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REVIEW ARTICLE

Advanced Exercise Prescription for Cancer Patients and its Application in Germany

Moritz Schumann[1] · Nils Freitag[1] · Wilhelm Bloch[1]

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Abstract

The scientific interest of exercise medicine for the treatment of cancer is ever expanding. Recently published and updated guidelines for exercise training in cancer patients by the American College of Sports Medicine (ACSM), the Clinical Oncology Society of Australia (COSA) or the Exercise and Sports Science Australia (ESSA) are leading the way towards an individualized approach for exercise prescription. These guidelines provide physicians and therapists with a comprehensive and detailed overview about the beneficial effects of exercise training and, more so, summarize the evidence on potential dose–response mechanisms, including pathways of exercise-induced stimuli to counteract tumour microenvironmental pathologies. However, the most optimal types and doses of exercise training across the cancer disease and treatment continuum are yet to be determined. Therefore, the purpose of this narrative review was to illustrate the current implications but also limitations of exercise training during the different stages of cancer therapy, as well as to discuss necessary future directions. As a second purpose, special attention will be given to the current role of exercise in the treatment of cancer in Germany.

Keywords Exercise medicine · Clinical exercise science · Exercise guidelines · Exercise therapy · Exercise oncology

Introduction

The scientific interest of exercise as medicine continues to grow rapidly. After the American College of Sports Medicine (ACSM) and the American Medical Association (AMA) launched their ground-breaking initiative of "Exercise is Medicine" in 2007 [82], the scientific publications focusing on exercise as medicine listed in PubMed have almost tripled. However, the history of exercise prescription dates back to ancient times and many of the recent developments are actually not novel but much rather are rediscovered after periods of exercise science research with a focus on athletic performance [93].

✉ Moritz Schumann
m.schumann@dshs-koeln.de

Nils Freitag
n.freitag@dshs-koeln.de

Wilhelm Bloch
w.bloch@dshs-koeln.de

[1] Department of Molecular and Cellular Sport Medicine, Institute of Cardiovascular Research and Sport Medicine, German Sport University Cologne, Am Sportpark Müngersdorf 6, 50933 Cologne, Germany

While initially the term exercise is medicine was understood as a means to improve population health and well-being by raising awareness of health care providers to focus on physical activity as a vital sign, nowadays it is much rather considered as a crucial part for the therapy of numerous chronic diseases [73]. In fact, current studies provide evidence for exercise to complimentarily support primary therapy of more than 26 chronic diseases, such as psychiatric, neurological, metabolic, cardiovascular, pulmonary, musculoskeletal, and oncological diseases [73]. Moreover, in a recent editorial published in the British Medical Journal, exercise medicine was referred to as a "miracle cure", highlighting current evidence on the beneficial effects of exercise in the prevention and treatment of chronic diseases [37]. However, also miracle cures follow a dose–response relationship and so does the *polypill* exercise, requiring a tailored prescription.

Considering the wealth of studies primarily focusing on exercise medicine, it is of little surprise that the field of exercise oncology is rapidly expanding as well, with indexed publications having increased by over 400% during the past decade. Interestingly, it was not until 2009 [46] and 2010 [84] when the first physical activity guidelines for cancer survivors were published. Since the evidence was scarce during that time, these guidelines initially followed a rather generic approach, and did not substantially differ from the WHO recommendations for healthy individuals or patients of other chronic diseases (i.e. 150 min of moderate aerobic activity or 75 min of vigorous aerobic activity, as well as two to three resistance exercise sessions per week) [98]. Intensified research efforts especially over the past decade, however, have eventually accumulated in recently published guideline papers by the Clinical Oncology Society of Australia (COSA) [19], Exercise and Sports Science Australia (ESSA) [45] and the ACSM [14, 72, 83], providing a first step towards precision exercise medicine in the treatment of cancer.

However, even though these guidelines provide thorough recommendations for scientists, practitioners and patients alike, the most optimal types and doses of exercise training across the cancer control continuum [20] are yet to be defined. In line with this, there seems to be a heterogeneous acceptance and understanding evolving around the beneficial effects of exercise for different cancer entities, and potential limitations or even harms of exercise in this vulnerable population often receive insufficient attention. Therefore, the aim of this narrative review is to illustrate the current implications and limitations of exercise training during the different stages of cancer therapy as well as to discuss necessary future directions. As a second purpose, special attention will be given to the current role of exercise in the treatment of cancer in Germany.

Implications for Physical Exercise in Cancer

According to the World Health Organization (WHO), cancer is the second leading cause of death globally, with over 9.6 million deaths in 2018 [12]. In fact, it is quite similar in Germany where only cardiovascular diseases cause more annual deaths [48]. However, concomitantly with the steady increase in cancer-related mortality and newly diagnosed malignant tumours, the survival rates are also increasing. On one hand, this dichotomous development can be explained by the change in demographics and, thus, a growing population of elderly as well as a higher incidence of cancer with increasing age [12, 48]. On the other hand, early detection of the disease and treatment options have significantly improved over the past decades, leading to improved survival rates [48]. Earlier cancer detection may also contribute to the increasing number of young adults diagnosed with cancer [61]. This, in turn, may prolong therapy and aftercare but also further increases the need of supportive strategies, such as psycho-oncological [97], nutritional [97] and exercise interventions [51, 73] as well as programs specifically tailored to facilitate return to work [11].

Although cancer is a complex and heterogeneous disease with numerous distinct underlying physiological and pathophysiological mechanisms, some similarities in the tumour genesis are observed across different cancer entities. These cancer hallmarks are summarized as follows: (i) sustaining proliferative signalling; (ii) evading growth suppressors; (iii) resisting cell death (apoptosis); (iv) enabling replicative immortality; (v) inducing angiogenesis; (vi) activating invasion and metastases; (vii) reprogramming of energy metabolism; and (viii) evading immune destruction [42]. Furthermore, systemic inflammation, tissue hypoxia and genome instability are contributing to the heterogeneity of cancer-related deconditioning by fortifying the underlying hallmarks [42]. The pathogenesis of tumour development is reviewed in detail elsewhere [42]. However, it is important to bear in mind that cancer tissue also affects surrounding healthy cells, causing dysfunction such as an altered metabolism, consequently inducing a number of side-effects, such as cachexia as well as immunosuppression, pain and fatigue [42, 71]. Thus, the treatment should target both the disease and the side effects of the disease, as well as the treatment-induced health consequences.

Considering the complexity in cancer genesis and entities as well as the heterogeneous and rapidly changing therapy approaches, treatment side effects, comorbidities and sequelae as well as individual therapy responses [42, 71], it is inevitable to continuously optimize both primary medical treatment as well as supportive therapies [71, 97]. It is well established that physical exercise induces physiological stimuli on molecular, cellular, tissue and systemic levels [56]. Thus, physical exercise may at least theoretically target both the disease itself as well as the disease and treatment-induced side effects [4, 7, 17, 56]. In a previous animal model, it was shown that exercise was actually similarly effective as cyclophosphamide treatment in attenuating tumour growth, while this response was almost doubled when exercise and chemotherapy were combined [8]. Moreover, a comprehensive overview on the acute and chronic regulating effects of exercise on the tumour microenvironment was recently published in *Nature Reviews Cancer* [56]. The authors summarized that exercise training might have the greatest effects in reprogramming cancer hallmarks by targeting the three key mechanisms of metabolism, angiogenesis and immune response [56]. Thus, the unique therapeutic benefits of exercise training may lie in its local and systemic modulating effects, which may be best controlled by tailored exercise prescriptions.

However, despite possible direct effects on tumour biology, it is indisputable that physical exercise should not be understood as a replacement of primary therapy but much rather may be considered an adjuvant treatment. As such, regular physical exercise is known to affect metabolic, endocrine, gastrointestinal, cardiopulmonary, neurological and immunological pathways, all of which might be affected by both cancerous cells and cancer treatment [4, 7]. Previous studies have shown numerous benefits of exercise training, including improved cardiovascular fitness [53] and muscle strength [91], reduced rates of lymphedema [57] and neuropathies [24], lowered cancer-related fatigue [21], reduced tumour growth [26] or relapse [30] and improved immunological function [51], as well as psychological well-being and quality of life [35].

However, despite the promising results of regular exercise for the adjuvant treatment of cancer, the majority of studies are lacking sufficient quality in reporting and transparency of exercise prescription and guidelines [27], making it difficult to apply their findings to other entities and real-life scenarios. Moreover, a large heterogeneity exists in terms of the timing of exercise interventions in the cancer control continuum (i.e. exercise administered prior to cancer therapy [prehabilitation], during targeted therapy, during rehabilitation and aftercare or during long-term survivorship) [17, 20], as well as in terms of the exercise mode (e.g. low-intensity vs. high-intensity training) and type (e.g. aerobic vs. strength training). The identification of dose–response relationships for specific types of training is likely a key in optimizing exercise prescription for cancer patients. However, research is often limited by ethical dilemmas, especially when certain types of training has been proven extremely beneficial and may no longer be withheld for certain cancer patient populations. Consequently, even well-controlled studies often utilize combined training approaches [63], making it impossible to identify sole contributions of individual training components.

Collectively, these concerns were summarized in a wider context by a recent editorial published in the British Journal of Sports Medicine 2016, where it was questioned whether research in exercise medicine is actually caught in an efficacy trap [6]. This question was reinforced by data on the exercise adherence, which often varies between only 40% and 50% [41]. However, even though this is quite similar to that reported in drug trials [6], it was postulated that there is a general confidence in licensed drugs being effective but this does not appear to be true for exercise training. Although it should be emphasized that this editorial did not specifically focus on exercise oncology, the concerns on missing efficacy are underlined by a current lack of clinical phase IV trials focussing on exercise interventions in oncological patients. Fortunately, some large-scale randomized controlled trials with the primary endpoint of overall survival are open for recruitment at present [67, 68, 70], some of these trials even being international multicentre trials with a supervised exercise period ranging from 6 to 12 months [69, 70]. However, despite overall survival also an in depth understanding of the underlying mechanisms by which exercise training can tackle both the disease and its side effects is fundamental. By that, it is likely that the next decade of research in exercise oncology will make another substantial step towards a precision exercise medicine approach.

Individualized Exercise Prescription for Cancer Patients

To develop concepts of individualized (i.e. tailored) exercise prescription, distinguishing between physical activity and structured exercise training is required. Physical activity is generally defined as skeletal muscle movement that results in elevated energy expenditure above resting levels and includes domains such as walking, hiking or gardening [32]. Exercise training on the other hand, expands on this definition by being a planned, structured and repetitive activity, aiming to improve physical performance. This is why exercise is characterized by specified criteria such as frequency, intensity, time, type, volume, and progression [32]. Considering exercise as medicine, the distinct definition of physical activity and exercise may also be achieved based on the primary goal, where physical activity is aimed at preventing chronic disease and disability. Exercise training, however, is prescribed towards a well-defined target like weight reduction, improved physical fitness, or even more profound the reprogramming of epigenetics or improvement of immune function.

In general, evidence from epidemiological studies suggests that greater volumes of physical activity contribute to a stronger decrease of morbidity induced by various types of chronic diseases [28]. Thus, a personalized approach for exercise prescription will further facilitate health care providers to define more accurately the optimal exercise regimen in the prevention or treatment of particular disease or treatment-induced side effects [75]. In fact, first studies indicating a potential dose–response mechanism in the reduction of cancer treatment-induced side effects are emerging [14]. Consequently, a sufficient and distinct training stimulus is required to induce meaningful physiological adaptations and improved clinical outcomes [4, 17]. Thus, individualizing exercise prescription may help to address possible variabilities in health-related outcomes. Furthermore, this would enable exercise programs to be tailored for the individual phenotype [18], also considering different needs based on the cancer therapy and treatment tolerance.

The need for individualized exercise prescription is highlighted by studies that specifically identify individuals that do not systematically improve exercise capacity, even though the training intervention was well-structured [78]. Ahtiainen and colleagues showed that approximately 7% of healthy individuals do not improve muscle mass following standardized strength training, while this number was increased to approximately 30% when gains in maximal strength are considered [1]. Moreover, extensive variations were observed for muscle hypertrophy (range from 11% to 30%) and maximal strength (− 8% to 60%), irrespective of age and sex [1]. Similar findings were also reported for changes in the aerobic capacity following a 20-week endurance training program, where 7% of the subjects improved maximal oxygen consumption by only 100 mL/min, while another 8% of the individuals improved up to 700–1000 mL/min,thus, indicating a great range of individual responses [10].

In cancer patients, the identification of low- and/or high-responders is often hindered by studies typically reporting the overall treatment effect of the entire study sample rather than individual responses [16, 53, 66, 91]. This may mask heterogeneous training responses and, therefore, might lead to false conclusions on the success of a given training program. This is also underlined by controversial results of studies assessing the effects of physical training performed concomitantly to medical treatment. While some studies have shown physiological and clinically meaningful adaptations [9, 64], in other studies prolonged exercise training did not induce beneficial changes [16, 66, 100].

Within a precision exercise medicine approach, the question arises on ways of avoiding low responders to a given training program. Based on the current literature, there are several aspects that need to be considered. Above all, it is obvious that an in-depth understanding of the mechanisms underlying the cancer genesis and/or treatment response in patient phenotypes is a necessity to tailored treatment strategies [18], including individualized exercise prescription and systematic long-term planning (i.e. training periodization) [75]. This approach is similar to clinical trials in which personalized doses of medical treatment have been successfully determined [99]. Another way to reduce the number of low responders might be to alter the training modalities, such as type, frequency, intensity or volume, concomitantly to the treatment (e.g. strenuous training in treatment-free weeks) [78]. In this context, also perceptual responses need to be considered. For example, high-intensity interval training may require less time compared to moderate-intensity continuous training but the associated shortness of breath, leg pain and fatigue observed during strenuous exercise may be bothersome [94]. It has previously been suggested that exercise at sub-threshold intensities is perceived pleasant for most individuals, while large inter-individual variability is observed when training at the second ventilatory or lactate threshold, and homogenously negative perceptions result from training at maximal intensities [36]. Thus, both physiological aspects but also subjective well-being need to be considered when designing proper exercise prescription in cancer treatment.

Other aspects might be related to both the timing and type of exercise within the cancer control continuum [17, 20, 29]. Exercise during therapy is often directly affected by the primary treatment and may, thus, require constant adjustments [55]. However, numerous studies have provided evidence to commence exercise already well before treatment (i.e. prehabilitation) [

Limitations of Exercise Medicine for Cancer Patients

Physical exercise is generally considered safe and relatively easy to implement throughout all phases of the cancer control continuum [17, 20]. However, the exercise-induced therapeutic potential is specific to the condition of the patient, determined by the disease, the disease status, as well as the primary therapy. Thus, exercise training may come along with contraindications that require careful consideration, similar to the primary therapy such as surgery, radiotherapy or drugs. These may include but are not limited to acute cardiovascular complications, such as unstable angina, severe aortic stenosis or uncontrolled hypertension [76], as well as alterations in hematologic parameters like low number of erythrocytes, platelets or haematocrit [45]. Furthermore, some types of exercise may be contraindicated in certain subpopulations, treatments or in individual diseased states. For example, caution is required for patients undergoing radiotherapy when exercise is performed in the pool, due to an increased risk of burn site irritation [90]. In addition, limitations may also exist for advanced cancer patients who are prone to develop bone metastases. However, while it was previously suggested to avoid heavy exercise load on metastasized areas to reduce the risk for fractures [88], evidence is emerging that strength training seems to be safe and feasible for these patients as well [43, 88].

Despite the type of exercise, certain exercise modalities including exercise intensity need to be considered as they may affect tumour-intrinsic factors, such as metabolism, growth and crosstalk with surrounding tissues [49]. Cancer cells are generally characterized by accelerated glycolysis and excessive lactate formation even under fully oxygenated conditions [95, 96], known as the Warburg Hypothesis [74]. According to this, the tumour bypasses regular mitochondrial function by glycolytic conversion of glucose molecules to lactic acid for ATP production [49]. Consequently, it is not surprising that blood lactate seems to play an important role in the tumour microenvironment and may affect tumour biology by its autocrine, paracrine and endocrine properties [13, 49, 58]. Current theories are indicating that cancer cells may switch between production and consumption of blood lactate insinuating a dynamic tumour metabolism [13, 49]. Furthermore, it is also discussed that tumours are consuming blood lactate produced by noncancerous cells, which is called the "reverse Warburg effect" [39]. In fact, these observations led some authors to conclude that increased blood lactate concentrations may contribute to tumour growth and increased rates of recurrence, as was previously shown in a mouse model [38, 39, 58].

In light of these concerns, it is crucial to understand the role of exercise-induced increased blood lactate concentrations to assure that the provided training stimulus does not augment carcinogenic mechanisms. Importantly, exercise-induced blood lactate accumulation following high-intensity exercise may actually impede glycolysis and lactate production in healthy individuals [50], potentially counteracting the carcinogenic microenvironment mechanisms [49]. Consequently, it appears that the systemic acidosis induced by strenuous exercise takes on a crucial role to interfere with the carcinogenic mechanisms potentially affecting tumour growth and/or recurrence [49, 89]. These facts are supported by a 40% decreased risk of overall cancer mortality in elite athletes exposed to long-term strenuous exercise compared to the general population [49, 80]. However, the role of exercise-induced blood lactate and, thus, the role of high-intensity exercise needs further investigations to identify its importance within the cancer control continuum.

To date, the majority of studies have assessed models of exercise prescription as an isolated adjuvant treatment strategy. However, exercise medicine should always be addressed in the context of other medical treatments, i.e. the primary therapy. In a recent review, a theoretical frame work was established, describing how exercise may affect a drug's absorption, distribution, metabolism, and excretion (i.e. pharmacokinetics) and, thus, potentially influence pharmacodynamics [62]. This is because acute exercise transiently diverts blood away from the liver and reduces the plasma volume, both of which may have profound effects on the blood concentration of a given drug. Moreover, chronic adaptations induced by regular exercise, such as changes in body composition and enhanced enzyme activities, may potentially alter drug pharmacokinetics to a significant extent [62]. While exercise-induced increases in peripheral blood flow have previously been associated with positive effects of drug delivery in cancer patients [4], other metabolic effects of exercise may actually interfere with the drug action, possibly becoming most problematic in cancer patients with comorbidities. It appears that interactions of exercise and drugs are among the most serious concerns for exercise prescription but to date only very few studies have addressed this specifically [62]. Thus, advancing exercise prescription requires also an in-depth analysis of possible interference of the exercise regimen with the primary medical therapy.

Similarly, interactions of exercise and cancer-induced fatigue (CRF) bear a potential for adverse health effects. CRF is among the most common side effects of cancer and cancer treatment, with over 80% of patients being affected during chemo- and/or radiotherapy [47]. The aetiology of CRF is complex and includes direct effects of the cancer and tumour burden as well as treatment side effects and comorbidities, such as thyroid dysfunction, sleep disturbances and psychosocial factors [47]. Currently, there is only very limited evidence about the efficacy for any pharmacological treatments of CRF [65] and evidence points towards beneficial effects of exercise training on CRF [21]. However, a recent meta-analysis summarizing the results of previously published reviews and meta-analysis revealed a quite clear lack of certainty regarding the benefits of exercise in CRF [54]. In fact, while the overall conclusion was that exercise does not seem to increase CRF burden, it was also suggested that the efficacy of exercise depends on the stages of CRF induced by the primary treatment, the patient's phenotype, as well as the already existing period of symptoms.

Interestingly, a recent randomized controlled trial including patients affected by CRF showed that up to 33% of cancer patients may actually experience an acute worsening of CRF following exercise [94]. This phenomenon is commonly referred to as post-exertional malaise and was initially described as a cardinal symptom in myalgic encephalitis and/or the chronic fatigue syndrome. In CRF patients, post-exercise malaise may last for several hours after the completion of a demanding physical or mental activity [94], possibly affecting long-term adherence to exercise as an adjuvant therapy. Therefore, an individually tailored and multicomponent approach may be advisable, and should include individual activity pacing [94]. Indeed, an often overlooked aspect of exercise prescription is a structured recovery process. In contrast to the vast knowledge on periodization models in elite athletes, also in terms of carefully planned periods with reduced training intensity and/or duration (i.e. tapering), this has to the best of our knowledge not yet been thorougly considered for exercise prescription in cancer patients. However, periods of planned de-load or structured reductions in volume, frequency or intensity might be an effective method to counterbalance cancer- and treatment-induced side effects.

Other limitations of exercise interventions in cancer patients may be induced by the interactions of concurrent exercise and active primary treatment. For example, due to the hormone-dependent tumour growth, advanced prostate cancer patients are commonly treated by androgen deprivation therapy (ADT). However, anabolic steroids such as testosterone are essential to muscle growth [5]. Consequently, significant reductions of circulating testosterone concentrations induced by ADT may induce adverse effects such as a loss of lean mass [31], bone mineral density [31] and muscle strength [2], impacting on independency and overall quality of life. Recent studies have shown that muscle mass is an important predictor of overall survival in patients with various cancer entities [59], and it was previously suggested that regular strength training will ameliorate the treatment-induced declines in muscle mass. However, in a recent meta-analysis, we showed that studies do not support this assumption at present, especially when training is commenced months after the initiation of ADT treatment [16]. These findings clearly highlight the limitations of sole exercise training for some patients and at the same time make a case for multimodal approaches, for example including nutritional interventions.

Even though in this section we have highlighted some considerations for possible detrimental effects of exercise in cancer treatment, studies reporting potential adverse effects are very rare. In a recent systematic review by Segal and colleagues, it appeared that exercise-related adverse events and severe adverse events were reported in only few studies [87]. In fact, out of the 29 included randomized controlled exercise trials, only two studies reported exercise-related adverse events, with three patients experiencing muscle soreness and two patients suffering a musculoskeletal injury [87]. All remaining studies stated either that no adverse events were exercise-related or did not report those at all. The latter is especially of concern, because reporting of adverse events systematically based on NCI Common Terminology Criteria for Adverse Events (CTCAE) is rare in exercise oncology related studies, implying that nearly all exercise regimens are safe in this population. However, this observation might be misleading due to limited reporting and evidence. This is for example underlined by a study assessing the effects of regular aerobic training in cancer patients with a concomitant stable heart failure, where the data indicated that all-cause mortality, as well as cardiovascular mortality and hospitalization, was higher at a 35 months follow-up in the training group as compared to the control group [52]. However, post-hoc analysis based on exercise adherence revealed that there was a higher risk for all-cause mortality and hospitalization in patients not adhering to the exercise volume of at least 90 min per week [52]. Based on the post-hoc analysis, it was concluded that supervised aerobic training might be safe and efficacious for patients able to adhere to the exercise prescription. This example clearly demonstrates that a thorough and detailed reporting of adverse events and adherence rates but also an individually tailored exercise prescription are warranted to conduct safe and efficient exercise programs.

Current Application of Exercise Prescription for Cancer Patients in Germany

The transition from research findings to clinical practice remains a significant challenge, similar in Germany. Empirical data have shown that it may take on average 17 years to translate even a small percentage of research into measurable practical outcomes [81]. The reasons for this gap between science and practice are manifold [25] but may include a lack of knowledge concerning evidence-based interventions, failure in understanding the need to introduce evidence-based exercise interventions, or barriers concerning the feasibility to integrate exercise programs within existing routines [22, 25]. It appears that many of these reasons are not specific to cancer but are much rather related to general practical aspects of implementation, requiring organization, sufficient expertise and funding [25]. While some of these aspects may not be directly influenced by research practices, factors concerning the research design should be considered. These often include research studies using exercise training protocols that are impractical to replicate or even impossible to implement in real-world healthcare settings [6] as well as a lack of data concerning dose–response relationships for clinically meaningful outcomes. It is obvious that this provides a significant challenge for us as scientists, to find the right balance between scientific rigor and practical applicability to further prove the effectiveness of exercise interventions in cancer patients and at the same time to improve the transition from lab to bedside.

The German healthcare system is a dual public–private system that foundation was laid by Otto von Bismarck in the 1880s, making it the oldest in Europe [40]. The system is considered a contribution-based social insurance, which is self-administered, decentralized and primarily funded by the public sector [40, 92]. Generally, it is based on four basic principles: (i) compulsory insurance; (ii) funding through insurance premiums; (iii) principle of solidarity and (iv) principle of self-governance [40, 92]. Following these principles, Germany guarantees healthcare to all citizens and, today, there are approximately 97% of the population insured in the public health insurance, while the majority of the remaining 3% are either covered by a private insurance or are in special arrangements for civil servants [92]. Contrary to other countries, the German system is not funded through general taxation but through sickness funds, which are financed by employees and employer payroll taxes. The principle of self-governance means that the federal government is not responsible for the organization of healthcare delivery but it shares responsibilities together with the 16 federal states for public health, including the management of hospitals and regulatory decisions [40, 92].

The federal joint committee is the independent authoritative for both appraisal and decision-making in the ambulatory and inpatient sectors [34, 92]. As such, the federal joint committee determines which medical care services are covered by the public health insurance and assesses the quality management and assurance of the medical services. Furthermore, the agency has the tasks to perform cost–benefit assessments and at the same time evaluates clinical practice guidelines, to submit recommendations on disease management for chronic diseases such as heart failure, diabetes and cancer. All these decisions and processes are based on the principles of evidence-based medicine [34, 92].

Considering the scientific evidence on beneficial exercise-induced effects across all stages of cancer prevention and treatment, it is obvious that exercise training has to be part of the usual care not only in Germany but also worldwide and, thus, should be covered by the health insurance systems. The evidence about the positive effects of exercise training for cancer patients has been reviewed, rated and incorporated in several German oncological guidelines (S3-Leitlinie) such as for mamma, prostate and hepatic carcinoma (Table 1) [3]. However, one has to bear in mind that in contrast to regulations, guidelines are not legally binding in Germany. Nevertheless, these guidelines provide a summary on the current medical knowledge, weigh the benefits and the harms of medical services, and provide detailed recommendations of potential proceedings.

However, despite the tremendous evidence, the federal joint committee has failed to include unified strategies of exercise oncology in the health insurance catalogue of covered medical services so far. Therefore, there is no uniform and nation-wide decision about the assumption of costs for measures of exercise oncology, contributing to the dilemma that exercise oncology is not yet part of the curriculum for medical students or therapists. Nevertheless, there are singularized attempts or alternatives to be aware of, such as medical device-based exercise [33] or medical doctor's prescription for exercise [60]. The medical device-based exercise is covered by the public health insurance, however, the number of applications (prescription quantity) is not uniformly regulated and, thus, mainly depends on the physician as well as the severity of the symptoms [33]. The prescription for exercise, on the other hand, is an initiative of the German Olympic Sports Confederation, the Federal Medical Association and the German Association of Sports Medicine and Prevention. In contrast to the medical device-based exercise, the medical doctor's prescription for exercise is not covered by the health insurance but has to be paid by the patient itself [60]. Importantly, both types of exercise prescription are dependent on the physician and his knowledge about these options as well as the beneficial effects of exercise in the treatment of cancer, highlighting the need for publically available research findings.

A third option for exercise prescription in the oncological treatment is the multidisciplinary oncological rehabilitation. This option is offered by both the health and pension insurance and the costs depend on the patient's status of retirement or employment [23]. The oncological rehabilitation can be administered immediately after hospital discharge, however, the outpatient or inpatient cancer treatment has to be completed. Furthermore certain medical requirements apply to the oncological rehabilitation, such as (i) the presence of an international classification of disease diagnoses (ICD), (ii) completion of the initial treatment (i.e. surgery or radiation therapy), (iii) treatability of the physical, mental, social or occupational disabilities, and (iv) sufficient resilience of the patient. In addition, certain administrative requirements have to be fulfilled such as six month of compulsory

Table 1 Overview of all available S3—guidelines for oncological treatment in Germany [3] with or without gathered and rated evidence about exercise training

Entity	Level of evidence	Further information	Detailed exercise prescription
Actinic keratosis/squamous cell carcinoma	n/a	n/a	n/a
Bladder cancer	cbr	Exercise may reduce side e ects such as fatigue, lymphedema and incontinence	n/a
Breast cancer	A–B 1a–2a	Patients should be motivated to exercise and normalize body mass (in case of an increased BMI). Aid should be given. Strength training programs should be o ered to patients, particularly to those treated with chemotherapy and hormone therapy. Patients should be advised and instructed in regular exercise therapy and physical activity to treat breast cancer-related fatigue. In the case of a chemotherapy-induced polyneuropathy, exercise therapy should be carried out to improve functionality, including balance-, sensorimotor-, coordination-, vibration- and motor skill training. Patients after surgical treatment for breast cancer and those who su er from lymphedema should be introduced to supervised, slowly progressive strength training for lymphedema treatment	150 min of moderate or 75 min of vigorous physical activity and two resistance exercise sessions a week
Cervical cancer	B	Patients should be o ered active forms of exercise training (strength and/or endurance training) to reduce fatigue	n/a
Chronic lymphocytic leukaemia	B	An individually adapted, regular physical training for patients with CLL is very likely to be beneficial for QoL and fatigue, while improving the specific oncological therapy	n/a
Colorectal cancer	B 2a–2b	Physical activity should be performed regularly to reduce the risk of colorectal cancer. Cohort studies indicate a link between physical activity and a reduced recurrence rate as well as improved survival. Patients should be encouraged to exercise	n/a
Endometrial cancer	cbr	Exercise may reduce side e ects such as fatigue, lymphedema and incontinence	n/a
Oesophageal carcinoma	cbr	Patients with oesophageal carcinoma should be motivated to exercise as much as possible. To reduce the fatigue burden caused by the tumour disease or tumour therapy, endurance training should be carried out based on individual resilience	n/a
Follicular lymphoma	n/a	Referring to the exercise recommendations within the guidelines for psycho-oncological and supportive therapy	n/a
Gastric carcinoma	cbr	Exercise therapy should be o ered to all patients. In patients with limited functional abilities, exercise should be carried out preoperatively as part of the "prehabilitation". Exercise therapy is also recommended to reduce side e ects	n/a
Germ cell tumours of the testis	n/a	n/a	n/a
Hepatocellular carcinoma	cbr	To maintain muscle mass, a light endurance and a special muscle building training should be recommended. To reduce cancer-related fatigue, endurance training based on the individual’s resilience should be carried out	n/a

Table 1 (continued)

Entity	Level of evidence	Further information	Detailed exercise prescription
Hodgkin lymphoma	A–B 1a	Exercise training is recommended during and after the therapy. To reduce cancer-related fatigue, endurance training based on the individual's resilience should be carried out	n/a
Laryngeal carcinoma	n/a	n/a	n/a
Lung cancer	B	During oncological therapy (also with high-dose chemotherapy), it is recommended that aerobic endurance training programs (e.g. interval training based on blood lactate concentrations and/or heart rate) may be carried out with an expected good e ciency (e.g. with regard to bone marrow regeneration) and to regain performance more quickly (level of evidence 1b). Similar programs are likely to be e ective in lung cancer patients as well	n/a
Melanoma	n/a	n/a	n/a
Oral carcinoma	n/a	n/a	n/a
Ovarian tumours	n/a	n/a	n/a
Pancreatic carcinoma	C 2b	Exercise training can be generally recommended for weight management	n/a
Prostate cancer	A	Exercise training as a rehabilitation should be recommended to patients on hormone therapy. The goals of (medical) exercise training are the avoidance or reduction of fatigue, the improvement of body composition (fat, muscle, bone mass), psychological stabilization and, thus, an improvement in QoL. Exercise training should take into account the existing restrictions and tumour-related lesions of patients	At least 30 min of moderate to heavy physical activity in addition to normal daily activities, at least five days a week. 45–60 min are desirable
Renal cell carcinoma	A	Depending on the indication and to improve the general condition and physical performance (including muscle mass), the patients are encouraged to participate in individual or group-based exercise therapy, with a focus on endurance, strength and / or coordination, machine-based exercise training, swimming, nordic walking, hiking and aqua fitness. To reduce cancer-related fatigue, endurance training should be carried out based on the individual's resilience. Exercise training improves the blood supply in the wound area and, thus, accelerates the breakdown of residual bruising or swelling, to improve wound healing. It is important to ensure that the exercise intensity is adjusted to the current phase of wound stabilization	n/a
Palliative care	B	Regular aerobic endurance and strength training should be o ered to patients with incurable cancer and tumour-related fatigue	n/a

Table 1 (continued)

Entity	Level of evidence	Further information	Detailed exercise prescription
Psycho-oncological care	A 1a	To reduce the fatigue syndrome in cancer patients (cancer-related fatigue), endurance training based on individual resilience should be carried out as part of exercise therapy	n/a
Supportive therapy	cbr	In the case of a chemotherapy-induced polyneuropathy, exercise therapy should be carried out to improve functionality, including balance-, sensorimotor-, coordination-, vibration- and motor skill training. Avoidance of immobilization and participation in regular physical exercise activities is recommended for the prevention and treatment of tumour- and/or therapy-associated osteoporosis	n/a

Level of evidence grade A–D: A—strong recommendation; B—recommendation; C—option; D—Level V evidence, little or no systematic empirical evidence; 1a—systematic review (with homogeneity) of RCTs; 1b—individual RCT (with narrow confidence intervals); 1c—all or none study; 2a—systematic review (with homogeneity) of cohort studies; 2b—individual cohort study (including low quality RCT)

cbr consensus-based recommendation, *n/a* no information provided, *QoL* quality of life

contribution within the last two years [23]. On average, the duration of an oncological rehabilitation is three weeks and includes a personal surcharge of 10 Euro per day. In addition to this singularized but nationwide available options, there are local attempts to provide free training, often in collaboration with nationally arranged experts groups.

Overall, the current options for cancer patients to benefit from exercise oncology services are rather short-dated and, thus, a tailored exercise prescription including a progressive and structured (i.e. periodized) exercise regimen is difficult to implement. This is in contrast to the overwhelming evidence that clearly indicates that such exercise programs are needed to counteract both, short-term and long-term side effects of the disease and/or its treatment. However, we believe that the recent comprehensive national and international research attempts provide an immense potential to improve the care of cancer patients during all stages of the cancer control continuum in the near future. As such, we also appeal to the German healthcare system to implement and guarantee a nation-wide system for structured exercise oncology.

Conclusion

Although the understanding of exercise prescription for the prevention and treatment of cancer has further improved over the past decades, tailored exercise prescription and periodization remains a rare phenomenon. The reasons for that are manifold but are often related to a combination of infrastructural shortages as well as knowledge gaps. To further facilitate the transfer of exercise interventions into the practice of cancer therapy, it is of utmost importance that studies go beyond simple feasibility and compliance outcomes and are performed with rigor designs (phase III and IV studies). This does not only include a homogenous study population and sufficient sample size but much rather also the inclusion of well-designed and structured training programs, targeting clinically relevant outcomes (such as overall survival), while concomittantly elucidating the underlying mechanisms. This is a key concern because in previous studies different types of training (e.g. aerobic and strength training) but also different training modes and intensity characteristics were often merged. Obviously, this facilitates recruitment of patients and reception of ethics approval but at the same time, these approaches may hinder both the interpretation and generalizability of the study results, especially considering the persistent disease-related heterogeneity in oncology. To overcome this, we suggest an even closer link between exercise science professionals and clinical oncologists. Consequently, basic methodological exercise research performed with healthy participants will build a solid base by exposing possible mechanisms, which may be relevant to counteract the pathogenesis of cancer and/or cancer treatment. These exercise regimens may then be transferred into clinical trials, verifying that the hypothesized outcome may indeed be achieved.

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