuals may be more amenable to adopting healthy lifestyle behaviours [50]. Research has demonstrated that individuals with a diagnosis of cancer may be more receptive to information about the role of healthful lifestyle behaviours (i.e. dietary modifications, physical activity, smoking cessation, etc.) with the potential to increase the adoption and maintenance of these behaviours [51]. Broadly speaking, it is recognized that this is a key time to introduce interventions aimed at modifiable risk factors that may increase the likelihood of the successful adoption and maintenance of these behaviours. Importantly, this teachable moment and the discussions of lifestyle behaviours have to be balanced with the broader patient experience and the impact of receiving a cancer diagnosis, making important decisions on course of treatment, financial obligations and work/family commitments. Thus, on an individual level, the "art" of exercise oncology is making an informed decision on how and when to introduce the topic of lifestyle behaviours.

Surveillance and Pretreatment

Clinical interest of exercise has emerged for patients who are managed with surveillance due to low volume, stage and grade of some cancers [52]. For example, active surveillance for prostate cancer describes a management strategy that involves no active treatment with regular monitoring with an intention to proceed to treatment with a curative intent when evidence of a clinically relevant change from a low-risk cancer becomes evident [53]. Preliminary evidence suggests that lifestyle and/or exercise interventions might have therapeutic potential for men on active surveillance [52]. In an early study in which patients made lifestyle changes during 1 year involving use of stress management techniques, dietary changes and physical activity (walking for 30 min, 6 days per week), a significant reduction of 4% in serum prostate-specific antigen (PSA) levels was observed in the intervention, whilst a 6% increase occurred in the non-intervention group [54]. After a follow-up period of 2 years, 27% of patients in the non-intervention group and 5% of patients in the intervention group had undergone conventional treatments (radical prostatectomy, radiotherapy and/or ADT) with a curative intent [55]. A recent study examining feasibility, safety and acceptability of aerobic exercise in the setting of active surveillance in 50 men with prostate cancer over 12 months reported improvements in body mass, systolic and diastolic blood pressure and quality of life [56]. Current exercise studies and efforts to expand these important initial findings are examining the potential of long-term exercise interventions implemented during surveillance to delay cancer progression and transition to active therapies [57].

The treatment preparation phase centres around the premise of "prehabilitation" and aiming to minimize the burden and impairments experienced from cancer treatments. First-line treatment for cancer is usually surgery to resect the tumour and surrounding tissue. Resultantly, impairments in the form and function of tissues and organs are a primary concern. Further, low muscle mass at diagnosis is consistently associated with greater treatment-related toxicities and overall mortality in a variety of cancers. Consistent evidence indicates that individuals diagnosed with cancer reduce levels of physical activity from pre- to post-diagnosis [58, 59]. This reduction in activity and subsequent "detraining" is likely to contribute to treatment-related toxicities, worsening of body composition and poorer prognosis. This highlights the urgent need to investigate interventions that can result in positive physiological adaptations in the pretreatment period that will potentially allow for greater treatment tolerance, reducing the magnitude of impairments resulting from therapy.

Interestingly, though the clinical utility of prehabilitative training is well supported, this remains one of the most difficult phases to study for a variety of issues. Primarily, the pretreatment period has varying durations, some lasting days or weeks, others lasting months. This makes the design and practical implementation of exercise interventions challenging. Additionally, the time surrounding a diagnosis brings a host of changes for patients, including psychological stress, financial burden and time management issues, all of which can affect an individual's proclivity to participate in an exercise program during this period. Consequently, this

remains an understudied area of research in exercise oncology. In an early single-arm pilot study, Jones et al. [60] reported that pre-surgical exercise training improved exercise capacity in lung cancer survivors undergoing pulmonary resection.

Licker et al. [61] examined the effects of high-intensity interval training (HIIT) prior to lung cancer surgery. Individuals with operable lung cancer were randomized to an HIIT group or no exercise control. The exercise group underwent ~25 days of HIIT (two 10-minute series of 15-second sprint intervals (at 80–100% peak work rate) separated by 15-second pauses and a 4-minute rest between the two series) prior to surgery. The primary outcome measure was a composite of death and in-hospital post-surgery complications. The 6-minute walk test, peak heart rate and peak oxygen consumption were also obtained. The results indicated that whilst exercise resulted in significant improvements in aerobic performance, there were no differences in early complications following surgery [61].

A review by Singh et al. [62] examined pre-surgical interventions and their effects on clinically relevant outcomes in cancer patients. The review included a mix of studies in lung, prostate and colorectal cancer patients. Overall, the results supported pre-surgical exercise through aerobic and resistance training, either on their own or in combination, to be beneficial in improving aerobic fitness, QOL and physical function. Importantly, the majority of studies included in the review were in lung cancer patients before a lung resection, so the evidence of the efficacy of prehabilitation is somewhat limited to this population. Additionally, very few studies included a control group or have carried out interventions to detect differences in outcomes between exercise interventions performed prior to, during or after treatment.

A recent study addressing some of the limitations reported above was conducted by Santa Mina et al. [63] where 87 prostate cancer patients were randomized to either receive a home-based exercise prehabilitation plus pelvic floor training or control condition of pelvic floor training alone prior to undergoing radical prostatectomy. Results indicated improved functional capacity and reduced preoperative and 6-month post-operative anxiety. Although not a primary study endpoint, post-operative complications as well as hospital length of stay was similar between groups at follow-up assessments.

Clearly, more research is required to expand on current findings in this phase of pretreatment. However, this is one of the most challenging areas of exercise oncology research as patients are typically trying to process and cope with a cancer diagnosis and get their affairs in order as they prepare for treatment. This, coupled with a relatively short time period between diagnosis and treatment, makes this a difficult window to recruit participants to conduct research.

During Treatment: Prevention/Reduction of Treatment-Related Toxicities

The investigation of exercise interventions during active cancer treatment is one of the fastest growing areas of exercise oncology. Ultimately, the goal of exercise during treatment is to manage treatment side effects, attenuate physical decline,

facilitate the completion of treatment and potentially enhance treatment efficacy. The effects of exercise during treatment have been summarized by numerous systematic reviews and meta-analyses, all with the general consensus that exercise can at minimum attenuate, if not improve, some of the treatment-related decline in skeletal muscle mass, muscular strength, cardiovascular function, fatigue and certain dimensions of quality of life [64–67].

Cardiac dysfunction is of critical concern in cancer treatment, particularly anthracycline chemotherapy agents, mediastinal irradiation and molecular targeted therapies [3, 9, 36, 37]. The magnitude of cardiac dysfunction is associated with the individual and cumulative dose and combination and/or sequence of drugs administered. Resultant cardiac arrhythmias, left ventricular dysfunction, myocardial ischemia, fibrosis and arterial thrombosis can lead to an increased risk for cardiovascular disease and related mortality in individuals with cancer [36, 68, 69]. Clearly, the prevention and/or attenuation of cardiac dysfunction from cancer therapies is of critical concern.

The evidence supporting the efficacy of exercise to mitigate the cardiotoxic effects of cancer treatment remains limited. Nevertheless, several randomized controlled trials show promise. Segal et al. compared the effects of resistance training or aerobic training versus usual care in individuals with prostate cancer initiating radiotherapy. Results demonstrated that both exercise groups attenuated a 5% decline in VO_2 peak observed in the usual care group [70].

Results from a trial by Courneya et al. evaluating an aerobic exercise program in individuals with Hodgkin or non-Hodgkin lymphoma during chemotherapy demonstrated that mean VO_2 peak increased by 4.6 ml/kg/min in the exercise group compared with a decrease of 0.6 ml/kg/min in the control group [71]. In a recent meta-analysis of clinical trials investigating the effects of exercise on cardiovascular outcomes in patients with cancer, Scott et al. demonstrated that exercise was associated with a significant increase in VO_2 peak (+2.80 ml/kg.min) compared with no change (+0.02 m/kg/min) in controls. However, the analysis included exercise interventions that were implemented before, during and after cancer treatment [72]. Currently, the extent by which exercise can attenuate cancer treatment-related cardiac dysfunction during cancer treatment is unclear [37]. Further, VO_2 peak may also be influenced by factors other than cardiac impairments, such as bone marrow suppression (and subsequent red blood cell production), muscular impairments and blood volume regulation in cancer patients, making it difficult to use VO_2 peak as an accurate indicator of cardiotoxicity [73]. Future work may be needed to investigate the type, dose and timing and mechanisms by which exercise may offer cardioprotection in individuals with cancer.

Individuals with cancer are exposed to a variety of factors that result in loss of muscle mass, including cancer therapies, tumour burden and malnutrition that are compounded by aging and inactivity. The importance of the maintenance of muscle mass during treatment cannot be overstated, with consistent evidence demonstrating the association between low muscle mass and treatment-related toxicities, cancer and all-cause mortality.

Galvão et al. [74] reported the results of a 12-week combined resistance and aerobic training intervention in men with prostate cancer receiving androgen

deprivation therapy with some undergoing concurrent radiation. Participants were randomly assigned to either an exercise (n = 29) or non-exercise control group (n = 28). The adjusted mean difference after the intervention for total body and regional lean mass was approximately 1 kg favouring the exercise group. Loss of lean mass after initiation of androgen deprivation has been extensively documented [7, 75], indicating the importance of targeted exercise to preserve musculoskeletal health in this group of patients.

Courneya et al. conducted a randomized controlled trial of aerobic exercise, resistance exercise or usual care (outlined in greater detail later) in individuals with breast cancer beginning adjuvant chemotherapy. Results of the trial revealed the resistance exercise group experienced a 1 kg increase in total body lean mass compared to the aerobic group (0.5 kg) and control group (−0.2 kg). Though promising, these results are in contrast to other trials that demonstrated no effect of exercise on muscle mass. Demark-Wahnefried et al. [76] found no effects of exercise on muscle mass in a combined home-based aerobic and resistance exercise intervention in individuals undergoing chemotherapy/radiotherapy and hormone therapy. Mustian et al. [77] found no effects of a combined home-based aerobic and resistance exercise intervention on muscle mass in breast and prostate cancer patients receiving radiotherapy. Taken together, these results indicate that supervised interventions may be superior to home-based intervention at targeting muscle mass in individuals with cancer.

Considering the association of low muscle mass with increased treatment toxicities, poorer prognosis and cancer-related and all-cause mortality, strategies to improve muscle mass are of clear clinical importance. However the extant literature remains mixed, with insufficient evidence to draw firm conclusions on the effect of exercise on muscle mass in individuals with cancer undergoing treatment [78]. The heterogeneity of results is likely linked to a variety of factors including quality and length of the exercise interventions, level of supervision provided, course of cancer treatment and prior activity levels. It should be noted however that, given the documented reductions in muscle mass with aging and various cancer treatments, the preservation of muscle mass (particularly when coupled with improvements in muscle strength) should also be seen as positive.

Fatigue is a ubiquitous, distressing symptom of cancer treatment, with approximately 50–90% of individuals receiving treatment experiencing fatigue [79]. Importantly, cancer-related fatigue is distinguishable from “regular” fatigue in that it is a complex, multifactorial syndrome, not fully ameliorated by rest. Several contributing factors have been proposed, including systemic inflammation, dysregulation of the hypothalamus-pituitary-adrenal axis, depression, anaemia and physical inactivity. There is consistent evidence to suggest that exercise is effective at ameliorating cancer-related fatigue. Peutz and Herring conducted a meta-analysis of exercise interventions on cancer-related fatigue during and after cancer treatment [80]. The results revealed similar magnitude effects both during and after treatment, with the greatest improvements in fatigue experienced by those with the lowest baseline scores and higher intervention adherence [80]. The results of a recent meta-analysis demonstrated that there is insufficient evidence to indicate if a

modality or specific prescription of exercise may be the most effective to target cancer-related fatigue [81]. A positive consequence of this is that most exercise modalities appear to have similar impact on fatigue with moderate-to-large effect sizes [81]. Similarly, Taaffe et al. recently reported in a large yearlong randomized controlled trial with 163 prostate cancer patients that different exercise modes had comparable effects on reducing fatigue during treatment [82]. Moreover, it appears that the greatest effects of exercise on fatigue are in those with greatest levels of fatigue at baseline [80, 82, 83]. Consequently, practitioners can make an informed choice of exercise selection based on availability of equipment, time, location and patient preferences.

Individuals receiving cancer treatment (i.e. hormonal therapy, chemotherapy and glucocorticoids) are at a heightened risk of bone loss. Recent evidence indicates that bone mineral density (BMD) loss associated with different cancer therapies can range between 2.0% and ~8% at 1 year [84]. This rate of bone loss is particularly concerning when compared to a rate of ~1% per year in apparently healthy individuals [84]. The accelerated decline in bone health can place individuals receiving cancer treatments at a heightened risk of fractures. Consequently, the importance of maintaining bone health during cancer treatment is critical.

It is being increasingly well recognized that bone may respond more favourably to high-impact exercises, highlighting the need of interventions to target specific outcomes of interest. In a yearlong trial, Newton et al. recently investigated the comparative efficacy of impact loading + resistance training, aerobic + resistance training and delayed aerobic exercise on bone mineral density in 154 prostate cancer patients undergoing androgen deprivation therapy [85]. Results of the trial revealed that impact + resistance exercise attenuated a decline in spine and hip BMD compared to aerobic + resistance exercise and delayed aerobic exercise. These findings are of clinical importance given that exercise is likely to be lower in cost than commonly used pharmacological therapies for bone loss (bisphosphonates) which also have low compliance [86].

An important concern among individuals who receive a cancer diagnosis is the psychological impact of the diagnosis and multifaceted burden of ensuing treatments. Consequently, individuals with cancer regularly experience anxiety, sleep disturbance and stress that is associated with decrements in aspects of health-related quality of life (HRQOL) and depression. In a recent meta-analysis of exercise interventions either during or at the initiation of treatment for cancer, Mishra et al. found that exercise interventions had a positive impact on overall health-related quality of life (HRQOL) and certain subdomains including physical functioning, role functioning and social functioning [87]. Moreover, improvements may be greater when prescribed at moderate-vigorous intensity versus lower intensity. This supports other works indicating the exercise may result in positive improvements in stress, anxiety and symptoms of depression [88, 89]. Collectively, there is a burgeoning body of evidence supporting the role of exercise offering some sort of psychosocial relief during cancer treatment. Further research is warranted to determine the sustainability of these effects after cancer treatment.

Exercise Timing: How Soon Should We Intervene?

There is an increasing interest among clinicians and researchers as to when would be the most opportune time to intervene with exercise. As such, questions of timing of exercise implementation for cancer patients remain an understudied area. In a recent trial of 104 prostate cancer patients, Taaffe et al. investigated the effects of an immediate versus delayed exercise intervention in men initiating androgen deprivation therapy [90]. Participants randomized to the immediate exercise group participated in 6 months of supervised aerobic, resistance and impact exercises, three times weekly. Participants in the delayed exercise group who underwent usual care for 6 months followed the same 6-month program as the immediate exercise group. Lumbar spine was preserved in the immediate exercise group compared to the delayed group (0.4% vs. −1.6%, respectively) at 6 months. Additionally, lean mass, appendicular skeletal mass and muscle density were preserved in the immediate exercise group and recovered at 12 months in the delayed exercise group. Results of this study indicate that initiating exercise at the onset of androgen deprivation therapy may be an important strategy to prevent or attenuate treatment-related musculoskeletal toxicities in prostate cancer patients.

Decisions on the appropriate timing of the intervention may be related to the cancer site or treatment course/burden. Capozzi et al. investigated the effect of a 12-week lifestyle and resistance exercise intervention either during radiation treatment or delayed until after treatment in individuals with head and neck cancer [91]. The primary outcome of body composition (more specifically, lean body mass) was assessed at 12 and 24 weeks. Both groups experienced similar reductions in body mass (exercise during radiation, −8.1 kg; exercise after radiation, −8.8 kg) and lean body mass (exercise during radiation, −4.9 kg; exercise after radiation, −5.4 kg) during treatment, which remained at 24 weeks. Interestingly, exercise attendance was 45% for the intervention during treatment for the exercise group during radiation and 61% for the intervention following treatment for the exercise group after radiation. The authors concluded that the implementation of an exercise program for individuals initiating treatment for cancer treatment may not be feasible for some individuals due to the stressful physical and psychological demands of head and neck cancer treatment.

These studies highlight some of the challenges of determining the most opportune time for exercise interventions in individuals diagnosed with cancer. Currently, there is a paucity of research investigating the timing of exercise interventions across the cancer continuum to optimize adherence to exercise and improvement in clinically relevant outcomes. Clearly, the anticipated benefits of exercise in ameliorating treatment-related toxicities must be balanced with the broader view of the treatment schedule and physical and psychological burden on the patient that may offer unique barriers to exercise distinct from other time points along the cancer continuum. Theoretically, exercise should be commenced as soon as possible to buffer treatment-related toxicities and preserve the function of physiological systems. However, it's likely that this recommendation is going to be site specific along with considerations for treatment and anticipated barriers contrasted against anticipated benefits.

Whilst mounting evidence demonstrates that exercise can attenuate many treatment-related toxicities, there are numerous tumour sites that remain understudied. Additionally, research investigating the effects of exercise on treatment toxicity should look to delineate between prevention and treatment, in addition to designing the intervention to target the specific outcome of interest. Importantly, maintenance of the patient's current condition may also be deemed as the best possible outcome, particularly given the magnitude of toxicity for each treatment.

During Treatment: Tolerance/Efficacy

Courneya et al. conducted a randomized controlled trial to examine the effects of different exercise modalities in breast cancer patients receiving chemotherapy [92]. Participants (n = 242) were randomized to an aerobic exercise, resistance exercise or usual care group for the duration of chemotherapy (median, 17 weeks; 95% CI, 9–24 weeks). The primary outcome was cancer-specific quality of life. Secondary outcomes included fatigue, physical fitness, body composition, chemotherapy completion rate, lymphedema and psychosocial functioning. Results of the study indicated that neither aerobic nor resistance exercise improved cancer-specific quality of life. Physical fitness, body composition and self-esteem were improved in the exercise groups. Interestingly, the chemotherapy completion rate was 89.9% in the resistance exercise group, 87.4% in the aerobic exercise group and 84.1% in the usual care group. The reasons for the improved completion rate are unclear, though the authors did allude to the association between a completion rate of ~85% and clinical outcomes.

Van Waart et al. compared the effectiveness of a home-based exercise program versus supervised exercise or usual care in patients with breast cancer undergoing chemotherapy [93]. Primary outcomes were cardiorespiratory fitness, muscle strength and fatigue. Secondary outcomes include physical activity, psychological distress and chemotherapy completion rates. Participants in the home-based group participated in at least 30 minutes of low-intensity activity, 5 days per week. Individuals in the supervised program participated in a combined aerobic and resistance exercise two times per week. Both exercise groups began after the first cycle of chemotherapy and lasted until 3 weeks after the last cycle. Results of the trial indicated that both exercise groups had less decline in cardiorespiratory fitness and physical functioning than the usual care group. Additionally, both exercise groups experienced less pain, nausea and vomiting than the usual care group. Interestingly, significantly less patients in the supervised exercise group required dose adjustments to chemotherapy (12%) than the home-based (34%) or usual care groups (34%). Further, the average percentage dose reduction was 10% in both exercise groups compared to 25% in the usual care group. In a randomized controlled trial of 12 weeks of supervised aerobic training or usual care, Courneya et al. [71] demonstrated that supervised exercise did not interfere nor did it enhance treatment

completion or response in lymphoma patients undergoing chemotherapy. Taken collectively, these preliminary findings allude to a potential protective effect of exercise against treatment-related toxicities. Ultimately, higher chemotherapy completion rates are associated with an improvement in disease-free and overall survival.

Bland et al. recently conducted a systematic review, synthesizing the literature examining the effects of exercise on chemotherapy completion rates [94]. Eight randomized controlled trials were included in the final analysis. Of those, only two studies demonstrated a favourable effect of exercise on completion rate, with the remaining six trials demonstrating no difference with exercise and control. Taken collectively, there is insufficient evidence to conclusively report whether exercise has a beneficial effect on the delivery of chemotherapy. Future studies are warranted to examine the effects of exercise on chemotherapy completion rates and the association of these changes with cancer endpoints. More specifics on this evolving area of exercise and treatment tolerance/efficacy will be discussed in further detail in subsequent chapters.

During Treatment: Patients with Advanced Disease and Palliation

Palliation is a cancer control outcome if treatment is either contraindicated or unsuccessful. The purpose of palliation is to relieve symptoms and to reduce/delay the decline in function and quality of life at the end of life. Research in this area is still very limited, although preliminary evidence shows promise. Oldervoll et al. [95] examined the effects of a combined aerobic and resistance exercise program in 231 advanced cancer patients. Individuals were undergoing chemotherapy ($n = 65$, 53.7%), radiotherapy ($n = 9$, 7.4%), hormonal therapy ($n = 21$, 17.4%) or targeted therapy ($n = 5$, 4.1%). Participants in the exercise group experienced significant improvements in the shuttle walk test and handgrip strength, with no improvement in fatigue [95]. It should be noted that of the participants that agreed to take part in the study, 54% completed the intervention, with an average attendance of 69%. This suggests some potential challenges in delivering interventions in the advanced-disease population.

Jensen et al. examined the feasibility of an exercise intervention in a large sample of 500 terminal cancer patients receiving treatment [96]. The authors found that the intervention was well tolerated by the patients, but similar to Oldervoll et al., there was some loss to follow-up through patient mortality. Research in the palliation phase of the cancer continuum is extremely difficult and it remains a relatively understudied area. There is clear potential for the use of exercise interventions in palliative care to target physiological and psychosocial wellbeing, though there is a paucity of conclusive evidence in this area.

Galvão et al. [97] examined the efficacy and safety of a modular multimodal exercise program in prostate cancer patients with advanced disease and bone metastases. The exercise program comprised of resistance, aerobic and flexibility training

taking into consideration the location and extent of bone metastases as a strategy to maintain or enhance physical function in this group of patients with advanced disease. As a result, the program was based on a mechanical perspective to avoid direct loading to the metastatic lesions. Patients in this study had extensive bone disease with metastatic lesions present in the pelvis (75.4%), femur (40.4%), rib/thoracic spine (66.7%), lumbar spine (43.9%), humerus (24.6%) and other sites (70.2%) and were either receiving or treated with ADT/chemotherapy. After 12 weeks of exercise training, patients in the exercise group reported improved self-reported physical functioning. No skeletal fractures or increased bone pain was reported as a result of the intervention. Given that metastases to bone occur in approximately 80% of men with advanced prostate cancer [98] leading to significant morbidity, limited function and decreased quality of life [99–101], these initial findings suggested potential clinically meaningful benefits of exercise to patients with advanced disease and bone metastases.

During Treatment: Cancer-Specific Endpoints

As presented in previous chapters, consistent evidence from epidemiological studies have shown that higher levels of physical activity post-cancer diagnosis are associated with increased cancer-specific and overall survival [102, 103]. These studies introduced an important concept that beneficial effects of physical activity/exercise after a cancer diagnosis could in fact extend beyond improving symptoms and treatment toxicities as initially suggested. Based on this foundation, larger trials were initiated in recent years to investigate if exercise during treatment in fact may improve survival and other disease-related cancer-specific endpoints in patients with colon cancer that have recently completed adjuvant treatment, patients with haematological cancers receiving allogenic stem cell transplantation, patients with metastatic castrate-resistance prostate cancer (mCRPC) receiving a variety of treatment modalities (AR-targeted therapy, ADT, chemotherapy) and patients with ovarian cancer receiving first-line chemotherapy.

Although not during treatment, the Colon Health and Life-Long Exercise Change (CHALLENGE) trial was the first trial designed to examine the effects of a structured physical activity intervention on disease-free survival in stage II or III colon cancer patients who have completed adjuvant therapy [104]. The study is ongoing, and preliminary feasibility results of 273 participants across 42 international centres have been initially reported [105].

The Physical Exercise Training versus Relaxation in Allogenic stem cell transplantation (PETRA) Study is a randomized controlled trial investigating the effects of partially supervised aerobic and resistance exercise in patients during and after allogenic stem cell transplantation [106]. Two-hundred and fifty-six patients have been randomized into an exercise or muscle relaxation training program for 1 year in a combination of supervised and self-directed exercise. The exercise program consists of 3 sets of 12 repetitions with 6–10 exercises for major upper and lower

body groups 2–3 times per week. Endurance training will be prescribed three times a week in the form of walking or jogging, with intensity monitored using the RPE scale. Participants in the relaxation group will receive a manual with background information and an audio CD on muscle relaxation, along with a standard physiotherapy program and access to a treadmill, during the inpatient period. The primary outcome is overall survival after 2 years.

Global Action Plan 4 Intense Exercise for Survival Among Men with Metastatic Castrate-Resistant Prostate Cancer (Interval-GAP4) is designed to examine the effects of high-intensity aerobic and resistance training on overall survival in men with mCRPC [107]. Secondary endpoints include time to disease progression, biomarkers of inflammation, energy metabolism, androgen metabolism and quality of life. Eight hundred and sixty-six participants will be randomized to either supervised exercise or self-directed exercise for 2 years. Individuals randomized to supervised exercise will participate in an individualized, periodized exercise program. The resistance exercise will be modified in accordance with sites of bone metastases using a protocol previously demonstrated to be safe in this population. The aerobic exercise will be a combination of high-intensity interval training and moderate-intensity continuous exercise.

Lastly, the ECHO trial [108] is evaluating the effects of an exercise intervention during first-line chemotherapy for ovarian cancer on progression-free survival. The exercise program is being undertaken during the period of chemotherapy with follow-up assessments at 6 and 12 months. These studies add substantially to the pioneering CHALLENGE trial [104] by providing evidence on the casual effects of exercise on survival in patients with cancer.

The protective effects of physical activity on cancer recurrence and disease-free survival most likely lie in improved metabolic function, attenuation of the accumulation of body fat along the maintenance of independent physical function. These trials are the biggest of their kind in cancer and have the potential to dramatically impact the field of exercise oncology. The results from these trials will provide critical insight into the causal effects of exercise interventions on cancer survival. If successful, they will be paramount in providing evidence supporting the uptake of exercise in cancer survival. Moreover, the cost analysis from these trials will provide valuable information that encourages policy reform and third-party coverage of these services.

Outcomes and Considerations for Future Inquiry in Exercise Oncology from Diagnosis Through Treatment

As outlined in the beginning of this chapter, the adapted PEACE framework highlights some key areas of focus for research in cancer, from exercise through the end of treatment. Specifically, the pretreatment phase is centred around delaying the progression of disease and buffering the anticipated physiological/psychological impairments associated with various treatments. Importantly, future research in the pretreatment phase should look to explore how improvements in fitness are

associated with post-treatment complications and/or length of hospital stays following surgical procedures. This may provide important information that supports third-party reimbursement for these services in the future.

Overall, the extant literature demonstrates that exercise is safe and feasible in a variety of cancer types, undergoing different cancer treatments. Future research may look to investigate the effects and mechanisms of exercise on mitigation of treatment-related toxicities. Specifically, research should seek to differentiate between *prevention* of toxicities and *improvement* of symptoms. For example, investigating the effects of exercise on cancer-related fatigue should consider enrolling individuals with documented cancer-related fatigue to potentially enhance the response to the exercise intervention. Further, the exercise dose-response in intervention studies has been rarely investigated in relation to a variety of outcomes and endpoints and should be a requirement for future studies to further refine information on exercise prescription in the setting of oncology.

Importantly, despite strong theoretical and biological rationale, the evidence supporting the effects of exercise on treatment efficacy is preliminary. Future research in this area requires large-scale trials, utilizing validated outcomes of treatment efficacy (i.e. relative dose intensity for chemotherapy) in addition to attempting to identify mechanisms and predictors of improvement treatment efficacy. Such research efforts could also be directed to other cancer-specific therapies in addition to the initial reports on exercise and chemotherapy response.

As discussed in Chap. 4, an important area of consideration is the effects of exercise on cancer/tumour biology. Recent reviews have highlighted the preclinical evidence demonstrating strong promise of exercise to enhance blood perfusion of tumours, enhance immune recognition and immune cell infiltration to tumours and regulate tumour signalling and metabolism [73, 109–111]. This is an exciting area for the field; however, these concepts have yet to be examined in humans. Thus, there is a strong and urgent need for clinical studies of exercise and tumour physiology (i.e. hypoxia and perfusion) to provide critical information on the mechanistic effects of exercise on cancer control in humans [109]. Further, this will allow for a greater understanding of the synergistic effect of exercise and anticancer therapies, along with how the exercise prescription may be modified to enhance this response.

Lastly, large randomized clinical trials are currently underway, investigating the effects of exercise on survival although limited at this stage to colon, haematological, prostate and ovarian cancer. Though these multinational trials can be challenging and time-consuming, they will be critical in furthering our understanding of how exercise may improve the quantity and quality of life in individuals with a diagnosis of cancer.

Summary

The field of exercise oncology research over the past 30+ years has consistently demonstrated the safety and efficacy of exercise on a number of endpoints in cancer patients undergoing treatment. Moreover, accumulating evidence indicates that

exercise may have a critical role in both the treatment preparation phase and during active treatment in preparing for and ameliorating treatment-related physiological and psychological impairments. As the field continues to evolve in its breath, scope and rigour, future large definitive trials will provide more conclusive information on the role of exercise in disease progression and survival.

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