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Exercise intensity prescription in cancer survivors

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Contents

Abstract

Thanks to the numerous positive effects of exercise [1-5] and its steadily growing importance in exercise oncology, exercise is recommended to all cancer survivors (CS) [3, 6-9]. The existing oncology exercise guidelines are based on the assumption that intensity specifications can be transferred from healthy individuals to CS. However, it was shown that cardio-metabolic parameters used for intensity prescription may be altered in CS due to cancer treatment [10, 11]. So-called second-generation trials are demanded which compare the effects of different training prescriptions aiming at elaborating the optimal exercise prescription for CS [12]. Consequently, before conducting the demanded studies, a fundamental question must first be clarified: "Is my selected dosage actually what it claims to be when I prescribe a certain intensity for a cancer survivor?". This was the leading question of this dissertation; Without its final clarification no progress can be made towards individualized training prescription. A precise intensity prescription is a prerequisite for eliciting the greatest possible training effects without provoking training overload. The TOP study was the first to systematically investigate whether currently used methods of intensity prescription are reliable for its use in CS.

The main questions were (I) whether maximal oxygen uptake (VO_{2max}) as the major parameter used for intensity prescription, is actually attained by CS during a cardiopulmonary exercise test (CPET), (II) whether three different established methods for intensity prescription for endurance exercise are equally suitable for targeting a specific intensity zone, and (III) whether commonly used methods of intensity testing and prescription in resistance exercise are also valid in CS. The TOP study was designed to answer these research questions; The results were discussed in three manuscripts which constitute the main body of this dissertation.

I. Manuscript 1 (chapter 5) targets the question whether CS attain their true VO_{2max} in a CPET. We analyzed data from 75 CS who underwent a supramaximal verification test to confirm the attainment of VO_{2max}. We found that VO_{2max} was not underestimated in the CPET on the group level, yet one third of CS did not attain their true VO_{2max}. We concluded that the verification test appears feasible and beneficial for distinguishing between patients who attained their true VO_{2max} and those who did not.
II. In manuscript 2 (chapter 6) we evaluated whether threshold concepts might be useful submaximal alternatives to $\%VO_{2max}$ in terms of meeting the vigorous intensity zone. We compared physiological and psychological responses of three training sessions defined by

three different prescription methods: blood lactate (bLa) thresholds, ventilatory thresholds, and %VO_{2max} as reference. The data showed that all intensity prescription methods met the targeted intensity zone on average, however the session prescribed via bLa thresholds provoked the most homogeneous bLa responses. Furthermore, not all CS were able to complete the training sessions, we therefore concluded that slightly lower percentages should be chosen to improve durability of the training sessions.

III. Manuscript 3 (chapter 7) focused on whether different maximum strength tests yield comparable results and are therefore applicable interchangeably. Maximal strength values derived from two indirect strength testing methods (h1-RM after Brzycki [13] and Epley [14]) were compared to one direct method of 1-RM determination, all performed at six different resistance machines. The results vary between the different methods with the occurrence of both, over- and underestimation of patients' strength performance. This should be considered when training intensities are to be described based on maximal strength values, and when comparing maximal strength data between studies using different testing procedures. Moreover, we aimed to investigate the prediction accuracy for targeting specific intensity zones in resistance exercise in CS, i.e., whether the achieved number of repetitions (NOR) corresponding to specific values of %1-RM/h1-RM were accurately predicted. We found in part extreme deviations between the targeted NOR and the NOR actually performed. We conclude that the prediction accuracy of all test procedures seems to be very poor for all tested strength training machines for the chosen intensities. The use of %1-RM/h1-RM for intensity prescription is therefore questionable for this population.

Our results demonstrate that currently used methods of exercise testing and prescription seem to have only limited applicability in CS. The overall conclusion for endurance exercise is that threshold concepts seem to be suitable alternatives to %VO_{2max} for intensity prescription, yet bLa thresholds should be favored if a defined metabolic strain is intended as this method evokes the most homogeneous bLa response between individuals. Furthermore, a verification test seems necessary to ensure VO_{2max} attainment, if percentages of VO_{2max} are used for intensity prescription, or if the effect of a training intervention is evaluated based on changes of VO_{2max}. Regarding resistance exercise, commonly used methods for testing are not safe (1-RM) or imprecise (h1-RM) which is also true when %1-RM/h1-RM is used for intensity prescription.

Directly approaching specified intensities might be an alternative method for intensity prescription in resistance training.

A phenomenon that connects all three manuscripts is that the individual data show in part extreme interindividual variations which tell different stories than the group means. Therefore, special attention should be paid to interindividual variability when prescribing exercise for CS. The choice of methods should fit the goals and possibilities of the patients. Subsequently, maximum accuracy is warranted in the context of studies, whereas in practice, more inaccuracies can be accepted, and the methods should be chosen accordingly. Independent of the setting, our results demonstrate that it is important not to blindly trust on calculated exercise intensity specifications but to consider them as orientation. For this, it is important to closely monitor the patients for signs of over- or underload, to ensure maximum safety and adequate training stimulus at the same time.

There will and can never be one method that fits all. People are individuals and training should be prescribed accordingly. The results presented in this dissertation contribute important insights about the accuracy of different exercise testing as well as prescription methods, and further advance the field of personalized exercise oncology. However, they only represent a first step in the still largely unresearched field of exercise prescription in CS and point to a need for further research.

Zusammenfassung

Dank der zahlreichen positiven Effekte von körperlicher Aktivität [1-5] und ihrer stetig wachsenden Bedeutung in der Onkologie, wird allen Krebsüberlebenden (CS) empfohlen körperlich aktiv zu sein [3, 6-9]. Die bestehenden onkologischen Leitlinienempfehlungen zu Sport und Bewegung basieren auf der Annahme, dass Intensitätsvorgaben von gesunden Personen auf CS übertragen werden können. Es wurde jedoch gezeigt, dass kardio-metabolische Parameter, die für die Trainingssteuerung verwendet werden, bei CS aufgrund der Krebstherapie verändert sein können [10, 11]. Es werden so genannte Studien der zweiten Generation gefordert, in denen verschiedene Trainingskonstellationen verglichen werden sollen, mit dem Ziel die optimale Trainingsvorgabe für CS zu finden [12]. Bevor die geforderten Studien durchgeführt werden können, muss jedoch zunächst eine grundlegende Frage geklärt werden: "Ist die von mir gewählte Trainingsintensität tatsächlich das, was sie zu sein vorgibt, wenn ich einem/einer CS eine bestimmte Intensität verschreibe?". Dies war die Leitfrage dieser Dissertation, ohne deren abschließende Klärung keine Fortschritte auf dem Weg zu einer individualisierten Trainingssteuerung gemacht werden können. Eine präzise Trainingssteuerung ist die Voraussetzung dafür, möglichst große Trainingseffekte zu erzielen, ohne dabei die Trainierenden zu überlasten. In der TOP-Studie wurde erstmals systematisch untersucht, ob etablierte Methoden der Intensitätssteuerung auch für die Trainingssteuerung in CS geeignet sind.

Die übergeordneten Forschungsfragen waren, (I) ob die maximale Sauerstoffaufnahme (VO_{2max}) als wichtigster Indikator der körperlichen Leistungsfähigkeit während eines kardiopulmonalen Belastungstests (CPET) tatsächlich von CS erreicht wird (II) ob drei verschiedene etablierte Methoden der Intensitätssteuerung für Ausdauertraining gleichermaßen geeignet sind, um eine bestimmte Intensitätszone anzusteuern, und (III) ob gängige Krafttests und Methoden der Intensitätssteuerung für Krafttraining auch bei CS gültig sind.

Die Ergebnisse der untersuchten Fragestellungen wurden in drei Manuskripten diskutiert, die den Hauptteil dieser Dissertation bilden.

I. Manuskript 1 (Kapitel 5) befasst sich mit der Frage, ob CS ihre echte VO_{2max} in einem CPET erreichen. Wir analysierten Daten von 75 CS, die sich einem supramaximalen Verifikationstest unterzogen, um das Erreichen der VO_{2max} während des CPETs zu beurteilen. Wir fanden heraus, dass die VO_{2max} im CPET im Mittel nicht unterschätzt wurde,

dennoch erreichte ein Drittel der CS nicht ihre echte VO_{2max}. Wir kamen zu dem Schluss, dass der Verifikationstest sicher durchführbar und geeignet zu sein scheint, um zwischen Patient:innen zu unterscheiden, die ihre echte VO_{2max} erreicht haben, und solchen, bei denen dies nicht der Fall war.

II. In Manuskript 2 (Kapitel 6) untersuchten wir, ob Schwellenkonzepte nützliche submaximale Alternativen zu $\%VO_{2max}$ sind hinsichtlich des Erreichens des intensiven Intensitätsbereichs. Wir verglichen die physiologischen und psychologischen Antworten während drei Trainingseinheiten, die mittels verschiedenen Steuerungsmethoden bestimmt wurden: Laktatschwellen, ventilatorische Schwellen und $\%VO_{2max}$ als Referenz. Die Daten zeigten, dass alle Steuerungsmethoden im Mittel den angestrebten Intensitätsbereich erreichten, wobei die mittels Laktatschwellen verschriebene Einheit die homogensten Laktatwerte hervorrief. Darüber hinaus waren nicht alle CS in der Lage, die Trainingseinheiten über die komplette vorgegebene Dauer durchzuführen, weshalb wir zu dem Schluss kamen, dass etwas niedrigere Prozentsätze gewählt werden sollten, um die Durchhaltbarkeit der Trainingseinheiten zu verbessern.

III. Manuskript 3 (Kapitel 7) beschäftigte sich mit der Frage, ob verschiedene Maximalkrafttests vergleichbare Ergebnisse liefern und somit austauschbar sind. Maximalwerte, die aus zwei indirekten Krafttestmethoden (h1-RM nach Brzycki [13] und Epley [14]) abgeleitet wurden, wurden mit einer direkten Methode der Maximalkrafttestung (1-RM) verglichen, die alle an sechs verschiedenen Kraftgeräten durchgeführt wurden. Die Ergebnisse variierten zwischen den verschiedenen Methoden, wobei es sowohl zu einer Über- als auch zu einer Unterschätzung der Maximalkraft der Patient:innen kam. Dies sollte bei der Verschreibung von Trainingsintensitäten, die auf Maximalkraftwerten basieren, sowie beim Vergleich von Maximalkraftdaten zwischen Studien mit unterschiedlichen Testverfahren berücksichtigt werden. Darüber hinaus wollten wir die Vorhersagegenauigkeit für das Ansteuern spezifischer Intensitätszonen beim Krafttraining in CS untersuchen, d. h. ob die erreichte Anzahl an Wiederholungen (NOR), die bestimmten Werten von %1-RM/h1-RM entspricht, genau vorhergesagt werden kann. Wir fanden zum Teil extreme Abweichungen zwischen der angestrebten NOR und der tatsächlich durchgeführten NOR. Wir schlossen daraus, dass die Vorhersagegenauigkeit aller Testverfahren für alle getesteten Krafttrainingsgeräte bei den gewählten Intensitäten ungenügend zu sein scheint. Die Verwendung von %1-RM/h1-RM zur Intensitätsvorgabe ist daher für diese Population fragwürdig.

Unsere Ergebnisse zeigen, dass die gegenwärtig verwendeten Methoden der Trainingsdiagnostik und -steuerung bei CS nur begrenzt anwendbar zu sein scheinen. Allgemein lässt sich für Ausdauertraining schlussfolgern, dass Schwellenkonzepte eine geeignete Alternative zu %VO_{2max} für die Intensitätssteuerung sind. Jedoch sollten Laktatschwellen bevorzugt werden, wenn eine definierte metabolische Belastung angestrebt wird, da diese Methode die homogensten Laktatantworten zwischen Individuen hervorruft. Darüber hinaus scheint ein Verifikationstest erforderlich, um das Erreichen der VO_{2max} sicherzustellen, wenn einerseits Prozentsätze der VO_{2max} für die Intensitätssteuerung verwendet werden und andererseits, wenn der Erfolg einer Trainingsintervention auf Grundlage von Veränderungen der VO_{2max} bewertet wird. Für das Krafttraining sind die üblicherweise verwendeten Testmethoden nicht sicher (1-RM) oder ungenau (h1-RM), was auch gilt, wenn %1-RM/h1-RM für die Intensitätsvorgabe verwendet wird.

Ein Phänomen, das alle drei Manuskripte verbindet, ist, dass die individuellen Daten zum Teil extreme interindividuelle Schwankungen aufweisen, die in eine andere Richtung weisen als die Gruppenmittelwerte. Daher sollte der interindividuellen Variabilität besondere Aufmerksamkeit gewidmet werden, wenn Training für CS verschrieben wird. Die Wahl der Methoden sollte zu den Zielen und Möglichkeiten der Patient:innen passen. Im Rahmen von Studien sollte eine maximale Genauigkeit gewährleistet werden, während in der Praxis mehr Ungenauigkeiten akzeptiert werden können und die Methoden sollten entsprechend ausgewählt werden. Unabhängig vom Setting zeigen unsere Ergebnisse, dass es wichtig ist, sich nicht blind auf berechnete Intensitätsvorgaben zu verlassen, sondern diese als Orientierung zu betrachten. Dabei ist es wichtig, Patient:innen engmaschig zu supervidieren und auf Anzeichen von Über- oder Unterforderung zu achten, um bei maximaler Sicherheit einen angemessenen Trainingsreiz zu gewährleisten.

Es wird und kann niemals die eine Methode geben, die für alle passt. Menschen sind Individuen und das Training sollte entsprechend gestaltet werden. Die in dieser Dissertation vorgestellten Ergebnisse liefern wichtige Erkenntnisse über die Genauigkeit verschiedener Belastungstests und Methoden der Intensitätssteuerung und bringen den Bereich der personalisierten Trainingsonkologie weiter voran. Sie stellen jedoch nur einen ersten Schritt in dem noch weitgehend unerforschten Gebiet der Trainingssteuerung in der Onkologie dar und verdeutlichen den Bedarf an weiterer Forschung.

List of scientific manuscripts included in the publication-based dissertation

I. **Schneider, J**., Schlüter, K., Wiskemann, J., and Rosenberger, F. (2019). *Do we underestimate VO2max in cancer survivors? Findings from a supramaximal verification test.* Applied Physiology, Nutrition, and Metabolism. doi: 10.1139/apnm-2019-0560

II. **Schneider, J**., Schlüter, K., Sprave, T., Wiskemann, J., and Rosenberger, F. (2020). *Exercise intensity prescription in cancer survivors: ventilatory and lactate thresholds are useful submaximal alternatives to VO2peak.* Supportive Care in Cancer. doi:10.1007/s00520-020-05407-y

III. **Schneider, J.**, Schlüter, K., Rosenberger, F., and Wiskemann, J. *Are percentages of the one-repetition maximum suitable for prescribing resistance exercise in cancer survivors? - Comparability and prediction accuracy of frequently used 1-RM procedures.* (Manuscript submitted for publication in Supportive Care in Cancer on 14th October 2022).

List of abbreviations

ACSM	American College of Sports Medicine
APMHR	Age-predicted maximal heart rate
CPET	Cardiopulmonary exercise test
CRF	Cardiorespiratory fitness
CS	Cancer survivor
bLa	Blood lactate
Bf_{max}	Maximal breathing frequency
H1-RM	Hypothetical one-repetition maximum
Hr_{max}	Maximal heartrate
HRR	Heart rate reserve
IAT	Individual anaerobic threshold
LT1	Aerobic blood lactate threshold
MLSS	Maximal lactate steady state
PPO	Peak power output
RER	Respiratory exchange ratio
RPE	Ratings of perceived exertion
SAE	Serious adverse event
Verif	Verification test
VO_{2max}	Maximal oxygen uptake
VO_{2peak}	Peak oxygen heart rate
VT	Ventilatory threshold
1-RM	One-repetition maximum

1. General introduction

Cancer is globally the second leading cause of death and the incidence of cancer diagnoses have continuously been increasing over the past decades [15, 16]. Yet, in more developed countries (e.g., in Europe, North America, and high-income countries in Asia and Oceania) survival rates have been increasing due to advancements in cancer treatment and management, as well as (improved) screening programs and consequent earlier detection of the disease [15]. In Germany, in 2016, breast cancer and prostate cancer, the most common cancer types in women and men, showed 5-year survival rates of 88% and 92%, respectively [17]. The increasing survival rates cause a steadily growing number of people affected by short and/or long-term side effects of cancer treatment. The treatment process can cause impairments of psychological health including fatigue, depression, anxiety, and reduction of self-esteem and quality of life [18-21]. Side effects impairing physiological health include muscle atrophy and subsequent loss of strength, cardiovascular toxicity as well as reduced cardiorespiratory fitness (CRF) [19, 22-24].

Exercise appears promising in counteracting the above-mentioned treatment-related side effects and in improving prognosis [1-5, 25]. Exercise-related beneficial effects include an increase in CRF, improvement in bone-health, reduction in depression, anxiety and fatigue, and thereby improvements in quality of life [5, 25, 26]. These exercise-related beneficial effects have led to endurance and resistance exercise being recommended to cancer survivors (CS) by various expert panels [7-9]. In this dissertation, the most commonly used definition is used defining a CS as a person who is living beyond a cancer diagnosis [27].

Early intensity prescription recommendations for CS were mostly general and vague [1]. Meanwhile more precise recommendations exist which deliver symptom specific exercise prescription [9]. These recommendations assume that methods for exercise prescription can be transferred from healthy individuals to CS, yet cardio-metabolic parameters commonly used for intensity prescription can be altered in CS due to cancer treatment [10, 11]. For instance, resting sinus tachycardia occurred in 50% of breast CS 20 months after chemotherapy (anthracycline-taxane-based) and/or immunotherapy (Trastuzumab) [28]. This has to be considered when using methods that include resting heart rate (HR_{rest}), e.g., heart rate reserve (HRR; i.e., maximal - resting heart rate (Hr_{max}- Hr_{rest})), as percentages of HRR may need to be adjusted for intensity prescription in CS. Precise intensity prescription is a prerequisite for eliciting the greatest possible training effects without provoking overload of CS.

In clinical oncology, tailored treatment strategies are becoming the new paradigm. This change of paradigm should also be pursued in the field of exercise oncology in which a "one size fits all" approach is still widely used. In the context of “exercise as medication” [29], understanding how to individualize intensity prescription adequately in this patient group is important. More specific exercise guidelines for CS are needed and therewith so-called second-generation trials, which elaborate the optimal exercise prescription, one of the top ten research questions in the field [12]. In that way, exercise may become a personalized therapeutic strategy and thus a complemental part of personalized oncology.

1.1. Exercise Intensity prescription

Exercise is defined as physical activity, performed in a systematic, planned, and repetitive manner, with the intermediate or final objective to improve or maintain physical performance (e.g., muscular strength or endurance) [30]. The underlying principle is that exercise represents an external stimulus on the body, which triggers disturbances of homeostasis (e.g., alterations of energy demand and supply, of metabolite accumulation, of muscle fiber recruitment, etc.), and thereby an individual metabolic reaction (i.e., strain) to this stimulus. Over time, these homeostatic perturbations lead to adaptive responses, which can be functional (e.g., improving muscle-nerve communication) or structural (e.g., triggering muscle hypertrophy) [31]. This interplay between homeostatic imbalance and adaptation plays a decisive role for the improvement of the functional state of the human body and thus for training effects [32].

Exercise is characterized by different components: frequency (e.g., 3 sessions per week), intensity (e.g., 70% Hr_{max}), time (e.g., 45 minutes per session) and type of exercise (e.g., cross trainer), hereafter called FITT criteria. Different constellations of the FITT criteria cause different exercise strain and subsequently different training effects [33]. Hence, the choice of the FITT criteria should depend on the goal, but also on the preferences and initial fitness of an individual [34]. Exercise intensity is the key component in determining physiological and metabolic adaptations to an exercise stimulus [35, 36]. The intensity of a training stimulus needs to reach a certain minimum threshold in order to elicit improvements of physical capacity (overload principle), however without overstraining the body [32]. The chosen exercise intensity therefore determines whether, which and how efficiently training effects are achieved. Intensity could be described as the response of a person’s physiological system to an exercise strain. As we are all individuals, each person responds differently to a given training load. Let's say two people run

at the same speed during a training session: Depending on their training condition, the intensity experienced can vary greatly. While one can easily continue for 40 minutes, the other one reaches his/her limits after 10 minutes. Therefore, the chosen speed would correspond to a moderate intensity (e.g., 65% Hr_{max}) for the first person, while corresponding to a vigorous intensity (e.g., 90% Hr_{max}) for the latter. Hence, intensity is always seen in relation to the individual performance of a person.

The challenge of intensity prescription is to provoke a specific exercise strain independently of the physical ability of a person, or in other words, placing individuals with heterogenous physical abilities at approximately equivalent metabolic conditions above resting levels. To stay with our example above, a speed that corresponds to a moderate intensity (e.g., 65% Hr_{max}) for both runners, e.g., the first one runs with a speed of 5 min/km, the second one with 7 min/km. Hence why exercise intensity is commonly expressed as certain percentage of a person's maximum physiologic capacity, such as percentages of maximal oxygen uptake (VO_{2max}), or of Hr_{max} [37]. However, these methods are criticized, as they may elicit interindividual metabolic variations at the same relative intensities [38]. Therefore, it cannot necessarily be assumed that a specific percentage of a maximum value causes the same metabolic strain in different individuals. This is particularly true for groups of people with heterogeneous fitness levels, which is particularly pronounced among CS, as they present a wide range of age, fitness levels, comorbidities, and cancer treatment-related side effects [11, 22, 23, 39-41]. This in addition to the fact that exercise intensity presents a positive dose-response relationship to health benefits, including CRF [39, 42, 43], cancer recurrence and cancer-specific [44] and all-cause mortality [45], underlines the difficulty of personalized exercise prescription in this group of patients, but at the same time highlights its relevance.

1.2. Intensity prescription in endurance exercise

For endurance exercise, a great variety of intensity prescription methods exists, ranging from simple methods based on subjective ratings of perceived exertion (RPE) [46] and broadly applied methods such as percentages of VO_{2max}, or Hr_{max} [43, 47], to highly precise methods such as blood lactate (bLa) thresholds and ventilatory thresholds (VT) [48-50].

RPE are primarily used in recreational sports with healthy individuals and patient populations, due to their easy application and inexpensiveness. In practice, a 6-20 scale or an adapted 1-10 scale is used to evaluate the subjective effort [46]. The different number ranges are grouped

into specific intensity zones which can be used for intensity prescription (e.g., vigorous intensity zone ("somewhat hard to very hard") corresponds to Borg 14-17 according to the ACSM guidelines for apparently healthy adults [43]). However, due to its subjective character, the Borg scale is considered the least accurate method of intensity prescription, which has also be shown in CS [51].

Fixed percentages of maximal attainable values like Hr_{max} or VO_{2max} are frequently used for intensity prescription in healthy individuals and in studies with CS [43, 47, 52]. These methods require a maximal exercise test to exhaustion, and in the case of VO_{2max} determination, with respiratory gas analysis i.e., cardiopulmonary exercise test (CPET, see 1.3 below). Even though this test procedure is quite laborious and requires experienced personnel, it allows the derivation of parameters that can be used for training prescription, in addition to a wide range of clinical parameters. Relative percent concepts offer greater accuracy than RPE but can nonetheless "[…] be criticized for assuming that a fixed percentage of a reference value represents the same intensity in all individuals" [53]. Furthermore, if maximal effort during CPET is not achieved, relative percent methods may not provoke the intended metabolic strain when used for intensity prescription.

Individual threshold concepts [49, 50] represent the most laborious intensity prescription methods, but are also considered the most precise ones [35, 38]. The rationale behind this assumption is that these concepts are anchored to the individual metabolic profile of a person. In other words, they are based on parameters which mirror a specific metabolic state of the body. The principle of threshold determination is that during a graded exercise test, the energy metabolism constantly adapts to the demanded effort. The course of the relationship between the performed workload and the provoked metabolic response allows to draw conclusions about the individual performance status of a person. At low intensities, energy is generated primarily via the aerobic system, though low concentrations of lactate (the by-product of anaerobic metabolism) are always present in the blood. BLa production and elimination are balanced and bLa concentration is therefore relatively stable. When the intensity is further increased, there is a point at which bLa concentration surpasses resting bLa concentration for the first time, reflecting the aerobic bLa threshold (LT1). During the formation of lactate, H^+ ions are produced, which are chemically buffered to H_2O and CO_2. The excess nonmetabolic CO_2 from lactate buffering (and to a smaller extent H^+-ions themselves) stimulates the respiratory

center of the central nervous system (via chemoreceptors), causing an immediate increase in alveolar ventilation [37]. Consequently, the increase of bLa during LT1 is mirrored by a disproportionate rise of CO_2-elimination in relation to O_2-consumption (i.e., higher VCO_2/VO_2 ratio), which is also defined as VT1 [54]. Thus, the metabolic condition of LT1 is the reason for the ventilatory condition measured during VT1. Beyond this point, energy is generated by aerobic and anaerobic metabolism, causing bLa concentration to further increase. The highest constant workload at which bLa production and elimination are still equilibrated is defined as the maximal lactate steady state (MLSS) [54]. The MLSS represents an exercise intensity an individual is capable to sustain for a prolonged period of time [37] and is also referred to as the individual anaerobic lactate threshold (IAT) [48, 55, 56]. At exercise intensities beyond the IAT the contribution of anaerobic metabolism increases considerably, causing bLa production to surpass bLa elimination, and therefore an excessive increase in bLa concentration. This bLa accumulation causes a metabolic acidosis (drop in pH due to high concentrations of H^+ ions), provoking hyperventilation disproportionate to the CO_2-elimination, defined as VT2. Exercising at intensities beyond IAT and VT2 can only be sustained for a limited amount of time. Increases of CRF is reflected by a rightward shift of an individual's bLa curve (i.e., lactate thresholds reached at higher absolute workloads) [57]; for a detailed review on lactate threshold concepts see Faude et al. [58].

From a practical point of view, the major advantage of threshold concepts is that maximal effort during CPET is not required. This renders threshold concepts valuable submaximal alternatives to relative percent concepts, which is particularly useful in sedentary patient populations, given the challenge of VO_{2max} attainment during CPET (see 1.3 below). Ventilatory thresholds have the additional advantage that they do not require blood sampling and still accurately reflect the metabolic state during the CPET.

Threshold concepts have a long tradition in high performance and recreational sports due to their ability to maximize physical performance [35, 58, 59], but their determination requires certain experience. For instance, taking blood samples for bLa threshold determination requires accurate handling. Nowadays various lactate threshold concepts are used, so it is difficult to speak of "the" bLa threshold. In the TOP study, we used Dickhut's concept, which defines IAT at 1 $mmol \cdot l^{-1}$ above minimum bLa equivalent [60]. All known bLa threshold concepts determine intensities that depend on the load increment of the CPET protocol [61]. Stepwise incremental

protocols with 3-minute stages are commonly used to determine bLa thresholds, which can be challenging for individuals with limited physical fitness since at least five stages are needed for reliable bLa threshold determination [58]. To better adapt to the physical performance of patient populations, a ramp protocol with 1-min steps is recommended by a Germany-wide expert panel [52]. This protocol was already used by some scientists (personal communication Kai Röcker), but has never been validated in CS. Of note, the bLa thresholds determined in the TOP study were not confirmed via multiple continuous exercise tests, which is why they could have turned out somewhat differently with other CPET protocols. They should therefore be described more cautiously as a reference point on the bLa performance curve that is useful for the assessment of endurance performance [61]. However, for reasons of simplicity the term IAT is nevertheless used in this dissertation.

In clinical oncology, tailored treatment strategies are becoming the new paradigm. Such a shift in paradigms should also be pursued in the field of exercise oncology as the "one size fits all" approach is still widely used. In the context of “exercise as medication” [29], it is important to understand how to individualize intensity prescription adequately in this patient group. More specific exercise guidelines for CS are needed as well as so-called second-generation trials which compare the effects of different training prescriptions aiming at elaborating the optimal exercise prescription; one of the top ten research questions in the field [12]. However, a fundamental prerequisite for comparing the effects of different intensity prescription methods is that it has to be known whether they can be employed to target specific intensity zones in CS, which was the central question to be answered by the TOP study. Another prerequisite for comparing the efficiency of different training prescriptions regarding CRF improvements, is a valid determination of CRF, further elaborated in the following chapter.

1.3. Determination of maximal oxygen uptake and its importance in exercise oncology

VO_{2max} is the product of the maximal cardiac output $\dot{Q}$ (L^{-1} blood·min^{-1}) and arterial-venous oxygen difference (ml^{-1} O_2·L^{-1} blood), therefore reflecting the functional capacity and integration of all physiological systems required for oxygen supply, transport, and use [37]. VO_{2max} therefore represents the criterion measure for CRF [34]. In a clinical setting, VO_{2max} is a well-established predictor of cardiovascular disease and mortality in the general population [62, 63] and in CS [11]. In exercise sciences, VO_{2max} is mostly used for assessing CRF and as monitoring tool for

changes of aerobic capacity and therefore for the assessment of training effectiveness. Yet, how to accurately determine VO_{2max} is a question nearly as old as the concept itself.

The gold standard for the determination of VO_{2max} in healthy individuals and those with restricted health (primarily in research and clinical settings) is a CPET [42, 64, 65]. The principle of a CPET is a systematic increase in work rate up to the tolerance limit of an individual [65]. CPETs are usually carried out on a treadmill or cycle ergometer with either continuous or stepwise work rate increments, referred to as ramp or stepwise protocols. CPETs are considered a safe and noninvasive method to measure CRF in CS [66] and are regarded as valuable for prescribing exercise and monitoring health changes in CS [1]. Reaching maximal physiological effort during CPET is a mandatory requirement for accurate VO_{2max} determination. Therefore, the validity and reliability of this testing procedure depends on reaching maximal exertion [67].

Individuals with restricted physical health, including CS, are not always capable or willing to spend maximal effort during a CPET [68]. Possible barriers to test completion can be a lack of motivation or of exercise literacy, anxiety to exert oneself to exhaustion, equipment discomfort (e.g., breathing mask), premature (muscular) exhaustion, or clinical symptoms [42, 68-71]. This might be particularly true for untrained, elderly, or clinical populations who are not used to the unpleasant sensations typically associated with strenuous physical exertion. Consequently, in breast and prostate cancer patients, VO_{2max} is particularly prone to be underestimated, as they tend to be older and less fit [11], and are commonly affected by side effects of cancer treatment [22, 23, 41].

Furthermore, the testing personnel might be reluctant to push the patient to the limits which could cause the highest reached VO_2 values to be submaximal with respect to maximal exhaustion. In clinical cohorts, the term "peak oxygen consumption" (VO_{2peak}) is therefore commonly used instead of VO_{2max}. Consequently, VO_{2peak} only represents an estimate of VO_{2max}. The terms VO_{2max} and VO_{2peak} should not be used interchangeably, as they do not represent identical conditions [71]. In this dissertation, the terms "VO_{2max}" and "true VO_{2max}" are used for reasons of clarity.

In CS, VO_{2max} is not only used as prescription and monitoring tool for exercise interventions, but also as clinical/diagnostic parameter [11, 72]. Previous studies report low VO_{2max} in CS which is often explained as a cancer therapy-related side effect [4, 40, 66]. For instance, according to a review by Peel et al. [40], VO_{2max} of breast CS after completion of adjuvant therapy was 25%

lower (22,2 $ml^{-1} \cdot min^{-1} \cdot kg^{-1}$ body weight) than VO_{2max} of age-matched healthy, sedentary women (29,7 $ml^{-1} \cdot min^{-1} \cdot kg^{-1}$ body weight). This phenomenon remains even years after termination of cancer treatment [73]. This difference is important, since small reductions in VO_{2max} are associated with a considerably increased risk of death from cardiovascular disease (≈ 18% per 1 MET (= 3,5 ml^{-1} O_2 $\cdot min^{-1} \cdot kg^{-1}$ body weight)) [63]. Possible causes for this cancer treatment-related reduction of CRF are manifold, involving multiple organ components of oxygen transport and consumption (i.e., pulmonary, vascular, cardiac and skeletal muscle function) [40], further elaborated in e.g., Lakoski et al. [10]. The best studied cause is a limitation in cardiac function in breast CS due to the cardiotoxicity of some chemotherapeutic agents (primarily anthracycline-containing regimens) as well as thoracic irradiation leading to long term cardiac abnormalities, including cardiac insufficiency [10]. With regard to prostate cancer, a considerable proportion of patients is treated with androgen deprivation therapy, which negatively impacts body composition (increase in fat mass, reduction of lean mass) and cardiometabolic variables (dyslipidemia, increase in glucose resistance) [19]. These changes in body composition and cardiometabolic variables are in turn associated with impaired CRF and an increased risk of cardiovascular mortality [74]. Common side effect of radiotherapy, chemotherapy and/or the tumor itself is cancer-related fatigue, which negatively impacts the activity level and therewith CRF [57]. Furthermore, most CS do not meet the international recommendations for physical activity already before their cancer diagnosis and tend to experience further declines in physical activity levels afterwards [39, 75]. The decline in physical activity levels during cancer treatment is further associated with the aggravation of fatigue, sustaining the fatigue cycle [57].

Consequently, against the backdrop of the methodological challenges mentioned above, low VO_{2max} values seen in CS may not only be a consequence of cancer treatment and/or reduction in physical activity following cancer diagnosis but could also be a consequence of failed maximal exhaustion during CPET in this patient collective. These problems emphasize the importance of objective criteria for verifying VO_{2max} attainment in such a heterogenous patient collective.

1.4. Evaluation of maximal oxygen uptake

Oxygen uptake plateau

The most widely recognized objective criterium for VO_{2max} verification is the occurrence of a VO_2 plateau, originally described by Taylor and coworkers [76]. A VO_2 plateau is supposed to occur

at the limits of tolerance, when VO_2 does not further increase despite increasing work rate, reflecting the upper limits of cardiovascular capacity. However, the VO_2 plateau concept has been criticized since it does not always occur simultaneously with maximal exhaustion [77, 78] and seems to depend on the CPET protocol [65]. Beltrami et al. [79] found that a VO_2 plateau occurred during sub-maximal exercise in healthy competitive soccer players. In individuals with low physical fitness including patients, the majority of studies do not report the quantity of VO_2 plateaus. Furthermore, it is generally believed that a VO_2 plateau occurs even less frequently in patient populations than in athletes [68]. For instance, a retrospective analysis of 78 CPETs from CS revealed that none of the participants reached a VO_2 plateau [69]. Low sensitivity (23%) and specificity (60%) of the VO_2 plateau criterion was also shown in a study with 100 unfit individuals suffering from obesity [80].

Secondary criteria for maximal exhaustion

As an alternative or supplement to the VO_2 plateau, there exist secondary criteria for maximal exhaustion, which are supposed to facilitate the evaluation of whether an individual has attained true VO_{2max}. These criteria include bLa concentration, respiratory exchange ratio (RER), age-predicted maximal heart rate (APMHR) and RPE. Yet, there is a lack of standardization regarding (i) the choice of criteria, (ii) the minimal quantity of criteria for confirming VO_{2max} attainment, and (iii) the specification of cut–off values for determination of VO_{2max} attainment [81]. Furthermore, these criteria are generally known to show poor sensitivity and specificity in healthy individuals [79, 82], irrespective of the fitness level [78]. Already in the 1980s, Niemelä and colleagues concluded that the VO_2 plateau concept seems useful for VO_{2max} affirmation, whereas the "value of other criteria and arbitrary endpoints is rather disappointing, especially if older and untrained subjects are concerned" [83]. Decades later, much of the literature on the use of secondary criteria for VO_{2max} attainment came to the same conclusion: As the use of these criteria had led to a considerable misjudgment of VO_{2max}, the authors advised against their employment for VO_{2max} assessment [68, 81, 82, 84]. Alternatively the use of higher cutoff values is recommended to avoid the erroneous assumption that subjects have attained VO_{2max} although they have not (i.e., type I error) [85]. Some authors propose alternative suggestions that classify recommendations for bLa and RER according to age and sex of the participants [67] or to the CPET protocol [70], but this has yet to be evaluated in CS.

It is generally questionable whether secondary criteria can be unconditionally applied in CS due to altered physiological responses [10, 11]. Secondary criteria have rarely been used and/or reported in previous studies with CS and their applicability in this patient collective has never been validated. One previous study investigated the accordance between the fulfillment of secondary criteria with the test leader's evaluation about the degree of exhaustion in patients newly diagnosed with cancer [70]. However, since this was a subjective evaluation of the test leader, no statement can be made about the reliability of the secondary criteria for determining true VO_{2max}.

Verification tests

One promising alternative for VO_{2max} affirmation are supramaximal verification tests (Verif) [86]. The principle of verification tests is that following a CPET, a second test with supramaximal constant load is performed, whereby supramaximal describes the workload, which is somewhat higher than the one reached during the preceding CPET. Most commonly, verification tests were carried out at 105% or 110% peak power output (PPO) on the same day, 5 to 60 minutes after the CPET [87-90]. VO_{2max} is confirmed when the verification test and the CPET yield consistent VO_{2max} values [91]. Verification tests are based on the initial assumption of the VO_2 plateau criterium that despite higher workload, VO_2 does not further increase [76].

The use of a verification test was first reported 40 years ago by Niemelä et al. [83], but this procedure was not able to assert itself into practice. However, for individuals with particular health restraints, the value of verification tests to accurately assess $\dot{V}O_{2max}$ has been increasing [80]. They have been safely implemented in healthy adults of different age, sex and activity levels [78, 86, 89, 90, 92-94], in obese adults with metabolic syndrome [80], and in children and adults with cystic fibrosis [84, 88], which suggests its well-tolerated applicability in a wide range of individuals. To the best of my knowledge, the TOP study was the first to investigate the feasibility and utility of verification tests in CS.

1.5. Intensity prescription in resistance exercise

Strength is composed of different components/qualities, such as maximum strength, strength endurance and several intermediate types. Resistance training prescription depends on which of these different types of strength will be (mainly) trained. For instance, to improve maximum strength, the training would consist of few repetitions (1-5) with near-maximal weights, whereas

improvement in strength endurance would require the opposite – a high quantity of repetitions (15-20) with relatively low weights.

The most widely used method for prescribing resistance exercise is by indicating intensity as percentage of the one-repetition maximum (1-RM). 1-RM refers to the maximal weight that a person is able to lift once with proper technique (see 1.6 below). In addition to the weight, the number of repetitions (NOR) that should be achieved with a specified weight is usually indicated when prescribing resistance exercise. For instance, according to Brzycki [13], exercising with a weight, corresponding to an intensity of 69% 1-RM, no more than 12 repetitions are possible. For the estimation of the relationship between %1-RM and the NOR, a variety of mathematical models exists (see 1.6 below), none of which are well supported by experimental data [95]. Studies with healthy individuals show that the NOR performed at selected percentages of 1-RM may vary considerably depending on e.g., muscle group [96, 97], training background [98] and gender [99]. Thus, it cannot be assumed that a given %1-RM is associated with the same/similar NOR in different individuals.

Resistance exercise is nowadays used in a wide range of oncology settings (i.e., different cancer entities, treatment types and timepoints during treatment) [100-104] and its benefits in cancer care are increasingly recognized [105]. Nevertheless, knowledge on the underlying principles behind intensity prescription of resistance exercise in CS is still poorly developed. For instance, no study has hitherto evaluated the accuracy between prescribed intensity (i.e., % 1-RM) and expected outcome (i.e., corresponding NOR). Hence, to stay with the above example, the question "do 69% of the 1-RM really correspond to (maximum possible) 12 repetitions and thus to my intended training stimulus?" cannot be answered for resistance training with CS, despite the fact that this is a fundamental question or even a prerequisite for accurate resistance training prescription. To prescribe exercise intensity based on %1-RM and its associated NOR, it seems obvious that the corresponding NOR that can be performed by CS at different %1-RM must first be established.

1.6. Determination of maximal muscle strength

Maximum strength can be divided into static and dynamic maximum strength. Static maximum strength describes the maximal capacity of the nerve-muscle-system during a volitional contraction against an insurmountable resistance, whereas dynamic maximum strength refers to the maximal strength that can be developed within a movement sequence [106]. Therefore,

maximum strength can be measured statically or dynamically. In a static or so-called isometric measurement, a muscle or muscle group is contracted against an insurmountable counterweight. In this type of testing, the maximum force delivered is usually referred to as maximum voluntary contraction (MVC, specified in Newton) [107]. The more commonly used method is the determination of dynamic strength expressed as the 1-RM (specified in kilograms or pounds) [106]. The principle of the test consists of a gradual increase of weight (after an initial warm-up) until the tested person is not able to lift the next higher weight. The 1-RM should be determined using as few attempts as possible (four attempts according to the ACSM [42]) in order to avoid muscular fatigue. According to the most recent international multidisciplinary roundtable's exercise guidelines for CS [9] the 1-RM test is considered as safe for assessing maximal strength in these patients. Even though adverse events resulting from this testing procedure have been reported [108, 109], 1-RM testing is a standard procedure for assessing maximal dynamic strength in intervention studies with CS [102, 110-114].

A variation of the 1-RM test is the determination of a hypothetical 1-RM (h1-RM), meaning that the person being tested performs repetitions to fatigue with a selected weight that this person is likely to lift between 5 and 12 times. The h1-RM is then calculated by means of different equations. This method offers a submaximal and therefore less strenuous alternative to the 1-RM test, which makes it particularly attractive for testing individuals with low resistance training experience, or restricted physical fitness. Yet, despite the popularity of these h1-RM prediction formulas, the underlying research that led to their derivation is largely unclear and unpublished [95, 115]. Another submaximal testing procedure is the x-RM test. The x-RM stands for the weight, that cannot be moved more or less than a certain number of times, for instance 10 and is then referred to as the 10-RM.

The mentioned measurements have in common that their results (MVC, 1-RM, h1-RM) are highly dependent on the used muscle group and test arrangement, i.e., seat position and force lever. Therefore, to ensure an accurate use of the test results for the training situation, it is crucial to use the same settings (e.g., joint angle) that were used during the test [107]. Consequently, the use of the mentioned methods for describing overall strength is limited and comparisons of the values between different tests require a strict standardization [107]. Therefore, it must be questioned whether comparing results from different 1-RM procedures of different studies in reviews or meta-analyses is informative.

2. Research gaps

VO_{2max} verification in cancer survivors

VO_{2max} plays an essential role as a parameter for intensity prescription, as well as in the assessment of a person's CRF and of the success of a training intervention. It is widely known that a reliable determination of VO_{2max} is challenging, especially in patients. Failed VO_{2max} attainment may considerably affect its informative value. Whether CS attain their true VO_{2max} is rarely verified and/or reported in the current literature, which could be related to the poor accuracy of criteria for its assessment. The verification test represents a promising alternative, but its feasibility and potential superiority compared to commonly used methods has not yet been investigated in CS.

Intensity prescription in cancer survivors

The positive effects of endurance and resistance exercise have led to their inclusion in all available exercise guidelines for CS. Even though these guidelines have become more accurate in recent years, they are based on guidelines for healthy individuals and thus on the assumption that the physiological responses to exercise do not differ between CS and healthy individuals. Guidelines, derived from cancer studies, are based on self-reported outcomes of the patients (e.g., physical function), which limits their validity [9]. It can therefore not be taken as granted that the specifications given for different intensity zones in the guidelines will actually result in the intended intensity zones in CS. It is not evident how these intensity zones can be adequately targeted in CS, since physiological parameters commonly used for intensity prescription can be altered as a result of cancer treatment [39]. Results of seldom studies dealing with this topic so far point in the direction that different intensity prescription methods can only be conditionally transferred from healthy individuals to CS. For instance, exercise stimuli prescribed based on $\%VO_{2max}$ turned out slightly lower than intended, as shown by a comparison of the ACSM recommendations for healthy individuals and CPET data from breast CS [116]. Consequently, the transfer of intensity specifications from healthy individuals to CS has first to be validated.

When it comes to resistance exercise, the difficulties regarding the accuracy of intensity prescription are even more pronounced than for endurance exercise. Training intensities for resistance exercise in healthy individuals and CS are commonly specified by means of %1-RM in combination with the corresponding NOR. This relationship (%1-RM and NOR) was adopted from guidelines for healthy individuals and has never been validated for CS. Already in healthy

individuals, the relationship between a certain %1-RM and its corresponding NOR show large variations depending on the muscle group [117], gender and training background [96, 97, 117, 118]. Due to the high heterogeneity of training background, age, and comorbidities of CS [11, 22, 23, 39-41] it can be expected that the accuracy is at least as poor as found in healthy individuals.

3. The TOP Study – data source

The TOP Study (German acronym for "Individuelle Trainingssteuerung bei onkologischen Patient:innen") had the overall aim of optimizing the positive training effects in breast and prostate cancer survivors through individualized training prescription. The study consisted of two parts: In TOP study part 1 the overall focus was on the methodology of intensity prescription and on testing maximal endurance and resistance capacity in CS, simply put on "acute effects". This study part followed a cross-sectional design. Each patient underwent the same endurance part consisting of one CPET with subsequent verification test, three vigorous continuous and two high intensity interval training (HIIT) sessions in randomized order. Cardiocirculatory (heart rate, HR), metabolic (bLa), and subjective (RPE) responses were assessed regarding their accuracy in targeting the vigorous intensity zone. The results of the continuous training sessions are discussed in manuscript 2. The HIIT sessions are not part of this dissertation, but the results can be found in Schluter et al. [119].

In addition to the endurance training part, each patient enrolled in TOP study part 1 performed a resistance training part consisting of two strength tests (1-RM and h1-RM), two familiarization sessions, and three exercise sessions with different intensities. The strength training part had two major objectives: Firstly, comparing the 1-RM to two different h1-RM methods regarding their accuracy for determining maximum strength, and secondly, to investigate how reliably specific intensity zones can be targeted when training weights are prescribed as percentages of maximum weights determined using the three methods mentioned above. The Results are discussed in manuscript 3.

The most suitable methods of the endurance and resistance training from part of study part 1 were applied in the second part of the TOP study, a four-arm randomized controlled training intervention trial, in which we compared different training regimes during a 12-week training period, regarding their efficacy for improving endurance and strength performance, thus focusing on "chronic effects".

In both parts of the study each patient performed a CPET and a verification test once (part 1) or at each measurement timepoint during the intervention (part 2). The CPET/verification data presented in manuscript 1 is composed of study part 1 (n=33) and of baseline data from study part 2 (n= 42). Apart from the CPET/verification data, part 2 of the study is not subject of this dissertation therefore, no further description is given. Some results of part 2 of the study can be

found in Schluter et al. [120] and Rosenberger et al. [108]. A more detailed description of the methodology of study part 1 and 2 can be found in the corresponding manuscripts. A simple illustration about the source of data of the three manuscripts of this dissertation is shown in Figure 1.

For patient recruitment, 40 and 120 patients (half breast and half prostate CS, respectively) 6 to 52 weeks after completed primary therapy were targeted (given the descriptive nature of TOP study part 1, the sample size was estimated based on a preceding similar study with healthy male participants). To fulfill these targets, patient recruitment ran from October 2016 until October 2019 (part 1 October 2016 to July 2017, part 2 December 2017 to October 2019). As the drop-out rate during study part 2 was higher than the one used for the initial sample size calculation, the targeted number of participants was increased to 150. Informed consent was obtained from all participants included in the study. Detailed inclusion and exclusion criteria are given in the manuscripts.

The TOP study was carried out by the National Center of Tumor Diseases (NCT), Heidelberg University Hospital and was funded by the Dietmar Hopp Foundation (Project number 1DH1811306). The study followed the ethical standards of the Declaration of Helsinki, was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S-347/2016) and is registered at clinicaltrials.gov (NCT02883699).

My contribution to this work included recruiting the study participants, conducting the endurance and strength tests as well as the training sessions (i.e., data acquisition), followed by the analysis of the data discussed in the three manuscripts incorporated in this dissertation. Two of the manuscripts were published in peer-reviewed journals, the third has been submitted; the decision is pending (status as of October 2022).

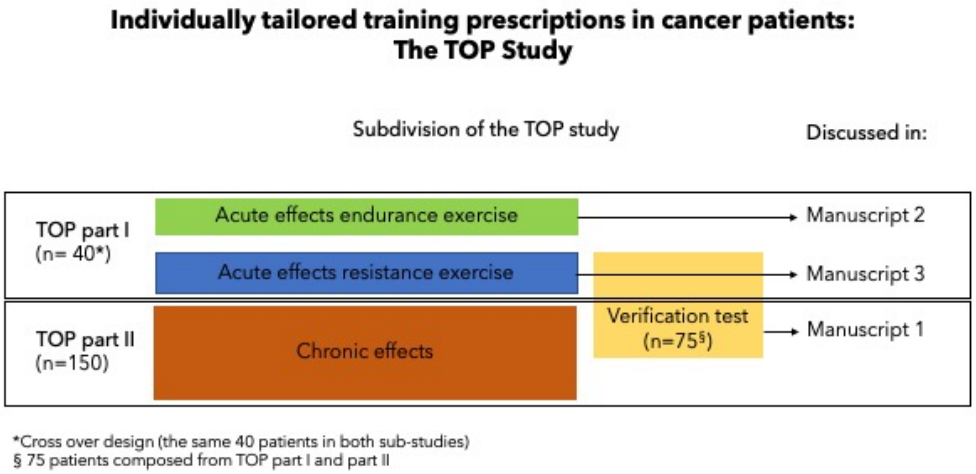

Figure 1: Overview of the subdivisions of the TOP study, and the corresponding manuscripts.

Further manuscripts that have emerged from the TOP study so far

- Schlüter, K., **J. Schneider**, T. Sprave, J. Wiskemann and F. Rosenberger (2019). *Feasibility of Two High-Intensity Interval Training Protocols in Cancer Survivors.* Medicine & Science in Sports & Exercise 51(12): 443–2450. doi:10.1249/MSS.0000000000002081

- Rosenberger, F., **Schneider, J**., Schlueter, K., Paratte, J.-L. and Wiskemann, J. (2021). *Vertebral fracture during one repetition maximum testing in a breast cancer survivor: A case report.* Medicine, 100(20), e25705-e25705. doi:10.1097/MD.0000000000025705

- Schlüter, K., **Schneider, J.,** Rosenberger, F., and Wiskemann, J. *Feasibility of high-intensity resistance training sessions in cancer survivors*. *The Journal of Strength & Conditioning Research*, 10.1519/JSC.0000000000004279. doi:10.1519/jsc.0000000000004279

- Pal, A.*, **Schneider, J**.*, Schlüter, K. et al. Different endurance exercises modulate NK cell cytotoxic and inhibiting receptors. Eur J Appl Physiol 121, 3379–3387 (2021). doi:https://doi.org/10.1007/s00421-021-04735-z *Shared first authorship

4. Outline

The aim of this thesis is to contribute to closing the indicated research gaps by addressing the following aspects:

Firstly, it was examined, (I) whether a supra maximal verification test is feasible and safe with CS, (II) whether CS reach theirtrue VO_{2max}during a CPET, and (III) if the verification test is more valuable for VO_{2max} confirmation than secondary criteria for maximal exhaustion (see manuscript 1, chapter 5).

Secondly, (I) different intensity prescription methods for endurance exercise were evaluated regarding their accuracy in targeting the vigorous intensity zone, and (II) the use of a 1-min ramp CPET protocol for LT determination in CS was assessed (see manuscript 2, chapter 6).

Thirdly, different approaches for prescribing strength training intensities are compared regarding their accuracy for (I) determining maximal strength, and (II) for targeting different intensity zones (see manuscript 3, chapter 7).

Finally, chapter 8 gives a summary of the three manuscripts and the results are discussed in the context of the current literature. The chapter is closed with conclusions, practical applications, and future perspectives.

5. Manuscript 1

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Do we underestimate VO_{2max} in cancer survivors? Findings from a supramaximal verification test

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Abstract
Cancer survivors demonstrate a reduced maximal oxygen uptake (VO_{2max}) which is clinically relevant in terms of overall survival. However, it remains uncertain whether they attain their "true VO_{2max}" in a cardiopulmonary exercise test (CPET). In the present study, a supramaximal verification bout (Verif) was applied in cancer survivors to confirm attainment of VO_{2max}. Seventy-five participants (61±12 years, n=43 females with breast cancer and n=32 males with prostate cancer, 6-52 weeks after primary therapy) performed a CPET on a cycle ergometer and a Verif at 110% peak power output. As verification criterion, VO_{2max} in Verif should not exceed VO_{2max} in CPET by >3%. On average, VO_{2max} was significantly lower in Verif compared to CPET (1.60±0.38 l/min vs. 1.65±0.36 l/min, p=.023). On the individual level, n=51 (68%) satisfied the verification criterion, whereas n=24 (32%) demonstrated a higher VO_{2max} in Verif. N=69 (92%) fulfilled ≥ 2 secondary criteria for maximal exhaustion in the CPET. While VO_{2max} was not underestimated in the CPET on average, still one third of cancer survivors did not attain their "true VO_{2max}". Verif appears feasible and beneficial to confirm "true VO_{2max}" in this population. Furthermore, it might be more reliable than secondary criteria for maximal exhaustion.

Novelty bullets:
- In about one third of cancer survivors, VO_{2max} is underestimated by a CPET.
- This underestimation of VO_{2max} is not necessarily indicated by secondary criteria for maximal exhaustion.
- A supramaximal verification bout appears feasible and helpful for the determination of VO_{2max} in cancer survivors.

Keywords: Breast cancer, prostate cancer, verification phase, maximal oxygen uptake (VO_{2max}), cardiopulmonary exercise test (CPET), verification bout.

Introduction

Maximal oxygen uptake (VO_{2max}) is an important clinical parameter for overall survival in the general population (Myers et al. 2002), and presumably as well in cancer survivors (Jones et al. 2012). Previous studies report an alarmingly low VO_{2max} in cancer survivors (Jones et al. 2012; Jones et al. 2016; Klassen et al. 2014; Peel et al. 2014). This is assumed to be caused by the disease itself, therapy-related side effects, and a reduced physical activity level (Gil-Rey et al. 2014b; Lakoski et al. 2012). However, it might also be possible that cancer survivors do not feel confident to spend maximal effort in the gold standard test for the determination of VO_{2max}, a cardiopulmonary exercise test (CPET).

Traditionally, secondary criteria for maximal exhaustion (e.g., maximal heart rate, HR_{max}) are used to confirm attainment of VO_{2max} (Midgley et al. 2007). However, these criteria are rarely used or reported in previous studies with cancer survivors. Therefore, it is difficult to draw conclusions about how frequently "true VO_{2max}" is attained in this population. Furthermore, secondary criteria for VO_{2max} attainment have been criticized for neglecting natural individual variability of maximal values and thus presenting a "one size fits all" approach (Poole and Jones 2017; Schaun 2017), the validity of which, especially in patient populations, is questionable. This challenges the notion that a low VO_{2max} seen in a cancer survivor is (solely) due to low aerobic capacity but might also reflect a slightly reduced compliance.

Another possibility to verify whether "true VO_{2max}" was attained in a CPET has emerged as an individualized supramaximal square wave "verification bout" performed to exhaustion shortly after the CPET (Midgley et al. 2006). Previous studies applied verification bouts in healthy adults of different age and activity level (Astorino et al. 2009; Dalleck et al. 2012; Sawyer et al. 2015; Scharhag-Rosenberger et al. 2011; Weatherwax et al. 2019) as well as in patients with cystic fibrosis (Causer et al. 2018). It was found to be safe, feasible and well-tolerated in this wide range of individuals. However, to the best of our knowledge, a verification bout has never been applied before in cancer survivors to confirm attainment of "true VO_{2max}".

Therefore, the present analysis aimed at investigating whether (1) "true VO_{2max}" is attained in a CPET in breast and prostate cancer survivors on the group and individual level, (2) a verification bout reveals different information compared to secondary criteria for VO_{2max} attainment and (3) a verification bout is feasible in this population. Albeit the terms peak oxygen uptake (VO_{2peak}) and VO_{2max} do not represent identical conditions and it was emphasized to not use them interchangeably (Green and Askew 2018), the term VO_{2max} is consistently used in this manuscript for reasons of clarity/better readability.

Methods

General design

The present exploratory cross-sectional analysis is based on data of the TOP study parts I and II (clinicaltrials.gov: NCT02883699, (Schlüter et al. 2019)). Baseline CPET data were analyzed, involving all complete data sets collected until 02/2019. Main outcome measure was VO_{2max} in the CPET (VO_{2CPET}) and the verification bout (VO_{2Verif}). Additional outcome measures were the secondary criteria for maximal exhaustion in the CPET: HR_{max}, maximal respiratory exchange ratio (RER_{max}), maximal blood lactate concentration (bLa_{max}), and maximal rating of perceived exertion (RPE).

Participants

Data from n = 75 cancer survivors (TOP study part I: n = 33, TOP study part II: n = 42), thereof n = 43 females with breast cancer and n = 32 males with prostate cancer, were analyzed. All participants met the following inclusion criteria: diagnosed with non-metastatic (M0) breast cancer or non-metastatic or metastatic (M0 or M1, except for bone or brain

metastases, with PSA evidence of stable disease) prostate cancer, 6 to 52 weeks after the end of primary therapy (i.e., surgery and/or radio therapy and/or chemotherapy), 18 to 75 years of age, and no regular vigorous endurance training (>1 session/week) since diagnosis or within the last 6 months. Exclusion criteria were diagnosis with additional other cancer and severe comorbidities that precluded participation in exercise testing or training (acute infectious diseases, severe cardiac, respiratory, renal or neurological diseases). All participants provided written informed consent to participate in the TOP study which followed the ethical standards of the Declaration of Helsinki and was approved by the ethics committee of the Medical Faculty of Heidelberg (S-347/2016).

CPET and verification bout

All participants performed a CPET plus verification bout on an electromagnetically braked cycle ergometer (Ergoselect 100, Ergoline, Bitz, Germany). The CPET started at 20 W and work rate increased every minute by 10 W until volitional exhaustion or medical reasons for early exercise termination. Cadence was kept between 60 and 80 rpm and patients were encouraged to exert maximal effort. The supramaximal verification bout was undertaken after 10 minutes of rest following the CPET (Scharhag-Rosenberger et al. 2011). The protocol started at 20 W and work rate was rapidly manually increased to 110% peak power output (PPO) of the CPET. The test was continued until volitional exhaustion and participants were again encouraged to exert maximal effort.

Gas exchange data were continuously measured using an open-circuit breath-by-breath gas analysis system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). The system was calibrated prior to each test according to the manufacturer's guidelines using a 3-l syringe, ambient air (20.09 % O_2 and 0.03 % CO_2) and a gas of known concentration (16.07 % O_2 and 4.94 % CO_2). VO_{2CPET} and VO_{2Verif} were defined as the highest 20 s average values during or immediately post-exercise, respectively. RER_{max} was defined as the highest 20 s average value during the CPET. A 12-lead electrocardiogram (ECG) was monitored continuously (CardioPart 12 Blue, amedtec, Aue, Germany) and HR_{max} was derived from the ECG as the highest 20 s average value during or immediately after the CPET (or read out manually in case of noisy ECG data mostly because of loss of electrodes due to severe sweating).

For the determination of bLa_{max}, capillary blood samples were taken from the hyperaemized (Finalgon balm) earlobe at the end of the CPET and 1-, 3-, and 5-min post-exercise. For each sample, one drop of blood was dissolved in a 1 ml cup of hemolysis solution using a 10 µl end-to-end capillary and analyzed using an enzymatic-amperometric method (Super GL compact, Hitado, Möhnesee, Germany). The highest value was considered bLa_{max}. To attain RPE_{max}, ratings of perceived exertion on a 6 to 20 BORG scale (Borg 1982) were assessed immediately post-exercise.

The verification bout was considered feasible when the patient was willing to perform the additional supramaximal test and when no adverse event occurred (e.g. pain or orthostatic problems)

VO_{2max} attainment

Attainment of "true VO_{2max}" in the CPET was accepted, when VO_{2max} in Verif did not exceed VO_{2max} in CPET by >3%. This verification criterion is based on the measurement accuracy of VO_2 determination reported by the manufacturer (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). Accordingly, the acceptable difference in HR_{max} between CPET (HR_{CPET}) and verification bout (HR_{Verif}) was set to 2% (HR_{Verif} - HR_{CPET}).

Attainment of VO_{2max} based on secondary criteria for maximal exhaustion was considered confirmed when two or more of the following criteria occurred: $RER_{max} \geq 1.1$,

HR_{max} ≥ 200 bpm minus age, bLa_{max} ≥ 8 $mmol \cdot l^{-1}$, RPE_{max} ≥ 18 (Ferguson 2014; Midgley et al. 2006; Midgley et al. 2007).

Statistical analyses

Normality of the exploratory data was tested using the Shapiro Wilk test and was present for all variables. Repeated-measures analysis of variance was used to test for differences between the CPET and the verification bout for VO_{2max} and HR_{max}. The same procedure was used to test for potential cancer entity-related differences between CPET and the verification bout, with entity as between-subjects variable. Differences between the tests for prostate cancer and breast cancer patients separately were assessed using paired t-tests. The agreement between VO_{2max} of the CPET and the verification bout was examined using Bland-Altman analyses (mean bias and 95% confidence intervals). Intraclass correlation coefficients (ICC) were calculated for relative and absolute VO_{2max} and HR_{max} to assess the reliability of VO_{2max} and HR_{max} between CPET and the verification bout. On an individual level, the number and proportion of participants satisfying the verification criterion (see above) was analyzed. Data are presented as means ± standard deviations (SD) unless stated otherwise and $p < 0.05$ was considered significant. All Data were analyzed using IBM SPSS Version 25 (IBM Corp, Armonk, NY).

Results

Participants' characteristics are shown in Table 1. All participants were willing and able to perform the supramaximal verification bout until volitional fatigue and no adverse events occurred.

Comparison of the CPET and the verification bout on the group level

The results of the CPET and the verification bout on the group level are displayed in Table 2 Mean CPET duration was 11.98 ± 2.91 min (range 6.33 – 18.67 min), mean duration of the verification bout was 2.17 ± 0.35 min (range 1.05 – 3.13 min). Prostate cancer survivors showed longer CPET durations compared to breast cancer survivors (13.99 ± 2.49 vs. 10.49 ± 2.23 min, p< .001), whereas the duration of the verification bout was not different between entities (2.18 ± 0.25 vs. 2.17 ± 0.41 min, p= .876), resulting in an interaction between cancer entity and test duration (p< .001).

Absolute and relative VO_{2CPET} were significantly higher than VO_{2Verif} (p= .023 and p= .033, respectively), although VO_{2max} was highly related between tests (ICC= .905 and .921, both p< .001). Mean differences between VO_{2CPET} and VO_{2Verif} were equal to -0.06 ± 0.21 l/min (range -0.84 – 0.31 l/min), -0.64 ± 2.53 ml/min/kg (range -9.29 – 3.76 ml/min/kg) and -2.97 ± 11.76% (range -44.45 – 20.67%), respectively (Figure 1).

Breast cancer patients showed VO_{2max} values between 10.1 and 30.23 ml/min/kg, whereas VO_{2max} of prostate cancer patients were ranging from 13.8 to 33.5 ml/min/kg. No effect of cancer entity on the differences between the CPET and the verification bout for both, absolute and relative VO_{2max} were found (women vs. men: 1.48 (range 0.91 – 2.09) vs. 1.88 (range 1.03 – 2.68) l/min, p= .084 and 21.3 (range 10.09 – 30.23) vs. 21.67 (range 13.79 – 33.51) ml/min/kg, p= .134). Yet, prostate cancer survivors showed higher absolute values of VO_{2CPET} compared to VO_{2Verif} (p= .039), whereas no difference in VO_{2max} between tests occurred in breast cancer survivors (p= .341).

HR_{max} was lower during the CPET compared to the verification bout (p= .044) and was highly related (ICC= .958; p< .001). No effect of cancer entity on the differences between the CPET and the verification bout for HR_{max} was found (p= .304). However, when analyzed separately for cancer entity, prostate cancer survivors showed higher HR_{max} values during the verification bout compared to the CPET (141 ± 23 vs. 139 ± 21 bpm, p= .041), whereas breast cancer survivors did not show differences between the verification bout and the CPET (159 ± 15 vs. 158 ± 15 bpm, p= .455).

Comparison of the CPET and the verification bout on the individual level and based on secondary criteria for maximal exhaustion

Fifty-one cancer survivors (68%) fulfilled the verification criterion, whereas 24 (32%) elicited a higher VO_{2Verif} than VO_{2CPET}, with differences ranging from 3.04 to 20.67% (Figure). Of those 24 participants who did not fulfil the verification criterion for VO_{2max}, six (25%) showed HR_{max} values that were > 2% higher during the verification bout compared to CPET. Twenty-one of those 24 participants (88%) showed durations of the verification bout of ≥ 2 min.

According to secondary criteria for VO_{2max} attainment, 69 of 75 CPETs (92%) were considered maximal (Table 3). Only in 46 of those 69 cases, VO_{2CPET} was confirmed by the verification bout (i.e., the verification criterion was fulfilled). Of those who did not fulfil the verification criterion (n= 24), 23 (96%) showed two or more secondary criteria for VO_{2max} attainment. In these 23 cancer survivors, the mean difference between VO_{2Verif} and VO_{2CPET} was 1.44 ± 0.8 ml/min/kg (reference value whole group mean difference -0.64 ± 2.53 ml/min/kg).

Discussion

Extremely low VO_{2max} values are often reported for cancer survivors; however, it can not necessarily be assumed that cancer survivors always attain their "true VO_{2max}" during a CPET. To the best of our knowledge, this is the first study which implemented a supramaximal verification bout in cancer survivors. The main findings of the present study are that (1) mean VO_{2CPET} was higher than mean VO_{2Verif}, however individual analyses showed that almost one third of cancer survivors did not reach their "true VO_{2max}" during the CPET; (2) a large proportion of this subgroup of participants (96%) would not have been identified deduced from secondary criteria for maximal exhaustion; and (3) the verification bout could be conducted in all breast and prostate cancer survivors and is therefore considered feasible in this patient population. Hence, our data demonstrate that a verification bout conducted 10 min after the CPET is beneficial for confirming the attainment of "true VO_{2max}" in a large proportion within the tested patient population and for identifying those participants who failed to attain VO_{2max} during CPET.

On the group level, mean VO_{2CPET} was significantly higher than $VO_{2Verif,}$ which is in line with results from Astorino and DeRevere (2018). However, others reported no differences between VO_{2CPET} and VO_{2Verif} (Dalleck et al. 2012; Midgley et al. 2009; Sawyer et al. 2015). Yet, when separated by gender, Astorino and DeRevere (2018) found VO_{2CPET} to be significantly higher than VO_{2Verif} in men, whereas no difference occurred in women. These findings are consistent with those observed here, in which we found no differences between VO_{2CPET} and VO_{2Verif} in breast cancer survivors, whereas differences in VO_{2max} between the two tests remained in prostate cancer survivors. These results likely reflect age or gender-specific differences (e.g., leg power output) between breast- and prostate cancer patients, rather than entity-specific differences.

The fact that the majority of the participants' VO_{2Verif} did not exceed VO_{2CPET} by more than 3% (i.e., satisfied the verification criterion), indicates that the majority attained VO_{2max} during CPET. Nevertheless, 32% of the tested participants did not satisfy the verification criterion, meaning that almost one third of the participants did not reach VO_{2max} during CPET. This is a higher proportion than reported in previous studies with healthy participants, stating differences between 11% (Astorino and DeRevere 2018) and 15% (Scharhag-Rosenberger et al. 2011) of the participants. However, both studies included young (18-45 years) healthy active participants. Astorino and DeRevere (2018) showed that participants with lower fitness demonstrated lager differences between VO_{2Verif} and VO_{2CPET},

which could be one possible explanation of the much higher proportion of participants who did not satisfy the verification criterion in the present study. Also, as already mentioned above, one possible reason for the lower proportion of participants who reached VO_{2max} during CPET in the present study could be a lack of exercise experience and comfort of spending maximal effort during CPET in this patient collective. Furthermore, a lack of exercise literacy, which is important for understanding the "deeper sense" of spending maximal effort during CPET is also a conceivable explanation for the missing maximal exhaustion of some patients. For those who did not fulfil the verification criterion, mean discrepancy between VO_{2Verif} and VO_{2CPET} was equal to 0.4 MET units (1 MET corresponds to 3.5 ml/min/kg of oxygen consumption (VO_2)). However, on the individual level, some cancer survivors showed differences above 3 ml/min/kg (0.86 MET). Since it has been reported that every 1-MET increase in VO_{2max} confers a 12-15% lower risk in all-cause mortality (Kodama et al. 2009; Myers et al. 2002), the clinical significance for underestimating VO_{2max} would likely be small. However, as we do not know whether this subgroup attained their "true VO_{2max}" during the verification bout, no conclusion can be drawn on the magnitude or clinical relevance of underestimation of VO_{2max} in this one third of cancer survivors.

Besides VO_{2max} is clinically relevant in terms of survival, it is also widely used for exercise intensity prescription in cancer survivors (Mann et al. 2013). Data from the present study raise the question whether percentages of VO_{2max} are suitable for training prescription in this patient population if VO_{2max} is underestimated in about one third of the participants. This one third of patients would exercise at a too low intensity which might reduce the beneficial effects on health and performance. Additionally, a valid detection of "true VO_{2max}" is prerequisite to accurately detect training adaptations. Therefore, underestimation of VO_{2max} could be a possible reason for the occurrence of exercise non-responders in intervention studies with patient collectives. Based on the results from the present study, one could conclude that sub-maximal threshold concepts like ventilatory or lactate thresholds might be more reliable for intensity prescription and the assessment of training adaptations in cancer survivors; a hypothesis that should be addressed in future studies. Threshold concepts not only confer the advantage that maximal exhaustion during CPET is not mandatory but are also assumed to be more potent in maximising the beneficial effects of exercise training in cancer survivors (Gil-Rey et al. 2014a).

Interestingly, HR_{max} during CPET was underestimated in only 25% of this third of patients (6/24), suggesting that percentages of HR_{max} may be more appropriate than percentages of VO_{2max} for intensity prescription with this patient collective.

Deduced from the present study, 23 of the 24 participants (96%) who did not satisfy the verification criterion, showed two or more secondary criteria for VO_{2max} attainment. Therefore, in one third of the examined patient population VO_{2CPET} would have been falsely considered as "true VO_{2max}" based on secondary criteria for VO_{2max} attainment. This raises the question whether these criteria are useful for cancer survivors. Accordingly, secondary criteria for maximal exhaustion have also shown to underestimate VO_{2max} in young cystic fibrosis patients (Saynor et al. 2013). Furthermore, these secondary criteria have previously been criticized for neglecting natural individual variability of maximal values (Poole and Jones 2017) and yet are still widely used as surrogate parameter for confirming VO_{2max} attainment (Midgley et al. 2007).

Concerning the validity of the CPETs regarding test duration, 99% of the performed CPETs were within the proposed valid range for VO_{2max} determination on cycle ergometers of 7 to 26 min (Midgley et al. 2008). The one cancer survivor with a CPET duration of < 7 min satisfied the verification criterion and fulfilled two of four secondary criteria for maximal exhaustion. Hence, we consider the respective CPET maximal. Altogether, the chosen protocol appears appropriate for

VO_{2max} testing in the population of cancer survivors.

Mean duration of the verification bout was comparable to previous studies (Sawyer et al. 2015; Scharhag-Rosenberger et al. 2011). However, on the individual level, 18 participants did not attain 2 min, which was stated as minimum duration for VO_{2max} attainment in verification bouts (Green and Askew 2018; Hill et al. 2002). Yet, of these 18 participants, only three did not satisfy the verification criterion, which suggests that duration of less than 2 min might be sufficient for VO_{2max} attainment in a verification bout in the examined patient population.

Limitations

Since one third of the participants' VO_{2Verif} exceeded VO_{2CPET} by > 3 %, no conclusion can be drawn on whether the attained VO_{2verif} represents "true VO_{2max}" in this subgroup. In this case (i.e., the verification criterion has not been fulfilled) an additional verification bout at a higher intensity would be necessary to assess whether VO_{2max} would further increase. For instance, Scharhag-Rosenberger et al. (2011) performed a second supramaximal verification bout at 115% PPO with healthy young individuals. However, as supramaximal verification bouts have never been applied in cancer survivors, we did not want to overstrain or frighten our participants but prove feasibility of the verification bout at 110 % PPO first. Another option might be to simply repeat the same test (CPET + Verification bout) on a separate day in those who failed to confirm the verification criterion at the first try. Since habituation to the test procedure could be one missing link for spending maximal effort during CPET for some patients, the second attempt might be more successful.

Furthermore, the verification criterion used in the present study is solely deduced from the measurement accuracy of the CPET device, since it was not possible to use values from previous studies with similar patient collectives. Thus, the chosen verification criterion is rather conservative since biological within-subject variations in VO_{2max} are not considered, which must be considered when interpreting the data (Midgley and Carroll 2009). However, it might also be argued that no relevant within-subject variation exists if two tests are only 10 min apart.

Moreover, the results from the present study can not necessarily be transferred to cancer entities other than breast and prostate cancer or to patients currently receiving physically demanding anti-cancer therapies like chemotherapy. And even though mean VO_{2max} of the breast cancer survivors of the present study was comparable to breast cancer collectives of similar age of previous studies (Peel et al. 2014), cardiorespiratory fitness is quite heterogeneous among breast cancer patients. Prostate cancer survivors showed lower VO_{2max} values than reported in previous studies (Segal et al. 2009; Wall et al. 2014), however, CPETs were conducted on treadmills in the named studies. Yet in the former study, patients were recruited prior to their radiotherapy and more than one third of the participants stated to currently undertake aerobic exercise at the beginning of the study. This variability of cardiorespiratory fitness should be considered when comparing the data of the present study to other breast and prostate cancer collectives. Another factor which has to be taken into account is that all participants showed a certain affinity for exercise as they all signed up voluntarily for this study. Lastly, the results of the present exploratory study have to be interpreted with caution, as the underlying main studies were statistically designed for other endpoints.

Conclusion

As the first study which implemented a supramaximal verification bout in cancer survivors, our results support findings from the majority of previous studies in the non-cancer field suggesting that this verification test procedure is a valid method for confirming CPET VO_{2max} in diverse populations (Astorino et al. 2009; Sawyer et al. 2015; Saynor et al. 2013; Weatherwax et al. 2019). In conclusion, although VO_{2max} was higher on average in the

CPET, one third of the examined study population did not reach their "true VO_{2max}" during the CPET. The clinical relevance for underestimating VO_{2max} for this subgroup of patients would likely be small; however, an additional verification bout at a higher intensity would be necessary to verify this assumption.

This suggests that VO_{2max} attainment during a CPET is not obvious in cancer survivors which could be an additional reason for the alarmingly low VO_{2max} of cancer survivors reported in previous studies (Jones et al. 2012; Jones et al. 2016; Klassen et al. 2014; Peel et al. 2014). A verification bout constitutes one remedy for discriminating between those who attain "true VO_{2max}" during the CPET and those who did not and has proven feasible in all 75 cancer survivors of the present study. Secondary criteria for maximal exhaustion do not seem to be suitable for the examined patient population since those participants who failed to attain VO_{2max} during the CPET would not have been identified by using secondary criteria for maximal exhaustion except for one participant.

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Author contributions:

F.R. and J.W. designed the study. F.R., J.W., K.S., and J.S. contributed to data acquisition. J.S. and F.R. analyzed and interpreted the data and wrote the manuscript. All authors revised and approved the manuscript.

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The authors declare no conflict of interest.

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Tables

Table 1: Participants' characteristics.

	Total	Breast cancer survivors	Prostate cancer survivors
n	75	43	32
Age	61.3 ± 12.0	57.5 ± 13.9	66.4 ± 5.9
BMI [kg/m^2]	26.5 ± 3.8	25.8 ± 4.0	27.5 ± 3.2
Time since diagnosis [months]	23 ± 30	16 ± 26	32 ± 33
Time since end of treatment[#] [months]	5 ± 3	4 ± 3	5 ± 3
Tumor staging, n (%)			
0	2 (3)	2 (5)	-
I	24 (32)	19 (44)	5 (29)
II	26 (35)	13 (30)	13 (76)
III	14 (19)	4 (9)	10 (59)
IV	2 (3)	0 (0)	2 (12)
unclear	7 (9)	5 (12)	2 (12)
Type of treatment received, n (%)			
Surgery	65 (87)	40 (93)	25 (78)
Chemotherapy	25 (33)	25 (58)	0 (0)
Radiation	61 (81)	36 (84)	25 (78)
Antihormonal therapy	46 (61)	34 (79)	12 (38)
VO_{2max} [ml/min/kg]	21.46 ± 4.48	21.30 ± 4.41	21.67 ± 4.55
PPO [W/kg]	129 ± 29	114 ± 22	150 ± 25

BMI, body mass index; VO_{2max}, maximal oxygen uptake; PPO, peak power output. [#]Surgery and/or radiotherapy and/or chemotherapy. All data are presented as mean ± SD unless stated otherwise.

Table 2: Comparison of the CPET and the verification bout.

	CPET	Verification bout
n	75	75
PPO [watt]	130 ± 29* (73 – 197)	143 ± 33* (80 – 215)
VO_{2max} [l/min]	1.65 ± 0.36* (0.91 – 2.68)	1.60 ± 0.38* (0.99 – 2.66)
VO_{2max} [ml/min/kg]	21.46 ± 4.48* (10.09 – 33.51)	20.82 ± 5.06* (10.92 – 36.91)
HR_{max} [bpm]	150 ± 20 (82 –180)	151 ± 21 (82 – 191)

CPET, cardiopulmonary exercise test; VO_{2max}, maximal oxygen uptake; PPO, peak power output; *p < .05 between the CPET and the verification bout. All data are presented as mean ± SD (range).

Table 3: Fulfilment of the verification criterion and the secondary criteria for maximal exhaustion.

	n	%
Total	75	100
VO_{2max} verification criterion fulfilled	51	68
VO_{2max} verification criterion **not** fulfilled	24	32
bLa_{max} ≥ 8 mmol/l	25	33
RER_{max} ≥ 1.1	63	84
HR_{max} ≥ 200 bpm minus age	57	76
RPE_{max} ≥ 18	63	84
None of the secondary criteria fulfilled	0	0
≥ 2 of the secondary criteria fulfilled	69	92
≥ 2 of the secondary criteria and VO_{2max} verification criterion fulfilled	46	61
2 of the secondary criteria fulfilled and VO_{2max} verification criterion **not** fulfilled	23	31

Verification criterion = VO_{2max} in Verif does not exceed VO_{2max} in CPET by >3%.

Figures

Figure 1

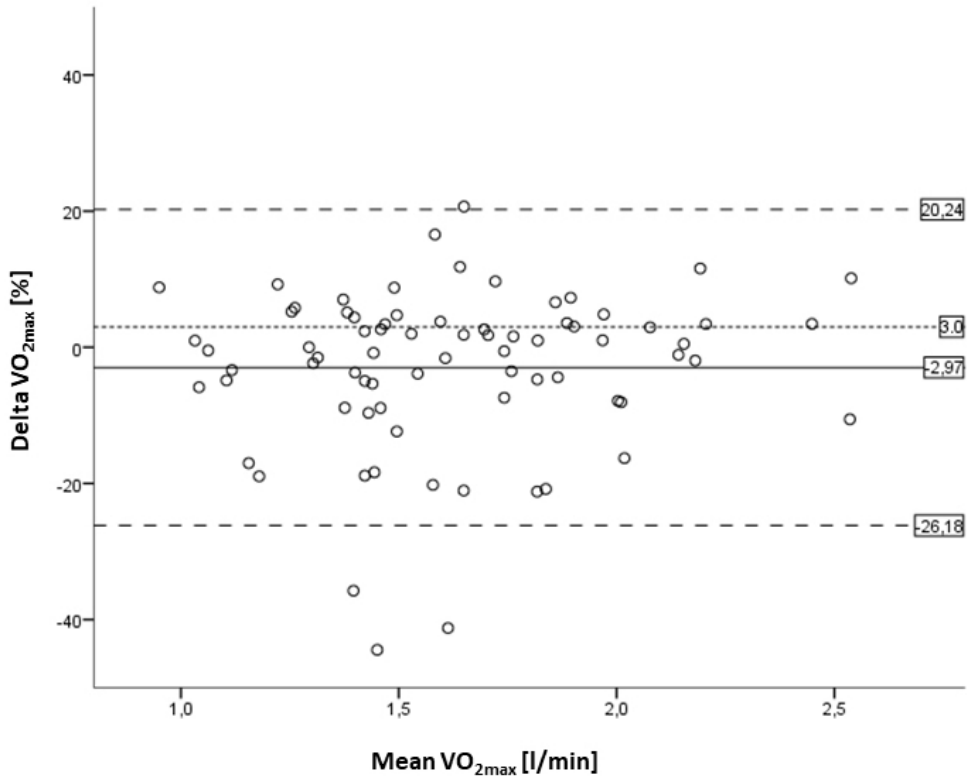

Figure captions

Figure 1: The agreement between maximal oxygen uptake (VO_{2max}) in the CPET and the verification bout. Displayed are the mean bias (floating solid line) and 95% confidence limits (floating dashed lines) in percent. The dotted line shows the verification criterion of a ≤ 3 % difference between VO_{2verif} and VO_{2CPET}, i.e., cases above the dotted line did not attain their "true VO_{2max}" in the CPET

6. Manuscript 2

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Exercise intensity prescription in cancer survivors: Ventilatory and lactate thresholds are useful submaximal alternatives to VO_{2peak}

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Abstract

Purpose: Most studies with cancer survivors use percentages of peak oxygen uptake (VO_{2peak}) for intensity prescription. Lactate or ventilatory thresholds might be useful submaximal alternatives, but this has never been systematically investigated. We therefore compared three training sessions prescribed in $\%VO_{2peak}$ (reference), lactate thresholds and ventilatory thresholds in terms of meeting the vigorous-intensity zone, physiological and psychological responses.

Methods: Twenty breast (58±10 years) and 20 prostate cancer survivors (68±6 years), 3.6±2.4 months after primary therapy, completed a maximal cardiopulmonary exercise test and three vigorous training sessions in randomized order: 38 min of cycling at 70% VO_{2peak} (M-VO_{2peak}), 97% of individual anaerobic lactate threshold (M-IAT) and 67% between ventilatory threshold 1 and 2 (M-VT). Heart rate (HR), blood lactate concentration (bLa), perceived exertion and enjoyment were assessed.

Results: Cancer survivors exercised at 75±23, 85±18 and 79±19 W during M-VO_{2peak}, M-IAT and M-VT ($p > .05$). Sessions could not be completed in 3, 8, and 6 cases. Session completers showed HR of 82±7, 83±9 and 84±8 $\%HR_{peak}$ and bLa of 3.7±1.9, 3.9±0.9 and 3.9±1.5 $mmol \cdot l^{-1}$, which was not different between sessions ($p > .05$). However, variance in bLa was lower in M-IAT compared to M-VO_{2peak} ($p = .001$) and to M-VT ($p = .022$).

Conclusion: All intensity prescription methods on average met the targeted intensity zone. Metabolic response was most homogeneous when using lactate thresholds.

Implications for Cancer Survivors: Submaximal thresholds are at least as useful as VO_{2peak} for intensity prescription in cancer survivors. Overall, slightly lower percentages should be chosen to improve durability of the training sessions.

Keywords: Aerobic training, endurance training, oncology, peak oxygen uptake, lactate threshold, ventilatory threshold

Introduction

Exercise is recommended for cancer survivors by expert panels worldwide because of its various beneficial effects [1-4]. Today, it represents a recognized part of supportive therapy. Regarding aerobic activity, 150 min of moderate or 75 min of vigorous-intensity exercise or an equivalent combination per week are recommended [1, 2]. Meeting these zones of moderate or vigorous intensity is crucial to elicit the intended training effects and avoid underload or overload of patients.

However, expert panel recommendations for cancer survivors either not specify how to target these intensity zones [1] or 60-85% of oxygen uptake reserve (VO_2R) or heart rate reserve (HRR) or >70% of peak heart rate (HR_{peak}) are suggested to target the vigorous-intensity zone [5, 6]. Percentages of VO_2R are rarely used due to the effort of resting oxygen uptake measurements and an analysis of cardiopulmonary exercise tests (CPETs) showed that percentages of HRR result in an intensity overload in cancer survivors due to their elevated resting heart rate [6, 7], whereas percentages of HR_{peak} appear appropriate [6, 8]. Most studies in cancer survivors prescribe certain percentages of peak oxygen uptake (VO_{2peak}) to target intensity zones [9, 10]. However, all relative percent concepts can be criticized for assuming that a fixed percentage of a reference value represents the same intensity in all individuals.

Alternatively, threshold concepts, i.e., blood lactate (bLa) or ventilatory thresholds [11, 12], which are anchored to the individual metabolic profile, are considered superior to fixed percentages of reference values [13, 14]. Furthermore, their determination does not require maximal exhaustion which appears valuable in cancer survivors who are not able or willing to spend maximal effort. Threshold concepts have a long tradition in high performance and recreational sports due to their capability of maximising physical performance [14-16] and are also considered superior in maximising beneficial effects of exercise in cancer survivors [6]. However, research on threshold concepts for intensity prescription in cancer survivors is scarce. So far, ventilatory thresholds have only been used for prescribing low to moderate but no vigorous-intensity exercise [17-19], whereas bLa thresholds have not been used for intensity prescription in cancer survivors yet. Their determination usually requires completing at least five stages of a stepwise incremental exercise protocol [20] which is not possible for many cancer survivors due to their low aerobic fitness [6, 21]. However, it appears worth testing whether bLa thresholds can be determined in a CPET protocol with 1-min stages [6, 21] and used for intensity prescription in cancer survivors.

Therefore, in the present study we compared three vigorous training sessions in terms of durability, physiological and psychological responses: a) a session prescribed in percentages of VO_{2peak} which, as the most commonly used method, served as reference here, b) a session prescribed by means of ventilatory thresholds, and c) for the first time with cancer survivors a session prescribed by means of bLa thresholds, all determined from one CPET. It was hypothesized that the threshold-based methods meet the vigorous-intensity zone as successful as percentages of VO_{2peak} but elicit a more homogeneous metabolic response as they are anchored to the individual metabolic profile. Knowledge on this will improve exercise intensity prescription for cancer survivors.

Methods

Participants: A total of 40 cancer survivors, 20 with breast and 20 with prostate cancer to represent the most common types of cancer in females and males, were recruited for participation. All participants met the following inclusion criteria: diagnosed with breast or prostate cancer, 6 to 52 weeks after end of primary therapy (i.e., surgery and/or radiotherapy and/or chemotherapy), 18 to 75 years of age, and no regular vigorous endurance or resistance training (> 1 session per week) within the last 6 months. Exclusion criteria were diagnosis with additional other cancer or severe comorbidities that preclude participation in exercise testing or training

(acute infectious diseases, severe cardiac, respiratory, renal or neurological diseases).

General design: Following a cross-sectional design, each patient performed four tests: a CPET and then three vigorous-intensity training sessions targeted by means of the three different prescription methods in randomized order (block randomization procedure). All tests took place once per week, separated by at least four days to avoid training adaptations, and were conducted on electromagnetically braked cycle ergometers (Ergoselect 100 or 200, Ergoline, Bitz, Germany).

Cardiopulmonary exercise tests: CPETs were preceded by a 2 min resting period on the cycle ergometer. They started at 20 W and increased every minute by 10 W until volitional exhaustion. Patients were encouraged to exert maximal effort. After a after a 10-min rest following the CPET, each patient performed a supramaximal verification test. The protocol started at 20 W and work rate was rapidly manually increased to 110% PPO of the preceding CPET [22]. Patients were again encouraged to exert maximal effort and the test was continued until volitional exhaustion.

A 12-lead electrocardiogram was continuously monitored (CardioPart 12 Blue, amedtec, Aue, Germany). Gas exchange data were continuously measured using a breath-by-breath gas analysis system (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). The system was calibrated prior to each test according to the manufacturer's guidelines. For bLa determination, capillary blood samples from the hyperaemized (Finalgon®) earlobe were taken at rest, at the end of each 1-minute increment, and after exercise cessation. They were analyzed using an enzymatic-amperometric method (Super GL compact, Hitado, Möhnesee, Germany). Blood pressure (Bp) and ratings of perceived exertion (RPE, 6 to 20 BORG scale [23]) were assessed every two minutes.

Peak power output (PPO) was interpolated when appropriate. VO_{2peak} and HR_{peak} were defined as the highest 20 s average value reached during or immediately after the CPET. Ventilatory threshold 1 (VT1) and 2 (VT2) were determined using the V-slope method (VCO_2/VO_2) [11] as primary and the VE/VCO_2 method [16] as secondary criterion. The individual anaerobic bLa threshold (IAT) was determined at 1 $mmol \cdot l^{-1}$ above minimum lactate equivalent (Ergonizer, Freiburg, Germany) [24]. This concept was originally designed for a 3 min-exercise stage protocol and adapted here to the CPET protocol.

CPETs were considered maximal when VO_{2peak} in the verification test did not exceed VO_{2peak} in the CPET by more than 3% (verification criterion). This verification criterion represents the measurement accuracy of VO_2 determination reported by the manufacturer (Ergostik, Geratherm Respiratory, Bad Kissingen, Germany). Furthermore, following secondary criteria, CPETs were considered maximal when two or more of the following criteria occurred: maximal respiratory exchange ratio (RER_{peak}) ≥ 1.1, HRpeak ≥ 200 minus age, peak bLa (bLa_{peak}) ≥ 8 $mmol \cdot l^{-1}$, RPE ≥18 [5, 25, 26]. However, all CPETs irrespective of maximal or not were used to derive training intensity from VO_{2peak} because this is the usual procedure in literature that should serve as a reference here.

Training sessions: Training sessions lasted 38 min to theoretically reach 75 min of vigorous-intensity exercise as recommended when performing two sessions per week [1]. All sessions were designed to target the vigorous-intensity zone: 70% VO_{2peak} [8, 27] (Method-VO_{2peak}, M-VO_{2peak}), slightly below (97%) IAT [15, 16, 20] (M-IAT) and two thirds (67%) between VT1 and VT2 [11, 16] (M-VT). Power output (W) corresponding to these points was prescribed. To assess the evoked strain, HR (Polar A300 monitor, Polar Electro Oy, Kempele, Finland), bLa, Bp, and RPE were recorded at rest and after 10, 20, 30 and 38 min of exercise. Exercise values were averaged over the four measurement time points. A lactate steady state (LASS) was defined as an increase in bLa of ≤ 0.9 $mmol \cdot l^{-1}$ during the last 18 min of each training session (≤ 0.05 $mmol \cdot l^{-1} \cdot min^{-1}$) [15, 28]. Enjoyment was assessed after each training session using a single item 7-point Likert scale, (*"How much did you enjoy the training session?";* 1= *not at*

all to 7= *very much*) adjusted from Rogers et al. [29] For safety assessment, adverse events were recorded.

Statistical analyses: The sample size was based on a preceding similar study with healthy male participants [30]. Normality was tested using the Shapiro Wilk test. Differences between the three training sessions for continuous data were assessed by one-way repeated-measures analysis of variance (ANOVA), or in the case of non-parametric or ordinal scaled data by Friedman's ANOVA. Differences between cancer entity were calculated using independent *t*-tests or the Mann Whitney-u test in the case of non-parametric or ordinal scaled data. Dependent dichotomous data were assessed using Cochran's Q Test with McNemar post-hoc test. For independent dichotomous data, the χtest was used. Pitman-Morgan test was used to test for differences of homogeneity of bLa and $\%HR_{peak}$ response between training sessions. Correction for multiple testing was applied using the Bonferroni-Holm post hoc test. $P < .05$ was considered significant. Data are presented as means ± standard deviations or individual courses. All Data were analysed using IBM SPSS Version 25 (IBM Corp, Armonk, NY) and MATLAB Version R2018a (MathWorks, Natick, MA).

Results

Participants' characteristics are shown in Table 4. VO_{2peak} could not be determined in one case due to fear of wearing a facemask, IAT could not be determined in one case because of a near linear bLa curve, and thus M-VO_{2peak} and M-IAT could not be performed in one case each. Seven out of the remaining 39 CPETs (18%) were not considered maximal based on secondary criteria for maximal exhaustion. Interestingly, according to the verification test, these seven CPETs were all considered maximal, whereas 13 other CPETs did not satisfy the verification criterion (i.e., VO_{2peak} reached during the verification test was more than 3% higher than VO_{2peak} reached during CPET). In other words, according to the verification test 33% of the performed CPETs were not considered maximal. Still all patients were included in the data analyses, to reflect what is usually done in practice. One patient's HR had to be excluded from data analyses because of measurement problems.

The results of the training sessions are presented in Table 5. Prescribed absolute power output did not differ between the training sessions (75±23, 85±19 and 79±19 W for M-VO_{2peak}, M-IAT and M-VT, all $p>.05$), but prescribed relative power output was lower for M-VO_{2peak} when compared to M-IAT ($p= .028$) and to M-VT ($p= .036$). M-VO_{2peak}, M-IAT, and M-VT were terminated prematurely in 3, 8, and 6 cases, respectively, which was not different between training sessions ($p= .093$). Sixteen of the 17 premature terminations were due to muscular exhaustion, whereas one resulted from knee pain, which was considered as a minor adverse event. No severe adverse event occurred. When comparing %PPO between session completers and those who terminated prematurely, there was no significant difference for M-VO_{2peak} (57 vs. 61 %PPO, $p= .484$), whereas %PPO of completers was significantly lower for M-IAT (62 vs. 72 %PPO, $p= .006$) and M-VT (58 vs. 70 %PPO, $p= .001$). For those who completed all exercise sessions, $\%HR_{peak}$ and homogeneity of $\%HR_{peak}$ as well as mean bLa and the number of participants who reached LASS did not differ between the training sessions (all $p> .05$). However, the variance of bLa during M-IAT was significantly lower compared to M-VO_{2peak} ($p= .001$, $n= 30$) and M-VT ($p= .022$, $n= 29$, Figure 1). RPE and enjoyment were not different between the training sessions.

Discussion

In the present study, intensity prescription by means of bLa and ventilatory thresholds was for the first time systematically investigated in breast and prostate cancer survivors after primary therapy and compared to the widely used percentages of VO_{2peak}. Our data indicate that within the examined patient population, 70% VO_{2peak}, slightly below (97%) IAT and two thirds (67%) between VT1 and VT2 were equally suitable to meet the vigorous-intensity zone. As expected, the

variance of bLa response was smaller when bLa thresholds were used for intensity prescription, but surprisingly not when ventilatory thresholds were used. In all three training sessions premature exercise terminations occurred, indicating that intensity was chosen slightly too high.

While prescribed absolute power output was not different between the training sessions, prescribed power output relative to the individual peak power output was higher for M-IAT and M-VT compared to M-VO_{2peak}. It must be noted that the used percentage within each intensity prescription method was chosen based on best knowledge and experience to meet the vigorous-intensity zone. This in a sense arbitrary choice naturally affected power output and the resulting physiological and psychological responses. This imbalance should be kept in mind when interpreting the findings. However, they could be levelled out in future by slightly adapting the used percentage within each intensity prescription method: When the early session terminations are additionally considered, 65% VO_{2peak}, 90% of IAT and 60% between VT1 and VT2 (instead of 70%, 97%, and 67%) might be prescriptions for more durable and comparable vigorous-intensity training sessions.

For those participants who completed all training sessions, mean percentage of HR_{peak} corresponded to the vigorous-intensity zone of 77-95% HR_{peak} given by the ACSM for apparently healthy adults [27]. This prescription was shown to be also valid in breast cancer survivors at the end of primary therapy [8]. Mean bLa responses to all three training sessions were nearly 4 $mmol \cdot l^{-1}$ which is roughly estimated to correspond to maximal LASS in untrained individuals and thus indicates that the upper limit of the vigorous training zone was met [15, 30]. Altogether, the cardio-metabolic exercise responses indicate that the vigorous-intensity zone was met on average in all three exercise sessions.

Surprisingly, although the cardio-metabolic responses reflected vigorous intensities, RPE reflected moderate intensities according to the ACSM guidelines for apparently healthy adults (RPE 12-13) [27]. Enjoyment was also rated relatively high. However, it must be considered that all training sessions were supervised in a one-on-one manner and albeit the supervising personal avoided conversations, some participants reported having enjoyed the undivided attention. Furthermore, socially desirable responding could have been an influencing factor. Therefore, subjective exercise responses should be interpreted cautiously.

Considering the homogeneity of physiological strain, the variance of bLa response was lower when bLa thresholds were used for intensity prescription compared to when VO_{2peak} was used. This was in accordance with our hypothesis. Variability in the degree of effort in the CPET might have contributed to the heterogeneity of metabolic strain when intensity was prescribed in percentages of VO_{2peak}. However, heterogeneous metabolic responses at given percentages of VO_{2peak} were also found in a previous study with healthy male participants who reached maximal exhaustion during CPET [30]. The authors therefore advised against using $\%VO_{2peak}$ for training prescription, although in that study, $\%VO_{2peak}$ was not compared to other intensity prescription methods. Surprisingly, variance in bLa response was not as low when ventilatory thresholds were used. This might be attributable to the more challenging determination of ventilatory thresholds as reflected by a lower inter- and intra-evaluator agreement compared to lactate thresholds [31].

In terms of cardiocirculatory strain, there were no statistically significant differences in the variance of heart rate response. However, single participants demonstrated heart rates above 100% HR_{peak} only in the sessions prescribed by means of bLa and ventilatory thresholds and not in the session prescribed by means of VO_{2peak} (Figure 1). Based on this, one might conclude that percentages of VO_{2peak} (or maximal values in general) for intensity prescription are superior to elicit a homogeneous cardiocirculatory strain while bLa thresholds for intensity prescription are

superior to elicit a homogeneous metabolic strain. While this appears obvious, confirmatory studies are to the best of our knowledge missing.

Although bLa thresholds have never been used before for intensity prescription in cancer survivors, they represent a general method for individually tailored exercise prescription in high-performance sports [15]. The challenge in the present study was to determine bLa thresholds from a CPET appropriate for cancer survivors. Typically, stepwise incremental exercise protocols with 3-min stages are used and at least five stages are needed for bLa threshold determination [12, 15, 20]. These five stages were easily reached in the present CPET protocol with 1-min stages and the resulting IAT proved useful for intensity prescription – if needed with the above-mentioned intensity reduction to 90% IAT. Lactate thresholds constitute the advantage that maximal exhaustion during CPET is not required. This is deemed particularly useful since in the present study 10% and 33% of the conducted CPETs were not considered maximal based on secondary criteria for maximal exhaustion and on the verification test, respectively. Altogether, the IAT derived from a CPET appears useful in cancer survivors which should be further investigated through training intervention studies.

To our knowledge, ventilatory thresholds have not yet been used for prescribing vigorous-intensity exercise in cancer survivors and only three prior studies with cancer survivors did so for prescribing low to moderate-intensity exercise [17-19]. These studies showed that cardiorespiratory fitness improved after 27 weeks [17], but not after 18 weeks [18, 19] of training at the VT1 performed thrice or twice per week, respectively. Since the intervention groups were compared to non-exercising control groups, no conclusion can be drawn on whether the missing effects were owing to the low exercise stimulus at the VT1 or to the method of intensity prescription itself. Results from studies with healthy participants suggest that moderate to vigorous exercise prescribed by means of ventilatory thresholds elicit superior training adaptations compared to a relative percent concept [14, 32]. More precisely, 100% of the participants who performed 12 weeks of training prescribed by means of ventilatory thresholds demonstrated an improvement in VO_{2peak}, whereas only 42% [14] and 60% [32] of those following the same intervention based on percentages of HRR were able to improve their VO_{2peak}. Altogether, ventilatory thresholds appear suitable for prescribing also vigorous-intensity exercise in cancer survivors.

Limitations

The strongest limitation of the present study is the somewhat arbitrary choice of percentages within the prescription methods. This cannot be avoided and although it limits direct comparability of the three training sessions, it does not hamper the conclusions drawn from this study. Furthermore, these findings (including the suggested adaptions of percentages within each intensity prescription method) are prerequisite for implementing the intensity prescription methods into training intervention studies. Another limitation is that threshold concepts might be considered somewhat sophisticated regarding clinical practice. Yet, as a first approach, we sought to systematically evaluate these methods that are appreciated in elite sports and can be determined without attaining maximal exhaustion in a CPET. In a second approach, it would be interesting to compare these highly objective methods to others that are easier to use, including subjective methods based e.g., on RPE.

Furthermore, the fact that we did not exclude all patients who had not attained their "true VO_{2max}" during CPET might be a limitation, since spending maximal effort during CPET is required for an adequate application of $\%VO_{2peak}$ for intensity prescription. However, the validity of secondary criteria for maximal exhaustion has been strongly criticised already for healthy individuals [33, 34] and their applicability has never been assessed in cancer survivors. And, as already mentioned above, we decided to include all patients in the data analyses as this more realistically reflects practice in previous research. Since there was no concordance between the two

methods (secondary criteria for maximal exhaustion and verification test) regarding the number of patients who failed to attain maximal exhaustion, it is questionable whether secondary criteria are even useful for cancer survivors. Furthermore, 33% not attaining "real VO_{2max}" during CPET raises the question of whether $\%VO_{2peak}$ is an appropriate intensity prescription method in cancer survivors, since in the present study, one third would have exercised at a too low intensity with this method. Even though this assumption is not reflected by the results, it could have more pronounced consequences regarding training responses for interventions with longer durations and/or in larger cohorts. Finally, it should be noted that the present findings are not necessarily transferable to patients with entities other than breast and prostate cancer or to those undergoing anti-cancer treatment.

Conclusion

Percentages of VO_{2peak} are commonly used for intensity prescription in cancer survivors, albeit they have been criticized for neglecting individual metabolic responses. Threshold concepts are linked to the metabolic profile and therefore promising submaximal alternatives for intensity prescription in cancer patients with heterogeneous fitness levels. However, this has never been systematically investigated before. We therefore conducted three training sessions prescribed as 70% VO_{2peak}, 97% IAT and 67% between VT1 and VT2, respectively, in breast and prostate cancer survivors and compared them in terms of durability as well as physiological and psychological responses.
Based on the cardio-metabolic responses, the vigorous-intensity zone was met on average through all intensity prescription methods. There were no significant differences in the number of premature terminations, cardio-metabolic responses, and subjective perception between the methods. Intensity prescription derived from bLa thresholds elicited a more homogenous blood lactate response compared to the other two methods. Thus, lactate thresholds appear more suitable if a defined metabolic strain is intended. Since early session terminations occurred in all training sessions, slightly lower percentages of the reference points might be preferable, e.g., 65% VO_{2peak}, 90% IAT, and 60% between VT1 and VT2. All three exercise sessions were equally enjoyed by the studied population and despite the, have been rated as moderate.
Therewith, submaximal thresholds are at least as useful as VO_{2peak} for intensity prescription in breast and prostate cancer survivors after primary treatment.

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Author contributions:
F.R. and J.W. designed the study. F.R., J.W., K.S., J.S. and T.S. contributed to data acquisition. J.S. and F.R. analyzed and interpreted the data and wrote the manuscript. All authors revised and approved the manuscript.

Compliance with Ethical Standards
Research involving Human Participants and/or Animals
The study followed the ethical standards of the Declaration of Helsinki, was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S-347/2016) and is registered at clinicaltrials.gov (NCT02883699).
This article does not contain any studies with animals performed by any of the authors.

Informed consent
Informed consent was obtained from all individual participants included in the study.

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Conflict of interest

All authors declare that they have no conflict of interest.
The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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Tables

Table 4: Participants' characteristics. Data presented as mean ± SD unless stated otherwise.

	Total	BCa	PCa
n	40	20	20
Age	62.9 ± 9.2	58.4 ± 9.7	67.5 ± 6.0
BMI [kg/m^2]	27.4 ± 3.9	27.1 ± 4.8	27.7 ± 2.7
Time since diagnosis [months]	20.8 ± 29.1	9.7 ± 3.5	32.0 ± 38.2
Time since end of primary treatment† [months]	3.6 ± 2.4	3.5 ± 2.0	3.8 ± 2.7
Type of treatment received, n (%)			
Surgery	36 (90)	20 (100)	16 (80)
Chemotherapy	10 (25)	10 (50)	0 (0)
Radiation	32 (80)	18 (90)	14 (70)
Antihormonal therapy‡	23 (58)	17 (85)	6 (30)
Current ß-Blocker intake, n (%)	11 (28)	5 (13)	6 (15)
VO_{2peak} [ml/min/kg], n	19.7 ± 4.1, 39	19.2 ± 3.4, 20	20.3 ± 4.7, 19
PPO [W/kg]	1.6 ± 0.4	1.5 ± 0.3	1.7 ± 0.4

BMI, body mass index; BCa, Breast cancer patients; PPO, peak power output; PCa, Prostate cancer patients; SD, standard deviation; VO_{2peak}, peak oxygen consumption; †Surgery and/or radiotherapy and/or chemotherapy. ‡21 of 23 participants were still undergoing antihormonal therapy at the beginning of the study.

Table 5: Comparison of the three exercise sessions. Intensity during sessions was prescribed as follows: 70% VO_{2peak} (M-VO_{2peak}), 97% IAT (M-IAT) and 67% between VT1 and VT2 (M-VT). Data presented as mean ± SD unless stated otherwise.

		M-VO_{2peak}	M-IAT	M-VT
Prescribed power output [W]	total (n= 38)	75 ± 23	85 ± 18	79 ± 19
	BCa (n= 19)	64 ± 17*†	71 ± 9*†	70 ± 16*†
	PCa (n= 19)	86 ± 24*†	98 ± 16*†	88 ± 19*†
Prescribed relative power output [% PPO]	total (n= 38)	57 ± 9	64 ± 9*	61 ± 8*
	BCa (n= 19)	57 ± 10	62 ± 7	62 ± 9
	PCa (n= 19)	57 ± 9	66 ± 11	59 ± 8
Number of premature session terminations	total (n= 38)	3	8	6
	BCa (n= 19)	2	3	4
	PCa (n= 19)	1	5	2
Relative heart rate [% HR_{peak}]	total (n= 28)‡	82 ± 7	83 ± 9	84 ± 8
	BCa (n= 14)	84 ± 6	84 ± 6	87 ± 6
	PCa (n= 14)	80 ± 7	83 ± 12	81 ± 8
Blood lactate concentration [mmol·l^{-1}]	total (n= 28)‡	3.7 ± 1.9	3.9 ± 0.9	3.9 ±1.5
	BCa (n= 14)	4.1 ± 1.8	4.2 ± 1.1	4.5 ± 1.1*†
	PCa (n= 14)	3.4 ± 2.0	3.6 ± 0.7	3.3 ± 1.6*†
Proportion of participants attaining LASS§ [%]	total (n= 36,31,34)	92	97	91
	BCa (n= 18,16,16)	90	80	94
	PCa (n= 18,15,18)	83	93	89
RPE breathing [scale 6 - 20]	total (n= 28)‡	12.7 ± 2.3	12.9 ± 1.8	12.8 ± 2.2
	BCa (n= 14)	13.4 ± 2.0	13.4 ± 2.0	13.6 ± 2.6*†
	PCa (n= 14)	11.9 ± 2.4	12.5 ± 1.5	12 ± 1.4*†
RPE legs [scale 6 - 20]	Total (n= 28)‡	12.8 ± 2.2	13.3 ± 2.1	13.0 ± 2.4
	BCa (n= 14)	13.4 ± 2.0	13.9 ± 2.4	13.9 ± 2.6*†
	PCa (n= 14)	12.3 ± 2.4	12.7 ± 1.5	12.1 ± 1.9*†
Enjoyment [scale 1 - 7]	Total (n= 28)‡	5.5 ± 1.4	5.5 ± 1.4	5.3 ± 1.3
	BCa (n= 14)	5.1 ± 1.7	5.3 ± 1.8	5.1 ± 1.5
	PCa (n= 14)	5.9 ± 0.9	5.8 ± 0.9	5.6 ± 0.9

BCa: Breast cancer patients; PCa: Prostate cancer patients; LASS, lactate steady state; RPE, rating of perceived exertion; SD, standard deviation; *Significant difference compared to M-VO_{2peak}: $p < 0.05$, *†Significant difference between cancer entities: $p < 0.05$, ‡Reduction from n= 38 to n=28 due to exclusion of data from participants with early session terminations; §Proportion of participants who attained LASS among those who completed the respective exercise session.

Figures

Figure 1

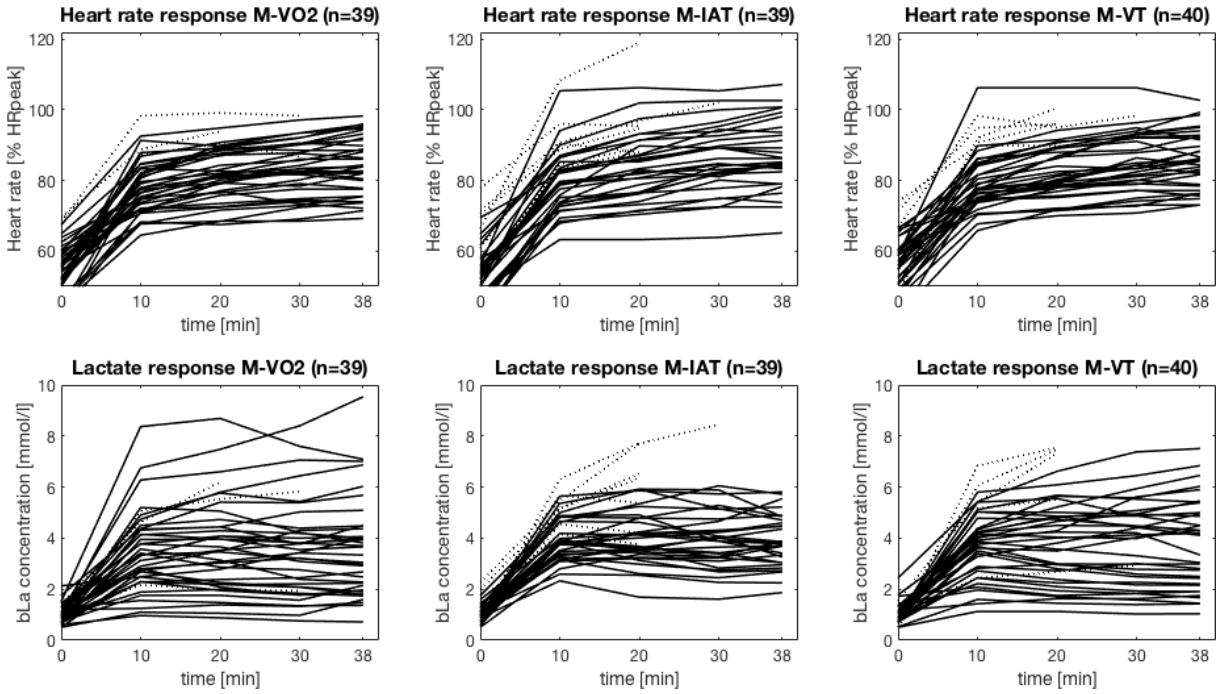

Figure Legends

Figure 1: Relative HR (a) and bLa (b) courses during M-VO_{2peak}, M-IAT, and M-VT (from left to right). Intensity during sessions was prescribed as follows: 70% VO_{2peak} (M-VO_{2peak}), 97% IAT (M-IAT) and 67% between VT1 and VT2 (M-VT). Dotted lines show courses of participants who terminated the session prematurely. The $\%HR_{peak}$ course of one patient is not displayed for M-VO_{2peak} due to a measurement problem.

7. Manuscript 3

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Are percentages of the one-repetition maximum (1-RM) suitable for prescribing resistance exercise in cancer survivors? - Comparability and prediction accuracy of frequently used 1-RM testing procedures

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Abstract

Purpose: To prescribe resistance training (RT) using percentages of (%) maximal strength (S_{max}), it is prerequisite that (I) methods for testing S_{max} are valid and (II) the relationship between $\%S_{max}$ and the corresponding number of repetitions (NOR) is known. This has never been investigated in cancer survivors (CS) and was the purpose of the present study.

Methods: Twenty breast (58 ± 10y) and 20 prostate CS (68 ± 6y), 3.6 ± 2.4 months after primary therapy, completed one one-repetition maximum (1-RM) test, one hypothetical 1-RM (h1-RM) test and three RT sessions (three sets at six different strength machines (SM)). H1-RM was calculated using two commonly used equations (after Brzycki and Epley), resulting in three S_{max} values for each SM, which were then compared to each other (1-RM as a reference). Each RT session was performed at a different intensity (≈92%, ≈69% and ≈47% of 1-RM/h1-RM). CS performed repetitions to fatigue and the resulting NOR were compared to the predicted NOR.

Results: S_{max} values differed between 1-RM and h1-RM values for each SM and between h1-RM values for some SM. Differences between performed and predicted NOR occurred among all intensities and methods.

Conclusion: Different strength tests yield different results for S_{max} and a certain %1-RM/h1-RM does not necessarily correspond to a specific NOR in all individuals, which questions the use of (I) h1-RM tests for determining S_{max} and (II) prescribing RT intensities based on %1-RM/h1-RM which is still the most common method used for RT intensity prescription in healthy individuals and patient populations, including CS.

Keywords: Breast cancer patients, prostate cancer patients, intensity prescription, weightlifting, multiple-repetitions maximum, Epley, Brzycki, repetitions to fatigue.

Introduction

Resistance training (RT) plays an important role to mitigate and prevent disease- and treatment-related side effects in cancer survivors1 (CS) and is associated with improved prognosis [1-3]. This is predominantly true for the two large groups of breast and prostate CS [4]. A large body of randomized controlled trials shows that RT improves fatigue, quality of life, physical functioning and bone health and does not induce or exacerbate upper extremity lymphedema [5]. Despite the fact that much more research has been done in the field of endurance training approaches, RT has been recommended as a key intervention in all available exercise oncology guidelines [5-9]. However, for quite a long time, RT recommendations were very vague by just stating that two or more days a week of RT are beneficial without providing more information [8, 10]. This has changed in the recently published roundtable of the American College of Sports Medicine publication by providing symptom specific FITT criteria (Frequency, Intensity, Time and Type of exercise) for the conduction of RT with CS. According to this recommendation, RT results in beneficial effects for CS if it is performed at least two times per week, using at least two sets of 8 to 15 repetitions at an intensity of at least 60% of the one-repetition maximum (1-RM) [5].

However, even having more precise RT prescriptions derived from performed studies, many questions regarding the conduction and evaluation of RT regimens remain open. For example, nearly all RT studies used 1-RM or hypothetical 1-RM (h1-RM) testing to determine initial RT load or to evaluate the efficacy of RT trials by applying pre-post-assessment study designs. Yet, to the best of our knowledge, different test methods have never been compared in terms of their accuracy in determining maximum strength in CS. Since various studies used various 1-RM testing procedures (1-RM or h1-RM as well as different equations for the calculation of the h1-RM) the question arises whether these different 1-RM/h1-RM procedures are comparable. The 1-RM test is considered safe and valid for determining maximal strength in CS [11] and is used as a standard procedure for assessing maximal dynamic strength in intervention studies with CS [12-17]. Yet, adverse events have also been reported in the past [18] and one serious adverse event (SAE) even happened in our working group [19]. This was at a timepoint when all 1-RM tests for this manuscript had already been performed, we would have chosen a different testing procedure otherwise. This together with the reports from previous studies indicate that the 1-RM test is not as safe as generally assumed. Furthermore, there has been no efforts made to evaluate the prediction accuracy of these maximal strength testing methods for exercise intensity prescription when training weights are prescribed as percentages of maximal values.

Therefore, the aim of our study was to evaluate the comparability and prediction accuracy of the most frequently used testing procedures (1-RM (served as a reference) vs. h1-RM testing with calculation formulas from Brzycki [20] and Epley [21]) in breast and prostate CS.

Methods

Participants

A total of 40 CS, 20 with breast and 20 with prostate cancer, participated in the study. All participants met the following inclusion criteria: diagnosed with non-metastatic breast or prostate cancer, 6 to 52 weeks after end of primary therapy (i.e., surgery and/or radiotherapy and/or chemotherapy), 18 to 75 years of age, and no regular vigorous endurance or resistance training (> one session per week) within the last 6 months. Exclusion criteria were a diagnosis with additional other cancer or severe comorbidities that preclude participation in

[1]In this manuscript, the term cancer survivor is defined as a person who is living beyond a cancer diagnosis and used interchangeably with the term cancer patient.

exercise testing or training (acute infectious diseases, severe cardiac, respiratory, renal, or neurological diseases). All participants provided written informed consent. The study followed the ethical standards of the Declaration of Helsinki, was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S-347/2016) and is registered at clinicaltrials.gov (NCT02883699).

General design

Following a repeated measures cross-sectional design, each patient performed two familiarization RT sessions, two strength tests, and three RT sessions with different intensities. All RT sessions (i.e., familiarization, testing and training sessions) were performed at six different resistance machines (Matrix, JOHNSON HEALTH TECH GMBH, Frechen, Germany). Three machines for the upper body (lat pulldown (LAT), rowing (R), shoulder press (SP)) and three for the lower body (leg press (LP), leg extension (LE), leg curl (LC)) were used. Each exercise session was supervised by an exercise professional (one-on-one) to ensure proper lifting technique, to provide verbal encouragement, and to document the testing results. No physical assistance was given at any time to help the patients with the concentric or eccentric phase of a lift. To ensure an adequate recovery period for each muscle group, resistance machines training the upper body were alternated with those training the lower body (i.e., LP, LAT, LE, R, LC, SP).

Familiarization sessions

The familiarization sessions were conducted with the intention to accustom patients to the proper lifting technique. They were conducted using minimal to moderate resistance and took place within the two weeks prior to the strength tests. In the first familiarization session, each machine was adjusted to ensure a proper lifting technique and configurations were protocolled for each patient for the following exercise sessions. In the second familiarization session the patients performed three sets with moderate weights at each of the six strength machines to get further accustomed to the proper lifting technique.

Strength tests

The two strength tests took place on the same day in randomized order (block randomization) and took approximately 90 min in total.

One-repetition maximum strength test

This test aims at determining the maximum weight that a patient is able to lift once through a full range of motion with the proper technique (1-RM test) and was conducted as follows: As an initial warm-up, each patient performed 10 repetitions with a low weight at the strength machine being tested (muscle-specific warm-up). Following the warm-up, a weight was selected that the patient was likely able to lift once with an adequate technique through a complete range of motion. If the patient was able to lift the weight properly, weights were increased progressively, at the discretion of the exercise professional, for the subsequent attempts until the 1-RM was determined. Total number of attempts should be limited to five, using 2-minute rest periods between attempts.

Hypothetical 1-RM strength test

For the determination of the hypothetical 1-RM (h1-RM), a multiple repetitions strength test (h1-RM test) was performed. For the h1-RM test, the exercise professional estimated a submaximal weight, which the patients were advised to lift for as many repetitions as possible with proper technique through a full range of motion. A weight was selected that the patient was likely able to lift 5-12 times. When the patient was able to lift the selected weight more than 20 times, the test had to be repeated at the end of the testing session after a minimum rest period of 15-minutes using a higher weight. Based on the

weight and the number of repetitions (NOR) that had been performed at each strength machine, two h1-RM weights were calculated using the following equations:

H1-RM according to Brzycki [20] (h1-RM_B): $1RM\ [kg] = w * \frac{36}{(37-r)}$ (w = kg, r = repetitions);

H1-RM according to Epley [21] (h1-RM_E): $1RM\ [kg] = (w * (1 + (\frac{r}{30}))$.

Consequently, deduced from the two strength tests, three values for maximal strength resulted for each resistance machine (one from the 1-RM test and two from the h1-RM test (i.e., h1-RM_B and h1-RM_E)).

Training sessions

After at least four days of recovery following the testing session, the three training sessions were conducted. One training session per week, also separated by at least four days, to avoid training adaptations.

All exercise sessions consisted of three sets on each of the six resistance machines. Each of the three exercise sessions was performed at a different intensity, corresponding to a specific NOR (i.e., four (4-RM), 12 (12-RM), and 20 repetitions (20-RM)). Based on the used equation, these repetition numbers correspond to a specific percentage of the individual maximal weight of a person. They were calculated from the three maximal weights (1-RM, h1-RM_B, h1-RM_E), rearranging the following equation:

$\%1 - \text{RM after Brzycki (1993)} = 102.78 - (2.78 * \text{r})$ (r= repetitions)

The resulting intensities were as follows:

4-RM = 91.7% 1-RM/h1-RM

12-RM = 69.4% 1-RM/h1-RM

20-RM = 47.2% 1-RM/h1-RM

Again, the three intensities imply a specific NOR that a person should be able to lift the associated weight (e.g., 4-RM presents the weight that a person should be able to lift four times (= the weight (hypothetically!) corresponding to 91,7% of his/her 1-RM/h1-RM)). All exercise sessions were performed as circuit training, meaning that all six strength machines were completed in the first circuit (first set, prescribed intensity e.g., 47.2% 1-RM). After the first set was completed, the patients began the second set (prescribed as e.g., 47.2% h1-RM_E) with the first machine again, followed by the second machine and so on. Given the fact that the calculated weights for each set were based on different equations (1-RM, h1-RM_B, h1-RM_E), three to some extent very different weights could result for the three sets on the same strength machine (e.g., leg press: 1-RM of 100 kg, h1-RM_B of 120 kg, h1-RM_E of 90 kg resulting in 4-RM training weights of 92 kg in set one, 110 kg in set two, and 83 kg in set three). The equation used for a particular set was randomized in order to adjust for muscular fatigue amongst the three sets. The order of the three different intensities for each exercise session was also randomized (e.g., week 1: 12-RM; week 2: 4-RM; week 3: 20-RM). A graphic overview of the methodical design is shown in Figure 2.

The expected repetitions that each intensity implies was not communicated to the patients, but instead patients were instructed to perform as many repetitions as possible (repetitions to fatigue). However, patients were stopped by the exercise professional after the 40th repetition.

Statistical analyses

The majority of data do not follow a normal distribution, which is why only non-parametric test statistics have been applied. Three analyzing procedures were employed:

(I) Differences between the three maximal weights determined by the 1-RM test and the two h1-RM strength tests (h1-RM_B and h1-RM_E) were calculated using a repeated

measures Friedman analysis with Wilcoxon rank post hoc test.

(II) Differences between the performed and the expected repetitions were calculated for each group (i.e., combination of intensity, machine, and model), using a Wilcoxon signed ranked test (non-parametric one-sample t-test) to compute whether the average repetition numbers of each group differ significantly from 4, 12, 20, respectively (18*3 statistical tests in total). However, as this test procedure might be too strict for the present research question, we elaborated an additional approach as follows.

(III) As an additional exploratory approach, we calculated the percentages of patients who performed less or more repetitions than a defined acceptable range (patients out of range, OOR) for each group (i.e., combination of intensity, machine, and model). The accepted range was set as: 3-5 repetitions for TM4, 10-14 repetitions for TM12 and 17-23 repetitions for TM20. We then calculated (based on random sampling) the percentage of patients expected to lie within these accepted ranges under the assumption of an underlying Poisson distribution (i.e., "what percentage of patients would naturally lie outside the set ranges, assuming the expectation value is equal to the predicted number of repetitions?"). This amounts to a threshold percentage of ≥ 58% OOR for the null hypothesis to be rejected at the 5% level ($p < 0.05$; i.e., in 5% of the cases, ≥ 58% patients OOR would occur, given a correct expected number of repetitions). The percentages of patients OOR was then tested for each group against the null hypothesis that the observed repetitions aligned to the expected number. This approach is hereafter called "%OOR method".

All data was analyzed using IBM SPSS Version 25 (IBM Corp, Armonk, NY) and MATLAB Version R2018a (MathWorks, Natick, MA).

Results

Patients' characteristics

The anthropometric and therapy-related characteristics of the patients (n= 40) are presented in Table 4. 1-RM weights and calculated predicted 1-RM weights (h1-RM_B and h1-RM_E) for each strength machine are presented in Table 7.

Agreement of maximal weights

Mean maximal weights are shown in Figure 3 (leg press) and

Figure 4 (remaining machines). Exact p-values are to be found in Table 8. Maximal weights of h1-RM_B differed from 1-RM for all strength machines except for R and LC, whereas h1-RM_E differed from 1-RM for all machines. Differences between maximal weights of h1-RM_B and h1-RM_E occurred for LP and LC.

1-RM weights plotted against h1-RM_B and h1-RM_E are shown in Figure 5 and Figure 6, respectively. For LP and LAT, both, h1-RM_B and h1-RM_E overestimated "real" 1-RM. For LE and SP, 1-RM was underestimated by both h1-RM methods, with relatively large mean differences (Figure 4). For R and LC, 1-RM was underestimated only by h1-RM_E. Hence, h1-RM_E exhibited a lack of similarity across all strength machines, whereas h1-RM_B evidenced a lack of similarity over four out of six machines. Both methods overestimated 1-RM for LP and LAT, whereas for the remaining machines they tended to underestimate 1-RM.

Accuracy of repetitions

The performed mean repetitions are presented in Figure 7. For TM4, the Wilcoxon test revealed significant

differences for three (LP, LAT, SP) five (LAT, LE, R, LC, SP) and four (LE, R, LC, SP) strength machines for 1-RM, h1-RM_B, and h1-RM_E, respectively (Table 9, Figure 6a). In TM12, differences occurred for four (LP, LAT, LE, SP), one (SP), and two (LAT, LC) machines for 1-RM, h1-RM_B, and h1-RM_E, respectively (Table 9, Figure 6b). In TM20 differences occurred for all strength machines for 1-RM and h1-RM_B, and for five (LAT, LE, R, LC, SP) machines for h1-RM_E (Table 9, Figure 6c).

Accuracy of repetition results evaluated by the %OOR method (see section Statistical analyses above) are summarized in Table 10 to Table 12 and are illustrated in Figure 8. TM4 showed insufficient accuracy (≥ 58% patients OOR) for four machines (LP, LAT, LE, SP) for 1-RM and all machines for h1-RM_B and h1-RM_E (Table 10, Figure 8a). In TM12, insufficient accuracy resulted for four (LP, LAT, LE, R), one (LP), and two (LP, LAT) machines for 1-RM, h1-RM_B, and h1-RM_E, respectively Table 11, Figure 8b). TM20 showed insufficient accuracy for four (LP, LAT, LE, LC), three (LP, LAT, R), and five (LP, LAT, LE, R, SP) strength machines for 1-RM, h1-RM_B, and h1-RM_E, respectively (Table 12, Figure 8c). Thus, accordance between the results of the Wilcoxon tests and the %OOR method was present in 14, 12 and 12 of 18 cases (three models*six strength machines) for TM4, TM12, and TM20, respectively.

In other words, TM4 exhibited insufficient accuracy for all machines among nearly all methods (except for R and LC for 1-RM) according to the %OOR method (Figure 8a). For TM12, h1-RM_B showed the highest accuracy (5 of 6 machines), followed by h1-RM_E (4 of 6 machines), and 1-RM with a sufficient accuracy for only two machines (Figure 8b). For TM20, 1-RM also showed accuracy for only two machines, which is comparably as low as h1-RM_B and h1-RM_E which presented a sufficient accuracy for three and one machine, respectively for this intensity (Figure 8c). Hence, h1-RM_B and h1-RM_E seem to be most suitable for TM12 and for strength machines involving smaller muscle groups such as R, LE, R, LC, and SP. None of the methods resulted in sufficient accuracy for LP and LAT (except for h1-RM_B for TM12) among all three intensities, suggesting that none of the methods seems suitable for these two resistance machines for the investigated intensities.

Discussion

From the perspective of feasibility, our results indicate that the classical and hypothetical 1-RM testing procedure can be well applied in breast and prostate CS following cancer treatment. However, strength testing results vary between the three investigated methods with the occurrence of over- as well as underestimation of patients' strength performance depending on training machines. Further, the NOR prediction accuracy of all three strength testing procedures seems to be very poor for all tested strength training machines and intensity regimens.

RT has become a central pillar in the supportive care of cancer patients in the last two decades. Studies show impressive effectivity regarding relevant clinical outcomes like chemotherapy compliance rates, onset of lymphedema as well as quality of life, fatigue, distress and functional well-being and RT is therefore recommended and prescribed in various exercise oncology guidelines [5-7]. Consequently, a variety of research groups has performed projects to enhance the application range and quality of RT regimens as well as to test different RT intensity protocols in CS. With regard to the application range, the field of RT research in CS has moved from the "classical" breast CS treated with curative intent [22] to studies that were enrolling cachectic head and neck [23], pancreatic [24], advanced renal cell [25] or lung CS [26] as well as CS with

unstable bone metastasis [27]. Other studies have successfully tested RT regimens not following the "classical" progressive hypertrophy RT approach (2-3 sets with 12 reps), but a maximal strength training protocol with 4x4 repetitions of dynamic leg press at approximately 90% of the 1-RM twice a week for 12 weeks in early stage breast CS [28]. On the other end, also gentle strength training approaches with 50% of the 1-RM just once a week for about six months were investigated [29]. Other studies also used intensity-varying approaches, like daily undulating training protocols (e.g., high intensity on Mondays, moderate on Wednesdays and again high intensity on Fridays) shown to be feasible and effective with regard to various clinically relevant endpoints [30, 31].

However, as already mentioned in the study descriptions before, the different studies used various 1-RM/h1-RM testing procedures to determine training intensities as well as to evaluate the efficacy of the invested RT intervention. In light of our results, it has to be questioned whether it is acceptable to incorporate RT studies with different 1-RM/h1-RM testing procedures in the same meta-analysis approach that might lead to invalid or inaccurate conclusions. Obviously, these questions are relevant to all RT studies and are not a unique problem of cancer patient populations. Furthermore, the question arises whether the participants in the above-mentioned studies really trained at the intended intensities. This is obviously a key question since a higher stress than normal must occur for fitness to improve [4]. Since the deviations between the h1-RM and the 1-RM results occurred in both directions in the present study, training weights could also turn out too high which bears the risk of overstraining the patients.

Generally, 1-RM test procedures were evaluated with regard to test–retest reliability and show mostly good to excellent results, regardless of e.g., previous RT experience, sex, and age of the participants [32]. However, patient cohorts are underrepresented in this type of research with only 4 out 32 studies having patients with disease conditions involved and CS are completely missing. There are studies showing in multiple following testing sessions (incorporating sufficient recovery time between sessions) that 1-RM performance significantly increased from the first to the last (4th) testing session by about 10-17% [33, 34]. These findings support our observation of patients being able to perform more repetitions in the first training session after 1-RM testing than expected by the prediction formulas which has been already shown for healthy older adults [35]. However, studies investigating such research questions in CS are currently missing. To the best of our knowledge, there is only one study that investigated the test-retest reliability of 10-RM tests for the leg press and bench press in breast CS [36]. The authors report a high to very high rate of reliability between the tests for both strength machines (ICC of 0.94 and 0.98, respectively). Even though these results contrast with the above-mentioned results from other studies, one has to keep in mind that the two test procedures (1-RM and 10-RM) are only comparable with each other to a limited extent.

Bringing the existing knowledge with our observation together, it has to be suggested that (I) h1-RM tests lead to errant maximal values with the occurrence of over- as well as underestimation of maximal values, (II) the NOR at given percentages of maximal values derived from 1-RM and h1-RM tests varies extremely between individuals. This implies that training intensities of the till to date published RT studies in oncology might be inaccurate regarding the intended training intensities when training intensities were prescribed as %1-RM/%h1-RM. Studies in the RT research area in non-cancer populations have partly addressed these questions with non-satisfying results mainly in accordance with our findings. For

example, a study published in the 1990s tested 91 participants to determine the NOR they could perform at 40, 60, and 80 %1-RM on various RT machines [37]. They observed large variations in the NOR that the participants were actually able to perform at the different intensities. Based on their findings the authors concluded that a given %1-RM will not always result in the same NOR. Interestingly, this finding was neither influced by gender nor by training status [37, 38] and also age does not seem to play an important role [39]. Another study undelines these findings, further showing that this phenomenon is true for all existing testing methods and equation procedures, and is not just limited to one of them [40]. According to our findings, the variations in the NOR tend to be greater for larger muscle groups of the lower extremity than those of the upper extremity [38].

Given the findings of our study as well as the current discussion in the field about how to optimize RT in general and in particular for CS, one aspect remains crucial: Reporting. It is well known from exercise oncology research that description and in particular reporting of exercise regimens need to be improved [41, 42]. Therefore, a variety of researchers have focused on comprehensive methods to describe and report RT adequately with a special focus on the cancer domain [43-45] as well as in general [46]. All approaches mentioned, move the field forward by suggesting relevant reporting parameters like objective volume load or velocity documentation or subjectively perceived intensity reporting. In addition, the cancer specific recommendations should incorporate reporting variables which are similar to medical/drug research outcomes in oncology, like relative exercise dose intensity, total cumulative planned and completed dose or dose modification, comparable to Schluter et al. [31]. Two implications can be drawn from the mentioned paper: (I) To be able to draw solid conclusions from RT trials concerning the effectivity and efficacy, a comprehensive approach for reporting RT regimens is mandatory; (II) No matter which additional method or recommendation will be used, it is of great importance to find a consensus regarding how these different reporting strategies can be best implemented and integrated to complement each other.

Our study is to our knowledge the first that addresses questions about strength test prediction accuracy and comparability for intensity prescription of RT in CS. However, there are limitations that have to be mentioned. Due to the study design with multiple 1-RM tests as well as multiple training sets with different intensities, there is a probability of biased findings due to the effect of increasing muscular fatigue with increasing number of sets and tests. We accounted for that by randomizing the order of the 1-RM testing procedures as well as the order of the intensity specifications the patients were asked to follow within one set. Due to the relatively low number of participants and to the nature of our research questions, we do have partly skewed data. However, we accounted for that by only applying non-parametric testing procedures within the analysis.

In conclusion, our study shows that from a feasibility perspective various 1-RM testing procedures can be applied in breast and prostate CS after acute cancer treatment and are well tolerated. Nevertheless, the finding that strength testing results vary largely between 1-RM procedures and over- as well as underestimate patients' strength depending on which method is used and which muscle group is tested, limits the comparability of studies using different 1-RM testing procedures. Findings from other studies suggest that the extent of misestimation of h1-RM procedures largely depends on the NOR achieved in the test [47-52]. Therefore, it can be assumed that even intraindividual values reported in studies are inaccurate. Consequently, it has

to be critically asked whether 1-RM/h1-RM testing procedures are adequate methods to be used to evaluate resistance-training efficacy in CS, and whether data from different 1-RM procedures are acceptable to be used for review and meta-analysis purposes. Future studies should invest this cross-sectional phenomenon on a longitudinal perspective to elucidate the potential problem of different non-comparable 1-RM procedures through the RT intervention period. Furthermore, given that the h1-RM methods showed the largest accuracy of repetitions for TM12, it can be concluded that these methods may be most suitable for intensity prescription of exercise sessions with similar numbers of repetitions to the h1-RM test. More simply put, if you intend to exercise at e.g., 10-RM a 10-RM test might be more suitable for determining the training weights. This would also be a safer alternative to the 1-RM test, which given the occurrence of SAE in the past, should better be replaced by a safer testing procedure for clinical populations.

Having discussed accuracy and methodological aspects of strength testing and intensity prescription of RT before, it has to be noted that there is quite a lot of discussion in the area of RT research about whether RT intensity is the central key variable when it comes to RT efficacy. A recent meta-analysis from studies performed with healthy participants shows that muscle hypertrophy can be reached by applying low- as well as high-load RT protocols [53]. However, maximal strength benefits were significantly greater in favor of high- vs. low-load training. This is mostly in line with recent findings from Lopez et al. in the cancer area. They found that the prescribed volume was inversely associated with gains in muscle strength, although there was no relationship between RT intensity and strength gains [54]. The authors therefore conclude that low volume RT might be a viable approach for breast CS to gain benefits from RT regardless of the training intensity. The possible opportunities again, stress the importance of accurate intensity assessment and prediction to set up an adequate resistance training regimen.

Regarding intensity prescription, given the fact that the accuracy of %1-RM/h1-RM (prediction of repetitions a patient can perform with a certain weight) was mostly inadequate, raises the question whether this method is adequate for intensity prescription in CS. From a practical point of view, exercise trainers should not rely on 1-RM/h1-RM testing procedure results and closely monitor their patients predominately through initial training weeks to be sure that the intended exercise intensity is reached. A more practical approach would be to directly approach the desired weight (gradually increase or decrease the weight until the patient can lift the weight the intended number of times). Prescribing the actual NOR to dictate the intensity and not vice versa is an approach which has already been advocated by other authors [55] and is also part of the Australian recommendations for CS [56]. Our results together with those from previous studies suggest that alternative methods than the ones commonly used for strength testing and RT prescription may be more suitable for CS, which should be investigated in future studies.

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Statements and Declarations

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Conflict of interest

All authors declare that they have no conflict of interest.

The authors have full control of all primary data and agree to allow the journal to review the data if requested.

Author contributions:

F.R. and J.W. designed the study. K.S. and J.S. acquired the data. J.S. analyzed the data. J.S and J.W. wrote the manuscript. All authors revised and approved the manuscript.

Compliance with Ethical Standards

Research involving Human Participants and/or Animals

The study followed the ethical standards of the Declaration of Helsinki, was approved by the Ethics Committee of the Medical Faculty of Heidelberg (S-347/2016) and is registered at clinicaltrials.gov (NCT02883699).

This article does not contain any studies with animals performed by any of the authors.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

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1. Tables

Table 6: Participants' characteristics. Data presented as mean ± SD unless stated otherwise. BMI, body mass index; BCa, Breast cancer patients; PCa, Prostate cancer patients; SD, standard deviation; $Surgery and/or radiotherapy and/or chemotherapy. ‡21 of 23 participants were still undergoing antihormonal therapy at the beginning of the study.

	Total	BCa	PCa
n	40	20	20
Age [years]	62.9 ± 9.2	58.4 ± 9.7	67.5 ± 6.0
BMI [kg/m^2]	27.4 ± 3.9	27.1 ± 4.8	27.7 ± 2.7
Time since diagnosis [months]	20.8 ± 29.1	9.7 ± 3.5	32.0 ± 38.2
Time since end of primary treatment$ [months]	3.6 ± 2.4	3.5 ± 2.0	3.8 ± 2.7
Type of treatment received, n (%)			
Surgery	36 (90)	20 (100)	16 (80)
Chemotherapy	10 (25)	10 (50)	0 (0)
Radiation	32 (80)	18 (90)	14 (70)
Antihormonal therapy‡	23 (58)	17 (85)	6 (30)
Current ß-Blocker intake, n (%)	11 (28)	5 (13)	6 (15)

Table 7: Descriptives of strength test results. Values are indicated in kilograms. LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing; SP, shoulder press.

	1-RM			h1-RM_B				h1-RM_E			
	median	min	max	median	min	max	delta 1-RM	median	min	max	delta 1-RM
LP	172.3	66.5	255.0	193.9	103.1	318.6	-29.5	185.5	94.5	277.9	-17.5
LAT	35.0	18.0	57.0	42.3	19.4	64.0	-5.7	38.4	19.1	55.7	-3.7
LE	43.0	23.0	81.0	31.3	12.5	74.6	13.7	29.3	12.3	77.4	14.4
R	39.0	18.0	57.0	35.3	16.3	66.3	0.9	34.0	16.8	56.0	2.3
LC	31.5	18.0	50.0	29.5	16.8	56.3	0.6	28.6	17.3	52.8	1.7
SP	22.3	10.0	66.1	17.7	7.8	56.8	3.1	17.8	7.3	46.4	3.8

Table 8: p-values of Friedman ANOVA comparing the results of the three tests. Bold numbers represent statistical differences (p< .05) to the results of the 1-RM test. LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing; SP, shoulder press.

	h1-RM_B vs. 1-RM	**h1-RM_E vs. 1-RM**	**h1-RM_B vs. h1-RM_E**
LP	**< 0.001**	**.003**	**.018**
LAT	**< 0.001**	**.002**	0.379
LE	**< 0.001**	**< 0.001**	1.000
R	.133	**.013**	1.000
LC	1.000	**.001**	**.016**
SP	**.009**	**< 0.001**	0.828

Table 9: p-values of Wilcoxon Rank test comparing the performed repetitions against the targeted number of repetitions for each training session. Bold numbers represent statistical differences (p< .05). LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing;

	TM4			**TM12**			**TM20**		
	1-RM	**h1-RM_B**	**h1-RM_E**	**1-RM**	**h1-RM_B**	**h1-RM_E**	**1-RM**	**h1-RM_B**	**h1-RM_E**
LP	**.000**	.053	.548	**.000**	.442	.090	**.000**	**.000**	.530
LAT	**.000**	**.019**	.100	**.000**	.230	**.000**	**.000**	**.000**	**.012**
LE	.836	**.000**	**.000**	**.000**	.325	.139	**.000**	**.000**	**.000**
R	.121	**.016**	**.000**	.373	.778	.136	**.014**	**.000**	**.027**
LC	.887	**.010**	**.000**	.872	.740	**.049**	**.040**	**.007**	**.029**
SP	**.006**	**.000**	**.000**	**.001**	**.046**	.255	**.001**	**.022**	**.000**

Table 10: Number (#) of patients out of range (OOR) for TM4. Absolute numbers and relative proportions. Percentages within the cut-off of <58% are highlighted in bold lettering. LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing; SP, shoulder press.

TM4	1-RM			h1-RM_B			h1-RM_E		
	#OOR	**n**	**%**	**#OOR**	**n**	**%**	**#OOR**	**n**	**%**
LP	31	36	86	30	36	83	33	36	92
LAT	30	38	79	28	39	72	25	39	64
LE	24	37	65	28	37	76	33	37	89
R	22	39	**56**	25	39	64	30	39	77
LC	18	37	**49**	26	37	70	28	38	74
SP	23	36	64	29	36	81	34	36	94

Table 11: Number (#) of patients out of range (OOR) for TM12. Absolute numbers and relative proportions. percentages within the cut-off of <58% are highlighted in bold lettering. LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing; SP, shoulder press.

TM12	1-RM			h1-RM_B			h1-RM_E		
	#OOR	**n**	**%**	**#OOR**	**n**	**%**	**#OOR**	**n**	**%**
LP	27	36	75	24	36	67	27	36	75
LAT	33	38	87	21	38	**55**	22	38	58
LE	27	38	71	15	38	**39**	17	38	**45**
R	23	37	62	15	39	**38**	12	39	**31**
LC	20	37	**54**	17	37	**46**	18	37	**49**
SP	19	34	**56**	12	33	**36**	18	34	**53**

Table 12: Number (#) of patients out of range (OOR) for TM20. Absolute numbers and relative proportions. percentages within the cut-off of <58% are highlighted in bold lettering. LAT, lat pulldown; LC, leg curl; LE, leg extension; LP, leg press; R, rowing; SP, shoulder press.

TM20	**1-RM**			**h1-RM_B**			**h1-RM_E**		
	#OOR	**n**	**%**	**#OOR**	**n**	**%**	**#OOR**	**n**	**%**
LP	30	36	83	23	37	62	25	36	69
LAT	36	37	97	33	39	85	26	38	68
LE	30	37	81	21	37	**57**	28	37	76
R	21	39	**54**	28	39	72	25	39	64
LC	26	38	68	18	38	**47**	18	38	**47**
SP	19	36	**53**	15	36	**42**	29	36	81

2. Figures

Figure 2: Graphic illustration of the methodological procedure of the study.

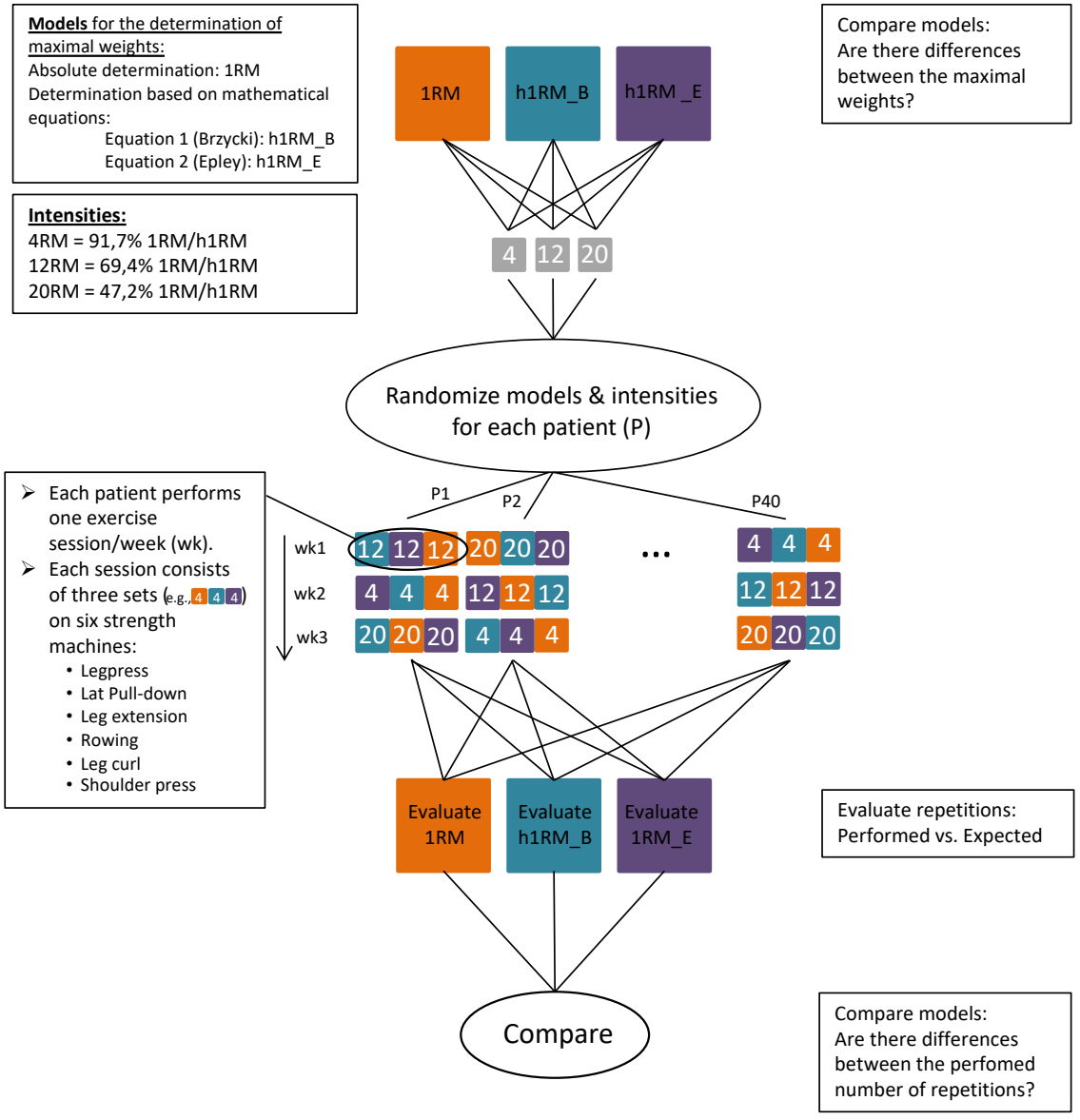


Figure 3: Median maximal weights of the 1-RM and h1-RM (h1-RM_B and h1-RM_E) tests. Bars marked with asterisk show significant differences to the 1-RM test. Significant differences between the two h1-RM tests are marked with "§".

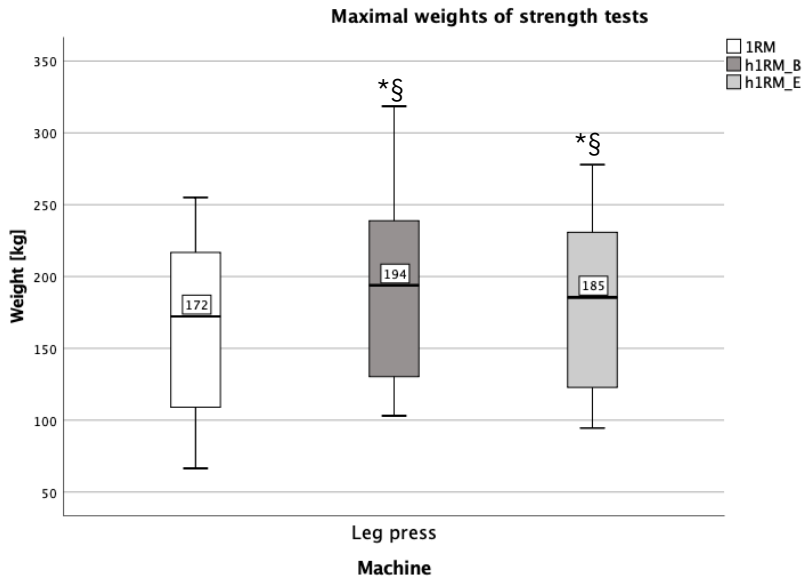


Figure 4: Median maximal weights of the 1-RM and h1-RM (h1-RM_B and h1-RM_E) tests. Bars marked with an asterisk show significant differences to the 1-RM test. Significant differences between the two h1-RM tests are marked with "§". Outliers are marked with circles (1.5x interquartile range (IQR)) and triangles (3xIQR).

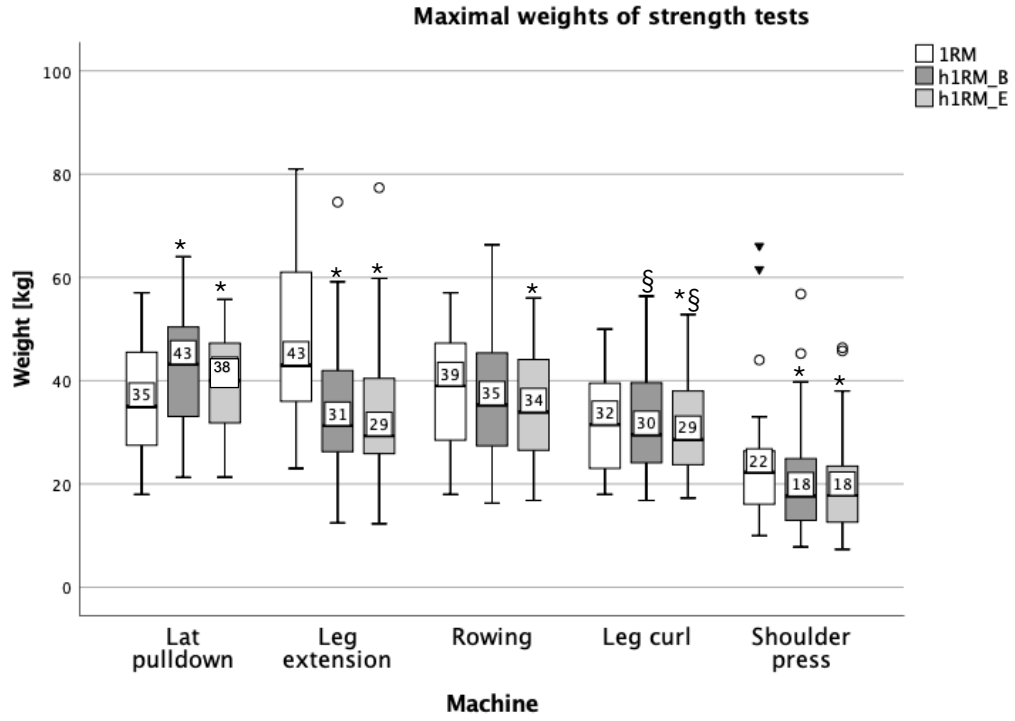


Figure 5: Maximal weights of 1-RM plotted against the predicted maximal weights of h1-RM_B.

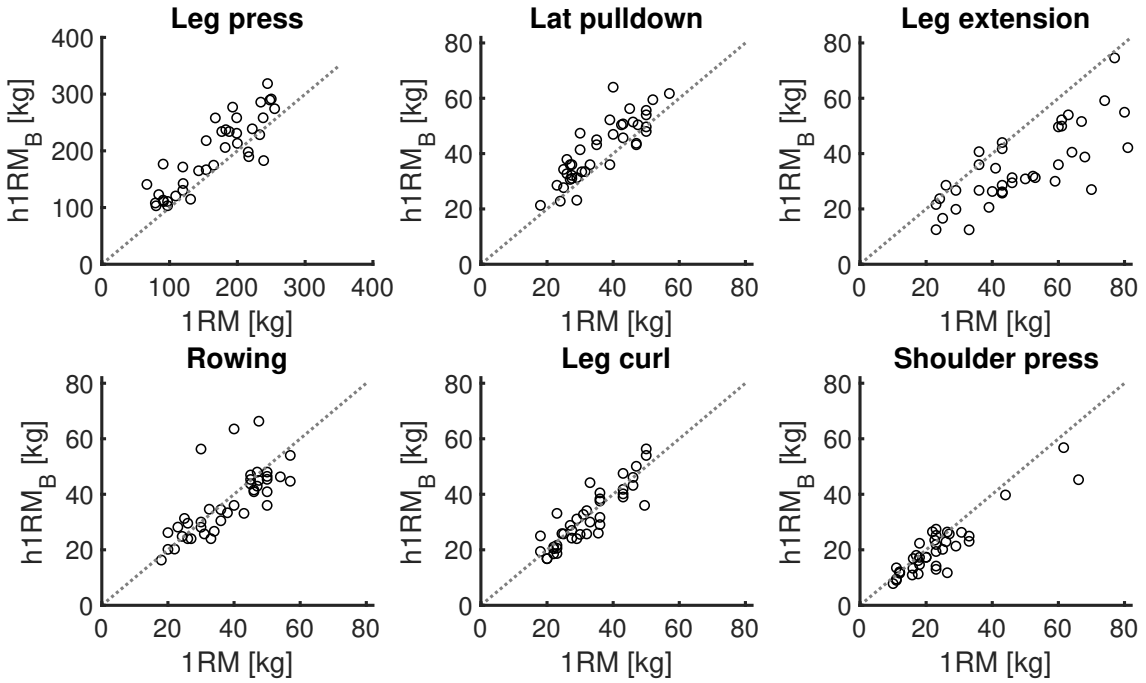


Figure 6: Maximal weights of 1-RM plotted against the predicted maximal weights of h1-RM_E.

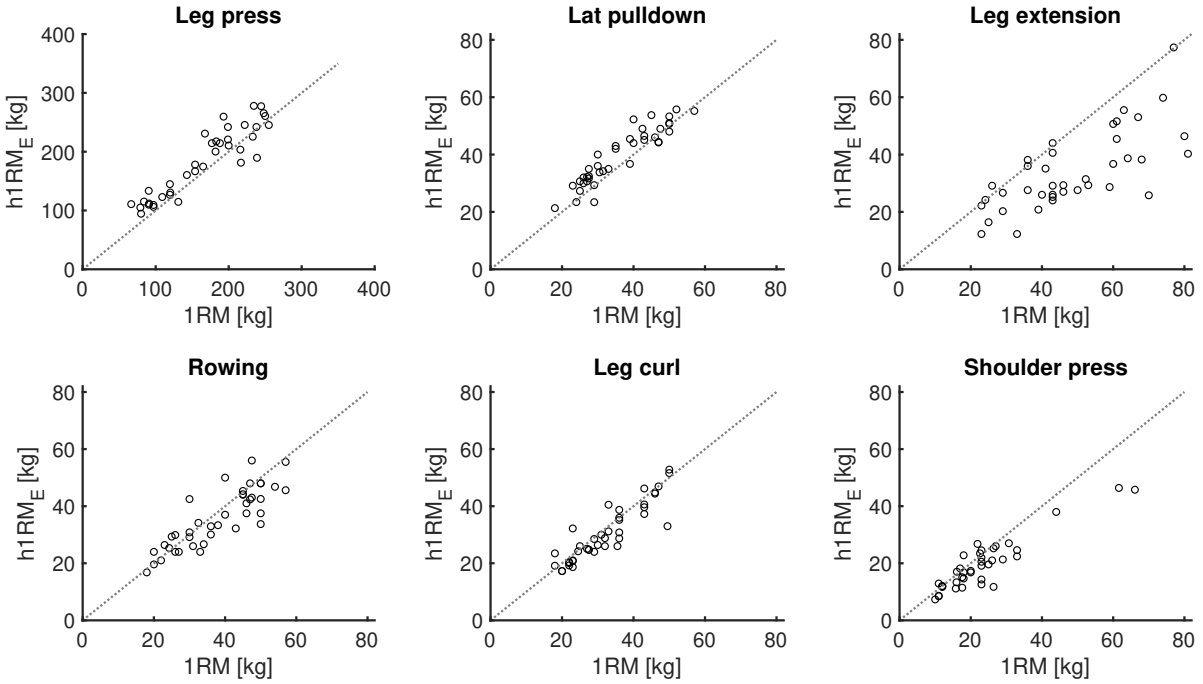


Figure 7: Mean number of repetitions for the three exercise sessions. Bars marked with an asterisk show significant differences to the targeted number of repetitions. Outliers are marked with circles (1.5x interquartile range (IQR)) and triangles (3xIQR).

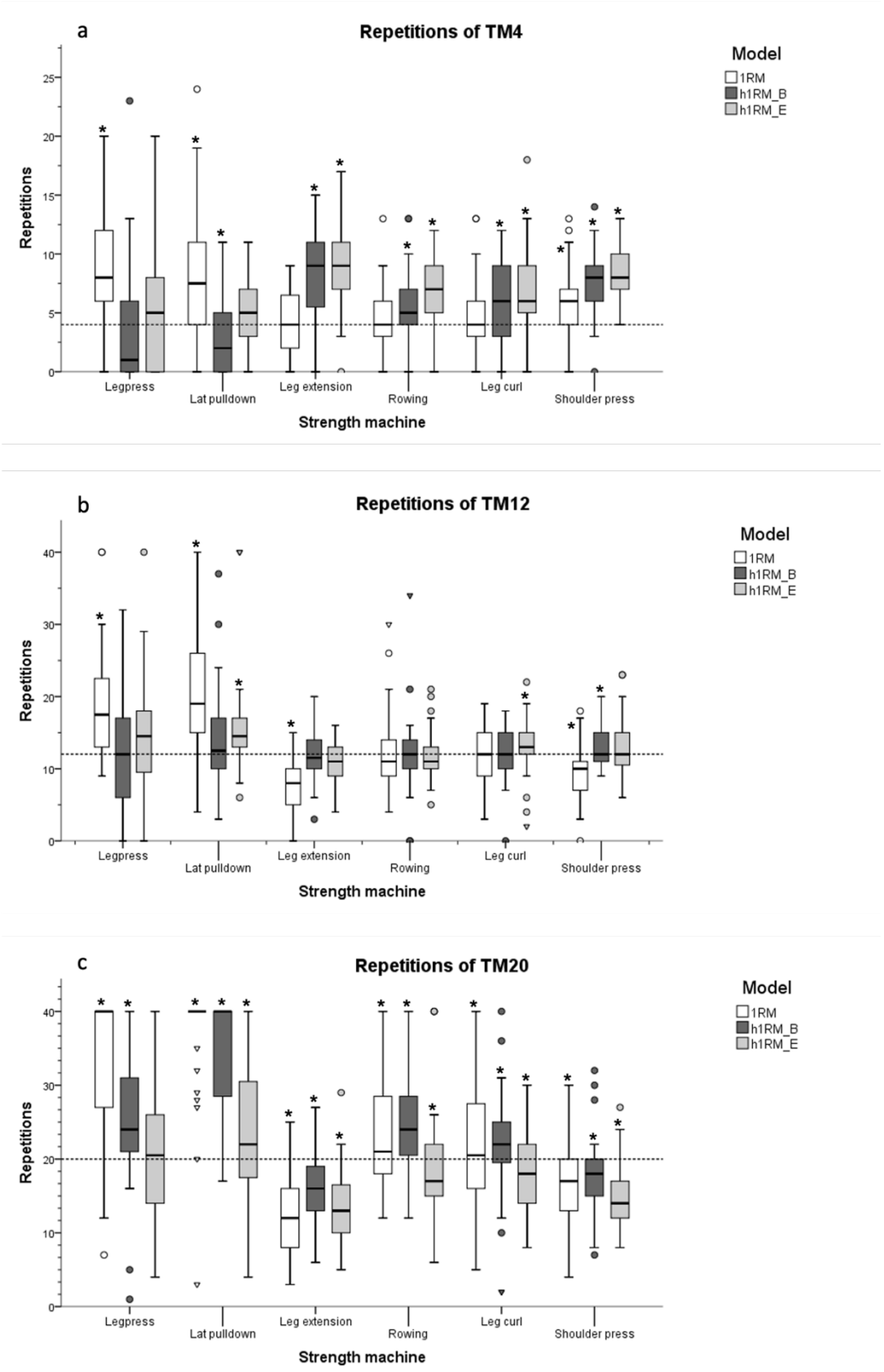
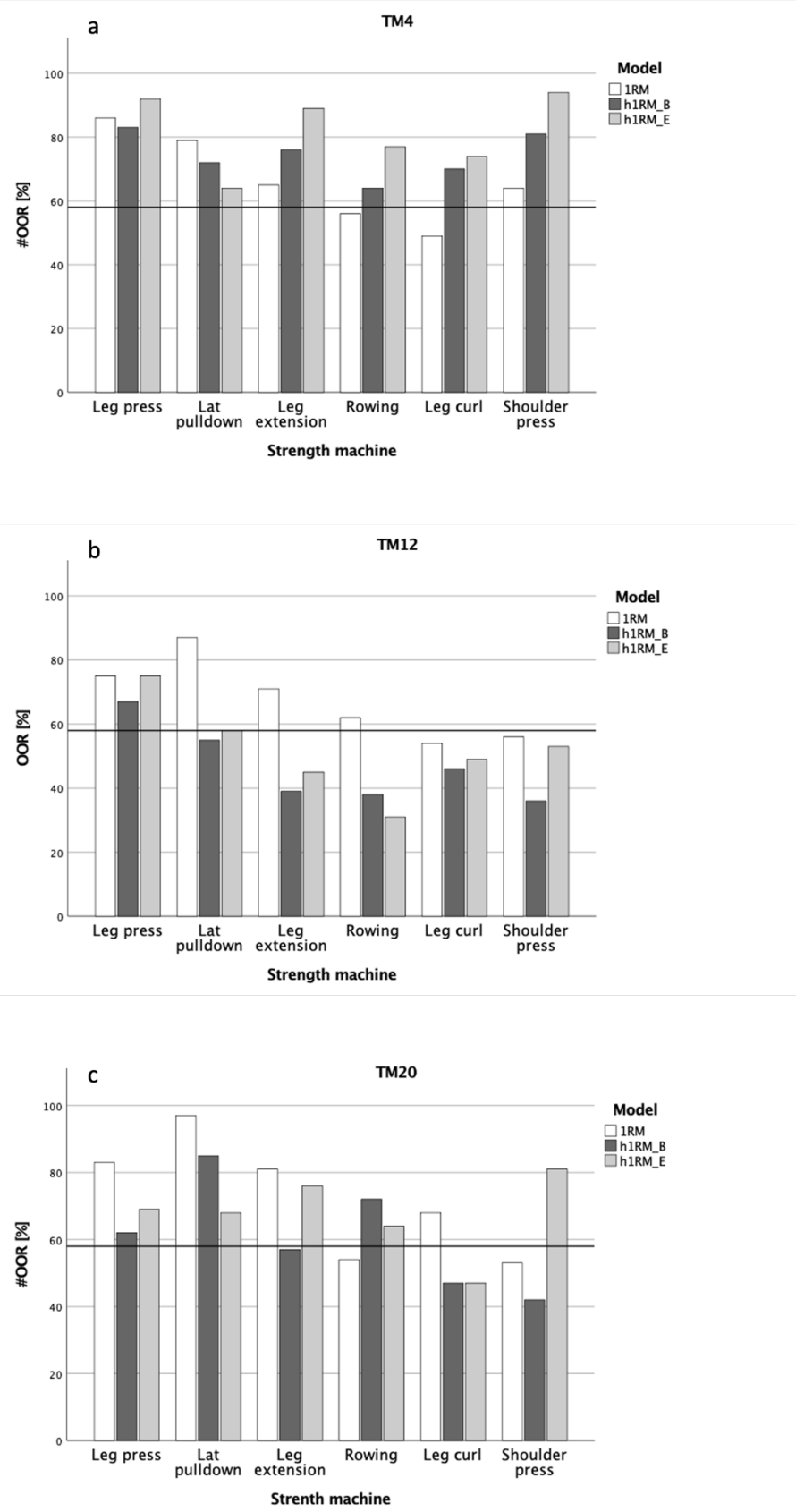


Figure 8: Relative numbers (#) of patients with repetitions outside the defined acceptable range (OOR).



8. General Discussion

The TOP study was designed with the intention to address fundamental questions about exercise intensity prescription by scrutinizing widely used methods in endurance and resistance exercise in breast and prostate cancer patients after primary therapy.

In the following chapter, the main results of the three manuscripts will be summarized (chapter 8.1) and discussed in the light of the current literature (chapter 8.2). Strengths and limitations are listed (chapter 8.3) and an overall conclusion is given (chapter 8.4). The closing part of the chapter proposes practical applications (chapter 8.5) and implications for future research (chapter 8.6).

8.1. Main findings

In manuscript 1, we incorporated supramaximal verification tests with 75 breast and prostate cancer patients. The tests were carried out 10 minutes after the CPETs at 110% PPO (obtained from the CPET) and lasted for about 2 minutes. The tests were feasible in all 75 patients without the occurrence of any adverse events and were therefore considered as safe. Mean CPET-derived VO_{2max} values were higher compared to those attained during the verification test. Yet, the individual data demonstrated that the CPETs underestimated VO_{2max} in 32% of the patients. Only one of these patients would have been identified as someone who failed to attain VO_{2max} based on secondary criteria for maximal exhaustion. Consequently, the verification test offers a high cost-benefit-ratio and is more reliable than secondary criteria for maximal exhaustion in the examined patient population.

In manuscript 2, driven by the question whether threshold concepts might be useful submaximal alternatives to $\%VO_{2max}$, we compared three training sessions in terms of meeting the vigorous intensity zone. The training sessions were performed at 70% VO_{2max} (served as reference), 97% of IAT, and 67% between VT1 and VT2. The data show that on average all intensity prescription methods met the targeted intensity zone. However, some patients were not able to maintain the demanded 38 min (i.e., early session terminations); slightly lower intensities than those selected would improve the durability of the training sessions. Furthermore, the acute bout prescribed by means of bLa thresholds provoked the most homogeneous bLa responses. Therefore, the three investigated intensity prescription methods seem to be equally suitable for targeting the

vigorous intensity zone in breast and prostate CS, yet bLa thresholds should be preferred if a more predictable metabolic training response is intended.

We furthermore implemented a 1-min ramp CPET protocol to investigate whether it is suitable for the determination of IAT in CS. All patients were able to complete enough stages required for an adequate determination of IAT, which proved useful for intensity prescription. To the best of my knowledge, manuscript 2 is the first publication to show that the 1-min ramp protocol is suitable for determining IAT in cancer patients.

Manuscript 3 focused on whether different maximum strength tests yield comparable results and are therefore applicable interchangeably. We compared maximal strength values derived from two indirect strength testing methods (h1-RM after Brzycki and Epley) and one direct method of 1-RM determination (served as reference). All three tests were performed at six different resistance machines (i.e., we obtained three maximal strength values for each resistance machine and compared separately for each machine, whether they differed between each other). We found that the strength test results vary in part considerably between the different methods with the occurrence of both, over- and underestimation of patients' strength performance. The magnitude of the deviations from the reference varies with the type of strength machine.

Moreover, we aimed to investigate the prediction accuracy of targeting specific intensity zones in resistance exercise in CS, i.e., whether the achieved NOR corresponding to specific values of %1-RM were accurately predicted. We conducted the h1-RM and 1-RM tests and derived the training weights for different intensity zones (i.e., %1-RM) and their (theoretically) corresponding repetitions. We then let CS perform repetitions to fatigue with the derived training weights and compared the conducted NOR to the specified repetition targets. We again found significant deviations between the target repetitions and the repetitions carried out. We concluded that the prediction accuracy of all test procedures seems to be very poor for all tested strength training machines for the chosen intensities.

8.2. Discussion

In the field of oncology, the word personalization is on everyone's lips. Exercise has become an important cornerstone in supportive cancer therapy, given its great potential in positively affecting cancer therapy side effects. In exercise oncology, the realization of a personalized

training prescription is one of the top ten research questions in the field [12]. The more individualized an exercise can be prescribed, the better it may contribute to personalized oncology. So-called second-generation studies are called for in which the effects of different training prescriptions should be compared in CS [12]. Yet before the demanded comparisons are possible, it first must be investigated whether the methods used so far are reliable for exercise prescription in CS.

Firstly, one substantial question has never been conclusively answered: "Can I rely on VO_{2max} as an indicator of CRF, on which I base my judgement about the effectiveness of a training intervention in CS?" VO_{2max} is the most commonly used parameter for monitoring physical fitness and therefore essential for the success of an exercise intervention in healthy individuals and patient groups including CS. Alarmingly low VO_{2max} values have been reported in the literature for CS [40]. It is generally believed that exercise naïve and/or clinical populations seldomly attain their highest physiological effort and thus VO_{2max} [68, 70]. The term VO_{2peak} is therefore frequently used when referring to the highest VO_2 reached during a CPET. Accepting VO_{2peak} as surrogate for VO_{2max} likely results in an underestimation of VO_{2max}. This illustrates the problem with using VO_{2peak} as a clinical parameter for the estimation of a patients' aerobic capacity and as a monitoring tool for changes of aerobic capacity (even if the latter requires intraindividual comparisons, it cannot be assumed that VO_{2max} is always underestimated to the same extent). Therefore, the above question would have to be answered with "no".

One possible consequence of failed VO_{2max} attainment is an underestimation of an individuals' CRF [71]. Another possible effect is that with repeated testing over time in an intervention setting, patients gain experience and confidence with the CPET procedure and perform better from test to test regardless of the actual increase in CRF [68]. For instance, McCarthy et al. [78] show that 33% of their healthy participants reached higher VO_{2max} values in a second CPET. This aligns with our results from manuscript 1 and manuscript 2 in which 32% and 33% of the participants did not attain VO_{2max} in the first CPET. The consequence of reaching higher VO_{2max} values in the second CPET would be an overestimation of the efficacy of a training intervention and therewith of its success. As counterargument, results from retrospective analysis of CPET data from a study with CS with mixed entities show that after two previous CPETs, only 2 out of 19 patients show verification markers of VO_{2max} during a third CPET [69]. The authors conclude that "repeated exposures did not improve participants' likelihood of obtaining true aerobic

capacity during testing"[69]. However, in the light of the limited accuracy and therewith applicability of VO_{2max} criteria (see 1.4 above), this conclusion is questionable.

Supramaximal verification tests are a promising approach for verifying VO_{2max} attainment and have been successfully used in a versatile group of individuals of different age, sex, health status and activity level [78, 80, 84, 86, 88-90, 92-94]. In manuscript 1, we show that supramaximal verification tests were feasible for all 75 patients without the occurrence of discomfort or adverse events. Since the TOP Study was the first to implement verification tests in CS, we used a protocol that was proven feasible in healthy individuals [90]. The supramaximal character of the test may cause concern about whether the intensity might be too high for this population. We faced no difficulties with the implementation and all patients were willing and able to perform the test. The clinical setting of our facility may have provided additional comfort for the patients to undergo the supramaximal test and to exert maximum effort. Also, for the testing personnel, the electrocardiogram and the nearby medical support may have provided additional confidence to encourage patients through this demanding test. Consequently, our data show that the verification test is safe to use with breast and prostate CS.

High proportions of individuals who did not attain VO_{2max} during CPET have been reported in studies with individuals with obesity [80] and cystic fibrosis [88]. The authors advise to apply a verification test to avoid gross underestimations of CRF. In contrast, Murias et al. [92] state that a verification test does not add any value for VO_{2max} determination, as VO_{2max} was not confirmed by a verification test in their study with 61 healthy individuals. In manuscript 1, mean VO_{2max} values were significantly higher during the CPET than during the verification test. At first glance, this would support the conclusion by Murias et al. [92], that the verification test does not add any benefit for VO_{2max} confirmation, since it underestimated VO_{2max} (on average!) in the investigated population. Yet this conclusion does not mirror the individual differences between the two tests, which is more relevant for our question on whether a verification test is suitable for identifying those whose VO_{2max} was underestimated by the CPET. Since "exercise testing is performed on individuals not groups" [91], results should also be considered this way in order to avoid misinterpretations. Based on these results, I would recommend that the assessment of whether VO_{2max} values differ between CPET and Verif should be completed on an individual basis, avoiding relevant differences going unnoticed. This assumption aligns with statements from other studies, in which large interindividual differences were also observed [78]. In fact, at

the individual level, 24 of 75 patients showed a VO_{2max} during Verif which was more than 3% higher compared to the CPET. Thus, VO_{2max} was underestimated by the CPET in 32% of the patients, supporting the findings by the first two mentioned studies by Causer et al. [88] and Moreno-Cabañas et al. [80]. When looking at the individual level of the third study mentioned above, VO_{2max} was underestimated by the CPET in 10% (6/61) of the participants [92]. The authors used the estimated measurement error of 2 $mL \cdot min^{-1} \cdot kg^{-1}$ as verification criterion, which represents a relative cut-off value of approximately 5% (mean VO_{2max} of 41 $mL \cdot min^{-1} \cdot kg^{-1}$). This criterion is 2 % higher than the verification criterion used in our study. It can therefore be assumed (and deduced from the Bland Altman plot displayed in their publication) that the number of individuals whose VO_{2max} differed between CPET and Verif would have been larger if a lower criterion had been chosen. Moreover, it is debatable whether 10% of underestimations of CPET VO_{2max} can according to the authors be seen as minor [92]. We can thus state that previous studies which implemented a verification test show that this test helps to identify those individuals whose VO_{2max} was underestimated in the CPET, with the proportion of these people being larger or smaller depending on the study. This may be on the one hand because there is no uniform consensus on which criterion is used as a cut-off (i.e., how much percent deviation between CPET and Verif is considered as different), and on the other hand because there is no uniform definition on the proportion of underestimated VO_{2max} values that can be rated as acceptable. Future studies comparing different criteria could help to clarify this issue.

A question which remains open is whether those patients who's VO_{2max} of the verification test has surpassed the one in the CPET, would reach even higher VO_2 values in an additional verification bout with a higher intensity. Hence, an additional test may be required for a final VO_{2max} confirmation in these patients. For this approach, it would be necessary to determine what intensity this additional test would need to be performed at, and whether it could be performed on the same day. This raises the question whether a second verification test on the same day would overstrain the patients and whether physical fatigue from the first two tests would counteract correct VO_{2max} determination. A second verification test on a separate day, however, would mean considerable additional work for patients and testing personnel. Furthermore, the day-to-day variability of VO_{2max} needs to be considered [121].

On the other hand, there was also a considerable number of participants (n=30, 40%) in manuscript 1 whose VO_{2max} was more than 3% higher in the CPET compared to Verif, meaning

that this group of CS were not able to reach a similar VO_{2max} during Verif (CPET VO_{2max} ± 3%) as the one reached during the CPET. In this group of patients, the intensity during Verif may have been too high and therewith the duration too short, causing muscular fatigue to occur before VO_{2max} could be attained. In fact, mean durations of those whose VO_{2max} was more than 3% higher during CPET compared to Verif tended to be lower than the mean duration of those CS who could at least reproduce their VO_{2max} during Verif (2,08 vs. 2,23 min CPET vs. Verif, p= 0,059). On the individual level, 10 CS whose CPET-derived VO_{2max} surpassed VO_{2max} of Verif by more than 3% were not able to sustain the verification bout for more than 2 min, which is considered the minimum duration for VO_{2max} attainment in verification bouts in healthy individuals [71, 122]. Yet, there were also CS that had Verif durations of less than 2 minutes who satisfied the Verif criterion (n=6) or whose VO_{2max} was more than 3% higher during Verif compared to the CPET (n=3). However, the question arises whether these patients would have reached even higher VO_{2max} values with a longer Verif duration with lower intensity. The intensity of 110% PPO of the verification tests performed in the TOP study was transferred from a study with healthy individuals [90] because these tests had never been performed with CS prior to the TOP study. Results from studies comparing VO_{2max} values of verification tests with different intensities to CPET-derived VO_{2max} values in young healthy males [123] and healthy older participants [124] show that compared to CPET-derived $VO_{2max,}$ a larger proportion of participants achieve similar or higher VO_{2max} values during submaximal (80% to 90% PPO) than during supramaximal (105% PPO) verification tests. This suggests that CS may require a longer test duration at a lower intensity than 110% PPO for their true VO_{2max} to occur during the verification test.

This hypothesis would also be important to clarify in order to better assess the magnitude and therewith the clinical relevance of VO_{2max} underestimation by CPET in CS. In manuscript 1, mean differences between the two tests (–0.64 ± 2.53 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$ VO_{2Verif} - VO_{2CPET}) were similarly small to those reported in previous studies with healthy individuals [91, 93]. Interindividual differences ranged between –9.29 and 3.76 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$, whereas VO_2 differences of more than ≥ 3.5 $mL{\cdot}min^{-1}{\cdot}kg^{-1}$ is considered clinically relevant [45, 125]. Consequently, the clinical relevance of our results from manuscript 1 would likely be low. However, this statement cannot be conclusively assessed until the most appropriate verification protocol for CS has been determined. Future studies should aim at identifying the optimal verification test intensity for CS which ensures sufficient test durations for VO_{2max} to occur.

Interestingly, in manuscript 1, 96% (n= 23) of those individuals who did not attain maximal exhaustion evaluated based on the verification test (n= 24), attained two or more secondary criteria for maximal exhaustion. Hence, almost none of the participants who failed to attain VO_{2max} would have been identified, using secondary criteria for maximal exhaustion. Of all 75 participants, only 68% (n= 51) did attain true VO_{2max} according to the verification test. Of those 68%, 10% (n=5) would have been wrongly assessed as sub-maximal based on secondary criteria. Consequently, secondary criteria for maximal exhaustion showed a high sensitivity of 0.91 (i.e., low rate of false negatives (n=5/75)) and poor specificity of 0.51 (i.e., high rate of false positives (n=23/75) in the assessed study population. This has been shown quite consistently in a large variety of previous studies [67, 79, 82, 84, 85]. Poole ,Jones [68] warned that natural individual variability of maximal values is neglected and VO_{2max} potentially underestimated by 30-40% when secondary criteria are used for assessing VO_{2max} attainment. This assumption is supported by Saynor et al. [84] who showed that traditional criteria for maximal exhaustion significantly underestimated VO_{2max} in patients with cystic fibrosis. Bjørke et al. [70] investigated the prevalence of fulfillment of common secondary criteria for VO_{2max} attainment (VO_2 plateau, Hf_{max}, RER, RPE and maximal breathing frequency (Bf_{max})) in CS, regarding the agreement with the test leader's evaluation of whether a CPET was carried out to exhaustion. Their results show that the test leader's evaluation was associated with the criteria RER_{peak}, RPE and Bf_{max}, whereas APMHR and VO_2 plateau do not show significant associations with the test leader's evaluation of whether a test was defined as to exhaustion. RER and RPE were the criteria with the highest rate of fulfillment (61% and 65%, respectively) which is comparable with results from manuscript 1, in which we obtained fulfillment rates of 84% for both, RER and RPE. Although it must be said that the test leader's evaluation is just another subjective, not validated secondary criterion for maximal exhaustion which is not necessarily congruent with the actual achievement of VO_{2max}. In my opinion, this is the biggest weakness of the study; the lack of a verification test does not allow conclusions to be drawn about how many CS reached their true VO_{2max}. It may well be that both, the secondary criteria, and the test leader's evaluation misclassified VO_{2max}, only in slightly different ways since 34% of the CPETs were misclassified as to exhaustion by the test leader. Again, no statement can be made as to whether these 34% were an actual false positive regarding true VO_{2max}, as secondary criteria were used as a reference. For instance, out of the mentioned 84% of patients fulfilling the RER (≥ 1.1) and RPE (≥ 18) criteria in manuscript 1, 30% did not attain true VO_{2max}during CPET according to the verification test (i.e., false positives of

RER and RPE criterion). Hence, misclassifications are to be expected when using these criteria, with a stronger tendency towards false positives (i.e., VO_2 values will be mistakenly classified as maximal), which supports findings from previous studies with study populations other than CS. It is therefore questionable to use secondary criteria as a reference for alternative criteria. Instead, VO_{2max} values should rather be confirmed by a verification test when serving as a reference.

One can thus state that there are always some individuals who do not attain maximal exhaustion during a CPET. The reasons can be versatile (see General Introduction, page 6). Another possibility for failed maximal exhaustion in some participants is that the chosen CPET protocol may not have been suitable for all patients. Previous studies already concluded that none of the different CPET protocols are suitable/valid for all individuals [126, 127]. Together with the results of manuscript 1, the necessity of a reliable method for VO_{2max} verification seems obvious. In my opinion a verification test should be incorporated into CPET protocols in future studies with CS if the VO_{2max} is to be used as a diagnostic parameter or for evaluating the success of an exercise intervention. For instance, when a patient has a VO_{2max} of 20 and 25 $mL \cdot min^{-1} \cdot kg^{-1}$ at baseline and postintervention, without validation of whether these values represent real maximal values, no conclusions can be drawn about the actual increase in VO_{2max}. Likewise, if training intensities are described as percentages of $VO_{2max,}$ a verification test should be performed to confirm $VO_{2max,}$ otherwise training intensities may turn out too low in a large proportion of CS. The test requires only a small amount of additional effort, as it can be performed directly after the CPET and takes only a few minutes with a much greater informative value than secondary criteria for maximal exhaustion. However, the correct protocol for CS still needs to be determined in future studies. In the interest of complete dosage reporting, VO_{2max} could be reported as "not verified" if no verification test is used in future studies. The use of secondary criteria has in my view no benefit, because VO_{2max} will be unsystematically misclassified as maximal or not maximal in a large proportion of people, what makes their use obsolete.

Despite the known difficulties to adequately determine VO_{2max}, $\%VO_{2max}$ is still one of the most commonly used intensity prescription method in healthy individuals [38], as well as in CS [103, 128, 129]. This raises the question whether the prescribed stimulus corresponds to the metabolic strain? Or in other words, "when a cancer patient exercises at a specific $\%VO_{2max}$ which is defined as e.g., "vigorous", does this stimulus really elicit a vigorous strain at the metabolic

level?" To answer this question, in manuscript 2, we compared the cardiometabolic responses of one acute bout (38 min) of vigorous intensity exercise at 70% VO_{2max} to two sessions with vigorous intensities prescribed by means of ventilatory (67% between VT1 and VT2) and bLa thresholds (97% IAT), respectively. We found that the cardiometabolic responses did not differ between the three investigated methods, and therefore conclude that 70% VO_{2max} is suitable for targeting the vigorous intensity zone in CS.

Nevertheless, we observed the trend that all cardio-metabolic parameters and the number of early terminations were (not significantly) lower in response to the exercise session based on $\%VO_{2max}$, when compared to the other two methods. It is possible that this trend would have resulted in statistically significant differences in a larger cohort, which has to be considered when interpreting the results from manuscript 2. Retrospective analyses of CPET data from breast CS at the end of primary therapy have shown that exercise stimuli prescribed based on $\%VO_{2max}$ turned out slightly lower than intended when compared to the ACSM recommendations for healthy individuals [116]. The authors specify adaptations which should be applied when exercise prescriptions for healthy individuals are used for CS. The intensity of 70% VO_{2max} used in manuscript 2 was within the specified range (67-91%VO_{2max}) for vigorous intensity endurance exercise with CS after primary therapy. Therefore, our data confirms that the specified range by Scharhag-Rosenberger et al. [116] can be used to adequately target the vigorous intensity zone in breast and prostate CS. Nevertheless, some patients were not able to maintain the demanded 38 min at 70% VO_{2max} which is why we recommend using lower percentages (e.g., 65%) to increase durability. Thus, in this training session the training strain tended to be lower (on the group level) than during the two sessions based on lactate and ventilatory thresholds, whereas some patients were overtaxed. Consequently, fixed percentages of maximal values might fit on average, but may be inaccurate on an individual level.

This has already been observed in previous studies; For instance, prolonged exercise at given percentages of VO_{2max} resulted in a large variability of bLa responses and therefore in heterogenous metabolic strains in a group of healthy participants [47]. In accordance, in manuscript 2, bLa responses were less homogenous when intensity was prescribed based on $\%VO_{2max}$ compared to the session in which intensity was based on bLa thresholds. In other words, despite the same percentage of VO_{2max} at which the patients exercised, there was a considerable variation in the exercise strain at the metabolic level. Also the other way around,

Meyer et al. [130] showed that percentages of VO_{2max} and Hf_{max} varied considerably at the IAT in healthy individuals. Hence, using fixed percentages of VO_{2max} seem to result in an unpredictable metabolic response; a point of criticism which has been raised before [38, 47]. Therefore, the question posed above cannot be conclusively answered with "yes" regarding $\%VO_{2max}$ since this prescription method results in great fluctuations regarding the exercise strain. This challenges the use of fixed percentages of VO_{2max} for prescribing exercise intensity, as a defined metabolic strain is necessary to achieve predictable adaptive responses, the basic aim of intensity prescription.

Wolpern et al. [35] and Weatherwax et al. [131] impressively demonstrate the consequences which can result from using fixed percentages of maximal values with regard to training effects. In their studies with healthy participants, 100% were able to improve their VO_{2max} following 12 weeks of training prescribed by means of ventilatory thresholds. Conversely, of those following the same intervention with intensities prescribed based on percentages of HRR, only 42% [35] and 60% [131], showed improvements in VO_{2max}. The authors conclude that threshold concepts "should be considered as a viable and practical method" [132] with the potential to "enhance training efficacy and limit training unresponsiveness" [35]. These and other previous studies led to the notion that threshold concepts are more accurate in eliciting a homogenous metabolic strain amongst different individuals, which is explained by the fact that they are anchored to the metabolic profile of an individual [38]. Also, in CS thresholds are considered more efficient for maximizing training effects [133], yet their use for targeting the vigorous intensity zone in CS has never been validated prior to the TOP study (manuscript 2). We investigated whether bLa and ventilatory thresholds are (equally) suitable for this purpose. To the best of my knowledge, in CS, VT were used for prescribing low- to moderate-intensity exercise in three previous studies [100, 134, 135] whereas bLa thresholds were used only once in CS [136]. However, these studies do not allow to draw conclusions about the accuracy of threshold concepts for exercise prescription in CS, as systematic comparisons between different methods are missing. Deduced from manuscript 2, bLa and ventilatory thresholds are suitable for targeting the vigorous intensity zone, however, bLa thresholds have proven to be more reliable regarding the provoked metabolic response. It can be assumed that a training prescribed by means of bLa thresholds elicits more predictable training effects in a heterogenous group of individuals which makes it particularly useful in CS. Yet, bLa threshold determination requires blood sampling and additional analyses, and might therefore remain reserved for research or elite sports.

In the light of the results from manuscript 1, threshold concepts are potent alternative methods to fixed percentages of maximal values for intensity prescription as the challenge of reaching maximal exhaustion can be bypassed. Yet for many people with restricted physical capacity, commonly used CPET protocols are not possible to be performed over the minimum duration required for bLa determination. These protocols comprise 3-min stages and at least five stages must be completed to reliably determine LT [50, 58]. This presents a limitation for LT determination in CS. In the TOP study we have adapted the CPET protocol to the possibilities of the patients and therefore incorporated a 1-min ramp protocol. Results from manuscript 2 show that the 1-min ramp protocol is useful for CPETs with CS when bLa and ventilatory threshold determination is intended.

Regarding the subjective perception of the intensity, the training sessions performed in manuscript 2 were rated as moderate (RPE 12-13 according to Garber et al. [43]) by the participants, albeit the fact that cardio-metabolic responses reflected the vigorous intensity zone. This has also been shown in a previous study with breast CS [129]. Therefore, from our data it can be hypothesized that RPE should not be used for training prescription in CS because intensities may be misestimated using this method.

The existing literature clearly shows that resistance training has great potential in preventing and alleviating oncology treatment related side effects in CS [7-9, 25, 26, 105]. This has led to strength training becoming an integral part of all available exercise oncology guidelines [6-9]. However, these guidelines presuppose assumptions some of which have never been validated for their use in CS. The TOP study aimed at verifying the following assumptions: (I) Maximal strength tests (direct or indirect, see 1.6 above) are safe, and (II) provide accurate estimates of maximal strength in CS. Furthermore (III), percentages of maximal strength are a valid method for prescribing resistance training intensities in CS.

Firstly, with regards to safety, there is a widespread belief that 1-RM tests [137-139] as well as h1-RM tests [140, 141] are safe with CS. This has also been recently stated in the updated international multidisciplinary roundtable's exercise guidelines for CS [9]. In manuscript 3, both, 1-RM and h1-RM tests could safely (i.e., no adverse events) be performed. Yet in the TOP study part 2, one 69-year-old CS experienced a lower back vertebral fracture during the 1-RM test at the leg press [108]. This serious adverse event (SAE) shows that this testing method is not as safe as assumed, especially for elderly clinical populations. Another SAE has already occurred in a

study with elderly, RT naive participants [109], and it is also assumed that adverse events were likely underreported in previous studies with CS [114, 142]. Furthermore, exercise studies tend to have a selection bias, since younger and fitter patients are often recruited with exercise experience pre-diagnosis, which makes it less likely for (S)AEs to occur [39]. This questions whether 1-RM testing is as safe as claimed for elderly and/or clinical populations. Using h1-RM or x-RM tests instead of 1-RM were proposed as a potentially safer assessment procedure in novice lifter [36] elderly clinical populations [108]. The x-RM test is also part of the ACSM guidelines for exercise testing [42] and has been successfully used in studies with CS [141]. We chose the 1-RM test because it is the most used method for assessing dynamic strength and we wanted our data to be as representative as possible. The occurrence of the SAE reported above, occurred after the completion of all 1-RM tests, used for the present dissertation. Had the SAE occurred at an earlier point in time, we would have reconsidered the use of this testing procedure and would have likely performed the h1-RM tests only or a x-RM test instead.

Concerning the second assumption on the accuracy of the different strength testing methods, to the best of my knowledge there is only one study published that presented coefficients of variation of bench press and leg press data from 1-RM tests performed with CS [113]. In manuscript 3 we compared two different hypothetical 1-RM testing methods to the direct 1-RM method. Although we used the 1-RM test as a reference, which means that we consider it to be a valid method for determining the maximum dynamic strength in CS, this assumption needs to be discussed in the light of the results of manuscript 1. As there is currently no existing method for verifying that maximal values have really been reached, the validity of the direct 1-RM test can be questioned as well. For instance, Ritti-Dias et al. [143] show that the reliability of the 1-RM tests varies between individuals with and without prior experience of resistance exercise. The performance (i.e., maximal weights) of non-experienced individuals increased by about 10% over the course of multiple repetitive testing sessions (with adequate recovery time in between), whereas no differences between test results occurred in individuals with previous experience in resistance exercise. The authors hypothesize that the increase in performance is due to improvements in neural adaptations and conclude that two to three 1-RM tests are necessary for an accurate assessment of maximal strength which is supported by other studies with similar results [117, 144]. This assumption could also be true for the CS in our study as the majority was inexperienced regarding resistance exercise. Even though we had the patients perform two familiarization sessions prior to the strength tests, these sessions were performed with moderate

weights and thus did not reflect the testing situations. One possible consequence could have been that the patients performed repetitions to failure with lower intensities than the intended 47, 69, 92%, respectively, resulting in higher NOR performed, which must be considered when interpreting the data of manuscript 3.

Another point of criticism regarding the use of strength tests has already been raised in the literature, stating that the performance in a strength test depends on how closely the used test resembles the training program [145, 146]. Therefore, strength depends on the test used to assess it, which in most cases is the 1-RM. In other words, the performance in a 1-RM test will improve most when the training was performed with high weights and few repetitions. This has been shown by Campos et al. [147], who compared a group of healthy men training with high relative loads (3-5-RM) to a group training with low relative loads (20-28-RM). The first group performed better in a 1-RM test than the latter, which however had a higher increase in performance in a repetitions to fatigue test at 60% 1-RM. CS commonly train the hypertrophy/strength-endurance component (i.e., 8-20 repetitions), which is also recommended by guidelines for RT with CS [9]. Consequently, improvements in strength may be overseen in CS when the 1-RM test does not mirror the training program. Therefore, whereas the 1-RM is more relevant in populations who want to improve their maximal strength (e.g., powerlifters), for CS, alternative/additional strength testing methods may be more appropriate which reflect the hypertrophy/strength endurance component. This assumption is supported by results from a retrospective analysis of data from older men and women in response to 12 (n = 110) and 24 (n= 85) weeks of supervised RT, which show that there were no non-responders when multiple strength measurements were applied since all participants improved in some way [148]. Consequently, the occurrence of the SAE together with the one-sided picture that the 1-RM test presents in terms of strength gain, indicate that this procedure should be replaced in older clinical populations including CS. A x-RM test is a safer alternative which may also better mirror the strength component that is usually trained in CS and is therefore likely more appropriate for these patients.

Regarding the accuracy of the h1-RM methods, our data show that depending on the resistance machine, significant deviations occur between the maximal values of nearly all methods and strength machines. This has already been shown before [96-99] and is particularly true when the repetition range is large. This has been thoroughly discussed in e.g., Wood et al. [115] and

Mayhew et al. [95] in their analysis of seven and 14 commonly used prediction equations for h1-RM, respectively. They conclude that the prediction accuracy was generally high for all equations across a wide range of strength machines when NOR performed during the test was ≤ 10. In the TOP study we performed the h1-RM test in a way that a weight was selected that can be moved 5-12 times, yet up to 20 repetitions were accepted. Consequently, it seems worth investigating whether performing the test in such a way that a maximum of 10 repetitions are possible would also provide more accurate estimates of the 1-RM in CS.

Our data also show that maximal weights at machines training large muscle groups (leg press, lat pull-down) tended to be over-estimated by the indirect methods, whereas those, training smaller muscle groups (rowing, leg extension and – curl, shoulder press) were more likely to be under-estimated by the indirect testing methods, which has been observed before [36]. Whether and to which extent the predicted 1-RM is under- or overestimated additionally seems to vary with training status [149]. This could lead to misinterpretations of training effects when h1-RM tests are used for training interventions. Additionally, training weights likely turn out incorrectly when derived from predicted 1-RM values, what should be considered especially for strength machines training large muscle groups to avoid unintentionally high training weights (further elaborated below).

Now that we have discussed that the h1-RM methods used in manuscript 3 are inaccurate for determining maximal strength, and that the 1-RM test does not necessarily guarantee the determination of the true maximal dynamic strength, we are facing the same problem as with endurance exercise: Inaccurate maximal values may lead to incorrect training loads if intensity prescription is based on percentages of these values. This must be kept in mind when using the above-mentioned testing methods of maximal strength for intensity prescription in CS, as training weights could lead to under- or overload depending e.g., on the used strength machine and method. This brings us to the third assumption above, regarding the validity of %1-RM for intensity prescription (i.e., the accordance of %1-RM and the estimated corresponding NOR). As already discussed for endurance exercise, knowing the relationship between a workload and its resulting metabolic strain is important to ensure correct training prescription. With resistance training, the problem is even more pronounced, since training weights are commonly prescribed by means of %1-RM/h1-RM and the corresponding NOR, in healthy individuals as well as in CS. This method has already been criticized for RT in healthy individuals, since the

NOR at selected %1-RM depends on gender [118], training status [98, 118, 149] and the used strength machine/muscle group [96, 97, 117, 118]. Compatible with this, in manuscript 3 we found in part extremely high variability in the NOR at selected %1-RM. For instance, at 69% 1-RM on the leg press, mean repetitions were 19, 11 and 14, depending on the maximal strength test used (1-RM, h1-RM_B, h1-RM_E, respectively). These values do not deviate extremely from the stated range of 8 to 12 repetitions defined by the exercise guidelines for CS [9] for 60-75% 1-RM. Yet, on an individual level, the NOR ranged from 0 to 40 in the most extreme cases and might have turned out even more extreme if the patients had not been stopped at 40 repetitions. Hence, when using percentages of maximal strength values, strong interindividual variability of exercise strain may occur with the methods used in manuscript 3. As already stated above, the results of the two different indirect methods used in manuscript 3 do not only deviate from the results of the 1-RM test, but in part also between each other. By implication, intensity prescription in the form of %h1-RM cannot provide accurate values.

This is even more far reaching in RT than for endurance training, as training intensities may not only turn out too low but also too high. Consequently, on the one hand, training weights may turn out below targeted intensities with the resulting possibility of missing training effects, whereas on the other hand, training weights that turn out too high may result in overload or even harm the patients in the long run. This would both contradict the underlying logic of personalized training prescription and is particularly concerning since a high proportion of studies implementing resistance exercise with CS derive their training weights using indirect strength tests [150]. From a practical perspective, however, it must be said that a training weight below targeted intensities would usually be increased quickly when the patient is able to perform the specified NOR with ease, provided the training is supervised by an exercise professional or the patients are well instructed and can safely manage the adjustment of the training weights themselves. In this case it would be rather unlikely that missing training effects would occur due to an unintentionally low starting weight in an intervention setting with adequate progression. However, training overload is particularly problematic in the elderly, including the CS of manuscript 1 (61.3 ± 12.0 years), manuscript 2 and manuscript 3 (both 62.9 ± 9.2 years), who are mostly inexperienced regarding resistance exercise and therefore likely more prone to training injuries [151]. Negative training experience which may result from training overload could discourage patients from continuing. This should be avoided, since CS

do already not generally meet the recommendations for physical activity and since activity levels typically decline even further during the treatment period [39].

One could avoid potentially overtaxing the patients by approaching the intended NOR without calculating them via maximum values, which have a poor cost-benefit ratio in view of their inaccuracy and cumbersomeness. This can be illustrated by an example from manuscript 3. The only case in which we obtained an acceptable accuracy of NOR was with both h1-RM methods for the 12-RM training session. This result is not very surprising since during the h1-RM test, a weight is selected that can be moved 5-12 times, which is then used (together with the completed NOR) to calculate the predicted 1-RM. Then the weight that can be moved 12 times is calculated from this value. With this weight, the patient may still be able to do more or less than 12 repetitions, so during the first training session, it may be necessary to adjust the weight to really find the one that the patient is able to move 12 times. A more practical approach would be to omit the intermediate step and simply approach directly to the desired weight (gradually increase or decrease the weight until the patient can lift the weight 12 times). That prescribing the actual NOR to dictate the intensity and not vice versa may be more suitable for several reasons has already been discussed in previous work [36]. This approach is also part of the Australian recommendations for CS in which intensity prescriptions for RT are specified either as 50-80% 1-RM or 8-12 repetitions [2].

8.3. Strengths and Limitations

The TOP study offers different novelties and strengths. It is the first study to implement supramaximal verification tests with a large number of cancer patients. Furthermore, we applied a CPET protocol with 1-min stages for LT determination and showed that it is suitable for this purpose and this cohort of CS. The highly laborious one on one supervision during all exercise sessions ensured a high accuracy of data. The randomized cross-over design of manuscript 2 and 3 allowed intra-individual comparisons. Furthermore, it allowed a comparison of objective cardiometabolic measures with patient reported outcomes. The use of sophisticated gold-standard methods like CPET as well as LT and VT determination, allows the comparison of data among studies using the same procedures, thus increasing the external validity of the results. Despite the vigorous exercise intensities in all three sub-studies, the TOP study part 1 has been terminated successfully without the occurrence of serious adverse events.

Furthermore, the TOP study focused on patients after primary treatment for breast and prostate cancer, as these are the two most frequent cancer entities in women and men, and the majority of exercise studies were conducted with these two types of CS [152]. The post-treatment timepoint was selected as it is considered the phase in which the acute effects of the cancer therapy have mostly dissipated [153] and their effects on the trainability are therefore likely small/neglectable. As opposed to the treatment and early post-treatment period in which more fluctuations in cardiometabolic parameters due to the medical treatment are to be expected, preventing reliable assessments of training effects.

The TOP study has also some limitations that need to be addressed. Most notably, the study design is somewhat complicated, especially regarding resistance exercise (manuscript 3). Combined with the small sample size, the statistical analysis of manuscript 3 was challenging (further elaborated below). Also, in manuscript 2, the sample size (n=40) was modest, which should be considered when interpreting the results. Regarding the patient population, it is possible that most patients participated in the study because of an already existing affinity to physical activity as we did not include a non-exercising control group. It can therefore be assumed that the assessed cohort presumably showed more affinity to physical activity than the "standard" CS. This bias could have been reflected in higher fitness levels, exercise experience, and willingness to push one's limits. However, due to our exclusion criteria, no CS were allowed to participate who regularly exercised more than once a week, so the effects mentioned should only be of minor importance. In fact, the CRF of our cohort was similar or even below that of other studies with breast [40] and prostate cancer patients [154] of comparable age. Nevertheless, this potential selection bias (i.e., volunteer bias) limits the internal validity of the study, "i.e., the characteristic of a clinical study to produce valid results" [155] which has to be kept in mind when interpreting the data. It also must be considered that the results of the TOP study are based on a cohort of middle-aged breast and prostate CS after primary treatment, which limits their generalizability.

Regarding the CPET methodology, the patients did not have a familiarization run on the cycle ergometer prior to the first test. Even though cycling requires relatively easy movement patterns and is mastered by a broad mass of people, it is still possible that the coordinative requirements hampered exercise naïve participants and in turn distorted VO_{2max} outcomes. That VO_{2max} increases from one CPET to the next in participants who are inexperienced with this procedure has been shown in previous studies with healthy individuals [78] and patient collectives [156].

The latter included men with prostate cancer who carried out two CPETs within one week and found VO_{2max} to increase significantly from the first to the second CPET despite high reliability between the tests ($r=0.92$, $p<0.001$). Consequently, it is possible that higher VO_{2max} values would have resulted in the TOP study if we had performed familiarization sessions. Yet, familiarization sessions for CPETs are not performed in most studies with CS and we wanted our study protocol to be as representative as possible. Furthermore, the VO_{2max} of the patients measured too low in the CPET would probably have turned out higher in the verification test. Therefore, these patients would have been identified by the verification test as those who did not reach true VO_{2max}.

The limitation also concerns the strength testing procedures. Even though the patients carried out two familiarization sessions prior to the maximal strength tests, these sessions did not reflect the testing procedures as they were performed with moderate training weights. The physical (coordination) and mental (courage) prerequisites may not have been fully developed when the patients conducted the 1-RM test for the first time, since they experienced the sensation of moving maximum weights, and thus really pushing to the limits, only during the actual testing procedure. Hence, like the above-mentioned argument on CPETs, it can be assumed that reaching "real" maximum values may have been hindered by the patients' inexperience regarding the 1-RM testing procedure. This assumption is supported by previous studies which came to the result that at least two prior tests are necessary in order to reach "real" maximum values during a 1-RM test in healthy participants without previous experience of resistance exercise [143, 144]. This is not the case in individuals with previous strength training experience. In our study, we only included CS who had not performed regular vigorous endurance or resistance training (> 1 session per week) within the 6 prior months. However, we did not account for training background in our data analyses, which must be considered as further limitation when interpreting the data.

It also must be mentioned that the results of manuscript 3 could be limited by the setup of the study. Patients conducted two maximum strength tests on the same testing session, and three sets with in part very different weights during each training session. In our analyses, we then compared the different maximum weights and the different NOR. Albeit the fact that we randomized the order of the testing procedures and the order of the methods for the three sets during the training sessions, the effect of increasing muscular fatigue may still have had an

influence on the data in different possible ways: (I) without muscular fatigue, maximal values could have turned out higher in the tests, (II) and the NOR could have turned out higher during training sessions, or (III) the NOR could also have turned out lower, since training weights would have turned out higher with higher maximal weights. In the case of (I) and (II), the training stimulus could have been overestimated in manuscript 3, whereas it could have been underestimated if case (III) was true.

Statistically the multiple randomization procedures should have been considered, which however was not possible because of the small sample size. Due to the complex set-up used in manuscript 3 and the challenging data analysis associated with it, we have developed an additional analysis procedure. However, this procedure has not been validated for these purposes and should therefore be considered as a purely experimental approach.

8.4. Conclusion

The field of exercise oncology has come a long way. Cancer patients were advised to take it easy and rest back in the 1980s; nowadays exercise is recommended by numerous expert panels to CS irrespective of the cancer entity, the type, and the timepoint of treatment [3, 6-9]. The various positive effects of exercise in CS have been proven [1-5], now it's time for exercise to become a personalized therapeutic strategy by exploiting its full potential through more individualized exercise prescriptions. The ultimate goal should be that exercise becomes an integral part of cancer treatment by prescribing a tailored exercise program that meets the patient's needs and goals in consideration of their medical situation (cancer type, stage, therapy and its side effects and comorbidities) and the resulting limitations to exercise [22] to each cancer patient as a standard. For this to happen, the essential prerequisite is to make sure that the methods used for exercise intensity testing and prescription in CS are reliable, which was the primary aim of this dissertation.

Our results demonstrate that currently used methods of exercise testing and prescription seem to have only limited applicability in CS. The overall conclusion for endurance exercise is that threshold concepts seem to be suitable alternatives to $\%VO_{2max}$ for intensity prescription, yet bLa thresholds should be favored if a defined metabolic strain is intended because this method evokes the most homogeneous bLa responses between individuals. Furthermore, a verification test seems necessary to ensure VO_{2max} attainment, when percentages of VO_{2max} are used for intensity prescription or if the effect of a training intervention is to be evaluated based on

changes of VO_{2max}. These methods guarantee the highest possible accuracy, but at the same time require a certain added effort, both for the patients and the staff, which is why they are primarily relevant for exercise studies with CS. Outside of studies more inaccuracies can be accepted providing that patients are not put in danger. For this, it is important to closely monitor the patients for signs of over- or underload, to ensure maximum safety and adequate training stimulus at the same time. Alternatively, if supervision is not possible, e.g., during everyday training outside of studies, patients should be well instructed to recognize these signs themselves. With regards to resistance training, a gradual approximation to specified intensities might be an alternative approach, which would not only facilitate strength training, both in practice and in the scientific field, but would ironically also make it safer and more accurate for achieving a targeted training stimulus.

Consequently, when designing an exercise program, one should weigh which test, and intensity prescription methods are reasonable for a certain purpose as well as how much inaccuracy one is willing to accept. The TOP study provides the data to assess which of the elaborated methods for exercise testing and prescription bring which inaccuracies or even dangers and therefore pave the way towards the demanded second-generation studies. However, our data demonstrate that in all three manuscripts, the individual data show in part extreme interindividual variability, which sometimes tells different stories than the group means. Concretely this means, if we assessed the reliability of the investigated prescription methods, and the informative value of the verification test solely based on group means, we would have rated the former as mostly satisfactory and the latter as inadequate. This highlights two potential problems: Firstly, the methodological problem of drawing conclusions from group means, which can have far-reaching consequences, especially for the interpretation of study data. Secondly the problem of the "one size fits all" approach of fixed percentages of maximal values resulting in a high interindividual variability of training strain.

It is important to have tools that can be used to determine training intensities for CS as well as to validate their accuracy, to which the TOP study has made an important contribution. Our results show that data analysis and interpretation should fit the question under investigation. There will and can never be one method that fits all. People are individuals and training should be prescribed accordingly in order to obtain an optimal effect for an individual person. To get there, it is important not to blindly rely on calculated exercise intensity specifications but to

employ them for guidance. Instead of trying to find one method providing the most predictable accuracy of training responses, a combination of existing methods may be more appropriate to better accommodate for the individuality of patients.

8.5. Practical applications

The following practical applications for exercise testing and intensity prescription can be derived from the results of this dissertation:

Implications for exercise testing with cancer survivors

- A verification test at 110% PPO, 10 min after CPET can be safely performed in breast and prostate CS and constitute a valuable tool for discriminating between those who attain VO_{2max} during CPET and those who do not (manuscript 1 and 2).
- Secondary criteria for maximal exhaustion do not add any value for confirming VO_{2max} as a considerable proportion of CS is misjudged (manuscript 1 and 2).
- The CPET protocol with 20 W starting power and increase of 10 W per minute is suitable for determining a reference point on the bLa curve (likely the IAT) useful for intensity prescription in breast and prostate CS after primary treatment.
- The 1-RM test is not safe with CS and should be replaced by an alternative sub-maximal strength test.
- Indirect 1-RM tests could safely be performed with CS, however, the results vary largely depending on the method and the tested muscle group. Comparisons between studies using different testing methods should therefore be interpreted cautiously (manuscript 3).
- A multiple repetitions maximum test could be a safer alternative which may also present a higher specificity of the strength component which is usually trained with CS.

Applications for intensity prescription in cancer survivors

- When percentages of VO_{2max} are used for intensity prescription, VO_{2max} attainment should be ensured (preferably by using a verification test), otherwise training intensities may turn out too low.
- bLa thresholds should be favored if a defined metabolic strain is intended because this method evokes the most homogeneous bLa response between individuals (manuscript 2).

- When prescribing vigorous intensity exercise in CS, 70% VO_{2max}, 97% of the IAT, and 67% between VT1 and VT2 are feasible. However, slightly lower percentages might be preferable to avoid early session terminations (e.g., 65% VO_{2max}, 90% of the IAT, and 60% between VT1 and VT2) (manuscript 2).
- For resistance training, determining training weights for specific NOR using percentages of 1-RM or h1-RM should serve only as rough orientation for the first training session, as very inhomogeneous training stimuli with potential overload for some patients (%h1-RM) are risked. Therefore, patients should be closely monitored during their exercise sessions and weights adapted if required (manuscript 3).
- A simpler alternative for training weight determination is to directly approach the intended training weight without describing it as a percentage of the 1-RM/h1-RM, by gradually increasing or decreasing the weight until the intended NOR is possible (manuscript 3).

8.6. Future directions

Previous research and the results of the TOP study give rise to new questions that should be considered in future studies on individualized intensity prescription in CS.

Verification test

To increase the informative value of Verif, future studies should establish a standardized protocol allowing a duration that is as long as necessary and as short as possible for VO_{2max} to occur in the largest possible proportion of CS. Also, uniform cut-off values should be specified defining which discrepancy between CPET and Verif derived VO_2 values is considered acceptable. Furthermore, future studies should explore how to manage individuals whose VO_{2max} is higher in the verification test than in the CPET. It should be investigated in which form (which intensity? same day or separate days? which temporal distance?) further verification tests can be included and whether the benefit outweighs the effort.

Intensity prescription in chronic exercise

In contrast to the background of the results on acute bouts of exercise, future research should verify the suitability of threshold concepts for intensity prescription in interventions with longer durations. Long-term adaptations to exercise can not necessarily be predicted using acute responses to training. Therefore, intervention studies are required to investigate whether

different training prescription methods will provoke different adaptations to training. The fact that the bLa threshold derived training bout elicited more homogenous metabolic responses (compared to VT and $\%VO_{2max}$), suggests that they may be more suitable for provoking consistent training effects in CS with heterogenous fitness levels. The TOP study part 1 provided important findings regarding the accuracy of different intensity prescription methods; The next step would be to compare the effectiveness of different training regimens in CS. In other words, what combination of intensity and volume elicits the most beneficial training effects? Most extant studies did not compare different training groups but training groups to control groups. Therefore, no conclusions can be drawn about the effectivity of different training regimens. In the TOP study part 2, we compared polarized endurance training to standard vigorous-intensity training regarding their effectivity on training effects. The results are not available yet, as the data analysis is still pending.

Molecular link

Although the positive effects of physical activity have been recognized, the underlying molecular mechanisms remain largely unexplored. A prominent focus of exercise oncology literature are the changes in metabolic and inflammatory parameters, which have been primarily investigated in response to endurance exercise in breast cancer patients [157]. However, the results are inconsistent and the hypotheses on potential biological mechanisms have to be regarded as preliminary [158]. Enhancing our knowledge about how different types and dosages of exercise affect relevant cancer outcomes and about the underlying mechanisms would be a big step towards exercise as tailored treatment strategy in oncology. An individual patient could be provided with the right dose of physical activity at the right time, depending on the goal, the medical condition, as well as the planned cancer treatment in relation to the patient's "metabolic constitution".

Within the TOP study part 2, we took blood samples from patients before and after maximal endurance or strength tests, as well as 3 months after a systematic endurance or strength training. We isolated peripheral blood mononuclear cells, which will be, among other aspects, used for phenotypic and functional characterizations of individual lymphocyte subsets. The increased differentiation of NK cell phenotypes is one of the numerous immunomodulatory effects of exercise, which in turn is associated with a better prognosis and improved overall survival in various cancers [159, 160]. This data will offer the opportunity to investigate acute and

chronic effects of different forms of exercise on immunological processes in breast and prostate cancer patients.

To enable the employment of exercise as cancer medication in a targeted manner it is crucial to understand the underlying mechanisms. However, for current exercise oncology research, this goal seems to be far in the future with many questions needing to be answered along the way; so future studies should better get started.

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List of figures

Author contributions

I. **Schneider, J**., Schlüter, K., Wiskemann, J., and Rosenberger, F. (2019). *Do we underestimate VO2max in cancer survivors? Findings from a supramaximal verification test.* Applied Physiology, Nutrition, and Metabolism. doi: 10.1139/apnm-2019-0560

F.R. and J.W. designed the study. F.R., J.W., K.S., and J.S. contributed to data acquisition. J.S. and F.R. analyzed and interpreted the data and wrote the manuscript. All authors revised and approved the manuscript.

II. **Schneider, J**., Schlüter, K., Sprave, T., Wiskemann, J., and Rosenberger, F. (2020). *Exercise intensity prescription in cancer survivors: ventilatory and lactate thresholds are useful submaximal alternatives to VO2peak.* Supportive Care in Cancer. doi:10.1007/s00520-020-05407-y

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III. **Schneider, J.**, Schlüter, K., Rosenberger, F., and Wiskemann, J. *Are percentages of the one-repetition maximum suitable for prescribing resistance exercise in cancer survivors? - Comparability and prediction accuracy of frequently used 1-RM procedures.* (Manuscript submitted for publication in Supportive Care in Cancer, 14th October 2022).

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Declaration in accordance to § 8 (1) c) and (d) of the doctoral degree regulation of the Faculty

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FAKULTÄT FÜR VERHALTENS- UND EMPIRISCHE KULTURWISSENSCHAFTEN

Promotionsausschuss der Fakultät für Verhaltens- und Empirische Kulturwissenschaften der Ruprecht-Karls-Universität Heidelberg / Doctoral Committee of the Faculty of Behavioural and Cultural Studies of Heidelberg University

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