Justification

KNGF Guideline on Oncology

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Koninklijk Nederlands Genootschap voor Fysiotherapie

Royal Dutch Society for Physical Therapy

Vereniging van Oefentherapeuten

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All sections of the guideline, including the summary, are available at **kngf.nl/kennisplatform**.

Koninklijk Nederlands Genootschap voor Fysiotherapie

De fysiotherapeuten van Nederland

VvOCM

Vereniging van Oefentherapeuten

The KNGF Guideline on Oncology is a publication of the Royal Dutch Society for Physical Therapy (Koninklijk Nederlands Genootschap voor Fysiotherapie – KNGF) and the Association of Cesar and Mensendieck Exercise Therapists (Vereniging van Oefentherapeuten Cesar en Mensendieck) (VvOCM).

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Note A.1 Introduction

An 'invitational conference' took place during the preparation phase in order to take stock of the barriers. In addition to 16 therapists and other healthcare providers who are involved in treating and guiding people living with or after cancer, patient representatives also provided input during the meeting. The barriers were then assessed during a focus group meeting in which nine therapists participated. The collected barriers were subsequently presented to the members of the guideline panel and review panel during the first guideline panel meeting or review panel meeting, respectively, whereby the most relevant barriers were selected, which were then converted into clinical questions.
One barrier was mentioned frequently, specifically that side effects and symptoms of cancer treatment can make physical therapy or exercise therapy treatment more difficult. These were designated as 'complicating factors'. Such a complicating factor can be a reason for modifying the physical therapy or exercise therapy treatment but can also have a negative effect on the prognosis and the result of the treatment and should, if only for this reason, be identified or diagnosed during intake.
Due to the limited duration of the project, it was not possible to compile an evidence-based recommendation for all frequently occurring problems. Based on the detected barriers, a longlist of complicating factors that are common in people living with or after cancer was therefore compiled. This longlist was then circulated among exercise therapists and physical therapists as a survey, with the goal of collecting information on the complicating factors about which there is the most clinical uncertainty. The respondents were asked to select five complicating factors from the longlist for which they would like to receive an evidence-based recommendation and then what type of advice they would like to get. The survey was completed by 117 exercise therapists and physical therapists. The table below shows the percentages of respondents that found the various complicating factors the most relevant for the guideline.

Longlist of complicating factors which, based on the results of the survey, were ranked according to the percentage of respondents that found this factor to be the most relevant for the guideline

Complicating factor	% of respondents
limited cardiac capacity	56%
metastasis	52%
disproportional fatigue	48%
chemotherapy-induced peripheral neuropathy (CIPN)	44%
neurological involvement resulting from tumour formation	41%
hormonal imbalance	35%
bone problems	35%
abnormal blood count	31%
vulnerability/frailty	26%

social/emotional functioning	18%
insufficient health literacy	17%
port-a-cath/PICC line	16%
distorted body image	15%
joint problems	15%
skin problems as a result of the treatment	10%

With the help of the results of the survey, the clinical questions could be carefully formulated and defined so that they could be answered within the limited timeframe.

Patient perspective

The patient perspective is guaranteed in the preparation phase, the development phase and the review phase. The Dutch Federation of Cancer Patients Organisations (Nederlandse Federatie van Kankerpatiënten organisaties – NFK) provided input about the barriers during the preparation phase, articulated the considerations from the patient perspective during the development phase and commented on the draft guideline during the review phase.

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AQUA. AQUA-Leidraad. Ten behoeve van de ontwikkeling van een richtlijn, module, zorgstandaard of organisatiebeschrijving, die betrekking heeft op (een deel van) een zorgproces en vastlegt wat noodzakelijk is om vanuit het perspectief van de cliënt goede zorg te verlenen. Diemen: Zorginstituut Nederland; 2021.

Note A.2 Cancer characteristics and treatment

The information required for answering the clinical question concerns textbook knowledge and was therefore gathered – in consultation with the guideline panel – in a non-systematic manner from the sources listed below, including a recently developed guideline and exercise intervention and the considerations of the guideline panel.

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Note A.3 Effects of treatment on movement-related functioning

The information required for answering the clinical question was gathered – in consultation with the guideline panel – in a non-systematic manner from the sources listed below, including a recently developed international guideline and the considerations of the guideline panel.

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Note A.4 The role of exercise in cancer

The information required for answering the clinical question concerns textbook knowledge and was therefore gathered – in consultation with the guideline panel – in a non-systematic manner from the sources listed below, including recently developed international guidelines and the considerations of the guideline panel.

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Note A.5 Organisation of healthcare

The information required for answering the clinical question concerns textbook knowledge and was therefore gathered – in consultation with the guideline panel – in a non-systematic manner from the source listed below and the considerations of the guideline panel.

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Note B.1 Choice of exercise intervention

In consultation with the guideline panel and the review panel, it was decided to provide this guideline with a current description of exercise interventions in order to promote an active lifestyle and improvement of the quality of life of patients living with or after cancer, and new insights for compiling a treatment plan for this patient group. This description is based on the sources listed below.

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Note B.2 Training recommendations

In consultation with the guideline panel and the review panel, it was decided to provide this guideline with a current description of training recommendations for exercise interventions in order to promote an active lifestyle and improvement of the quality of life of patients living with or after cancer, and the associated new insights for compiling a treatment plan for this patient group. This description is based on the sources listed below.

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Note B.3 Measurement instruments

In consultation with the guideline panel and the review panel, it was decided to provide this guideline with a current description of measurement instruments for exercise interventions in order to promote an active lifestyle and improvement of the quality of life of patients living with or after cancer, and the associated new insights for compiling a treatment plan for this patient group. This description is based on the sources listed below.

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Note B.4 Personalised guidance

In consultation with the guideline panel and the review panel, it was decided to provide this guideline with a current description of complaints or problems that are related to cancer (treatment) in relation to exercise interventions in order to promote an active lifestyle and improvement of the quality of life of patients living with or after cancer, and the associated new insights for compiling a treatment plan for this patient group. This description is based on the sources listed below.

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Note B.5 The safety of exercise interventions

In consultation with the guideline panel and the review panel, it was decided to provide this guideline with a current description of **the safety of exercise interventions** in order to promote an active lifestyle and improvement of the quality of life of patients living with or after cancer, and **the associated new insights** for compiling a treatment plan for this patient group. This description is based on the sources listed below.

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Note C.1 Bone metastasis

Search

The information needed for formulating recommendations about the safety of exercise interventions in patients with bone metastasis was gathered with the assistance of the recently conducted systematic review by Weller (2021). This study describes, among other things, the safety, feasibility and effectiveness of exercise interventions in patients with bone metastasis based on the evidence of controlled studies. The literature review was performed on 16 July 2020 in the electronic databases MEDLINE, Embase, PubMed CINAHL, PEDro and CENTRAL.
The selection criteria used by Weller (2021) are included in the following table.

Selection criteria

Type of studies	randomised or controlled study
Type of patients	age 18 years or older diagnosed with cancer (of which at least some of the participants have bone metastasis)
Type of intervention	more than one exercise session
Type of comparison	usual care, attention paid to the control group or alternative exercise intervention (strength training versus endurance training)
Type of outcome	side effects and physical functioning

Characteristics of the included studies

A total of 16 studies were included that investigated the feasibility and effectiveness of strength training (5 studies), endurance training (1 study), a combination of strength and endurance training (7 studies) or an exercise intervention in the context of a game (3 studies) in both a supervised and an unsupervised setting. In addition, one study was included that compared the effectiveness of strength training and endurance training. Thirteen studies included both patients with and without bone metastasis, and four studies included only patients with bone metastasis. Of the 1,489 participants included in the review, 645 (43%) had bone metastasis; the average age of the participants was 65 years. Based on the data from three studies, the age varied between 32 and 87 years. Nine studies investigated the effectiveness of a supervised exercise intervention; in six studies a combination of supervised and unsupervised sessions was offered and in two studies the intervention consisted of unsupervised sessions. The supervision was done by qualified physical therapists, exercise physiologists or sports professionals.
Nine studies reported side effects in both the intervention and the control group, seven studies only in the intervention group and one study reported no side effects, only fatigue complaints. Seven studies used a classification tool to assess the severity of the side effects. Three studies reported serious side effects in patients both with and without bone metastasis. Of the 57 serious side effects, 27 occurred in the intervention group and 30 in the control group. Four serious side effects (in 0.5% of the total number of participants in the exercise intervention) could be attributed to the exercise intervention. All side effects could be attributed to football training and did not occur in the area with the bone metastasis. The serious side effects consisted of: two fractures, one Achilles tendon rupture and one infection stemming from a scratch that was caused

by a shin guard. No serious side effects were reported in the four studies that included only patients with bone metastasis.
Nine studies did not include patients with pain or unstable bone metastasis. Four studies required the approval of the physician for participation, and eight studies required a minimum performance status (Eastern Cooperative Oncology Group [ECOG] performance status 0–1/2; Karnofsky performance status (KPS) > 70). In addition, the training recommendations were modified in connection with the bone metastasis in seven of the included studies. For example, strength exercises were prescribed whereby the load on the area with the bone metastasis was minimised and/or resistance bands were used instead of equipment.
No significant negative effects were reported in any of the 17 studies. With regard to the control group, a significant improvement in physical functioning was reported in seven studies, a significant reduction in fatigue was reported in three studies and a significant improvement in quality of life was reported in four studies as a result of the exercise intervention. Six studies reported a significant improvement in body composition and objectively measured muscle strength. Two studies reported a significant decrease in pain as a result of the exercise intervention. No significant effect on fatigue or quality of life was reported in the four studies that included only patients with bone metastasis. However, a significant improvement in physical functioning (3 studies) and muscle strength (2 studies) was reported. One study also reported a significant decrease in pain as a result of the exercise intervention, while three studies found no difference in pain between the intervention and the control group.

Individual study quality

The design and execution of the individual studies (risk of bias; RoB) have been assessed in the meta-analysis by Weller (2021) with the help of the Cochrane Risk of Bias 2.0. The Risk of Bias In Non-Randomized Studies of Interventions (ROBINS) was used to assess the study by Rosenberger (2017). See appendix C.1-1 for the RoB assessment of all individual studies included by Weller.

Quality of the literature found

One of the items of the RoB tool describes the deviations from the prescribed intervention. Because the description of this item was deemed to be unclear in eight of the 17 studies (47%) and that uncertainty might have affected the results found, the evidentiary value of the meta-analysis was lowered by one level. This resulted in the quality of the evidence being assessed as moderate. See the following table for the GRADE evidence profile.

GRADE evidence profile of the studies on side effects as a result of exercise interventions in the presence of bone metastasis

RCTs (*n*)	Quality assessment					Summary of results			Quality
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)	Effect size		
							intervention	control	
17	1 level[1]	none	none	none	unknown	645	27 serious side effects	30 serious side effects	moderate

[1] Down-graded by 1 level due to uncertainty about continuation and possible deviations from the prescribed intervention.

Conclusions based on the literature

There is evidence of moderate quality that exercise interventions in patients with stable bone metastasis do not increase the risk of serious side effects compared to no exercise intervention, but only if the exercise intervention is adapted to the location of the bone metastasis.

Considerations

The recommendations are not only determined by findings in the literature. Other considerations also play a role. The considerations concerned:

- Desirable effects: For patients with bone metastasis, an exercise intervention can produce important benefits on the outcome measures, such as physical functioning, and on muscle strength.
- Undesirable effects: The risk of serious side effects as a result of an exercise intervention in patients with bone metastasis is very small, but only if the exercise intervention is adapted to the location of the bone metastasis. The evidence is limited to stable metastasis. With unstable metastasis, a comprehensive risk assessment is necessary, as is consultation with the healthcare providers involved.
- Quality of desirable effects: The evidentiary value is moderate.
- Balance between desirable and undesirable effects: Given that there are no indications that an exercise intervention in patients with stable bone metastasis leads to any increased risk in any way but might be effective in improving physical functioning and muscle strength, the desirable effects surpass the undesirable effects. The risks of the exercise intervention must be weighed together with the patient against the benefits of exercise and the health risks of not exercising.
- Value of desirable effects: Withholding an effective exercise intervention can lead to injury. One example of this is that the risk of falling increases due to inactivity. Withholding an effective intervention can therefore result in increased falling and hence the risk of fractures. The importance of an adequate physical condition for the patient and proper execution of the exercises is clearly associated with optimising activities of daily life, the patient's general wellbeing, the reduction of the risk of falling and daring to exercise despite the bone metastasis.
- Variation in value of desirable effects: The effectiveness and safety of exercise interventions in patients with unstable bone metastasis are unknown. The guidance of patients with bone metastasis differs from patient to patient. With unstable bone metastasis, additional attention is needed in guiding the patient due to the increased risk of incidents.
- Required resources (costs): There are no additional costs associated with the intervention (compared to regular treatment by the physical therapist or exercise therapist).
- Variation in required resources (costs): Not applicable.
- Cost-effectiveness: No evidence is available about the cost-effectiveness of an exercise intervention in patients with bone metastasis.
- Acceptability: Exercise should be encouraged as much as possible for patients with stable bone metastasis. Guidance of patients with unstable bone metastasis requires a comprehensive risk assessment in consultation with the treating physician and any other involved practitioners. To reduce risks, if these are present, functional training can be used as much as possible, while only using one's own weight, gravity and functional weights which the patient would also use

in daily life. Physicians, nurses or nursing specialists could express concerns about the safety of the load on patients. It is essential for there to be agreement among all involved practitioners, based on explicit clinical considerations, about what can be done safely and what cannot, so that clear advice can be given to the patient and the patient isn't exposed to unnecessary risks but also no effective healthcare is withheld.
Feasibility: Implementation of exercise interventions in patients with stable bone metastasis is feasible in daily practice in a primary care setting, with good information from the treating physician about the nature and location of the bone metastasis being essential. The therapist should be guided as little as possible by impairments but must realise that certain exercises are associated with an increased risk (e.g. transverse forces or compression forces at a location with demonstrated metastasis). In order to make a good risk assessment, it is necessary to receive information from the treating physician about the location of the metastasis and to use this information when assessing the safety of exercise therapy and training. The therapist checks with the referrer as to whether the patient has stable or unstable bone metastasis and whether there are neurological symptoms, osteoporosis, pain related to the location of the metastasis, previous fractures, which treatment was administered due to the bone metastasis and what the assessed risk of falling is. Based on these risk factors, a suitable physical therapy or exercise therapy treatment plan can be compiled in consultation with the treating physician or nursing specialist. The information gathered by the therapist was selected in consultation with the guideline panel and the review panel and is aligned with the international guidelines currently in development. The nature of the bone metastasis is included in this consideration in connection with a possible greater risk of fractures in the presence of osteolytic metastasis than in the presence of osteoblastic metastasis or mixed osteolytic/osteoblastic metastasis.

Conclusion The guideline panel recommends collecting as much relevant information as possible and compiling a suitable physical therapy or exercise therapy treatment plan in consultation with the treating physician or nursing specialist.

Measurement instruments

Bone metastasis occurs primarily in the parts of the bone that are heavily supplied with blood, such as the spine, pelvis and long bones. In 70% of patients, bone metastasis stems from breast, lung, prostate, thyroid or renal cell carcinoma. In approximately 70% of patients with bone metastasis, the symptoms consist of bone pain and decreased mobility. Bone metastasis can be visualised with the help of an X-ray, MRI, bone scintigraphy or CT scan. If appropriate, a biopsy can also be done in addition to radiological exams when no other previously proven bone metastasis has been identified. Therefore, bone metastasis will always be diagnosed by a physician. Any impairments or threat to the exercise capacity will have to be assessed during the intake for an exercise intervention. When selecting measurement instruments for measuring the exercise capacity and other functions of the musculoskeletal system, the physical therapist or exercise therapist takes into account the location and nature of the bone metastasis, similarly to when offering training. Use of direct 1RM tests is not recommended. In the event of doubt about the execution of an exercise intervention in patients with bone metastasis, the therapist consults with the primary treating physician.

The evidence-to-decision form for safe administration of exercise interventions in patients with bone metastasis is included as appendix C.1-2.

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Note C.2 Cardiotoxicity

Search

A systematic review was performed for the following question: What is the difference in the number of side effects (O) in people living with or after cancer and therapy-related cardiotoxicity (P) who get an exercise intervention (I) compared to people who do not get an exercise intervention (C)?

On 19 March 2021, a systematic search was performed with relevant search terms for randomised controlled studies (RCTs), systematic reviews and meta-analyses in the databases MEDLINE, Embase, Cochrane and PEDro, among others. The justification for the search is included in appendix C.2-1.

The table below lists the selection criteria of the search.

Selection criteria	
Type of studies	RCTs, systematic reviews and meta-analyses
Type of patients	people living with or after cancer and therapy-related cardiotoxicity
Type of intervention	exercise intervention
Type of comparison	no intervention
Type of outcome	number of side effects

Characteristics of the included studies

Based on title and abstract, 60 articles were selected whose entire text was evaluated. Ultimately, two randomised studies were included that investigated the safety of exercise interventions in patients with decreased cardiac capacity.

Jones (2014) describes the safety of an aerobic exercise intervention in patients with cancer and heart failure. Ninety patients with an average age of 66 years were randomised to an intervention group that received an aerobic exercise intervention or a control group that received standard care. The exercise intervention consisted of three supervised group sessions of 20 to 45 minutes per session with an intensity of 60 to 70% of the heart rate reserve (HRR) for 12 weeks. Additionally, the participants were advised to be physically active five days per week for 40 minutes at a heart rate of 60 to 70% of the HRR. Tsai (2019) investigated the feasibility of an exercise intervention in 25 patients aged between 28 and 76 years. Participants who were randomised to the intervention group could choose between a supervised exercise intervention lasting 16 weeks or an unsupervised exercise intervention lasting 12 weeks. In both cases, the exercise intervention consisted of endurance training three times per week of 30 minutes per session, with a Borg score of 12.

Jones (2014) reported a higher incidence of side effects in the group that participated in the exercise intervention compared to the group that receive standard care (45% vs. 23%; $p = 0.046$) in the two years following the intervention. This difference was caused by a higher incidence of exacerbation of heart failure and severe arrhythmia. Post-hoc analyses suggest that patients who were not able to keep up the exercise intervention have an increased risk of hospitalisation or death in the two years after the intervention. In the study by Tsai (2019), two side effects were documented that were related to the exercise intervention. Premature ventricular contractions were observed in one participant during the exercise. After re-evaluation, the participant received permission to continue with the exercise intervention. A second participant experienced severe fatigue during minimal exertion. After being examined by a cardiologist, this participant also received permission to resume the exercise intervention, and the participant no longer reported severe fatigue after this. Both studies concluded that an aerobic exercise intervention is safe for patients with treatment-related heart failure. Jones (2014) reported that an exercise intervention is particularly safe for patients who are able to maintain an exercise intervention.

Individual study quality

The design and execution of the randomised studies was assessed with the help of the risk of bias (RoB) tool of the Cochrane Collaboration. The assessment of the RoB of the individual studies is included as appendix C.2-2.

Quality of the literature found

The quality of the study design and the execution of the study was lowered by two levels in connection with the limited quality of the collected data. In one of the studies, patients who were randomised to the intervention group could themselves choose between a supervised and an unsupervised intervention. In addition, the side effects were monitored based on self-reporting by the participants, and the participants themselves were aware of the group to which they were randomised. In this case, the non-blinding could have resulted in overestimating or underestimating side effects. Between the two studies that were discussed, there is heterogeneity in the type of side effects that were reported, and in both cases these were small studies. Therefore, they were down-graded for inconsistency and imprecision. The quality of the evidence is assessed to be very low. See the following table for the GRADE evidence profile.

GRADE evidence profile of the studies on the effects of exercise interventions on therapy-related cardiotoxicity in people living with or after cancer

RCTs (*n*)	Quality assessment					Summary of results			Quality
	Study design and execution (RoB)	Inconsistency	Indirectness	Imprecision	Publication bias	Patients (*n*)	Effect size		
							intervention	control	
2	2 level[1,2]	1 level[3]	none	1 level[4]	none	115	21 side effects[a]	10 side effects[a]	very low
							2 side effects as a result of the intervention[b]	0 side effects[b]	

[1] No blinding and self-reporting of side effects. [2] Patients who were randomised to the intervention group could themselves choose between a supervised and an unsupervised intervention. [3] Heterogeneity in the type of side effects that were reported. [4] Small study size.[a] Jones 2014. [b] Tsai 2019.

Conclusions based on the literature

An aerobic exercise intervention in patients with therapy-related cardiotoxicity may be associated with an increased risk of side effects. Based on the very low quality of the literature found, no conclusion can be drawn about the safety of exercise interventions in patients with cardiotoxicity.

Considerations

The recommendations are not only determined by findings in the literature. Other considerations also play a role. The considerations concerned:

- Desirable effects: It may be possible for patients living with or after cancer who have reduced cardiac capacity to perform aerobic training safely, especially patients who are able to maintain an exercise intervention.
- Undesirable effects: An aerobic exercise intervention in people living with or after cancer and therapy-related cardiotoxicity may be associated with increased risk of cardiovascular events. It is unclear whether side effects occur as a result of the exercise intervention.
- Quality of desirable effects: The evidentiary value is very low.
- Balance between desirable and undesirable effects: The balance between desirable and undesirable effects cannot be properly assessed based on the scientific evidence. Caution should be exercised when offering an exercise intervention.
- Value of desirable effects: The therapist will discuss the use of an intervention with the patient, as well as the risks of the exercise intervention and the benefit this intervention can yield.
- Variation in value of desirable effects: The expected desirable effects depend on the patient's exercise tolerance and expectations, the risk assessment and the feasibility of the intervention.
- Required resources (costs): A CPET can be of added value for the risk assessment or if no progress is made and there are worries about the patient's capacity. The CPET request is made in consultation with the physician or general practitioner. In scientific research, a CPET was unable to fully cover the risk of possible side effects in patients with cancer and who were diagnosed with heart failure.
- Variation in required resources (costs): A CPET is associated with additional costs. Depending on the risk assessment for the individual patient, it must be considered whether a CPET is of added value.
- Cost-effectiveness studies: Studies on cost-effectiveness were not found.
- Acceptability: The therapist discusses the risk of possible side effects with the patient and also explains that omitting the training will not improve the cardiovascular risk profile.
- Feasibility: The feasibility of the desirable effects for the patient depends on the patient's capacity and the risk assessment of side effects.

Conclusion The guideline panel decides to recommend therapy provided that valsalva manoeuvres are avoided. In addition, based on risk factors and consultation with the treating physician, it must be assessed whether a maximal exertion test with ECG should be requested in order to determine whether physical training can be safely given.

Measurement instruments

The European Society of Cardiology (ESC) recommends an echocardiography prior to high-intensity physical activity in patients who were treated with cardiotoxic medication. Diagnosing cardiac toxicity and left ventricle dysfunction is a task of the cardiologist or oncologist. Measurements of left ventricular ejection fraction are typically used to assess the cardiac function of patients who have received chemotherapy or radiation therapy. However, echocardiography measurements are more sensitive to the detection of ventricular dysfunction.

The physical therapist or exercise therapist can consult with the treating physician about requesting a maximal exertion test for patients with limited physical capacity. The physical capacity can be determined with the aid of the Six Minute Walk Test (6MWT) as described in the KNGF Guideline on COPD (KNGF 2020). The results of the maximal exertion test can be used to determine whether physical training can be applied safely, for identifying limiting factors and for making an informed choice between forms of therapy and the intensity of physical training (Campbell 2019).

The evidence-to-decision form for applying measurement instruments for cardiotoxicity is included as appendix C.2-3.

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Note C.3 Chemotherapy-induced peripheral neuropathy

Search

In order to answer the clinical question, a systematic review was performed for the following question: What is the difference in incidents (0) in people living with or after cancer and chemotherapy-induced peripheral neuropathy (P) who receive an exercise intervention (I) compared to people who receive no exercise intervention (C)?
On 19 March 2021, a systematic search was performed with relevant search terms in the databases MEDLINE, Embase, Cochrane and PEDro, among others. The justification for the search is included in appendix C.3-1.
The table below lists the selection criteria of the search.

Selection criteria

Type of studies	RCTs, systematic reviews and meta-analyses
Type of patients	people living with or after cancer and chemotherapy-induced peripheral neuropathy
Type of intervention	exercise intervention
Type of comparison	no exercise intervention
Type of outcome	number of incidents

Characteristics of the included studies

Based on title and abstract, 41 articles were selected whose entire text was evaluated. No studies were found that investigated specific adjustments for CIPN with respect to necessity or effectiveness. Ultimately one systematic review was included (Tanay 2021). It included the most recent literature about the feasibility of exercise interventions and interventions aimed at behavioural change in patients with CIPN. The goals of the review were as follows (among other things): assess the evidence of the behavioural and exercise interventions aimed at limiting CIPN symptoms, determine the components of an interventions and summarise the effectiveness of interventions on decreasing CIPN symptoms and improving quality of life, balance and muscle strength. By means of a systematic search strategy, articles were identified which were published between January 2000 and May 2020. Eight randomised studies, four pre-/post-test design studies and one quasi-experimental study were included, with a total of 743 participants (64% was diagnosed with breast cancer). Based on the data from four studies, the age of the participants varied between 19 and 82 years. All studies investigated the effect of an exercise intervention: four after the cancer treatment had been completed, six studies during the cancer treatment and three studies both during and after treatment.

1. Exercise interventions

The exercise interventions in the study by Tanay (2021) were all developed based on scientific evidence and guidelines of the American College of Sports Medicine, and were geared to patients with neuropathy and cancer or elderly people with balance problems. They lasted three to 36 weeks and were given two, three or five times per week. The duration of a session was 10 to 60 minutes and the intensity varied from low to moderately intensive. Some exercise interventions consisted of one type of training, and others out of a combination of endurance training, strength training and balance and flexibility exercises. Treadmills, bicycle ergometers and cross trainers, balance boards, free weights and exercise mats were also used. Five studies investigated a fully unsupervised intervention, seven studies a fully supervised intervention and one study a combination of unsupervised and supervised exercise sessions. None of the included studies described specific adjustments for CIPN. No unfavourable side effects from the exercise intervention were reported. Reasons for not complying with or completing the exercise intervention were: lack of motivation, too busy to achieve training goals, balance problems not related to neuropathy, no benefit gained from the intervention, transportation problems, a medical incident (not related to the exercise intervention) or mental/emotional problems. Tanay (2021) describes that it is difficult to assess the feasibility of exercise interventions due to variability in intervention duration, the structure of the intervention and the type of exercises. Moreover, the various types of interventions were not directly compared to each other within a single study. This makes it problematic to select an intervention that therapists can recommend to patients with CIPN.

2. Behavioural interventions

Interventions that increase the patient's knowledge about CIPN, improve self-management skills and enable access to symptom management result in fewer complaints of CIPN (Tanay 2021). Such behaviour-oriented strategies must contain components that increase patients' knowledge and encourage them to change their behaviour and the way they think or respond emotionally to their symptoms. Motivational interviewing, goal setting, action statements, training diaries and/or using exercise monitors are proven effective ways to achieve better therapy compliance for exercise interventions.

3. Effectiveness of exercise interventions with CIPN

During a systematic search with respect to this guideline, 15 systematic reviews were identified on 19 March 2021 describing the effectiveness of exercise interventions with respect to CIPN complaints. Because there is a lot of overlap between the scientific evidence in these reviews amongst each other, it was decided to describe the evidence of the three most recently published systematic reviews (Kanzawa-Lee 2020; Lin 2021; Tanay 2021).
Using the search strategy of Kanzawa-Lee (2020) in April 2019, 13 studies were included, of which seven were randomised and six were quasi-experimental. Seven of these studies were also described in the study by Tanay (2021). The number of participants in these 13 studies varied from 21 to 355 with an average age of 56 years (varying between 18 and 81 years). The oncological treatment consisted of platinum derivatives, taxanes or a combination of various types of chemotherapy. In nine studies the participants were still in treatment; in four studies the treatment had already been completed. The interventions consisted of yoga, endurance training, strength training, balance training or a combination of different intervention types. The exercise interventions varied from 23 to 210 minutes per week, one to seven days per week for three to 36

weeks at a moderate to high intensity (50-80% of the heart rate reserve, 40-75% of the V02peak or a Borg score of 13-15) Balance training consisted primarily of four exercises during 15 to 30 seconds that were repeated two to three times per week. The studies that were also included by Tanay (2021) have already been described above.
Three observational studies described a significant improvement in CIPN symptoms when these symptoms were measured with the Total Neuropathy Score (TNS) and the Total Neuropathy Score-clinical version (TNSc). This concerned an individualised, eight-week exercise intervention for three days per week, with balance, strength and endurance training of one hour per session, a three-week exercise intervention consisting of 15 sessions with a focus on balance exercises, and a twice weekly exercise intervention with strength and balance exercises of 60 minutes per session lasting 12 weeks.
Variable effects were found in the randomised studies: two studies reported a significant decrease in CIPN complaints in the intervention group but not in the control group after an unsupervised exercise intervention of combined endurance and strength training at moderate intensity lasting six weeks (355 participants, all diagnosed with breast cancer) or a supervised exercise intervention of strength, endurance and sensory motor training two days per week for 36 weeks (61 participants, all diagnosed with lymphoma). In two other studies no significant difference was found between the intervention and the control group. These interventions consisted of twice weekly balance exercises of 45 minutes per session for four weeks (22 participants, all diagnosed with various types of cancer) or individualised balance and endurance training twice per week for 12 weeks (37 participants, all diagnosed with colon cancer). One study reported stable CIPN complaints due to a twice weekly exercise intervention of balance and strength training lasting eight weeks, but a significant decrease in complaints in the control group (30 participants, all diagnosed with colon cancer). Kanzawa-Lee (2020) described a total of nine studies with a significant positive effect on CIPN complaints; six of these studies were also included in the review done by Tanay (2021).
Tanay (2021) reported that in nine studies with an exercise intervention with components aimed at improving balance, a statistically significant improvement of the balance scores was measured with the Berg Balance Scale (BBS), the Fullerton Advanced Balance (FAB) scale or another balance test. These findings are confirmed in the review by Kanzawa-Lee (2020), which describes that in all studies where balance was measured, a positive effect was reported in the intervention group compared to the control group (6 studies). Tanay (2021) describes that five of the eight studies reported a significant improvement in quality of life after an exercise intervention. In the review by Kanzawa-Lee (2020), this is four of the eight studies. Both Tanay (2021) and Kanzawa-Lee (2020) describe that exercise interventions can result in improvements in balance, physical functioning and symptoms of CIPN in adults with CIPN; however, the evidence is limited in quantity and quality. Furthermore, current studies are too varied to be able to conclude what the most effective training recommendations are for improving CIPN complaints and quality of life.
Lin (2021) published a systematic review which combines the effects of five studies into a meta-analysis. However, this meta-analysis was not conducted correctly, and the results have therefore not been included in this guideline.

Consolidation of the results

To get an idea of the magnitude of the effects of exercise interventions on CIPN symptoms and functional balance, an attempt was made to consolidate the effects of randomised studies. A total of 11 randomised studies were identified which compared the effect of an exercise intervention

to a control treatment without exercise intervention. Various types of interventions were investigated in these studies (endurance training, strength training, balance exercises, sensory motor training and nerve gliding), and the outcomes were measured with various gauges. Thanks to this heterogeneity and the lack of suitable data in many published articles, the project group decided not to consolidate the effects. You can find an overview of the studies and the outcomes found in appendix C.3-2.

Individual study quality (RoB)

The design and execution of the individual studies were assessed in the systematic review by Tanay (2021) based on the criteria of the Effective Public Health Practice Project (EPHPP) quality assessment tool. The Consolidated Standards of Reporting Trials (CONSORT) extension checklist was used to assess the studies that were included in the review by Kanzawa-Lee (2020). The RoB table for assessing the individual studies is included as appendix C.3-3 and C.3-4.
The included reviews provide limited information about the magnitude of the effect on various outcome measures and are largely restricted to reporting the statistical significance of the outcomes. The clinical relevance of the findings is therefore difficult to assess.

Quality of the literature found

The evidence is based on both randomised studies and observational studies, due to which a low quality of evidence is used as the starting point. The quality of the study design and execution was lowered by two levels due to the low to moderate quality of the individual studies. There is heterogeneity in the investigated intervention, between the various studies and the reported outcome measures. Due to this, the quality with regard to inconsistency was lowered by one level. The quality of the evidence is assessed to be very low.
The GRADE evidence profile of the studies on the effects of exercise interventions in people with CIPN living with or after cancer is shown in the following table.

GRADE evidence profile of the studies on the effects of exercise interventions in people with CIPN living with or after cancer

RCTs and observational studies(*n*)	Quality assessment					Summary of results		Quality
	Study design and execution	Inconsistency	Indirectness	Imprecision	Publication bias	Participants	Outcome measure	
13	2 level[1,2]	1 level[3]	none	none	none	743	None of the included studies described specific adjustments for CIPN. No unfavourable side effects were reported.	very low

[1] The quality of the individual studies is moderate to low. [2] Evidence based on both RCTs and observational studies. [3] The heterogeneity in intervention and outcome measures.

Conclusions based on the literature

Due to the very low quality of the found literature, no conclusion can be drawn about adjustments that are necessary when offering exercise intervention to people living with or after cancer and with CIPN. The results appear to indicate that exercise interventions are feasible without specific adjustments. Due to the heterogeneity in the various types of interventions and outcome measures, it is not possible to draw a definitive conclusion based on the scientific literature about the most effective exercise intervention for patients with CIPN.

Considerations

The recommendations are not only determined by findings in the literature. Other considerations also play a role. The considerations concerned:

- Desirable effects: The literature has reported significant positive effects of an exercise intervention on CIPN symptoms, although clinical interpretation is difficult due to a lack of effect estimation.
- Undesirable effects: No undesirable side effects of exercise interventions were reported in patients with CIPN.
- Quality of desirable effects: The evidence is of very low quality.
- Balance between desirable and undesirable effects: Given that no undesirable effects were reported, the desirable effects of the intervention outweigh the undesirable effects.
- Value of desirable effects: In connection with the patient's wellbeing, it is important to improve the patient's condition and manner of exercising. Based on the clinical experience of the guideline panel members and the people they represent, it has become clear that patients with CIPN can develop fear of movement and have a higher risk of falling. Avoidance behaviour can lead to decreased activity or to inactivity. This has negative consequences for the health in general and the functions of the musculoskeletal system in particular. The literature supports the added value of interventions aimed at self-management. The listed interventions (such as goal setting, activity monitoring, coping with symptoms) are generally a part of an exercise intervention, and the physical therapist or exercise therapist can, therefore, play a role in improving self-management in patients with CIPN.
- Variation in value of desirable effects: In practice, patients often don't see a physical therapist or exercise therapist with a primary need for assistance concerning neuropathy. In most cases, the patient will also experience other complaints, which can result in variation in the desirable effects.
- Required resources (costs): Because no specific adjustments are needed, no additional costs are associated with the intervention.
- Variation in required resources (costs): Not applicable.
- Cost-effectiveness: No evidence is available about the cost-effectiveness of an exercise intervention in patients with CIPN. Exercise interventions during chemotherapy under the guidance of a physical therapist may be cost-effective, depending on the willingness to pay and the opinion on the disease burden from the societal perspective (Van Waart 2017). The costs from the healthcare perspective are limited and are very low compared to the total costs of healthcare for people with cancer.
- Acceptability: Exercise interventions are acceptable for therapists and patients with CIPN. There are no indications of undesirable side effects of exercise interventions in patients with CIPN.
- Feasibility: Exercise interventions during or after cancer treatment are already often applied. Exercise interventions in patients with CIPN are considered feasible.

Conclusion The guideline panel decides to recommend exercise therapy if adjustments are made in the exercise intervention based on the complaints of the individual patient with CIPN, insofar as this is necessary for being able to safely and effectively implement the desired exercise programme.

Measurement instruments

CIPN complaints can be assessed based on various physical tests and questionnaires. For example, complaints with the hands can be identified with the help of squeeze force, or wrist extension/dorsiflexion force by manually measuring muscle strength (Knoerl 2020). Because complaints first manifest in the extremities, the inability to provide resistance to moderate counter-pressure is an indication of significant loss of strength, which may indicate CIPN. Objective functional tests, such as the Timed Up & Go (TUG) test, can be used as a measurement instrument to assess the functional mobility and the risk of falling of patients with CIPN. This test has a high degree of reliability but has the disadvantage that many patients achieve the maximal score. If a maximal score has been obtained, or when there is a need to better assess the patient's problems, the FAB scale can be used. This measurement instrument has added value beyond the BBS because many patients function relatively well. The FAB scale has a higher distinctive value. The BBS can be considered for a patient with worse balance, however.
The effects of CIPN are also reflected in the gait. Patients walk more carefully, with slower and smaller steps. Paying attention to the walking capacity at longer distances and for complications, such as slipping, stumbling or falling, is important because problems don't manifest themselves as quickly at short distances and in a controlled environment. The standard values of the Six Minute Walk Test (6MWT) cannot be applied in order to get an idea of the aerobic endurance when there is neuropathy in the feet.
Additionally, sensory and functional complaints can be measured with the help of questionnaires such as the Functional Assessment of Cancer Therapy/Gynaecologic Oncology Group Neurotoxicity (FACT/GOG-Ntx) or the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Chemotherapy (EORTC QLQ-CIPN20). The questionnaires contain questions with which functional problems can be evaluated, such as getting dressed, walking, and picking up and holding objects. Research has shown the internal consistency, reliability, responsiveness and validity of these questionnaires to be high.
The action plan of the Clinimetric Framework (Raamwerk Klinimetrie) was employed when selecting the measurement instruments (KNGF 2016). By going through the eight steps in the framework, the choice of measurement instruments is justified, after which the recommended and optional measurement instruments are differentiated.

Step 1: What do you want to measure?

In this module parameters are designated that could be assessed during the diagnostic and therapeutic process for patients with CIPN. These parameters can be objectified when taking the medical history for the purposes of setting goals, monitoring during the intervention or the (final) evaluation. These parameters fall under the ICF domain 'Activities and participation' / 'Functional mobility' / 'Risk of falling'.

Step 2: Why do you want to measure?

The parameters listed in step 1 can be measured with a prognostic, diagnostic and evaluative goal.

Step 3: What kind of measurement instrument do you want to use to measure?

A search was conducted for measurement instruments that are suitable for objectifying both parameters. The starting point was the systematic review conducted by the EDGE Task Force, which was created by the American Physical Therapy Association to provide advice about clinimetrics for people with cancer (Huang 2019).
Of the two measurement instruments that are strongly recommended in this review, the Fullerton Advanced Balance (FAB) scale was analysed within the scope of this guideline, because the FAB scale is already being used in Dutch physical therapy and exercise therapy practice.
Of the three measurement instruments that are additionally recommended by the EGDE Task Force the Timed Up & Go (TUG) test was specifically examined within the scope of this guideline, because the TUG is aligned well with the diagnostic goal and because this instrument is also already frequently being used in Dutch physical therapy and exercise therapy practice.

Step 4: How can you find a measurement instrument?

The measurement instruments are available at www.meetinstrumentenzorg.nl.

Step 5: What is the practicability?

Fullerton Advanced Balance (FAB) scale
The FAB scale consists of 10 static and dynamic activities in various situations, with the goal of identifying balance problems. When there is a limited amount of time available or when less comprehensive diagnostics are needed, there is also a short version available consisting of items 4 through 7.
The Airex® mats will have to be purchased if they are not available at the physical therapy or exercise therapy practice, but they are not expensive. Taking the test lasts 10 to 12 minutes.

Timed Up & Go (TUG) test
The TUG test measures the time a patient needs to stand up from a chair, walk comfortably (energetically most efficient) for 3 metres, turn around, walk back and sit down again. The patient may use their own walking aid and/or orthotic, but no physical assistance or encouragement may be given. The test is practical and simple to perform.

Step 6: What is the clinimetric quality?

Fullerton Advanced Balance (FAB) scale
The FAB scale is reliable and valid and is strongly recommended by the EDGE Task Force (Huang 2019). The test has high sensitivity (74.6%) and specificity (52.6%) (Hernandez 2008). The test-retest reliability is very high: 0.98 (Wampler 2007).

Timed Up & Go (TUG) test
The NICE guidelines and the EDGE Task Force recommend a TUG test for assessing walking and balance (Huang 2019; NICE 2013). Marschollek (2011) found a sensitivity of 90% and a specificity of 22% at a standard value of 20 seconds. The TUG test is especially informative for a quality assessment (NVKG, 2017).

Steps 7 and 8: Are standard values available and how do you calculate and interpret the data?

Fullerton Advanced Balance (FAB) scale
Standard data (Hernandez 2008):

- Score ≤25: The patient is at risk of falling in 7 out of 10 cases.

Apart from the scoring, when performing each component it can be assessed what the quality of the performance is of the requested activity, in order to obtain insight into which components (function, skill and self-confidence, etc.) of functional balance are the most problematic.

Timed Up & Go (TUG) test
Standard data (Podsiadlo 1991):

- Score <20 sec: The patient walks independently and safely.
- Score >30 sec: Assistance is needed when walking.

The evidence-to-decision form for applying exercise interventions for CIPN is included as appendix C.3-5.

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Note C.4 Fatigue

Search

The project group decided to answer this question based on existing guidelines and findings that were reported in a recently published systematic review. This literature review was conducted with the following question: What is the difference in fatigue (O) in people living with or after cancer (P) who receive an exercise intervention (I) compared to people who receive no exercise intervention (C)? The following were examined:

1. The effects of supervised exercise interventions on fatigue both during and after the cancer treatment compared to no exercise intervention.
2. The effects of unsupervised exercise interventions on fatigue both during and after the cancer treatment compared to no exercise intervention.
3. The difference in effect between exercise interventions for different patient characteristics and training recommendations (frequency, intensity, type, time; FITT).
4. The effect of High Intensity Interval Training (HIIT) compared to an exercise intervention of continuous intensity on fatigue in people living with or after cancer.

For the first three aspects, already published systematic meta-analyses have been included (Buffart 2017, 2018; Van Vulpen 2020). The objective of these studies was to use the individual participant data of randomised intervention studies to investigate moderators of the intervention effects on fatigue, quality of life and physical functioning.
For the fourth aspect, a systematic review was conducted within the scope of this guideline on the effectiveness of HIIT on fatigue compared to an exercise intervention of continuous intensity on fatigue in people living with or after cancer. On 12 February 2021, a systematic search was performed with relevant search terms for randomised controlled studies (RCTs), systematic reviews and meta-analyses in the databases MEDLINE, Embase, Cochrane and PEDro, among others. The justification for the search is included in appendix C.4-1.
The table below lists the selection criteria of the search.

Selection criteria

Type of studies	RCTs, systematic reviews and meta-analyses
Type of patients	people living with or after cancer
Type of intervention	high intensity interval training (HIIT)
Type of comparison	exercise intervention of continuous intensity
Type of outcome	fatigue

Characteristics of the included studies

Based on a systematic review by Buffart (2017) in PubMed, Embase, PsycINFO and CINAHL, 69 randomised studies on exercise intervention appeared to be suitable for inclusion. The original data of 36 of these studies was included in a database for the purposes of this guideline. Of the remaining studies, it was not possible to collect the original data. No difference in effect was found between the studies that were and were not included.
In the meta-analysis of Van Vulpen (2020), 36 individual studies were included. No fatigue was reported in five studies. The data from the other 31 studies were used to investigate the effects of an exercise intervention on fatigue. In those 31 studies, a total of 2,437 patients with different types of cancer were randomised to an exercise intervention and 1,929 participants to the control group. The great majority of these patients (78%) were female. 70% were diagnosed with breast cancer; the average age was 54 years. The studies investigated whether demographic and clinical characteristics and a lot of or a little fatigue prior to the exercise intervention impacted the effect of the exercise intervention, and the effect of the various training recommendations was also investigated.
The same studies were included in the meta-analysis of Buffart (2018) as in the meta-analysis of Van Vulpen (2020).

1. Effectiveness of supervised exercise interventions on fatigue

The results of the study by Van Vulpen (2020) show that a supervised exercise intervention during and after cancer treatment can lead to less fatigue (*z*-score β= -0.23 (95% CI -0.29 to -0.17). The effects were investigated with a mixed effect model and corrected for the initial values. A random intercept at the study level was applied and the differences between the groups were reported in *z*-scores (interpretation: 0.2-0.5 = small effect; 0.5-0.8 = moderate effect; ≥0.8 = large effect).

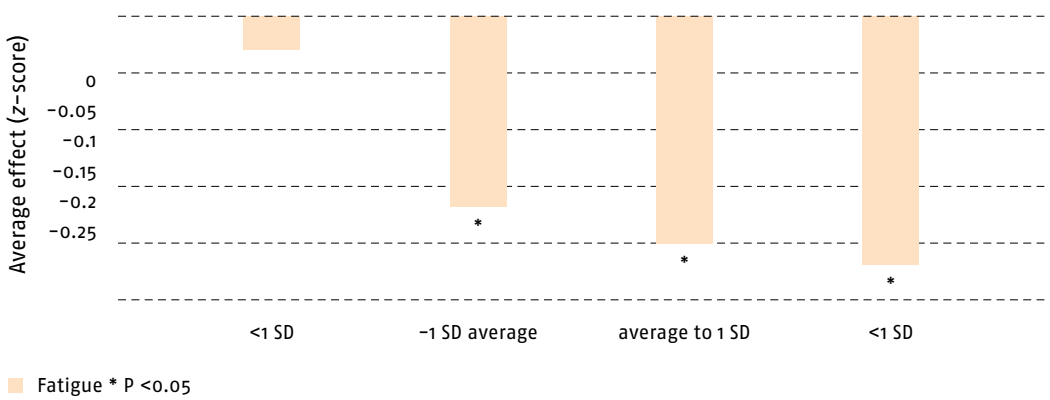
2. Effectiveness of unsupervised exercise interventions on fatigue

The meta-analysis by Van Vulpen (2020) shows that unsupervised exercise interventions result in a very small and insignificant effect (*z*-score β= −0.04; 95% CI −0.13 to 0.04).

3. Difference in effect between exercise interventions for different patient characteristics and training recommendations

Patient characteristics

A study where the same data was used as in Van Vulpen's study investigated whether there are differences in the effectiveness of exercise interventions on fatigue between patients who have more or less fatigue prior to the intervention (Buffart 2018). This was investigated by dividing the patients in subgroups based on the fatigue experienced prior to the intervention. The results of these analyses show a significant effect of the fatigue prior to the intervention (*z*-score β= −0.05; 95% CI −0.10–0.00) with larger effects for patients who experience more than average fatigue prior to the intervention (*z*-score β= −0.22; 95% CI −0.37 to −0.07) compared to patients who had little fatigue (*z*-score β= −0.03; 95% CI −0.13 to 0.08). See the figure below.



Average effect (*z*-score) of an exercise intervention on fatigue for subgroups based on the experienced fatigue prior to the intervention (Buffart 2018)

An average fatigue score corresponded in this study to a value of 12.1 for general fatigue measured using the Multidimensional Fatigue Inventory and a value of 37.1 measured with the Functional Assessment of Chronic Illness Therapy (FACIT) fatigue scale. For both supervised and unsupervised interventions, Van Vulpen (2020) found no difference in effect between groups based on age, gender, education level, civil status, body mass index (BMI), type of cancer or type of treatment.

Training recommendations

In the meta-analysis by Van Vulpen (2020), based on individual patient data no indication was found for differences in effects on fatigue between supervised interventions that differed in frequency, session duration, intensity or type. This study did find indications that interventions lasting 12 weeks or less showed larger effects compared to interventions lasting longer than 12 weeks, especially if the intervention lasted longer than 24 weeks (≤12 weeks: *z*-score β= −0.29, 95% CI −0.39 to −0.20; >12–24 weeks: *z*-score β= −0.25, 95% CI −0.41 to −0.10; >24 weeks: *z*-score

β= −0.11, 95% CI −0.22 to 0.00). The authors of the review attribute this to decreasing therapy compliance and/or increasing contamination starting at 12 weeks, although a possible plateau effect is not ruled out. These findings are in contrast to the findings that are described in the ACSM guidelines, where a larger effect was found in programmes that lasted longer than 12 weeks and that had a longer session duration.

4. Effectiveness of HIIT compared to exercise interventions of continuous intensity

The search in the scope of this guideline yielded 185 hits. Based on the title and abstract, 124 studies were excluded. This left 61 studies, of which 23 were systematic reviews that were all evaluated on their full text, for which ultimately one systematic review was included because it compared the effectiveness of HIIT with training of continuous intensity and no training (Mugele 2019). Only one study was included in this systematic review that compared the effect of HIIT on fatigue to an exercise intervention of continuous intensity (Schmitt 2016). This small study was conducted in 28 women with an average age of 53 years who were treated for various types of cancer. The intervention consisted of six 75-minute sessions at a low to moderately intensive continued intensity or eight HIIT sessions over a three-week period. Fatigue was measured before the intervention and after the end of the intervention using the Multidimensional Fatigue Inventory (MFI) (the higher the score, the greater the fatigue). Both HIIT (−1.31 ± 2.02 points) as well as low to moderate intensity training (−3.23 ± 2.52 points) resulted in a decrease of general fatigue. Low to moderate intensity training resulted in a larger decrease of general fatigue compared to HIIT (p = 0.04), but this difference was not found for the other subscales of fatigue, measured with the MVI (physical fatigue, mental fatigue, decreased motivation and decreased activity).
Thirty studies concerned randomised studies. One concerned a study that was published after the systematic review by Mugele (2019) and appeared to be relevant to answering the clinical question (Piraux 2020). This study compared the effects of HIIT with strength training and no training, respectively, in patients with prostate cancer during treatment with radiation therapy. A total of 78 patients were included, of which 27 were randomised to the HIIT training group, 25 to the group receiving strength training and 26 to the control group. Fatigue was measured using the Functional Assessment of Chronic Illness Therapy – Fatigue (FACIT-F) (the lower the score the greater the fatigue). The results show that both HIIT (p = 0.012) and strength training (p = 0.039) can limit an increase in fatigue compared to the control group. No differences were found between the effects of strength training and HIIT (effect size not reported).
The remaining eight studies were not systematic reviews or RCTs. These studies hence did not fulfil the inclusion criteria and were therefore not included in the further analysis.

Individual study quality (RoB)

The design and execution of the individual studies ('risk of bias'; RoB) were assessed with the help of the Cochrane Collaboration Risk-of-Bias (RoB) tool in the systematic review by Van Vulpen (2020) (reported in Buffart, 2017). The Cochrane RoB tool was also used for assessing the studies of Schmitt (2016) and Piraux (2020). For the assessment of the RoB of the individual studies, see appendix C.4-2.

Quality of the literature found

With regard to the first three aspects, despite the lack of blinding in almost all of the studies, it was decided not to down-grade for study design and quality, given that blinding in such studies is impossible and other aspects within the RoB tool were scored very well.

Based on the 'trim-and-fill' procedure conducted by Van Vulpen (2020) and Buffart (2018), there is a reason to assume that there is some publication bias. The quality of evidence for the effects of a supervised exercise intervention on fatigue was down-graded due to this and assessed as moderate. There is a large variation in the effects and the confidence interval of studies that compared an unsupervised exercise intervention with no exercise intervention. The quality of the evidence was therefore down-graded based on inconsistency and publication bias, with which the quality of the evidence for the effects of unsupervised interventions on fatigue is low.
The evidence for differences in effects between exercise interventions that vary in FITT principles stems from the study by Van Vulpen (2020). The quality of the evidence is moderate, because down-grading also took place for this comparison due to publication bias.

With regard to the fourth aspect, down-grading took place for individual study quality because the randomisation procedures were not clearly described. In addition, down-grading took place for inconsistency because the effect size was not clearly reported. The publication bias could not be evaluated for the comparison between studies in which HIIT was compared to an exercise intervention of continuous intensity. The quality of the evidence is low.
The GRADE evidence profile of the studies found is included in the following table.

GRADE evidence profile of the studies on the effects of exercise interventions on fatigue in people living with or after cancer

RCTs (*n*)	Quality assessment					Summary of results		Quality
	Study design and execution	Inconsistency	Indirectness	Imprecision	Publication bias	Participants	Effect size (95% CI)	
1. Supervised exercise intervention compared to no exercise intervention								
23	none[1]	none	none	none	1 level[5]	2,974	-0.23 (-0.29 - 0.17)	moderate
2. Unsupervised exercise intervention compared to no exercise intervention								
9	none[1]	1 level[3]	none	none	1 level[5]	1,446	-0.04 (-0.13; 0.04)	low
3a. Difference in effect of exercise interventions for patients with different characteristics								
31	none[1]	none	none	none	1 level[5]	4,421	lots of fatigue: -0.22 (-0.37; -0.07) little fatigue: -0.03 (-0.13; 0.08)	moderate
3b. Difference in effect between exercise interventions with different training recommendations								
31	none[1]	none	none	none	1 level[5]	4,421	interaction effects have not been demonstrated	moderate
4. High intensity interval training compared to exercise interventions of continuous intensity								
2	1 level[1,2]	1 level[4]	none	none	none[6]	74	no effect (no data reported)	low

[1] Not down-graded for blinding (see 'Quality of the literature found' for an explanation). [2] Allocation. [3] Variation in confidence interval. [4] Effect size not reported. [5] Publication bias evaluated based on Egger's test. [6] Not evaluated.

Conclusions based on the literature

There is a small effect of supervised exercise interventions compared to no exercise intervention on the fatigue outcome measure. The quality of evidence is moderate.
There is no effect of an unsupervised exercise intervention compared to no exercise intervention on the fatigue outcome measure. The quality of evidence is low.
There is a greater effect of exercise interventions in patients with more than average fatigue compared to patients with less than average fatigue. No difference in effect was demonstrated between interventions of low to moderate intensity and moderate to high intensity, between an intervention of <3 sessions per week and ≥3 sessions per week, and between strength training and aerobic training. The quality of evidence is moderate.
No difference in effect was found on fatigue between exercise interventions whereby HIIT is applied, compared to exercise interventions where training of continuous intensity is applied. The quality of evidence is low.

Considerations

The recommendations are not only determined by findings in the literature. Other considerations also play a role. The considerations concerned:

- Desirable effects: The literature has reported small positive effects of an exercise intervention on fatigue. The effectiveness of supervised exercise interventions is greater than that of unsupervised exercise interventions. There are no demonstrable differences between the effects of exercise interventions of continuous intensity and HIIT on fatigue. The guideline panel points out that other than effects on experienced fatigue, exercise interventions also contribute to improved overall fitness, an improved cardiovascular risk profile and a better quality of life. It is also important for fitness to play a positive role during the treatment and have favourable effects on the outcomes of the treatment. That's why more health outcomes other than just fatigue might be involved when considering an exercise intervention.
- Undesirable effects: No undesirable effects of exercise interventions were reported in the identified studies.
- Quality of desirable effects: The evidentiary value for the effects of a supervised exercise intervention on fatigue is moderate. The quality of evidence concerns the evidence of highly standardised exercise interventions. In the exercise therapy and physical therapy practice, a higher degree of adaptation to the individual will be required, whereby in addition to physiological effects of exercise interventions, cognitive behavioural components will also be applied (such as goal setting, psychoeducation, coaching on activity regulation) and possible substitution with or addition of functional types of training aimed at daily activities that are valuable for the patient.
- Balance between desirable and undesirable effects: Given that no undesirable effects were reported, the desirable effects of the intervention outweigh the undesirable effects.
- Value of desirable effects: The effects of exercise interventions on fatigue are small and it is unlikely that the threshold for clinical relevance will be exceeded with those effects. However, in scientific research, it is often a selection of active participants that is included and it is reported that the control group is also frequently very active. The effect of an exercise intervention on fatigue complaints may be greater in practice than is reported in scientific research.

- Variation in value of desirable effects: A significant moderation effect of the fatigue prior to an intervention was reported (z-score β= −0.05; 95% CI −0.10 to 0.00) with larger effects for participants who experienced higher than average fatigue prior to the intervention (*z*-score β= −0.22; 95% CI −0.37 to −0.07) compared to participants with little fatigue (*z*-score β= −0.03; 95% CI −0.13 to 0.08).
- Required resources (costs): There are no additional costs associated with the intervention.
- Variation in required resources (costs): Because no standard programmes are offered in the exercise therapy and physical therapy practice but rather customised care, costs may vary. A graded-activity programme for patients with fear of movement likely needs more time to arrive at the desired results than a training programme that can immediately be offered at sufficient intensity. The presence of risks due to (very) low capacity, co-morbidity or low motor skills can also result in a longer than average treatment duration.
- Cost-effectiveness: Information about cost-effectiveness is limited. Unsupervised exercise interventions during treatment with chemotherapy are probably not cost-effective from the social perspective. Exercise interventions during chemotherapy under the guidance of a physical therapist or exercise therapist may be cost-effective, depending on the willingness to pay and the prevailing assessment of the disease burden (Van Waart 2017). The costs from the healthcare perspective are limited and are very low compared to the total costs of healthcare for people with cancer (VRA 2018).
- Acceptability: Exercise interventions are acceptable for therapists and people during or after cancer treatment. The experience experts consulted for this guideline did indicate that they value broader advice than merely training guidance on site at the physical therapist's or exercise therapist's practice. In particular obtaining insight into (finding the right balance between) load and capacity in activities of daily life are explicitly mentioned here.
- Feasibility: Exercise interventions during or after cancer treatment are already often applied and are considered feasible.

Conclusion The guideline panel decides to recommend therapy for people living with or after cancer and fatigue. If the patient is already experiencing severe fatigue, anxiety/stress, depression or sleep problems at the time of the cancer diagnosis or if no progress has been made after a 12-week exercise intervention, despite adequate physiological stimulus, a multidisciplinary treatment or cognitive behavioural
approach should be considered.

Measurement instruments

All measurement instruments included in the KNGF Standard on Exercise Intervention in Oncology and the Medical Specialised Rehabilitation in Oncology Guideline of the Dutch Society of Rehabilitation Physicians (VRA 2018) are included in the consideration.
The Load Meter can be used as a detection tool for load in general and for underlying causes of that load, such as fatigue. It is important to apply a multidimensional approach for the diagnosis and to examine the physical, emotional and cognitive dimensions of fatigue.
The Multidimensional Fatigue Inventory (MFI) is recommended for diagnosing fatigue. Additional research may be required for assessing the underlying causes of fatigue. For example, this may be a blood test or a questionnaire about anxiety and depression (Hospital Anxiety and Depression Scale [HADS]). Mutual coordination with the involved primary oncology specialists or the GP is important for this.

Diagnosing anxiety or depressive disorders is outside the scope of the physical therapist's or exercise therapist's field of expertise. Screening for these mood disorders is recommendable, however. If a patient has a score that exceeds the applicable cut-off points, it can be discussed with the patient whether further diagnosis and/or treatment by a qualified healthcare provider is desirable.
The action plan of the Clinimetric Framework (Raamwerk Klinimetrie) was employed when selecting the measurement instruments (KNGF 2016). The action plan consists of eight steps: The choice of measurement instrument is justified for each step, after which the recommended and optional measurement instruments are differentiated.

Step 1: What do you want to measure?

Fatigue is a parameter within the ICF domain 'functions and anatomical characteristics' that can be assessed when taking the medical history for the purposes of setting goals, monitoring of the intervention and the (final) evaluation during the diagnostic and therapeutic process.

An additional measurement instrument can be used for the differential diagnostics.

Step 2: Why do you want to measure?

This parameter can be measured with both a diagnostic goal as well as an evaluative goal.

Step 3: What kind of measurement instrument do you want to use to measure?

A measurement instrument was sought that is suitable for objectifying the fatigue parameter. For fatigue, the Multidimensional Fatigue Inventory (MFI) was analysed because it is recommended in the Medical Specialised Rehabilitation in Oncology Guideline (2.0) (VRA 2018).

Step 4: How can you find a measurement instrument?

The measurement instrument is available at www.meetinstrumentenzorg.nl.

Step 5: What is the practicability?

The MFI is a self-reporting instrument and consists of 20 assertions and statements concerning five dimensions of fatigue and its consequences. The MFI is very practical and is mostly used in clinical healthcare in the Netherlands for measuring cancer-related fatigue (VRA 2018). Completing the MFI takes about 5 minutes.

Step 6: What is the clinimetric quality?

The MFI is reliable, valid and sensitive to changes (Meek 2000; Minton 2009). The internal consistency of the subscales was investigated among Dutch patients with cancer who underwent radiation therapy and was assessed as good to very good (Cronbachs α= 0.79 to 0.93; Smets 1996). The same study found supporting evidence for sufficient construct validity and structural validity. In one large study among the general population, the structural validity did not hold up and the 'General Fatigue' sub-scale turned out to be the most reliable measure of fatigue (Kieffer 2021). Another recent study that included a large study with 1,818 patients with cancer also did not find any evidence for the underlying 'structure' factor but nevertheless recommends that the subscales be scored as intended (Hinz 2020).

Steps 7 and 8: Are standard values available and how do you calculate and interpret the data?

The higher the score on the MFI, the greater the level of fatigue and the more fatigue is a limiting factor. The scoring tool of the Netherlands Comprehensive Cancer Organisation (IKNL) can be used to calculate the score.

The scale scores can be used to evaluate the fatigue of an individual patient over the course of time. The *z*-scores can be used for comparison with a reference group of (German) people after cancer. With the help of this tool, the deviation of the patient's score compared to the reference group can be calculated for each dimension. Because there is doubt about the validity of the division into sub-scales, the guideline panel recommends using these scores as a conversation aid and not as a definitive diagnostic tool. The *z*-scores are included as appendix C.4-3.

The evidence-to-decision form for exercise interventions for fatigue is included as appendix C.4-4.

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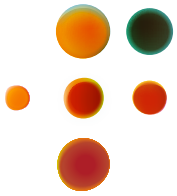
The KNGF aims to create the conditions in which high-quality physical therapy care can be provided that is accessible to the entire Dutch population, whilst recognising the professional expertise of the physical therapist.
The KNGF represents the professional, social and economic interests of over 18,000 registered physical therapists.



The physical therapists of the Netherlands

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