Module 26.3

Physical Activity and Exercise Training in Cancer Patients

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Learning Objectives

- To understand the impact of cancer and its treatment on cardiorespiratory fitness, physical function and quality of life;
- To discuss the evidence for physical activity and exercise in cancer, across the disease trajectory, with a focus on symptom burden and physical function;
- To understand how to prescribe, structure and monitor a physical activity and exercise intervention;
- To discuss the barriers to physical activity and exercise intervention as applied to cancer practice.

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Key Messages

- Reduced physical function, incorporating exercise intolerance, physical inactivity and dependency, is a common consequence of cancer and its treatment;
- Most physical activity and exercise guidelines for cancer survivors suggest that physical activity should be an integral and continuous part of care for all cancer survivors;
- The full potential of exercise in cancer patients is more likely to be realized with careful and considered individual prescription;
- There is sufficient evidence to support the promotion of physical activity and exercise for adult cancer patients before, during, and after cancer treatment, across all cancer types, including those with advanced disease;
- Combined aerobic and resistance exercise training, targeting fitness and muscle function, may be particularly relevant in patients with cachexia. Evidence for the added value of nutritional support alongside exercise is emerging;
- Patient, family and professional beliefs about the value and benefits of physical activity and exercise can influence patients' attitudes and motivation to participate in programmes.

1. Introduction

Reduced physical function is a common consequence of cancer and its treatment. It is apparent across most cancer types, all stages of disease, and is associated with poorer functional independence, worse anti-cancer treatment tolerability and higher all-cause mortality (1).

Patients with cancer have considerable impairments in cardiorespiratory fitness; defined as the capacity to deliver oxygen from the air to the skeletal muscles for energy production (2). This is associated with heightened symptoms, functional dependence, and an increased risk of cardiovascular morbidity and mortality (3). Causes include existing patient characteristics, e.g. age or comorbid conditions, the direct effects of anticancer therapy, e.g. chemotherapy-induced anaemia or radiation-induced pneumonitis (4, 5), as well as the indirect consequences secondary to therapy, e.g. deconditioning due to physical inactivity (1).

Physical function is broader than cardiorespiratory fitness, influenced also by muscular fitness; what skeletal muscle can do with oxygen once it is delivered, plus the patient's tolerance for exercise-induced symptoms like breathlessness and fatigue (6). Muscular fitness can be reduced at the point of diagnosis owing to the natural effects of older age, poor lifestyle and co-morbidities. Anti-cancer treatment can have adverse effects on muscle mass (7, 8). Reduced muscular fitness generally continues unless the cancer can be eradicated due to limiting symptoms, physical inactivity and a deconditioning spiral. Physical function can decline to a level that threatens the patient's physical independence. One-third and half of adults with cancer respectively have difficulty or require assistance to perform basic and instrumental activities of daily living, most frequently walking, dressing and transfers (9).

Cancer cachexia accelerates the decline in physical function (10) and increases the risk for physical disability (11, 12). The definition of Fearon et al. emphasizes the key role of muscle loss in the development of frailty and disability (13, 14). Reduced muscle mass is a cardinal feature of cachexia. It is most apparent when intra-muscular fat is accounted for (15) and leads to impaired oxidative capacity. Muscle quality (force/unit mass) may

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also be compromised in some cases (16) though this is most apparent in male patients and those reporting substantial weight loss (17). Further, physical inactivity is an almost inevitable consequence of the negative energy balance in cachexia that results from reduced food intake and metabolic disturbance (18, 19).
The above are all indications for increased physical activity and exercise (i.e. a form of physical activity that is planned, structured and repetitive and aims to improve fitness, performance or health (20) as recommended by the ESPEN expert group for action against cancer-related malnutrition (21). This module briefly outlines the evidence supporting the provision of physical activity and exercise in cancer, provides a framework for prescribing and monitoring interventions, and discusses the barriers and facilitators to getting physical activity and exercise into cancer practice.

2. Physical Activity and Exercise Prescription

2.1 Guideline Recommendations

Most physical activity and exercise guidelines for cancer survivors suggest that physical activity should be an integral and continuous part of care for all cancer survivors (22). For exercise, the American College of Sports Medicine (ACSM), as an example, recommend that patients with cancer should participate in at least 150 min of moderate exercise (e.g. brisk walking, light swimming) or 75 min of vigorous exercise (e.g. jogging, running) each week (23). This recommendation may be more of a long-term goal and is not often an appropriate initial prescription for sedentary patients during anti-cancer treatment. However, most exercise studies in the cancer literature have tested an exercise prescription that closely adheres to this plan. Other guidelines focusing on physical activity, recommend that daily and regular physical activity is performed, but encourage any steps to move from a sedentary to a more active lifestyle (24, 25).

2.2 Individualized Prescription

Key to a safe and effective exercise prescription is the structured individualization of the programme to patients' needs (26). This can be challenging given the variation in pathophysiology, management, and prognosis between different tumour types and patients. The full potential of exercise in cancer patients is more likely to be realized with careful and considered individual prescription. The principles of training can help guide the application of more effective exercise (27).

- *Individualization* describes the customized application of training towards the physiological status of the patient;
- *Specificity* addresses the notion that selected exercise stress must be specific to the primary system(s) and outcome(s) of interest;
- *Progressive overload* describes how stress must increase over time to confer continued physiological adaptation;
- The *rest and recovery* principle describes the necessity of nutrients and rest (or reduced training load) to replace the required constituents of the impacted system(s).

The F.I.T.T. principle provides a structure to design a physical activity or exercise programme by considering exercise: frequency (sessions per week), intensity (how hard per session), time (session duration), and type (exercise modality). Jones and colleagues (26) provide a general approach to individualized, progressive exercise prescription in

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cancer patients focusing on aerobic training. The type of exercise (aerobic or resistance) should be influenced both by patient needs and preference.

2.3 Screening and Monitoring

Physical activty and exercise training is generally safe in cancer patients. However, patient frailty, co-morbid conditions, and side effects of cancer treatment add to complexity (28). Safe exercise training can be facilitated by a careful history and physical examination for cardiac, pulmonary, neurological, and musculoskeletal signs and symptoms (29). Tools such as the Physical Activity Readiness Questionnaire or PARmed-X provide a structure to screen and indicate any need for further evaluation (29).

The prevailing view is that when there are clinically significant abnormalities in blood counts (platelets $<220x10^9/L$; haemoglobin <80g/L; white blood cell count $<2.0x10^9/L$; neutrophils $<1.5x10^9/L$; blood glucose <5.5mmol/L/100mg/dL) or fever (oral temperature >38.0 C/100.4 F) training should be limited and guided by a physician (30). Additional safety precautions include avoidance of high-intensity physical activity or exercise when immunosuppressed, experiencing severe pain, fatigue, or compromised bone health (22, 30, 31). If experiencing sudden onset of swelling, physical dysfunction or pain the use of the affected body part/region should be avoided (22, 30, 31). Patients with compromised immune function, undergoing radiation or with indwelling catheters or feeding tubes should stay away from swimming pools (22). For patients who are frail, experiencing dizziness or peripheral sensory neuropathy, avoiding activities requiring balance is recommended, and patients with a stoma are advised to start with low-resistance exercise and progress slowly to avoid herniation (22, 31). For patients with cognitive impairment additional support should be provided as required and training should be simplified (22, 30). Finally, professionals should also stay up to date on advances in cancer treatment, and any emerging safety issues (28).

Blood pressure, heart rate, and oxygen saturations (SpO_2) can easily be obtained at screening, before and throughout training, to assess baseline status and haemodynamic response to exercise, and to identify adverse cardiorespiratory signs and symptoms (30). Patient self-monitoring and reporting of chest pain, palpitations, and breathlessness on exertion should be encouraged (30).

3. Effects of Exercise

3.1 Summary of Overall Effects

There is sufficient evidence to support the promotion of physical activity and exercise for adult cancer patients (32, 33). Several reviews and meta-analyses provide strong evidence that physical activity and exercise is safe and acceptable before, during, and after cancer treatment, across all cancer types (33), and including those with advanced stages of disease receiving treatments with palliative intent (34). About two-thirds of cancer patients offered a physical activity or exercise programme will accept and about half will complete it (35).

Overall, exercise in cancer patients during and after treatment is associated with maintenance of or improvements in physical and psychosocial outcomes (36), including increased cardiorespiratory fitness (4), reduced fatigue (37), anxiety and depression (38), and better health-related quality of life (39). Most exercise studies have been conducted in patients with early stage breast cancer during and immediately after receiving therapy

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with a curative intent (33), including adjuvant chemotherapy (40, 41). Fewer studies including patients with lung or upper-gastrointestinal cancer, haematological malignancies, or advanced stage cancer have been conducted. However, this literature is rapidly growing and evidence for these groups is accumulating. A review limited to advanced cancer identified 24 trials with most reporting significant between- and/or within-group improvements in physical function, quality of life, fatigue, body composition, psychosocial function, and sleep quality (42). The latest studies in pancreatic (43, 44), lung cancer (44, 45) and gastrointestinal cancer (46) show good safety and feasibility, and suggest potential for benefit on outcomes around body composition and physical function.
Observational data suggest that sufficient levels of physical activity may also enhance tolerance to cancer treatments (40) and improve disease-free and overall survival (47). Higher levels of physical activity are generally associated with lower mortality risk in survivors of breast, colon, and prostate cancer (40, 47). The link between physical activity and cancer outcomes has strong biological plausibility related to sex hormones, inflammatory markers, immune function, and antioxidant pathways (48). Exercise may theoretically also impact on tumour progression and metastasis via alterations in systemic and circulating factors, to influence the tumour microenvironment and cellular signalling. (49). However, heterogeneity precludes meaningful conclusions from the current evidence and causal data are lacking.

3.2 Exercise Type

Most exercise trials in cancer patients have followed physical activity guidelines for the general population and focus on completing moderate-intensity aerobic training on at least three occasions each week. The additional use of individualized resistance exercise, targeting muscle strength and mass, may be particularly relevant in patients with cachexia, where muscle dysfunction contributes directly to functional impairment (21). Exercise may attenuate some of the immunological and hormonal abnormalities found with cancer cachexia (50), and provides a strong anabolic stimulus to counteract the accelerated decline in muscle mass and function (51).
A systematic review concluded that both aerobic and resistance exercise can improve upper and lower body muscle strength more than usual care (52). There was some indication that resistance exercise is more effective for improving muscle strength than aerobic exercise (52). It would be surprising if this was not the case, given the specificity principle of exercise training, and the lack of a finding of significance probably reflects the low volume and small size of comparative studies. A more recent meta-analysis further supported the role of resistance training to target cancer-related muscle dysfunction (53). Pooling individual patient data from 28 trials, exercise significantly improved upper body muscle strength (β=0.20, 95% Confidence Interval (CI) 0.14 to 0.26), lower body muscle strength (β=0.29, 95% CI 0.23 to 0.35) and lower body muscle function (β=0.16, 95% CI 0.08 to 0.24) with larger effects for supervised interventions and when resistance exercise was included, more so when training sessions were >60 min duration (53). More research of this nature is required to demonstrate the relative effects of different exercise programmes (21), and to identify patient and clinical moderators of effect to explain 'for whom' or 'under what circumstances' interventions work best.

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3.3 Combined Exercise and Nutrition

The principles of optimizing physical and nutritional function in patients with cancer cachexia would seem appropriate to be applied to a broader rehabilitation concept in all patients with cancer. In patients with incurable cancer the high prevalence of cachexia means that any rehabilitation intervention for this group should consider key components of nutritional support. A recent review of combined exercise and nutritional rehabilitation interventions in incurable cancer identified eight studies. Factors associated with programme completion were better baseline nutritional or functional status and lower levels of systemic inflammation. Despite limited data, programmes led to improvements in many outcomes important to patients, most notably those relating to physical endurance and depression (see **Table 1**).

Table 1
Combine exercise and nutrition programmes in incurable cancer

Patient-Important Outcomes	Studies / participants	Quality of the body of evidence (GRADE)	Comments
Quality of Life	3 / n=214 (54-56)	LOW (C)	Two moderate quality studies with conflicting results, one low quality study showing improvement; studies have limitations and inconsistencies in outcome variables.
Overall Function	2 / n=81 (57, 58)	VERY LOW (D)	Two studies with low and very low quality examined changes in functional status scores, one finding significant and one non-significant improvements. Sparse data with limitations.
Fatigue	3 / n=203 (54, 56, 57, 59)	LOW (C)	Two low, one very low-quality studies with limitations showing significant improvements in fatigue in spite of sparse data, and one high quality (underpowered) study showing non-significant improvements in intervention group compared to control.
Physical Endurance/ Strength	6 / n=342 (54, 56-60)	MODERATE (B)	Six studies with overall 'low' quality, with limitations: variable consistency in significance levels but overall magnitude of effect seen was improvement in spite of low statistical power of studies: GRADE of evidence increased (+2).
Depression	6 / n=371 (54, 55, 57, 59-61)	MODERATE (B)	Overall low-quality studies with limitations but GRADE of evidence increased (+2) due to studies all showing consistent significant improvements in depression/ psychological subscales.
Nutrition / Weight	5 / n=285 (54, 56-59)	VERY LOW (D)	Five studies of overall low quality with serious limitations and indirectness (variable interventions). Two low/very low-quality studies showed improved PG-SGA scores but the highest quality RCT showed only significant increases in protein intake. Evidence not strong enough to be upgraded.

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3.4 Exercise Delivery

There is a dose-response to exercise, and amending the mode of delivery can support more sustained and intense intervention (47). Supervised interventions which often permit a higher training intensity have more beneficial effects on physical function than unsupervised interventions (62) and moderate-to-vigorous exercise is the best level of intensity to improve physical function (33). Home- and community-based physical activity interventions may be a potential tool to combat functional decline without the need for specialist centres (63). Community-based group interventions produce larger effect sizes than home-based interventions completed alone (63). For interventions at home, with light supervision, effects on function are greater when a higher weekly energy expenditure is prescribed (62).

4. Practice Barriers and Facilitators

4.1 Patients and Families

Patient beliefs about the value, enjoyment and benefits of physical activity and exercise can influence their attitude and motivation to participate. Those who don’t see themselves as exercisers are more likely to count everyday activities as ‘being active’ and may be less motivated to participate in more formal exercise programmes (64-66). Use of simple programmes with walking as the primary modality can be useful (67).
Cancer symptoms, e.g. breathlessness and fatigue, can act as barriers especially if they increase in intensity during or after physical activity (68). Patients may lack knowledge and confidence on how to exercise safely and have fears relating to over-exertion, potential harm or disease progression (64-66). How physical activity and exercise is proposed to patients is an important influencer. Advice from any health-care professional reduces barriers (65), but some patients perceive doctors to be the most influential (69). Some patients can be attracted by seeing potential benefit around fitness whilst others may be more willing to participate if programmes are promoted to help them to carry on with usual routines and roles of normal life, to return to work or to improve their mental well-being (65, 70). There is wide variation in patient preferences, suggesting that multiple options would be most beneficial (67). Professionals should embrace patients’ interests and preferences to facilitate optimal uptake of physical activity interventions.
Family and friends are also important. Patients report that it can be difficult to overcome family advice to rest (66). Time too is a barrier, especially when receiving cancer treatment. For some, physical activity and exercise need to fit into daily routines or alongside scheduled hospital visits and not require extra appointments at the hospital. For others, lack of support is a barrier and group activities are more acceptable (65, 70). Advice should be individualized and the simple message to avoid a sedentary lifestyle and licensing usual physical activity is a start. For other patients, recommendations to take a daily walk or an invitation to join a physical exercise programme may be more fitting (21).

4.2 The Role of Professionals

Clinicians report a lack of knowledge about the benefits and risks associated with physical activity and exercise and that this influences their ability to give good advice. They are aware of the above barriers experienced by patients, as well as the complex interaction of cancer type and staging, treatments, symptoms, age, comorbidities etc (70, 71). These

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same factors reduce clinicians' confidence around the provision of safe advice, especially when symptoms or psychological distress are severe.
Some clinicians, like patients, do not realize the benefits for patients, especially those with a poor prognosis. Others are uncertain how they can change patient behaviours during short clinical encounters (71). Brief goal setting, setting of graded tasks and instruction of how to perform behaviours, can help to encourage previously inactive patients to achieve international physical activity guidelines (72). Strategies containing interactive elements, e.g. patient diaries, tailored to the individual needs of patients, are more successful in improving uptake of physical activity (73).

4.3 Organizational Factors

Access to physical activity and exercise services may be limited. There is a lack of provision for exercise in cancer care compared to other health conditions. Location, difficulties associated with transport and cost also act as barriers (65, 71, 74) and in exercise studies the location of the centre is a prominent predictor of adherence (68). Home-based programmes may improve acceptability but supervision is less prominent in these delivery models (64).
Workplace cultures can act as a barrier or facilitator to physical activity. There is uncertainty around whose role it is to give information and in what format. The physical environment and routine of wards and out-patient clinics can promote or inhibit PA. Larger healthcare system issues also have an impact. Fragmented care teams, and lack of physiotherapists in care teams and/or lack of referral pathways to physiotherapy act as system level barriers (65, 71, 74). Sharing of advice between health professionals can help build collective confidence and expertise, moving towards a position in which every team member feels they can contribute towards multimodal care (75).

5. Summary

Cancer and its treatment reduce physical function often through an effect on cardiovascular, respiratory and muscular systems. Cachexia accelerates the decline in physical function, primarily through loss of muscle mass and function, leading to earlier physical disability and dependence. Physical activity and exercise have a sound theoretical basis and strong evidence around their effects on reducing symptom burden and improving physical function in cancer, leading to improved health related quality of life. Several frameworks are available to support the professional to provide safe and effective exercise training, including screening, prescription and progression. The combination of aerobic and resistance training is most appropriate for patients with cancer cachexia and/or those where muscle performance limits physical function. Additionally, programmes combining nutrition with exercise may be most appropriate for patients with cachexia and incurable cancer. Intensive, supervised exercise programmes are most effective but may not be acceptable or practical for all patients. Advice to improve physical activity levels, working to overcome patient, professional and organizational barriers, is recommended.

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