

# Exercise-based Multimodal Programming: A Treatment Gap for Older Adults with Advanced Cancer

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Approximately 60% of new cancer diagnoses occur in patients aged 65 years and older.<sup>1</sup> Normal aging is associated with a decline in health and physical function.<sup>2</sup> A cancer diagnosis and subsequent treatment can accelerate this age-related physical decline, increasing the risk of adverse health events and mortality.<sup>1</sup> Aerobic and resistance exercise is an effective therapy to improve physical fitness and quality of life and to reduce cancer-related fatigue in individuals diagnosed with cancer, including advanced cancer.<sup>3</sup> The American College of Sports Medicine guidelines recommend maintenance of physical activity during active cancer treatment,<sup>3</sup> but guidelines specific to advanced cancer or elderly populations are lacking. Older patients with cancer are vastly underrepresented in clinical trials, including exercise-based trials,<sup>4</sup> due in part to the challenges introduced by the observed heterogeneity among older adults with respect to comorbid conditions, functional status, motivation, and safety-related concerns of the treating health care professionals.<sup>4</sup> Older adults are more likely to fear physical activity due to potential injury and to lack of guidance regarding how to start exercising.<sup>5,6</sup>

Similar to older adults, few exercise studies have targeted cancer populations with advanced cancer, potentially due to the increased risks (eg, pathological fracture, spinal cord compression) and challenges of exercise implementation.<sup>7</sup> Yet the majority (63%–92%) of patients with advanced cancer are willing and able to be physically active.<sup>8</sup> The combination of older age and advanced cancer diagnosis may create unique barriers to exercise such as increased symptom burden, particularly fatigue,<sup>2,9</sup> and reduced independence in transportation and reliance on caregivers,<sup>10</sup> that can reduce willingness and ability to partake in supervised exercise. Therefore, the feasibility of traditional “best-practice” supervised exercise interventions<sup>11</sup> can be limited among this population. These physical, psychological, and environmental barriers limit the generalizability of exercise prescriptions that were established as safe, feasible, and effective in younger or early-stage cancer populations. Therefore, the implementation of exercise-based programming among older adults with advanced cancer requires accommodations to overcome these barriers.

In this issue of *The Oncologist*, Mikkelsen et al<sup>12</sup> adeptly took on the challenge of developing and evaluating a multimodal exercise intervention in 84 older adults (≥65 years) with advanced cancer (stage III/IV).<sup>12</sup> The single-center, two-arm, randomized controlled trial compared the effect of a 12-week intervention consisting of group-based resistance training twice per week, protein supplementation post-training sessions, an individualized walking program, and 2 total individualized, nurse-led, motivational, and supportive counseling sessions to usual cancer care on physical function, symptoms, quality of life, and chemotherapy outcomes during first-line palliative chemotherapy, immunotherapy, or targeted therapy for pancreatic, biliary tract, or non-small-cell lung cancer.<sup>12</sup> Each aspect of the intervention was designed to address barriers specific to older adults with these advanced cancer types, including age-related limitations and comorbidities such as cachexia and sarcopenia.<sup>13</sup> The goals of the intervention were to avoid high energy consumption and an energy deficit but also to avoid inactivity, and to provide support for symptom management as well as individually determined life domains identified by a geriatric assessment and a palliative assessment.<sup>13</sup> Potential safety concerns and barriers to attendance were mitigated by resistance exercise supervision and individualization by a physiotherapist and provision of a home-based program if they were unable to attend the supervised group sessions. Importantly, the perspectives of patients in the target population were incorporated into the design of the intervention.<sup>12,13</sup>

Over one-third of eligible patients agreed to participate and the primary reason for declining was being too overwhelmed (33%). Among participants of both sexes (57% female), with a median age of 72 years, the multimodal exercise program was feasible as demonstrated by adherence rates of 69% and 75% to the resistance and walking exercise prescriptions, respectively, and a group difference of an increase in >2500 daily steps favoring the intervention group. While two grade 3 adverse events occurred that were potentially related to the exercise program (5% of intervention participants), they were appropriately managed by the exercise study staff by

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referral for diagnosis and management, allowing one of the patients to return to the exercise program with no further problems. Importantly, the intervention resulted in significant between group differences in physical function, including in the 30-second chair stand test (2.4 stands), 6-minute walk test (41 m), and hand grip strength (2.4 kg). A likely mechanism underpinning these improvements may be the 0.9 kg increase in lean mass measured by dual-energy x-ray absorptiometry. Additionally, symptom burden, symptoms of depression and anxiety, and quality of life improved in the intervention group. However, there were no group differences in any clinical outcomes, including hospitalization, treatment toxicity, chemotherapy dose intensity, or survival.

Despite the absence of an effect on chemotherapy outcomes or survival in the Mikkelsen et al study, the employed exercise-based multimodal program was both feasible and safe and the effects on physical function and patient-reported outcomes are clinically relevant for this patient population who experience accelerated decline in physical function and higher symptom burden.<sup>2,9</sup> Mikkelsen et al<sup>12</sup> have helped to fill an important gap in knowledge regarding the benefits of exercise for older adults with advanced cancer by capitalizing on established exercise motivators for older adults to participate in physical activity. Specifically, the intervention provided social benefits (via group-based exercise), use of motivational interviewing, and goal setting to enhance self-efficacy and behavior change, support from exercise professionals (physiotherapists) to reduce fear, and may have also provided a sense of control or purpose in life.<sup>6,14</sup>

Although the benefits of exercise in cancer populations in general are well known, a recent systematic review reported that 58% of oncology health care professionals report discussing physical activity with their patients, while only 18% refer patients to rehabilitation or an exercise specialist.<sup>15,16</sup> An oncologist's recommendation to exercise without a referral to exercise professionals has been shown to increase the exercise behavior of patients with early-stage breast cancer.<sup>17</sup> However, among older adults with cancer, one study of 591 patients identified that 65% presented with a physical, cognitive, or social functional deficit that could be addressed by referral to an exercise, physical, or occupational therapy professional.<sup>18</sup> The same study identified a substantial treatment gap among older adults (ie, difference in number of patients who need care and those who receive it), as only 9% of patients received therapy within 12 months. Cited barriers to physician referral of patients to exercise professionals include lack of time and the health care professionals' concerns about patient safety during physical activity.<sup>15,16</sup> Addressing this issue of lack of referral, or more specifically these barriers to referral, for older adults with cancer is key to reducing the treatment gap. Indeed, once referred, uptake of exercise programming is high (76%) among older inactive patients (aged 60+ years), even relative to younger age groups (56% for ages 16-44 and 67% for ages 45-59).<sup>19</sup> Particularly for older adults who have advanced cancer, physician referral to a supervised rehabilitation program like that in the study of Mikkelsen et al<sup>12</sup> may be a significant step toward reducing the treatment gap and addressing key functional health outcomes in this population.

There are several directions and considerations for future exercise clinical trials and programming for older adults, including those with advanced cancer. To advance knowledge on this topic, further identification of key exercise motivators,

facilitators, and preferences is needed among diverse groups of older adults with cancer to understand and address exercise barriers throughout the cancer continuum. A patient-centered approach that incorporates accommodations for the identified preferences but also evaluates and addresses individual patients' limitations and needs is likely to be optimal. Further research is needed to determine the exercise prescription (frequency, intensity, duration, type), setting (ie, supervised, home-based, telehealth, or hybrid), possible adjunct therapies (ie, protein supplementation) to optimize the balance between feasibility and impact on functional health outcomes. Older adults with early stage or advanced cancer are likely to benefit from individually tailored exercise prescriptions that incorporate mobility, agility, and balance training to increase patient safety, comfort, and confidence prior to the prescription of moderate-vigorous intensity exercise recommended in the guidelines. Adjunct therapies can enhance or potentiate the effects of exercise among older adults. For example, the study by Mikkelsen et al<sup>12</sup> included protein supplementation and counseling, which may have had synergistic effects on the improvements in physical function, lean mass, and symptoms. Lastly, intervention trials should also be designed with endpoints relevant to older adults, including those that will capture changes in cognitive function, mobility, balance, fall risk, physical function, and cachexia or sarcopenia.

In conclusion, the study of Mikkelsen et al<sup>12</sup> contributes new findings to the limited body of literature illustrating that exercise-based multimodal programming is feasible, safe, and benefits the physical function and patient-reported outcomes of older patients with advanced cancer. This study overcame numerous challenges associated with interventions directed at older populations, to contribute new evidence that may address the barriers to referral and resultant treatment gap in this population.

## Author Contributions

S.D.S., A.A.K.: conception/design. All authors: manuscript writing, final approval of the manuscript.

## Conflict of Interest

The authors indicated no financial relationships.

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