The Role of Exercise in Cancer Treatment: Bridging the Gap

Gary T. Kimmel, MD[1]; Barbara K. Haas, RN, PhD[2]; and Melinda Hermanns, PhD, RN, BC, CNE[2]

Abstract

In recent years, there has been a burgeoning amount of evidence-based scientific data demonstrating the benefit of exercise during and following cancer treatment. This compelling evidence has resulted in major stakeholders in cancer management, including the American College of Sports Medicine, American Society of Clinical Oncology, National Comprehensive Cancer Network, American Cancer Society, Oncology Nursing Society, and the Commission on Cancer, advocating exercise as an integral component of cancer care. Despite the acknowledgment of exercise as an essential component, it remains virtually absent in routine cancer treatment. This article discusses the role of exercise in cancer treatment utilizing a community-based program. The rationale presented is that a scalable and replicable standard of care model is a plausible avenue to assimilate exercise into routine oncology practice.

Introduction

Exercise has been established as beneficial throughout the cancer management continuum. Its benefits may exceed or improve those of many routine treatment protocols (24). Acknowledging the long-term multitude of benefits, exercise should be included as an integral component of cancer treatment. Since the majority of persons with cancer have one or more comorbidities, the importance of studying the influence of exercise on cancer outcomes in the presence of a concomitant chronic disease is emphasized. Exercise may be administered best on a case-by-case, structured, and individualized basis in partnership with the patient for perpetuity. This approach provides achievement of optimal duration, frequency, intensity, and diversity for long-term adherence, thus providing maximum benefit. The rationale with a recommended strategy to bridge the gap between the demonstrated scientific benefits of exercise and its relative absence in cancer treatment is suggested.

[1]Cancer Foundation For Life®, Tyler, TX; and [2]College of Nursing, University of Texas at Tyler, Tyler, TX

Address for correspondence: Gary T. Kimmel, MD, Cancer Foundation For Life®, 1713 Troup Highway, Tyler, TX 75701; E-mail: g.kimmel@att.net.

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Exercise throughout the Cancer Treatment Continuum

Studies have demonstrated consistently that exercise enhances physical and psychosocial function, resulting in an improved quality of life (11,26). Improvements in the side effects of chemotherapy treatment include reduced nausea, fatigue, anxiety, and depression and increased integrity of bone and muscle mass (28). Exercise may improve timely completion of full-dose chemotherapy regimens, enhancing treatment benefit (5). Increased tumor sensitivity may occur in individuals exercising during chemotherapy administration (21). Aerobic exercise may be beneficial in the prevention and treatment of the cardiotoxic effects of doxorubicin and trastuzumab as well as in the improvement of cardiorespiratory fitness (28,34,38). The benefit of upper extremity exercise in the management of lymphedema in breast cancer has been documented, dispelling the myth of restricting use of the affected extremity (32). Sixty percent of patients with breast cancer gain weight during adjuvant chemotherapy, which increases the risk of recurrence. Exercise can ameliorate this risk factor (18).

Observational studies have demonstrated a remarkable 50% improvement in survival among persons with breast and colon cancer who exercise (16,25). Walking 150 minutes a week at a brisk pace achieved these benefits in persons with breast cancer, while more intense exercise of 6 hours a week was required in persons with colon cancer. Irwin *et al.* (17) studied more than 900 patients with breast cancer for a median follow-up of 6 years. Participants engaging in moderately intense physical activity demonstrated a 60% reduction in risk of death from all causes (17). In prostate cancer, 3 hours a week of vigorous activity (jogging, biking, swimming, tennis, and weight training) resulted in a 70% risk reduction in high-grade, advanced, or fatal prostate cancer (13). The magnitude of the effect that exercise has on a wide variety of physiologic functions is profound. Some of the favorable metabolic effects are evidenced in anti-inflammatory response, immune system, cognitive function, hematopoietic system, estrogen production, insulin-like growth factor 1 production, apoptosis, deoxyribonucleic acid

damage, and genomic aberration (gene expression and mutation) (9,22). Although common cancers such as breast, colon, and prostate cancer have been studied the most, research has expanded to include many other cancer types that benefit from exercise (2,6,19,31).

Survival data suggests that the frequency, type, and intensity of exercise required to achieve benefit vary depending on the type of cancer (13,16,25). The duration of the physical and psychosocial debilitation from cancer with the demonstrated long-term benefits of exercise in patients with cancer dictate that it be viewed as a permanent behavioral lifestyle. One community-based exercise program for persons with cancer accepts patients with all types and stages of cancer, degrees of disability, comorbidities, and any point in time in the treatment continuum for perpetuity (14). With an average age of 65, 70% of participants had one or more comorbid diseases (hypertension, diabetes, cardiovascular, obesity, Parkinson's, etc.). Exercise significantly contributes to the improvement of quality of life and survival partly through improvement in coexisting chronic diseases. Sedentary lifestyle may be viewed as a chronic disease, as inactivity is a progenitor of chronic disease and increase in all-cause mortality (4,12,23). The presence of comorbidities significantly influences participants' exercise routine. Although 150 minutes of exercise per week is recommended (35), significant improvement may be observed with much less exercise (36). Very small initial doses of exercise can result in outcomes previously unimagined. Two case studies illustrate this observation.

Case #1: Henry is a 63-year-old man in complete remission following surgery, radiation, and chemotherapy for brain lymphoma. Treatment side effects resulted in confinement to a wheelchair following physical therapy. Henry had been an avid biker and was highly motivated to resume bicycling. Evaluation revealed extreme muscle wasting in both lower extremities, with marked weakness in all major muscle groups. Henry initiated treadmill walking at home at 0.5 mph for 2 min, suspending his weight on the side rails of the treadmill with his arms. He would rest for 2 to 3 min, sitting on a stool on the treadmill deck, and perform a second session. This was repeated four times daily. Henry progressed 10% to 20% weekly in the duration and speed of his walk. In 4 months, he was walking without assistance for 30 min and had resumed riding his bicycle for up to 30 miles daily.

Case #2: Bill is a 71-year-old man with penile carcinoma and regional lymph node metastasis in remission, with advanced Parkinson's disease being treated with maximum medical therapy and deep brain stimulation. He had completed all prescribed physical therapies. A progressive shuffling gait became incapacitating, resulting in wheelchair dependence. Lower extremity muscle strength was excellent. However his gait disturbance prevented him from taking even a few steps without a shuffling hesitation associated with loss of balance. Walking at 0.3 mph was initiated with a gait belt and the ability to take two to three shuffling steps before stopping. Walking would be resumed when he could assume an erect posture and balance. Although progression was initially very slow, by 30 d of daily visits to the exercise center, Bill was taking several steps in succession. Flexibility, stability ball, and elliptical activities had been added to his exercise sessions. Walking speed and duration gradually progressed, and by 150 d, he was ambulating independently at 2.3 mph for 20 to 30 min with resolution of the shuffling gait.

This clinical experience demonstrates that minimal activity progressing over unlimited time can result in remarkable benefit. Exercise used as a perpetual therapeutic tool can achieve physical and mental outcomes in the management of disease that significantly may exceed those achieved with traditional medical treatment.

These case studies illustrate that although defining the amount of exercise to achieve optimal benefits in specific cancer types is relevant, the major factors determining the type, duration, frequency, intensity, and variety of exercise are complex. Variables to be considered include support (physicians, physician assistants, nurse practitioners, nursing staff, spouses, and caregivers), type and stage of cancer, current level of fitness, age, cancer treatment morbidity, comorbid diseases, and quality of the exercise program. Perhaps the most important factors in creating an effective exercise program that provides a nurturing relationship are the patient's will to improve and the knowledge, competence, and compassion of the staff.

Relatively little attention has been given to the palliative benefits of exercise in the cancer treatment paradigm. Individuals with far-advanced cancer or those in the terminal phase of the cancer experience also may benefit significantly from exercise (1). Experience suggests that selected patients with the will to live and who exercise often enjoy an enhanced quality of life. Oncologists may be reluctant to inform patients of their short-term prognosis when beneficial treatment modalities have been exhausted (8). These patients often pursue alternative therapies that are costly, ineffective, and sometimes toxic. Life tempered with finite time embellishes the value of each enjoyable moment. An exercise program may provide the opportunity to experience unanticipated gratification and peace during the end of life journey.

Exercise in the Cancer Treatment Paradigm

Major stakeholders now recommend exercise during and following cancer treatment. The American College of Sports Medicine (ACSM) assembled a panel of experts to create guidelines for exercise of cancer patients that was endorsed by the American Society of Clinical Oncology (ASCO) (33). The Commission on Cancer, which provides certification for cancer care providers, recommends that rehabilitation services be a component of comprehensive cancer treatment. The National Comprehensive Cancer Network (NCCN) recently added exercise guidelines to their inclusive treatment recommendations. The American Cancer Society (ACS) and Oncology Nursing Society (ONS) also recommend exercise as an integral component of cancer care (29,30). Although exercise currently is recommended across the cancer care continuum, it is not yet a routine component of cancer treatment. The explanation for not incorporating exercise into cancer treatment is multifactorial (37). Traditionally the oncologist has focused on prescribing surgery, radiation, or chemotherapy. Oncologists are less familiar with the benefits of exercise in comparison with those of traditional treatment. In addition, there is no Standard of Care

Model (SCM) exercise program for physician referral that is recognized as safe and effective regardless of cancer type, stage, degree of disability, and presence of comorbidities. The lack of a SCM for exercising persons with cancer results in little uniformity of exercise administration. A wide variety in exercise program application and quality may result in compromised benefit and enthusiasm for incorporation into oncology practice. In addition, there is no insurance provider reimbursement for cancer rehabilitation. Finally physicians have little enthusiasm for discussing lifestyle changes when the result is a small percentage of favorable outcomes in the absence of effective programs to refer their patients to.

Incorporating Exercise into Cancer Treatment

Whether patients are cured, in remission, or in relapse, psychological and physical toxicities of the disease or its treatment may persist for years. There is a growing body of evidence that prolonged maintenance therapy, particularly with targeted drugs, may be beneficial in many cancers including breast cancer, myeloma, lymphoma, sarcoma, and non-small cell lung cancer. Thus the potential increase in toxicity of cancer therapy enhances the role of long-term exercise in ameliorating these adverse treatment effects. Although exercise programs for weeks to several months in duration demonstrate the short-term benefits of exercise, the majority of the patients revert to a sedentary lifestyle within 6 months following completion of an exercise program of finite duration (27). Therefore it is imperative that exercise be viewed as a perpetual component of cancer treatment.

The development of a subspecialization has resulted in fractionation of medical care, with patients often receiving care from two or more physicians. The oncologist must have confidence that the exercise program is effective and safe to refer most patients regardless of coexisting diseases or the degree of disability without the necessity of subspecialist clearance. This eliminates a potentially formidable obstacle.

The following discussion is based on the *FitSTEPS for Life*® (FSFL®) programs' 12-year experience and is an exemplar of a successful exercise program for persons with cancer. Since the inception of the FSFL® program, over 14,000 referred patients have attended more than 350,000 exercise sessions at 13 community-based locations. The program has been demonstrated to be safe and effective, and its benefits are sustainable over time (14,15). The FSFL® began in 2001 when exercise was not considered yet a component of cancer treatment. All adult patients with cancer are eligible to participate for an unlimited duration at no personal expense. Funding from hospitals, cancer clinics, physicians, participants, grants, individual gifts, fund-raisers, and private and public foundations sustains the FSFL®. Reluctant oncologists initially referred only individuals with end-stage cancer or those remarkably debilitated from cancer therapy or a comorbid disease. This turned out to be enlightening for both the oncologists and the FSFL®. Many of these early participants achieved unprecedented benefits of improved quality of life and predicted survival. Now most patients are referred much earlier in their cancer treatment paradigm.

The exercise intervention is based on the *Social Cognitive Theory* (SCT) of Bandura who stated that "Health mandates without supporting resources, explicit plans of action, and a system for monitoring progress will not beget a healthy society. Successful models of personal change rely on guided mastery experiences in managing problem situations as the principle vehicle of change" (3).

The elements of the SCT based program include the following:

1. a structured, individualized, and well-defined exercise program,
2. convenient and accessible locations,
3. easily mastered exercise components to build self-efficacy,
4. monitored exercise sessions with positive feedback and achievable goal setting, providing participant incentive to progress and adhere to the program, and
5. an established exercise "community" providing accountability, self-modeling with an inspiration to succeed.

It is best to begin exercise at the time of diagnosis. This is the most "teachable moment" for the patient with cancer (10). These participants are most receptive to accepting recommendations that may improve tolerance to treatment and survival. Exercise is perceived as an inherent part of cancer treatment, enhancing adherence. It enables patients to participate actively in their treatment, providing a sense of control rather than a feeling of being a victim of cancer.

The physician is the most powerful influence in motivating patients to engage in a lifestyle change (20). The FSFL® program requires a physician referral. Physician authorization includes identifying restrictions to be imposed during exercise, authenticating the program to the patient, and reducing liability. Providing brochures to educate patients in the waiting and examining room stimulates patient inquiries about FSFL® and enhances physician referrals. An FSFL® navigator in the physicians' office may more-than-double patient referrals (Table). The navigator visits patients in the waiting room and chemotherapy suite as well as those attending chemotherapy and radiation therapy classes. The reduction in physician and staff time to explain the program and benefits of exercise enhances referrals. In the absence of a navigator, physician assistants, nurse practitioners, and nursing staff provide the resources to engage patients in an available exercise program.

The initial dosing of exercise "medicine" may be contrasted with chemotherapy administration. Chemotherapy protocols are given frequently for a finite number of cycles, titrating the dosage to toxicity. If remission is achieved, the patient is observed off chemotherapy or placed on maintenance therapy at a tolerable dose. An exercise program is initiated best in incremental doses, avoiding "toxicity," and increased over time with titration to a dose the patient can sustain for a lifetime. During the period of titration, patients are improving physical and mental function, building self-efficacy, and becoming a member of an exercise community. As opposed to a gymnasium, an environment with individuals of varying degrees of disability experiencing shared challenges instills collegial inspiration with a sense of control, creating enthusiasm for participation. These factors enhance long-term adherence, achieving maximal benefit.

Table.
Navigator influence on patient referrals to FSFL®.

	2009	2010	2011	2012	2013
First quarter: January, February, and March	25	26	13	69	51
Second quarter: April, May, and June	15	26	60	83	66
Third quarter: July, August, and September	19	21	94	67	72
Fourth quarter: October, November, and December	23	19	86	63	—
Yearly total	82	92	253	282	213 YTD

The expertise of the staff is the core component of a successful exercise program. All staff members hold exercise science degrees and are trained in managing debilitated patients with comorbidities. An average of 40 h of training is required to develop competency in providing the FSFL® program. Staff training, program supervision, and research project management are conducted by ACSM-certified cancer exercise trainers.

A history including cancer diagnosis and treatment, presence of comorbid diseases, and list of medications are obtained initially. Participants are educated about the benefits of exercise, and short-term and long-term goals are established. Stressing the importance of a long-term commitment to exercise, three or more times weekly, is emphasized. Patients unable to attend an exercise facility consistently are instructed on home exercises and receive telephone counseling for exercise progression, addressing obstacles, providing solutions, and setting goals. Spouses and caregivers (with physician referral) are encouraged to participate in the FSFL® program to enhance adherence.

During the baseline evaluation, height, weight, and abdominal girth measurements are obtained. Assessment of core strength, balance, flexibility, and presence of neuropathy and lymphedema in patients with breast cancer is performed. Aerobic capacity is evaluated by treadmill walking. The patient determines the speed and duration of activity, with pulse oximetry, blood pressure, heart rate recovery, and RPE scale monitored to establish the initial dose of aerobic exercise. Preexercise testing is costly and unnecessary in the FSFL® experience to safely and effectively administer an exercise program. One or more exercise components may be added (flexibility, stretch band, stability ball, dumbbells, elliptical, etc.) at the initial visit, as indicated. Exercise component selection is prioritized to address the participant's most compromised physical function. This achieves the most rapid improvement and builds self-efficacy and motivation to continue the program. Exercise sessions progress weekly by increasing intensity (10% to 20% weekly) and adding new exercise components. Participants are taught how to perform the exercises and record monitored metrics. Gradually they become more self-reliant and take ownership of their exercise sessions. After a few weeks or months, most are capable of performing exercise sessions with minimal supervision, thus enabling 6 to 10 participants per staff member to exercise safely and simultaneously.

New referrals, beginners, and significantly debilitated patients are scheduled when the center is least busy for additional individual supervision and instruction. Exercise classes are provided to enhance fitness, build camaraderie, and increase accountability and adherence. Staff increases exercise intensity, monitors technique, and adds new components to keep the program dynamic and gratifying. Participants achieve a plateau where they are exercising to tolerance that can be adhered to consistently for a long term. All patients are provided leisure time home exercise components, enhancing the achievement of an active lifestyle.

The FSFL® data using the SF-8 demonstrate significant improvement in physical and mental health within 1 month. Thus long-term adherence may be enhanced by consistent program participation for at least a month. Participant dropout rate is difficult to determine in this relatively morbid population. The FSFL® attrition rate is approximately 45%, translating to 55% adherence, which is higher than the 48% national average (15). Patients are prepared for lapses and reassured that these are common and that they are always welcome to return. It is not uncommon for individuals to return after an absence for weeks, months, or even years. To validate the anecdotal data, we tracked dropouts and restarts for 1 year. At the end of the year, the number of persons returning to the program (n = 1,675) approximated the number of those who dropped from the program (n = 1,735). The data are summarized in Figure 1. Participants are considered dropouts if they have not visited an FSFL® facility for 3 months or more. Although exercise attrition rate may appear high, prescription medication regimens have a similar compliance rate (7).

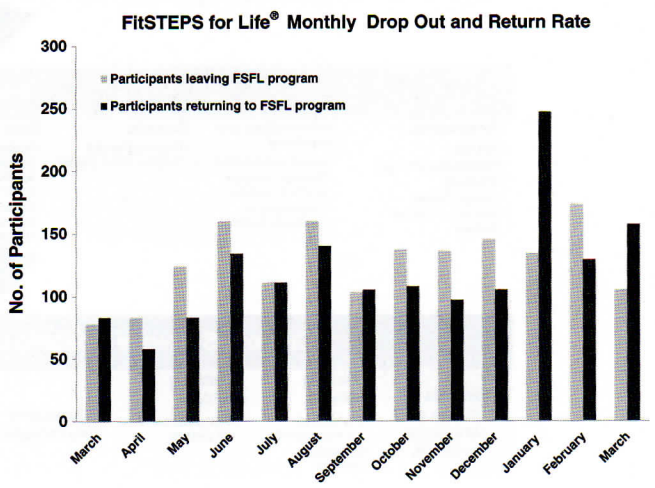

Figure 1: FSFL® dropouts and restarts.

Bridging the Gap: Proposing a Standard of Care Model (SCM)

The acknowledgment that treatment of a disease is appropriate is based on established standard of care criteria. Accepted protocols for surgery, radiation, and chemotherapy are developed for the treatment of most cancers. The NCCN is an excellent example of such a resource for clinicians. Treatment protocols improve with new research findings. Despite the irrefutable scientific evidence that exercise significantly improves the cancer treatment paradigm, it fails to be incorporated into oncology practice and no such standard of care protocols exist. The endless number of exercise programs with a variety of applications by individuals with various levels of skill and training precludes the development of a maximally beneficial exercise intervention. Until a SCM is provided to cancer care providers, patients' benefits from exercise will be compromised significantly and incorporation of exercise into clinical practice remains problematic. To bridge the gap between the scientific evidence and the absence of incorporation of exercise into clinical practice, it is recommended that a SCM be developed.

The seminal features of a SCM exercise program are summarized in Figure 2. Participants are instructed to learn their individualized exercise program for self-application with periodic staff assessment to enhance exercise session effectiveness. This builds self-efficacy and enables the staff to supervise safe and effective exercise sessions for multiple participants simultaneously. Measured metrics monitored during exercise sessions include pulse oximetry, blood pressure, heart rate, heart rate recovery, and RPE. Group classes improve conditioning, build camaraderie, and enhance adherence. In addition to aerobic and resistance strength training, core exercises are emphasized utilizing the stability ball, BOSU ball, Fit ball, foam pad, and seated safety squat. Individuals unable to attend an exercise facility consistently are provided home exercise components with regularly scheduled telephone counseling.

The SCM is a robust resource for research, with multiple institutions using the same intervention to contribute protocols and large numbers of study patients, thus greatly expediting the acquisition of research data that are clinically applicable. It serves as a valuable resource for academic institutions with exercise science and health care degrees to provide student internships, postgraduate work, and research opportunities. Students assist clinical staff providing hands-on experience and reducing cost of program administration. Multiple institutions utilizing the same exercise intervention may contribute additions and modifications that enhance program effectiveness.

A SCM may provide the impetus for stakeholders to partner in the incorporation of exercise into clinical practice, bridging the gap between the scientific data that demonstrates the benefits of exercise in cancer treatment and its absence in the cancer treatment paradigm.

Establishing a SCM

In consideration of the known benefits and barriers to incorporating exercise into cancer treatment, the following

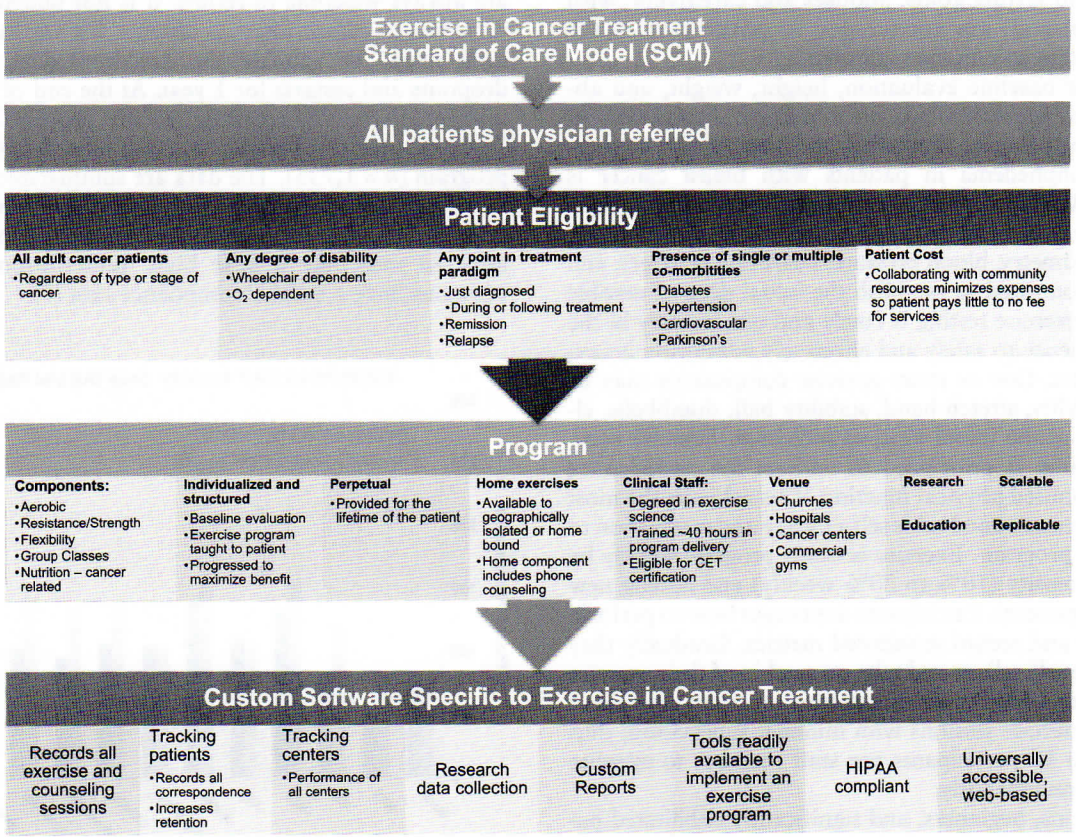

Figure 2: Standard of Care Model (SCM).

action plan is proposed to integrate a SCM into the cancer treatment paradigm:

1. First distinguished contributors in the academic field of exercise science and medical oncology, along with prominent cancer care providers, must endorse the concept of a SCM as the prototype to assimilate exercise into routine cancer treatment. Several leaders and experts already have acknowledged this proposal and endorsed such a letter.
2. This letter is to be distributed to major stakeholders (*e.g.*, ACS, ASCO, ACSM), requesting their collective support for a SCM incorporating principles from a program, such as FSFL®, to be the exemplar model for exercise as cancer treatment.
3. Collaborate with ACSM to establish a SCM.
4. Continue current efforts to expand partnerships with cancer care providers across the country to integrate a SCM, such as FSFL®, as a component of cancer treatment.
5. Recommend that the Commission on Cancer and NCCN use SCM for certification requirement and cancer treatment guidelines, respectively.
6. Conduct multisite research using a SCM to endeavor the accumulation of clinically relevant treatment outcomes.
7. Conduct cost-effectiveness research using a SCM to analyze the cost-to-benefit ratio of adding exercise to the cancer treatment paradigm. Favorable outcomes may provide evidence, resulting in Medicare and insurance carriers' reimbursement of exercise programs for cancer survivorship care.
8. Disseminate SCM research through professional organizations (*e.g.*, ASCO, ONS, ACSM).
9. Ensure continued modification of SCM to accommodate the burgeoning growth of information on best practices for the utility of exercise in cancer treatment.

Conclusions

Major stakeholders in cancer management recommend that exercise be provided for cancer patients during and following treatment. The rationale and method for the establishment of exercise as a beneficial cancer treatment were presented. The complexity of confounding variables present in patients with cancer makes acquiring meaningful relevant research challenging and arduous. A disseminated SCM provides a robust resource to accumulate relevant scientific research to further the development of protocols for cancer treatment.

Implementation of exercise as cancer treatment is illustrated from the experience of a community-based FSFL® model. A SCM was recommended to bridge the gap between the scientific evidence of exercise benefits and its lack of incorporation as a routine treatment in oncology practice. Failure to provide such a model to oncologists makes the incorporation of an optimally beneficial exercise intervention into clinical practice problematic. An action plan has been proposed to achieve this initiative. It is time for exercise to play a seminal role in cancer treatment.

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