Maintenance of Fitness and Quality-of-Life Benefits From Supervised Exercise Offered as Supportive Care for Breast Cancer

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ABSTRACT

Background: Overwhelming randomized controlled trial evidence demonstrates that exercise has positive health impacts during and after treatment for breast cancer. Yet, evidence generated by studies in which exercise programs are delivered outside a tightly controlled randomized trial setting is limited. The purpose of this study was to assess the effectiveness of an evidence-based exercise program with real-world implementation on physical fitness and quality of life (QoL).

Patients and Methods: Oncologists referred women with early-stage breast cancer who were scheduled to receive adjuvant chemotherapy. The program consisted of supervised aerobic and resistance exercise of moderate to vigorous intensity 3 times per week until the end of treatment (chemotherapy $\pm$ radiotherapy), then twice per week for 10 weeks, followed by once per week for 10 weeks. Health-related physical fitness and QoL were assessed at baseline, end of treatment, end of program, and 1-year follow-up. **Results:** A total of 73 women were enrolled. Estimated peak VO_2 ($\text{VO}_{2\text{peak}}$), QoL, and body weight were maintained between baseline and end of treatment, whereas muscular strength improved ($P < .01$). By the end of the program, $\text{VO}_{2\text{peak}}$, heart rate recovery, waist circumference, and some aspects of QoL were improved (all $P < .01$) relative to baseline. One year later, $\text{VO}_{2\text{peak}}$, QoL, and waist circumference were maintained relative to end of program, whereas the improvements in strength and heart rate recovery had dissipated (all $P < .01$). **Conclusions:** Evidence-based exercise programming delivered with real-world implementation maintained $\text{VO}_{2\text{peak}}$, strength, and QoL during adjuvant treatment and improved these measures after treatment completion among women with breast cancer. Continued guidance and support may be required for long-term maintenance of strength improvements in this population.

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Background

A critical aspect of breast cancer survivorship care includes addressing the negative sequelae of breast cancer therapy on health-related fitness and quality of life (QoL). The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Breast Cancer state that support for exercise, healthy eating, and weight management are important standards for survivorship care.¹ However, within most cancer treatment centers, exercise programming is not offered and access to registered dietitians is limited.

Although exercise training can be beneficial during and after treatment, intervention during chemotherapy may be especially important as supportive care in managing treatment-related side effects. With respect to exercise during adjuvant chemotherapy for breast cancer, randomized controlled trials (RCTs) have demonstrated that supervised aerobic or resistance exercise training has superior effects to both usual care and home-based exercise on health-related physical fitness and QoL.^{2,3} Furthermore, the large (N=300), multicenter, randomized CARE trial (ClinicalTrials.gov identifier: NCT00249015) demonstrated that a combined aerobic and resistance training intervention provided equivalent or greater benefits across these health domains relative to aerobic exercise alone.⁴ Synthesis of these major efficacy trial results suggests that the most effective format of exercise programming for women with breast cancer during adjuvant chemotherapy is supervised aerobic and resistance exercise training.

With efficacy established, a key element in developing an evidence-based approach for using exercise and healthy eating as supportive therapy during chemotherapy for breast cancer is translating these benefits into effective clinical programming. The effectiveness of an intervention is measured by its ability to produce a similar effect under real-world conditions.⁵ Defining features of an effectiveness trial include minimal exclusion criteria; flexible, individualized delivery of the intervention; and reduced expectations for adherence.⁵ Little is known about the effectiveness of supervised exercise training in patients with breast cancer when the program is

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implemented in a clinical setting outside the stringent conditions of an RCT.⁶

The NExT study (ClinicalTrials.gov identifier: NCT01806181) assessed the effectiveness of exercise and healthy eating programming offered to women receiving adjuvant chemotherapy for early-stage breast cancer. Exercise programming during treatment was closely modeled after the combined aerobic and resistance exercise arm of the CARE efficacy trial.⁴ The NExT exercise program is unique from programs used in previous studies by continuing for an additional 20 weeks after treatment completion, with a gradual step-down in supervised exercise. The program's reach, its implementation, and the effectiveness and maintenance of self-reported physical activity and the physical component summary of the RAND-36 have been reported previously.⁷ In brief, goals for successful reach were attained (>50% referral rate, >70% uptake, and retention) and aerobic and resistance physical activity and the physical component summary increased by the end of the program, but only aerobic physical activity and the physical component summary remained higher than baseline at 1-year follow-up.

The goal this study was to assess the changes in objective measures of health-related physical fitness (eg, aerobic fitness, muscular strength, body composition) and QoL throughout the program, and maintenance of these changes for 1 year after program completion. Based on previous findings derived from efficacy trials, it was hypothesized that the NExT program would attenuate negative treatment-related effects on aerobic fitness, strength, body weight, and QoL, and result in improvements in aerobic fitness, strength, body weight, and QoL after treatment completion. It was also hypothesized that the step-down approach would result in maintenance of improvements for 1 year after program completion.

Patients and Methods

Study Design and Participants

The NExT study was a single-arm intervention offered to English-speaking adult women with stages I–IIIA breast cancer who were scheduled to receive adjuvant chemotherapy at the Vancouver Center of the British Columbia Cancer Agency (BCCA). Participants were recruited via a “prescription” from a medical oncologist. Participants had to be able to complete the baseline assessment before completion of >50% of chemotherapy treatment and be deemed safe to exercise by their oncologist. Patients with a body mass index >40 kg/m², uncontrolled cardiovascular disease or diabetes, or disabilities impeding exercise were excluded. The 12-month recruitment period originally planned as a measure of yearly intake for a potential clinical

program was extended to 15 months after securement of additional funding. The BCCA Research Ethics Board approved this study and participants provided informed consent.

Intervention

Participants were invited to take part in the exercise training program and a single nutrition information session. The exercise program had 3 distinct phases: (1) treatment (baseline/enrollment to completion of chemotherapy ± radiotherapy, 3 times/wk); (2) post-treatment (10 weeks, twice/wk); and (3) maintenance (10 weeks, once/wk) (Figure 1). The exercise program has been described previously in detail.⁸ In brief, supervised aerobic and whole-body resistance sessions were supplemented with encouragement of home-based exercise to work toward achieving the NCCN recommendation of 150 minutes of moderate-intensity aerobic activity and 2 or 3 sessions of whole-body resistance training per week (Figure 1).¹ The single, 2-hour, small group-based nutrition session involved discussion of topics ranging from nutritional management of treatment side effects, achieving adherence to Canada's Food Guide and Canadian Cancer Society guidelines, and Dietary Reference Intake.

Outcome Measures

Demographics were collected via questionnaire. Treatment and diagnosis characteristics were extracted from

Figure 1. NExT exercise prescription for each of the 3 phases of exercise training program. Check marks indicate supervised aerobic session prescription; supervised whole-body resistance sessions were performed at the same sessions. Open boxes indicate home-based session of aerobic type unless otherwise specified; a log book provided the prescriptions, including the RPE scale to measure intensity of exercise, and a place to record exercise performed. Arrows indicate progression.

Abbreviations: HRR, heart rate reserve; RPE, Rating of Perceived Exertion.

^aAerobic intervals (4 times: 4 minutes hard, 4 minutes easy⁸) were prescribed for participants without a history of cardiovascular disease, current heart medications, dyspnea/asthma issues, or injuries limiting exercise intensity.

^bParticipants could perform the supervised program at their own gym according to the intervention prescription or were provided with a resistance band program.

medical records. Assessments included physical fitness tests and questionnaires, and were performed at the following time points: (1) baseline/enrollment, (2) end of treatment (1 week after radiotherapy if received, or the length of one chemotherapy cycle after the last cycle), (3) end of program (completion of intervention, 20 weeks after end of treatment), and (4) 1-year follow-up (1 year after end of program without further intervention).

Health-related physical fitness was assessed using methods that were deemed to be practical and cost-effective for a clinical program. Because of the focus on practicality, familiarization sessions were not performed. These assessments were used to individualize exercise prescriptions and to evaluate progress and program effectiveness. Waist circumference was measured as the average of 2 measurements ≤ 0.5 cm apart around the top of the iliac crest.⁹ Aerobic fitness was estimated using a modified Balke treadmill test that was terminated at 70% of age-predicted heart rate reserve.¹⁰ When the target heart rate was reached, the speed and grade were immediately returned to 2.0 mph and 0%, respectively, for an active recovery. Heart rate was recorded at the end of each 3-minute stage of the test and at 2 minutes into recovery. Participants were asked to minimize talking and handrail holding during the test and recovery period. For each test, a linear regression of the heart rate at the end of each stage and the corresponding VO_2 was performed and solved for age-predicted peak heart rate ($206 - [0.88 \times \text{age}]$)¹¹ to estimate peak VO_2 ($\text{VO}_{2\text{peak}}$). VO_2 was calculated for each workload of the test using a metabolic equation,¹² which we have previously shown to be accurate in this population.¹³ Heart rate recovery, a known correlate of $\text{VO}_{2\text{peak}}$ in patients with breast cancer,¹⁴ was calculated as the peak heart rate during the test minus the heart rate at 2 minutes into recovery. One-repetition maximums (1-RMs) for chest press and leg press were estimated from validated prediction equations using maximal weight lifted for 7 to 10 repetitions as previously used in efficacy trials, such as the CARE trial.^{4,15} As an indicator of feasibility of our fitness assessment methods, we tracked the number of failures and reasons for failure of completion of assessments.

General and breast cancer-specific health-related QoL was assessed by the RAND-36¹⁶ and the Functional Assessment of Cancer Therapy–Breast (FACT-B), respectively.¹⁷ The questionnaire scales that relate most to physical components of QoL are reported because they are most likely to respond to interventions that change physical morbidity.¹⁸ QoL was also assessed at the completion of chemotherapy to compare the change scores across chemotherapy reported in the CARE efficacy trial as the primary and secondary outcomes.

The differences between means for each measure were compared with the established minimally important differences (RAND-36 = 3; FACT-B trial outcome index = 5; FACT-General = 3).^{19,20}

Statistics

Each health-related physical fitness and QoL outcome was analyzed using a generalized linear mixed model in SPSS Statistics, version 24 (IBM Corporation, Armonk, NY), which does not require that participants with missing data be dropped from the analysis. All available data, including for participants who dropped out of the intervention, were included. A random intercept was included to account for intraindividual similarities across time points, and time point was included as a repeated and fixed effect. Significant time effects were interpreted with post hoc contrasts for each of the 3 follow-up time points relative to baseline, end of treatment relative to end of program, and end of program relative to 1-year follow-up. Differences between time points were considered significant when $P \leq .01$, using the Bonferroni adjustment for multiple comparisons. To compare variables in common between the NExT and CARE trials, change scores were calculated for QoL at the end of chemotherapy and for physical fitness at the end of treatment to match the format of data reported in CARE.

Results

Participants

Between August 2013 and October 2014, a total of 109 patients were referred; 93 were eligible and 73 enrolled (78% of eligible) (flow diagram previously published⁷). Table 1 describes the baseline characteristics of study participants; 5 participants withdrew before completion of any exercise sessions, and another 4 withdrew during chemotherapy. Of these 9 withdrawals, 4 returned to complete outcome measures during the intervention period but not at 1-year follow-up. Among participants who did not withdraw, 83% completed 1-year follow-up assessments.

The treatment phase duration was 25 ± 8 weeks and the entire program was 45 ± 8 weeks, on average. Average attendance during treatment, posttreatment, and maintenance phases were $60\% \pm 26\%$, $52\% \pm 33\%$, and $50\% \pm 38\%$, respectively.

Body Weight and Waist Circumference

Body weight did not change over time ($P = .11$) (Table 2). Waist circumference did not change between baseline and end of treatment ($P = .03$) or between end of treatment and end of program ($P = .02$), but it was significantly lower at end of program and at 1-year

Table 1. Patient Demographics, Cancer Diagnosis, and Treatment Characteristics (N=73)

Characteristic	n	%
Demographics		
Age, mean $\pm$ SD (range), y	50.8 $\pm$ 10.6 (29–77)	
Marital status^a		
Married/Common-law	49	71
Divorced/Separated	5	7
Single	11	16
Widowed	3	4
Ethnicity^a		
White	44	64
Asian	22	32
South Asian	2	3
Black or African American	1	1
Education^a		
High school diploma	5	7
Technical/Community college	18	26
Some university	8	12
Bachelor's degree	17	25
Higher than bachelor's degree	21	30
Work status during treatment		
Working during	11	15
Not working	55	75
Part-time/Casual	7	10
Medical history		
Menopausal status		
Postmenopausal (natural)	27	37
Surgery/Hysterectomy	6	8
Perimenopausal	12	16
Menopausal	28	38
Comorbidities		
Hypertension	12	16
Mental illness	11	15
Arthritis/Osteoporosis	8	11
Asthma/Lung disease	7	10
Cardiovascular disease/arrhythmias	5	7
Metabolic disease	3	4
Previous cancer	3	4
Thyroid disorder	3	4
Fibromyalgia/Multiple sclerosis	2	3

(continued)

^aMissing 4 responses from participants who withdrew before completing demographics questionnaire.

follow-up relative to baseline ($P<.01$). Waist circumference did not change between end of program and 1-year follow-up ($P=.86$).

Table 1. Patient Demographics, Cancer Diagnosis, and Treatment Characteristics (N=73) (cont.)

Characteristic	n	%
Cancer diagnosis and treatment		
Tumor stage		
I	17	23
II	47	64
III	9	12
Chemotherapy regimen		
Anthracycline-containing	51	70
Taxane-containing	70	96
Cyclophosphamide-containing	73	100
Primary surgery		
Breast-conserving surgery	53	73
Mastectomy	20	27
Radiotherapy	67	92
Hormone therapy		
Aromatase inhibitor	16	22
Selective estrogen receptor modulator	44	60
None	13	18

^aMissing 4 responses from participants who withdrew before completing demographics questionnaire.

Aerobic Fitness

Estimated VO_{2peak} could not be calculated in 16 of 249 (6%) completed assessments due to β -blocker use ($n=11$), heart rate monitor failures ($n=3$), and failure to complete stage 2 before achieving target heart rate ($n=2$). No significant change was seen in VO_{2peak} from baseline to end of treatment ($P=.34$) or from end of treatment to end of program ($P=.02$) (Table 2). VO_{2peak} was significantly higher at end of program relative to baseline ($P<.01$). At 1-year follow-up, VO_{2peak} was not different from baseline ($P=.13$) or end of study ($P=.06$). VO_{2peak} baseline values and percentage change during treatment were similar between the NExT and CARE trials (Figure 2A, C).

Relative to baseline, heart rate recovery did not change by end of treatment ($P=.19$), but it was improved by end of program relative to both end of treatment and baseline (both $P<.01$) (Table 2). However, this improvement was transient, because at 1-year follow-up, it was not different from baseline ($P=.45$) and was significantly lower than at end of program ($P<.01$).

Muscular Strength

The chest press test was not completed in 36 of 249 assessments (14%) due to breast surgery-related limitations ($n=25$), non-cancer-related injury ($n=10$), and time limitations ($n=1$). The leg press test was not completed in 10 assessments (4%) due to non-cancer-related

Table 2. Health-Related Physical Fitness Changes Over Time

Characteristic	Baseline (N=73)	End of Treatment (n=57)	End of Program (n=59)	1-Year Follow-Up (n=46)
Body weight, kg	69.9 ± 17.7	68.8 ± 15.7	67.7 ± 17.0	67.2 ± 14.3
Waist circumference, cm	89 ± 14	87 ± 13	85 ± 13 ^a	84 ± 12 ^a
VO ₂ peak, mL/kg ⁻¹ /min ⁻¹	27.4 ± 6.5	28.0 ± 7.3	29.7 ± 7.1 ^a	28.3 ± 7.9
Heart rate recovery, beats/min	29 ± 8	30 ± 10	33 ± 10 ^{a,b}	29 ± 11 ^c
Upper body strength, kg	22 ± 8	28 ± 11 ^a	34 ± 11 ^{a,b}	28 ± 10 ^{a,c}
Lower body strength, kg	87 ± 24	103 ± 29 ^a	115 ± 27 ^{a,b}	106 ± 26 ^{a,c}

^aSignificantly different from baseline with $P \leq .01$.

^bSignificantly different from end of treatment with $P \leq .01$.

^cSignificantly different from end of program with $P \leq .01$.

injury (n=9) and time limitations (n=1). The pattern of change for estimated 1-RM was the same for chest press and leg press, with end of treatment, end of program, and 1-year follow-up significantly improved from baseline (all $P < .01$) (Table 2). An additional significant improvement between end of treatment and end of program (both $P < .01$) was seen, but a significant decrease was observed from end of program to 1-year follow-up (both $P < .01$). Baseline chest press and leg press 1-RMs were similar between the NExT and CARE trials, whereas percent change during treatment was substantially larger for NExT (Figure 2C).

Quality of Life

Between baseline and end of treatment, no QoL measures changed (all $P > .06$). Between end of treatment and end of program, the RAND-36 physical functioning, role limitations due to physical health, energy/fatigue, and general health scales and FACT-General scores were improved (all $P < .01$) (Figure 3). These improvements in the RAND-36 role limitations due to physical health and the FACT-General score at end of program were significant relative to baseline (both $P < .01$). At 1-year follow-up, all scores were higher than baseline (all $P < .01$), except for general health ($P = .15$). Relative to end of program, only the FACT-B trial outcome index was improved ($P < .01$) at 1-year follow-up. Among the baseline values of QoL measures in common between the NExT and CARE trials, role limitations due to physical health was lower in NExT, whereas all other measures were similar (Figure 2B). The percentage change scores for QoL during chemotherapy were larger for NExT (using the end-of-treatment time point) than for the CARE trial for physical functioning, role limitations due to physical health, and the physical component summary (Figure 2D).

Discussion

Although numerous randomized trials have demonstrated the efficacy of exercise training in generating positive effects on health-related physical fitness and QoL in women

with breast cancer, the NExT trial contributes new information regarding the effectiveness of exercise training when delivered in a setting more closely resembling a real-world model of a clinical program. Expected changes in the absence of intervention during treatment include a reduction in aerobic fitness, muscular strength, and QoL, and a gain in body weight. In line with our hypothesis, participants in the program experienced meaningful health benefits during adjuvant treatment, including maintenance of aerobic fitness, QoL, and body weight and improvement of upper and lower body muscular strength.

To allow for direct comparison of results with those of the CARE efficacy trial,⁴ the same QoL and fitness assessments were used at similar time points in NExT. Differences with the NExT trial included use of a sub-maximal treadmill test to estimate rather than measure VO₂peak and the performance of fitness assessments after the completion of all primary treatments (chemotherapy ± radiotherapy) due to feasibility and staffing limitations. Participant demographics and diagnoses were comparable between the trials, but the chemotherapy regimens differed. It is unknown how different regimens might affect fitness and QoL outcomes. At baseline, QoL, VO₂peak, and strength were closely matched between the studies (Figure 2A, B). As expected for a primary defining feature of an effectiveness trial,⁵ exercise adherence was lower in NExT (60% ± 26% attendance) than in the CARE trial and other similar RCTs (70%–83% attendance).^{2–4,21–24} In comparing the QoL change scores in the 2 studies over the same time period (duration of chemotherapy only), the average deterioration in physical functioning, role limitations due to physical health, and the physical component summary were smaller, albeit with greater variability, in NExT. For fitness changes, upper and lower body strength increased in both studies during treatment, but a greater average change was seen after an average of 25 weeks of intervention in NExT compared with an average of 16 weeks in CARE. In terms of statistical changes within

Figure 2. Comparison of (A) baseline fitness, (B) baseline QoL, (C) percentage change in fitness, and (D) percentage change in QoL for the CARE efficacy trial's combined aerobic and resistance exercise arm and the NExT effectiveness trial's single exercise arm that was modeled after CARE. Data are mean $\pm$ SE. Note that although change in QoL is assessed with similar timing in the 2 studies (start and end of chemotherapy), in the NExT trial, fitness was assessed only after completion of both chemotherapy and radiotherapy (and a longer exercise intervention), due to feasibility and staffing limitations, as opposed to after chemotherapy only in the CARE trial.

Abbreviations: 1-RM, one-repetition maximum; QoL, quality of life.

Data from Courneya KS, McKenzie DC, Mackey JR, et al. Effects of exercise dose and type during breast cancer chemotherapy: multicenter randomized trial. *J Natl Cancer Inst* 2013;105:1821–1832.

each study, in the CARE trial the intervention only partially attenuated the treatment-related deterioration in VO₂peak and QoL; significant reductions still occurred. In NExT, changes in aerobic fitness, strength, body weight, and QoL were mitigated during treatment. A possible reason for the greater change in NExT is that participants were also encouraged to perform home-based aerobic exercise during treatment twice per week.

Regarding body composition, the CARE trial reported a body weight gain that was primarily due to increased lean mass as measured by dual-energy x-ray absorptiometry.⁴ We did not use advanced body composition assessment methods in NExT, but the lack of change in body weight combined with the nearly significant decrease in waist circumference may suggest findings similar to those of the CARE trial.

This study was also unique in that the total duration of exercise programming was considerably longer, with supervised sessions offered across the trajectory of breast cancer treatment.²⁵ Despite reduced frequency of supervised sessions between the end-of-treatment and the end-of-program time points, there were improvements in strength, heart rate recovery, and QoL. Although we hypothesized, based on previous results of exercise efficacy trials,²⁵ that aerobic fitness and body composition would improve with exercise training performed in the period after treatment completion, we saw only a trend toward improvement in VO₂peak and waist circumference between end of treatment and end of program.

Evidence is limited and inconsistent regarding maintenance of improvements in fitness and QoL after

Figure 3. Health-related QoL changes for RAND-36 norm-based scores and FACT-General and FACT-B scores. Data are estimated marginal mean $\pm$ SE.

Abbreviations: FACT, Functional Assessment of Cancer Therapy; FACT-B, Functional Assessment of Cancer Therapy–Breast; QoL, quality of life.

*Significantly different from baseline.

†Significantly different from end of program.

‡Difference from baseline mean exceeds minimally important difference.

completion of a supervised exercise intervention during treatment of breast cancer.²⁶ Three studies have reported that exercise effects on aerobic fitness, muscular strength, and QoL are not maintained without continued intervention.^{2,23,27} One study reported maintenance of positive changes in QoL and aerobic fitness at 6 months after intervention,²⁸ but dissipation of these benefits at 18 and 60 months was reported.²⁹ Given the substantially longer duration of the NExT intervention, along with the step-down in supervised exercise frequency and increase in prescribed home-based exercise, we hypothesized that benefits would be maintained for 1 year. The objectively measured changes in aerobic fitness and muscular strength reported in the present study mirror changes in self-reported exercise habits previously reported for the NExT program.⁷ Aerobic and resistance exercise levels were higher at end of program relative to baseline, but at 1-year follow-up, only the aerobic levels remained higher than baseline and unchanged relative to end of program.⁷ This suggests that there may be more barriers to engaging in resistance training (eg, access to equipment, less familiarity) and that more guidance and support, including behavior modification strategies (eg, goal setting, self-monitoring), are needed to promote maintenance of muscular strength outside a

supervised exercise program. However, an important finding for long-term health and functioning is that muscular strength at 1-year follow-up was still higher than at baseline.

The primary strength of our study design is the resemblance to real-world conditions with respect to the expectations regarding exercise adherence and the generalizability of the study population. Our study sample was much broader than in most prior RCTs with respect to age, ethnicity (one-third nonwhite), comorbid conditions, and work status during treatment (one-fourth worked at least part-time during treatment). A similar program could be implemented in clinical practice with minimal personnel cost (we estimated ~\$41,000 USD/y) and use of clinical space and the purchase or donation of used exercise equipment.⁷

This study is not without limitations. There was no usual care control group for comparison. The single-arm design was chosen because it would more closely mimic operations of a real-world clinical program and thereby would attract a more similar population. Our use of estimated VO_2peak from a submaximal exercise test without gas analysis and the lack of familiarization testing sessions are limitations for interpretation of the fitness changes and for comparison with

efficacy trials using these methods. These test formats were chosen to increase translatability to a real-world clinical program. The exercise component of the intervention was disproportionate relative to the nutrition component. For future studies and clinical programs, we recommend more ongoing nutritional education and feedback on dietary habits from a dietitian.

Conclusions

When delivered in real-world conditions, an exercise intervention based on synthesis of evidence from efficacy trials resulted in meaningful health benefits, including mitigation of the commonly observed treatment-related deterioration in aerobic fitness and QoL, improvement of muscular strength, and maintenance of body weight. We have also shown that a step-down approach

to supervised exercise frequency after completion of primary adjuvant treatment seems to be beneficial for inducing lasting change for up to 1 year.

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