Doctoral thesis submitted to
the Faculty of Behavioural and Cultural Studies
Heidelberg University
in partial fulfillment of the requirements of the degree of
Doctor of Philosophy (Dr. phil.)
in Sport Science

Title of the publication-based thesis

Development and prevention of chemotherapy-induced peripheral neuropathy and associated impairments of postural control: The role of physical activity and structured exercise programs

presented by
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year of submission
2020

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”Wie komm ich am besten den Berg hinan?
Steig nur hinauf und denk nicht dran!“

Friedrich Nietzsche

Danksagung

Wenn ich auf die vergangen viereinhalb Jahre zurückschaue, fühlt es sich an, als würde eine lange Reise hinter mir liegen. Eine Reise auf der es gilt neue Sprachen zu lernen, auf dem Ozean sicher zu navigieren, Vulkane zu erklimmen, in dichten Urwäldern oder trockenen Wüsten nicht verloren zu gehen und so dem Ziel Schritt für Schritt näher zu kommen. Ich blicke heute auf eine sehr prägende, lehrreiche Zeit zurück und bin stolz diese Reise gemeistert zu haben. Doch einen solch langen, teils anstrengenden Weg geht man nicht allein. Daher möchte ich mich bei allen bedanken, die mich begleiteten, mir den Weg erleichterten und meinen Rucksack mit mir trugen.

Zuallererst möchte ich den Patienten danken, die sich bereit erklärten, an unserer PIC Studie teilzunehmen. Ich erachte es als nicht selbstverständlich, sich unmittelbar nach der Diagnose Krebs und bevorstehender Chemotherapie auf eine Sportinterventionsstudie einzulassen. Ohne diese Menschen, gäbe es die vorliegende Arbeit nicht. Die vielen starken, tapferen und dankerfüllten Persönlichkeiten sind mir ein Vorbild und bleibende Erinnerung. Ich bin dankbar, dass ich Sie begleiten durfte!

Der nächste große Dank gilt meinem Doktorvater PD Dr. Joachim Wiskemann. Chronologisch betrachtet zunächst einmal für deine Hartnäckigkeit mich nach Heidelberg in deine Arbeitsgruppe ONKOLOGISCHE SPORT UND BEWEGUNGSTHERAPIE am Nationalen Centrum für Tumorerkrankungen (NCT) zu holen. Ich danke dir für die übertragene Verantwortung und das damit entgegengebrachte Vertrauen, den Raum für offene Gespräche, für die Freiheiten in der Ausgestaltung meiner Arbeit sowie die Unterstützung bei der Findung und Umsetzung meiner wissenschaftlichen Ziele.

Mein Dank gilt auch meinem Zeitbetreuer Prof. Dr. Thorsten Stein und Dr. Steffen Ringhof, die ihre Expertise rund um die Posturographie mit mir teilten und auch darüber hinaus geschätzte Ratgeber waren. Besonders danken möchte ich auch PD Dr. Markus Weiler für sein bemerkenswertes Engagement, die konstruktiven Ratschläge und den unverzichtbaren, aufmerksamen Blick aus der neurologischen Perspektive. Darüber hinaus danke ich Prof. Dr. Lars Donath, der sich bereit erklärt hat, als Zweitgutachter für die vorliegende Dissertation zu fungieren.

Weiterhin geht ein besonderer Dank an die Mitarbeiter und Unterstützer der PIC Studie. Allen voran möchte ich meiner Kollegin Christine Boos danken. Nach den drei Jahren gemeinsamer Studienarbeit kann ich nur ein Fazit ziehen: Jede Doktorandin braucht eine Christine. Danke für deinen herausragenden Einsatz, deine stets lösungsorientierte Art und moralische Unterstützung in jeder Lebenslage. Ebenso möchte ich mich bei Laura Jansen für ihren großartigen Windschatten, nicht nur auf den Straßen, sondern auch im Arbeitsalltag am NCT bedanken.

Darüber hinaus bin ich den geduldigen Weglotsen Dr. Martina Schmidt und Sabine Holzmeier im dichten Dschungel der SAS Macro Programmierung dankbar. Prof. Dr. Friederike Rosenberger möchte ich für ihre supportive, positive Art danken, mit der sie unsere Arbeitsgruppe begleitet. Ebenso danke ich dem restliche Team der AG Onkologische Sport und Bewegungstherapie für das wertschätzende Arbeitsklima und den lebhaften Austausch.

Ich danke auch denen, die bereit waren, die unzähligen Entwürfe dieser Dissertation Korrektur zu lesen und somit einen wertvollen Beitrag leisteten, diese Dissertation in die nun präsentierte Form zu bringen, allen voran Annegret Preuß.

Ein tiefempfundener Dank gilt meinem jahrelangen Freund und geschätzten (ehemaligen) Arbeitskollegen Matthias Limbach, der mir den Start in die neue Aufgaben am NCT Heidelberg und das Verlassen meiner damaligen Heimat Freiburg zu einem leichtfüßigen Abschnitt gemacht hat. Angeliki Tsiouris, die immer nur „20 Minuten" entfernt war, wenn ich sie brauchte und Kathrin Schlüter für das morgendliche „Go Go Go" und die intensive Wegbegleitung so kurz vor dem Gipfel. Ein besonderer Dank geht auch an meine anderen Reisegefährten Dorothea Clauss, Alexander Haussmann, Sophie Scherer, Justine Schneider und Isabel Weinstein, allesamt liebe und wertvolle Menschen, die die Enttäuschung um die ausgebliebenen Fanfarenklänge bei der ersten Paper Submission mit mir teilten und mir mit ihren Einschätzungen und Taten nicht nur auf dem Weg der Promotion immer zur Seite standen.

Darüber hinaus möchte ich meinen Eltern dafür danken, dass sie es mir immer ermöglichten, all meinen Interessen nachzugehen und dass ihre Tür für mich stets offen steht. Ich danke meiner Schwester für ihre ständigen Ermutigungen und bedingungslose (häufige last-minute) Unterstützung. Und zu guter Letzt möchte ich mich aus tiefstem Herzen bei Daniel bedanken, für die Sicherung in den ausgesetzten Wegpassagen, die motivierende Begleitung im Flachland und vor allem dafür, dass du immer an mich geglaubt hast.

Heidelberg, September 2020

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Abstract

"Avoid inactivity!" is a central statement in the physical activity guidelines, not only for healthy people but also for cancer patients. This clear appeal is based on a body of evidence that has grown exponentially over the last decade, showing that exercise is not – as originally thought – harmful to cancer patients, but can positively influence a number of acute, persistent and late treatment-related side effects. While tumor-related fatigue is probably the most frequently investigated side effect in exercise oncology research, chemotherapy-induced peripheral neuropathy (CIPN) has been addressed much less frequently.

CIPN refers to a condition of peripheral nerve damage and degeneration processes caused by various neurotoxic chemotherapeutic agents. Affected patients mainly suffer from sensory symptoms, such as tingling, burning, pain, and numbness in hands and/or feet. A more severe CIPN may also be accompanied by motor symptoms, including e.g. paresis. The frequently resulting functional limitations, which are particularly evident in impaired fine motor skills and postural control deficits, play a key role in the loss of independent performance of various activities of daily living. CIPN thus has a major negative impact on quality of life, but possibly also on recurrence and mortality rates due to chemotherapy dose-modifications with increasing CIPN symptom burden.

Effective prevention and treatment measures, however, do not yet exist, creating an urgent need for further research. The cumulative dissertation at hand is therefore intended to contribute to this research area by (a) comprehensively analyzing the association between CIPN and postural control of cancer patients before, during and up to six months after neurotoxic chemotherapy, and (b) addressing the preventive potential of exercise on the onset of CIPN during neurotoxic chemotherapy. The underlying three manuscripts are based on the data of a randomized controlled trial (PIC study, prevention of chemotherapy-induced peripheral neuropathy through sensorimotor training), designed to evaluate the preventive potential of regular sensorimotor exercise training (SMT) and resistance training (RT) during neurotoxic chemotherapy compared to usual care (UC). Within this RCT, comprehensive state-of-the art assessment techniques were used to quantify postural control (center of pressure (COP) analysis via force plate) as well as CIPN signs and symptoms (Total Neuropathy Score, EORTC QLQ-CIPN20 questionnaire).

The first manuscript investigated postural control in cancer patients (sub-sample of the UC group, n = 35) before and after neurotoxic chemotherapy and compared these data to healthy aged, gender, height, and weight one-to-one matched controls (HMC, n = 35). Despite a larger proportion of patients showing reduced sensory nerve quality at baseline, postural control did not differ from the HMC population. However, three weeks after completion of neurotoxic chemotherapy, cancer patients showed significantly increased temporal and spatial COP measures in bipedal balance tasks, compared to baseline and HMC. These balance deficits were most evident under visual deprivation. Together with the increased CIPN signs and symptoms shown, this may indicate that the neurotoxic agents have impaired the somatosensory feedback, which was further supported by negative correlations, especially between COP parameters and electrophysiologically assessed sensory and motor nerve function (nerve conduction studies, NCS).

The second manuscript completes the postural control analysis i.a. with a description of

postural control development within six months after chemotherapy. Interestingly, our UC patients (n = 54) recovered from postural instability despite persisting CIPN signs and symptoms and pathologic NCS findings. Due to this counterintuitive course and because the correlation analyses in Manuscript I revealed only moderate associations of postural control with clinically assessed CIPN signs and symptoms three weeks after neurotoxic chemotherapy, we analyzed whether postural control in cancer patients treated with neurotoxic agents is additionally affected by other factors than CIPN alone. Based on regression models, the influence of age, BMI, sensory and motor nerve function (NCS), physical activity and muscle strength on the course of postural control during and after neurotoxic chemotherapy was analyzed. The regression model showed that worse baseline sensory nerve function was a preventive factor for the impairment of postural control, while worse baseline motor nerve function predicted a greater impairment of postural control. However, no influencing factors for the regeneration of postural control in the follow-up period were found within our models. We assumed, that (pre-)therapeutically disturbed somatosensory inputs may induce adaptive processes, such as muscular co-contractions or sensory reweighting, that have compensatory effects and allow recovery of postural control, while CIPN signs and symptoms and pathologic peripheral nerve function persist.

Finally, the third manuscript aimed to provide evidence on the preventive potential of exercise on CIPN. Therefore, the complete PIC study cohort of N = 159 cancer patients were analyzed. Our primary intention-to-treat analysis revealed that neither SMT nor RT was able to prevent the onset of CIPN signs and symptoms during neurotoxic chemotherapy. However, as mean attendance rates within the exercise groups were relatively low (overall 61 %), we excluded non-adherent patients for exploratory per-protocol analysis (attendance rate < 67 %). The results showed that subjectively perceived sensory symptoms in the feet increased less during chemotherapy in the adherent exercisers (pooled group: SMT + RT) compared to UC. Moreover, on the functional level, we identified a better course of muscular strength in favor of this group, but only a trend-level preventive effect for postural control. Additionally, we observed better results in terms of overall quality of life, physical and role functioning, and fatigue in the adherent exercisers, as well as enhanced chemotherapy compliance by means of relative dose intensity.

In conclusion, this cumulative dissertation provides comprehensive information about postural control in cancer patients before, during and up to six months after neurotoxic chemotherapy and its associations to CIPN signs and symptoms, but also CIPN-independent influencing factors. However, the methods used cannot provide a final explanation for the regeneration of postural control despite persisting nerve damage after the end of chemotherapy, which needs to be investigated in future analyses. On the other hand, the present work makes an important contribution to the evaluation of the preventive potential of exercise on CIPN during neurotoxic chemotherapy by demonstrating that SMT and/or RT alleviate subjectively perceived sensory CIPN symptoms in the feet, if an appropriate training stimulus is achieved. Additionally, better chemotherapy compliance was observed in these patients, which may further positively affect recurrence and mortality rates. Even if these results are based on secondary analyses and need to be verified by future studies, they are in line with the large body of evidence in exercise oncology recommending regular exercise throughout the entire cancer continuum.

List of scientific manuscripts for the publication-based dissertation

Manuscript I

Müller, J., Ringhof, S., Vollmer, M., Jäger, L. B., Stein, T., Weiler, M., & Wiskemann, J. (2020). Out of balance – Postural control in cancer patients before and after neurotoxic chemotherapy. Gait and Posture. doi:10.1016/j.gaitpost.2020.01.012

Manuscript II

Müller, J., Kreutz, Ch., Ringhof, S., Köppel, M., Kleindienst, N., Sam, G., Schneeweiss, A., Wiskemann, J, & Weiler, M. (under review). Chemotherapy-induced peripheral neuropathy: Longitudinal analysis of predictors for postural control. Submitted to *Scientific Reports* on September 12, 2020.

Manuscript III

Müller, J., Weiler, M., Schneeweiss, A., Haag, G.M., Steindorf, K., Wick, W., & Wiskemann, J. (submitted). Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: a randomized controlled trial. Submitted to *Annals of Oncology* on October 1, 2020.

1

General background

The World Health Organization International Agency for Research on Cancer (WHO-IARC, Global Cancer Observatory) estimated that 18.1 million people were newly diagnosed with cancer in 2018 [1]. It is expected that this number will increase by more than 60% to 29.5 million people by 2040 [1]. However, this alarming development is contrasted by significantly improved disease-free and overall survival in the last decades due to continuous improvements of cancer early detection and treatment [1-3]. The latter, however, is often accompanied by the use of more aggressive treatment regimes, thus bringing treatment-related long-term side effects into focus [4]. Therefore, some tumor diseases require the administration of certain chemotherapeutic agents, which can lead to painful nerve damage. The incidence of so-called chemotherapy-induced peripheral neuropathy (CIPN) is variable and significantly influenced by the total dose and the drug type administered. Overall, 57.7% to 78.4% of patients report CIPN symptoms within the first month after completion of neurotoxic chemotherapy [5].

Affected patients primarily suffer from a disturbed sensory perception, which, in addition to feelings such as numbness, burning, tingling and pain in hands and feet, can also result in balance and gait instability [6]. The symptoms may ease after some time, but often accompany many patients throughout their lives [7]. Until a few years ago, it was assumed that CIPN rarely led to severe limitations for those affected [8]. A growing body of literature today, however, describes that CIPN symptoms are associated with considerable restrictions in everyday life and thus also in the overall quality of life [9,10], which is reflected not least in higher healthcare costs of CIPN patients ($17'344 higher on annual average than controls without CIPN symptoms) [11]. In addition, CIPN may have a negative effect on cancer recurrence rates and overall survival, as chemotherapy may be postponed, reduced or even discontinued completely with increasing CIPN symptom burden [12].

At present, however, neither effective prevention nor rehabilitation measures exist. The latter therefore focus on the symptom management [2]. Exercise seems to be a promising approach to positively influence functional limitations, such as balance (postural) instability (e.g. [13]). Based on the results of a – in my opinion – landmark study of research on diabetic peripheral neuropathy [14], as well as retrospective analyses [15] and animal model studies in the field of CIPN [16], the hypothesis can be derived that exercise may also have a preventive (neuroprotective) effect. This has already been addressed by means of some secondary [17-19] but also primary analyses of randomized controlled trials (RCTs) [20-22]. However, the results are not yet con-

clusive, which, in addition to a rather rudimentary CIPN diagnosis, is probably also due to small sample sizes especially in the latter studies. For this reason, the present dissertation investigates the preventive potential of regular sensorimotor exercise training during neurotoxic chemotherapy in N = 159 cancer patients (PIC study, prevention of chemotherapy-induced peripheral neuropathy through sensorimotor training). Furthermore, the influence of neurotoxic chemotherapies on postural control is investigated in longitudinal sub-analyses based on the waiting-list control group of the PIC study and healthy matched controls.

In order to classify the present dissertation within the overall scientific context, the following section briefly outlines the developments and results of the research area of exercise oncology (Chapter 1.1). Thereafter, CIPN including its symptoms and functional limitations, pathophysiology, diagnostics and potential forms of prevention and treatment measures are discussed in more detail. Based on the current state of research on exercise oncology in the field of CIPN (Chapter 1.3), the research gaps addressed in the present dissertation are derived in Chapter 1.4. These are followed by an outline of the methodology of the PIC study (Chapter 2) and the associated papers (Chapter 3 – 5). Finally, the research findings are discussed in summary in Chapter 6.

1.1 Exercise oncology

In the past, cancer patients were advised to rest and avoid physical overexertion, especially during active cancer treatment [23]. Nowadays, however, it is clear that "avoid activity" does not lead to the intended strengthening of the body for the often debilitating therapies and must rather be replaced by "avoid inactivity" [24,25]. This paradigm shift is based on a body of evidence that has grown exponentially over the last decade in the field of exercise oncology [26]. While the first meta-analysis in 2005 summarized the results of 32 randomized controlled trials (RCTs) [27], current literature provides umbrella reviews, which summarize the numerous effects of physical activity[1] from more than 140 individual reviews and met-analyses throughout the entire cancer continuum [28,29]. The investigated outcomes address various health issues resulting from the disease, its treatment, and related comorbid conditions [3]. The effects found include improvements on physical fitness and function (e.g. peak oxygen consumption, strength, and flexibility), body composition (e.g. lean body mass), psychological function (e.g. mood, depression, anxiety), cancer related fatigue, overall and health-related quality of life as well as several biomarkers associated with cancer progression [28,29]. These beneficial effects on biopsychosocial levels have been demonstrated for most cancer entities and independently of the specific timing of exercise, i.e. during and after active cancer treatment [28] – albeit partly with varying effect sizes [29]. However, physical activity (especially after diagnosis) cannot only improve the overall quality of life, but may also prolong the survival of patients with breast, colon and prostate cancer (based on observational studies) [30,31]. In addition, more recent research approaches also focus on so-

[1] In the present dissertation, the term "physical activity" covers the entire movement behavior related to occupation, everyday life and leisure time of an individual. The term "exercise", on the other hand, refers to targeted training sessions, which primary includes traditional exercise modalities, i.e. endurance and/or resistance training, but sometimes also less common exercise modalities (e.g. yoga, sensorimotor exercise training) [28]. Therefore, when referring to an exercise intervention the specific modality will be named in detail.

called prehabilitation, which may reduce postoperative complications and thus achieve a faster recovery of functional status [32,33]. It is also discussed whether the tolerability of active cancer treatment (especially chemotherapy) can be increased by prehabilitation [28].

Additionally, specific training recommendations have been extracted from the current literature, which focus on tumor- and/or treatment-related side effects and are hence independent of the entity [25]: A minimum total dose of 90 minutes moderate endurance training plus ideally two sessions of resistance training per week is advised to cancer patients today to positively influence many of the investigated outcomes, including anxiety, depressive symptoms, fatigue, physical functioning, and health-related quality of life. For other outcomes and training modalities (e.g. yoga or therapeutic exercises), however, the existing evidence is still too heterogeneous to derive specific training recommendations, or preliminary training recommendations need to be verified by further studies.

In conclusion it can be stated that exercise in cancer patients is not only safe – taking into account possible contraindications [24,34] – but can also positively influence a number of acute, persistent and late treatment-related side effects [28]. However, the side effects have not been addressed in the same frequency in exercise oncology research so far: While cancer-related fatigue was probably the most frequently investigated [28], CIPN has rarely been the subject of scientific research – presumably also due to the relative complexity of the diagnosis. The present dissertation is therefore intended to contribute to closing this research gap by addressing CIPN prevention through exercise during the active treatment phase of chemotherapy.

1.2 Chemotherapy-induced peripheral neuropathy

CIPN is a common side effect which may be observed from the first administration of neurotoxic drugs [35,36]. The following substance classes and their associated drugs are known to cause injuries to the peripheral nervous system and thus CIPN symptoms [6,37-39]:

- Platinum compounds — cisplatin, carboplatin, oxaliplatin
- Taxanes — paclitaxel, nab-paclitaxel, docetaxel
- Vinca alkaloids — vincristine, vinblastine, vinorelbine, vindesine
- Epothilones — ixabepilone
- Immunomodulatory agents — thalidomide, lenalidomide
- Proteasome inhibitor — bortezomib

A systematic review and meta-analysis including 31 studies with data from 4,179 adult patients summarized a CIPN prevalence of 68.1% (57.7–78.4) in the first month after completion of neurotoxic chemotherapy [5]. Affected patients primarily suffer from sensory and motor dysfunctions, which in about 30% (6.4–53.5) of patients persist for six months [5], but may still be present five and twelve years after therapy [40,41]. The resulting functional limitations, such as balance (postural) instability and gait difficulty, can even be partly measured five to ten years after completion of neurotoxic therapy [42,43]. Overall, CIPN symptoms and functional limitations may have a moderating effect on patients' independence and quality of life [6], but also on cancer

recurrence and mortality due to dose reductions during therapy [12].

In order to get a comprehensive picture of this neurotoxic side effect, the symptoms, functional limitations (especially postural instability) and pathophysiology as well as the diagnosis, prevention and treatment measures will be discussed in detail in the following. Whenever necessary, reference is made to the literature on diabetic research (diabetic peripheral neuropathy (DPN)), since some aspects of CIPN have not yet been sufficiently investigated.

1.2.1 Symptoms

Since the above mentioned neurotoxic agents affect different parts of the peripheral nervous system, the clinical picture of CIPN can be characterized by sensory, motor, and autonomic symptoms [6]. Somatosensory (afferent) peripheral nerve fibers are usually injured first due to their thinner or non-existent myelin layer [7]. Therefore, symptoms such as paresthesia (e.g. tingling, numbness, burning, disturbed sensitivity to cold or heat) and dysesthesia (painful sensations) are most frequently reported by CIPN patients (sensory neuropathy) [6]. In addition, impairments of the somatosensory function due to changes in deep sensitivity and proprioception are crucial in the development of postural instability (see Chapter 1.2.2). The symptom pattern of a more severe CIPN can further be accompanied by motor symptoms due to neurotoxic lesions of the motor (efferent) peripheral nerve fibers (motor neuropathy) [6]. For example, DPN patients show less muscle strength than healthy controls [44,45]. However, comparable studies for CIPN patients have not yet been published. In high-grade CIPN, this reduced muscle strength can further develop into severe paresis (particularly of foot dorsiflexors) [46]. Additionally, as a combined consequence of motor and sensory nerve injury, fine motor skills are often hampered, which becomes apparent in many activities of daily living (ADL), such as closing buttons [47]. The sensory and motor symptoms described primarily occur in the periphery of the extremities and spread proximally with increasing disease severity. The large surface area of these longest nerve fibers may lead to a higher exposure to neurotoxic agents and is therefore discussed as the reason for this so-called "glove and stocking" distribution [6]. Damage to the autonomic nervous system is very rare in CIPN, but may lead to impaired organ function, e.g. constipation, orthostatic hypotension, urinary dysfunction, sexual dysfunction [35].

1.2.2 Postural instability

The symptoms described above may result in further functional limitations. As already indicated, the loss of sensory perception can be associated with various motor impairments. Besides the impairment of fine motor skills, the negative impact of CIPN on postural control is one of the major side effects limiting the patient's quality of life and susceptibility to falls [6,48]. The destabilizing effect of CIPN was first described by Wampler et al. [49] for breast cancer patients and was repeatedly substantiated by further studies [42,43,50-54] (see exemplary graphic representation in Figure 1). Since one focus of the present dissertation lies on the change of postural control under the influence of neurotoxic chemotherapy, the theoretical background as well as the basic terminology in this context will be explained as far as relevant in the following.

Without postural control[2], normal activities of daily living, such as climbing stairs, walking or simply standing upright, would not be possible [56]. Herein, the main tasks of postural control are the maintenance of POSTURAL ORIENTATION and of POSTURAL STABILITY [57]. That means that sensory information about the whole body and its segments in relation to a reference point (postural orientation) is centrally integrated and processed, with the aim of maintaining the body's center of mass (COM) above the base of support (BOS) through the interaction of various sensorimotor processes (postural stability) [56,58,59].

In the literature three different TYPES OF BALANCE CONTROL are distinguished: steady-state, reactive, and proactive balance [55]. However, in most of our motor activities these three forms do not occur separately but in combination [55]. In the PIC study and most of the other studies presented later, steady-state balance was assessed via static posturography (see Figure 1), which describes a state of balance in a constant and predominantly predictable environment/situation (e.g. standing quietly) [55]. Reactive postural control describes, as the name indicates, the postural control process after a disturbing stimulus (e.g. stumbling over an object). Whereas the third form describes exactly the opposite and is characterized by a proactive muscle contraction before a potentially destabilizing stimulus (e.g. lifting a heavy object) [55].

In order to maintain balance in the described situations, the interaction of sensory, motor and central processes is crucial, which together form the INDIVIDUAL POSTURAL CONTROL SYSTEM [55]. Within this system, the interaction of feedforward and feedback mechanisms is necessary. Feedforward mechanisms generate anticipatory postural adjustments, e.g. in the form of muscle contractions before a potentially destabilizing voluntary movement, and are therefore predominant in proactive balance situations (reviewed in e.g. [60]). On the other hand, feedback mechanisms serve the error detection and correction of body sway motions [61]. Feedback mechanisms are predominant in steady-state and reactive balance situations and therefore of primary interest in the present dissertation: The sensory system provides the essential information on the basis of visual, vestibular and somatosensory receptors [59]. The weighted sum of these inputs is used by the central nervous system (CNS) to detect postural sway and subsequently to generate adequate corrective internal forces via a motor command [59] (usually by recruiting muscular synergies [55]) to maintain or restore balance and thus to prevent a fall [55,58]. The ENVIRONMENT can influence how sensory, motor, and cognitive systems are organized to control balance [55]. For example, an instable surface can modify the muscular activation (e.g. increased muscular co-contraction) [55] and may also cause a shift in the processing of sensory information due to conflicting sensory inputs (e.g. down-weighted processing of somatosensory information and an elevated processing of visual and vestibular information; sensory reweighting theory) [59,62].

The neural mechanisms of the postural control system initiate different POSTURAL CONTROL STRATEGIES depending on the situation and available sensory information. Herein, the fixed-support strategies (ankle and hip strategy) serve to keep the COM above the BOS [55]. In unperturbed steady-state situations (with feet side-by-side), postural stability in anterior-posterior (AP) direction is primarily controlled by the ankle strategy which is based on somatosensory in-

[2] Postural control is often used interchangeably with the terms balance, equilibrium and posture [55].

formation (one-segment inverted pendulum with the subtalar joint as fixed point) [63,64]. In case of faster perturbations or, e.g. when the support surface is smaller than the feet and thus the COM is close to the boundary of the BOS, the postural stability cannot further be controlled only by the ankle-strategy [55]. Consequently the hip strategy is applied which produces large and rapid motion at the hip joints accompanied by antiphase rotations of the ankles (two-segment inverted pendulum) [55,63]. The hip-strategy relies more on vestibular information [64] and does not only compensates AP but also medio-lateral (ML) sway motions in side-by-side stance by a load/unload strategy via abductors and adductors [63]. In standing positions where the feet are not side-by-side but in line (e.g. tandem stance) the fixed-support postural control strategies for AP and ML sway are reversed (AP: hip strategy, ML: ankle strategy) [63,65]. However, if these strategies are unable to control the COM above the BOS, the BOS is ideally increased, e.g. by a step, in order to bring the COM back within the boundaries of a now enlarged BOS and thus prevent falling (change-in support/stepping strategy) [55].

The apparently simple task of standing quietly is, in summary, dependent on the successful complex interaction of the sensorimotor system [59]. Consequently, impairments in one or more of these subsystems may lead to POSTURAL INSTABILITY [57]. With regard to CIPN, somatosensory feedback is impaired, due to chemotherapy-induced damage of preferentially afferent sensory nerves [66,67]. Thus, information relevant for maintaining an upright posture are disturbed or absent, i.e. information about surface condition (pressure and touch receptors in the skin), body segments position as well as muscle tension and length (muscle and joint receptors: muscle spindle, Golgi tendon organ, Pacinian corpuscle) [48,56,59]. Accordingly, researchers were able to demonstrate a significant correlation between postural instability while standing quietly and sensory peripheral neuropathy in DPN patients [68]. However, postural instability in CIPN patients may also induce gait difficulties [51,69,70] and a higher risk of falling [69] and might further be amplified by reduced muscle strength, which can be seen in cancer patients after chemotherapy [71] (biomechanical prerequisites for postural control (see e.g. [57]).

In general, limitations in lower limb functionality play a key role in the loss of independent performance of various ADLs, which in turn has a negative impact on the quality of life [6,48]. For this reason, it is tremendously important to treat not only the "direct" symptoms but also the functional limitations in CIPN patients. The treatment approaches currently being pursued are described in Chapter 1.2.6. However, the following chapters will first address the underlying pathophysiological mechanisms (Chapter 1.2.3) as well as how CIPN can be diagnosed (Chapter 1.2.4) and potentially prevented (Chapter 1.2.5).

1.2.3 Pathophysiology

The pathophysiology of CIPN has a paradoxical aspect: It is still unclear why some chemotherapeutic agents, which actually damage fast-dividing tumor cells, also damage post-mitotic neurons [37]. As mentioned before, the anticancer drugs most commonly associated with CIPN are taxanes, platinum derivatives, and vinca alkaloids [6]. In addition to these classic anticancer drugs, the newly developed immunotherapy has also increased the risk of neurological (immune-related) adverse events [39]. However, the onset and persistence of CIPN symptoms depends not only on the drug type but also on the cumulative dose, comorbidities (especially pre-therapeutic peripher-

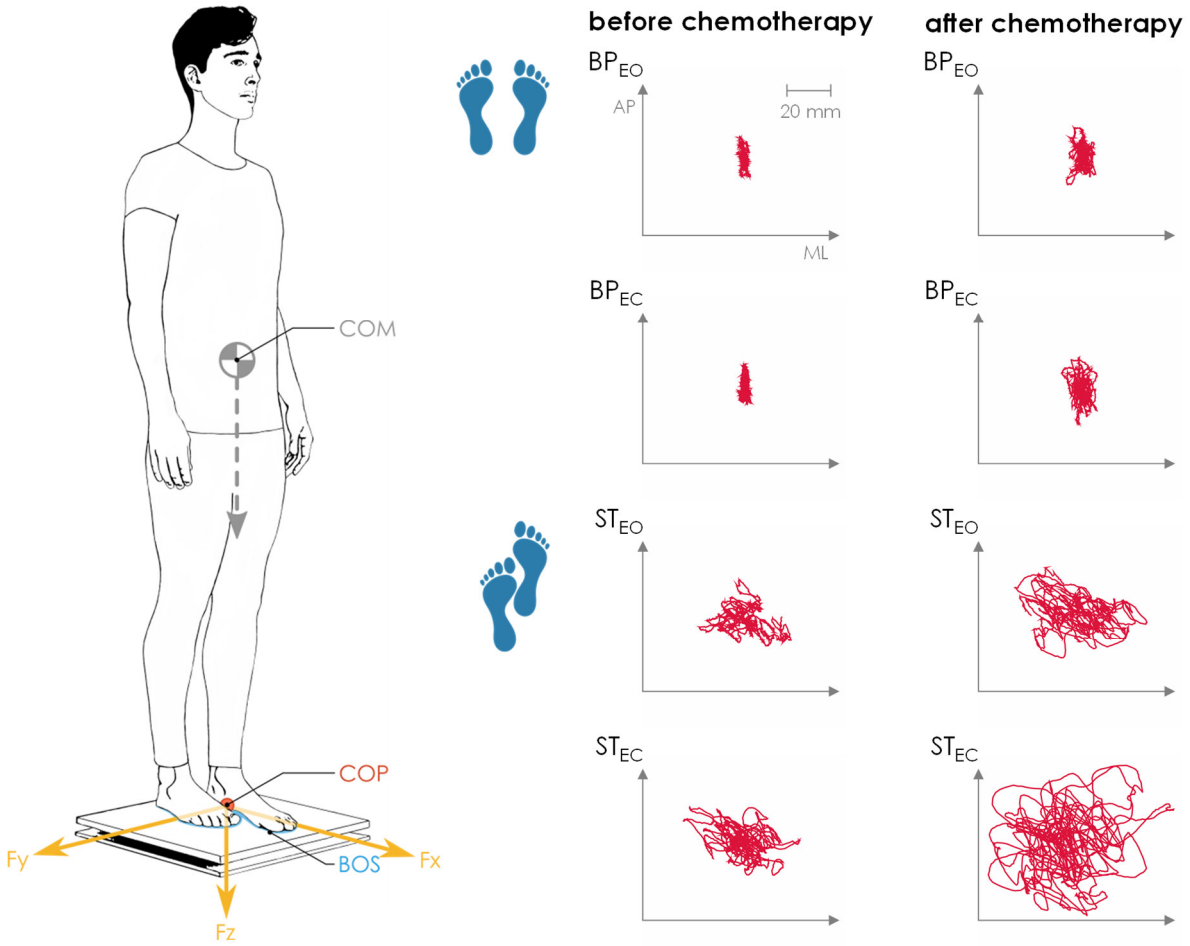

Figure 1. Assessment of postural control using a force plate. This combined figure shows a) on the left side a schematic representation of a static posturography on a force plate and b) on the right side exemplarily the resulting center of pressure (COP) statokinesigrams of a breast cancer patient before and after 25 weeks of neurotoxic chemotherapy (Paclitaxel; PIC study, patient no. 017) in four different standing positions: bipedal stance (BP) and semi-tandem stance (ST), both with open (EO) and closed eyes (EC). For a better understanding a short overview of the theoretical background of posturography will be given: The high center of mass (COM) within the human body together with the small support area and the many joints result in the fact that even quite standing (steady-state balance) is not absolutely motionless [63]. These permanent sway movements (predominantly in anterior-posterior direction) reflect the efforts of the postural control system to counteract the destabilizing gravitational forces [63]. The primary goal is to control (the vertical projection of) the COM within the boundaries of the base of support (BOS) and thus to prevent the loss of balance [55]. The measurement of the COM is therefore a possibility to detect the addressed sway movements [72]. However, this (direct) measurement of COM is difficult to implement from a temporal and methodological perspective, so that indirect measurements are often preferred to quantify postural control [72]. In this context, the most commonly used method is (static) posturography using a force plate, which measures the ground reaction forces under the area of the feet [72,73]. Based on the measured forces (F_x, F_y, F_z), COP can be calculated, which can be seen as a combination of sensorimotor response to the COM displacement and the COM position itself [55,72,74]. A large number of time, frequency and spatial domain measures can be calculated from COP data to quantify postural control (e.g. [73,75-77]) with the mean velocity (time domain), mean or median frequency (frequency domain) and standard deviation or total area (spatial domain) being the most commonly reported measures [78]. These measures are typically presented separately for anterior-posterior (AP, based on F_x) and mediolateral (ML, based on F_y) sway direction (not total area) with higher values indicating higher sensorimotor activity and thus poorer postural control [72].

al neuropathy), and genetic factors [5,39,79-81]. Lifestyle factors such as obesity and low moderate-to-vigorous physical activity also appear to influence the severity and duration of CIPN [40,82-84].

The underlying mechanisms of nerve damage and degeneration are complex and have not yet been fully understood [6,85]. In addition to the heterogeneity of the neurotoxic anticancer therapies mentioned above [37], this is also due to the different neurological structures which they affect [7]. Several reviews have been published addressing the different pathophysiological modes of action (e.g., [6,7,37]). To give an overview, the results of Park et al. [7] are summarized in the following:

Figure 2 illustrates the structures of the peripheral nervous system which are potentially impaired by neurotoxic agents. Starting proximally, the sensory cell bodies in the dorsal root ganglion (DRG) are a highly vulnerable structure that is located outside the protective blood-nerve barrier and thus come into contact with the neurotoxic agents more quickly. For example, platinum derivatives accumulate here, which can lead to cell death through DNA damage. Taxanes, vinca alkaloids, thalidomides and bortezomib are also associated with damage to the DRG. DRG are generally responsible for the transmission of afferent signals via sensory nerve fibres to the posterior grey column [86]. The damage to the DRG can thus be one explanation for the predominant sensory CIPN symptoms. In addition, some neurotoxic agents also lead to direct axonal toxicity, such as oxaliplatin. Oxaliplatin impairs the ion channel function, which disturbs or even inhibits transmission of electrical stimuli and information at the synaptic cleft. Contrary, this damage can also result in peripheral nerve hyperexcitability. In comparison, bortezomib and cisplatin affect the myelin layer (demyelinating damage). The myelin layer enables saltatory conduction [86], the damage of which consequently also impairs the transmission of electrical stimuli.

In addition to the primarily direct axonal damage described above, some neurotoxic agents lead to impairments in the supply structures of the axon, e.g. the microtubules, causing it to gradually degenerate. Among other things, microtubules are responsible for various substance transports within the nerve cell [19]. Taxanes, vinca alkaloids and bortezomib can destroy the microtubules, which can lead to restrictions in the axonal transport processes as well as the energy supply and ultimately cause cell death. In addition, a restriction in energy supply is also caused by direct damage to the mitochondria. For example, paclitaxel is associated with structure-changing processes in axonal mitochondria. In addition to the axonal degeneration, the repolarization of the axon is also not possible without adenosine triphosphate (ATP), which originates from the mitochondria [19]. Damage to the surrounding blood vessels – e.g. by thalidomide – also leads to interruption of substance transport chains and thus to an undersupply of the axon.

In summary, the pathophysiological mechanisms of CIPN differ in terms of whether the neurotoxic agent causes direct damage to the axon or its myelin layer or initiates degeneration of the axon [7]. Since damage to the myelin layer predominantly associated with the administration of bortezomib and cisplatin and/or high toxicity (see Figure 2), axonal damage (both direct and indirect) is generally more frequent in CIPN than demyelination [7,87]. Nevertheless, both pathophysiological mechanisms result in a disturbed communication between the peripheral and the central nervous system, causing the described symptoms and functional limitations. As already

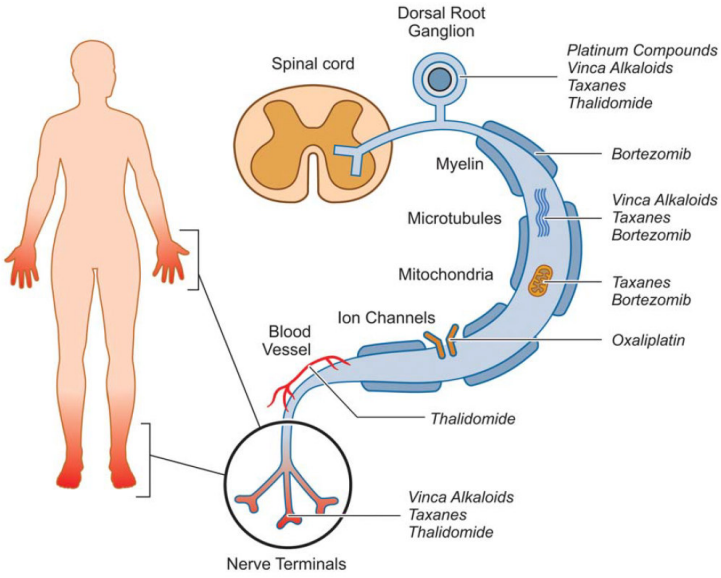

Figure 2. Pathophysiological mechanisms of neurotoxic chemotherapeutic agents. This figure was reprinted from [7] with kind permission of John Wiley and Sons [license number: 4823641403145].

previously discussed, from a human movement science perspective it is particularly important to note this inadequate stimulus transmission hampers somatosensory perception, which is associated with impairments in postural control. Before addressing the question of how to prevent and counteract these symptoms and functional limitations, the next chapter summarizes the diagnostic approaches to CIPN.

1.2.4 Diagnostic

The diagnosis of CIPN is as complex as its pathophysiology and the resulting clinical appearance. More than 100 different diagnostic approaches have been identified in the literature, which vary significantly in terms of reliability, validity, sensitivity and patients' compliance [88]. However, a gold standard for quantitative assessment and monitoring of CIPN does not yet exist [6,89]. In clinical-oncological practice, CIPN is most frequently assessed with so-called Common Toxicity Criteria (CTC) [89,90]. In the scientific setting, however, CTCs are not appropriate for monitoring the progress of CIPN because of their broad and partly poorly defined grading criteria [6,90,91]. Hence, for comprehensive CIPN assessment, current reviews recommend a combination of neurological and electrophysiological examinations plus patient-reported outcome (PRO) measures [88,89,92,93].

Nerve conduction studies (NCS; electrophysiology) are considered the most effective non-invasive method for determining the type of neuronal damage (axonopathy vs. demyelination) [87,94]. For this purpose, the nerve to be examined is electrically stimulated percutaneously (Figure 3). The resulting electrical excitation propagation is derived distally from the stimulation site above the innervation area of the sensory nerve or the innervated muscle (motor nerve). The most important outcome parameters are nerve conduction velocities (NCV) as well as sensory (SNAP) and compound motor action potential amplitudes (CMAP) [87,94]. Given the primary-

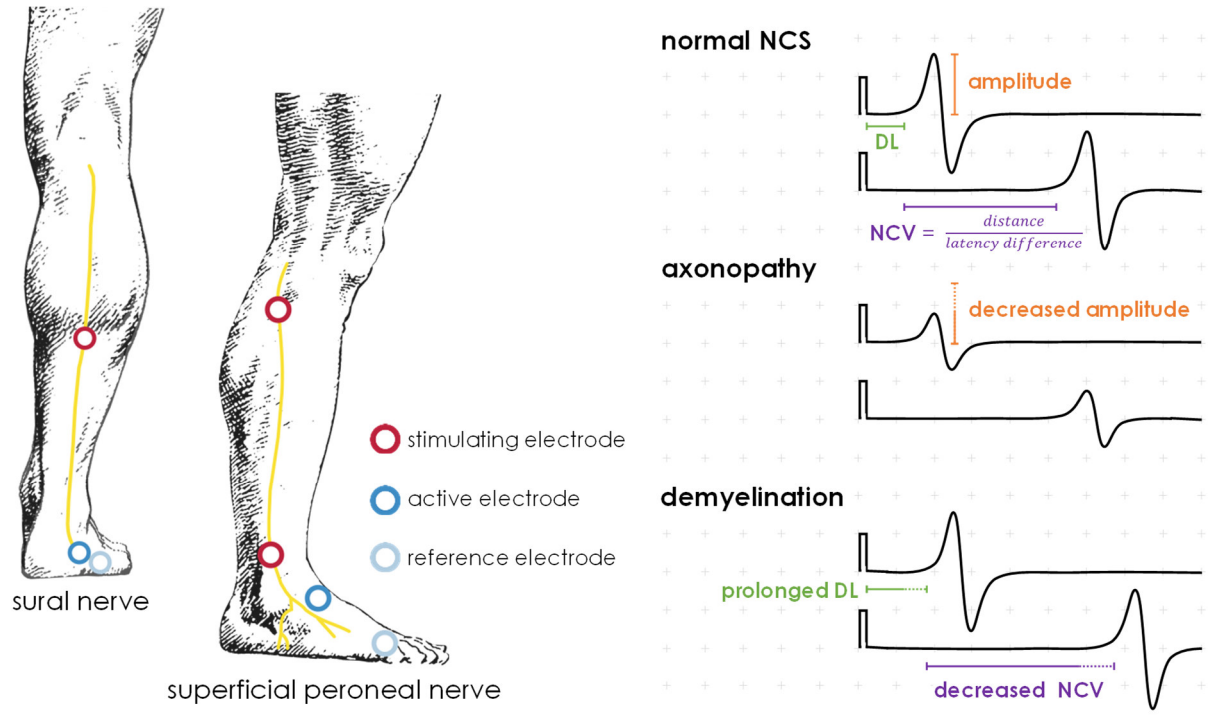

Figure 3. Nerve conduction studies (NCS) and their outcome parameters. The left side of this figure illustrates the characteristic setup of a NCS assessment to examine sensory (sural nerve) and motor (superficial peroneal nerve) nerve function of the lower extremities. The right side of this figure shows simplified diagrams of normal NCS outcome parameters and patterns of neuronal damage (axonopathy and demyelination).

ly axonal mechanism of neurotoxicity in CIPN, reductions of CMAP and particularly SNAP amplitudes can typically be found earlier, whereas reduction of NCVs are commonly first observed at more advanced stages of the disease [87,94,95]. However, NCS only reflect neuronal damage of the large myelinated and best surviving nerve fibers [87,96]. If only a small proportion and/or only the small non-myelinated nerve fibers (such as Aδ and C fibers) are affected, the results of NCS show normal values [87,96]. Therefore, comprehensive CIPN assessment should also include a thorough neurological examination of sensory nerve fiber functions.

The neurological examination of sensory nerve fiber functions assesses neuronal damage of myelinated and non-myelinated nerve fibers by applying various stimuli, e.g. cold/warm or sharp/blunt, and recording patients' reported perception [97]. In general, superficial sensation (sensation of touch, pain and temperature) and deep sensation (sense of position, movement and vibration) are analyzed [98]. Table 1 provides an overview of the stimuli used. Deep tendon reflexes and muscular strength are often additionally assessed as part of these so-called bedside assessments [98]. The impossibility of standardizing stimulus intensity leads to a predominantly qualitative evaluation [98]. Taking this limitation into account, quantitative sensory testing (QST) was developed, which enable an inter-examiner standardization of stimulus intensities. Due to the special equipment and training required and the very time-consuming assessments, QST has found little application in day-to-day clinical practice as well as in science [88,93,98].

Table 1. Neurological examination for the diagnosis of CIPN.

Sensory quality	Bed-side assessments	Receptor	Peripheral nerve fiber
Superficial sensation			
Touch sensation	monofilament, piece of cotton wool etc.	mechanoreceptors	Aβ
Temperature sensation	cold vs. warm water, thermo sticks (metal vs. plastic), thermorollers	thermoreceptors	Aδ (cold), C (warmth), free nerve ending (heat/cold pain)
Pain sensation [surface pain]	wooden cocktail stick	nociceptors	Aδ (early, sharp pain), C (late, dull pain), free nerve ending
Deep sensation			
Vibration sensation	graduated tuning fork (e.g. Rydell-Seiffer, 128 Hz)	Meissner's corpuscles (low frequency), Pacinian corpuscle (high frequency)	Aβ
Movement and joint positioning sensation	passive movement of toes/fingers (patient reports the direction) or extremities (patient imitates position with the opposite site)	muscle and joint receptors: muscle spindle, Golgi tendon organ, Pacinian corpuscle	Aα, Aβ

This table was modified from [99,100] and extended by further information from [101].

Neurological examinations of sensory nerve functions (and QST) are more sensitive in detecting minor symptom changes than NCS [102], but they do not provide information on the type of neuronal damage (axonopathy vs. demyelination). The combination of these two diagnostic approaches in so-called composite scores offers a higher sensitivity and reliability than the single examination alone [88,98]. Therefore, composite scores are considered the best available evidence-based CIPN assessment technique [88,98].

The Total Neuropathy Score (TNS) and its various modifications (TNS reduced (TNSr), TNS clinical (TNSc), TNS modified (TNSm)) is the most widely applied composite score in CIPN research [88,89,93]. The TNS scores both large and small fiber function, divided in four assessment parts: patient-reported symptoms, neurological examination (pin prick, reflexes, deep-sensitivity, strength), NCS and semi-quantiative sensory examination of the vibration perception threshold via vibrameter [88]. Each TNS item is rated on a 0 to 4 scale and summed up to a total score, with higher values reflecting more severe peripheral neuropathy. The less time-consuming modifications TNSr (without vibrameter) and TNSc (without vibrameter and NCS) are found to be valid, reliable and accurate in grading CIPN and sensitive in showing CIPN progression compared to the full TNS [89,103]. The detailed psychometric properties are comparatively presented by Park et al. [89]. Following the recommendation in the current literature to use the TNS or its modifications as CIPN assessment in clinical studies [88,89,92,93], the TNSr was implemented in

the later addressed PIC study. A table showing the assessments and the scoring used is given in the supplementary material of the present dissertation (Table S1, p. 114).

Low correlations between objective CIPN assessments and individual symptom perception of the patient [104,105] indicate that the subjective components of CIPN signs and symptoms are not satisfactorily captured by the assessments described above. Furthermore, objective CIPN assessments are often not sensitive enough to minor symptom changes [6]. For these reasons, scientists demand that PROs must be a crucial part of CIPN assessment [88,89,92,93]. The questionnaires FACT/GOG-Ntx and EORTC QLQ-CIPN20 are the most frequently used and represent therapy/symptom-specific modules of the core questionnaires FACT/G and EORTC QLQ-C30 [90,106]. The questionnaires measure the subjectively perceived impact of CIPN symptoms on everyday life and health-related quality of life (recall period of seven days). Both questionnaires are similarly constructed and show good psychometric properties and a good usability [88,92,107-110] – for summary see Park et al. [89]. For these reasons, both questionnaires are used alongside the TNSr in the PIC study to comprehensively assess CIPN signs and symptoms. The questionnaires are shown in Table S2 (p. 115) and Table S3 (p. 116).

In summary, it can be stated that the available literature cannot recommend any assessment for satisfactory CIPN diagnosis without reservation. This is not least due to the complex nature of the pathogenesis and the resulting clinical appearance of CIPN. However, the combination of the TNS and at least one PRO currently seems to be the best consensus between reliability, sensitivity, time and cost expenditure as well as patients' compliance in repetitive measurement settings [88,89,92,93]. Future studies will probably also use nerve MRI, ultrasound, skin biopsies and other assessments to further comprehensively describe the clinical picture of CIPN – at least in clinical studies – and perhaps sometime in the future to define a gold standard [98]. Regardless of how CIPN is diagnosed, measures to reduce symptoms and, at best, to prevent onset must be implemented, not least to limit the negative effects of CIPN on quality of life. The preventive and treatment approaches pursued are described in the following.

1.2.5 Prevention

Scientists have been researching pharmaceutical and non-pharmaceutical preventive measures for many years, with unsatisfactory results so far. Therefore, the current guidelines of the American Society of Clinical Oncology (ASCO) and the German S3 guideline for supportive therapy conclude that preventive measures for CIPN are currently lacking [80,111]. However, these guidelines did not take into account the recently published approaches regarding cyotherapy (cooling of hands and feet during chemotherapy administration), which may prevent/alleviate some CIPN symptoms [112,113] and thus may have a positive effect on chemotherapy completion rate [114]. Compression is also being investigated to achieve comparable results (e.g. by using surgical gloves that are too small [115]). However, this approach has been less effective so far, possibly due to methodological deficits in the study design.

Physical activity is another preventive approach that was not incorporated into the guidelines mentioned above, due to absence of randomized controlled trials. Possibly encouraged by Balducci et al. [14], who showed that endurance training can prevent the development of DPN, physical activity was investigated as a CIPN prevention measure, particularly in the last two years.

Since this preventive approach forms the basis for the present dissertation, the underlying studies are discussed in detail in Chapter 1.3.1.

1.2.6 Treatment

Clinicians are often faced with a dilemma after the diagnosis of CIPN, as no effective CIPN treatment currently exists [6,116]. In general, CAUSAL THERAPY addresses the change of pathophysiological causes. After the onset of CIPN and an associated reduction in quality of life, the first step therefore is often a dose-reduction or even the discontinuation of chemotherapy. Both measures must be reconciled with a potentially increased risk of cancer recurrence and mortality [80,92]. On the other hand, SYMPTOMATIC THERAPY approaches focus on symptom management by reducing pain, improving physical functioning, and thus positively influencing quality of life [2]. The pharmacological and non-pharmacological approaches used are outlined below.

PHARMACOLOGICAL TREATMENTS. Pharmacological treatment approaches of CIPN are (still) at the forefront of treatment options. However, very few drugs have proven their efficacy in clinical trials [38]. The drugs frequently used are anticonvulsants, antidepressants or opiates [38]. However, in the current guidelines cited above, only duloxetine was classified as potentially effective for the treatment of CIPN-related pain (moderate recommendation) [80,111]. Contrary to these recommendations, pregabalin is prescribed very frequently, although its efficacy has only been shown for DPN, but not for CIPN [38,117]. This, as well as the assumption that by 2027 three CIPN drugs will be launched with three completely different modes of action, underline once again that the pathophysiology of CIPN is still not sufficiently understood, and that there is an urgent need for further research [39].

NON-PHARMACOLOGICAL TREATMENTS. This area includes for example food supplements (e.g. vitamin E), acupuncture, massages, biofeedback and neurostimulation. Stubblefield et al. [6] found in their review that transcutaneous electrical nerve stimulation (TENS) can be effective in CIPN pain management. A similar conclusion was drawn in reviews concerning acupuncture treatments, which may improve not only pain but also subjectively perceived CIPN symptoms, but not nerve conduction velocity [118,119]. Additionally, photobiomodulation (low level laser therapy) may provide a modest effect on CIPN symptoms [38]. However, the available studies on these and other non-pharmacological treatments are generally sparse and in some cases anecdotal, so that no evidence-based recommendations can be provided to date [6,120].

Another, yet unmentioned, non-pharmacological treatment approach could be physical activity/exercise interventions. The cited guidelines only provided a positive expert consensus on exercise [80,111], as only one randomized controlled exercise intervention trial existed at the time of writing [17]. Meanwhile, however, seven RCTs have been published, which will be discussed in more detail in Chapter 1.3.2.

1.3 Exercise interventions during and after neurotoxic chemotherapy

A literature review was conducted in February 2020 and updated in June 2020 to identify relevant studies addressing CIPN prevention or treatment approaches based on exercise interventions (Figure 4). This review was guided by the criteria of other reviews [121,122][3], but was by definition not intended to be a systematic review. The following simple search term combination was developed for Medline (PubMed) and further modified for PEDro and Cochrane databases: "(chemotherapy induced peripheral neuropathy OR CIPN) AND exercise".[4] Based on the results of the literature search, additional reference lists (e.g. of clinical and/or practical guidelines) were hand searched for further relevant literature sources.

The criteria for considering studies for this review are addressed below, following the PICO structure [124]. In order to be included in the literature review, the studies (published before 13th June, 2020) had to investigate the effect of an exercise intervention on CIPN in adults (≥ 18 years) in a randomized controlled study design, either in a preventive or treatment approach. For this purpose, at least one objective or subjective CIPN assessment had to be used in a pre-post comparison. Studies including patients during or after non-neurotoxic chemotherapy and thus analyzed an inadequate patient cohort against the background of the research question of this review were excluded. The titles and abstracts and, if necessary, the full text were used to examine the inclusion and exclusion criteria. The remaining full texts were then critically analyzed (Figure 4). The results are presented separately below according to the following questions: (a) Can the occurrence of CIPN signs and symptoms be prevented by various exercise interventions? (b) Can CIPN signs and symptoms be treated by various exercise interventions? The PEDro Scale was used to demonstrate the methodological quality of the RCTs included [125].

1.3.1 Literature review: Exercise as preventive measure for CIPN

A total of 180 studies resulted from the literature search after duplicates had been removed. After examination of inclusion and exclusion criteria, six randomized controlled trials were identified that address the prevention of CIPN by means of various exercise intervention approaches during neurotoxic chemotherapy [17-22]. The quality of the studies varies between 3 [18,21], 6 [19,20,22] and 7 [17] on the PEDro scale. The single PEDro items are shown in the Table S4 (p. 118).

CANCER POPULATION. In total, the RCTs included 618 cancer patients (mean: 103; median: 44; range: 19 [22]-420 [19]), across all stages (UICC I–IV), of which the majority were breast cancer patients (61 %, n = 374), followed by lymphoma (10 %, n = 62) and lung cancer patients (9 %, n = 56). Most studies included patients receiving taxane-based chemotherapy only [20-22]. In

[3] Immediately after completion of the first round of the literature review presented here, a review with a comparable focus was published online (March 19, 2020) [123]. Since the authors only included studies published until April 2019 in their review (n=8), the literature search conducted here resulted in a total of 13 RCTs.

[4] The keywords were intentionally kept in such a narrow way as to automatically exclude polyneuropathic symptoms of other aetiologies. Since "exercise" is a MeshTerm in the Medline (PubMed) search, it was not extended by e.g. "training" etc., since these search terms are automatically integrated in the MeshTerm "exercise". In the Cochrane databases, however, "exercise OR training" was used as search string.

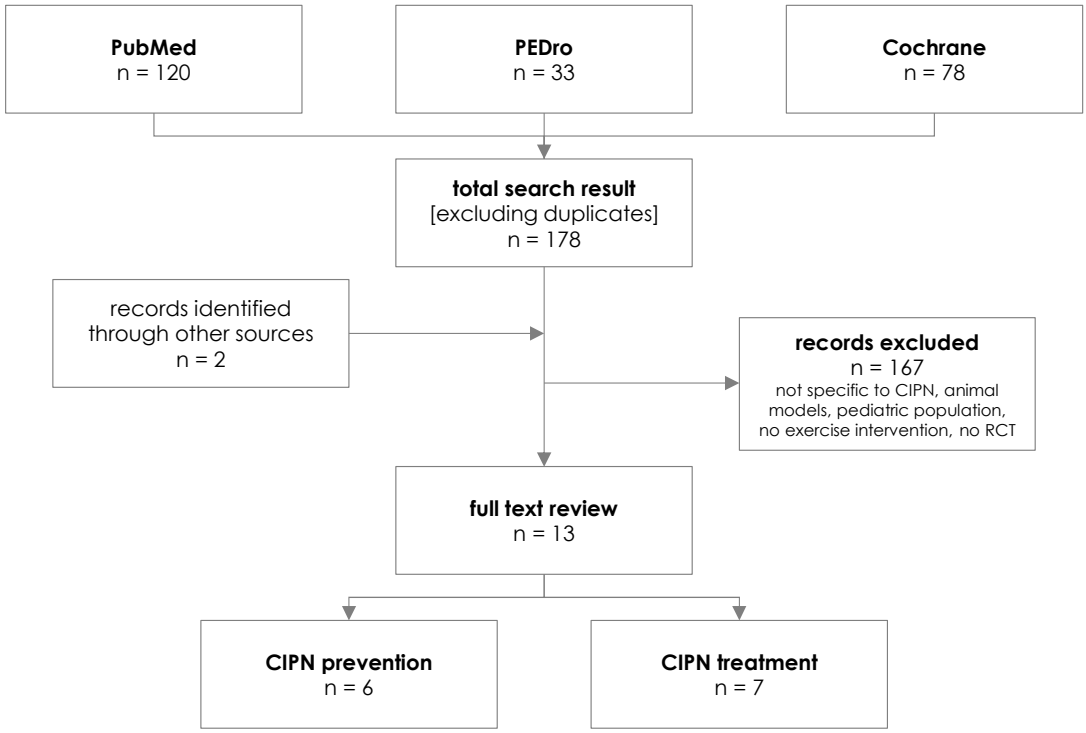

Figure 4. Screening process of literature.

one study, only platinum-based chemotherapy was administered [18], while the largest cross-entity study included patients receiving taxanes, platinum derivatives and/or vinca alkaloids [19]. One study reported the administration of neurotoxic chemotherapeutic agents, but did not further specify these [17].

INTERVENTION DESCRIPTION. All studies used a multi-modal intervention approach, combining either balance, resistance and endurance training [17,20,21] or resistance and endurance training alone [18,19,22]. The detailed training descriptions, as far as they were reported in the manuscripts, as well as the compliance/adherence rates can be found in Table S5 (p. 119). The results of the studies are presented chronologically within the intervention categories mentioned above and discussed in summary form at the end of this chapter.

MULTI-MODAL EXERCISE INTERVENTIONS: BALANCE, RESISTANCE AND ENDURANCE TRAINING. Streckmann et al. [17] were among the first to address a possible preventive effect of an exercise intervention on the development of CIPN by publishing the results of a secondary analysis (primary endpoint: health-related quality of life (QOL), EORTC QLQ-C30). The authors conducted an intervention study with N = 61 lymphoma patients (IG = 30, CG = 31). Within this study, n = 37 patients (IG = 20, CG = 17) received neurotoxic chemotherapy and were therefore monitored for CIPN occurrence during the intervention and thus chemotherapy (deep sensitivity via Rydel-Seiffer tuning fork, pathological values: < 60 years 5/8, ≥ 60 years 4/8). CIPN prevalence

did not significantly differ between groups at baseline (IG = 7, CG = 12). However, CIPN symptoms decreased by about 88 % (n = 7/8) in the IG and by 0 % (n = 0/12) in the CG during the 36-week intervention ($p < .001$). Caution should be exercised, however, when interpreting these results as patients with CIPN-related chemotherapy dose reductions were excluded from the analyses. The corresponding number of cases was not reported. Moreover, significantly better values within the IG compared to the CG were found for QOL (only within the first 12 weeks of intervention) and postural control (lower sway path and less failed attempts in monopedal stance). However, since these analyses were based on an intention-to-treat approach (N = 61), which also included patients with non-neurotoxic chemotherapy, the results cannot be used for further interpretation in the context of this dissertation. A further sub-analysis of the "neurotoxic" cohort regarding these outcomes would have been desirable.

Vollmers et al. [21] addressed the aspect of postural control in their study. They presented a per-protocol analysis of N = 36 (IG = 17, CG = 19) breast cancer patients undergoing multimodal exercise intervention during taxane-based chemotherapy (total length was not reported). The authors presented significant time × group effects for static postural control in bipedal stance (COP 95 % prediction ellipsis; IG: -0.49, CG: -1.14; $p < .039$) and for the Fullerton Advanced Balance Scale (IG: +1.35, CG: -2.84; $p < .001$). Static postural control also significantly improved in monopedal stance in the IG, but time × group differences were not tested. It is critical to note that baseline data were neither reported nor tested for group differences. The authors reported to have used the EORTC CIPN20 questionnaire for CIPN diagnosis, an adequate presentation of results, however, is missing. The authors merely summarized (p. 1789): "The assessments for psychological parameters and adverse events showed hardly any significant improvements in the IG compared to the CG. For some parameters, the scores in the IG were even non-significantly worse than in the CG." This incomplete and poorly structured presentation of results, in addition to the superficial description of the intervention, the lack of adherence data and the small sample size, require an extremely cautious interpretation of results and thus conclusions on the preventive potential of this intervention for CIPN.

Bland et al. [20] analyzed the effects of a multi-modal exercise intervention during 10-week taxane-based chemotherapy in N = 27 (IG = 12, CG = 15) breast cancer patients. Contrary to the studies previously described, a comprehensive CIPN diagnostic procedure was used: subjective perception of CIPN symptoms via EORTC CIPN20 questionnaire (primary endpoint) and clinical assessment via QST (deep sensitivity: tuning fork; pain: pinprick). CIPN sensory and motor symptoms (EORTC CIPN20) increased during chemotherapy and decreased again in both groups in the following 10 – 15 weeks. Thus, the authors could not show that the intervention had a positive effect on the primary endpoint (milder course of the sensory, motor and autonomic subscales of the EORTC CIPN20 questionnaire in the IG compared to the CG). However, a sub-analysis indicated that at least the progression of specific CIPN symptoms (moderate to severe numbness in toes and feet) can be prevented within the first three taxane cycles. This "slowing-down effect", however, was no longer detectable at the end of chemotherapy. Furthermore, the intervention had no effect on clinically diagnosed CIPN (QST), but on the overall quality of life (time × group effect, $p = .01$), so that after the intervention the IG reported an 11.5 points

higher quality of life than the CG (scale 0–100; p = .05). An interesting result has been provided by the sub-analysis of the chemotherapy tolerance. Here it is shown that despite increasing CIPN symptoms, all subjects (n = 12/12) of the IG received a critical minimal dose of at least 85% of the initially calculated dose [126,127], whereas this was only the case in 67% (n = 10/15) of the patients in the CG (p < .05).

The reasons for the predominant absence of effects in the latter study can be manifold. Firstly, it is conceivable that the exercise load/intensity was too low, mainly due to the reduction of training intensity (but increased duration) in the post-chemotherapy week. Furthermore, it is possible that the adherence rate decreased in the course of the study, i.e. with increasing toxicity. This could also explain the "slowing-down effect" described above. The authors themselves argued that cumulative toxicity might have blunted the training effect. Another reason could be the "contamination" of the CG by independently performed physical activity. However, the activity level was not assessed in this study. Even if the sub-analyses show a promising direction, they must be validated in a larger cohort, taking into account the methodological problems mentioned above.

MULTI-MODAL EXERCISE INTERVENTIONS: RESISTANCE AND ENDURANCE TRAINING. In a secondary per-protocol analysis, Henke et al. [18] investigated the effect of combined resistance and endurance training on CIPN symptoms in N = 29 (IG = 18, CG = 11) lung cancer patients during the first three platinum-based chemotherapy cycles. The intervention showed no effect on the prevention of CIPN, which was assessed with a single item of the EORTC QLQ-LC13 questionnaire. However, the authors were able to show an intervention effect on the Bartel index, which describes patients' independence in carrying out ADL. A sub-analysis addressing the relationship between ADL and CIPN symptoms would have been of interest. The lacking preventive effect on CIPN in this study is most likely due to the insufficient CIPN diagnostics used, and the study design in general (small sample size, secondary analysis).

Visovsky et al. [22] also assessed CIPN symptoms subjectively by using the FACT taxane questionnaire (Functional Assessment of Cancer Therapy Taxanes) in their pilot study. In the presented intention-to-treat analysis (adjusted for age, breast cancer related symptoms, total paclitaxel dose, baseline physical activity), only a trend-level intervention effect regarding the perceived CIPN symptoms (IG: +30, CG: +48; p = .07) was observed in N = 19 analyzed breast cancer patients after 12 weeks of intervention (detailed group alignment was not reported). Furthermore, no significant differences were found for gait and balance (timed-up-and-go test, TUG) as well as QOL during the intervention or follow-up period. The missing effects may be attributable to the small sample size, but also to possibly poor adherence rates (which were not reported) and/or to the type of intervention: Home-based interventions are often less effective than supervised interventions in the oncological context [25].

Kleckner et al. [19] also conducted a home-based intervention, but with a markedly greater sample size of N = 420 initially included patients. The reported results regarding CIPN prevention were based on a secondary analysis of data from a phase III RCT, which investigated the effects of exercise on fatigue. For the CIPN analysis N = 355 (IG = 170, CG = 185) patients pro-

vided sufficient datasets and were included. In comparison to the other CIPN prevention studies, multiple entities and thus also different neurotoxic agents (taxanes, platinum derivatives, vinca alkaloids) were included. However, as in most studies, CIPN diagnosis was very rudimentary: Patients were asked to rate their perceived CIPN symptoms regarding (a) numbness and tingling and (b) hot/coldness in hands/feet during the last seven days on a numeric rating scale (0–10) at different time points. Both groups report more symptoms regarding numbness and tingling after the 6-week intervention and thus after chemotherapy (IG: +0.38, CI = 0.04, 0.71, p = .027; CG: +0.58, CI = 0.20, 0.95, p = .003; effect size 0.11 [128]) and hot/coldness (IG: +0.38, CI = 0.06, 0.70, p = .022; CG: +0.77, CI = 0.42, 1.13, p < .0001; effect size 0.11 [128]). However, linear regression analysis showed that the increase in hot/coldness symptoms was stronger in CG than in IG (coefficient = -0.46, CI = -0.01, -0.91, p = .045). For the symptoms numbness and tingling, however, only a trend-level effect was observed (coefficient = -0.42, CI = -0.85, 0.02, p = .061). Despite the small intervention effect of exercise on CIPN, this study (with an adequate sample size) motivates to further investigate this possible preventive effect with an adapted study design. It can be assumed that with an intervention length adapted to chemotherapy – which in most cases would exceed the six weeks presented in this study – the indicated small effects might become greater and thus clinically relevant [128]. In addition, it has to be pointed out again that a supervised exercise intervention would probably have been more effective.

SUMMARY OF CIPN PREVENTION. The possible preventive potential of exercise interventions with regard to CIPN was investigated in six RCTs. Based on the absence of adverse events, exercise interventions during neurotoxic chemotherapy seem to be safe. However, two studies did not report whether adverse events occurred [18,21].

Nevertheless, the results found in these studies are sometimes divergent, and in most cases the underlying assessments were only addressed by a single study. The investigation of peripheral deep sensitivity was the only outcome that was addressed by two different studies. A combination of resistance, endurance and balance training showed a positive effect on deep sensitivity in one study [17], but not in another comparable study [20]. No further intervention effect was found for the other objectively assessed CIPN signs and symptoms (see Table 2). This is also in line with the subjectively assessed CIPN symptoms. Only the perception of hot/coldness was positively influenced by a combination of resistance and endurance training during neurotoxic chemotherapy [19]. On the basis of the EORTC CIPN20 questionnaire, however, the potential preventive effect was not confirmed [20,21]. Furthermore, singular intervention effects on static postural control [21], the ability to carry out ADLs [18] and the global QOL [20] were achieved by various exercise interventions. However, the latter contrasts with the zero effect of a combined resistance and endurance intervention [22].

Although the zero results of the studies numerically exceed the positive intervention effects, a global negative conclusion – that the presented exercise interventions cannot prevent the occurrence of CIPN during neurotoxic chemotherapy – would not be tenable against the background of the traditional aphorism "absence of evidence is not evidence of absence". The reason for this is the predominantly small sample size, partially fragmented presentation of results and an

Table 2. Randomized controlled exercise intervention studies for CIPN prevention: summary of findings.

	intervention effect	no intervention effect
CIPN signs (objective assessments)		
▪ deep sensitivity (tuning fork)	BAL+RT+END [17]	BAL+RT+END [20]
▪ pain (pin-prick)		BAL+RT+END [20]
CIPN symptoms (PRO)		
▪ FACT/GOG-Ntx		RT+EN [22]
▪ EORTC QLQ-CIPN20		BAL+RT+END [20,21]
▪ EORTC QLQ-LC13		RT+EN [18]
▪ hot/coldness (NRS, 0 – 10)	RT+EN [19]	
▪ numbness/tingling (NRS, 0 – 10)		RT+EN [19]
Functional outcomes		
▪ static balance performance	BAL+RT+END [21]	
▪ timed-up-and-go test (TUG)		RT+EN [22]
Other CIPN related outcomes		
▪ quality of life	BAL+RT+END [20]	RT+EN [22]
▪ ability to carry out ADL (Bartel Index)	RT+EN [18]	
▪ RDI	BAL+RT+END [20]	

The table lists all CIPN relevant outcomes that were investigated in the cited CIPN prevention studies (left column). The column "intervention effect" indicates which interventions showed a significant time × group interaction. If no intervention effect was found, this is indicated in the column "no intervention effect". General abbreviations: +, combination of two or more training modalities within one session; ADL, activities of daily living; BAL, balance training; END, endurance training; EORTC QLQ-CIPN20, EORTC quality of life questionnaire for CIPN symptoms; EORTC QLQ-LC13, EORTC quality of life questionnaire for lung cancer patients (includes a single CIPN item); FACT/GOG-Ntx, FACT/GOG questionnaire for neurotoxicity assessment; NPRS, numeric pain rating scale; NRS, numeric rating scale; PRO, patient reported outcomes; RDI, chemotherapy relative dose intensity; RT, resistance training.

overall rather rudimentary CIPN diagnosis, whose outcomes were frequently only addressed in a single study. In addition, training modalities were very divergent, which made a comparison of the individual interventions partly impossible. The present methodological issues are addressed in more detail in Chapter 1.4.2, as they served as a basis for the intervention design and the statistical analyses of the PIC study. Further, adequately designed studies are therefore needed in order to generate evidence-based statements on the preventive potential of exercise interventions during neurotoxic chemotherapy on CIPN.

1.3.2 Literature review: Exercise as treatment measure for CIPN

Seven randomized controlled trials were identified that addressed the treatment of CIPN through various exercise intervention approaches after neurotoxic chemotherapy [13,53,129-133]. The quality of the studies varied between 4 [17,129], 6 [13,130-132] and 7 [133] on the PEDro scale. The detailed PEDro score is shown in the supplementary material (Table S4, p. 118). Due to the focus of the present dissertation on CIPN prevention, the results of the mentioned RCTs for

CIPN treatment are only presented in summary form. Detailed information about exercise intervention descriptions and adherence rates can be found in Table S6 (p. 122).

CANCER POPULATION. The RCTs comprised a total of 354 cancer patients (mean: 51; median: 40; range: 22 [131]–131 [130]) across all cancer stages (UICC I–IV). Compared to the prevention studies discussed above, the cancer entities in these CIPN treatment studies were more distributed: 19% breast cancer (n=70), 18% colorectal cancer (n=64), 10% ovarian cancer (n=38), 8% lymphomas (n=29). Only one study included a homogeneous cohort [132], all the others included multiple entities. This is also mirrored in the various neurotoxic agents that caused CIPN. One study enrolled patients after taxane or platinum-based chemotherapy [133], two other studies additionally included patients after vinca alkaloids [53,129,130] and one study further included patients after administration of bortezomib [130]. Three studies did not specify the exact substance classes [13,131,132].

INTERVENTION DESCRIPTION. Guided by the CIPN symptoms, the main focus of the interventions was on balance and/or vibration training, either as a single or multi-modal training approach. The multi-modal approaches comprised a combination of balance and resistance training [133] or balance, resistance and endurance training [132]. Two studies tested a quasi-singular intervention, with the CG containing a part of the intervention of the IG. In these studies either balance and endurance training were combined, with the CG only receiving endurance training [13], or patients received a combination of whole body vibration training (WBV) and multiple exercises that focused on transportation movements, with the CG only performing the latter [130]. Another study compared pure balance training with a passive CG [131], while another study added an active CG (WBV training) to the study design mentioned before [53]. One study tested the efficacy of yoga for the treatment of CIPN signs and symptoms [129].

SUMMARY OF MAIN FINDINGS. The question of the efficacy of the various interventions can only be answered on several levels, in an outcome-oriented way. Considering the OBJECTIVE CIPN ASSESSMENTS, a wide range of assessments can be found within three studies [13,53,130]. However, a common denominator was only found for the evaluation of reflexes and deep sensitivity. The results showed that balance training can possibly improve reflex activity [53] (note: small sample size, n=10), whereas WBV training seemed to have no effect [53,130]. The improvement of deep sensitivity was reported in relation to endurance [13] and balance training [53]. However, the latter result contrasted with the results of Kneis et al. [13], who could not replicate this effect with their balance intervention. The authors discussed that the assumed neuro-regenerative effect of balance training might have been eliminated by the endurance training which was performed prior to the balance exercises. Likewise, WBV training did not influence the perception of deep sensitivity [53]. All other objective CIPN parameters were only assessed in single studies and were not positively influenced by the various exercise interventions (see Table 3).

On the SUBJECTIVE LEVEL of CIPN symptom perception, the intervention effects were similarly divergent. The most frequently used PRO tool was the FACT GOGntx questionnaire.

Combined with the results of the EORTC QLQ-CIPN20 questionnaire, positive time effects (pre-post comparison within a group) were shown for endurance [13], balance [13] and WBV training [130] as well as massage and passive mobilization [130]. However, only one study showed a significant time × group effect on perceived CIPN symptoms with a combination of resistance, endurance and balance training [132]. In contrast, several studies showed zero effects for endurance [13], balance [53] and WBV training [53] as well as Yoga [129]. Due to the small sample size in the study of Streckmann et al. [53] – whose results certainly need to be proven with a larger sample size – it can be summarized that the various interventions probably have a positive influence on the subjective perception of symptoms. However, this conclusion must be validated by further studies showing significant time × group effects. The same request also applies to the assessment of pain, the influence of which was also shown to be contradictory (see Table 3).

The most frequently investigated FUNCTIONAL OUTCOME was postural control. Here it was shown that singular balance training [13,131] or in combination with endurance and resistance training [132] had a positive effect on static postural control. Although these results contrasted with the results of Streckmann et al. [53], the absence of an intervention effect could be explained by a ceiling effect, as these patients had already participated in a systematic training program before the study. Furthermore, various muscular functions were improved by multi-modal [132], singular endurance [13] and WBV training [130]. However, since these parameters have only been investigated in individual studies so far, further studies are needed to verify these results.

Interestingly, the vast majority of studies did not show an intervention effect on QOL despite supervised exercise and acceptable adherence rates [13,53,129]. The simplest explanation could relate to the length of intervention which varied between four and twelve weeks. Although Buffart et al. [134] and Sweegers et al. [135] showed that the intervention duration did not significantly moderate the effect of exercise on QOL, the current exercise oncology guidelines summarize that the intervention length must be at least 12 weeks to show improvements in QOL [25]. However, the cited meta-analyses and guideline only referred to resistance or endurance training. With regard to balance and WBV training, not enough studies have been published so far to provide comparable analyses. Based on the available literature, however, it is possible that the energy expenditure in these studies was too low – even if this had only been a moderator for unsupervised training in the meta-analysis mentioned above [135]. The missing effects of the yoga intervention partly reflect the results of a current review [136] – but could also simply be explained by the very small sample size.

In summary, most of the interventions for the treatment of CIPN signs and symptoms seemed to be safe, although adverse events were not addressed in two studies [129,130]. The results of the present RCTs indicate that various exercise modalities might have a positive influence on perceived CIPN signs and symptoms and existing balance deficits. Further individual findings on objectively measured CIPN parameters (reflexes, deep sensitivity) as well as muscle function were identified, but should be validated in future appropriately powered studies. Furthermore, future studies should include a follow-up period to investigate the sustainability of the intervention effects.

Table 3. Randomized controlled exercise intervention studies for CIPN treatment: summary of findings.

	intervention effect	no intervention effect
CIPN signs (objective assessments)		
▪ nerve conduction studies		SMT [53], WBV [53]
▪ vibration sense	END [13], SMT [53]	SMT [13], WBV [53]
▪ tendon reflexes	SMT [53]	WBV [53,130]
▪ QST: warm detection threshold	WBV [130]	
▪ QST: heat pain detection threshold		WBV [130]
▪ QST: cold detection threshold		WBV [130]
▪ QST: mechanical detection threshold		WBV [130]
▪ light touch		SMT [53], WBV [53]
▪ sense of position		SMT [53], WBV [53]
▪ lower leg strength		SMT [53], WBV [53]
CIPN symptoms (PRO)		
▪ FACT/GOG-Ntx	END+RT+SMT [132], EX^{t} [130], SMT^{t} [13], WBV^{t} [130]	END [13], SMT [53], WBV [53], Yoga [129]
▪ EORTC QLQ-CIPN20	END^{t} [13], SMT^{t} [13]	
▪ CIPNAT	RT+SMT^{g} [133]	
▪ S-LANSS	RT+SMT^{g} [133]	
▪ Pain-DETECT		SMT [53], WBV [53]
Functional outcomes		
▪ static balance performance	END+RT+SMT [132], SMT [13,131]	END [13], SMT [53], WBV [53]
▪ gait (speed & step time variability)		SMT [131]
▪ muscle strength	END+RT+SMT [132]	
▪ lower body's muscle power (CMJ)	END^{t} [13]	SMT [13]
▪ chair-rising test (CRT)	EX^{t} [130], WBV^{t} [130]	
Other CIPN related outcomes		
▪ quality of life (PRO: EORTC QLQ C30 / FACT)	RT+SMT^{g} [133]	END [13], SMT [13,53], WBV [53], Yoga [129]
▪ fear of falling (PRO: FES-I)		SMT [131]

The table lists all CIPN relevant outcomes that were investigated in the cited CIPN treatment studies (left column). The column "intervention effect" indicates which interventions showed a significant time × group interaction. If these were not reported or tested, the following abbreviations apply: ^{t} significant time effect in the intervention group (pre-post intervention), ^{g} significant group effect after intervention (intervention vs. control group at post intervention). If no intervention effect was found, this is indicated in the column "no intervention effect". Note: In Clark et al. [84] only the Yoga intervention was considered. General abbreviations: +, combination of two or more training modalities within one session ADL, activities of daily living; BAL, balance training; CIPN, chemotherapy-induced peripheral neuropathy; CIPNAT, chemotherapy induced peripheral neuropathy assessment tool; CMJ, counter movement jump; CRT, chair rising test; END, endurance training; EORTC QLQ-CIPN20, EORTC quality of life questionnaire for CIPN symptoms; EX, general physical exercises; FACT/GOG-Ntx, FACT/GOG questionnaire for neurotoxicity assessment; FES-I, Falls Efficacy Scale – International; Pain-DETECT, pain questionnaire; PRO, patient reported outcomes; QST, quantitative sensory testing; RT, resistance training; S-LANSS, Leeds assessment for neuropathic symptoms and signs; WBV, whole body vibration training.

1.4 Gaps in previous research and research questions

Especially in the past 10–15 years, the knowledge about the positive influence of physical activity on treatment-related side effects has grown steadily, with tumor-related fatigue probably being the most frequently investigated side effect in exercise oncology studies [28]. In contrast, CIPN and its effects on postural control have been addressed much less frequently. The need for research in this area is mainly based on the major negative impact of CIPN on the quality of life, the functional status (e.g. increased risk of falling) and possibly also on recurrence and mortality rates due to chemotherapy dose-modifications with increasing CIPN symptom burden [9,10,12]. The specific research questions based on this generally defined research gap are addressed separately below and relate to (a) the postural control of cancer patients before, during and after neurotoxic chemotherapy and (b) the preventive potential of sensorimotor exercise and/or resistance training on the development of CIPN during neurotoxic chemotherapy.

1.4.1 Postural control in response to neurotoxic chemotherapy

The current literature provides some studies investigating postural control – objectified by body sway movement analysis, e.g. using a force plate – in response to neurotoxic chemotherapy [42,43,49-54]. Other studies also investigated postural control in cancer patients but did not specify neurotoxic potential of chemotherapy or did not control for CIPN symptoms [137,138]. Therefore, the former studies are of particular interest to derive the research gap for the postural control part of the present dissertation.

Most of these studies provide cross-sectional data after completion of chemotherapy [42,43,49,52-54] with the majority showing deterioration of postural control compared to (healthy) matched controls, especially within the first six months after completion of chemotherapy [42,49,52,54]. However, only one pilot study has described how postural control changes during chemotherapy [50,51]. This longitudinal investigation mirrors the cross sectional findings, showing that postural control in breast cancer patients gradually deteriorates with increasing taxane-based chemotherapy cycles and remains impaired one to three months after completion of chemotherapy [50,51]. None of these studies, however, considered whether cancer patients may have an impaired postural control prior to chemotherapy, e.g. due to cancer-related factors such as deconditioning [71]. Furthermore, these studies differ in their methodological approach and quality, resulting in a still rather fragmented picture of postural control in response to neurotoxic chemotherapy. Options for improving the main constraints of these studies are discussed below and serve as a basis for the analysis of postural control in the present dissertation.

The first methodological issue relates to the MATCHING CRITERIA used in the cross-sectional studies. Only some of these studies used adequate matching criteria that potentially influence postural control (gender, age, height and weight) [43,49,52,53] or adjusted their statistical analyses for (some of) these factors [42]. If adequate matching criteria were used, most of the studies used frequency-matching [43,52], or the exact procedure remains unclear [49,53]. With regard to anthropometric data, however, not only the distribution of height and weight within the considered population seems to be important when analyzing postural control, but also their rela-

tionship within an individual. Therefore, a one-to-one matching procedure would have been more appropriate.

The second aspect concerns the analysis of POSTURAL CONTROL itself. In order to generate a comprehensive picture of postural control in various cohorts, it is generally recommended to use different testing conditions, which manipulate different sensory inputs, as well as to report different COP parameters [139]. However, this is only partially taken into account in the literature mentioned above. Most authors analyzed a maximum of two (simple) testing conditions [42,50-53]: bipedal with eyes open [42]; bipedal vs. monopedal [52,53]; bipedal eyes open vs. bipedal eyes closed [50,51]). Regarding the quantification of postural control, most studies only report a single COP parameter [43,49,51-53]. Only three studies considered postural sway in sagittal (anterior-posterior) and frontal (medio-lateral) plane separately in order to characterize postural control in detail [42,50,54].

The third point for improvement of the mentioned studies concerns the CIPN ASSESSMENT. According to current recommendations, CIPN should be reported both clinically and based on patients' subjective perception in scientific studies (see Chapter 1.2.4). However, only three studies used clinical and patient reported outcome tools to describe CIPN signs and symptoms comprehensively [51-53]. Kneis et al. [52] and Streckmann et al. [53] additionally completed their CIPN description by electrophysiological data. All the other studies mainly used PRO assessments only.

The last point concerns potential RISK OR PROTECTIVE FACTORS for the deterioration of postural control within this patient population. The pathophysiology of CIPN strongly supports a causative relationship of CIPN with impairments of postural control, but previous correlation analyses merely demonstrated low to moderate associations between various diagnostic approaches of CIPN and COP analyses [51,52]. Therefore, it seems plausible that postural control in cancer patients treated with neurotoxic agents is additionally affected by factors other than CIPN alone, possibly including baseline peripheral nerve function, muscle strength and/or power [140], and physical inactivity [141].

Taking into account the methodological issues listed, the overall objective was to merge the previously fragmented findings of the primary cross-sectional studies in order to generate a coherent picture of postural control in cancer patients in response to neurotoxic chemotherapy. To this end, Manuscript I and II deal with the following aspects: (a) longitudinal assessment of postural control and CIPN in cancer patients during and after neurotoxic chemotherapy, by quantifying postural control with various COP parameters in different standing positions and comprehensive CIPN assessment according to current recommendations, (b) comparison of these data to adequately one-to-one age, gender, height, and weight matched healthy controls, (c) analysis of relevant influencing factors other than CIPN on the change in postural control during and after neurotoxic chemotherapy. Therefore, the first two manuscripts of the present dissertation pursue the following main research questions:

Research questions of Manuscript I

- Does postural control in cancer patients before neurotoxic chemotherapy differ from healthy, one-to-one matched controls, e.g. due to cancer-related deconditioning?
- How does postural control change during neurotoxic chemotherapy compared to healthy one-to-one matched controls with regard to different testing conditions and various COP parameters?
- To what extent is postural control, after completion of neurotoxic chemotherapy, related to neurologically objectified and patient-reported CIPN signs and symptoms as well as fear of falling?

Research questions of Manuscript II

- To what extent does postural control as well as neurologically objectified and patient-reported CIPN signs and symptoms change in cancer patients during neurotoxic chemotherapy [repeated measurements] and three and six months afterwards?
- Which risk or protective factors are related to the change of postural control during and after neurotoxic chemotherapy?

1.4.2 CIPN prevention through exercise

As already described in detail in Chapter 1.3.1, there are currently six RCTs that address the preventive potential of various exercise interventions on CIPN in a total of 678 cancer patients. However, the results are not yet conclusive, which might be due to several methodological issues regarding study design, CIPN assessments, exercise intervention design and statistical analyses. The individual aspects are discussed below and serve as the basis for the study design and statistical analyses of the PIC study.

The first point concerns the general STUDY DESIGN. Only three of the presented studies reported a CIPN-relevant primary endpoint [20-22], one of which is a pilot study [22]. The remaining three studies were secondary analyses [17-19], the results of which – as in the case of all secondary analyses – have to be verified with appropriately designed RCTs. The sample sizes of the former RCTs designed for CIPN prevention appear to be relatively small: 19 [22], 31 [20] and 43 [21] patients included – despite power calculations reported in two studies [20,22]. Future studies on CIPN prevention should therefore base their sample size on an adequate power calculation and consider the multidimensionality of CIPN signs and symptoms within their assessments – not only with regard to the primary endpoint (see next point).

Thereafter, the second methodological issue relates to the CIPN ASSESSMENTS. In the presented RCTs CIPN was rather rudimentarily assessed, which was probably due to the large proportion of secondary analyses. Four studies only used subjective assessments [18,19,21,22], ranging from simple, not psychometrically tested symptom queries to the use of recommended questionnaires. Only one study assessed deep sensitivity via tuning fork [17], another study combined clinical and subjective CIPN assessments [20]. Accordingly, only one study met the current literature recommendations by combining subjective and objective assessments for CIPN diagnostics (see Chapter 1.2.4).

Another point of criticism is the timing of the BASELINE MEASUREMENT – which additionally makes between-study comparisons difficult. Most studies performed baseline measurement before administration of neurotoxic chemotherapy agents, but after non-neurotoxic chemotherapy [20-22]. Only one study performed a "pure" baseline measurement [19], while in two studies the exact timing is unclear [17,18]. These blurred baseline values can be one reason for the partial absence of effects. CIPN diagnostics should therefore precede the initial administration of any chemotherapeutic agent. Furthermore, a follow-up period after completion of chemotherapy/exercise intervention is desirable to evaluate the sustainability of the potentially achieved effects. However, only two of the presented studies reported a follow-up period of about three months [20,22], which should be the minimum according to other authors [38].

The EXERCISE INTERVENTION DESIGN of the existing studies also needs to be considered more closely. Despite the exercise categorization presented in Chapter 1.3.1, the training modalities of the individual study were very divergent, which further limits comparability. As it is not yet clear whether exercise is effective in CIPN prevention, it is recommended to implement single interventions. This would allow analyses identifying the most effective exercise modality. Subsequently, these could then be combined in order to possibly further strengthen the preventive effect. Furthermore, these single-exercise interventions should be implemented in a supervised setting, which is known to be more effective than home-based interventions [28]. However, two of the available CIPN prevention studies conducted the exercise program in a home-based setting [19,22]. The selected training setting could therefore be an additional reason for the partial absence of effects, as well as low adherence rates – which might emerge in connection with the training setting, but also independently of it. Although adherence rates were addressed in five studies [17-21], only one study [20] followed current recommendations and also reported, for example, adherence to prescribed training intensities [142]. Only by means of detailed adherence reporting it is possible (for other scientists) to evaluate whether insufficient training intensities or volumes were the cause of (partial) absence of intervention effects.

The last methodological issue which needs to be addressed concerns the consideration of mediators and moderators as well as confounders and covariates within the STATISTICAL ANALYSES [143]. Kleckner et al. [19] showed in a sub-analysis, that age, sex, and breast cancer can moderate the effect of physical activity on CIPN symptoms. However, only Visovsky et al. [22] included age and breast cancer related symptoms as well as total paclitaxel dose, and baseline physical activity in their analyses. Furthermore, it would be important to monitor pharmacological (e.g. Duloxetin) and non-pharmacological CIPN prevention and/or treatment measures (e.g. cyotherapy, compression) during neurotoxic chemotherapy – which, however was not addressed by any of the studies described. Additionally, exercise intervention studies should control the physical activity level outside the prescribed exercises in order to detect potential "contamination" of the CG. However, this was only done by one study [17].

To sum up, current literature does not provide sufficient evidence to conclude on the preventive potential of exercise interventions for CIPN. The predominant absence of intervention effects might be (partly) due to the methodological problems discussed above and can therefore not be interpreted as "evidence of absence". In order to address these methodological problems

and to provide high quality evidence, the PIC study was designed, which investigates the following research questions.

Research questions of Manuscript III

- Can sensorimotor exercise and/or resistance training – compared to usual care – prevent the occurrence of neurologically objectified and patient-reported CIPN signs and symptoms during neurotoxic chemotherapy?
- Do potential changes in CIPN associated functional limitations – in terms of postural control and muscle strength – and quality of life differ between the three study groups during neurotoxic chemotherapy?
- How do the previously addressed outcomes develop inter- and intra-individually three and six months after the end of chemotherapy and thus intervention period?
- Does chemotherapy tolerance – measured by relative dose intensity (RDI) – differ between the three study groups?

Before the research questions addressed are answered within the three manuscripts, the following chapter gives a general overview of the study design of the PIC study and lists the methods used.

2

General methods

The manuscripts of the present cumulative dissertation are based on the data of a prospective, three-armed, single-center, randomized-controlled intervention trial. The primary question of the PIC study focused on the preventive potential of a sensorimotor exercise (SMT) or resistance training (RT) during neurotoxic chemotherapy compared to a waiting-list control group receiving usual care (UC). The length of the intervention period (pre–post$_0$) was dependent on the length of the individual chemotherapy. The intervention period was completed by a six-month follow-up in total (post$_3$, post$_6$). Figure 5 provides a detailed overview of the study design. The study was conducted at the National Centre for Tumor Diseases (NCT) in Heidelberg (Germany) between March 2016 and May 2019. Ethical approval was obtained by the ethics committee of the Medical Faculty University of Heidelberg (S-630/2015). The study was registered on ClinicalTrials.gov (NCT02871284).

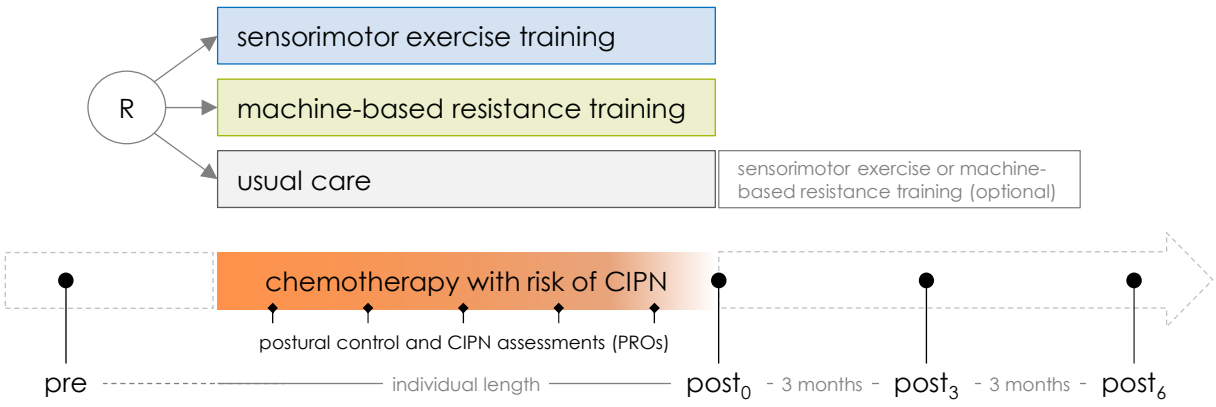

Figure 5. Study design of the PIC study.

2.1 Participants

Patients who were 18 years of age or older and agreed to undergo a chemotherapy protocol containing at least one neurotoxic agent were eligible for the PIC study. The detailed inclusion and exclusion criteria are listed in Table 4. Oncologists from the NCT or a clinical-oncological cooperation center in the Rhine-Neckar metropolitan region informed their patients about the possi-

bility of participating in the study. If patients were interested, the study personnel (one sports scientist, one study nurse) gave detailed study information, examined the inclusion and exclusion criteria and finally obtained the patients' informed consent after a 24-hour reflection period. The sample size estimation for the PIC study was based on the main outcome criterion, the change of the TNSr from baseline (pre) to the end of the intervention ($post_0$). Further information is given in Manuscript III. A total of N=170 patients were recruited and assigned to one of the groups mentioned above via stratified block randomization by an external epidemiologist (randomization strata: gender, class of the neurotoxic chemotherapeutic agent).

2.2 Interventions

After baseline testing (pre), patients were randomly assigned to an exercise intervention (SMT or RT) or UC group. The intervention modalities of these groups are briefly described below. A more detailed description can be found in Manuscript III and its corresponding supplementary material (p. 128ff.).

SENSORIMOTOR EXERCISE TRAINING. The SMT focused on the lower extremities to improve postural control. During an introductory one-to-one training session the patients were taught the general SMT principles by a sport scientist. Additionally, they were given a training manual including illustrated SMT exercises (see Figure S1, p. 129) as well as necessary training materials (one Airex® Balance Pad and one Redondo® ball). The exercises were designed to progressively increase the difficulty of the balance tasks on an individual basis. For this purpose, the base of support (e.g. bipedal vs. monopedal stance), the surface (e.g. solid ground vs. Airex® Balance Pad) and the visual control (e.g. open vs. closed eyes) were varied and if possible combined with additional tasks (e.g. throwing a ball). The IG participants trained twice a week for 45 minutes each at the NCT and once weekly for 15 minutes at home, resulting in a total training time of 1.75 hours per week. Alternatively, e.g. if travel distance to the NCT was too far, the patients could also conduct the SMT at home (3×35 min).

RESISTANCE TRAINING. The main part of the RT was machine-based, which was scheduled 2×/week for 45 minutes each at the Institute for Sport and Sport Science (University of Heidelberg) or at one of the other cooperative training centers of the OnkoAktiv network. The machine-based RT consisted of a maximum of eight exercises per session and primarily involved the major muscle groups of the body. After two familiarization sessions, a one-repetition-maximum strength test (1RM) was performed at each resistance machine. Its results were used to define initial training weights (8–12 RM / 70–80% 1RM). If patients were able to move the target weight in 3×12 repetitions in three consecutive training sessions, the training weight was increased to the next higher load existing. Conversely, the training weight was reduced if less than eight repetitions were completed in the first set of an exercise. In addition to the machine-based training, the active CG carried out progressively designed stabilizing trunk exercises at home once a week for 15 minutes.

Table 4. Study inclusion and exclusion criteria.

Inclusion criteria	▪ age ≥ 18 years ▪ diagnosed with cancer and assigned to receive a chemotherapeutic regimen containing at least one of the following agents: - a platinum analog, e.g. cisplatin, carboplatin, oxaliplatin - a vinca alkaloid, e.g. vincristine - a taxane, e.g. paclitaxel, docetaxel - suramin - thalidomide or lenalidomide - bortezomib ▪ physical capability that allows the performance of the training program implemented within the exercise intervention groups
Exclusion criteria	▪ known peripheral neuropathy of any kind or any peripheral neuropathic signs or symptoms at baseline ▪ positive family history for any hereditary peripheral neuropathy ▪ known metastasis to the central or peripheral nervous system ▪ any physical or mental handicap that would hamper the performance of the training program implemented within the exercise intervention groups ▪ known history of alcohol or illegal drug abuse or any constellation of lab values suggesting alcoholism, e.g. elevated GGT, MCV, CDT

Abbreviations: CDT, carbohydrate-deficient transferrin; GGT, gamma-glutamyl transferase; MCV, Mean corpuscular volume.

USUAL CARE. The waiting-list control group was given UC without additional exercise intervention or information about physical activity during cancer treatment. However, the patients in this group were regularly seen and phoned (see below) in order to ensure the same frequency of contact with the study personnel in all groups. After completion of chemotherapy, UC patients had the opportunity to participate in one of the interventions described above ($post_0$-$post_6$).

2.3 Assessments

In order to answer the research questions outlined in Chapter 1.4, the CIPN diagnostics (clinical, electrophysiological and patient-reported) and static posturography were the most relevant assessments in the present dissertation, which have already been described in previous chapters (Chapter 1.2.2 and 1.2.4). In addition, further parameters were addressed in secondary analyses, which are marked with an asterisk in Table 5. To avoid redundancies, detailed information on these assessments can be found in the respective manuscripts. Table 5 also lists all the other outcome parameters assessed in the PIC study, in order to provide a comprehensive overview.

The study assessments were further complemented by demographic, clinical and behavioral data (general dietary habits, alcohol consumption and smoking as well as concomitant CIPN prevention and treatment approaches during chemotherapy not intended by the PIC study), which were queried from the patients and supplemented by medical records. Information on chemotherapy regimens (including type, individual dose, dose-reductions, postponements and discon-

tinuations) was derived from the in-house pharmacy database or requested in a comparable form from external cooperation centers.

All assessments listed in Table 5 were assessed before the start (pre) and three weeks after completion of chemotherapy ($post_0$) as well as twice during a six-month follow-up period ($post_3$, $post_6$) (Figure 5, p. 41). Between pre and $post_0$ assessments, static postural control and subjectively perceived CIPN symptoms were measured repeatedly prior to each or, in case of a weekly administration schedule, prior to every second application of chemotherapy. Additionally, all patients received weekly phone calls to assess exercise adherence and potential adverse events related to the intervention, if applicable, as well as current nutritional status and fall history. Since the individual manuscripts, on which the present dissertation is based, refer to different data of the PIC study, each manuscript contains an introductory figure which highlights the analyzed study group(s) and assessment time points (Figure 6, p. 45; Figure 7, p. 57; Figure 8, p. 69).

Table 5. PIC study outcomes and assessments

Outcome	Assessment
CIPN signs and symptoms	▪ Clinical and electrophysiological evaluation: Total Neuropathy Score (TNS reduced*) [primary outcome] ▪ Subjectively perceived symptoms (PROs): - EORTC QLQ-CIPN20* - FACT/GOG-Ntx
Postural control	▪ Static*: temporal, spatial and frequency domain measures of the COP, force plate (AccuSway OptimizedTM, AMTI Watertown, USA) ▪ Dynamic/perturbed: sway path and time to recover after perturbation (Posturomed®, HAIDER BIOSWING GmbH, Pullenreuth, Germany)
Muscle strength	▪ Isometric* and isokinetic measurement of lower and upper extremities (IsoMed 2000-system B-series version, D&R Ferstl GmbH, Hemau, Germany)
Endurance capacity	▪ CPET*: quasi-ramp exercise test (start: 20W, increment: 10W/min) on a stationary bicycle until voluntary exhaustion
Quality of life	▪ PRO: EORTC QLQ-C30*
Fear of falling	▪ PRO: Fall Efficacy Scale International (FES-I*)
Physical activity behavior	▪ PROs: - Short Questionnaire to Assess Health-enhancing physical activity (SQUASH) - Self-developed questionnaire* (see p. 117)
Cancer related fatigue	▪ PRO: Multidimensional Fatigue Inventory (MFI)
Depression / Anxiety	▪ PRO: Patient Health Questionnaire-4 (PHQ-4)
Sleep quality	▪ PRO: Pittsburgh Sleep Quality Index (PSQI)
Blood laboratory values	▪ Routine and exclusive study blood samples

The table lists all the outcome parameters and their operationalization that were investigated in the PIC study. Assessments that are marked with an asterisk (*) are addressed in the manuscripts, on which the present dissertation is based on. Abbreviations: EORTC QLQ-C30 European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire; EORTC QLQ-CIPN20, EORTC quality of life questionnaire for CIPN symptoms; FACT, Functional Assessment of Cancer Therapy, questionnaire for neurotoxicity assessment; COP, center of pressure; CPET, cardiopulmonary exercise test; PRO, patient-reported outcome.

3

Manuscript I

Müller, J., Ringhof, S., Vollmer, M., Jäger, L. B., Stein, T., Weiler, M., & Wiskemann, J. (2020). Out of balance – postural control in cancer patients before and after neurotoxic chemotherapy. *Gait and Posture, 77*, 156–163. doi:10.1016/j.gaitpost.2020.01.012

Highlights

- Cancer patients show significant balance deficits following neurotoxic chemotherapy
- Balance deficits are most apparent under visual deprivation
- Balance deficits are most strongly associated with nerve conduction velocity

Data used of the PIC study

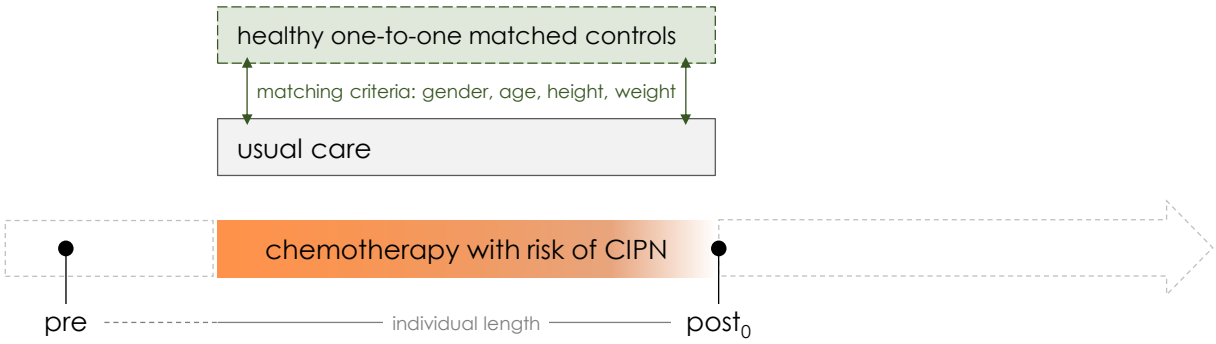

Figure 6. Patient data used for Manuscript I based on the PIC study.

The **supplementary material** for this manuscript can be found on page 125.

Authorship contributions (categories based on the recommendations of Gait and Posture): conception or design of study [JM, MW, JW], acquisition of data [JM, MV, LBJ], analysis and/or interpretation of data [JM, SR, MW], supervision [SR, TS, JW], drafting the manuscript [JM], revising the manuscript critically for important intellectual content [all authors], approval of the version of the manuscript to be published [all authors], agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved [all authors].

Out of balance – Postural control in cancer patients before and after neurotoxic chemotherapy

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Abstract

BACKGROUND: Chemotherapy-induced peripheral neuropathy (CIPN) is a serious side effect deriving from neurotoxic chemotherapeutic agents. The underlying nerve injury can affect proprioception causing impaired postural control, gait difficulties and a higher risk of falling. Overall, the symptoms and functional limitations negatively affect patients' independence and quality of life.

RESEARCH QUESTION: Our objective was to analyze postural control in cancer patients before and after neurotoxic chemotherapy and to compare these data to healthy controls.

METHODS: Participants were 35 cancer patients (PAT) and 35 healthy, one-to-one gender, age, height, and weight matched controls (HMC). Postural control of HMC was tested once, whereas PAT were tested prior to (PAT_{pre}) and three weeks after completion of neurotoxic chemotherapy (PAT_{post}). Temporal, spatial and frequency domain measures of the center of pressure (COP) were calculated using a force plate. The following balance conditions were analyzed: bipedal stance with open (BP_{EO}) and closed eyes (BP_{EC}), semi-tandem (ST_{EO}, ST_{EC}) and monopedal stance (MP_{EO}). CIPN was assessed clinically (Total Neuropathy Score) and via questionnaire. Time and group differences were determined by using Wilcoxon-signed-rank tests. Spearman correlation was applied to analyze associations between severity of CIPN and postural control.

RESULTS: PAT_{post} showed significantly increased temporal and spatial measures of the COP ($p<.05$) – both after neurotoxic chemotherapy (PAT_{pre}–PAT_{post}) and in comparison to HMC. Withdrawal of visual control resulted in greater temporal and spatial COP displacements in PAT_{post} than in the comparative groups (PAT_{pre}, HMC). Correlation analyzes revealed moderate associations of COP measures with clinical CIPN measures and low to none for the questionnaires.

SIGNIFICANCE: Three weeks after completion of neurotoxic chemotherapy, PAT_{post} showed significant balance deficits compared to PAT_{pre} and HMC. Especially the deficits in the standing conditions with closed eyes may indicate an impaired proprioception. This hypothesis is supported by the finding that stronger CIPN symptoms were associated with poorer postural control. However, future studies need to take further influencing factors on postural control into account (e.g. strength) in order to generate efficacious rehabilitation measures.

KEYWORDS: Balance ▪ Cancer ▪ Chemotherapy ▪ Peripheral neuropathy ▪ Postural stability ▪ Proprioception

1 Introduction

Continuous improvements of cancer diagnostics and treatment significantly improved disease-free and overall survival in the last decades. However, prolonged survival is sometimes accompanied with increased frequency and intensity of side effects such as fatigue and various treatment toxicities. Approximately 68 % of all cancer patients are diagnosed with chemotherapy-induced peripheral neuropathy (CIPN) one month after neurotoxic chemotherapy including platinum derivatives, vinca alkaloids, taxanes, etc. [1]. The clinical picture is characterized by symptoms such as tingling, numbness, burning and/or pain in hands and/or feet

[1]. From a pathophysiological perspective, the various neurotoxic agents usually affect small C-fibers first and then rapidly continue to injure large (myelinated) sensory nerve fibers [2]. As a result, stimuli transmission is impaired, which in turn can have a negative effect on proprioception. Consequently, CIPN can also lead to gait difficulties or postural instability, which may have moderating effects on patients' independence and quality of life [3], but also on cancer recurrence and mortality [4] by reducing overall physical activity behavior [5].

Impairments of postural control in cancer patients have been demonstrated in cross-sectional comparisons with healthy matched controls after completion of (neurotoxic) chemotherapy [6–11] as well as longitudinally in a breast cancer population currently undergoing neurotoxic chemotherapy [12,13]. However, some authors did not account for the presence of CIPN [7,8], which due to its pathophysiology can have a significant influence on postural control. Only Kneis et al. [6] comprehensively described CIPN signs and symptoms by using clinical, electrophysiological and patient reported outcome tools. Additionally, none of these studies considered whether cancer patients may have an impaired postural control prior to chemotherapy, e.g. due to cancer-related factors such as deconditioning [14]. Therefore, the aim of this study was to compare postural control in cancer patients prior to neurotoxic chemotherapy with healthy, one-to-one matched controls and to analyze the potential impact of CIPN on postural control after neurotoxic chemotherapy in order to generate a coherent picture of postural control in cancer patients.

2 Methods

2.1 Participants

Thirty-five cancer patients (PAT) and 35 healthy, one-to-one matched controls (HMC) participated in our prospective exploratory study. PAT were derived from the waiting list control group of a single-center, randomized-controlled 3-arm intervention trial (PIC-Study; ClinicalTrials.gov identifier: NCT02871284; Ethics Committee Medical Faculty University of Heidelberg: S-630/2015) designed to assess the preventive effects of different exercise interventions in cancer patients undergoing neurotoxic chemotherapy. They were included in case they had assigned to receive a neurotoxic chemotherapy which had not been started at time of study assignment and baseline testing. The

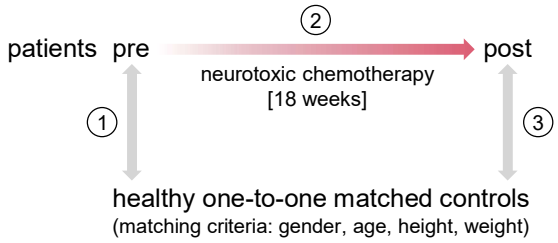

Fig. 1. Study design. The three numbers refer to the comparisons considered: 1) group comparison of patients prior to neurotoxic chemotherapy (PAT_{pre}) and healthy matched controls (HMC), 2) temporal comparison referring to the period of neurotoxic chemotherapy, 3) group comparison of patients after neurotoxic chemotherapy (PAT_{post}) and HMC.

HMC were recruited separately via advertising posters primarily on the University Campus and matched regarding gender, age, height, and weight. The HMC had no diagnosis of cancer and were free of any impairment that potentially impedes balance control and/or nerve function (supplementary material provides detailed inclusion and exclusion criteria).

HMC data were assessed once at time of study enrollment, whereas PAT were tested prior to (PAT_{pre}) and in median 3 weeks after completion of neurotoxic chemotherapy (PAT_{post}) (Fig. 1). The period between last chemotherapy and post-measurement corresponded to a hypothetical, largest possible period for all PATs to have overcome initial/short-term side effects, such as nausea, but if applicable (e.g. in neoadjuvant breast cancer patients) to perform the measurement before surgery. Written informed consent was obtained from all participants. Demographic, clinical and behavioral data were collected from medical records and study-specific forms, if applicable.

2.2 Assessment procedures

POSTURAL CONTROL was assessed during quiet standing on a force plate (AMTI, AccuSway optimized, Watertown, USA). Five measurement conditions were used: bipedal stance with eyes open (BP_{EO}) and eyes closed (BP_{EC}), semi-tandem stance (ST_{EO}, ST_{EC}), and monopedal stance (MP_{EO}) on the non-preferred leg [15]. Prior to data collection, participants were asked to test the different standing conditions. Afterwards, each condition was assessed twice for 30 s with at least 30 s break in between, during which participants were allowed to sit down if necessary. Measurements took place barefooted. Distance between feet in BP condition was based on individual hip width. Participants were instructed to stand comfortably upright and as still as possible with arms aligned aside, focusing on a visual cue attached to the wall on eye level 1.1 m away from

the force plate. Data collection was started with a 5 s delay to avoid perturbations caused by initiation of the trial.

Center of pressure (COP) data were collected with a sample rate of 100 Hz and further processed in MATLAB (Version 2018a; MathWorks, Inc; Natick, MA) using custom scripts based on standard recommendations [16]. Trials with a sample time of less than 30 s were excluded from further COP analyses. After applying a 4th order Butterworth low-pass filter (cut-off: 5 Hz), different temporal, spatial and frequency domain measures of the COP were calculated to quantify balance performance: mean sway velocity in anterior-posterior (VEL_{AP}) and medio-lateral directions (VEL_{ML}), 95 % confidence ellipse area (AREA), and mean frequency in anterior-posterior ($FREQ_{AP}$) and medio-lateral directions ($FREQ_{ML}$). Based on the overall mean velocity of the COP signal, the best trial (lowest value) out of two for each condition was selected for analyzes. Additionally, we recorded the number of failed attempts and the best duration (max. 30 s) participants were able to stand on one leg (MP_{EO}).

CIPN symptoms were diagnosed objectively applying the TOTAL NEUROPATHY SCORE in the reduced version (TNSr). The TNSr consists of two parts: clinical examinations of signs and symptoms and nerve conduction studies (NCS; motor: compound muscle action potential of peroneal nerve (CMAP), sensory: sensory nerve action potential of sural nerve (SNAP)). The detailed testing procedure is described elsewhere [17]. Each TNS item was rated on a 0–4 scale and summed up to a total score (TNSr, range 0–36) and without CMAP and SNAP results to a clinical subscore (TNSc, range 0–28). Higher scores reflect more severe peripheral neuropathy. The TNSr and TNSc are found to be reliable and accurate in grading CIPN and sensitive in showing CIPN progression [17]. Nerve conduction velocities (NCVs) of the peroneal and sural nerves were reported separately for more detailed quantification of CIPN [2].

PATIENT-REPORTED CIPN SYMPTOMS were assessed with the EORTC-CIPN20 questionnaire. The original questionnaire contains 20 items, which are rated on a 4-point Likert scale referring to the past seven days. Based on current research findings, it is recommended to calculate the mean sum score over 15 items (CIPN15: range 0–100), with higher scores associating higher symptom burden [18].

FEAR OF FALLING was assessed using the Falls Self-Efficacy Scale- International (FES-I). The questionnaire shows good applicability and psychometric properties [19]. According to the manual, a sum score was calculated (range 16–64) with higher scores indicating a greater fear of falling. Additionally, the number of falls during chemotherapy (PAT) or within the last six

Table 1. Participant characteristics.

	Patients	Healthy Matched Controls	p
Demographic profile			
Sex [f:m, n]	33:2	33:2	-
Age [years, median (range)]	51 (38 - 73)	53 (37 - 72)	.39
Married [n (%)]	24 (71 %)	24 (71 %)	1.0
Completed university [n (%)]	9 (26 %)	18 (51 %)	**.02**
Medical profile			
Height [cm, median (range)]	166.0 (154.0 - 178.0)	167.0 (159.0 - 180.0)	.08
Weight [kg, median (range)]	69.0 (49.2 - 101.5)	70.2 (53.5 - 98.8)	.06
BMI [kg/m², median (range)]	24.3 (18.35 - 3)	25.2 (19.4 - 34.8)	.28
Comorbidities [n (%)]			
- none	5 (14 %)	9 (26 %)	.23
- respiratory	2 (6 %)	1 (3 %)	1.0
- cardiovascular	12 (34 %)	3 (9 %)	**.01**
- musculoskeletal	22 (63 %)	18 (51 %)	.33
- neurological	0 (0 %)	1 (3 %)	.31
- endocrine/metabolic	3 (9 %)	3 (9 %)	1.0
[diabetes]	0 (0 %)	1 (3 %)	1.0
- psychiatric	1 (3 %)	0 (0 %)	1.0
Oncological diagnosis [n (%)]			
Breast cancer	31 (89 %)	-	-
Pancreatic cancer	2 (6 %)	-	-
Rectal cancer	1 (3 %)	-	-
Oral cancer	1 (3 %)	-	-
Disease status (UICC) [n (%)]			
I	12 (34 %)	-	-
IIa	7 (20 %)	-	-
IIb	4 (17 %)	-	-
IIIa	2 (6 %)	-	-
IIIb	1 (3 %)		
IV	4 (17 %)	-	-
Chemotherapy			
Duration [weeks, median (range)]	18 (4 - 25)	-	-
Time between last chemotherapy and post0 assessment [days, median (range)]	21 (3 - 55)	-	-
Taxane-based [n (%)]	20 (57 %)	-	-
Platinum-based [n (%)]	4 (11 %)	-	-
Vinca alkaloid [n (%)]	1 (3 %)	-	-
Taxane-platinum combination [n (%)]	8 (23 %)	-	-
Taxane-taxane combination [n (%)]	2 (6 %)	-	-
Behavioral profile			
Smoking [n (%)]			.33
- never smoker	14 (40 %)	21 (60 %)	
- former smoker	17 (49 %)	12 (34 %)	
- current smoker	3 (9 %)	2 (6 %)	
Alcohol [yes/no]	25 (71 %)	29 (83 %)	.73
Physical activity [n (%)]			.10
- none	2 (6 %)	1 (3 %)	
- 0–<9 MET*h/week	10 (29 %)	3 (9 %)	
- 9–<18 MET*h/week	7 (20 %)	6 (17 %)	
- ≥ 18 MET*h/week	16 (46 %)	25 (71 %)	

Abbreviations: CT, chemotherapy; MET, metabolic equivalent of task. Bold p-values are considered statistically significant different ($p<.05$).

Table 2. Center of pressure-based measures of postural control – percentage differences between groups.

		PAT_{pre} – HMC		PAT_{pre} – PAT_{post}		PAT_{post} – HMC	
		Δ (Q1–Q3) [%]	**p**	**Δ** (Q1–Q3) [%]	**p**	**Δ** (Q1–Q3) [%]	**p**
BP_{EO}							
VEL	AP	-4.3 (-25.3–4.1)	.052	24.8 (7.4–49.1)	**.000**	10.7 (-10.3–48.0)	.095
	ML	6.3 (-17.9–34.0)	.162	12.4 (-12.8–44.6)	**.042**	22.8 (-6.1–71.5)	**.004**
AREA		4.7 (-45.1–65.0)	.724	40.2 (-19.8–163.2)	**.013**	46.8 (-24.3–156.2)	**.013**
FREQ	AP	-11.7 (-51.1–29.2)	.212	17.8 (-20.1–88.0)	**.015**	3.3 (-29.2–95.8)	.411
	ML	7.1 (-28.3–26.9)	.736	-4.2 (-29.8–34.5)	.479	-7.4 (-30.6–37.3)	.712
BP_{EC}							
VEL	AP	-4.7 (-28.7–22.7)	.459	35.2 (2.8–62.2)	**.000**	17.2 (-15.3–71.7)	**.042**
	ML	0.0 (-26.3–67.1)	.585	23.7 (-15.6–84.5)	**.019**	31.5 (-8.0–100.3)	**.006**
AREA		12.7 (-26.9–83.4)	.333	57.1 (10.5–160.3)	**.001**	82.1 (3.9–269.7)	**.000**
FREQ	AP	-3.6 (-31.6–28.7)	.911	-7.0 (-17.2–45.1)	.962	-2.2 (-27.9–34.9)	1.00
	ML	-12 (-40.8–33.2)	.089	-1.3 (-28.5–52.5)	.911	-16.8 (-36.3–12.1)	**.044**
ST_{EO}							
VEL	AP	-1.8 (-30.5–22.3)	.479	4.5 (-3.2–25.5)	**.028**	0.3 (-19.1–38.1)	.885
	ML	-6.5 (-25.2–27.3)	.421	16.7 (-6.4–36.7)	**.002**	8.1 (-12.9–50.4)	.157
AREA		14.0 (-23.6–58.4)	.130	22.0 (-22.9–67.7)	.071	27.0 (-13.1–93.9)	**.006**
FREQ	AP	-3.8 (-42.8–49.1)	.402	2.3 (-38.6–65.4)	.873	-16.7 (-59.0–72.0)	.183
	ML	-29.2 (-41.6–21.5)	**.006**	27.1 (-8.2–55.3)	**.003**	0.1 (-31.3–24.1)	.653
ST_{EC}							
VEL	AP	8.9 (-26.9–53.4)	.325	14.0 (-2.5–46.9)	**.005**	17.6 (-21.8–112.3)	**.027**
	ML	-3.8 (-24.3–42.5)	.821	22.4 (5.1–51.3)	**.000**	24.2 (-16.7 – 80.0)	**.015**
AREA		40.7 (-20.6–113.7)	.063	47.3 (4.5–77.7)	**.000**	81.1 (1.7–187.8)	**.000**
FREQ	AP	8.6 (-21.6–48.0)	.445	-4.8 (-30.8–17)	.152	0.2 (-47.8–54.4)	.795
	ML	-13.8 (-34.4–35.8)	.455	13.9 (-14.2–36.4)	.071	10.2 (-30.1–53.3)	.308
MP_{EO}							
VEL	AP	6.2 (-30.6–40.5)	.688	2.7 (-10.0–33.9)	.359	-3.8 (-35.4–38.1)	.623
	ML	-2.9 (-28.4–14.3)	.144	2.5 (-7.8–16.8)	.192	-4.3 (-29.9–28.7)	.438
AREA		4.3 (-33.2–73.0)	.716	9.6 (-25.4–33.3)	.496	0.1 (-17.8–51.5)	.438
FREQ	AP	-3.9 (-42.3–48.7)	.376	7.1 (-17.1–27.0)	.542	5.5 (-44.6–40.4)	.623
	ML	-6.7 (-31.8–15.5)	.194	4.1 (-24.7–20.6)	.779	-9.9 (-34.5–14.1)	.083
time			.875		**.016**		**.016**
FA			1.00		**.043**		**.047**

Differences between groups are shown as median percentage differences (Δ) and interquartile range (25–75 %). Bold p-values are considered statistically significant different as revealed by Wilcoxon-signed-rank tests ($p<.05$). **Abbreviations:** PAT_{pre}, patients before neurotoxic chemotherapy; HMC, healthy one-to-one matched controls; PAT_{post}, patients 3 weeks after neurotoxic chemotherapy; Q1–Q3, interquartile range (25–75 %); BP, bipedal stance; ST, semi-tandem stance; MP, monopedal stance; EO, eyes open; EC, eyes closed; VEL, COP mean velocity; AREA, 95 % confidence ellipse area; FREQ, COP mean frequency; AP, anterior-posterior; ML, medio-lateral; FA, failed attempts.

months (HMC) was recorded.

Physical activity behavior was assessed with a self-developed questionnaire [20] referring to the last 12 months. Participants were asked to give an average on how often they had done the following activities: continuous walking for at least 20 min, cycling and other sports activities (free text). Based on intensity, time/duration and type of physical activity average MET*h/week were calculated [21].

2.3 Statistical analysis

Demographics, comorbidities and behavioral profile were compared between PAT and HMC using Chi-square test. Based on deltas between groups (Δ_1: PAT_{pre} – HMC; Δ_2: PAT_{pre} – PAT_{post}; Δ_3: PAT_{post} – HMC), Wilcoxon-signed-rank-test was used to calculate group (Δ_1, Δ_3) and time differences (Δ_2). To investigate whether withdrawal of visual control (EC conditions) had a greater impact on postural control in PAT than HMC an additional Wilcoxon test was applied. Here delta specific EO differences of the different COP parameters were compared with equivalent EC differences (e.g. BP_{EO}_ AREA_Δ_1 vs. BP_{EC}_AREA_Δ_1 and ST_{EO}_AREA_Δ_1 vs. ST_{EC}_AREA_Δ_1). Mann-Whitney-U test was used to detect baseline differences in postural control between PAT who failed and PAT who successfully completed MP_{EO} after chemotherapy. Spearman-Correlation was applied to analyze associations

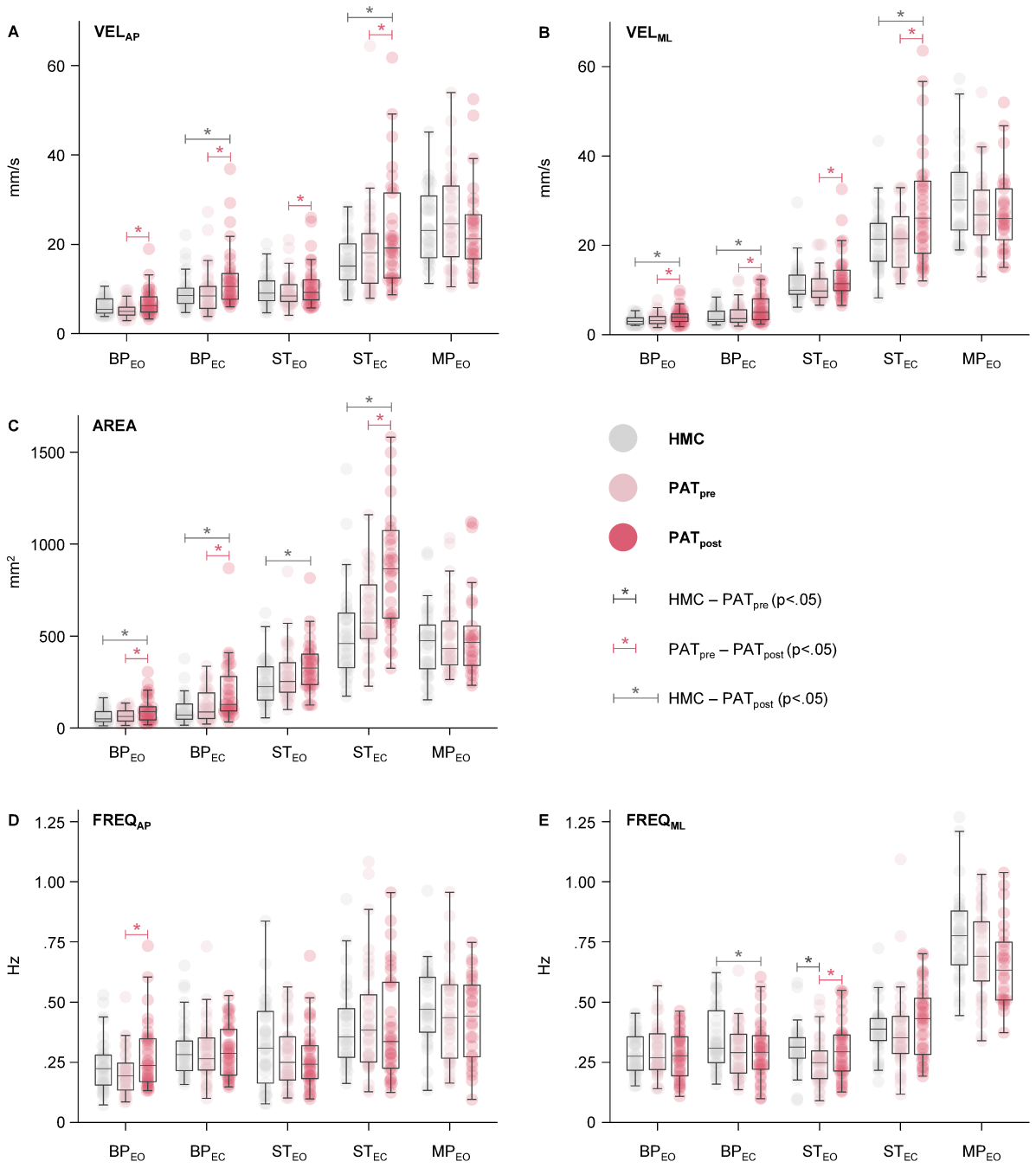

Fig. 2. Center of pressure-based measures of postural control. Box and jitter plots showing the center of pressure (COP) data for healthy matched controls (HMC), cancer patients prior to (PAT_{pre}) and after chemotherapy (PAT_{post}). The following COP parameters are displayed: mean sway velocity in A) anterior-posterior (VEL_{AP}) and B) medio-lateral directions (VEL_{ML}), C) 95 % confidence ellipse area (AREA), and mean frequency in D) anterior-posterior ($FREQ_{AP}$) and E) medio-lateral directions ($FREQ_{ML}$). Each graph shows the five tested measurement conditions: bipedal stance with eyes open (BP_{EO}) and eyes closed (BP_{EC}), semi-tandem stance (ST_{EO}, ST_{EC}), and monopedal stance (MP_{EO}). Significant differences between groups are marked (*).

between balance performance (COP parameter) and severity of CIPN symptoms (TNSr, TNSc, and CIPN15 scores) as well as fear of falling (FES-I) amongst the PAT_{post} population. Statistical analyses were completed using SAS Enterprise Guide 7.1 (SAS Institute Inc., USA). The level of significance was set to $p<.05$. Due to the exploratory nature of this study, α-error correction was not applied.

Table 3. CIPN signs and symptoms and falls.

	HMC	PAT_{pre}	PAT_{post}	PAT_{pre} – HMC	PAT_{pre} – PAT_{post}	PAT_{post} – HMC
	median (Q1–Q 3)	median (Q1–Q3)	median (Q1–Q3)	p-value	p-value	p-value
TNS						
TNSr [score]	0 (0–0)	1 (0–2.5)	6 (3–11)	**<.001**	**<.001**	**<.001**
TNSc [score]	0 (0–0)	0 (0–1)	5 (2–8)	**<.001**	**<.001**	**<.001**
NCS						
CMAP [µV]	8.8 (7.0–10.7)	8.2 (5.9–10.2)	5.7 (4.3–7.5)	.189	**<.001**	**<.001**
SNAP [mV]	13.8 (10.9–18.1)	11.8 (9.3–15.6)	7.9 (5.3–10.8)	.138	**<.001**	**<.001**
NCV (per) [m/s]	50.4 (47.9–52.2)	48.9 (45.8–52.1)	47.9 (45.3–51.7)	.673	.095	.169
NCV (sur) [m/s]	48.1 (45.2–50.5)	47.6 (45.3–52.6)	46.5 (44.1–50.0)	.500	.107	.866
PRO						
CIPN15 [score]	0 .0 (0.0–2.2)	0 (0–2.2)	8.9 (2.2–17.8)	.476	**<.001**	**<.001**
FES-I [score]	17 (16–18)	16 (16–17)	17 (16–19)	.336	**<.001**	.330
Falls [n]	0 (0–1)[a]	0 (0–1)[a]	0 (0–2)[a]	1.00	.375	.625

Table shows descriptive statistics for each group separately as median and interquartile range (Q1–Q3) and p-values as revealed by Wilcoxon-signed-rank tests. Bold p-values are considered statistically significant different (p<.05). **Annotations**: [a] To avoid ambiguities in the context of the continuous text, the range of falls was displayed instead of the interquartile range (25–75 %). **Abbreviations**: HMC, healthy one-to-one matched controls; PAT_{pre}, patients before neurotoxic chemotherapy; PAT_{post}, patients 3 weeks after neurotoxic chemotherapy; Q1–Q3, interquartile range (25–75 %); TNSr/TNSc, total neuropathy score (reduced/clinical); NCS, nerve conduction studies; CMAP, compound muscle action potential of peroneal nerve; SNAP, sensory nerve action potential of sural nerve; NCV, nerve conduction velocity; per, peroneal nerve; sur, suralis nerve; PRO, patient reported outcomes; CIPN15, sumscore based on EORTC QLQ-CIPN20 questionnaire; FES-I, sumscore based on FES-I questionnaire.

3 Results

Participants' characteristics are listed in Table 1. Analyzes showed no differences between PAT and HMC regarding demographic profile. However, HMC more often had a university degree (p=.02) than PAT and had less cardiovascular comorbidities (p=.01). Most PAT received taxan-based chemotherapy (57 %) which lasted a median of 18 weeks.

3.1 Postural control

Results of descriptive and inferential statistics are listed in Table 2 and plotted in Fig. 2. PAT_{pre} – HMC: Analyzes revealed one significant different COP parameter regarding the addressed comparison: $FREQ_{ML}$ in ST_{EO} (PAT_{pre}<HMC; S=162, p=.01).

PAT_{pre} – PAT_{post}: After completion of chemotherapy, 11 of 12 analyzed temporal and spatial domain measures of the COP in bipedal standing conditions (BP and ST) were significantly increased compared to baseline assessment (p≤.04), but not for MP_{EO} (p>.19). However, the time PAT were able to stand on one leg decreased (S=17, p=.02) pre to post and number of failed attempts increased significantly (S=20.5, p=.04). Detailed analyzes of the six PAT who failed the MP_{EO} task after chemotherapy revealed (significantly) increased COP values before chemotherapy compared to the patients who succeeded in the task (VEL_{AP} U=157, p=.01; VEL_{ML} U=144, p=.05; AREA U=131, p=.18; $FREQ_{AP}$ U=153, p=.02; $FREQ_{ML}$ U=146, p=.04). Two of ten analyzed frequency domain measures were significantly increased (BP_{EO}: $FREQ_{AP}$ S=145, p=.02; ST_{EO}: $FREQ_{ML}$ S=173, p<.01).

PAT_{post} – HMC: PAT had significantly higher values than HMC for all temporal and spatial domain measures in bipedal standing conditions with closed eyes (p≤.04). For bipedal standing positions with open eyes the following results were obtained: BP_{EO} – PAT had significantly higher VEL_{ML} (S=170, p<.001) and AREA (S=148, p=.01); ST_{EO} – PAT showed higher values in AREA (S=162, p=.01). COP variables of the temporal and spatial domain measures in MP_{EO} did not differ significantly (p>.41), but PAT had significantly lower standing times (S=17, p=.02) and higher failure rates (S=25.5, p=.05) than HMC. Regarding FREQ analyzes only one significant difference occurred in BP_{EC} (PAT_{post}>HMC: $FREQ_{ML}$ S=122, p=.04).

EO vs. EC conditions: When PAT_{post} were compared with PAT_{pre} and HMC, closed eyes conditions showed greater differences between groups than conditions with open eyes for VEL_{AP} (p<.001–.14; nonsignificant for BP condition), VEL_{ML} (p<.01–.02) and AREA (p<.001–.04), but not for $FREQ_{AP}$ (p=.19–.70) nor $FREQ_{ML}$ (p=.16–.72). No differences were found for the comparison of PAT_{pre} and HMC.

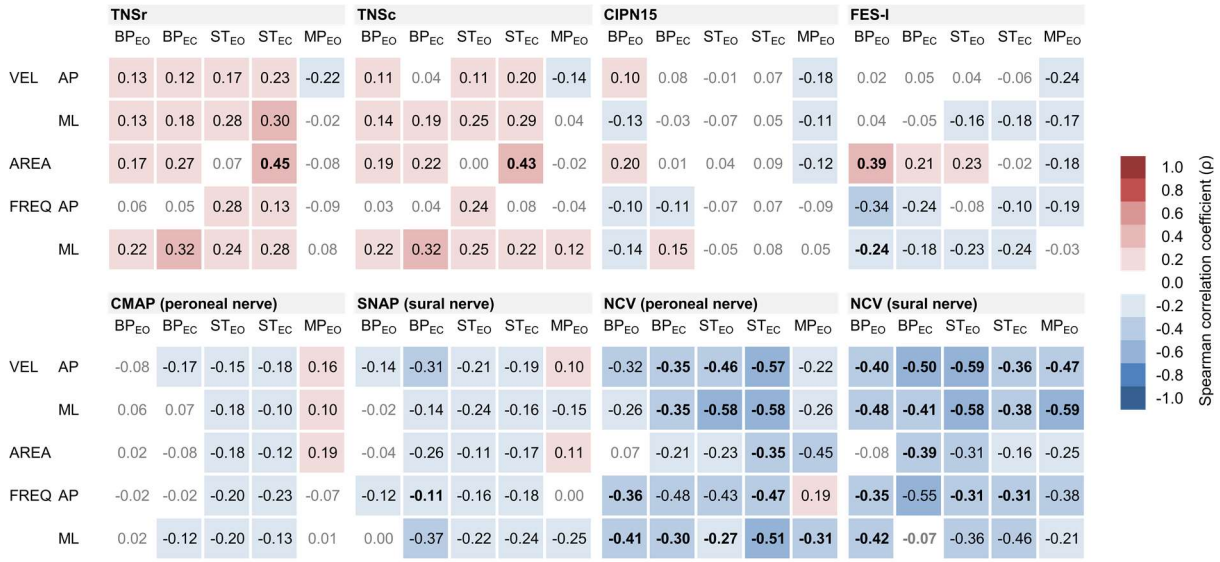

Fig. 3. Correlation matrix heatmap. The darker the color the stronger the association between postural control parameters and clinically diagnosed CIPN (TNSr, TNSc), patient reported outcomes (CIPN15, FES-I) or results of nerve conduction studies (CMAP, compound muscle action potential of peroneal nerve; SNAP, sensory nerve action potential of sural nerve; NCV, nerve conduction velocity). Bold Spearman correlation coefficients (ρ) are considered statistically significant different (p<.05).

3.2 Total Neuropathy Score

PAT_{pre} – HMC: TNS scores were significantly higher (TNSr: S=73.5, p<.001; TNSc: S=43.5, p<.001) for PAT compared with HMC. No differences were found for CMAP, SNAP or NCVs. PAT_{pre} – PAT_{post}: During neurotoxic chemotherapy PATs' CMAP (S=284.5, p<.001) and SNAP (S=249.5, p<.001) decreased significantly but not NCVs (peroneal: S=93.5, p<.10; sural: S=86.5, p<.11), which was accompanied by a significant increase of the TNSr (S=187.5, p<.001) and TNSc score (S=197, p<.001) (Table 3). PAT_{post} – HMC: Comparison revealed significant lower CMAP (S=207, p<.001) and SNAP (S=205.5, p<.001) as well as higher TNS scores (TNSr: S=217.5, p<.001; TNSc: S=217.5, p<.001) for PAT but no differences in NCVs (peroneal: S=67.5, p<.10; sural: S=8, p<.11).

3.3 Patient reported outcomes

No differences occurred when PAT_{pre} were compared with HMC. PAT_{post} showed significant higher CIPN15 and FES-I score after finishing neurotoxic chemotherapy (p<.001; Table 3). In comparison to HMC, the CIPN15 score was significantly higher in PAT_{post} (p<.001; Table 3).

3.4 Associations between postural control and CIPN

For TNSr/TNSc, correlations were primarily low to moderate for all COP parameters and tended to be higher for more difficult bipedal standing positions (|ρ|=0.05–0.45, p<.001–.83; Fig. 3). Correlations between COP parameters in bipedal standing positions and CMAP were primarily low and tended to be more pronounced for SNAP. For NCVs, primarily significant moderate to high negative correlations for all COP parameters were found. No or just small, nonsignificant negative correlations were found between CIPN15 and FESI scores and the various COP parameter in the different standing positions. Overall, correlations for MP_{EO} were very heterogeneous across considered parameters.

4 Discussion

The aim of our study was to generate a coherent picture of postural control in cancer patients by combining matched cross-sectional (PAT_{pre} – HMC, PAT_{post} – HCM) and longitudinal (PAT_{pre} – PAT_{post}) comparisons of postural control with a particular focus on CIPN. Our results showed that cancer patients' postural control is not impaired prior to chemotherapy. However, postural control deteriorated during neurotoxic chemotherapy which corresponds to an ageing process of 25 years [22] and these balance deficits could also be confirmed in comparison to healthy one-to-one matched controls. Since the results of bipedal and monopedal standing conditions allow different conclusions, discussion is divided according to these testing positions.

4.1 Postural control in bipedal standing positions

Since PAT_{pre} did not differ from HMC in almost all COP parameters, it can be concluded that possibly existing pre-therapeutic cancer-related factors did not impair postural control. Consequently, the detected balance deficits (PAT_{pre} – PAT_{post}, PAT_{post} – HMC) are probably associated with the side effects of neurotoxic chemotherapy. Statistical analyzes revealed a deteriorated postural control in bipedal standing positions (BP, ST) after neurotoxic chemotherapy, wherein both AP and ML mean sway velocity and sway area of the COP significantly increased, but not frequency. The most obvious differences were seen in bipedal standing conditions with closed eyes: Withdrawal of visual control resulted in greater COP displacements after neurotoxic chemotherapy than before. In combination with the negative correlation between some COP parameters and objectively assessed CIPN symptoms (more severe CIPN symptoms were associated with poorer postural control), it could be assumed that this result was due to an impairment of proprioception, which might have been compensated by visual control in conditions with open eyes [23]. Although, we cannot define causative relationships with the correlation presented, from a physiological perspective it is most likely that the underlying nerve damage diagnosed with the TNSr has a negative influence on postural control. It is worth noting that COP parameters correlated more strongly with NCVs than with CMAP or SNAP amplitudes. Given the primarily axonal mechanism of neurotoxicity in CIPN, reduction of NCVs are commonly first observed at more advanced stages of the disease, whereas reductions of CMAP and particularly SNAP amplitudes can typically be found earlier [2]. Therefore, it is plausible that relevant balance deficits occur after the extent of axonal injury has reached a critical degree, e.g., when large, myelinated nerve fibers (Ia afferents) are impaired, leading to delayed somatosensory input. However, the overall rather low correlations regarding TNSr may indicate that other influencing factors exist. This assumption is supported by results from Wampler et al. [24], who explained 44 % of the variance of a balance test (sensory organization test) with the modified TNS ($r=-0.66$, $p=.002$). Future studies should therefore analyze other factors potentially influencing postural control, e.g. strength [25], cognitive impairments [26], and physical inactivity [27], in addition to CIPN.

COMPENSATION STRATEGIES. Naturally, the central nervous system counteracts delayed somatosensory input with compensation strategies such as muscular co-contractions. Kneis et al. [6] showed significant correlations between COP sway path and co-contraction indices in CIPN patients. Muscular co-contractions are typically accompanied by higher sway frequencies [28]. However, frequency domain measures remained unchanged after neurotoxic chemotherapy in our study. Likewise, no differences were found in the comparison between HMC and PAT_{post} which is comparable to Schmitt et al. [7]. In light of this, we assume that the deterioration of somatosensory input was not compensated by muscular co-contractions but rather caused a delay of postural reactions, which became evident by the increased temporal and spatial COP parameters. However, since our study was not designed to detect postural control strategies such as muscular co-contractions, future studies should implement EMG studies to verify the speculative conclusion presented.

4.2 Postural control in monopedal standing positions

Although enhanced temporal and spatial COP parameters indicate balance deficits in bipedal standing positions, these findings could not be replicated in monopedal stance. This might be due to a ceiling effect, since patients excluded from analyses (standing time < 30 s in both trials) already had a significantly worse postural control prior to chemotherapy than patients, who successfully completed MP_{EO}. Consequently, only patients with appropriate pre-postural control were analyzed. However, lower monopedal standing time and a higher number of failed attempts may also indicate balance deficits in PAT_{post}, both in comparison to PAT_{pre} and HMC. In conclusion, MP_{EO} might only be sensitive in detecting COP based balance deficits in this cohort, if test time is reduced.

4.3 Falls

Balance deficits are an important predictor of falls. Winters-Stone et al. [29] reported an almost twice as high fall rate of CIPN symptomatic compared to asymptomatic patients 6 years after treatment. In our cohort, however, only three patients fell during chemotherapy (n=1 twice), but fear of falling increased significantly. This divergence in results may be related to the different time periods considered: While patients are more likely to be aware of the altered sensory perception during chemotherapy and may therefore walk more cautiously, this increased focus might be reduced as part of an habituation process or increased dual-task requirements during everyday life, thereby increasing the risk of falling.

4.4 Practical implications

Since balance deficits in general or in combination with CIPN are associated with gait difficulties and higher risk of falling [29], and therefore might have a negative impact on activities of daily living as well as quality of life [3], it is necessary to detect and counteract balance deficits early. Regarding detection, we assume that the patient reported outcome tools used in our study (CIPN15, FES-I) are inadequate to detect balance deficits due to the lack of correlation with COP parameters. Therefore, future studies should invest in the development of balance tests which are easy to implement in a clinical environment and can be used as a monitoring parameter during chemotherapy. Based on our results, ST_{EC} could be a promising standing position for a precise detection of balance deficits.

In addition to early diagnosis, preventive measures or at least early countermeasures must be implemented after positive CIPN diagnosis. However, high-quality studies addressing preventive approaches during neurotoxic chemotherapy are currently lacking. Regarding rehabilitative approaches, sensorimotor exercise and strength training approaches might be useful to enhance balance in this cohort (e.g. [30]). Referring to our findings, we would recommend exercises that target proprioception and sensitivity of the vestibular organ, e.g. by training on unstable surfaces with closed eyes. Vibration training might also be a promising approach, as it has shown a tendency to improved sensory perception in CIPN patients [31].

4.5 Limitations

Although we provided a comprehensive picture of postural control in cancer patients with a particular focus on CIPN, there are some limitations to be addressed. First, generalizability is hampered due to the fact that mainly breast cancer patients were enrolled in this trial. Since this also applies to all other published studies [6–11], it is important to verify these results in other cohorts. Second, our study population was heterogeneous regarding treatment protocols. The different neurotoxic agents might have led to variations in CIPN symptom development. However, our sample size was too small to run subgroup analyzes. Future studies should therefore address potential different effects on postural control of the various neurotoxic chemotherapeutic agents. Third, although we applied a comprehensive ono-to-one matching procedure, our healthy control group had a higher educational status (more university degrees). Being aware of the link between education and health [32], it is conceivable that our cancer patients generally had an unhealthier lifestyle, which might have caused pre-therapeutic nerve damage (significantly higher clinically diagnosed CIPN symptoms compared to HMC). However, our assessed behavioral profile does not support this assumption.

5 Conclusion

Prior to chemotherapy, postural control in cancer patients was unimpaired, but markedly deteriorated after neurotoxic chemotherapy. Besides peripheral nerve injury, other factors influencing postural control may exist and should be addressed in future studies to effectively develop both preventive and rehabilitative measures.

Funding

This work was supported by an intramural funding program: Proof of concept trials 3.0, National Center for Tumor Diseases, Heidelberg, Germany (PIC study, G876).

Declaration of Competing Interest

The authors declared no conflict of interest.

Acknowledgement

We thank all patients and healthy controls for participating in this study. We gratefully acknowledge Christine Boos and Laura Jansen for study implementation and conduction, Georges Sam (Department of Neurology, Heidelberg University Hospital) for excellent technical assistance in electro diagnostics, the clinical cooperation partners (Andreas Schneeweiss, Martin Haag, Stefan Welte) for recruitment assistance, NCT Cancer Registry and NCT Trial Center for data management support, Axel Benner and Nikolaus Kleindienst for statistical support, and the OnkoAktiv Network.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.gaitpost.2020.01.012.

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4

Manuscript II

Müller, J., Kreutz, C., Ringhof, S., Köppel, M., Kleindienst, N., Sam, G., Schneeweiss, A., Wiskemann, J., & Weiler, M. (under review). Chemotherapy-induced peripheral neuropathy: Longitudinal analysis of predictors for postural control. Submitted to *Scientific Reports* on September 12, 2020.

Highlights

- Neurotoxic chemotherapy deteriorates postural control in cancer patients
- Postural control recovers after neurotoxic chemotherapy while CIPN persists
- Baseline sensory and motor nerve functions are related to postural control

Data used of the PIC study

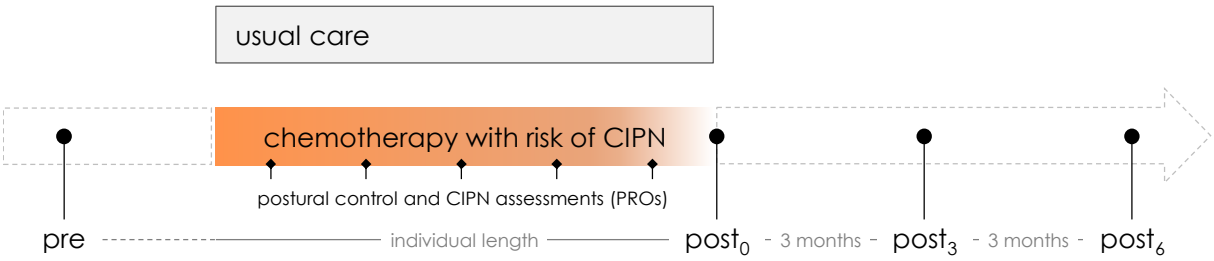

Figure 7. Patient data used for Manuscript II based on the PIC study.

The **supplementary material** for this manuscript can be found on pages 126f.

Authorship contributions (according to CRediT taxonomy): conceptualization [JM, JW, MW], data curation [JM, JW, MW], formal Analysis [JM, MK, NK], funding acquisition [JW], investigation [JM, CK, GS, JW, MW], methodology [JM, JW, MW], project administration [JM, JW, MW], resources [AS, JW, MW], software [SR], supervision [JW, MW], validation [SR, MK, NK, JW, MW], visualization [JM], writing – original draft [JM], writing – review & editing [all authors].

PLEASE NOTE: The manuscript was accepted by *Scientific Reports* on January 12, 2021, and subsequently published in a revised version (January 27, 2021): Müller, J., Kreutz, Ch., Ringhof, S., Köppel, M., Kleindienst, N., Sam, G., Schneeweiss, A., Wiskemann, J, & Weiler, M. (2021). Chemotherapy-induced peripheral neuropathy: Longitudinal analysis of predictors for postural control. *Scientific Reports 11*(2398). https://doi.org/10.1038/s41598-021-81902-4.

Chemotherapy-induced peripheral neuropathy: Longitudinal analysis of predictors for postural control

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Abstract

Impaired postural control is often observed in response to neurotoxic chemotherapy. However, potential explanatory factors other than chemotherapy-induced peripheral neuropathy (CIPN) have not been adequately considered to date due to primarily cross-sectional study designs. Our objective was to comprehensively analyze postural control during and after neurotoxic chemotherapy, and to identify potential CIPN-independent predictors for its impairment. Postural control and CIPN symptoms (EORTC QLQ-CIPN20) were longitudinally assessed before, during and three weeks after neurotoxic chemotherapy, and in three and six months follow-up examinations (N=54). The influence of peripheral nerve function as determined by nerve conduction studies (NCS: compound motor action potentials (CMAP) and sensory action potentials (SNAP)), physical activity, and muscle strength on the change in postural control during and after chemotherapy was analyzed by multiple linear regression adjusted for age and body mass index (BMI). Postural control, CIPN signs/symptoms, and CMAP/SNAP amplitudes significantly deteriorated during chemotherapy ($p<.01$). During follow-up, patients recovered from postural instabilities ($p<.01$), whereas CIPN signs/symptoms and pathologic NCS findings persisted compared to baseline ($p<.001$). The regression model showed that low CMAP and high SNAP amplitudes at baseline predicted impairment of postural control during but not after chemotherapy. Hence, pre-therapeutically disturbed somatosensory inputs may induce adaptive processes that have compensatory effects and allow recovery of postural control while CIPN signs/symptoms and pathologic peripheral nerve function persist. Baseline NCS findings in cancer patients who receive neurotoxic chemotherapy thus might assist in delineating individual CIPN risk profiles more precisely to which specific exercise intervention programs could be tailor-made.

KEYWORDS: Balance ▪ Cancer ▪ Chemotherapy-induced peripheral neuropathy ▪ Electrophysiology ▪ Proprioception

1 Introduction

Chemotherapy-induced peripheral neuropathy (CIPN) is a common, potentially severe and dose-limiting adverse effect of cancer treatment. The compounds most commonly associated with CIPN are taxanes, platinum derivatives, and vinca alkaloids, applied either alone or as combined therapies [1]. The clinical picture of CIPN comprises sensory symptoms including tingling, burning, pain, and numbness and, in more severe cases, additional motor symptoms such as muscle cramps, weakness, and wasting [1]. In about 30% of patients, CIPN symptoms may persist for six months and longer after completion of neurotoxic chemotherapy [2]. The underlying causes of CIPN are various pathophysiological changes in the somatosensory (afferent) and motor (efferent) peripheral nerve fibers, which may lead to difficulties in postural control, concomitant with gait instabilities [3], and an increased risk of falls [4], associated with further medical complications, and consider-

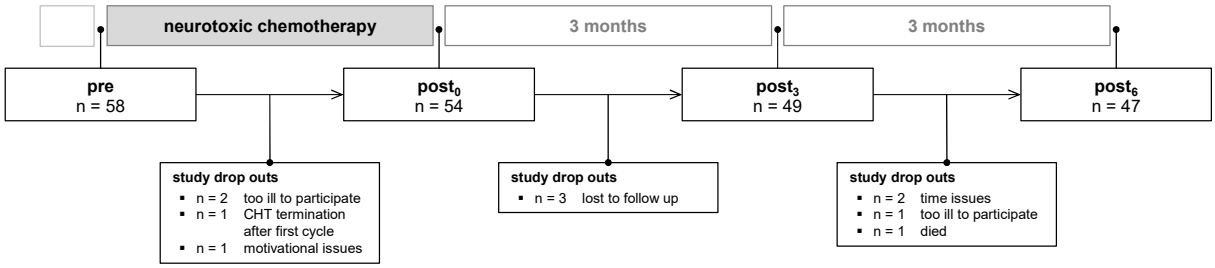

Figure 1. Study design and flow-chart.

ably deteriorated quality of life [1].

Several studies investigated static postural control in cancer patients in response to neurotoxic treatments, applying quantitative center of pressure (COP) analyses using a force plate [3-10]. However, available data are heterogeneous as to the time point of COP analysis, and the investigation of risk or protective factors. During taxane-based chemotherapy, postural control gradually deteriorated with increasing chemotherapy cycles and remained impaired one to three months after completion of chemotherapy [3]. Cross-sectional studies mirror this finding by showing that postural control is impaired immediately after completion of chemotherapy compared with healthy controls [7-9]. However, the longer the treatment-free period (time between completion of chemotherapy and COP analysis), the more divergent the results became [4-6], until about ten years after completion of chemotherapy differences became no longer detectable [10].

The pathophysiology of CIPN strongly supports a causative relationship of CIPN with impairment of postural control, but previous correlation analyses merely demonstrated low to moderate associations between various diagnostic approaches of CIPN and COP analyses [3, 5, 7]. Therefore, it is plausible that postural control in cancer patients treated with neurotoxic agents is additionally affected by factors other than CIPN alone, possibly including baseline peripheral nerve function, muscle strength and/or power [11], and physical inactivity [12].

Since comprehensive analyses on overall predictors of postural control in the context of neurotoxic chemotherapy are lacking, we present here longitudinal data on postural control in patients with different cancer types during and after neurotoxic chemotherapy. Specifically, the main goals of our study were to (i) determine the extent of change of postural control along with patient-reported and neurologically objectified CIPN signs/symptoms; and (ii) identify risk and protective factors that influence postural control during and after neurotoxic chemotherapy.

2 Results

A total of 58 cancer patients were included in our analysis. Four patients became ineligible after baseline testing and were excluded from further analyses (Figure 1). Patient and treatment characteristics of the remaining 54 patients are summarized in Table 1. Thirty-seven percent of the patients were diagnosed with abnormal sensory nerve action potential (SNAP) amplitudes before starting neurotoxic chemotherapy. Patients were tested before (pre) and three weeks after completion of neurotoxic chemotherapy ($post_0$). Between pre and $post_0$ assessments, postural control and subjectively perceived CIPN symptoms were evaluated repetitively prior to each or, in case of a weekly administration schedule, prior to every second application of chemotherapy. Follow-up data were generated three ($post_3$) and six months ($post_6$) after $post_0$ (Figure 1). During follow-up, 26% of the patients started a structured training: sensorimotor exercise training (n=6, mean attendance rate: 62.0%), resistance training (n=7, mean attendance rate: 41.5%), or endurance training (n=1, attendance rate: 100%).

POSTURAL CONTROL DURING NEUROTOXIC CHEMOTHERAPY. Four measurement conditions were analyzed: bipedal and semi-tandem stance, each with eyes open (BP_{EO}; ST_{EO}) and eyes closed (BP_{EC}; ST_{EC}). During neurotoxic chemotherapy, a fluctuating increase in COP_{AREA} was observed with an almost parallel increase in patient-reported CIPN symptoms (Figure 2). This descriptive observation was confirmed at the interference statistical level (Table 2): postural control deteriorated in all standing conditions (pre-$post_0$: $p<.0001$) except for ST_{EO} (pre-$post_0$: $p=.04$). CIPN signs/symptoms also worsened (pre-$post_0$: $p<.0001$), as did muscle strength assessed by maximal voluntary isometric contraction (MVIC, pre-$post_0$: $p=.001$). No significant difference was observed in physical activity behavior (PA).

The regression models showed that – after adjusting

for age and body mass index (BMI) – high baseline SNAP amplitudes were a significant predictor for the decline in postural control in EO and EC conditions during subsequent neurotoxic chemotherapy (EO_{AREA}: β=0.37, p=.03; EC_{AREA}: β=0.44, p<.01). In EC conditions, low baseline compound muscle action potential (CMAP) amplitudes were an additional significant predictor (EC_{AREA}: β=-0.43, p<.01). All other predictors were not significant (Table 3).

POSTURAL CONTROL DURING FOLLOW-UP. Six months after completion of neurotoxic chemotherapy, patients recovered from postural disturbances ($post_0$-$post_6$: p<.004), thus differences to baseline assessment were no longer detectable (pre-$post_6$: p>.08). Compared to $post_0$, patients were more physically active (p<.01) and gained in muscle strength (p=.01). However, CIPN signs/symptoms were still worse compared to pre (pre-$post_6$: p<.001; Table 2). Sub-analyses did not show different results when patients who performed a structured exercise intervention during follow-up were excluded from analyses (Table S1). The analyses of changes in postural control did not reveal any significant predictors, neither in EO nor in EC standing conditions.

3 Discussion

In our study, postural control as well as patient-reported, neurologically, and electrophysiologically assessed CIPN signs/symptoms deteriorated during neurotoxic chemotherapy. Despite unchanged pathologic CIPN signs/symptoms during follow-up, postural control regenerated six months after neurotoxic chemotherapy. The regression models showed that high SNAP and low CMAP amplitudes at baseline predicted greater impairment of postural control during chemotherapy, but not during follow-up.

DETERIORATION OF POSTURAL CONTROL DURING NEUROTOXIC CHEMOTHERAPY. The deterioration of postural control concomitant with increasing CIPN signs/symptoms mirrors the results of various cross-sectional case-control studies [5, 7, 9], randomized controlled intervention trials (e.g. [13]), and one longitudinal observational study during neurotoxic chemotherapy [3]. The latter proved deterioration in postural control in BP_{EO} and BP_{EC} within the first three cycles of a taxan-based chemotherapy [3]. In contrast, our study covered the complete chemotherapy period and included additional standing conditions. In the ST conditions, a visual improvement of postural control (lower COP_{AREA}) within the first three to four chemotherapy cycles was observed. This might have been due to an initial learning effect which was not observed in the less remote BP conditions [14]. This assumed learning effect may also serve as an explanation why p-

Table 1. Patient characteristics.

	Patients
Demographic profile	
Number of patients [sex f:m, n]	54 (47:7)
Age [years, mean ± SD]	54.4 ± 11.6
Married [n (%)]	41 (79%)
Completed university [n (%)]	16 (31%)
Medical profile	
Height [cm, mean ± SD]	166.2 ± 5.9
Weight [kg, mean ± SD]	70.7 ± 13.6
BMI [kg/m², mean ± SD]	25.6 ± 4.8
Comorbidities [n (%)]	
- none	7 (13%)
- cardiovascular	19 (35%)
- musculoskeletal	32 (59%)
- neurological	4 (7%)
- endocrine/metabolic [diabetes]	4 (7%) 2 (4%)
- psychiatric	3 (6%)
Oncological diagnosis [n (%)]	
Breast cancer	43 (80%)
Pancreatic cancer	3 (6%)
Esophagus cancer	2 (4%)
Prostate cancer	2 (4%)
Tongue base cancer	1 (2%)
Stomach cancer	1 (2%)
Rectal cancer	1 (2%)
Ovary cancer	1 (2%)
Disease status (UICC) [n (%)]	
1 | 1A	1 (2%) | 13 (24%)
2 | 2A | 2B	1 (2%) | 12 (22%) | 7 (13%)
3 | 3A | 3B | 3C	0 (0%) | 6 (11%) | 2 (4%) | 1 (2%)
4 | 4A | 4B	6 (11%) | 3 (6%) | 1 (2%)
unknown	1 (2%)
Chemotherapy	
Duration [weeks, mean ± SD]	17.6 ± 5.6
Time between last chemotherapy and $post_0$ assessment [days, mean ± SD]	22.5 ± 9
Taxane-based [n (%)]	27 (50%)
Platinum-based [n (%)]	6 (11%)
Vinca alkaloid [n (%)]	1 (2%)
Taxane-platinum combination [n (%)]	18 (33%)
Taxane-taxane combination [n (%)]	2 (4%)
Behavioral profile	
Smoking [n (%)]	
- never smoker	20 (38%)
- former smoker	25 (48%)
- current smoker	7 (13%)
Alcohol consumption (WHO) [n (%)]	
- non-drinker (0 g/day)	18 (35%)
- harmless use (f: ≤ 12 g/day, m: ≤ 24 g/day)	28 (54%)
- harmful use (f: > 12 g/day, m: > 24 g/day)	6 (12%)

Abbreviations: **$post_0$**, i.e., assessment point at completion of neurotoxic chemotherapy.

Table 2. Descriptive statistics and results of paired t-tests.

	pre [mean ± SD]	**post$_0$** [mean ± SD]	**post$_3$** [mean ± SD]	**post$_6$** [mean ± SD]	**pre - post$_0$** [p-value]	**post$_0$ - post$_3$** [p-value]	**post$_0$ - post$_6$** [p-value]	**pre - post$_6$** [p-value]
Postural control [95% confidence ellipse area]								
BP_{EO} [mm²]	64.1 ± 44.2	94.7 ± 58.8	74.8 ± 51.8	73.2 ± 49.9	**<.0001** [t = 4.9; DF = 53]	.206 [t = -1.3; DF = 38]	**.004** [t = -3.1; DF = 38]	.345 [t = 1.0; DF = 38]
BP_{EC} [mm²]	98.4 ± 75.6	168.0 ± 113.6	138.3 ± 160.8	121.1 ± 88.9	**<.0001** [t = 5.4; DF = 53]	.617 [t = -0.5; DF = 38]	**<.0001** [t = -4.4; DF = 38]	.087 [t = 1.8; DF = 38]
ST_{EO} [mm²]	263.9 ± 134.7	308.7 ± 148.7	228.0 ± 110.0	239.2 ± 103.0	.042 [t = 2.1; DF = 53]	**.003** [t = -3.2; DF = 38]	**<.0001** [t = -4.9; DF = 38]	.097 [t = -1.7; DF = 38]
ST_{EC} [mm²]	655.2 ± 673.9	943.8 ± 756.7	746.3 ± 442.9	688.6 ± 594.3	**<.0001** [t = 6.1; DF = 53]	.025 [t = -2.2; DF = 38]	**<.0001** [t = -5.0; DF = 38]	.862 [t = -0.2; DF = 38]
EO composite score [mm²]	164.0 ± 81.4	201.7 ± 91.2	151.4 ± 73.2	156.2 ± 68.3	**.002** [t = 3.2; DF = 53]	**.003** [t = -3.2; DF = 38]	**<.0001** [t = -5.6; DF = 38]	0.235 [t = -1.2; DF = 38]
EC composite score [mm²]	376.8 ± 355	555.9 ± 407.8	442.3 ± 276.1	404.9 ± 329.9	**<.0001** [t = 7.2; DF = 53]	.027 [t = -2.2; DF = 38]	**<.0001** [t = -6.1; DF = 38]	0.875 [t = 0.2; DF = 38]
CIPN signs/symptoms								
TNSc [sum score]	1.3 ± 2.1	5.8 ± 3.8	6.1 ± 4.6	5.0 ± 3.9	**<.0001** [t = 9.1; DF = 53]	.486 [t = 0.7; DF = 39]	.162 [t = -1.4; DF = 39]	**<.0001** [t = 6.5; DF = 39]
CMAP [mV]	7.4 ± 2.9	5.5 ± 2.3	6.2 ± 2.7	5.9 ± 2.6	**<.0001** [t = -8.0; DF = 53]	**.001** [t = 3.2; DF = 39]	**<.001** [t = 3.7; DF = 39]	**<.001** [t = -3.8; DF = 39]
SNAP [µV]	11.3 ± 5.1	8.3 ± 5.0	9.1 ± 5.1	8.9 ± 5.5	**<.0001** [t = -5.7; DF = 53]	.329 [t = 1.0; DF = 39]	.039 [t = 2.1; DF = 39]	**<.001** [t = -3.4; DF = 39]
CIPN15 [sum score]	3.3 ± 5.8	14.6 ± 15.3	14.9 ± 18.4	13.3 ± 17.0	**<.0001** [t = 5.7; DF = 53]	0.793 [t = 0.3; DF = 48]	.628 [t = -0.5; DF = 46]	**<.0001** [t = 4.4; DF = 46]
Physical activity and strength								
PA [min/week]	57.2 ± 94.4	35.7 ± 86.3	54.9 ± 100.6	147.7 ± 265.5	.205 [t = -1.3; DF = 53]	.353 [t = 0.9; DF = 48]	**.002** [t = 3.3; DF = 46]	.039 [t = 2.1; DF = 46]
MVIC [Nm]	141.1 ± 34.5	131.1 ± 35.5	129.9 ± 26.0	143.2 ± 19.1	**.001** [t = -3.2; DF = 53]	.049 [t = 2.0; DF = 27]	**.003** [t = 2.9; DF = 27]	.493 [t = -0.7; DF = 27]

Descriptive statistics are shown for each assessment point separately (mean and standard deviation) and p-, t-values and DF as revealed by paired t-tests. Bold p-values are considered statistically significant (p<.0125). **Abbreviations**: **BP**, bipedal stance; **CIPN15**, sum score based on EORTC QLQ-CIPN20 questionnaire; **CMAP**, compound muscle action potential of peroneal nerve; **DF**, degrees of freedom (paired t-test); **EC**, eyes closed; **EO**, eyes open; **MVIC**, maximal voluntary isometric contraction; **PA**, physical activity; **pre**, assessment point before neurotoxic chemotherapy; **post$_0$**, assessment point three weeks after neurotoxic chemotherapy; **post$_3$**, assessment point three months after post$_0$; **post$_6$**, assessment point six months after post; **SD**, standard deviation; **SNAP**, sensory nerve action potential of sural nerve; **ST**, semi-tandem stance; **t**, t-value (paired t-test); **TNSc**, total neuropathy score (clinical).

values in the ST_{EO} condition did not survive correction for multiple comparisons. When data were corrected for this learning effect (by defining the fourth measurement as baseline), p-values remained significant after Bonferroni correction (data not shown).

Searching for predictive factors of deterioration in postural control during neurotoxic chemotherapy, we performed a multiple linear regression analysis. Overall, the addressed predictors had a higher explanatory potential in EC than in EO conditions (adjusted R^2=0.11 vs. 0.21). However, only two predictors were significant: SNAP in the EO and EC condition, and CMAP in the EC condition. Of note, SNAP and CMAP amplitudes correlated inversely with the impairment of postural control: while worse baseline sensory nerve function (as expressed by low SNAP amplitudes) was a preventive factor for the impairment of postural control, worse baseline motor nerve function (as expressed by low CMAP amplitudes) predicted a greater impairment of postural control.

Vestibular, visual and especially somatosensory inputs provide the basis for a stable upright posture [15]. Hence, dysfunction of one or more of these systems may interfere with postural control but can also induce compensation processes [16]. In our study, a large proportion of patients (37%) had started neurotoxic chemotherapy with an impaired somatosensory function. This presumably age-related dysfunction [17] might have led to postural control mechanisms such as muscular co-contraction [18] or sensory reweighting in terms of down-weighted processing of somatosensory information and an elevated processing of visual and vestibular information to stabilize postural control (sensory reweighting theory [15, 16]).

Based on these theoretical considerations, the following causal relationship might be valid: the more the somatosensory system is impaired before chemotherapy is started (as suggested by low SNAP amplitudes), the more likely adaptive processes can be assumed – either in the sense of muscular co-contraction or reweighting of somatosensory information through central adaptation – and the less postural control gets impaired by further chemotherapy-induced damage of predominantly sensory nerves. Our follow-up data

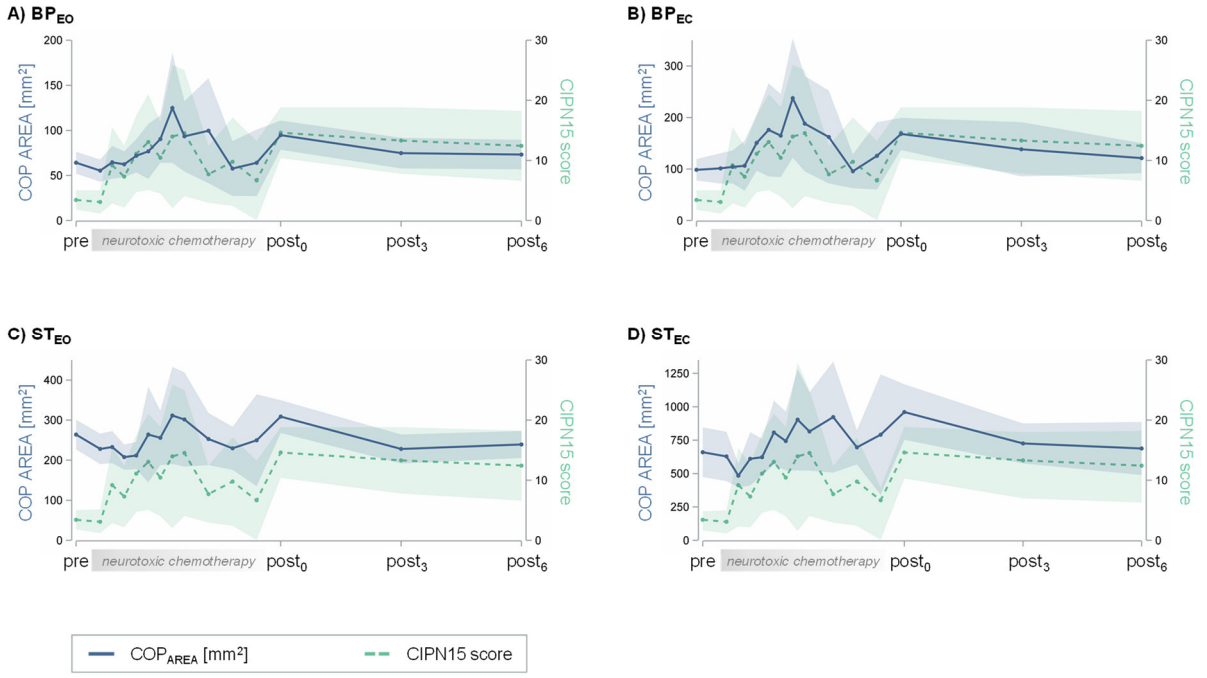

Figure 2. Postural control and CIPN symptoms over time. The time-scale of the data points in the 'neurotoxic chemotherapy' portion of the x-axis correspond to the chemotherapy cycles. Since the minimum interval between two postural control measurements was two weeks, but the individual lengths of the chemotherapy cycles in our study varied between one to three weeks, the reported sample sizes per cycle (*in brackets*) differ as follows: 32 (*2*), 34 (*3*), 34 (*4*), 32 (*5*), 18 (*6*), 21 (*7*), 7 (*8*), 14 (*9*), 13 (*11*), 10 (*13*), 7 (*15*). The blue line graphs show the averaged course (+95% CI, blue shading) of postural control (COP_{AREA}) over the entire study period in the following standing conditions: A) bipedal stance with eyes open (BP_{EO}), B) bipedal stance with eyes closed (BP_{EC}), C) semi-tandem stance with eyes open (ST_{EO}), D) semi-tandem stance with eyes closed (ST_{EC}). The turquoise line graphs show the averaged EORTC-CIPN15 scores (+95% CI, turquoise shading) at the corresponding measurement points.

provide additional weight to this hypothesis: despite the persistence of CIPN signs/symptoms and electrophysiologically objectified peripheral nerve damage, postural control regenerated in all standing conditions six months after the end of chemotherapy.

Besides an intact somatosensory system, a sound efference (as expressed by peroneal CMAP amplitudes) is required to guarantee postural control [19]. Patients with more severe impairment of motor nerve function before starting on neurotoxic chemotherapy (e.g., due to ageing [17]) thus might be at higher risk of a deterioration in postural control during chemotherapy. Though muscle strength plays a crucial role in stabilizing an upright posture [19], a reduction in maximum isometric quadriceps strength during neurotoxic chemotherapy in our patients does not predict a deterioration in postural control. It is likely that in our comparatively simple testing conditions the ankle strategy was primarily used to stabilize the upright posture by activating ankle plantar and dorsi flexors [20]. With increasing difficulty of the balance task, hip strategy is used and thus quadriceps and hamstrings, but especially the hip muscles, are more activated [20]. Hence, more comprehensive muscular assessments, including hip, thigh and ankle muscles, are needed to delineate more clearly the influence of muscle strength and power on postural control in CIPN patients, providing a framework for planning effective prevention measures.

Contrary to the results of exercise intervention studies in CIPN patients partly undergoing neurotoxic chemotherapy (e.g. [13]), physical activity in our patients did not show any influence on the change in postural control. However, the structured exercise programs implemented in those studies differed considerably from the self-chosen exercise efforts in our patients that were of rather low intensity, frequency, and duration. Therefore, it may be assumed that type and total load of physical activity in our patients was insufficient to influence postural control.

REGENERATION OF POSTURAL DISTURBANCE SIX MONTHS AFTER NEUROTOXIC CHEMOTHERAPY. The observed regeneration of postural control six months after completion of chemotherapy is contrasted by unchanged pathologic CIPN signs/symptoms. Regarding previous intervention studies in CIPN patients (e.g. [21]), it is conceivable that this improvement might have been caused by enhanced physical activity during

Table 3. Multiple linear regression analysis for predicting changes in postural control during and after neurotoxic chemotherapy.

	pre - post$_0$ [n=54]					**post$_0$ - post$_6$** [n=39]				
	B (95% CI)	**β**	**t-value**	**p-value**	**adj. R^2**	**B (95% CI)**	**β**	**t-value**	**p-value**	**adj. R^2**
EO					**0.12**					**0.11**
CMAP	-3.88 (-12.71, 4.94)	-0.13	-0.86	.389		-3.47 (-14.58, 7.64)	-0.13	-0.64	.529	
SNAP	6.25 (0.66, 11.84)	0.37	2.20	**.028**		-3.85 (-9.79, 2.09)	-0.30	-1.32	.196	
age	0.8 (-1.41, 3)	0.11	0.71	.479		-0.01 (-2.17, 2.16)	0.00	-0.01	.993	
BMI	2.88 (-2.01, 7.77)	0.16	1.15	.248		-2.95 (-7.56, 1.67)	-0.24	-1.30	.203	
PA	0.25 (-0.01, 0.52)	0.26	1.86	.063		-0.11 (-0.23, 0.02)	-0.28	-1.77	.086	
MVIC	-0.48 (-1.55, 0.58)	-0.13	-0.89	.373		-	-	-	-	
EC					**0.21**					**0.11**
CMAP	-26.33 (-43.43, -9.24)	-0.43	-3.02	**.003**		22.37 (-7.58, 52.32)	0.31	1.52	.138	
SNAP	15.59 (4.83, 26.35)	0.44	2.84	**.005**		-0.23 (-16.23, 15.78)	-0.01	-0.03	.977	
age	2.14 (-2.2, 6.49)	0.14	0.97	.334		2.5 (-3.33, 8.34)	0.15	0.87	.389	
BMI	6.36 (-3.44, 16.15)	0.17	1.27	.204		-7.79 (-20.24, 4.65)	-0.24	-1.27	.212	
PA	0.53 (0, 1.06)	0.25	1.95	.051		-0.05 (-0.38, 0.28)	-0.05	-0.30	.769	
MVIC	-0.61 (-2.72, 1.51)	-0.08	-0.56	.575		-	-	-	-	

Results of multiple linear regression analysis investigating the influence of various predictors on changes in postural control during (pre - post$_0$) and after (post$_0$ - post$_6$) neurotoxic chemotherapy are shown. Bold p-values are considered statistically significant ($p<.05$). **Abbreviations**: **adj. R^2**, adjusted R^2; **B**, unstandardized regression coefficient; **β**, standardized regression coefficient; **BMI**, body mass index; **CI**, 95% confidence interval; **CMAP**, compound muscle action potential of peroneal nerve; **EC**, eyes closed; **EO**, eyes open; **MVIC**, maximal voluntary isometric contraction of quadriceps [$\Delta_{pre\text{-}post0}$]; **PA**, physical activity; **post$_0$**, assessment point three weeks after neurotoxic chemotherapy; **post$_6$**, assessment point six months after post$_0$; **pre**, assessment point before neurotoxic chemotherapy; **SNAP**, sensory nerve action potential of sural nerve.

the follow-up period. However, the results of our follow-up regression analysis did not support this hypothesis. It is possible that the exercise behavior might have been too unstructured or simply ineffective in improving postural control [22], and/or biased by recalling these information. Overall, no significant influence of the investigated predictors was found in the regression analysis.

PRACTICAL CONSIDERATIONS. Even though regeneration of postural control six months after completion of neurotoxic chemotherapy occurs spontaneously to some degree, specific interventions for the prevention or rehabilitation of postural impairments are still indispensable. Our results do not allow a differentiation between functional regeneration and non-functional compensation, e.g. in terms of muscular co-contractions. Although co-contractions enable a safer, more stable gait in the absence of somatosensory information [23], they also increase the risk of falling [24]. Hence, the reduction of co-contractions, for instance via a sensorimotor exercise training [25], is desirable as a functional regeneration measure to lower the increased risk of falling in CIPN patients, associated with additional medical complications, and higher healthcare costs [4]. Moreover, in CIPN patients, a primary sensorimotor exercise training may reverse the impaired processing of somatosensory inputs by increased stimulation of less affected peripheral nerves [26]. Since SNAP and CMAP amplitudes at baseline may be predictive with regard to the extent of deterioration of postural control during neurotoxic chemotherapy, cancer patients should routinely receive thorough neurologic and electrodiagnostic examinations before starting on a neurotoxic therapy regime. These baseline findings might help to define individual CIPN risk profiles more precisely to which specific exercise intervention programs could then be tailor-made.

LIMITATIONS AND FUTURE DIRECTIONS. Our results are based on a sub-analysis of a larger, randomized, controlled clinical trial. Eighty-seven percent of the study participants were female, and 80% had breast cancer so our data might be biased by sex and cancer type to some degree. However, we used comprehensive state-of-the art assessment techniques to quantify postural control as well as CIPN signs/symptoms. Moreover, we provide an unprecedented longitudinal dataset of cancer patients treated with neurotoxic agents. Constrictively, the present sample size allowed us to analyze only a limited number of potential influencing factors within our regression models. The rather low explanation of variance yet indicates that additional influencing factors might be relevant for planning efficacious preventive and rehabilitative interventions.

CONCLUSION. The deterioration of postural control in cancer patients during neurotoxic chemotherapy may be related to baseline sensory and motor nerve functions. Six months after the completion of chemothera-

py, COP parameters indicate a regeneration of postural control, while CIPN signs/symptoms persist unchanged. Whether the improvement of postural control during follow-up is based on functional regeneration or non-functional compensation strategies needs to be investigated by larger future studies.

4 Methods

PARTICIPANTS AND STUDY DESIGN. The cancer patients included in the present longitudinal exploratory analysis were derived from the waiting list control group of a prospective, three-armed, single-center, randomized-controlled intervention trial (PIC study; ClinicalTrials.gov identifier: NCT02871284, May 6, 2016; Ethics Committee Medical Faculty University of Heidelberg: S-630/2015, Febuary 2, 2016). The main inclusion criterion of the secondary analysis at hand was that patients received a neurotoxic chemotherapy which had not been started at the time of study assignment and baseline testing (see Table S2 for detailed inclusion and exclusion criteria). Written informed consent was obtained from all patients in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013). During follow-up, patients were offered an exercise program within the present study (home-based sensorimotor exercise, or supervised resistance or endurance training) or to participate in another exercise intervention study (supervised endurance or resistance training; TOP-Study, ClinicalTrials.gov identifier: NCT02883699).

ASSESSMENT PROCEDURES. All assessments were performed at the National Center for Tumor Diseases (Heidelberg, Germany). Demographic, clinical and behavioral data were collected from medical records and study-specific forms.

Postural control was assessed during 30 s quiet standing on a force plate (AMTI, AccuSway optimized, Watertown, USA). The detailed testing procedure is described elsewhere [7]. Four measurement conditions were analyzed: bipedal and semi-tandem stance, each with eyes open (BP_{EO}; ST_{EO}) and eyes closed (BP_{EC}; ST_{EC}). The positioning of the feet in relation to each other was accurately noted for each condition in order to guarantee reproducibility in the subsequent trials. COP data were collected with a sample rate of 100 Hz and further processed in MATLAB (Version 2018a; MathWorks, Inc; Natick, MA) using custom scripts based on standard recommendations[27]. After applying a 4th order Butterworth low-pass filter (cut-off: 10 Hz), 95% confidence ellipse area of the COP (COP_{AREA}) was calculated to quantify balance performance. The best trial (lowest COP_{AREA} value) out of two for each condition was selected for further analyses.

CIPN symptoms were assessed using the patient-reported EORTC-CIPN20 questionnaire. According to current recommendations, a mean sum score of 15 instead of 20 items was calculated (CIPN15: range 0-100) [28]. Additionally, CIPN signs/symptoms were assessed with the clinical version of the Total Neuropathy Score (TNSc, range 0-28) [29]. Both scores express higher CIPN signs/symptoms in higher values. In addition, nerve conduction studies (NCS) to assess CMAP of the peroneal nerve and SNAP of the sural nerve were carried out by a technician with longstanding experience in clinical neurophysiology and peripheral neuropathy. CMAP amplitudes $\leq$ 3.8 mV and SNAP amplitudes $\leq$ 9.5 µV were assessed as pathological [29]. CMAP and SNAP amplitudes are presented as average over both legs. Skin temperature was controlled at a minimum of 32°C.

Physical activity behavior (PA) was assessed with a self-developed questionnaire [7] referring to four different periods: 12 months prior to chemotherapy (pre), the time of chemotherapy (pre-$post_0$) and both follow-up phases ($post_0$-$post_3$, $post_3$-$post_6$). The patients were asked to give an average of how often they exercised during these periods. Based on frequency and duration, average activity minutes per week [min/week] were calculated. Patients who participated in the training program during follow-up recorded their training sessions in training diaries. The resulting activity minutes per week were additionally added.

Maximal voluntary isometric contraction (MVIC) was measured for quadriceps at 36° flexion (IsoMed 2000-system B-series version, D&R Ferstl GmbH, Hemau, Germany). Patients were asked to produce maximum force over a period of six seconds. Resulting maximal peak torque was averaged over both legs.

STATISTICAL ANALYSIS. Statistical analyses were carried out using SAS Enterprise Guide 7.1 (SAS Institute Inc., USA). To allow for intention-to-treat analyses while avoiding bias related to imputation of data, multiple stochastic regression imputation (SAS proc MI; n=10) was performed to impute 1.2% (pre), 2.0% ($post_0$), 2.6% ($post_3$) and 1.9% ($post_6$) of values, which were at least missing at random. Results of the subsequent inferential statistical analyses were based on multiple imputation based on the SAS proc MIANALYZE.

Changes in postural control, CIPN signs/symptoms, MVIC and PA over study time were assessed by pair-wise t-tests (1: pre-$post_0$, 2: $post_0$-$post_3$, 3: $post_0$-$post_6$, 4: pre-$post_6$). The level of significance was set to $p<.0125$ (Bonferroni-Holm corrected). The described intermediate measurements of postural control and CIPN symptoms (CIPN15 score) between pre and $post_0$ were only used for descriptive illustration.

Multiple linear regression was used to analyze the relation between several predictors and the course of postural control (a) during chemotherapy (Δpre-$post_0$) and (b) follow-up ($\Delta post_0$-$post_6$). According to McCrary et al. [30], postural control was included in the regression analyses as a composite score: time differences (Δpre-$post_0$, $\Delta post_0$-$post_6$) were calculated from the averaged COP_{AREA} of the two standing conditions with eyes open (EO_{AREA}=mean(BP_{EO}, ST_{EO})) and eyes closed (EC_{AREA}=mean(BP_{EC}, ST_{EC})). The following predictors were analyzed: CMAP (a: pre, b: $post_0$), SNAP (a: pre, b: $post_0$), PA (a: pre-$post_0$, b: $post_0$-$post_6$), and change in muscular strength (a: Δpre-$post_0$). The analyses were adjusted for age and BMI (a: pre, b: $post_0$) by including those factors in the multiple linear regression models. Supplement digital content provides additional regression analyses for each standing position separately (Table S3).

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Acknowledgement

We thank all patients for participating in this study. We gratefully acknowledge Christine Boos, Laura Jansen, and Paula Hoffmann for study implementation and conduction, the clinical cooperation partners (Frederik Marmé, Martin Haag, Stefan Welte) for recruitment assistance, the NCT Cancer Registry and NCT Trial Center for data management support, and the OnkoAktiv Network.

Funding

This project was supported by an intramural funding program: Proof of concept trials 3.0, National Center for Tumor Diseases, Heidelberg, Germany (G876).

Competing Interest

The authors declare no competing interests.

Additional information

Supplementary information is provided by Tables S1, S2, and S3: Table S1 provides results of additional paired t-tests, excluding patients who conducted a systematic training program during follow-up. Table S2 provides detailed inclusion and exclusion criteria of the study. Table S3 provides results of additional multiple linear regression analyses for each standing position separately.
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5

Manuscript III

Müller, J., Weiler, M., Schneeweiss, A., Haag, G.M., Steindorf, K., Wick, W., & Wiskemann, J. (submitted). Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: a randomized controlled trial. Submitted to *Annals of Oncology* on October 1, 2020.

Highlights

- Exercise alleviates the development of subjectively perceived sensory CIPN symptoms in the feet during chemotherapy
- Patients with a sufficient training stimulus show a higher chemotherapy tolerance (RDI)
- Exercise improves muscle strength and various aspects of quality of life during chemotherapy

Data used of the PIC study

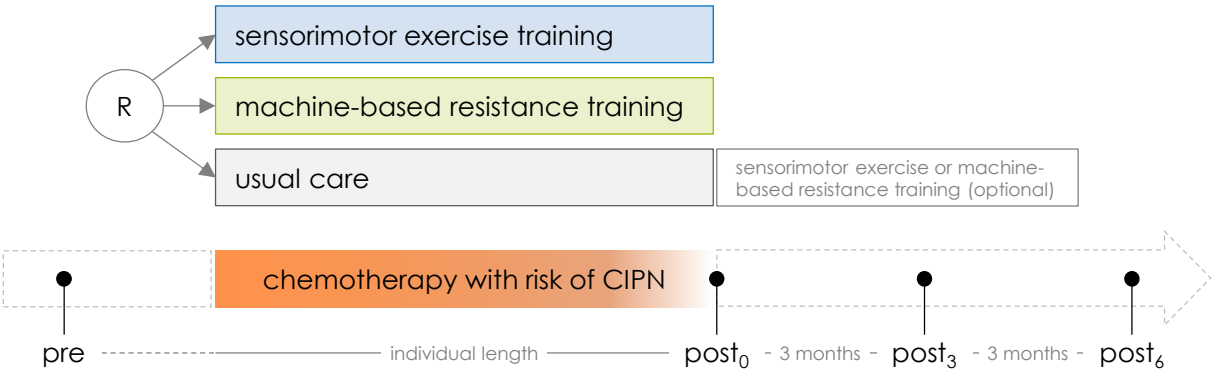

Figure 8. Patient data used for Manuscript III based on the PIC study.

The **supplementary material** for this manuscript can be found on pages 128ff.

Authorship contributions (according to CRediT taxonomy): conceptualization [MW, AS, KS, WW, JW]; data curation [JM, MW, JW]; formal analysis [JM]; funding acquisition [JW]; investigation [JM, MW, JW]; project administration [JM, JW]; resources [MW, AS, GMH, KS, WW]; supervision [JW]; validation [MW, KS, JW]; visualization [JM]; writing – original draft [JM]; writing – review & editing [all authors].

PLEASE NOTE: The manuscript was rejected by *Annals of Oncology* on November 2, 2020, and resubmitted to *British Journal of Cancer* on February 25, 2021, where it was accepted for publication in a revised version (June 17, 2021): Müller, J., Weiler, M., Schneeweiss, A., Haag, G.M., Steindorf, K., Wick, W., & Wiskemann, J. (2021). Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: a randomised-controlled trial. *British Journal of Cancer*. https://doi.org/10.1038/s41416-021-01471-1.

Preventive effect of sensorimotor exercise and resistance training on chemotherapy-induced peripheral neuropathy: a randomized controlled trial

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Abstract

BACKGROUND: Chemotherapy-induced peripheral neuropathy (CIPN) is a common side effect of neurotoxic chemotherapeutic agents that severely impairs patients' quality of life. Evidence-based preventive measures do not yet exist. Therefore, the aim of the present study was to examine the preventive potential of sensorimotor exercise training (SMT) and resistance training (RT) on CIPN.

PATIENTS AND METHODS: Patients (*N*=170) were randomized to SMT, RT or usual care (UC). Both exercise groups trained three times per week for a total of 105min/week during the application period of neurotoxic chemotherapy (mean intervention length: 20 weeks). CIPN signs/symptoms were assessed objectively via Total Neuropathy Score (TNSr; primary endpoint) and subjectively (EORTC QLQ-CIPN20 questionnaire). CIPN functional limitations were quantified by balance (center of pressure) and muscle strength (isokinetic) measurements. Quality of life was assessed using EORTC QLQ-C30 questionnaire. Relative chemotherapy dose intensity (RDI) was calculated based on medical records. The follow-up period covered six months after the end of chemotherapy.

RESULTS: Intention-to-treat analyses (*N*=159) revealed no differences regarding CIPN signs/symptoms. Per-protocol analyses (N=89) indicated that the subjectively perceived sensory symptoms in the feet increased less during chemotherapy in the adherent exercisers than in the UC group (*P*=.039, *ES*=1.27) and these patients received a higher RDI (*P*=.045); we further identified a better course of muscular strength in favor of the adherent exercisers (*P*<.001, *ES*=0.57), as well as better results in terms of overall quality of life, physical and role functioning and fatigue (*P*≤.016, *ES*≥0.48). No between-group differences were observed for balance. During follow-up, CIPN signs/symptoms persisted overall in all groups.

CONCLUSIONS: SMT and/or RT alleviates subjectively perceived sensory CIPN symptoms in the feet and other symptoms associated with cancer therapy if an appropriate training stimulus is achieved. Additionally, higher RDIs were observed in these patients, which may further affect the risk of relapse or tumor progression.

KEYWORDS: Balance ▪ Cancer ▪ Physical activity ▪ Quality of life ▪ Strength ▪ Supportive care

1 Introduction

Tingling, burning, numbness, and pain in hands and/or feet may be observed from the first administration of neurotoxic drugs such as taxanes, platinum compounds or vinca alkaloids.[1,2] The severity and persistence of the so-called chemotherapy-induced peripheral neuropathy (CIPN) is mainly dependent on drug type and cumulative dose, but probably also on comorbidities and lifestyle factors such as obesity and low moderate-to-vigorous physical activity.[3,4] The primary sensory symptoms and resulting functional limitations, such as balance and gait difficulties, may persist over several years/decades[5-8], causing reduced individual independence and quality of life[6], but also probably increased cancer recurrence

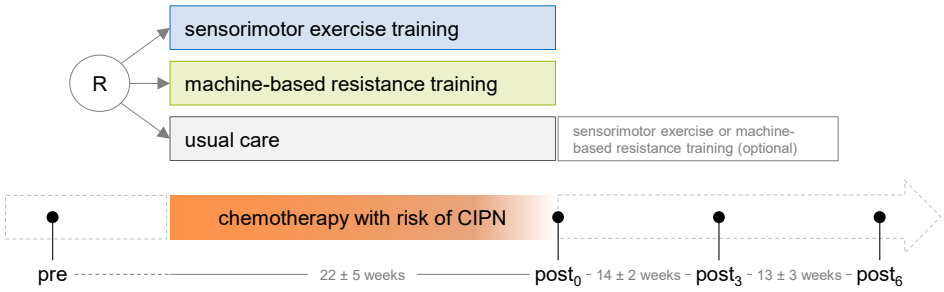

Figure 1. Study design.

and mortality rates, due to chemotherapy dose reductions and early treatment termination.[9]

The reduction of chemotherapy dose is currently the only way to prevent progression of CIPN symptoms. However, the body of research is constantly growing investigating the effects of various prevention and rehabilitation measures, such as exercise therapy. After chemotherapy, exercise is shown to positively affect various aspects of CIPN.[10-15] However, the preventive potential has been so far less investigated and the results are sometimes divergent. Positive intervention effects were found for deep sensitivity[16], perception of hot and coldness[17], and static balance performance.[18] All other studies were not able to detect a positive influence on CIPN signs/symptoms or functional limitations[19-21], which might be due to the following methodological issues: Small sample sizes (N=19-43)[16,18-21], blurred baseline values by performing baseline measurement after the first chemotherapy administration[16,21], and rudimentary CIPN assessment.

On this basis, we conducted a single-center randomized-controlled three-arm intervention trial. The primary aim of the PIC study was to evaluate the preventive potential of sensorimotor exercise training (SMT) and resistance training (RT) versus usual care (UC) during neurotoxic chemotherapy on clinically objectified CIPN signs/symptoms by means of the Total Neuropathy Score (TNSr). We hypothesized that patients randomized to the SMT or RT group would have a smaller change on the TNSr score over the course of neurotoxic chemotherapy in comparison to patients receiving UC.

2 Methods

2.1 Study design and participants

The PIC study was a single-center randomized-controlled three-arm exercise intervention trial. Ethical approval was obtained (Ethics Committee Medical Faculty University of Heidelberg: S-630/2015) and the trial was registered before activation (ClinicalTrials.gov: NCT02871284). Patients were eligible if they were ≥ 18 years of age and were admitted to receive a neurotoxic chemotherapy which had not been started at time of study assignment and baseline testing (see Table 1 for further details).

2.2 Procedures

Potentially eligible patients were identified by their physicians or through hospital records at the National Center for Tumor Diseases (NCT Heidelberg, Germany) or regional cooperation clinics between March 2016 and June 2018. After providing written informed consent and completed baseline testing (pre), patients were randomly assigned to an exercise intervention (SMT or RT) or UC group. The allocation was done by an independent person based on blocked randomization lists stratified by gender and type of treatment (taxanes, platinum derivates, vinca alkaloids, combined neurotoxic chemotherapy). Three weeks after completion of the individual chemotherapy regime $post_0$ assessment took place. Follow-up assessments were scheduled three ($post_3$) and six months ($post_6$) after $post_0$ (Figure 1). All assessments were carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki, 2013).

2.3 Outcomes

CIPN SIGNS AND SYMPTOMS. The primary endpoint was the Total Neuropathy Score in its reduced version (TNSr).[22] The TNSr represents a sum score of patient-reported and clinical examinations of CIPN signs/symptoms as well as nerve conduction studies (NCS; motor: compound muscle action potential of peroneal nerve (CMAP), sensory: sensory nerve action potential of sural nerve (SNAP)), with higher values reflecting a greater symptom burden. In addition, the TNSc (TNSr without NCS), TNSm (without NCS and autonomic symptoms) and the result variables of the NCS are reported separately: CMAP, SNAP, and nerve conduction velocities

Table 1. Study inclusion and exclusion criteria.

Inclusion criteria	▪ age ≥ 18 years ▪ diagnosed with cancer and assigned to receive a chemotherapeutic regimen containing at least one of the following agents: a platinum analog, e.g. cisplatin, carboplatin, oxaliplatin; a vinca alkaloid, e.g. vincristine; a taxane, e.g. paclitaxel, docetaxel; suramin; thalidomide or lenalidomide; bortezomib ▪ physical capability to follow the training program implemented within the exercise intervention groups
Exclusion criteria	▪ known peripheral neuropathy of any kind or any peripheral neuropathic signs or symptoms at baseline ▪ positive family history for any hereditary peripheral neuropathy ▪ known metastasis to the central or peripheral nervous system ▪ any physical or mental handicap that would hamper the performance of the training program implemented within the exercise intervention groups ▪ known history of alcohol or illegal drug abuse or any constellation of lab values suggesting alcoholism, e.g. elevated GGT, MCV, CDT

(NCV). All TNS assessments were blinded and performed according to general standards.[22] Furthermore, CIPN symptoms were assessed based on patients' perception by using the CIPN questionnaire of the European Organization for Research and Treatment of Cancer (EORTC QLQ-CIPN20).[23] In contrast to the initially published scoring manual, the mean sum score was calculated over 15 instead of 20 items, with higher values expressing higher CIPN symptoms.[24] Since our main exercise intervention (SMT) particularly focused on the lower extremities, we exploratory defined two separate scores for sensory (items 2, 4, 6, 9) and motor symptoms (items 8, 14, 15) in the feet, in accordance to the lower extremity score.[25]

FUNCTIONAL ASSESSMENTS. Postural control was assessed with a force plate (AMTI, AccuSway optimized, Watertown, USA). The detailed testing procedure is described elsewhere.[26] Briefly, patients were asked to stand as still as possible in bipedal stance with eyes closed (BP_{EC}) for 30sec. The best trial out of two was reported (lowest center of pressure (COP) value for total mean velocity). Additionally, we determined the average time of two trials patients were able to stand on one leg with open eyes (MP_{EO}). Maximal voluntary isometric contraction for quadriceps was measured with an isokinetic dynamometer (IsoMed 2000-system B-series version, D&R Ferstl GmbH, Hemau, Germany). The test setup included a maximum force generation against the dynamometer arm for 6sec at a knee angle of 36°. Maximal peak torque was measured in the dominant leg which was defined based on the higher peak torque of the right and left leg at baseline. Endurance capacity was measured by performing a cardiopulmonary exercise test on a bicycle utilizing a quasi-ramp protocol (start: 20W for 2min, increment: 10W/min) until volitional exhaustion. Oxygen update was measured using a breath-by-breath gas analysis system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). The highest 30sec average value was considered as peak oxygen uptake (VO_{2peak}).

PATIENT REPORTED OUTCOMES. Quality of life (QoL) was assessed with the validated EORTC QLQ-C30 questionnaire (version 3.0).[27,28] Fear of falling was assessed via Fall Efficacy Scale (FES-I).[29] Additionally, the number of falls was assessed (a) at baseline (pre), referring to the last six months, and (b) weekly during chemotherapy via telephone calls.

Demographic, clinical and behavioral data (including minutes of exercise per week[26]) were collected from medical records and study-specific forms. Relative dose intensity (RDI) and relative cumulative dose were calculated according to guidelines.[30] Concomitant CIPN prevention and treatment measures (e.g. cryotherapy, Duloxetin intake) were queried from the patients.

EXERCISE ADHERENCE AND TOLERABILITY. Based on training documents completed by the patients, adherence data were evaluated.[31] The reasons for missed training sessions and training related adverse events were queried in weekly telephone calls.

2.4 Exercise interventions

SENSORIMOTOR EXERCISE TRAINING. The SMT was scheduled 3×/week for 35min each. During an introductory one-to-one training session the patients received a catalogue of exercises, including 45 illustrated exercise cards, and necessary training materials (e.g. Airex balance pad). The patients exercised either at home or in an open supervised training session at the NCT. Each exercise was carried out 3×30sec with at least 30sec pause between sets. Patients were asked to progress their training based on individually perceived difficulty. Figure S1 and Table S1a provide further details.

RESISTANCE TRAINING. The RT included a machine-based RT 2×/week for 45min each, and a 15min home-based training once a week. The detailed training descriptions can be found in Table S1b. Briefly, the machine-based RT consisted of a maximum of eight exercises per session and was performed in an experienced

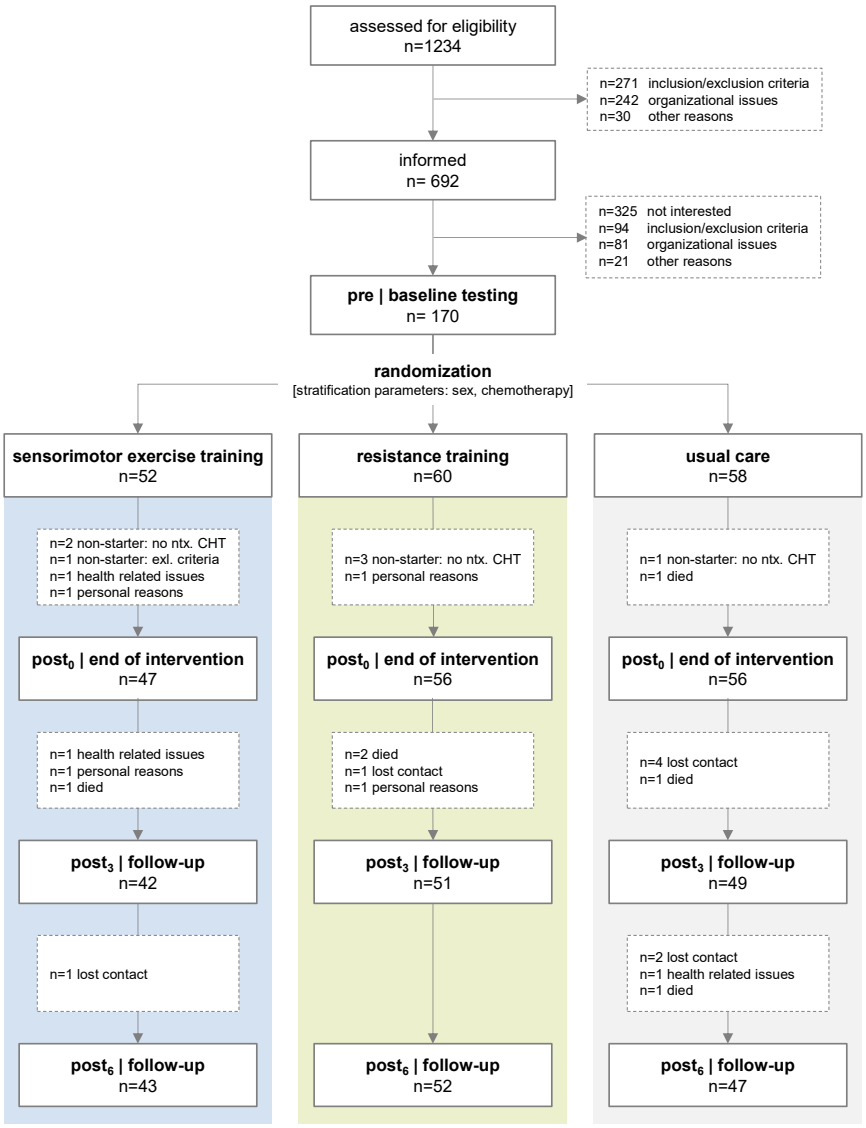

Figure 2. Consort flow chart.

exercise oncology training facility (OnkoAktiv Network). After two familiarization sessions, a one-repetition-maximum strength test (1RM) was conducted at each resistance machine. Its results were used to define initial training weights based on current guidelines (70-80% 1RM).[32] The home-based RT consisted of progressively designed core stability exercises.

USUAL CARE. The control group received usual care (UC) without additional information about physical activity. After completio n of chemotherapy ($post_0$-$post_6$), UC patients had the opportunity to participate in one of the interventions described above.

All patients received weekly phone calls to monitor nutritional status and fall history as well as training compliance and potential adverse events related to the intervention program, if applicable.

2.5 Statistical analysis

The sample size estimation was based on the main outcome criterion, the change of the TNSr from pre to $post_0$. Sample size calculation was performed by Monte-Carlo simulations of the power for the Kruskal-Wallis Test. Simulations were performed with the following input parameters i) equal allocation between the three groups, ii) equidistant population means, iii) normalized equal distribution, iv) α=5%. Under these assumptions a sample size of 246 (82 per group) was calculated to achieve a power of 80%. Assuming a maximal drop-out rate of 20%, it was planned to recruit 300 patients.

Baseline differences were tested by Kruskal-Wallis or Chi^2/Fisher's exact test in case of categorical variables. The primary analyses followed an intention-to-treat (ITT) approach. Secondary analyses included a per-

protocol (PP) approach where patients with an attendance rate of lower than 66.67% of planned training sessions were excluded from analyses.[33] Additionally a second exploratory PP_{EX} analyses with both exercise groups combined (only adherent exercisers; EX) vs. UC was conducted. Analysis of covariance (ANCOVA) was used to test i) intervention effects (pre-post$_0$), and ii) changes during follow-up (post$_0$-post$_3$, post$_0$-post$_6$) with the change scores of the respective comparison being the dependent variable, the intervention groups (SMT vs. RT vs. UC; EX vs. UC) as independent variable and stratification variables (gender and treatment), age, and baseline (pre-post$_0$) or post$_0$ measure (post$_0$-post$_3$, post$_0$-post$_6$) as covariates. No adjustments for multiple comparisons for the follow-up comparisons and secondary outcomes and analyses were made, as these were considered to be explorative. Standardized effect sizes (*ES*) were calculated for within-group and between-group comparisons for all outcomes by respectively dividing the adjusted mean change or the adjusted between-group difference by the baseline standard deviation. For ease of presentation of the between-group comparisons, *ES* received a positive sign if it was in favor of the first group of the following comparisons: SMT vs. UC, RT vs. UC, SMT vs. RT, and EX vs. UC. All statistical tests were two-sided, and $P<.05$ was considered statistically significant. SAS Enterprise Guide 7.1 (SAS Institute Inc., USA) was used for all analyses.

3 Results

One hundred and seventy patients (mean age 53.3 years) were randomized after baseline testing, of which $N=159$ completed the intervention period and were included in the ITT analysis (Figure 2). Most patient were female (85%) and had breast-cancer (74%) (Table 2, Table S2). Due to a poor recruitment rate (25%), we were unable to achieve our intended sample size within the given project time.

3.1 Adherence to the Interventions

Table S1a/b provide detailed information about exercise adherence. Briefly, mean intervention length was 20 weeks for both groups. Mean attendance rate was 68% in the SMT and 55% in the RT group. The reasons for missed training sessions are listed in Table S3. Thirty-five patients were classified as adherent and included in PP/PP_{EX} analyses (SMT: $N=20$, RT: $N=15$). Non-adherent patients had lower physical and cognitive function as well as higher fatigue and insomnia baseline val-

Table 2. Patient characteristics.

	Total	SMT	RT	UC
Demographic profile				
Number of patients [n]	163 (100%)	49 (30%)	57 (35%)	57 (35%)
Number of female patients [n]	138 (85%)	41 (84%)	48 (84%)	49 (86%)
Age [years, mean ± SD]	53.3 ± 11.5	51.7 ± 10.8	53.4 ± 11.7	54.5 ± 11.9
Married [n (%)]	124 (78%)	38 (78%)	43 (78%)	43 (78%)
University degree [n (%)]	54 (34%)	22 (45%)	15 (27%)	17 (31%)
Medical profile				
Height [cm, mean ± SD]	167.3 ± 6.8	168.5 ± 7.5	167.5 ± 6.7	166.0 ± 6
Weight [kg, mean ± SD]	72.9 ± 14.3	74.2 ± 15.7	74.8 ± 13.3	70.0 ± 13.7
BMI [kg/m², mean ± SD]	26.1 ± 5.0	26.2 ± 5.6	26.7 ± 4.7	25.4 ± 4.8
Comorbidities [n (%)]				
- none	21 (13%)	9 (18%)	4 (7%)	8 (14%)
- cardiovascular	60 (37%)	19 (39%)	20 (35%)	21 (37%)
- musculoskeletal	94 (58%)	22 (45%)	40 (70%)	32 (56%)
- neurological	14 (9%)	3 (6%)	7 (12%)	4 (7%)
- endocrine/metabolic	21 (13%)	7 (14%)	10 (18%)	4 (7%)
[diabetes]	7 (4%)	2 (4%)	3 (5%)	2 (4%)
- psychiatric	9 (6%)	3 (6%)	3 (5%)	3 (5%)
Oncological pre-diagnosis	20 (12%)	7 (14%)	3 (5%)	10 (18%)
Oncological diagnosis [n (%)]				
Breast cancer	121 (74%)	36 (73%)	41 (72%)	44 (77%)
Pancreatic cancer	9 (6%)	2 (4%)	3 (5%)	4 (7%)
Prostate cancer	5 (3%)	2 (4%)		3 (5%)
Stomach cancer	5 (3%)	2 (4%)	2 (4%)	1 (2%)
Esophagus cancer	4 (2%)	1 (2%)	1 (2%)	2 (4%)
Colon cancer	4 (2%)	3 (6%)	1 (2%)	
Brain cancer	3 (2%)		3 (5%)	
Ovary cancer	3 (2%)	1 (2%)	1 (2%)	1 (2%)
Tongue base cancer	2 (1%)		1 (2%)	1 (2%)
Rectal cancer	2 (1%)		1 (2%)	1 (2%)
Anus / anal canal cancer	1 (1%)		1 (2%)	
Bronchus / lung cancer	1 (1%)		1 (2%)	
Cervix uteri cancer	1 (1%)		1 (2%)	
Bladder cancer	1 (1%)	1 (2%)		
Malignant neoplasm without specification of site	1 (1%)	1 (2%)		
Disease status (UICC) [n (%)]				
I/II	102 (65%)	30 (67%)	36 (63%)	36 (64%)
III/IV	56 (35%)	15 (33%)	21 (37%)	20 (36%)
Chemotherapy				
Duration [weeks, mean ± SD]	17.2 ± 5.3	17 ± 5.2	16.7 ± 5.1	17.8 ± 5.7
Time between last chemotherapy and post$_0$ [days, mean ± SD]	22.9 ± 9.2	22 ± 9.3	23.5 ± 8.9	23 ± 9.4
Taxane-based [n (%)]	87 (53%)	27 (55%)	30 (53%)	30 (53%)
Taxane-platinum combination [n (%)]	52 (32%)	15 (31%)	18 (32%)	19 (33%)
Platinum-based [n (%)]	19 (12%)	7 (14%)	6 (11%)	6 (11%)
Vinca alkaloid [n (%)]	4 (2%)		3 (5%)	1 (2%)
Platinum-vinca alkaloid combination [n (%)]	1 (1%)			1 (2%)
Relative dose intensity				
relative dose intensity [%, mean ± SD]	93.2 ± 8.6	94.5 ± 8.4	93.1 ± 8.0	92.2 ± 9.4
- min. 85% of planned dose intensity [n (%)]	124 (85%)	41 (93%)	44 (81%)	39 (81%)
relative cumulative dose [%, mean ± SD]	93.9 ± 10.6	93.7 ± 12.7	93.9 ± 8.8	94.2 ± 10.4
- min. 85% of planned dose [n (%)]	121 (81%)	38 (84%)	44 (81%)	39 (78%)
Behavioral profile				
Smoking [n (%)]				
- never smoker	66 (42%)	18 (37%)	27 (50%)	21 (38%)
- former smoker	63 (40%)	19 (39%)	18 (33%)	26 (47%)
- current smoker	29 (18%)	12 (24%)	9 (17%)	8 (15%)
Alcohol consumption (WHO) [n (%)]				
- non-drinker (0 g/day)	42 (26%)	12 (24%)	12 (22%)	18 (33%)
- harmless use (f: ≤ 12 g/day, m: ≤ 24 g/day)	94 (59%)	29 (59%)	34 (62%)	31 (56%)
- harmful use (f: > 12 g/day, m: > 24 g/day)	23 (14%)	8 (16%)	9 (16%)	6 (11%)

Abbreviation: post$_0$, i.e., assessment point at completion of neurotoxic chemotherapy

Table 3. Intention-to-treat analysis: CIPN signs and symptoms.

Outcome	group	pre	post$_0$	post$_3$	post$_6$	pre-post$_0$	between-group comparison [pre-post$_0$]			
		mean ± SD	mean ± SD	mean ± SD	mean ± SD	adjusted [a] mean change (95% CI)	compar-ison	adjusted [a] between-group difference (95% CI)	p value	ES (95% CI)
Total Neuropathy Score										
TNSr	SMT	1.4 ± 2.0	7.2 ± 4.1	8.2 ± 4.2	7.1 ± 4.0	4.5 (2.8 to 6.2)	SMT vs. UC	0.3 (-1.6 to 2.3)	.908	-0.15 (-0.57 to 0.27)
[sum score, 0-36]	RT	1.6 ± 1.5	7.6 ± 4.7	6.5 ± 4.3	6.8 ± 4.1	4.7 (3.1 to 6.2)	RT vs. UC	0.5 (-1.4 to 2.4)	.809	-0.21 (-0.62 to 0.19)
	UC	2.3 ± 3.1	7.8 ± 4.7	7.6 ± 5.1	6.5 ± 4.0	4.2 (2.5 to 5.8)	SMT vs. RT	-0.2 (-2.2 to 1.8)	.982	0.07 (-0.36 to 0.49)
TNSc	SMT	0.5 ± 1.2	4.9 ± 3.1	5.8 ± 3.5	5.3 ± 3.4	3.2 (1.8 to 4.5)	SMT vs. UC	-0.1 (-1.7 to 1.5)	.983	0.08 (-0.33 to 0.48)
[sum score, 0-28]	RT	0.7 ± 1.1	5.6 ± 3.6	5.1 ± 3.6	5.0 ± 3.6	3.7 (2.5 to 5.0)	RT vs. UC	0.4 (-1.1 to 2)	.773	-0.28 (-0.68 to 0.12)
	UC	1.4 ± 2.1	5.8 ± 3.7	5.7 ± 4.4	4.9 ± 4.0	3.3 (2.0 to 4.6)	SMT vs. RT	-0.6 (-2.1 to 1)	.673	0.36 (-0.06 to 0.77)
TNSm	SMT	0.4 ± 1.0	4.2 ± 2.8	5.2 ± 3.2	4.8 ± 3.1	2.8 (1.6 to 4.0)	SMT vs. UC	-0.1 (-1.5 to 1.4)	.995	0.04 (-0.37 to 0.45)
[sum score, 0-24]	RT	0.7 ± 1.1	5.1 ± 3.4	4.5 ± 3.2	4.4 ± 3.1	3.6 (2.4 to 4.7)	RT vs. UC	0.7 (-0.7 to 2.1)	.438	-0.51 (-0.91 to -0.1)
	UC	1.2 ± 1.9	5.0 ± 3.2	4.9 ± 3.8	4.3 ± 3.5	2.8 (1.6 to 4.0)	SMT vs. RT	-0.8 (-2.2 to 0.6)	.395	0.55 (0.13 to 0.97)
Nerve conduction studies										
CMAP [µV]	SMT	7.6 ± 3.0	5.7 ± 3.0	5.5 ± 2.5	6.4 ± 2.6	-1.4 (-2.2 to -0.7)	SMT vs. UC	0.1 (-0.9 to 1)	.984	0.02 (-0.38 to 0.42)
	RT	8.0 ± 2.5	6.1 ± 2.7	5.7 ± 2.7	6.4 ± 2.6	-1.3 (-1.9 to -0.6)	RT vs. UC	0.2 (-0.6 to 1.1)	.813	0.08 (-0.30 to 0.46)
	UC	7.4 ± 2.9	5.4 ± 2.4	6.2 ± 2.8	5.9 ± 2.7	-1.5 (-2.2 to -0.8)	SMT vs. RT	-0.2 (-1.1 to 0.8)	.913	-0.06 (-0.45 to 0.34)
SNAP [mV]	SMT	10.8 ± 4.3	7.6 ± 3.9	7.2 ± 3.6	8.0 ± 3.8	-3.2 (-4.5 to -1.8)	SMT vs. UC	-0.6 (-2.3 to 1)	.612	-0.14 (-0.55 to 0.26)
	RT	10.6 ± 4.3	8.1 ± 4.4	8.4 ± 4.1	8.2 ± 4.5	-2.5 (-3.6 to -1.3)	RT vs. UC	0.1 (-1.5 to 1.6)	.996	0.01 (-0.38 to 0.40)
	UC	11.3 ± 5.0	8.2 ± 5.1	8.9 ± 5.1	9.2 ± 5.5	-2.5 (-3.8 to -1.3)	SMT vs. RT	-0.7 (-2.3 to 0.9)	.562	-0.16 (-0.56 to 0.25)
NCV (peroneal) [m/s]	SMT	48.0 ± 3.7	46.8 ± 3.7	46.1 ± 4.3	46.3 ± 4.1	-2.3 (-3.5 to -1.1)	SMT vs. UC	-0.2 (-1.6 to 1.2)	.943	-0.05 (-0.46 to 0.35)
	RT	48.8 ± 3.6	46.9 ± 4.1	48.2 ± 4.2	47.9 ± 3.8	-2.2 (-3.2 to -1.2)	RT vs. UC	-0.1 (-1.4 to 1.2)	.988	-0.02 (-0.41 to 0.36)
	UC	48.7 ± 3.8	47.2 ± 4.4	47.3 ± 4.4	47.3 ± 3.8	-2.1 (-3.2 to -1.0)	SMT vs. RT	-0.1 (-1.5 to 1.3)	.981	-0.03 (-0.44 to 0.38)
NCV (sural) [m/s]	SMT	48.4 ± 5.0	46.4 ± 4.8	46.8 ± 4.7	45.8 ± 5.2	-3.1 (-5.2 to -0.9)	SMT vs. UC	0.0 (-2.7 to 2.6)	.999	-0.01 (-0.42 to 0.40)
	RT	48.0 ± 4.7	45.9 ± 5.9	45.8 ± 6.1	45.6 ± 4.8	-3.1 (-5.0 to -1.2)	RT vs. UC	-0.1 (-2.6 to 2.4)	.997	-0.01 (-0.41 to 0.38)
	UC	48.4 ± 6.5	46.3 ± 5.3	45.3 ± 3.6	46.1 ± 3.9	-3.0 (-5.1 to -1.0)	SMT vs. RT	0.0 (-2.6 to 2.7)	1.00	0.00 (-0.41 to 0.42)
Patient reported CIPN symptoms [EORTC QLQ-CIPN20]										
CIPN15	SMT	1.9 ± 4	14.2 ± 14.5	15.2 ± 19.1	12.1 ± 13.5	9.8 (3.7 to 16.0)	SMT vs. UC	2.2 (-5.2 to 9.5)	.761	-0.47 (-0.87 to -0.07)
[sum score, 0-100]	RT	2.2 ± 3.5	15.4 ± 17.9	14.4 ± 16.3	12.1 ± 14.3	10.4 (5.1 to 15.7)	RT vs. UC	2.7 (-4.3 to 9.7)	.624	-0.59 (-0.98 to -0.2)
	UC	3.6 ± 5.9	14.3 ± 15.3	14.8 ± 18.7	13.3 ± 17.2	7.7 (2.0 to 13.4)	SMT vs. RT	-0.6 (-7.9 to 6.8)	.983	0.12 (-0.28 to 0.52)
Sensory symptoms feet	SMT	2.0 ± 4.9	17.5 ± 18.0	18.8 ± 22.4	14.4 ± 18.2	9.5 (1.6 to 17.3)	SMT vs. UC	-1.5 (-10.9 to 7.9)	.925	0.23 (-0.17 to 0.63)
[sum score, 0-100]	RT	1.4 ± 3.3	19.4 ± 21.1	18.8 ± 22.2	17.1 ± 20.2	11.9 (5.0 to 18.7)	RT vs. UC	0.9 (-8.2 to 10)	.971	-0.14 (-0.52 to 0.24)
	UC	4.2 ± 9.3	21.5 ± 21.7	21.0 ± 23.4	18.4 ± 23.1	11 (3.6 to 18.3)	SMT vs. RT	-2.4 (-11.8 to 7)	.819	0.37 (-0.03 to 0.77)
Motor symptoms feet	SMT	2.9 ± 6.3	10.4 ± 13.7	14.7 ± 21.6	8.5 ± 12.7	4.8 (-1.0 to 10.7)	SMT vs. UC	1.4 (-5.6 to 8.4)	.885	-0.17 (-0.56 to 0.23)
[sum score, 0-100]	RT	2.8 ± 4.9	12.3 ± 15.8	12.9 ± 17.7	11.5 ± 15.4	6.6 (1.6 to 11.7)	RT vs. UC	3.2 (-3.5 to 9.9)	.499	-0.38 (-0.76 to 0.01)
	UC	6.1 ± 11.9	12.3 ± 18.2	14.2 ± 24	13.4 ± 23.0	3.5 (-2.0 to 8.9)	SMT vs. RT	-1.8 (-8.8 to 5.2)	.815	0.21 (-0.18 to 0.61)
Symptoms hands	SMT	2.0 ± 5.1	15.4 ± 16.2	15.0 ± 19.8	13.0 ± 14.4	12.5 (5.7 to 19.2)	SMT vs. UC	4.6 (-3.5 to 12.6)	.373	-0.69 (-1.1 to -0.28)
[sum score, 0-100]	RT	3.2 ± 6.3	15.6 ± 19.9	14.2 ± 16.4	11.1 ± 16.0	11.1 (5.3 to 17.0)	RT vs. UC	3.2 (-4.4 to 10.9)	.582	-0.49 (-0.87 to -0.1)
	UC	3.5 ± 8.0	12.8 ± 15.3	13.1 ± 19.6	11.7 ± 14.6	7.9 (1.6 to 14.2)	SMT vs. RT	1.3 (-6.7 to 9.4)	.918	-0.20 (-0.6 to 0.19)

Table shows descriptive statistics of clinically, electrophysiologically assessed and subjectively perceived CIPN signs and symptoms for all assessment points. Adjusted mean change (within groups) and between-group differences are only presented for intervention time as revealed by intention-to-treat analyses. Bold value indicates statistical significance at the level of 5%. **Notes**: [a] Regression models were adjusted for baseline value, sex, age, and therapy-randomization strata. **Abbreviations**: **CIPN15**, sum score based on 15 items of the EORTC QLQ-CIPN20 questionnaire; **CMAP**, compound muscle action potential of peroneal nerve; **NCV**, nerve conduction velocity; **pre**, assessment point before neurotoxic chemotherapy; **post$_0$**, assessment point 3 weeks after neurotoxic chemotherapy; **post$_3$**, assessment point three months after post; **post$_6$**, assessment point six months after post; **SD**, standard deviation; **SNAP**, sensory nerve action potential of sural nerve; **TNSc**, total neuropathy score (clinical); TNSm, total neuropathy score (modified); **TNSr**, total neuropathy score (reduced).

ues on the EORTC QLQ-C30 subscales (all P<.024, Table S4).

Twenty-three patients reported mild training associated adverse events without indication for medical treatment (SMT: N=10, RT: N=13; see Table S5 for details).

During follow-up, 26% of the UC patients started a structured training: SMT (N=6, mean attendance rate: 62.0%), RT (N=7, mean attendance rate: 41.5%), or endurance training (N=1, attendance rate: 100%). Reported exercise minutes per week increased descriptively in this group ($post_0$-$post_6$: +34.9 (-40 to 109.8), P=.359).

3.2 CIPN Signs and Symptoms

Table 3 provides summarized data for CIPN signs/ symptoms revealed by ITT analyses. Complementary values (e.g. ES for within-group comparisons) as well as results of secondary outcomes and complete PP/ PP_{EX} analyses are presented in Table S6.

Overall, the TNSr score increased significantly in all three groups during chemotherapy with small, non-significant between-group differences; comparable results were found for the TNS variations (TNSc, TNSm) and NCS parameters (ITT, Table 3). PP/ PP_{EX} analyses provided comparable results with larger effect sizes (Figure 3).

During the intervention period, between-group comparisons of the increased EORTC CIPN-20 total and sub-scores revealed no significant differences between groups (ITT). PP_{EX} analysis showed a significant between-group comparison in favor of EX regarding sensory symptoms in the feet (PP_{EX} pre-$post_0$: P=.039, ES=-1.27).

During follow-up, TNSr and its variations as well as NSC parameters did not change according to inferential statistics. EORTC CIPN-20 total score revealed a significant decrease in SMT and RT (ITT $post_0$-$post_6$: P<.038) and for symptoms in the hands for all groups (ITT $post_0$-$post_6$: P<.045). Between-group comparisons revealed marginal, non-significant differences with overall small effect sizes during the follow-up periods. PP and PP_{EX} analyses showed overall comparable results.

3.3 Functional Assessments

COP mean velocity in BP_{EC} increased significantly during the intervention period in all groups (ITT pre-$post_0$: P<.015). PP showed a tendency towards unchanged adjusted mean change values for SMT (pre-$post_0$: P=.235). For all analyses approaches, between-group differences were non-significant with small effect-sizes. During follow-up, all groups showed decreased COP mean velocities (ITT $post_0$-$post_6$: P<.019), however, this effect only

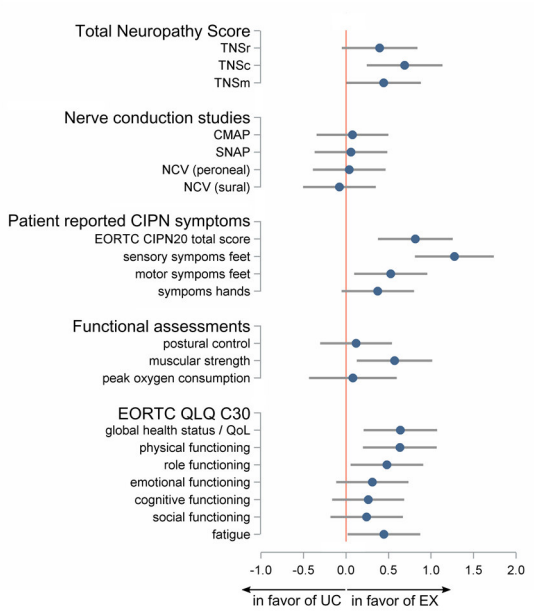

Figure 3. Effect sizes for CIPN signs and symptoms and other symptoms associated with anti-cancer therapy (PP_{EX} analysis).

remained significant for SMT group in both PP analyses. Between-group differences were non-significant and had small effect sizes for all analyses.

In all analyses approaches, mean MP_{EO} standing time remained unchanged for SMT and RT, but significantly decreased in UC, resulting in a significant between-group comparison for ITT analysis in favor of both exercise groups (pre-$post_0$: SMT vs. UC P=.045, ES=0.27; RT vs. UC P=.023, ES=0.28). During follow-up comparisons did not reveal any significant differences (ITT, PP, PP_{EX}).

RT and SMT sustained their baseline muscle strength status while UC showed decreased values (ITT pre-$post_0$: P=.016). PP analyses revealed a significant gain of muscle strength for RT (pre-$post_0$: P=.003) and PP_{EX} analysis for adherent EX (pre-$post_0$: P=.027). Consequently, between-group comparisons revealed a significant difference in favor of RT compared to UC (pre-$post_0$: ITT P=.045, ES=0.30; PP P<.001, ES=0.81) as well as for SMT compared to UC (PP pre-$post_0$: P=.041, ES=0.38) and for EX compared to UC (PP_{EX} pre-$post_0$: P<.001, ES=0.57). During follow-up, no significant between-group comparisons and overall small effect-sizes were found.

3.4 Patient-reported Outcomes

During intervention period, primary ITT analyses of the EORTC QLQ-C30 scores revealed non-significant between-group differences and mainly small effect sizes. However, PP analyses showed significant group differences between RT and UC for global health status (pre-

post$_0$: *P*=.018, *ES*=0.85) and social functioning (pre-post$_0$: *P*=.047, *ES*=0.52). PP_{EX} analyses additionally showed significant between-group differences in favor of adherent EX for physical functioning (pre-post$_0$: P=.014, ES=0.63), role functioning (pre-post$_0$: *P*=.02, *ES*=0.48) and fatigue (pre-post$_0$: *P*=.016, *ES*=0.45), and borderline significance for pain (pre-post$_0$: *P*=.057, *ES*=0.32). Overall, follow-up period revealed mainly non-significant between-group comparisons with small effect sizes for all analyses approaches.

Fear of falling increased in UC during chemotherapy (ITT pre-post$_0$: *P*=.037, *ES*=0.57), but not in SMT and RT. However, pre-post$_0$ changes did not differ between groups in all analyses approaches, nor did number of falls during intervention period (see Table S7 for details).

3.5 Chemotherapy Completion Rate

Chemotherapy dose reductions and early terminations were evenly distributed between groups and most often associated with CIPN symptoms (Table S8). Mean RDI did not differ between study groups (ITT *P*=.461, Table 1), except when comparing EX with UC (PP_{EX}: EX: 96.6 ± 4.8, UC: 92.2 ± 9.4; *P*=.045). So did clinically relevant threshold of 85% RDI (EX: 94%, UC: 76%; *P*=.032). Concomitant CIPN prevention or treatment measures did not differ between groups (Table S8).

4 Discussion

The PIC study aimed to investigate the preventive effect of sensorimotor exercise training (SMT) or resistance training (RT) versus usual care (UC) on CIPN during neurotoxic chemotherapy. Our primary ITT analysis revealed that none of the exercise programs were able to impact the progression of neurologically objectified and patient-reported CIPN signs/symptoms. Due to high numbers of missed training sessions in both groups, we excluded non-adherent patients for exploratory per-protocol analyses. Subjectively perceived sensory symptoms in the feet increased less during chemotherapy in the adherent exercisers (pooled group: SMT+RT) compared to UC. Furthermore, compliance to chemotherapy was found to be enhanced in this group. On the functional level, we identified a better course of muscular strength in favor of the adherent exercisers, as well as better results in terms of overall quality of life, physical and role functioning, fatigue, and a trend-level effect for pain.

Only a few RCTs have investigated the preventive effect of exercise on CIPN during neurotoxic chemotherapy[16-21], of which only two used clinical instruments to assess CIPN symptoms[16,19]: In accordance with our ITT results, Bland et al.[19] did not demonstrate an intervention effect of a multimodal exercise program during taxane-based chemotherapy with regard to quantitative sensory tests (deep sensitivity: tuning fork; pain: pinprick). In contrast, a sub-analysis of a comparable exercise program showed a reduction of CIPN symptoms by tuning fork evaluation in the intervention group but not in the control group.[16]

Similarly, the results of the other studies regarding the subjective perceived CIPN symptoms are largely consistent with our ITT analyses. The studies which used psychometrically tested questionnaires, that focus on CIPN symptoms in the whole body, were not able to find a significant intervention effect (EORTC QLQ-CIPN20[19]) or only observed a trend-level effect (FACT/GOG-Ntx[20]). Kleckner et al.[17] used a numeric-rating-scale (NRS 0-10), which only focused on two symptom-combinations in hands and feet. The authors reported a trend-level effect for perception of numbness/tingling and a significant intervention effect for hot/coldness in favor of the intervention group. Comparable results were observed for adherent exercisers within our PP_{EX} analysis, who developed less sensory symptoms in the feet during chemotherapy compared to UC. A sub-analysis by Bland et al.[19] mirrors these findings by showing that multimodal exercise can prevent the progression of moderate to severe numbness in toes and feet within the first three taxane cycles. In our opinion, this is a highly relevant finding, since CIPN-induced dose modifications of chemotherapy are mainly based on patients' subjective perception. Therefore, the better chemotherapy tolerance (mean RDI) observed in the adherent exercisers (97%) compared to UC (92%) may be associated with the shown lower perceived CIPN symptoms in this group. Although evidence does not yet allow final conclusions to be drawn as to whether exercise actually has a positive influence on chemotherapy tolerance[34], these findings are in line with Bland et al.[19] and point towards a promising direction.

FUNCTIONAL STATUS AND PATIENT-REPORTED OUTCOMES. Various studies have shown that neurotoxic chemotherapy can have a negative effect on postural control[26,35,36], which may be partly prevented by a multimodal training program.[18] Our COP data did not replicate this result and showed only a marginal trend in favor of the SMT group. Based on the mean standing time in MP_{EO} position, however, SMT and RT showed a more favorable progression of postural control than UC. The improved standing time in the RT group during neuro-

toxic chemotherapy could have been achieved by increased muscle strength observed in the RT-adherent patients.[37] Since cancer patients normally show a chemotherapy-induced deterioration of muscle strength[38] – as also shown in our UC group – the increase but also the maintenance of muscle strength by RT or SMT is an important finding.

Although CIPN and associated poor postural stability are known to increase risk of falling[5,7], the fall prevalence of 8% in our total cohort during chemotherapy is markedly lower compared with another study showing annual fall rates of 43-57% after cancer treatment.[39] Generally less everyday activities during chemotherapy may explain this difference, which might also be in line with the majority of our patients (71%) reporting low concerns about falling during chemotherapy (FES-I value <20).[40]

Finally, the adherent exercisers were able to enhance QoL during chemotherapy. The difference compared with UC (+12.9 points) can be seen as clinically meaningful[41], and is in accordance with Bland et al.[19]. Additionally, we observed better results in favor of adherent exercisers in terms of physical and social functioning as well as fatigue and a trend-level effect for pain which are in line with a large body of exercise oncology studies.[32]

CIPN SIGNS AND SYMPTOMS DURING FOLLOW-UP. Neurologically objectified CIPN signs/symptoms did not change during the follow-up period of six months, whereas EORTC CIPN-20 total score decreased significantly in RT and SMT as well as CIPN symptoms in the hands in all groups. However, group means were still elevated compared to baseline values. These results are in line with many other studies addressing the long-term persistence of CIPN symptoms after completion of chemotherapy.[42] Structured exercise interventions helped to positively influence objectively assessed[10-12] and subjectively perceived CIPN signs/symptoms.[10,12-14] However, the proportion of patients who followed a structured exercise program within our study and their adherence were probably too small to show this effect.

LIMITATIONS AND FUTURE DIRECTIONS. In line with Bland et al.[19] we were unable to achieve our target sample size. Nevertheless, in comparison to most exercise intervention studies focusing on CIPN prevention, we provide the largest sample size for ITT and PP analyses with comprehensive and recommended CIPN diagnostics.[43] However, as our primary ITT analyses did not confirm our initial hypothesis – probably due to the lack of adequate training stimulus – we excluded non-adherent patients from analyses. Although most of the PP results are in line with other studies, they need to be verified by future studies by amending the following aspects: i) larger sample-size of adherent exercisers, e.g. by means of measures to increase exercise adherence (see practical considerations), ii) higher CIPN assessment density during chemotherapy in order to detect variations in the effectiveness of exercises[19] and consequently to be able to make adjustments, and iii) modification of CIPN diagnostics towards several specifically tailored procedures that focus on the targeted training region instead of depicting the entire peripheral nerve status as our primary endpoint, TNSr.

PRACTICAL CONSIDERATIONS. In order to preventively influence as many facets of CIPN as possible, it would be advisable to recommend a multimodal training approach consisting of SMT and RT[16,19], and possibly also endurance training.[16,17,19] However, this multimodal training approach can only be effective if an adequate training stimulus is achieved through sufficient exercise adherence. Approximately one third of all missed training sessions were based on time constraints and motivational issues. Adherence enhancing measures, which go beyond the conducted telephone calls and include well-founded motivational content, may increase exercise adherence and thus the prevention effect in terms of perceived symptoms and functional limitations.[44] These might also help the non-adherent patients who had lower physical and cognitive function as well as higher fatigue and insomnia values at baseline compared to the adherent patients, to enhance their attendance rate.

CONCLUSION. SMT and/or RT might be effective strategies to prevent sensory CIPN symptoms in the feet during neurotoxic chemotherapy and enhance chemotherapy tolerance as well as QoL. However, as these results are based on PP analysis, future studies need to confirm these findings.

Acknowledgments

We would like to thank all patients for participating in this study. We gratefully acknowledge Christine Boos, Charlotte Kreutz, and Laura Jansen for study implementation and conduction; all other members of the working group Exercise Oncology for further study assistance; Georges Sam (Department of Neurology, Heidelberg University Hospital) for excellent technical assistance in electrodiagnostics; the OnkoAktiv Network for training implementation; Frederik Marmé and Stefan Welte for medical support and help with recruitment; the NCT

Cancer Registry and NCT Trial Center for data management support; Richard Schlenk and Martina Schmidt for statistical support.

Funding

This project was supported by an intramural funding program: Proof of concept trials 3.0, National Center for Tumor Diseases, Heidelberg, Germany (G876).

Disclosure

The authors declared no conflict of interest.

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6

General discussion

CIPN is a frequent and very unpleasant side effect of neurotoxic chemotherapeutic agents. The symptoms and resulting functional limitations have a severe impact on patients' quality of life and may be associated with a reduced survival time due to CIPN-induced chemotherapy dose reductions [12,41]. The multifaceted impact of this side effect and the lack of effective preventive measures are therefore the reason for the extensive need for further research.

Within this globally defined research framework, the present cumulative dissertation focused on two main aspects: Firstly, together with a multidimensional CIPN assessment, the postural control of cancer patients before, during and after neurotoxic chemotherapy was comprehensively investigated (Manuscript I & II) and potential risk or protective factors were evaluated (Manuscript II). On the other hand, the preventive potential of exercise on CIPN onset during neurotoxic chemotherapy was analyzed, focusing on sensorimotor exercise (SMT) and/or resistance training (RT) in comparison to usual care (UC; Manuscript III). The main findings of the examined research questions are summarized in the following Chapter (6.1) and are then integrated into a broader research context (Chapter 6.2). Based on the strength and limitations of the PIC study (Chapter 6.3), implications for further exercise oncology studies are derived (Chapter 6.4). This dissertation closes with recommendations for patient care (Chapter 6.5), followed by the overall conclusion (Chapter 6.6).

6.1 Summary of main findings

The data presented in the present dissertation show that postural control – operationalized via temporal and spatial measures of the COP – deteriorates in different bipedal standing conditions during neurotoxic chemotherapy, with a simultaneous increase in objectively and subjectively assessed CIPN signs and symptoms (Manuscript I & II). In comparison to healthy, gender, age, height and weight matched controls (HMC), the withdrawal of visual control had a greater impact on postural control in cancer patients than in HMC, which is consistent with an impaired somatosensory feedback due to neurotoxic chemotherapy (Manuscript I). Furthermore, negative correlations, especially between COP parameters and objectively assessed CIPN signs and symptoms indicated that postural instability is more likely to occur when the nerve damage has already reached a greater extent (Manuscript I). However, contrary to initial assumptions, this deterioration of postural control could not be prevented by SMT or RT during chemotherapy. Only in the

SMT patients who achieved an adequate training adherence and thus stimulus, a marginal trend towards unchanged postural control during chemotherapy was observed. However, when operationalizing postural control via mean standing time in monopedal stance, SMT and RT showed a more favorable progression than UC (Manuscript III). In the follow-up period, postural control regenerates despite unchanged CIPN signs and symptoms (Manuscript I & II). A superiority in the sense of a faster regenerative effect in the exercise groups within the analyzed standing conditions was not found (Manuscript III).

Based on the moderate correlation of COP measures with clinically assessed CIPN signs and symptoms, the above-mentioned correlation analyses suggest that there are other factors influencing the deterioration of postural control than CIPN alone. Therefore, we analyzed the influence of baseline nerve function (CMAP, SNAP), physical activity during neurotoxic chemotherapy as well as change of muscle strength on the change of postural control in a multiple linear regression under the control of age and BMI. However, only two predictors showed significant impact: worse baseline sensory nerve function (as indicated by low SNAP amplitudes) was a preventive factor for the impairment of postural control, while worse baseline motor nerve function (as indicated by low CMAP amplitudes) predicted a greater impairment of postural control. Within the analyzed models, however, no significant influencing factors for the above described regeneration of the postural control during follow-up was found.

The last main research question of the present dissertation dealt with the preventive effect of SMT and/or RT versus UC on CIPN during neurotoxic chemotherapy. Our primary intention-to-treat (ITT) analysis revealed that none of the exercise programs were able to impact the progression of objectively and subjectively assessed CIPN signs and symptoms. However, since we found poor training adherence rates in the overall cohort, we conducted an exploratory per-protocol (PP) analysis, which considered only patients who completed at least 67% of the prescribed training sessions. The results showed that subjectively perceived sensory symptoms in the feet increased less during chemotherapy in the adherent exercisers compared to UC. Moreover, on the functional level, we identified a better course of muscular strength in favor of the adherent exercisers, as well as better results in terms of overall quality of life, physical and role functioning, fatigue, and a trend-level effect for pain. Further, chemotherapy compliance (relative dose intensity) was found to be enhanced in this group.

6.2 Integration of study results into the broader context

The study results of the individual manuscripts will be integrated into the broader research context, separately for the topics (a) postural control in response to neurotoxic chemotherapy and (b) exercise-induced prevention of CIPN signs and symptoms as well as associated functional limitations and quality of life. Thereby the discussion about postural control is additionally divided into bipedal and monopedal standing conditions, starting with the former.

6.2.1 Postural control in response to neurotoxic chemotherapy

Even before the start of an antitumor therapy, the cancer itself can lead to reduced physical function [71], which may also have a negative effect on postural control. However, this has not been

considered in previous analyses of postural control in cancer patients. Although our patients more often show a reduced sensory nerve quality at baseline (PAT_{pre}: 37 %, HMC: 13 %, p = .020; data not shown), postural control did not differ from the HMC population in almost all analyzed COP parameter and standing positions (Manuscript I).

During neurotoxic chemotherapy, however, postural control deteriorated while CIPN signs and symptoms simultaneously increased (Manuscript I & II) leading to significant impairments compared to HMC (Manuscript I). Only one other study presented results from a longitudinal dataset and proved this gradual deterioration in postural control in BP_{EO} and BP_{EC} within the first three cycles of a taxane-based chemotherapy [51]. Our data additionally provide information over the entire period of different neurotoxic chemotherapy protocols and are further supplemented by the analysis of two additional standing conditions as well as extensive CIPN diagnostics. Thus, when considering the studies [17,51,52,54] together with our results, the current literature provides sound evidence of deterioration in postural control in response to neurotoxic chemotherapy, both longitudinally and in comparison to healthy (matched) controls.

Since impaired postural control is associated with reduced ADLs and an increased risk of falling [40,42], there is an urgent need for preventive measures to counteract this deterioration. The literature describes that multimodal intervention approaches consisting of balance, strength and endurance training in CIPN patients (partly) undergoing neurotoxic chemotherapy can improve postural control [17,21,132]. However, the corresponding analysis within the PIC study can only reflect these results to a certain extent: Manuscript III only showed a tendency that a regular SMT can prevent deterioration of postural control during neurotoxic chemotherapy, but the comparison with the other study groups (RT, UC) only revealed a small superiority of SMT. At this point, however, it must be mentioned that due to the content focus in Manuscript III, only one COP parameter in a single standing condition was analyzed. Subsequent analyses should therefore cover the scope of analysis of Manuscript I by examining all recorded standing conditions as well as various COP parameters separately, according to the anatomical directions. In addition, frequency bands should also be examined. They may provide information about potential exercise-induced postural control strategies (see Chapter 6.4.2 for further details).

Six months after the end of chemotherapy, postural control regenerated in all standing conditions (Manuscript II) without showing a superiority for the adherent exercisers e.g. in terms of a faster regeneration (Manuscript III). The striking aspect of this finding is that the regeneration of postural control occurred despite persistence of CIPN signs and symptoms and electrophysiologically objectified peripheral nerve damage (Manuscript II & III). In line with our findings, case control studies also indicate an improvement in postural control after chemotherapy, independent of any intervention: therefore, differences between cancer patients and (healthy) controls were only detectable when postural control was assessed close to the end of chemotherapy ([54]: 3.8 weeks). The longer the time period between the end of chemotherapy and COP assessments was, the more inconsistent the observed differences were ([52]: five months, differences in MP_{EO} but no differences in BP_{EO}; [53]: two years, no differences in BP_{EO} and MP_{EO}; [42]: five years, three principal components resulted in three different results in BP_{EO}). After 15 to 43 years, differences were no longer detectable [43]. These studies in combination with our

results may lead to the assumption that despite the presence of CIPN signs and symptoms, compensatory/adaptive mechanisms might have occurred (e.g., muscular co-contractions, sensory reweighting), which may ensure that persisting CIPN and subsequent impaired somatosensory input cease to have a negative effect on postural control. These compensatory/adaptive mechanisms are discussed in more detail in the next section within the context of the analyzed factors of postural control. However, since the patients in our study and the cited studies tended to have mild to moderate CIPN signs and symptoms, it remains unclear whether our hypothesis of intervention-independent postural regeneration due to compensatory/adaptive mechanisms still retains its validity in the presence of a higher symptom burden.

INFLUENCING FACTORS ON POSTURAL CONTROL IN BIPEDAL STANDING POSITIONS. When postural control is considered in the context of neurotoxic chemotherapy, it is most likely that chemotherapy-induced damage of preferentially afferent sensory nerves causes the deterioration of postural control [66,67]. This assumption is supported by correlation analyses showing associations between various diagnostic approaches of CIPN and COP analyses [51,52]. Our data characterize this relationship even more specifically: Postural control is particularly impaired when the nerve damage has already reached a greater extent, i.e. the neurotoxic agents have already damaged the myelin sheath of the large nerve fibers (Ia afferents), which is reflected in reduced nerve conduction velocities (Manuscript I). Although correlation analyses per se do not allow conclusions about the causal relationships, from a pathophysiological perspective it is most likely that nerve damage affects postural control and not vice versa. However, the cited studies above and our data merely demonstrate low to moderate correlations, leading to the assumption that other factors than CIPN alone exist that affect postural control in cancer patients treated with neurotoxic agents.

Consequently, we analyzed the influence of baseline nerve function (CMAP, SNAP), physical activity during neurotoxic chemotherapy as well as change of muscle strength on the change of postural control in a multiple linear regression under the control of age and BMI. Overall, the results revealed higher explanatory potential in EC than in EO conditions (adjusted R^2=0.11 vs. 0.21). However, only baseline SNAP and CMAP amplitudes were significant predictors in our models analyzed: while worse baseline sensory nerve function (as indicated by low SNAP amplitudes) was a preventive factor for the deterioration of postural control, worse baseline motor nerve function (as indicated by low CMAP amplitudes) predicted a greater deterioration of postural control (Manuscript III). It should be noted that these predictors correlate inversely and, in the case of SNAP amplitude, counterintuitively with the deterioration of postural control, which needs further consideration.

The processing of visual, vestibular and especially somatosensory information is the basis for a stable upright posture [59,144]. Therefore, impairment of one or more of these systems may negatively affect postural control, but may also induce compensation/adaptation strategies. In the PIC study, a large proportion of patients (37%) showed reduced somatosensory nerve function at baseline. It is thus conceivable that reduced somatosensory inputs prior to chemotherapy induce compensatory/adaptive processes to stabilize posture [145], and that this pre-therapeutic

compensation may also guarantee less impairment in response to neurotoxicity. Based on theoretical considerations, muscular co-contraction and sensory-reweighting need to be further discussed as compensation/adaptation strategies.

Regarding MUSCULAR CO-CONTRACTIONS as a potential postural control strategy, the literature provides conflicting information. On the one hand, it is discussed that impairments of the somatosensory feedback, e.g. due to ageing [146] or diabetic peripheral neuropathy [147], can induce muscular co-contractions to "compensate" for this information deficit, which may be reflected in lower COP deviations [146,147]. With regard to our data, this may indicate that pre-existing muscular co-contractions may be supportive when somatosensory inputs from the peripheral nervous system are further injured by neurotoxic agents, resulting in a smaller COP_{AREA} increase compared to patients with better peripheral sensory nerve function at baseline. On the other hand, however, this rather speculative approach is contrasted by current results in CIPN patients: Kneis et al. [52] reported a positive correlation between ankle muscle co-contraction and the COP total path ($r=0.68$, $p<.001$). However, this study did not include longitudinal analyses. Thus, further EMG studies are needed to assess the contribution of pre-existing muscular co-contractions on postural control when the somatosensory system is additionally impaired by neurotoxic chemotherapy.

Moreover, SENSORY REWEIGHTING within the central nervous system may also serve as an explanation for the negative standardized regression coefficients regarding the predictive value of baseline SNAP: age-related functional or undetected pathophysiological changes within the somatosensory feedback system might have led to a down-weighted processing of somatosensory information and an elevated processing of visual and vestibular information to stabilize postural control (sensory reweighting theory [59,145]). In diabetic research, comparable sensory reweighting processes are discussed in the presence of neuropathy (for review see [148]). Notably, similar findings have recently been provided also for CIPN patients who were shown to down-weight somatosensory information in comparison to healthy matched controls [149].

Based on these theoretical considerations derived from the existing, albeit not always distinct, literature, the following causal relationship could be valid for our patients: the more impaired the somatosensory feedback is before the start of chemotherapy (low SNAP amplitudes), the more likely compensatory or adaptive processes can be assumed (muscular co-contractions or sensory reweighting) and the less postural control is affected by further chemotherapy-induced injury of predominantly sensory nerves. The case control studies cited above [42,43,52,53] as well as our follow-up data lend additional weight to this hypothesis by showing that postural control regenerates within six months after the end of chemotherapy, despite the persistence of CIPN signs and symptoms, and electrophysiologically objectified peripheral nerve damage.

Besides intact somatosensory feedback from the periphery, a sound efference (as expressed by peroneal CMAP amplitudes) is required to guarantee postural control [55]. Our regression analysis revealed, that patients with more severe impairment of motor nerve function at baseline (e.g., due to ageing [150]) might be at higher risk of deterioration of postural control during chemotherapy. Therefore, baseline nerve conduction studies assessing SNAP and CMAP could be useful to identify patients at increased risk of postural control deterioration during neurotoxic

chemotherapy. These patients could then be monitored more closely and, by means of targeted exercises, postural instability may be prevented or at least reduced (Manuscript III, [17,21,132]).

Regarding the other predictors analyzed, the data suggest that a reduction in quadriceps strength during neurotoxic chemotherapy in our patients cannot predict deterioration in postural control. Although muscle strength plays a crucial role in stabilizing an upright posture [55], our results are in line with other studies that failed to demonstrate an association between intervention-related increases in leg extensor strength and improvements of postural control [151,152]. This also reflects the low correlation between static balance ability and maximum strength ability – predominantly of the knee extensor – described in a meta-analysis of slightly older cross-sectionally assessed subjects (eight studies, back-transformed $r = 0.27$) [140]. With our relatively simple standing conditions, it is likely that ankle plantar and dorsi flexors were primarily used to stabilize posture via the ankle strategy [63]. The more difficult a balance task gets, the more hip strategy is used and thus quadriceps and hamstrings, but especially the hip muscles, are more activated [63]. Consequently, future studies should conduct a more comprehensive muscular assessment, including hip, thigh and ankle muscles, to delineate more clearly the influence of muscle strength and power on postural control in CIPN patients.

Physical activity during chemotherapy – which was reported retrospectively by our patients – showed no influence on the change in postural control. This is in contrast to the results of exercise intervention studies in CIPN patients partly undergoing neurotoxic chemotherapy [17,132]. However, the self-selected exercise efforts in our patients, which were of rather low intensity, frequency and duration, differed significantly from the structured exercise programs performed in the studies cited. Therefore, it can be assumed that the type and overall level of physical activity in our patients was not sufficient to influence postural control.

Searching for explanatory factors for the improvement of postural control within the first six months after completion of chemotherapy, our models analyzed were unable to identify any significant influencing factors. The previously discussed postural control strategies could be considered again as an explanation, but can only be partially verified within our study design in further analyses (see Chapter 6.4.2).

POSTURAL CONTROL IN MONOPEDAL STANCE. Although enhanced temporal and spatial COP parameters indicate deterioration of postural control in bipedal standing positions during chemotherapy, these findings were not reproduced in MP_{EO} stance (Manuscript I). Here, a ceiling effect must be considered, since the patients excluded from COP analyses (standing time less than 30 seconds in both trials) already had significantly worse postural control prior to chemotherapy than patients who had successfully completed MP_{EO}. Consequently, only patients with appropriate postural control at baseline were analyzed. However, when analyzing mean standing time in MP_{EO} – which can be seen as a simplified form of postural control assessment – deterioration of postural control is proved. Furthermore, the preventive effect of SMT and RT on the deterioration of postural control seems to be more evident when based on the revealed p-values and effect sizes than in the analyses of the COP parameters in this standing condition (Manuscript III).

However, these results should not encourage future studies to use only the mean MP_{EO} standing time as postural control assessment due to lower diagnostic accuracy compared to COP analyses [139]. Instead, it should be concluded from these results that MP_{EO} might only be sensitive in detecting COP based balance deficits in this cohort, if test time is reduced. The use in clinical practice as e.g. monitoring parameter during chemotherapy is also restricted: Although there are strong associations between reduced standing time (less than 5 seconds) and increased risk of falling [153], this test alone cannot predict all falls that occur during lifetime [153] and is preferred to be used in subjects with severe postural limitations [139]. A cost-effective, valid "quick test" for postural control does not and may never exist. But there are some non-instrumented assessment procedures that are more applicable in clinical routine than force plate analyses. A current panel of experts recommends the use of either the Berg Balance Scale or the Mini Balance Evaluation System test (required time 10–20 minutes) [154]. Although, to my knowledge neither of these two tests has been evaluated on cancer patients undergoing chemotherapy with the risk of CIPN development, they could possibly be used in clinical routine for early detection and thus counteract postural impairments in time.

6.2.2 CIPN prevention through exercise

The analyses in the scope of Manuscript III showed that CIPN signs and symptoms – operationalized by clinical-neurological, electrophysiological and patient-reported outcome assessments – increased not only in the UC during chemotherapy, but also in the SMT and RT group. Our initial hypothesis that SMT and/or RT can prevent this progression was (consequently) not confirmed by our primary ITT analysis. Considering instrument based assessment procedures in other studies, our results are in line with Bland et al. [20], who found no intervention effect of a multimodal exercise program using QST (deep sensitivity: tuning fork; pain: pinprick). In contrast, however, a comparable intervention revealed a reduction of CIPN symptoms by means of tuning fork diagnostic in the IG but not in the CG [17]. However, caution should be exercised when interpreting this result, as patients were excluded from the analysis if they had experienced a dose reduction of neurotoxic drugs due to CIPN [17].

Considering the evaluation of CIPN signs and symptoms via patient-reported outcomes, our ITT results show a consistent picture with other studies, when psychometrically tested questionnaires were used that reflect the peripheral nerve status of the entire body through a sum score: While a trend-level intervention effect was observed with the FACT/GOG-Ntx questionnaire [22], no intervention effect was identified based on the total score of the EORTC QLQ-CIPN20 (Manuscript III, [20]). However, when the subjectively perceived symptoms are separated in lower and upper extremities and/or symptom characteristics (sensory, motor), intervention effects were demonstrated: Based on a NRS assessment (scale 0–10), Kleckner et al. [19] observed a trend-level effect for perception of numbness/tingling in hands and/or feet and a significant intervention effect for hot/coldness in favor of a home-based resistance and endurance training. These results are comparable with our PP analyses: While in the PP analysis (comparison of SMT with RT and UC) the effect sizes increased in favor of the adherent SMT and RT patients (for all CIPN assessments), between-group differences remained non-significant, probably due to small sample sizes in the exercise groups. For this reason and because between-group dif-

ferences of SMT and RT compared with UC pointed in the same direction, we performed another exploratory PP_{EX} analysis by combining the two exercise groups. Here it is shown that the adherent exercisers develop less sensory symptoms in the feet during chemotherapy compared to the UC group. A sub-analysis by Bland et al. [20] provides a comparable result by showing that exercise can prevent the progression of moderate to severe numbness in toes and feet within the first three taxane cycles of breast-cancer treatment. As an intermediate conclusion, it can be stated that the prevention effects of exercise are primarily observed in the subjective perception of sensory CIPN symptoms. These effects appear to be achieved only if (a) an adequate exercise adherence and thus training stimulus is achieved, and if (b) the underlying CIPN assessments focus on the body regions that were primarily stimulated by the training.

Although these preliminary results need to be verified by future studies, the prevention of subjectively perceived sensory CIPN symptoms is a highly relevant outcome, since decisions on therapy modifications in case of persistent CIPN symptoms are based on the subjectively perceived limitations/strain of the patient. Accordingly, the lower perceived CIPN symptoms shown in the adherent exercises may be associated with the better chemotherapy tolerance (mean RDI) observed in this group (97%) compared to UC (92%). Albeit this result is in accordance with Bland et al. [20] and points towards a promising direction, the influence of exercise on chemotherapy compliance and thus probably on progression-free and overall survival [155] has only been tested in a limited number of studies [156]. Future studies additionally need to carefully consider other patient-related factors, such as multimorbidity, that might affect both exercise and chemotherapy tolerance and thus need to be integrated as confounding variables in future analyses [157,158].

FUNCTIONAL STATUS AND PATIENT-REPORTED OUTCOMES. At this point only the most relevant outcomes will be discussed against the background of CIPN, namely muscular strength, falls and fear of falling as well as quality of life. MUSCLE STRENGTH in cancer patients is associated with prognostic factors such as cancer-specific and all-cause mortality [159]. Therefore its maintenance or ideally its increase during and after chemotherapy should be targeted. This goal was achieved by our adherent RT patients who gained significant and clinically relevant muscle strength during chemotherapy compared to UC (ES = 0.81). The fact that RT can positively impact muscle strength during chemotherapy has already been reported in many other studies (for review see e.g. [160]). However, it is interesting to note that SMT was also able to prevent decrease in muscular strength throughout the chemotherapy period, probably due to an improved neuronal activation of the leg muscles [161]. Even if the effect is markedly lower in comparison to UC (ES = 0.38), this is a relevant result in terms of the easier feasibility of the training. Six months after the end of chemotherapy all groups descriptively regain their baseline level of muscular strength. However, due to a high proportion of missing data (43%), we cannot rule out that the course of muscular strength in the follow-up is overestimated since patients who did not participate might have had a poorer physical condition.

Although it is known that CIPN and associated postural instability as well as reduced lower limb muscle strength increases the risk of falling [40,42,162], the FALL PREVALENCE of 8% in our

total cohort during chemotherapy appears to be rather low, compared with another study showing annual fall rates of 43–57 % in cancer patients without and with CIPN symptoms, respectively [69]. This difference might be explained by the higher age of these patients (+10 years), but also by the longer time after diagnosis (+6 years). Additionally, an enhanced focus on locomotion in everyday life due to the acute change in sensory perception and generally less everyday activities during chemotherapy may further explain this difference. The latter point might also be in line with the majority of our patients (71 %) who report low concerns about falling during chemotherapy (FES-I value < 20) [163]. Although the fear of falling did not change during the follow-up period, it was markedly lower than in a CIPN patient cohort in another study [131].

Finally, QOL analyses provide another important finding within the PIC study. The adherent exercisers were able to improve their QOL during chemotherapy on a clinically meaningful level compared to UC (+ 12.9 points) [164], which is in accordance with Bland et al. [20]. Although not statistically significant, effect sizes for QOL were higher in RT (ES = 0.85) than in SMT (ES = 0.49), which might be explained by the supervised setting [135]. Additionally, adherent exercisers showed better results in terms of physical and social functioning, fatigue and a trend effect on pain, which is consistent with a large number of exercise oncology studies [25]. However, it must be critically noted that in future studies, pain assessment should be expanded, as it is a key symptom in many CIPN patients and may not be adequately assessed by a single questionnaire item. During follow-up, QOL improved in all groups equally and beyond baseline value.

6.3 Strengths and limitations

The three manuscripts presented in the cumulative dissertation at hand provide an unprecedented longitudinal dataset of cancer patients during neurotoxic chemotherapy and six months afterwards with the particular focus on postural control development and the preventive potential of SMT and RT on CIPN signs and symptoms. The underlying analyses of these major outcomes were based on state of the art assessment techniques. In particular, the assessments of CIPN signs and symptoms were specifically selected to reflect the multi-dimensionality of this neurotoxic side effect of chemotherapeutic agents, which has often been neglected in other published exercise oncology studies focusing on CIPN prevention [17-19,21,22]. In comparison to these studies, we also ensured that the baseline measurements were performed prior to the first administration of chemotherapy in order to avoid blurred baseline values. Additionally, we provided an appropriate follow-up period, taking into account the so-called coasting effect, i.e. the increase in CIPN symptoms especially within the first month after the end of chemotherapy [38,79]. Moreover, we provide the largest sample size for ITT and PP analyses in comparison to most exercise oncology studies mentioned above.

However, we were unable to achieve our target sample size in the PIC study, and (thus) our primary ITT analyses did not confirm our initial hypothesis. However, the high non-attendance rate in both exercise interventions, accompanied by a resulting insufficient training stimulus, could explain the absence of an intervention effect, too. Therefore, we excluded patients with an inadequate training compliance for exploratory PP analyses. Although most of the PP results are

in accordance with other studies, these analyses are based on small sample sizes for the intervention groups (SMT: n = 20, RT: n = 15) and are per se not confirmatory. Hence, the presented results need to be verified by future studies, not least to rule out a potential selectivity issue of the PP population, i.e. by showing that the higher training adherence and no other accompanying factors led to the intervention effects shown. Besides the non-confirmatory analyses, there are further limitations in the PIC study which are discussed below and may help to improve the study designs of these future studies and thus improve the reliability of the results.

Firstly, as most patients had breast cancer and were female, the generalizability of all three manuscripts presented is hampered. Since this applies to most other published studies analyzing postural control [6–11] and CIPN prevention via exercise [19-22], it is important to put emphasis on the recruitment of other entities. Secondly, these future studies should also address the question whether different chemotherapy protocols might lead to variations in postural control and CIPN symptom development as well as effectiveness of training [165]. The sample sizes within the individual chemotherapy protocols in our study were too small to initiate corresponding subanalyses. A further limitation of our cohort was that more than one third of the patients included already showed impairments in sensory nerve quality at baseline (Manuscript I, II). Further subanalyses should investigate (a) if e.g. specific cancer factors might have influenced this outcome, as we did not observe this high percentage of impaired sensory nerve function in our HMC population, and (b) whether patients with pre-existing nerve damage respond differently to further neurotoxic influences as well as to exercise interventions. The last point again addresses the high percentage of non-adherent patients, and thus refers to the feasibility of a planned/implemented intervention in future studies. Although the most common reason for missed training sessions within the PIC study were side effects of the chemotherapy, a considerable percentage of missed training sessions might have been avoided by e.g. structured, behavioral theory based telephone calls [166], thus possibly increasing the number of cases analyzed and probably also the intervention effect (see Chapter 6.4.4 for further discussion). To help other researchers to adequately plan their studies against this background, we have integrated a comprehensive analysis of intervention feasibility in terms of various adherence indicators in the supplementary material of Manuscript III (p. 128ff.). Additionally, these data are intended to help future studies with training reporting, not least to be able to summarize specific – and urgently needed – exercise recommendations for patients undergoing neurotoxic chemotherapy against the background of CIPN prevention.

6.4 Implications for further exercise oncology studies

Although some recommendations have already been derived in the previous sections, this chapter additionally elaborates some key aspects that should be given special attention in the planning and implementation of future exercise oncology studies with the focus on the prevention of CIPN signs and symptoms, but also on associated functional limitations such as postural instability.

6.4.1 CIPN assessment

Our primary endpoint the TNSr – the most widely applied composite score in CIPN research [88,89,93] – reflects the peripheral neurological status of the entire body. However, our PP analysis (Manuscript III), the results of Kleckner et al. [19], the sub-analysis of Bland et al. [20] and also (albeit with limitations) the clinical diagnostics of Streckmann et al. [17] suggest that a preventive effect for CIPN signs and symptoms can only be detected in the body regions that are targeted by the training implemented (in this case the lower extremities). Conversely, studies that used a global test procedure, i.e. a questionnaire sum score, did not show any intervention effects related to CIPN prevention [21,22]. Therefore, future exercise intervention studies should plan their CIPN assessments in such a way that, in addition to the presentation of the global peripheral nerve status, a differentiation into upper and lower extremities is possible, ideally separated according to sensory and motor symptoms. However, the basic principles of CIPN diagnostics should still be considered: Both subjective and objective assessments should be used, which can represent all facets of CIPN through their multidimensionality.

In addition, a higher evaluation density should be aimed at in order to detect a potential fading intervention effect during the course of neurotoxic chemotherapy, as shown by Bland et al. [20]. However, the assessment of the complete TNS or its variations would be too time-consuming for both the investigators and the chemotherapy patient. A sole measurement of the subjective perception of symptoms by means of questionnaires would therefore be justified at this point. On the one hand, the EORTC questionnaire, for example, already offers the above mentioned possibility of differentiation of symptoms, and on the other hand, the subjective perception plays a decisive role in the decision about dose modifications of the therapy. Here, (mostly) no objective procedures are used, due to the poor implementation options in clinical practice.

6.4.2 Postural control assessment and analyses

Even though our study results, together with the work of other authors already provide a comprehensive picture of postural control in cancer patients in response to neurotoxic chemotherapy, there are some aspects that need further consideration. In the follow-up period, a regeneration of postural control was observed without the influence of specific interventions or general physical activity (Manuscript II, III). As an explanatory approach, postural control strategies such as muscular co-contraction or sensory reweighting were discussed. However, the verification of these hypotheses will be the subject of future analyses and studies.

Based on the given COP dataset, further frequency band analyses may provide information about a sensory reweighting strategy within our cohort. In general, frequency band analyses can be used to draw conclusions about the sensory information used to maintain postural control in a specific postural task [167]. Three different frequency bands are defined, whereby the frequency ranges vary slightly depending on the author [139,168]: low, medium and high frequency bands, corresponding respectively to visual, vestibular and somatosensory information processing [169]. Due to the impaired somatosensory feedback in CIPN patients, it is most likely that the high frequency range is underrepresented in various balance tasks compared to healthy subjects [170]. Kneis et al. [149] support this consideration and additionally showed that CIPN patients ($n = 8$)

up-weighted somatosensory information to maintain postural control after SMT. A study in DPN patients observed comparable results after balance training [167]. These individual results should be supplemented by frequency band analysis in our cohort – both longitudinally in all study groups as well as in comparison to the healthy matched controls – in order to provide further insights into potentially existing chemotherapy- and training-induced postural control strategies. However, the influence of muscular co-contractions as potential postural control strategy in CIPN patients cannot be further investigated within our data. Future studies should therefore simultaneously record COP parameters and muscular activity via EMG to provide information about muscular co-contractions [139].

Many other assessment options are available that may provide further reinforcing insights into postural strategies of CIPN patients and ultimately form the basis for planning appropriate prevention measures. These include, for example, the manipulation of further sensory information, the inclusion of dynamic standing conditions and 3D motion capture systems in order to differentiate between ankle and hip strategies [139]. But the discussion of these individual points would go beyond the scope of the present dissertation. However, in the effort to learn more about postural control strategies, an accurate assessment of possible influencing factors beyond environmental conditions must not be neglected [61]. Some of these have already been discussed in detail in this dissertation, e.g. muscle strength and physical activity/inactivity. Based on the findings, that approx. 15–25 % of (breast cancer) patients experience cognitive impairments after completion of chemotherapy [171] and cognitive impairments may negatively affect postural control [172], it should finally be emphasized that cognitive capacity should be included in further exercise oncology studies when assessing postural control.

6.4.3 Selection of exercise interventions

The cited CIPN prevention studies have only covered traditional exercise modalities so far. The introduction of whole-body vibration (WBV) training in exercise oncology might be a promising approach when focusing on CIPN symptoms. In diabetes research there are first studies showing the positive influence of WBV on DPN symptoms and functional limitations [173]. For CIPN, Schönsteiner et al. [130] were able to achieve an improvement in symptoms and muscular status (CRT) using multimodal training including WBV (N = 131). Streckmann et al. [53] also showed a tendency towards improved sensory perception in CIPN patients, in a pilot-study (N = 30). The translation into the preventive context is currently being tested in a study [34].

However, the mentioned WBV studies focused only on the lower extremities. As mentioned above, exercise interventions seem to show only a preventive effect on CIPN symptoms in the target region of the training modalities implemented. Since sensory and motor CIPN symptoms of the hands are probably more noticeable to patients in everyday life as they affect fine motor skills, targeting the hands is also crucial. A vibration training of the upper extremities e.g. with a vibration dumbbell seems to be feasible in breast cancer patients [174]. Whether this training also has a preventive effect on CIPN symptoms in the hands needs to be investigated by future studies. Additionally, exercise modalities that do not fit into the "classical" definition could be promising. For example, Hammond et al. [175] examined the effectiveness of home-based nerve-gliding exercises in N = 48 (IG = 22, CG = 26) breast cancer patients during taxane-based

chemotherapy (ITT). Nerve-gliding exercises are "theorized to help by elongating the nerve, restoring mobility, and decreasing neural edema by promoting axoplasmic flow" ([176] p. 236). After the intervention, differences in pain pressure thresholds between the two groups were found (QST).

6.4.4 Monitoring and patient support

The regular participation in an exercise intervention is the basic requirement for an adequate training stimulus. However, the adherence rate in our study was rather low due to different reasons/ barriers (Manuscript III). The most common reason for missed training sessions was based on therapy-related side effects (approx. 45%), while time constraints and motivational issues were mentioned as the second most common reason (in summary approx. 30%). Although the first point cannot probably be changed, the use of targeted monitoring strategies, which in term of content go beyond the telephone calls performed in the PIC study, may help to overcome the barriers that are more likely to be based on motivation and volition. In the literature, monitoring strategies are discussed that are derived from behavioral models [166] – e.g. the concept of the transtheoretical model [177] or social cognitive theory [178] – and include, e.g. goal setting and action statements [179]. An option which is probably easy to implement and widely applicable would be the integration of these theory based principals in mobile health applications. However, the evaluation of feasibility and efficacy is still lacking, not only in the oncological setting [180,181].

Since we found significant baseline differences between adherent and non-adherent patients, with the latter having lower physical and cognitive function and higher levels of fatigue and insomnia, these patients should be given special attention in the monitoring process. A baseline screening to identify these patients and a subsequent more intensive monitoring would therefore be desirable to support these patients who seem to have an overall poorer health status, and could therefore possibly benefit most from an adequate implementation of exercise interventions [25].

6.5 Recommendations for patient care

In addition to the conclusions for future scientific work, it is also important to derive recommendations for patient care from the data presented, and the studies already published. The answer to the question of what we should advise our patients in practice is nearly as multifaceted as CIPN itself, since different exercise interventions can influence different CIPN signs and symptoms. The development of (subjectively perceived) sensory symptoms in the feet seems to be prevented by SMT and RT (comparable effect sizes of the two groups, Manuscript III), as well as by multimodal training approaches [17,19,20]. With regard to CIPN-associated functional limitations, however, there is a trend towards better postural control for SMT, while muscular strength development is in favor of RT (Manuscript III). Therefore, in order to influence as many facets of CIPN as possible in a preventive way, it is advisable to recommend a multimodal training approach, consisting of at least SMT and RT and presumably also endurance training [20] and specific exercises for the hands [176].

The derivation of detailed training recommendations of this multimodal training approach regarding frequency, intensity and time is not straightforward due to the high diversity of the studies and partly missing data (for details see Table S5, p. 119). For this reason, the following recommendations are to be understood as broad framework, which can and should be modified in the individual patient situation – e.g. depending on an enlarged risk for certain symptoms or already existing symptoms – and will certainly have to be considered/reported in a more differentiated manner in future studies. SENSORIMOTOR EXERCISE TRAINING should be performed 2–3× per week, with a total time of (estimated) 15 [20], 20 [17] to 35 minutes (Manuscript III) per session. Each balance task should be carried out 3×20–30 seconds. The difficulty of the balance tasks should increase throughout the training period, e.g. by modifying the support surface and visual control, and include dual-task aspects. These dual-tasks may comprise cognitive aspects but also specific hand exercises, such as nerve-gliding exercises [176]. The training can be performed in a supervised [17,20] or in a home-based setting (Manuscript III). RESISTANCE TRAINING was most often performed in a supervised setting 2–3× per week, (Manuscript III, [17,20]) and targeted four [17], five [20] or up to eight (Manuscript III) major muscle groups. The intensity varied between 50% [20] and 70% of the 1RM (Manuscript III). In addition, the PIC study and Bland et al. [20] included home-based resistance (band) exercises (RPE 14–16) while Kleckner et al. [19] implemented only home-based resistant band exercises (low to moderate intensity: RPE 3–5). Supervised ENDURANCE TRAINING was performed on a treadmill, cycle ergometer, or elliptical trainer 2–3× per week for 10–40 min per session [17,20]. Intensity was chosen between 55–75% HRR [20] or 70–80% HR_{max} [17]. Home-based endurance training was also performed additionally twice per week [20] or daily as single training [19]. The intensities for the latter varied between RPE 12–14 (for 15–30 min) [20] and 60–85% HRR (low to moderate intensity) [19]. The total length of this multimodal exercise approach should correspond to the total length of the individual chemotherapy (Manuscript III, [17,20]).

These exercise prescriptions are in line with the current general exercise recommendations for cancer patients and may therefore not only be effective in the prevention of CIPN, but also have a positive effect on other treatment-related side effects [25]. Regardless of which exercise modalities, durations and intensities appear to be effective at this point in time, it is important to take patient preference into account. It is less demanding to achieve an effective training stimulus if patients appreciate the program and therefore exercise regularly over a long period of time [28,182]. The aforementioned behavioral models may help to find the "right" training program for each patient.

6.6 Conclusion

Chemotherapy-induced peripheral neuropathy is a common, highly compromising side effect of neurotoxic chemotherapy, which is not only associated with unpleasant sensations in the hands and feet, but can also seriously impair postural control. Therefore, the focus of the present dissertation consisted of two aspects: On the one hand, a comprehensive understanding of the development of postural control in response to neurotoxic chemotherapy was provided. The knowledge gained may help to establish risk profiles, generate appropriate exercise intervention

measures and furthermore provide a basis for future analyses. On the other hand, the preventive potential of exercise on the onset of CIPN during neurotoxic chemotherapy was evaluated. It was shown that regular exercise during neurotoxic chemotherapy alleviates the occurrence of symptoms such as tingling, burning, and numbness in the targeted training region. The present dissertation thus complements the results of the research area of exercise oncology and makes the general tenor sound even louder: "Avoid inactivity!".

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List of abbreviations

ADL	activities of daily living
AP	anterior-posterior
ATP	adenosine triphosphate
BMI	body mass index
BOS	base of support
BP	bipedal stance
CG	control group
CIPN	chemotherapy-induced peripheral neuropathy
CMAP	compound motor action potentials
CNS	central nervous system
COM	center of mass
COP	center of pressure
CPET	cardiopulmonary exercise test
CTC	Common Toxicity Criteria
DNA	deoxyribonucleic acid
DPN	diabetic peripheral neuropathy
DRG	dorsal root ganglion
EC	eyes closed
EMG	electromyography
EO	eyes open
HR_{max}	maximum heart rate
HMC	healthy matched controls
HRR	heart rate reserve
IG	intervention group
ITT	intention-to-treat analysis
ML	medio-lateral
MP	monopedal stance
MRI	magnetic resonance imaging
NCS	nerve conduction studies
NCV	nerve conduction velocity
NRS	numeric rating scale
PP	per-protocol analysis
PRO	patient-reported outcome
QOL	quality of life
QST	quantitative sensory testing
RCT	randomized controlled trial
RDI	relative dose intensity
RM	repetition maximum
RPE	rate of perceived exertion
RT	resistance training
SMT	sensorimotor exercise training
SNAP	sensory action potentials
ST	semi-tandem stance
TENS	transcutaneous electrical nerve stimulation
TNS	Total Neuropathy Score
TNSc	Total Neuropathy Score clinical
TNSm	Total Neuropathy Score modified
TNSr	Total Neuropathy Score reduced
TUG	timed-up-and-go test
UC	usual care
WBV	whole-body vibration
1RM	one-repetition maximum

Supplementary material

Additional information on CIPN assessment

Total Neuropathy Score reduced version

The following table contains the reduced version of the Total Neuropathy Score (TNSr) as it was used in the PIC study. The numbers next to the boxes correspond to the scoring of each single item (0–4), which together form the total (sum) score.

Table S1. Total Neuropathy Score reduced version.

Sensory symptoms	☐ 0 None	☐ 1 Symptoms limited to fingers or toe	☐ 2 Symptoms extend to ankle or wrist	☐ 3 Symptoms extend to knee or elbow	☐ 4 Symptoms above knees or elbows, or functinally disabling
Motor symptoms	☐ 0 None	☐ 1 Slight difficulty	☐ 2 Moderate difficulty	☐ 3 Require help or assistance	☐ 4 Paralysis
Number of autonomic symptoms	☐ 0 None	☐ 1 One	☐ 2 Two	☐ 3 Three	☐ 4 Four or five
Pin sensibility	☐ 0 Normal	☐ 1 Reduced in fingers and/or toes	☐ 2 Reduced up to wrist and/or ankle	☐ 3 Reduced up to ellbow and/or knee	☐ 4 Reduced above elbow and/or knee
Vibration sensibility	☐ 0 Normal	☐ 1 Reduced in fingers and/or toes	☐ 2 Reduced up to wrist and/or ankle	☐ 3 Reduced up to ellbow and/or knee	☐ 4 Reduced above elbo and/or knee
Strength	☐ 0 Normal	☐ 1 Mild weakness	☐ 2 Moderate weakness	☐ 3 Severe weakness	☐ 4 Paralysis
Tendon reflex	☐ 0 Normal	☐ 1 Ankle reflex reduced	☐ 2 Ankle reflex absent	☐ 3 Ankle reflex absent, others reduced	☐ 4 All reflexes absent
Sural amplitude	☐ 0 > 9,5 µV	☐ 1 7,6 - 9,5 µV	☐ 2 5,1 - 7,5 µV	☐ 3 2,6 - 5,0 µV	☐ 4 0 - 2,5 µV
Peroneal amplitude	☐ 0 > 3,8 mV	☐ 1 3,1 - 3,8 mV	☐ 2 2,1 - 3 mV	☐ 3 1,1 - 2 mV	☐ 4 0 - 1 mV

CIPN questionnaires

In the PIC study two patient reported outcomes (PRO) were used to assess the subjective perception of CIPN symptoms. The individual items as well as the response options of the FACT GOGntx and EORTC CIPN20 questionnaire are shown in Table S2 and table S3 respectively (German versions).

Table S2. German version of the FACT GOGntx questionnaire.

Bitte geben Sie jeweils an, wie sehr jede der folgenden Aussagen im Laufe der letzten 7 Tage auf Sie zugetroffen hat, indem Sie die entsprechende Zahl ankreuzen.

	überhaupt nicht	**ein wenig**	**mäßig**	**ziemlich**	**sehr**
1. Ich habe ein Taubheitsgefühl oder Kribbeln in den Händen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
2. Ich habe ein Taubheitsgefühl oder Kribbeln in den Füßen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
3. Ich habe ein unangenehmes Gefühl in meinen Händen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
4. Ich habe ein unangenehmes Gefühl in meinen Füßen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
5. Ich habe Gelenkschmerzen oder Muskelkrämpfe	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
6. Ich fühle mich insgesamt schwach	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
7. Ich habe Hörprobleme	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
8. Ich bekomme Ohrenklingeln oder Ohrensausen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
9. Ich habe Schwierigkeiten Knöpfe zu schließen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
10. Ich habe Schwierigkeiten, die Form kleiner Gegenstände zu spüren, wenn ich sie in meiner Hand halte	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4
11. Ich habe Schwierigkeiten beim Gehen	☐ 0	☐ 1	☐ 2	☐ 3	☐ 4

Table S3. German version of the EORTC CIPN 20 questionnaire.

Der folgende Fragebogen beinhaltet verschiedene Fragen zu Ihrem Befinden. Bitte kreuzen Sie von den Antworten diejenige an, die am besten auf Sie zutrifft. Machen Sie hierbei pro Frage bitte nur ein Kreuz und lassen Sie bitte keine Frage aus.

Während der letzten Woche …	**überhaupt nicht**	**wenig**	**mäßig**	**sehr**
1. Hatten Sie ein Kribbeln in Fingern oder Händen?	☐ 0	☐ 1	☐ 2	☐ 4
2. Hatten Sie ein Kribbeln in Zehen oder Füßen?	☐ 0	☐ 1	☐ 2	☐ 4
3. Hatten Sie ein Taubheitsgefühl in Ihren Fingern oder Händen?	☐ 0	☐ 1	☐ 2	☐ 4
4. Hatten Sie ein Taubheitsgefühl in Ihren Zehen oder Füßen?	☐ 0	☐ 1	☐ 2	☐ 4
5. Hatten Sie stechende oder brennende Schmerzen in Ihren Fingern oder Händen?	☐ 0	☐ 1	☐ 2	☐ 4
6. Hatten Sie stechende oder brennende Schmerzen in Ihren Zehen oder Füßen?	☐ 0	☐ 1	☐ 2	☐ 4
7. Hatten Sie Krämpfe in Ihren Händen?	☐ 0	☐ 1	☐ 2	☐ 4
8. Hatten Sie Krämpfe in Ihren Füßen?	☐ 0	☐ 1	☐ 2	☐ 4
9. Hatten Sie Probleme beim Stehen oder Gehen, weil Sie den Boden unter Ihren Füßen nicht mehr spürten?	☐ 0	☐ 1	☐ 2	☐ 4
10. Hatten Sie Schwierigkeiten, warmes von kaltem Wasser zu unterscheiden?	☐ 0	☐ 1	☐ 2	☐ 4
11. Hatten Sie Mühe, einen Stift zu halten und damit zu schreiben?	☐ 0	☐ 1	☐ 2	☐ 4
12. Hatten Sie Mühe, mit Ihren Fingern mit kleinen Gegenständen umzugehen (zum Beispiel kleine Knöpfe zuzumachen)?	☐ 0	☐ 1	☐ 2	☐ 4
13. Hatten Sie Mühe, ein Glasgefäß oder eine Flasche zu öffnen, weil Ihre Hände zu schwach waren?	☐ 0	☐ 1	☐ 2	☐ 4
14. Hatten Sie Mühe beim Gehen, weil Ihre Füße nach unten abknickten?	☐ 0	☐ 1	☐ 2	☐ 4
15. Hatten Sie Mühe beim Treppensteigen oder beim Aufstehen von einem Stuhl, weil Ihre Beine schwach waren?	☐ 0	☐ 1	☐ 2	☐ 4
16. Wurde Ihnen beim Aufstehen aus einer sitzenden oder liegenden Position schwindelig?	☐ 0	☐ 1	☐ 2	☐ 4
17. Hatten Sie eine verschwommene Sicht?	☐ 0	☐ 1	☐ 2	☐ 4
18. Hatten Sie Hörprobleme?	☐ 0	☐ 1	☐ 2	☐ 4
Bitte beantworten Sie die folgende Frage nur, wenn Sie Autofahrer sind 19. Hatten Sie Probleme beim Gebrauch der Pedale?	☐ 0	☐ 1	☐ 2	☐ 4
Bitte beantworten Sie die folgende Frage nur, wenn Sie männlich sind 20. Hatten Sie Schwieigkeiten, eine Erektion zu bekommen oder zu erhalten?	☐ 0	☐ 1	☐ 2	☐ 4

Questionnaire for the assessment of physical activity in the PIC study

Liebe Patientin, lieber Patient,

wir möchten gerne wissen, wie sehr Sie in dem oben angekreuzten Zeitraum körperlich aktiv waren, getrennt nach körperlicher Aktivität im Alltag (diese Seite) und sportliche Aktivität (Rückseite). Sollten Sie im Rahmen der PIC-Studie während der Chemotherapie ein Training absolviert haben, brauchen Sie dies nicht erneut zu dokumentieren.

Vielen Dank!
Ihr PIC-Studienteam

1. **Waren Sie während des oben *angekreuzten Zeitraums* länger als 20 Minuten am Stück <u>zu Fuß unterwegs</u> (z.B. zum Spazierengehen, Weg zur Arbeit, für Erledigungen)?**
   Hinweis: (Nordic) Walking bitte bei Sport eintragen (siehe Rückseite).

   ☐ nein
   ☐ ja, in ☐☐ Wochen während des oben angekreuzten Zeitraumes →

   Häufigkeit: an ca. ☐ Tagen pro Woche
   Dauer: meist etwa ☐☐☐ Minuten pro Tag

   Körperliche Anstrengung
   ☐ gering
   ☐ moderat
   ☐ teilweise stark
   ☐ überwiegend stark

2. **Sind Sie während des oben *angekreuzten Zeitraums* <u>Fahrrad gefahren</u>?**
   Hinweis: Rennradfahren oder Mountainbiking bitte bei Sport eintragen.

   ☐ nein
   ☐ ja, in ☐☐ Wochen während des oben angekreuzten Zeitraumes →

   Häufigkeit: an ca. ☐ Tagen pro Woche
   Dauer: meist etwa ☐☐☐ Minuten pro Tag

   Körperliche Anstrengung
   ☐ gering
   ☐ moderat
   ☐ teilweise stark
   ☐ überwiegend stark

3. **Haben Sie während des *oben angekreuzten Zeitraums* <u>Sport getrieben</u>?**

   ☐ nein
   ☐ ja → welche Sportart(en)

   Sportart 1: ☐

   Zeitraum: in ☐☐ Wochen während des oben angekreuzten Zeitraumes
   Häufigkeit: n ca. T ☐ agen p o W che
   Dauer: meist etwa ☐☐☐ Minuten pro Tag

   Körperliche Anstrengung
   ☐ gering
   ☐ moderat
   ☐ teilweise stark
   ☐ überwiegend stark

   Wo bzw. mit wem haben Sie diesen Sport meistens betrieben?
   ☐ im Verein
   ☐ im Fitnesscenter
   ☐ in einem zeitlich begrenzten Kurs (z.B. Volkshochschule)
   ☐ privat mit Partner, Freunden, Bekannten
   ☐ alleine

   Sportart 2: ☐

   Zeitraum: in ☐☐ Wochen während des oben angekreuzten Zeitraumes

Additional information on exercise intervention studies in CIPN patients

The following section provides further information on the exercise intervention studies that focus on CIPN prevention or treatment (see Chapter 1.3). This includes details on the PEDro score (Table S4, p. 118) and a comprehensive description of the underlying exercise interventions, drop-out and adherence rates for the preventive (Table S5, p. 119) and treatment approach separately (Table S6, p. 122).

Table S4. Sample sizes and PEDro scores for exercise oncology studies focusing on CIPN prevention and treatment.

	N	PEDro [single items]											total score
		Eligibility criteria	Random allocation	Concealed allocation	Baseline comparability	Blind subjects	Blind therapists	Blind assessors	Adequate follow-up	Intention to-treat analysis	Between-group comparisons	Point estimates and variability	
CIPN prevention													
Bland 2019	31	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Henke, 2014	44 [a]	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3
Kleckner 2018	420 [a]	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6
Streckmann 2014	61 [a]	No	Yes	No	Yes	No	No	Yes	Yes	Yes	Yes	Yes	7
Visovsky 2014	19 [b]	Yes	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6
Vollmers 2018	43	Yes	Yes	No	No	No	No	No	No	No	Yes	Yes	3
CIPN treatment													
Clark 2012	36 [b]	Yes	Yes	No	Yes	No	No	No	No	No	Yes	Yes	4
Dhawan 2019	45	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	Yes	7
Kneis 2019	50	No	Yes	Yes	Yes	No	No	No	No	Yes	Yes	Yes	6
Schönsteiner 2017	131	No	Yes	No	Yes	No	No	Yes	Yes	No	Yes	Yes	6
Schwenk 2016	22	Yes	Yes	Yes	Yes	No	No	No	Yes	No	Yes	Yes	6
Streckmann 2018	40 [b]	Yes	Yes	No	No	No	No	Yes	No	No	Yes	Yes	4
Zimmer 2017	30	Yes	Yes	No	Yes	No	No	No	Yes	Yes	Yes	Yes	6

Notes: [a] secondary analyses / results, [b] randomized controlled pilot study.

Table S5. CIPN prevention: Detailed exercise prescription, drop-out and compliance/adherence rates.

Reference Type, setting, frequency and total length of intervention	**Exercise intervention**	**Drop-outs**	**Compliance / Adherence**
Bland 2019 [20] multi-modal: balance + resistance + aerobic supervised + home-based supervised: 3×/week home-based: 2×/week 10 weeks [mean; complete CT period] + 2-3 weeks after last CT cycle	<u>supervised aerobic exercise</u> - treadmill, cycle ergometer, elliptical trainer - intensity & duration ("CT periodization"): 1st week after CT: 50–55% HRR, 40 min/session other weeks: 75% HRR, 25–35 min/session [HRR was calculated on resting heart rate measured during à 5 min seated rest period before every exercise session] <u>supervised resistance exercise</u> - upper + lower body: 5 exercise machines, free weights, resistance bands - intensity & duration/sets: 1×10 50% h1RM >> 2×10–12 65% h1RM [progression over study period; in weeks of CT only one set] - additionally: hand & foot exercises with resistance bands and balls; 2 exercises for abdominal strength <u>supervised balance exercises</u> - 2 single-leg standing exercises for 6–8 repetitions à 20–30s - progression: stable >> unstable surface <u>homebased aerobic exercise</u> (started in week 4): - exercise facilities or (if not available) walking outside - duration: 15 >> 30 min/session (progression over study period) - intensity: RPE 12–14	during intervention n=4 [IG: n=1 requested withdrawal, n=2 became ineligible; CG: n=1 became ineligible] during follow-up n=2 [CG: n=1 cancer recurrence, n=1 personal reasons]	<u>supervised sessions</u> - general attendance: 78 ± 23% - aerobic exercise intensity and duration: 77 ± 30% and 78 ± 24% - resistance and balance exercise prescription, including prescribed exercises, weight, sets, and repetitions: 78 ± 37% <u>home-based exercise</u> - frequency: 87 ± 23% [most frequently reported as walking outside] - All participants met or exceeded the prescribed home-based aerobic exercise duration - Adherence to home-based exercise intensity based on target RPE: 78 ± 19%
Henke 2014 [18] multi-modal: resistance + aerobic supervised aerobic: 5×/week resistance: every other day of the week 1st–3rd cycle of CT [length not reported]	<u>aerobic exercise</u> - walking in hallway - duration: 6 min/session - intensity: moderate, 55–70% HRR (adjustment depending on dyspnoea perception) [HRR was based on Karvonen formula; patient's HR_{max} was estimated according to $HR_{max} = 208\text{-}0.7 \times age$] - staircase walking exercises (10-step staircase, walking up and down) - duration: 2 min/session <u>resistance exercise</u> - 2 free exercises: bridging exercise, abdominal exercise 2 elastic band exercises (4.6 Ibs resistance at 100% elongation): biceps curl, triceps extension - sets: 3 per exercise (1 min break) - intensity: 50% of maximal capacity/amount of repetitions tested at baseline - goal: increasing repetitions - training adaptation: After two cycles of CT, the maximal amount of repetitions possible for each exercise was tested again <u>conventional physiotherapy</u> [usual care; was also offered to CG] - breathing techniques [5×/week] - optional manual therapy (in case of dyspnea, soft tissue or joint problems)	during intervention n=15 [IG: n=1 non-compliance, n=1 changed hospital, n=4 death; CG: n=7 non-compliant, n=2 death]	not reported [patients were excluded from analysis, if compliance was < 75%]

Kleckner 2018 [19] multi-modal: resistance + aerobic home-based 7×/week 6 weeks	aerobic exercise - daily walking prescription, individually tailored - intensity: 60–85 % HRR (low to moderate) - duration: variable, depending on baseline step count - progression/goal: increase average step count by 5–20 % per week [based on pedometer values] resistance exercise - 10 elastic band exercises: squat, side bend, leg extension, leg curl, chest press, row, calf raise, overhead press, biceps curl, triceps extension + 4 optional band exercises: front raise, lateral raise, internal rotation, external rotation - intensity: 3–5 RPE (low to moderate) - duration: variable, depending on how fast exercises were performed - progression [weekly]: total number of sets and repetitions (maximum of 4×15 repetitions) and band resistance	during intervention n=65 [IG: n=15 other medical issues, n=15 no reasons, n=8 overwhelmed, n=2 changed mind, n=1 non-compliant, n=1 cannot exercise; CG: n=9 no reason, n=8 medical, n=2 non-compliant, n=2 overwhelmed, n=1 researcher error, n=1 CT too late]	aerobic exercise: - not explicitly reported - increased average daily steps by 649 (approx. 0.32 miles) resistance exercise: - 77 % of exercisers reported performing at least some resistance exercise - mean: 28.4 min/session, RPE 4; 3.5x/week
Streckmann 2014 [17] multi-modal: balance + resistance + aerobic supervised 2×/week 36 weeks	balance exercise - 4 postural stabilization tasks per session - duration: 3×20s per task (20s rest between each set, 1 min rest between every task) - progression: increasing task difficulty and surface instability resistance exercise - 4 exercises [not further specified] - duration: 1 min/exercise - intensity: maximum force - for inpatients: elastic band exercises aerobic exercise - bicycle-dynamometer or treadmill - intensity: 70–80 % HR_{max} - duration: 10–30 min total duration: approx. 60 min	during intervention n=10 [IG: n=4; CG n=6; reasons not reported]	average compliance for all time points and all interventions was 65 % (highest for SMT, lowest for strength, highest in stationary phases, lowest after completion of therapy)
Visovsky 2014 [22] multi-modal: resistance + aerobic home-based strength: 1–3×/week endurance: 5–7×/week 12 weeks	resistance exercise - resistance band exercises: biceps curls, triceps extensions, front and lateral raises, shoulder press, calf raises, lunges, supine leg curls and supine leg extensions - intensity "according to their self-report of exercise experience" - week 1–3: 1–2×8 repetitions [1–2×/week] week ≥ 4: 2–3×8–12 repetitions [3×/week] aerobic exercise - walking and progressive interval training - week 1–3: brisk walking 5–7 days/week week ≥ 4: interval based workout consisting light to moderate intensity exercises for 30 min duration [CG: educational materials avoiding those related to physical activity]	not reported	not reported

Vollmers 2018 [21] multi-modal: balance + resistance + aerobic supervised 2×/week during CT [length not reported] + 6 weeks after CT termination	aerobic exercise [warm up] - bicycle ergometer - duration: 8–10 min - intensity not reported balance exercise - monopedal stand on Posturomed with eyes open resistance exercise - 6 machine based exercises - duration: 2×20 repetitions - intensity: RPE 13–15	during intervention n=7 [IG: n=4; CG n=3; general reasons: missed appointments, retrieval of patients consent]	not reported [patients were excluded from analysis, if compliance was < 70%]

Abbreviations: CG, control group; CT, chemotherapy; h1RM, hypothetical one repetition maximum; HR_{max}, maximum heart rate; HRR, heart rate reserve; IG, intervention group; RPE, rating of perceived exertion.

Table S6. CIPN treatment: Detailed exercise prescription, drop-out and compliance/adherence rates.

Reference Type, setting, frequency and total length of intervention	**Exercise intervention**	**Drop-outs**	**Compliance / Adherence**
Clark 2012 [129] Yoga supervised + home-based 1×/week 6 weeks	<u>reiki</u> - performed by 5 Reiki masters in 1:1 sessions - duration: 60 min/week + daily reflections of Reiki sessions <u>yoga</u> - Hatha Yoga: breathing, stretching, relaxation - duration: 60 min/week + daily home practice <u>meditation</u> - mindfulness meditation practice - duration: 60 min/week + daily home meditation practice <u>education (CG)</u> - focus on biological, psychological, and social components of CIPN - duration: 60 min/week + daily home revision of class material	during intervention n=10 [Reiki: n=2 no reason provided; Yoga n=1 cancer recurrence, n=1 work schedule interfered with participation; Meditation n=1 cancer recurrence, n=1 medical concerns; CG n=1 family crisis, n=2 no reason provided, n=1 transportation issues]	<u>reiki</u> - 90 % of prescribed supervised sessions - 3/7 reflected their experiences at home: 5 days for 17 min/day (mean values) <u>yoga</u> - 73 % of prescribed supervised sessions - 5/7 participants practiced at home: 18 days for 14 min/day (mean values) <u>meditation</u> - 83 % of prescribed supervised sessions - All participants practiced at home: 22.2 days for 25 min/day (mean values) <u>education</u> - 95 % of prescribed supervised sessions - 1/5 reviewed class materials at home: 4 days for less than 2 min/day
Dhawan 2019 [133] multi-modal: balance + resistance home-based 7×/week 10 weeks	<u>resistance and balance exercises</u> - 12 exercises: lying position: ankle motion, hip abduction, straight leg raise sitting position: digit abduction/adduction, wrist motion, elbow flexion and extension, knee flexion and extension, toe tapping standing position: one legged stand, toe stand, hip extension, tandem forward walking - duration: 30 min/session - intensity and sets and repetitions were not reported	during intervention n=4 [IG: n=1 lost to follow-up, n=2 declined to give post-test; CG: n=1 lost to follow-up]	a total of 68 % adhered to exercise regimen [1]
Kneis 2019 [13] multi-modal: balance + aerobic supervised 2×/week 12 weeks	<u>aerobic exercise</u> - duration: up to 30 min - intensity: moderate, below the individual anaerobic threshold (IAT), monitored with RPE scale <u>balance exercise</u> - 3–8 exercises per session - duration: 3×20–30s (total duration: 30 min) - progression: increasing exercise difficulty by reducing the support surface and visual input, adding motor/cognitive tasks, and instability induction	during intervention n=9 [IG: n=2 time conflict, n=2 orthopaedic problem, n=1 recruiting failure; CG: n=1 time conflict, n=2 therapy indication, n=1 recruiting failure]; additionally n=4 were excluded from per-protocol analysis [IG: n=2 training compliance <70 %; CG: n=1 time conflict, n=1 personal reasons]	overall (intention-to-treat analysis): 92 % (range: 25–100 %) per-protocol analysis (>70 % adherence): - IG: 92 % (range: 71–100 %) - CG: 100 % (range: 71–100 %)

Schönsteiner 2017 [130] multi-modal: WBV + "exercises" + mobilisation supervised + home-based 2×/week (WBV, massages + passive mobilisation) 7×/week (home exercises) 7,5 weeks (15 Interventionen, 2× per Woche), allerdings unklar, weil Gesamtlänge nicht berichtet wird	<u>WBV</u> (supervised) - duration: 19 min - warm-up: 3 min, 9>>13 Hz, horizontal position (0° elevation) main training: 3 min, 14 Hz, 30° elevation >> 18 Hz, 60°–90° elevation + 3 min, 19>>23 Hz, upright position (90° elevation) cool-down: 9 min, 9>>13 Hz, 30°>>0° elevation <u>physical exercises</u> (home based) - 21 exercises: focus on posture and transport movements [detailed description available in supplementary material] - duration: 1×3–10 repetitions (depending on exercise) - intensity: body weight <u>massage and passive mobilization</u> (passive treatment) - duration: 30 min per side	during intervention n=27 [IG: n=4 IC withdrawal, n=1 dyspnea, n=1 nausea, n=2 death, n=2 infection, n=1 surgery, n=4 progress, n=1 thrombosis; CG: n=4 IC withdrawal, n=2 surgery, n=2 progress, n=1 thrombosis, n=2 diarrhea]; during follow-up n=10 [IG: n=2 IC withdrawal, n=3 progress, n=1 surgery; CG: n=1 IC withdrawal, n=2 progress, n=1 withdrawal]	not reported
Schwenk 2016 [131] balance supervised 2×/week 4 weeks	<u>balance exercise</u> - exergaming system (LegSys™) provided visual performance feedback during static and dynamic balance tasks: ankle point-to-point reaching task, visual obstacle crossing task - duration: 45 min	during intervention n=3 [IG: n=2 lack of transport to study center; CG: n=1 medical event unrelated to the study]	not reported
Streckmann 2019 [53] balance | WBV supervised 2×/week 6 weeks	<u>balance exercise</u> - 4 exercises / session - duration: 3x20 s, rest 40 s between each set + 1 min between each exercise - progression: unstable surfaces <u>WBV</u> - side-alternating vibration platform (Milbration, Milon), - 4 progressing sets of 30s to 1 min vibration, frequency from 18–35 Hz, amplitude of 2–4mm; rest 1 min between exercises; standing on forefoot (or if too unstable, with an 80/20 % distribution)	during intervention n=1 [CG: n=1 due to progress of the disease, in-hospital treatment]	97.5 % (mean compliance for all time points and interventions)

Zimmer 2017 [132] multi-modal: balance + resistance + aerobic supervised 2×/week 8 weeks	<u>balance training</u> - e.g. balance pads, balancing on lines - duration: 10 min - additionally 5 min coordination practices: cherry pit pillows, brasils <u>endurance training</u> - cross-trainer, bicycle ergometer, walking - duration: 10 min - intensity: RPE 12–13 = 60–70 % HR_{max} <u>resistance training</u> - circuit training including 5 stations: bench press, lat pulldown, leg press, seated row, abdominal exercise - duration: 2×8–12 repetitions [total duration: 20 min] - intensity: 60–80 % h1RM, RPE 6 (scale 0–10) <u>cool down</u> - relaxing, stretching, breathing and mobilization exercises - duration: 10–15 min	During intervention n=4 [IG: n=1 pneumonia, n=1 died; CG: n=1 disease progression, n=1 psychological reasons]; during follow-up n=2 [CG: n=1 died; n=1 depression]	mean training frequency: 88.3 %

Abbreviations: CG, control group; CIPN, chemotherapy-induced peripheral neuropathy; HR_{max}, maximum heart rate; IG, intervention group; MC, matched controls; RPE, rating of perceived exertion; WBV, whole body vibration training. Notes: [1] missing (correct) description of the calculation: tables show that 150 min/week was counted as "attended" instead of 210 min/week (7×30min).

Supplementary material for Manuscript I

This section provides the supplementary material referred to in the first manuscript. However, the general inclusion and exclusion criteria of the PIC study were not listed again. These can be found on page 43 (Table 4).

Table S2. Healthy one-to-one matched controls' inclusion and exclusion criteria.

Inclusion criteria	▪ age ≥ 18 years ▪ physical capability that allows to follow the requirements of the study protocol
Exclusion criteria	▪ any malignant disease ▪ ever receive chemotherapy and/or radiation therapy ▪ known polyneuropathy of any kind or any polyneuropathic signs or symptoms ▪ family history positive for any hereditary polyneuropathy ▪ known vitamin B12 deficiency ▪ any neurological disorder or physical or mental handicap that potentially impede balance control and/or nerve function ▪ any surgery of the lower limbs within the last 12 months ▪ known history of alcohol or illegal drug abuse

Supplementary material for Manuscript II

This section provides the supplementary material referred to in the second manuscript. As mentioned before, the general inclusion and exclusion criteria of the PIC study were not listed again (see p. 43). Table S1 provides results of additional paired t-tests, excluding patients who conducted a systematic training program during follow-up. Table S2 provides detailed inclusion and exclusion criteria of the study (see Table 4, p. 43). Table S3 provides results of additional multiple linear regression analyses for each standing position separately.

Table S1. Descriptive statistics and results of paired t-tests, excluding patients who conducted a systematic training program during follow-up.

	pre [mean ± SD]	**post$_0$** [mean ± SD]	**post$_3$** [mean ± SD]	**post$_6$** [mean ± SD]	**pre - post$_0$** [p-value]	**post$_0$ - post$_3$** [p-value]	**post$_0$ - post$_6$** [p-value]	**pre - post$_6$** [p-value]
Postural control [95% confidence ellipse area]								
BP_{EO} [mm²]	64.1 ± 44.2	94.7 ± 58.8	76.4 ± 52.3	80 ± 54.7	<.0001 [t = 4.9; DF = 53]	.070 [t = -1.9; DF = 35]	.002 [t = -3.4; DF = 26]	.574 [t = 0.6; DF = 26]
BP_{EC} [mm²]	98.4 ± 75.6	168.0 ± 113.6	155.3 ± 185.7	141.1 ± 96.3	<.0001 [t = 5.4; DF = 53]	.609 [t = -0.5; DF = 35]	<.0001 [t = -4.1; DF = 26]	.155 [t = 1.5; DF = 26]
ST_{EO} [mm²]	263.9 ± 134.7	308.7 ± 148.7	223.4 ± 84.1	247.0 ± 102.9	.042 [t = 2.1; DF = 53]	.001 [t = -3.8; DF = 35]	<.0001 [t = -5.1; DF = 26]	.045 [t = -2.1; DF = 26]
ST_{EC} [mm²]	655.2 ± 673.9	943.8 ± 756.7	762.6 ± 460.3	748.4 ± 673.6	<.0001 [t = 6.1; DF = 53]	.024 [t = -2.3; DF = 35]	<.0001 [t = -3.8; DF = 26]	.558 [t = -0.6; DF = 26]
$EO_{composite\ score}$ [mm²]	164.0 ± 81.4	201.7 ± 91.2	149.9 ± 57.2	163.5 ± 69.9	.002 [t = 3.2; DF = 53]	<.0001 [t = -4.1; DF = 35]	<.0001 [t = -5.9; DF = 26]	.099 [t = -1.7; DF = 26]
$EC_{composite\ score}$ [mm²]	376.8 ± 355	555.9 ± 407.8	459.0 ± 295.2	444.8 ± 373.6	<.0001 [t = 7.2; DF = 53]	.025 [t = -2.2; DF = 35]	<.0001 [t = -4.8; DF = 26]	.771 [t = -0.3; DF = 26]
CIPN signs/symptoms								
TNSc [sum score]	1.3 ± 2.1	5.8 ± 3.8	7.1 ± 4.8	5.9 ± 4.2	<.0001 [t = 9.1; DF = 53]	.368 [t = 0.9; DF = 36]	.932 [t = -0.1; DF = 27]	<.0001 [t = 6; DF = 27]
CMAP [mV]	7.4 ± 2.9	5.5 ± 2.3	6.4 ± 2.3	6.2 ± 2.4	<.0001 [t = -8.0; DF = 53]	.001 [t = 3.2; DF = 36]	<.0001 [t = 4.3; DF = 27]	.005 [t = -2.8; DF = 27]
SNAP [µV]	11.3 ± 5.1	8.3 ± 5.0	9.6 ± 5.7	8.9 ± 6.0	<.0001 [t = -5.7; DF = 53]	.316 [t = 1; DF = 36]	.111 [t = 1.6; DF = 27]	.005 [t = -2.8; DF = 27]
CIPN15 [sum score]	3.3 ± 5.8	14.6 ± 15.3	17.3 ± 20.4	15.3 ± 19.0	<.0001 [t = 5.7; DF = 53]	.834 [t = 0.2; DF = 44]	.741 [t = 0.3; DF = 33]	<.0001 [t = 3.6; DF = 33]
Physical activity and strength								
PA [min/week]	57.2 ± 94.4	35.7 ± 86.3	33.8 ± 55.5	115.7 ± 267.4	.205 [t = -1.3; DF = 53]	.786 [t = 0.3; DF = 44]	.014 [t = 2.6; DF = 33]	.190 [t = 1.3; DF = 33]
MVIC [Nm]	141.1 ± 34.5	131.1 ± 35.5	131.6 ± 29.2	143.3 ± 18.9	.001 [t = -3.2; DF = 53]	.086 [t = 1.7; DF = 24]	.303 [t = 1; DF = 17]	.411 [t = -0.8; DF = 17]

Descriptive statistics are shown for each assessment point separately (mean and standard deviation) and p-values, t-values and DF as revealed by paired t-tests. Bold p-values are considered statistically significant different (p<.0125). **Abbreviations**: **BP**, bipedal stance; **CIPN15**, sum score based on EORTC QLQ-CIPN20 questionnaire; **CMAP**, compound muscle action potential of peroneal nerve; **DF**, degrees of freedom (paired t-test); **EC**, eyes closed; **EO**, eyes open; **MVIC**, maximal voluntary isometric contraction; **PA**, physical activity; **pre**, assessment point before neurotoxic chemotherapy; **post$_0$**, assessment point three weeks after neurotoxic chemotherapy; **post$_3$**, assessment point three months after post$_0$; **post$_6$**, assessment point six months after post; **SD**, standard deviation; **SNAP**, sensory nerve action potential of sural nerve; **ST**, semi-tandem stance; **t**, t-value (paired t-test); **TNSc**, total neuropathy score (clinical).

Table S3. Multiple regression analysis for predicting the change in postural control during and after neurotoxic chemotherapy.

	pre - post$_0$ [n=54]					**post$_0$ - post$_6$** [n=39]				
	B (95% CI)	**β**	**t-value**	**p-value**	**adj. R^2**	**B (95% CI)**	**β**	**t-value**	**p-value**	**adj. R^2**
BP$_{EO}$					**-0.03**					**-0.08**
CMAP	-2.17 (-7.11, 2.77)	-0.14	-0.86	.389		-4.44 (-13.49, 4.62)	-0.22	-1.00	.326	
SNAP	2.16 (-0.91, 5.24)	0.24	1.38	.168		0.15 (-4.69, 4.99)	0.02	0.06	.950	
age	0.04 (-1.21, 1.29)	0.01	0.07	.947		0.48 (-1.29, 2.24)	0.11	0.55	.585	
BMI	0.98 (-1.81, 3.76)	0.10	0.69	.492		-1.38 (-5.14, 2.39)	-0.15	-0.74	.463	
PA	0.09 (-0.07, 0.24)	0.16	1.11	.268		0.01 (-0.09, 0.11)	0.03	0.16	.870	
MVIC	-0.01 (-0.62, 0.6)	0.00	-0.03	.979		-	-	-	-	
BP$_{EC}$					**0.07**					**-0.06**
CMAP	-5.29 (-15.09, 4.51)	-0.16	-1.06	.290		-8.4 (-24.65, 7.86)	-0.23	-1.05	.301	
SNAP	4.33 (-1.8, 10.46)	0.23	1.38	.166		3.44 (-5.25, 12.13)	0.20	0.81	.426	
age	1.27 (-1.21, 3.74)	0.15	1.00	.315		0.68 (-2.49, 3.84)	0.08	0.43	.667	
BMI	6.68 (1.18, 12.18)	0.34	2.38	.017		-3.05 (-9.8, 3.70)	-0.19	-0.92	.365	
PA	0.2 (-0.1, 0.5)	0.18	1.29	.199		-0.05 (-0.23, 0.13)	-0.10	-0.57	.570	
MVIC	0.1 (-1.1, 1.3)	0.02	0.16	.871		-	-	-	-	
ST$_{EO}$					**0.08**					**0.11**
CMAP	-5.59 (-22.01, 10.83)	-0.10	-0.67	.504		-2.51 (-22.67, 17.65)	-0.05	-0.25	.802	
SNAP	10.35 (-0.02, 20.71)	0.33	1.96	.050		-7.86 (-18.63, 2.92)	-0.34	-1.48	.147	
age	1.55 (-2.57, 5.67)	0.11	0.74	.460		-0.5 (-4.42, 3.43)	-0.05	-0.26	.799	
BMI	4.78 (-4.36, 13.92)	0.15	1.03	.305		-4.52 (-12.9, 3.86)	-0.20	-1.10	.280	
PA	0.42 (-0.08, 0.92)	0.23	1.65	.099		-0.22 (-0.44, 0)	-0.32	-2.03	.051	
MVIC	-0.96 (-2.96, 1.04)	-0.14	-0.94	.346		-	-	-	-	
ST$_{EC}$					**0.14**					**0.09**
CMAP	-47.37 (-81.26, -13.49)	-0.41	-2.74	.006		53.14 (-7.41, 113.69)	0.37	1.79	.083	
SNAP	26.85 (5.54, 48.15)	0.40	2.47	.014		-3.89 (-36.25, 28.47)	-0.06	-0.24	.808	
age	3.02 (-5.63, 11.67)	0.10	0.69	.493		4.33 (-7.46, 16.13)	0.13	0.75	.460	
BMI	6.03 (-13.47, 25.54)	0.09	0.61	.544		-12.54 (-37.7, 12.63)	-0.19	-1.01	.318	
PA	0.86 (-0.2, 1.91)	0.22	1.59	.111		-0.05 (-0.71, 0.62)	-0.02	-0.14	.890	
MVIC	-1.31 (-5.51, 2.89)	-0.09	-0.61	.541		-	-	-	-	

Table shows results of multiple linear regression analysis investigating the influence of various predictors on changes in postural control during (pre - post$_0$) and after (post$_0$ - post$_6$) neurotoxic chemotherapy. Bold p-values are considered statistically significant different ($p < .05$). Abbreviations: **Adj. R^2**, adjusted R^2; **B**, unstandardized regression coefficient ; **β**, standardized regression coefficient; **BMI**, body mass index; **BP**, bipedal stance; **CI**, 95% confidence interval; **CMAP**, compound muscle action potential of peroneal nerve; **EC**, eyes closed; **EO**, eyes open; **MVIC**, maximal voluntary isometric contraction of quadriceps; **PA**, physical activity; **post$_0$**, assessment point 3 weeks after neurotoxic chemotherapy; **post$_6$**, assessment point 6 months after post; **pre**, assessment point before neurotoxic chemotherapy; **SNAP**, sensory nerve action potential of sural nerve; **ST**, semi-tandem stance.

Supplementary material for Manuscript III

This section provides the supplementary material referred to in the third manuscript:

- Figure S1. Selected sensorimotor exercise training cards.
- Table S1a. Sensorimotor exercise training: Prescribed and actual exercise dose and adherence outcomes.
- Table S1b. Resistance training: Prescribed and actual exercise dose and adherence outcomes.
- Table S2. Detailed information of cancer stages.
- Table S3. Reasons for missed training sessions.
- Table S4. Patient characteristics and significant baseline differences between adherent and non-adherent exercisers.
- Table S5. Adverse events related to the exercise programs.
- Table S6. Results revealed by ANCOVA for ITT, PP and PP_{EX} analyses.
- Table S7. Number of falls.
- Table S8. Information on chemotherapy dose modifications, early termination and concomitant CIPN treatment and prevention measures.

Figure S1. Selected sensorimotor exercise training cards. The exercises primarily included static balance exercises in an upright position – every fifth exercise was of dynamic character. For progression purposes, the exercises varied in the following aspects: base of support (e.g. bipedal vs. monopedal stance), surface (e.g. solid ground vs. Airex Balance Pad), head position (e.g. straight vs. head back), and visual control (open vs. closed eyes) and were combined with additional tasks if possible (e.g. throwing a ball). The patients were instructed to increase exercises difficulty in each training session and over the entire training period from easy to difficult (the higher the number in the left corner of a card, the more difficult the exercise). Every exercise was rated on a numeric rating scale after it was carried out (NRS: 1 - very easy, 2 - easy, 3 - intermediate, 4 - difficult, 5 - very difficult). If an exe rcise was too easy (NRS 1 or 2), the training card was removed from the catalogue in order to continue with more difficult exercises in the following training sessions.

Table S1a. Sensorimotor exercise training: Prescribed and actual exercise dose and adherence outcomes.

	PRESCRIBED	ACTUAL	
FREQUENCY	3x/week	▪ Attended training weeks [% of planned length]	68.1 ± 29.3
		▪ Attended training sessions [% of planned sessions] [o/w supervised]	53.3 ± 27.5 [4.6 ± 12.2]
		▪ Treatment interruption [n per patient] [1]	1.5 ± 1.6
		▪ Length of treatment interruption [weeks]	2.5 ± 1.4
		▪ Permanent treatment discontinuation [n] [2]	11 (23%)
INTENSITY	various difficulties progression: based on individual perception (see Figure EX1 for details)	▪ Missed progress [% of attended training sessions] [3]	19.1 ± 14.7
		▪ Sessions requiring dose reduction(s) [% of attended training sessions] [4]	23.9 ± 15
TIME	total length according to CHT regime 3x35 min/week	▪ Total length [weeks]	20.7 ± 4.7
		▪ Total training duration per week [min]	81.5 ± 21.7
		▪ Number of exercises per session [mean]	7.8 ± 1.9
TYPE	**Sensorimotor exercise training** STATIC AND DYNAMIC (16%) EXERCISES IN UPRIGHT POSITION FOR IMPROVING POSTURAL CONTROL/BALANCE. EXERCISES WERE PROGRESSIVELY DESIGNED AND VARIED REGARDING BASE OF SUPPORT, SURFACE, HEAD POSITION, VISUAL CONTROL, AND ADDITIONAL TASKS. EACH EXERCISE WAS PERFORMED 3×30 SECONDS WITH AT LEAST 30 SECONDS PAUSE BETWEEN SETS.		

The adherence outcomes are presented as mean ± SD (unless otherwise indicated) and are based on the data of 48 patients. Four patients out of 52 (8%) did not start their assigned sensorimotor exercise training due to: study exclusion (n=3, see flow-chart), an unplanned inpatient admission at the beginning of the study made the patient feel that the additional training program was too much (n=1). Abbreviations and additional explanations/definitions: [1] missing at least three consecutive sessions (Nilsen et al. 2018 Med Sci Sports Exerc); [2] permanent discontinuation of exercise intervention within the first two thirds of the planned duration; [3] patients indicated that at least one of the performed exercises was very easy or easy (NRS 1 or 2) without increasing the difficulty in the following training sessions (i.e. using at least one training card with a higher number); [4] patients indicated that the average dose/difficulty of a training session was reduced, i.e. the mean value of the card numbers has decreased from one training session to the next.

Table S1b. Resistance training: Prescribed and actual exercise dose and adherence outcomes.

	PRESCRIBED		ACTUAL		
	SUPERVISED	HOME-BASED		SUPERVISED	HOME-BASED
FREQUENCY	2x/week	1x/week	▪ Attended training weeks [% of planned length]	55.1 ± 28.4	55.1 ± 29.9
			▪ Attended training sessions [% of planned sessions]	42.7 ± 25.7	55.1 ± 29.9
			▪ Treatment interruption [n per patient] [1]	2.0 ± 1.9	
			▪ Length of treatment interruption [weeks]	2.3 ± 1.0	
			▪ Permanent treatment discontinuation [n] [2]	10 (19%)	
INTENSITY	start at 70-80%1RM progression: 3×12 repetitions in three consecutive training sessions	RPE 14-16	▪ Mean intensity over time	68.4 ± 15.4 [3]	14.4 ± 1.7 [4]
			▪ Training weight increases [%] [5]	19.9 ± 13.4	n/a
			▪ Training weight reductions [%] [5]	9.7 ± 10.9	n/a
			▪ Missed progress [6]	70.3 ± 26.9	n/a
TIME	total length according to CHT regime		▪ Total length [weeks]	20.3 ± 5.5	
	2x 45 min/week [8 exercises/session]	15 min/week [3 exercises/session]	▪ Total training duration per week [min]	68.6 ± 17.8	17 ± 6.1
			▪ Numbers of exercises per session [median]	8.3 ± 1.4	2.8 ± 0.4
TYPE	**Supervised machine-based resistance training + home-based core stability exercises** SUPERVISED: LEG PRESS, KNEE EXTENSION AND FLEXION, ROWING, LATERAL PULL DOWN, SHOULDER INTERNAL AND EXTERNAL ROTATION, BUTTERFLY, BUTTERFLY REVERSE || HOME-BASED: 15 DIFFERENT CORE STABILITY EXERCISES IN VARIOUS POSITIONS: SUPINE POSITION, PRONE POSITION, QUADRUPED POSITION, PLANK POSITION				

The adherence outcomes are presented as mean ± SD (unless otherwise indicated) and are based on the data of 54 patients. Seven patients out of 60 (12%) did not start their assigned resistance training program due to: time constraints (n=3), study exclusion (see flow-chart, n=2), medical contraindication (port thrombosis, n=1), training contents did not please (n=1). Abbreviations and additional explanations/definitions: [1] missing at least three consecutive sessions (Nilsen et al. 2018 Med Sci Sports Exerc); [2] permanent discontinuation of exercise intervention within the first two thirds of the planned duration; [3] %1RM [percent of one repetition maximum]; [4] BORG Rating of Perceived Exertion (RPE); [5] number of training weight increases/reductions per exercise (compared to the previous training session) in relation to the total number of exercises during the intervention period; [6] training weight was not increased after patient moved the target weight in 3×12 repetitions in three consecutive training sessions.

Table S2. Detailed information of cancer stages according to UICC [n (%)].

	Total	SMT	RT	UC
1	8 (5%)	4 (8%)	2 (4%)	2 (4%)
1A	32 (20%)	9 (18%)	9 (16%)	14 (25%)
1B	1 (1%)	1 (2%)		
1C	1 (1%)		1 (2%)	
2	2 (1%)		1 (2%)	1 (2%)
2A	33 (20%)	7 (14%)	14 (25%)	12 (21%)
2B	23 (14%)	9 (18%)	7 (12%)	7 (12%)
3	7 (4%)	3 (6%)	3 (5%)	1 (2%)
3A	15 (9%)	4 (8%)	5 (9%)	6 (11%)
3B	6 (4%)	1 (2%)	3 (5%)	2 (4%)
3C	5 (3%)	1 (2%)	3 (5%)	1 (2%)
4	14 (9%)	4 (8%)	4 (7%)	6 (11%)
4A	5 (3%)		2 (4%)	3 (5%)
4B	3 (2%)	2 (4%)		1 (2%)
WHO II°	2 (1%)		2 (4%)	
WHO III°	1 (1%)		1 (2%)	
unknown	5 (3%)	4 (8%)		1 (2%)

Table S3. Reasons for missed training sessions.

	SMT	RT
Side effects of anticancer treatment [%]	43.1	47.4
Time constraints [%]	25.9	22.4
Motivation [%]	11.2	5.3
Medical contraindications [%]	7.4	4.5
Feeling unwell [%]	5.7	4.2
Organizational reasons [%]	4.8	12.0
Pain [%]	1.4	1.4
Others [%]	0.3	2.4
Mental constrains [%]	0.2	0.5

Table S4. Patient characteristics and significant baseline differences between adherent and non-adherent exercisers.

	Adh. EX	Non-adh. EX	p-value
Patient characteristics			
N	35	71	-
Sex [f:m, n]	27:8	62:9	.179
Age [mean ± SD]	52.1 ± 10.9	52.9 ± 11.5	.752
BMI [mean ± SD]	26 ± 5.1	26.7 ± 5.2	.573
Married [n (%)]	29 (74%)	52 (85%)	.245
Completed university [n (%)]	16 (30%)	21 (47%)	.088
Breast cancer [n (%)]	25 (71%)	52 (73%)	.844
Stage III/IV [n (%)]	12 (36%)	24 (35%)	.875
EORTC QLQ C30 [baseline values, mean ± SD]			
Physical functioning	91.8 ± 15.4	88.1 ± 13.6	.024 *
Cognitive functioning	88.2 ± 21.1	78.6 ± 20.9	.007 *
Fatigue	21.4 ± 23.7	36.0 ± 26.2	.004 *
Insomnia	24.5 ± 28.8	43.8 ± 34.3	.006 *

We tested all primary and secondary outcome variables, but only the significant differences are shown besides patient characteristics. Abbreviations: adh., adherent; EX, exercisers.

Table S5. Adverse events related to the exercise programs.

	SMT	RT
Patients reporting at least one AE [n]	10	13
Adverse events		
Pain ▪ after 1RM test	-	2
▪ musculoskeletal	4	14
▪ other	1	3
Fatigue	2	4
Dizziness	9	2

Table S6. Results revealed by ANCOVA for ITT, PP and PP_{EX} analyses.
This supplementary table refers to an Excel table with three different sheets that can be downloaded from https://heibox.uni-heidelberg.de/f/bdf29dfdda654e778251/?dl=1 [password: DissertationMüller]. The link is only active for the time of grading of the present dissertation. As soon as the corresponding paper has been accepted by a journal, this table can be found in the supplementary materials on the journal website.

Table S7. Number of falls.

	pre	**pre-post$_0$**	**post$_0$-post$_3$$^+$**	**post$_3$-post$_6$$^+$**
SMT [n (%)]	2 (4%)	5 (11%)	4 (10%)	5 (12%)
RT [n (%)]	6 (11%)	2 (4%)	1 (2%)	1 (2%)
UC [n (%)]	4 (7%)	6 (11%)	3 (6%)	4 (9%)
p-value	.485	.290	.280	.047

Table S7 shows the number of falls according to different time periods within the PIC study. The first time period (pre) refers to the 12 months prior to study inclusion. **Note**: The follow up time-periods marked with a "+" have high numbers of missing values (post$_0$-post$_3$: n=18, post$_3$-post$_6$: n=42), therefore p-values should be interpreted with caution.

Table S8. Information on chemotherapy dose modifications, early termination and concomitant CIPN treatment and prevention measures.

	Total	SMT	RT	UC	*p value*
CHT dose modifications	49 (32%)	12 (26%)	22 (40%)	15 (28%)	.239
- neuropathy	24 (15%)	8 (16%)	9 (15%)	7 (13%)	.917
- hematopoietic disturbances	8 (5%)	2 (4%)	5 (8%)	1 (2%)	
- skin reactions	5 (3%)		2 (3%)	3 (6%)	
- obstipation/diarrhea	5 (3%)		4 (7%)	1 (2%)	
- mucositis	4 (2%)		4 (7%)		
- chemotherapy intolerance symptoms	3 (2%)	1 (2%)		2 (4%)	
- arthralgia/myalgia	2 (1%)		1 (2%)	1 (2%)	
- cardiac signs or symptoms	1 (1%)		1 (2%)		
- thrombopenia	1 (1%)	1 (2%)			
- edema	1 (1%)	1 (2%)			
- liver reactions	1 (1%)			1 (2%)	
- nausea/vomiting	1 (1%)		1 (2%)		
- difficulty swallowing	1 (1%)	1 (2%)			
- psychological strain	1 (1%)		1 (2%)		
- reduced overall condition	1 (1%)		1 (2%)		
- extravasate	1 (1%)		1 (2%)		
- patient's wish	1 (1%)			1 (2%)	
- multiple reasons	3 (2%)	2 (4%)		1 (2%)	
- not known	2 (1%)		1 (2%)	1 (2%)	
CHT early termination	33 (21%)	10 (21%)	11 (20%)	12 (22%)	.960
- neuropathy	9 (6%)	4 (9%)	2 (4%)	3 (6%)	.573
- patient's wish	4 (3%)	1 (2%)	2 (4%)	1 (2%)	
- skin reactions	2 (1%)	1 (2%)	1 (2%)		
- hematopoietic disturbances	1 (1%)			1 (2%)	
- cardiac signs or symptoms	1 (1%)			1 (2%)	
- thrombopenia	1 (1%)			1 (2%)	
- hemoptysis	1 (1%)			1 (2%)	
- liver reactions	1 (1%)			1 (2%)	
- mucositis	1 (1%)		1 (2%)		
- obstipation/diarrhea	1 (1%)		1 (2%)		
- arthralgia/myalgia	1 (1%)			1 (2%)	
- progressive disease	1 (1%)	1 (2%)			
- multiple reasons	5 (3%)	3 (6%)	2 (4%)		
- not known	4 (3%)		2 (4%)	2 (4%)	
Concomitant CIPN treatment / prevention measures					
- CIPN specific medication	16 (10%)	6 (12%)	5 (9%)	5 (9%)	.792
- pain oil	5 (3%)	1 (2%)	2 (4%)	2 (4%)	
- painkillers	2 (1%)	1 (2%)	1 (2%)		
- Vitamin B/D	103 (63%)	32 (65%)	39 (68%)	32 (56%)	.371
- food supplements	27 (17%)	10 (20%)	12 (21%)	5 (9%)	
- ice	66 (40%)	19 (39%)	23 (40%)	24 (42%)	.941
- massages	56 (34%)	15 (31%)	19 (33%)	22 (39%)	.675
- general mobility exercises	14 (9%)	4 (8%)	5 (9%)	5 (9%)	
- (Kneipp) bathing	7 (4%)	2 (4%)	4 (7%)	1 (2%)	
- handworks/handcrafts	7 (4%)	1 (2%)	3 (5%)	3 (5%)	
- acupuncture	4 (2%)	2 (4%)	2 (4%)		
- electrostimulation/TENS	1 (1%)		1 (2%)		
- vibration	1 (1%)		1 (2%)		
- yoga	1 (1%)		1 (2%)		
- others	6 (4%)		6 (11%)		

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I declare that I did not use the submitted dissertation in this or any other form as an examination paper until now and that I did not submit it in another faculty.

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