

As the field of exercise oncology is rapidly expanding, exercise has been increasingly recognized as an important therapeutic intervention to combat several cancer- and treatment-related adverse effects (1–5). There is a plethora of evidence highlighting the benefits of resistance training (RT) in this regard (2,4–9). Despite the promise of RT within exercise oncology, recent literature has highlighted improving the training prescription as central for progress in this area to continue (10). To improve prescription, it is important to examine how training variables (i.e., volume, intensity, frequency, type, and duration) and key principles (individualization, progressive overload, and specificity) are used within the current literature, but authors have often neglected to report these details (11,12). Further, several systematic reviews have demonstrated the consistent underreporting regarding the specifics of RT variables in clinical interventions (13–16), which significantly limits the applicability of findings and hinders the ability to progress in the design of precise interventions. Further, RT variables should be sequenced in a manner which aims to maximize specific outcomes of interest (i.e., periodization) (12); however, this is rarely the case in exercise oncology, possibly leading to a lower magnitude of benefit.

Despite underwhelming reporting of specific training variables, several reporting guides for clinical exercise interventions do exist, such as the CONSORT statement (17) and Consensus on Exercise Reporting Template (CERT) (18). The CERT provides guidelines for reporting the dosage of prescribed exercise using number of sets, repetitions, and duration (18). However, authors usually provide a range rather than exact numbers of these variables (i.e., three to five sets of 8–12 repetitions) making it difficult to quantify metrics such as total volume load (sets \times repetitions \times weight lifted) in which precise numbers are needed. Further, “adherence” to a program is typically defined as attendance (i.e., whether or not an individual shows up to a session), which gives little insight into the actual dose of exercise received by participants (i.e., number, type, and reasons for deviations from the prescribed dose). In fact, the “actual dose” more accurately reflects the *adherence* to a protocol as the extent to which an individual *adheres* to the prescribed program (set, repetitions, load, etc.). Without these details, particularly the dose of exercise that was *actually achieved* rather than *prescribed*, results could lead to over reporting of actual dose of RT completed. Therefore, current reporting standards may be insufficient to capture the necessary detail and true nuances of RT prescription. Recently, Nilsen et al. (19) presented a novel method for reporting exercise dose and adherence specific to aerobic training. The purpose of this study was to investigate the reported dose, adherence, and tolerance of RT from a recent trial in individuals with advanced prostate cancer.

METHODS

Participants

This is a follow-up analysis using data from a prior two-arm, randomized controlled trial to assess the effect of exercise compared with usual care in individuals with advanced prostate

cancer. Details of inclusion criteria and recruitment have been previously reported (20). After study completion and posttest assessment, the usual care group was invited to perform the same exercise program prescription and assessments. Data contributed by these additional patients were pooled to extend the number of assessable patients with data on RT. The flow of participants through the study can be found in Figure 1. The study was approved by the University Human Research Ethics Committee, and all patients provided written informed consent.

Exercise Program

The RT component of this program has been previously described in detail (20,21). Briefly, six resistance exercises that targeted the major upper- and lower-body muscle groups and were part of modular multi-modal exercise program were performed thrice weekly for 12 wk and supervised by an exercise physiologist. The exercise selection was modified based on the location and extent of bone metastases to avoid loading skeletal bone lesions as previously described and used in prior research in this population (20). Specifically, the core exercises included leg press, leg extension, leg curl, chest press, seated row, and triceps pulldown. Exercise modifications or substitutions were required based on the location and extent of metastases. Modifications included substituting an exercise with another that did not load the specific site (for example, leg press was avoided for individuals with bone metastases in the pelvic region), or unilateral limb loading of the region unaffected by bone metastases (if metastases were present in left femur, individuals were encouraged to perform unilateral knee extension/flexion with right limb). In the instance of extensive metastases, this resulted in avoidance of multiple exercises. For more information on the modular aspects of the exercise prescription, readers are directed to previous publications detailing this approach (20,21).

The RT program was designed to progress from lighter resistance and more repetitions to heavier resistance and fewer repetitions using 12 to 8 repetitions for two to four sets per exercise (Table 1). Load (kg) was increased using 5% to 10% increments for the next set or training session if the patient was able to perform more repetitions than the repetition maximum (RM) specified during a given set. Any modification to the exercise prescription (exercise selection, altering sets, and/or repetitions) was undertaken at the discretion of the supervising exercise physiologist.

Volume metrics. Prescribed training volume and completed training volume (sets \times repetitions \times load) was calculated for each individual exercise, summed to provide a total session volume. Further, total volume from all sessions was summed to derive both the total prescribed and actual cumulative volume per patient. Exercise-relative dose intensity (ExRDI) was also calculated and was defined as the ratio of total actual to total prescribed cumulative dose, expressed as a percentage. An ExRDI of 100% indicates that a patient was able to perform the RT prescription, without dose modification, whereas an ExRDI of 70% would indicate that a patient required some sort of dose modification (reduction in sets, repetitions or weight) by 30% of the prescribed dose.

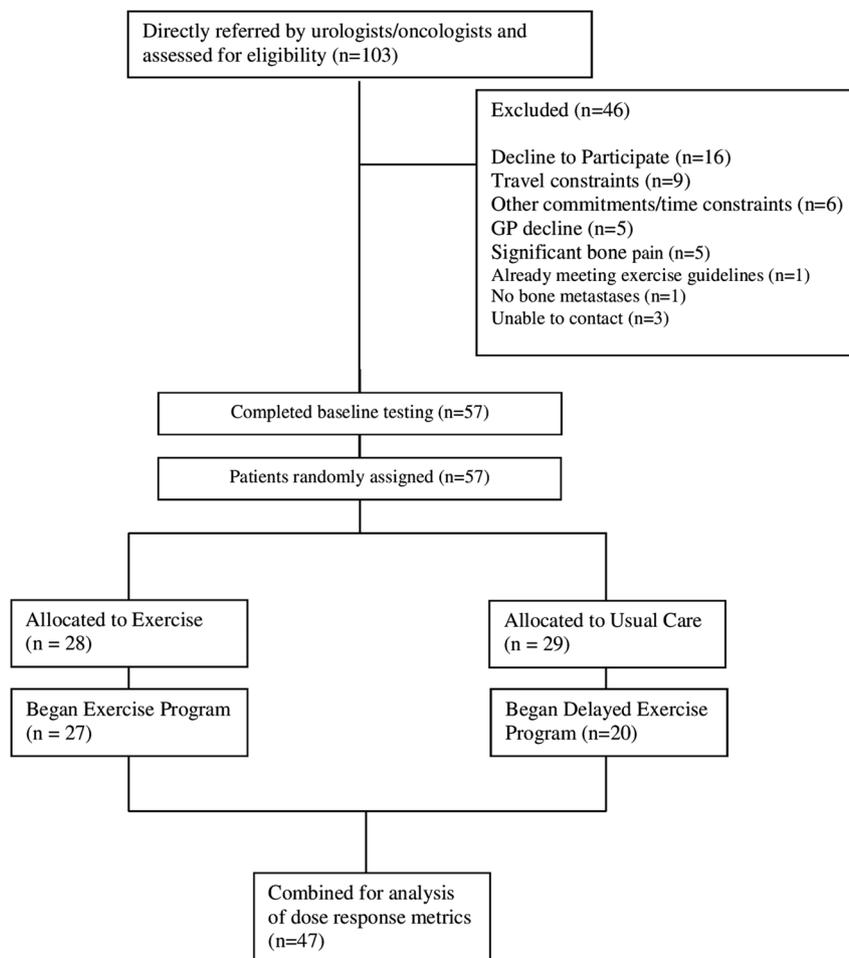


FIGURE 1—CONSORT diagram.

Dose modification quantification. Attendance was quantified as a percentage of how many total sessions a participant attended, regardless of how much training was completed during the session. We defined adherence outcomes as proposed in previous research (19): *missing session* defined as missing single or two consecutive sessions; *exercise interruption* defined as missing three or more consecutive exercise sessions; and *permanent exercise discontinuation* defined as the permanent discontinuation of exercise before week 12. Further, loss to follow-up (i.e., participants with baseline data but no data for postintervention assessment) was also recorded. *Session dose modification* was defined as any session requiring the prescribed dose (number of set and/or repetitions and/or training load reduced) to be modified during the session. Dose escalation was defined as any session where dose was modified to progress individuals (i.e., load was higher than initially prescribed).

Metrics are presented as the number and percentage of patients requiring at least one of the above-presented criteria, and number and percentage of sessions that met the above described criteria. This information was also collated to garner information on adherence per session, per patient, and per exercise.

Statistical Analysis

Descriptive statistics (mean ± SD and frequencies) were used for baseline characteristics. Dose and tolerability variables for RT were summarized by mean (SD and range, where appropriate), including all patients who initiated the exercise intervention program. A paired sample *t* test was used to determine the difference between planned and actual cumulative RT dose. Descriptive statistics were calculated using Microsoft Excel (2016) with other analyses conducted using SPSS (version 22.0, IBM, Chicago, IL).

RESULTS

Patient characteristics are presented in Table 2. Patients were age 70.15 ± 8.90 yr and presented with extensive metastatic

TABLE 1. Resistance exercise prescription.

Weeks	Session	Sets	Repetitions
1–2	1–6	2	12
3–4	7–12	3	12
5–6	13–18	3	10
7–9	19–27	4	10
10–12	28–36	4	8

TABLE 2. Participant characteristics at baseline.

Variables	Mean (SD)
Age (yr)	70.15 (8.90)
Height (cm)	174.51 (4.87)
Weight (kg)	86.87 (13.50)
Comorbidities	
Hypertension, <i>n</i> (%)	21 (47)
Hypercholesteremia, <i>n</i> (%)	21 (47)
Cardiovascular disease, <i>n</i> (%)	11 (25)
Diabetes, <i>n</i> (%)	8 (18.2)
Osteoporosis, <i>n</i> (%)	0 (0)
Gleason score	8.05 (1.17)
PSA	34.7 (100.7)
Months since diagnosis	50.02 (56.91)
Months since metastases	10.70 (18.04)
Bone lesion site	
Pelvis, <i>n</i> (%)	34 (77.3)
Femur, <i>n</i> (%)	16 (36.4)
Rib/thoracic vertebrae, <i>n</i> (%)	27 (61.4)
Lumbar vertebrae, <i>n</i> (%)	17 (38.6)
Humerus, <i>n</i> (%)	8 (18.2)
All regions, <i>n</i> (%)	3 (6.8)
Other site, <i>n</i> (%)	29 (65.9)
Treatment	
Current ADT, <i>n</i> (%)	41 (93.2)
ADT months	5.3 (6.7)
Radiation, <i>n</i> (%)	22 (50)
Radiation for bone, <i>n</i> (%)	7 (15.9)
Brachytherapy, <i>n</i> (%)	5 (11.4)
Chemotherapy, <i>n</i> (%)	8 (18.2)

lesions in the pelvis (77.3%), femur (36.4%), rib/thoracic vertebrae (61.4%), lumbar vertebrae (38.6%), humerus (18.2%), and other sites (65.9%). Ninety-three percent of patients were undertaking androgen deprivation therapy.

Conventional Attendance Metrics

Using conventional metrics, training session attendance was 79.5% (range, 19.4%–100%) Four participants were lost to follow-up due to increased bone pain ($n = 2$), health deterioration ($n = 1$), or a fall at home ($n = 1$).

Exercise Dose Quantification and Adherence Metrics

The prescribed total cumulative exercise dose across the intervention was $139,886 \pm 69,150$ kg (range, 7872–300,546 kg) (Fig. 2A), which yielded a mean weekly training volume of 3886 ± 37 kg (range: 2062–4848 kg). The completed cumulative total exercise dose across the intervention was $112,835 \pm 83,499$ kg (range: 7104–240,788 kg) (Fig. 2A). There was a statistically significant difference between the prescribed and completed cumulative dose ($P = <0.001$). The prescribed and completed training volume per session is depicted in Figure 2B. The ExRDI was $77.4\% \pm 16.6\%$ (range: 19.3%–99.4%) (Fig. 2C), indicating that the dose was modified/interrupted for ~22.6% of the sessions.

The dose was interrupted in 24 (51%) of the participants due to a variety of health-related (e.g., general illness, treatment related pain, etc.) and non-health related (e.g., vacation) reasons (Table 3). Forty-four patients (87%) missed one or more exercise sessions during the intervention, with most missed sessions due to conflicting appointments and general

illness. The dose was modified in 41 (87%) of patients and 149 (9%) of sessions. Specifically, dose was modified via the reduction in load ($n = 79$; 53%), reduction in sets ($n = 19$; 13%), repetitions ($n = 9$; 6%), different exercise selection ($n = 2$; 1%) or exercise removal ($n = 38$; 25%). Dose was modified for a variety of health-related ($n = 94$; 5%) and non-health-related reasons (e.g., time-constraints, equipment availability, previously missed session) ($n = 55$; 3%). On the other hand, dose escalation occurred in 19 (40%) of the patients. Adjustments were undertaken by exercise physiologists to ensure an appropriate load was assigned, and the principle of progressive overload was followed. Additionally, adherence per patient is presented in Figure 3A, and adherence per exercise in Figure 3B.

DISCUSSION

This retrospective analysis was conducted to examine the specific dosage of training that was completed in our previous exercise oncology trial (20) to make recommendations going forward on how to calculate more precise metrics for training completion in clinical intervention studies and improve the applicability of study design and interpretation of the results. There were three important findings of a RT intervention in prostate cancer patients with bone metastases: 1) the prescribed total volume of RT was higher than the actual completed volume as reflected by an ExRDI of 77.4%; 2) RT was interrupted in half of the patients and missed (i.e., participants did not attend for one or two consecutive sessions) in ~90% patients; and 3) training dose throughout the intervention was modified in ~85% of patients. Similar to the present findings, Nilsen et al. conducted a retrospective analysis of a 24-wk aerobic training program in prostate cancer patients undergoing ADT and reported an ExRDI of ~77%, with training interrupted and/or modified in 44% and 96% of patients, respectively. Additionally, Scott et al. (22) reported that aerobic training was interrupted in 46% of patients, missed in 100% of patients and modified in 49% of patients in a 36-session aerobic training trial in individuals with metastatic breast cancer. Overall, the results of this retrospective analysis are in concert with others and reveal the methods of exercise dose reporting outlined by Nilsen et al. (19) for aerobic exercise can be effectively adapted for RT.

The purpose of performing this retrospective analysis on this population was to provide an illustration of *how* these metrics can be applied to resistance exercise trials in individuals with cancer. A novel aspect of adopting advanced adherence metrics when reporting RT interventions is the ability to determine the tolerability of different exercises in individuals at different stages of disease, or different cancer populations. Despite the modular aspect of this program, dose modifications during individual training sessions were still required as a result of bone pain or upper-/lower-extremity pain and accumulated fatigue. Thus, implementing this strategy and tracking dose modification metrics may provide valuable information concerning the tolerability of specific exercises where the frequency and magnitude of dose modifications will likely vary

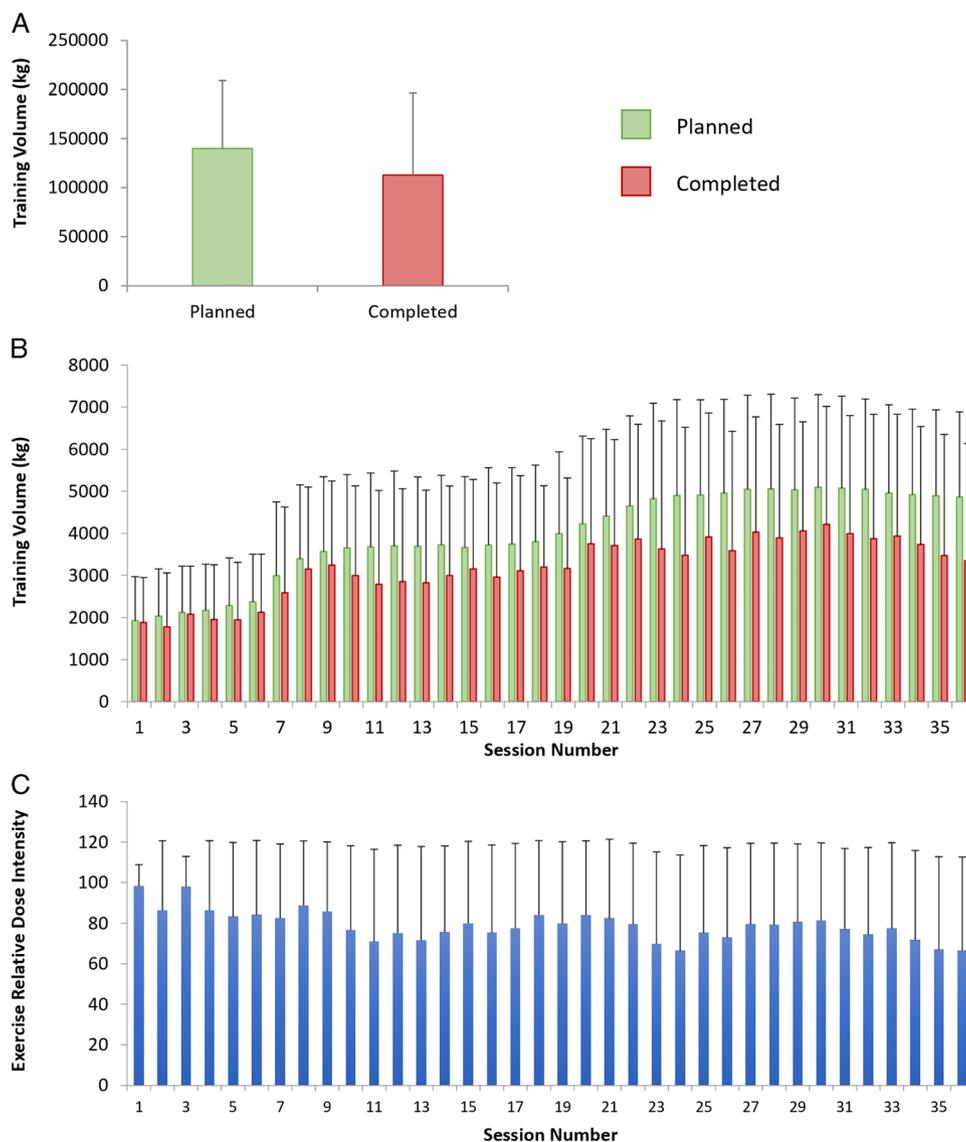


FIGURE 2—Data are mean \pm SD. Prescribed vs actual cumulative training volume (A) and mean training volume per session (B) (Green colored bars indicate prescribed dose, whereas red colored bars indicate actual or completed dose.); ExRDI per session across the intervention (C).

across the cancer spectrum and intervention time course, as will the reasons for these interruptions/modifications (22). For example, having to substitute or modify upper body RT exercises (i.e., incorporating physical therapy exercises for postsurgery, rather than traditional RT exercises) in women with breast cancer as a result of treatment-related dysfunction could potentially explain reasons why limited or no improvements were seen in upper body strength (23). Another example could be individuals with head and neck cancer undergoing chemotherapy and/or radiotherapy who need consistent dose reductions as a result of low energy from malnutrition or other acute treatment toxicities (24).

This process of dose modification essentially refers to the concept of autoregulation, where the training stimulus is modified in accordance with an individual's "readiness to train." In this sense, subjective/objective measure of sleep, fatigue, energy, recovery (or other relevant indices) can be used to provide

an individualized, appropriate training stimulus (12,23). Further, it has been posited that the flexibility of autoregulation within a periodized program may help ward off staleness, improve enjoyment, and ultimately foster the long-term maintenance of activity (12). Irrespective, reporting dose modifications via exercise selection in these circumstances can lend further insight into the feasibility of delivering an exercise intervention during periods of illness, dysfunction, or transient toxicity, which provides important information for practitioners to understand the expectations and challenges of working with specific populations.

Implementing traditional metrics, outlined by Nilsen et al. (19), of adherence in exercise trials, such as loss to follow-up and session attendance alone, have limited utility because they may lack breadth and specificity that is critical to defining adherence and tolerance of the RT dose prescribed in the intervention. For example, Scott et al. (22) reported that some type

TABLE 3. Reasons for dose modifications.

Variable/Reasons	No. Patients ^a	Pct.	No. Sessions	Pct.
Permanent discontinuation	4	9	65	4
Health-related				
Increased bone pain	2	5	23	2
Health deterioration	1	3	28	2
Fall at home	1	3	14	1
Exercise interruption ^b	24	51	154	9
Health-related				
General illness	6	13	25	1
Treatment-related pain	2	4	17	1
Conflicting appointments	4	9	9	1
Fatigue	1	2	3	0
Nausea	2	4	4	0
Non-health-related				
Vacation	15	32	96	9
Missing sessions ^b	41	87	135	8
Health-related				
Conflicting appointments	31	66	79	5
General illness	16	34	16	1
Fatigue	4	9	5	0
Nausea	3	6	3	0
Treatment-related pain	1	2	1	0
Upper-extremity pain	1	2	2	0
Non-health-related				
Other	10	21	15	1
Vacation	3	6	4	0
No reason	1	2	1	0
Dose modifications ^b	40	85	149	9
Health-related				
Fatigue	16	34	29	2
Lower extremity pain	11	23	43	2
Upper extremity pain	11	23	15	1
Bone pain	3	6	5	0
Nausea	2	4	2	0
Non health-related				
Other ^c	28	60	47	3
Not recorded	6	13	6	0
Time constraints	2	4	2	0
Dose escalation	19	40	30	2

Definitions: *permanent discontinuation*: permanent discontinuation of exercise prior to week 12; *exercise interruption*: missing ≥ 3 consecutive supervised sessions; *missing sessions*: missing single or 2 consecutive sessions; *dose modification*: ≥ 1 session required dose modification, and the total number of sessions requiring a dose reduction; *dose escalation*: any session where dose was modified to progress individuals (i.e., load was higher than initially prescribed).

^aAll metrics are collectively counted as one entity in the same patient unless otherwise indicated.

^bNumber of reasons for dose modification sums to greater than the total number of patients listed since several patients required dose modification for different reasons.

^cOther: time constraints, equipment availability, previously missed session.

of dose modification and early session termination occurred in 49% and 36% of all training sessions, respectively in their trial; however, conventional metrics would have classified the modified and terminated sessions as 100% adherence. Clearly, this traditional metric limitation highlights the need to calculate adherence in a more precise manner. Specifically, if sessions in which dose modification occurs are counted as 100% attendance then this does not provide an accurate picture of the participant's feasibility and tolerability of exercise, particularly in advanced cancers or periods of intense cancer treatments, highlighted by almost half of the sessions in the study by Scott et al. (22) being modified in some way. Consequently, adaptations may be compromised when exercise dosage is decreased. For example, Scott et al. (22) had a predetermined feasibility threshold set at an ExRDI of 70%, the authors reported that individuals who did not meet this threshold experienced an 11% decline in peak oxygen consumption whereas those with an

acceptable feasibility (ExRDI $\geq 70\%$) experienced a significant improvement in cardiorespiratory fitness (22). Ultimately, it seems clear that altering a training session dose can affect study outcomes, and this should be considered when examining the feasibility of exercise interventions in various cancer populations, and should impact training recommendations in practice.

Importantly, simply using ExRDI (and other metrics) only addresses reporting and not the *quality* of an intervention. The CONSORT and CERT statements provide excellent frameworks for the reporting of randomized controlled trial components. However, the specifics of these guidelines are open to interpretation and can be limited when it comes to capturing the complexity of RT dose received, as noted by several systematic reviews, which demonstrated that RT intervention characteristics remain consistently underreported (13–16). Thus, the methods of reporting adherence outlined in this article should be utilized in parallel with the reporting guidelines outlined by CONSORT or CERT (18). Ultimately, the applicability of exercise is medicine, and the investigation of exercise dose–response on several clinical endpoints becomes irrelevant, unless there are accurate metrics in place to quantify the actual dosage undertaken by the patient. Combining ExRDI with appropriate reporting of intervention characteristics will allow for more accurate description of the dose of exercise prescribed and tolerability of that dose. Subsequently, this will allow for greater insight into the tolerability of exercise, ability to better compare exercise dose across different populations and provide a more specific framework for exercise prescription and modification.

RT prescription is complex, with many variables that can be manipulated (exercises, sets, repetitions, load, rest period, time under tension, etc.). Consequently, there is unlikely to be a consensus on a gold-standard method to quantify RT load, and choice of method will be a combination of population studied, reason for use, and feasibility. For example, methods to quantify volume from machine, dumbbell or free weights are likely to be different than those from plyometric exercises or resistance bands and should be tracked separately. Additionally, calculating volume load with group-based circuit training or home training may be difficult and impractical. Additionally, tracking relative volume (i.e., sets \times repetitions \times percentage of one-repetition maximum) as opposed to absolute (sets \times repetitions \times load) would add a greater degree of accuracy in accounting for individual strength levels and offering further insight into the magnitude of progression. Nevertheless, we contend that the calculation of volume load is a simple and quick method that can allow for better monitoring, adjusting, and reporting of the RT prescription (25).

It is important to note that traditional metrics, such as attendance and loss-to follow up, are not without value. For example, from a behavioral perspective, regular attendance at exercise sessions/programs may demonstrate that an individual has developed the self-regulatory skills to set a goal of participating in an exercise session and translated that intention/goal into action by enacting a plan and overcoming barriers that could have impeded attendance (26–31). Consequently, attendance and loss

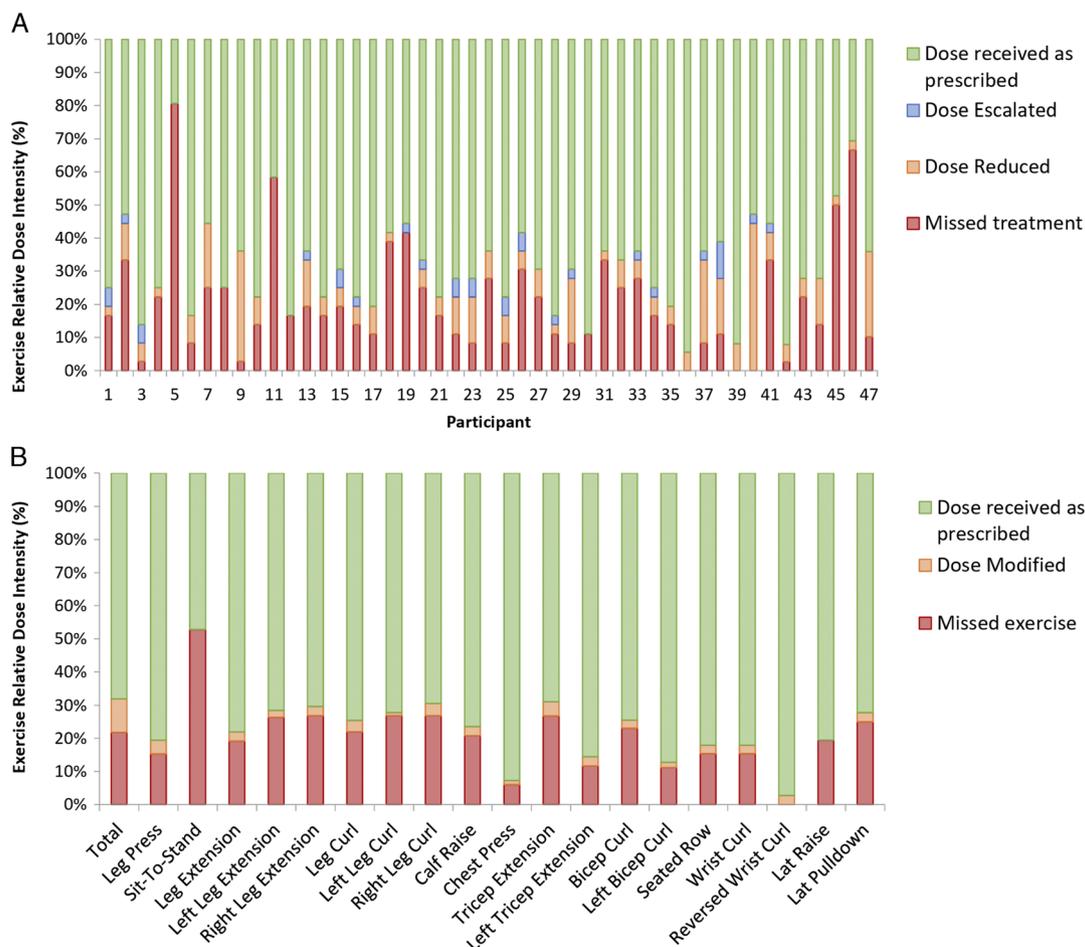


FIGURE 3—Adherence to protocol per patient (A) and per exercise (B). The green bars represent dose received as prescribed; orange bars depict dose modified; blue bars depict dose escalated; red bars depict missed sessions (A) or exercise (B).

to follow-up (i.e., retention) may offer value and insight into the efficacy of an intervention aimed at behavior change. Ultimately, combining these metrics will allow for an expansion of attendance and provide both breadth and specificity in future interventions evaluating elements of an exercise intervention, such as adherence, dose, and tolerance.

Notably, the proposed metrics may also be applied to other populations where the exercise dose might require modifications to accommodate comorbidities or conditions (e.g. chronic obstructive pulmonary disease, knee osteoarthritis or diabetes). We have included a master template (see Supplemental Digital Content 1, master template for calculating RT dose metrics, <http://links.lww.com/MSS/B719>) that can be adapted to other RT interventions to assist researchers/practitioners looking to adopt these metrics. In summary, previously described methods for reporting aerobic exercise interventions in cancer can be

adapted to provide valuable information on the tolerability and adherence to RT in exercise interventions for cancer patients.

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C. M. F., T. S. N., and D. G. each had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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