**Title:** Multiphasic prehabilitation across the cancer continuum: A narrative review and conceptual framework

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**Abstract**

The field of cancer survivorship has significantly advanced the person-centred management of cancer and treatment-related sequelae. Within cancer survivorship, the last decade has seen remarkable growth in the investigation of prehabilitation, that is, a multi-modal, pre-treatment intervention to prevent or attenuate the burden of oncologic therapies. While the majority of evidence which remains in the surgical setting continues to mount, prehabilitation is being adapted to target modifiable risk factors that predict poor treatment outcomes in patients receiving other systemic and localized anti-tumour treatments. With the rapid evolution of the science and proposed models that are more inclusive of the variability in cancer journeys, rethinking potential value and application of prehabilitation across the cancer continuum is timely and important. Accordingly, we propose ‘prehabilitation across the cancer continuum’ as a conceptual framework to encompass the variability in cancer treatment experiences while adopting the most inclusive definition of the cancer survivor.

**Introduction**

For more than thirty years, cancer survivorship has grown to become a well-established and internationally endorsed component of gold-standard, person-centered care that starts at diagnosis and continues to end of life. The seminal report on survivorship by the Institute of Medicine and the National Research Council, entitled “From Cancer Patient to Survivor: Lost in Transition” recently celebrated a decade’s worth of influence through its articulation of ten recommendations to improve oncology care.1 These recommendations specifically focus on the “period following first diagnosis *and* treatment and prior to the development of a recurrence of the initial cancer or death”, in response to insufficient attention to patients’ needs during this time. With remarkable progress in this field, pause for reflection on the application of survivorship principles at the core of these recommendations (e.g., strategies to “identify and manage late effects of cancer and its treatment”)2 is warranted, particularly, how these principles apply to the periods *between* diagnoses (primary and recurrence) and treatment(s).

Cancer rehabilitation programs aim to help a person (re)gain physical, social, psychological, and vocational functioning within the limits imposed by cancer and its treatment3 and are often the crux of cancer survivorship services. Because the field of cancer rehabilitation predates survivorship terminology, its integration (although still a work in progress), reflects its medical origins in impairment-driven care. While representing a marked advancement in oncology, contemporary cancer rehabilitation has largely been reactive to treatment sequelae rather than proactive in preventing or attenuating well-known consequences of common treatments. The ‘future’ of cancer rehabilitation in 1974 highlighted approaches to prevent or minimize disability that could be reasonably predicted; however, only recently have models been proposed with services initiated at the time of diagnosis and continued throughout the continuum of treatment.4, 5 The focus of recent interventions on building resilience *prior to* treatment through conditioning and medical optimization is commonly referred to as *pre*habilitation.

Cancer prehabilitation is defined as “a process on the continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a person’s health to prevent or reduce the incidence and the severity of current and future impairments.”6 The term prehabilitation captures the nuance of its role within the cancer treatment experience; that is, an intervention before oncological treatment with the aim to prevent or minimize the severity of anticipated treatment-related impairments. Prehabilitation is not oncology-specific, but is a growing field unto itself that has historically been applied to surgery where preoperative physiological and psychosocial health are well-established predictors of peri- and postoperative outcomes.7, 8 Reviews of prehabilitation in surgical oncology identify empirical limitations in the current evidence, yet acknowledge encouraging findings including improved functional capacity, length of hospital stay, surgical complication rates, health-related quality of life (HRQoL), and prolonged disease-free survival.9–13

The rapid growth of cancer prehabilitation over the past decade has contributed to a push for clinical implementation within perioperative care models;14, 15 however, there are a few gaps in foundational prehabilitation frameworks that limit its potential impact to broader cancer survivorship research and practice. First, while prehabilitation models have nearly exclusively focused on the period between diagnosis and surgery, cancer is often treated with multiple lines of therapy, each with unique treatment-related sequelae and challenges to completion. Accordingly, multiple phases of prehabilitation may be needed to prepare for consecutive treatments and their unique anticipated adverse effects. Second, while prehabilitation is arguably an integral part of gold-standard survivorship care, it does not supersede traditional post-treatment rehabilitation, but rather, complements it. As such, the two teams must work synergistically in the various phases of treatment to ensure efficient delivery and contiunuity of care. Lastly, prehabilitation has yet to be applied to the breadth of the ‘cancer survivor’ definition, using the fullest sense of the term that is inclusive of family, friends, and caregivers, particularly in preparation for end of life for the person with cancer.16 While the burden of the disease on palliative care patients has been widely recognized, interventions that proactively optimize their wellbeing remain unaccounted for. Conceptual frameworks that embrace the multiphasic nature of cancer treatment and encompass the breadth of the cancer survivor definition represent a major shift in the role and opportunity for prehabilitation in cancer care.

To support evolving clinical and research endeavours in oncologic prehabilitation, we propose a conceptual framework which argues that multimodal prehabilitation should be delivered across the cancer continuum. In this framework, prehabilitation is a dynamic, person-centered, and proactive health intervention that incorporates the relevant modalities to prepare survivors for imminent treatment(s), disease outcomes, and long-term health and well-being. In the sections that follow, we briefly review the multimodal nature of prehabilitation, as well as provide an overview of the evidence and theoretical rationale for multiphasic prehabilitation planning, organized by phase of treatment (i.e, neoadjuvant, primary, and adjuvant treatment).

**Multimodal Prehabilitation**

While early prehabilitation trials were predominantly unimodal (e.g., exercise or diet alone), contemporary prehabilitation models have adopted a multimodal approach to address the complex needs of people with cancer. Multimodal prehabilitation may be defined as the incorporation of two or more intervention components specifically selected for their potential cumulative or synergistic effects on health outcomes. Multimodal prehabilitation interventions have often comprised of two or more of the following: i) aerobic and resistance training to attenuate cardiorespiratory and musculoskeletal deconditioning, respectively; ii) dietary interventions to counteract disease and/or treatment-related malnutrition and to support anabolism and the metabolic cost of exercise; iii) psychological interventions to reduce stress and associated morbidity; iv) cessation of adverse health behaviours (e.g., alcohol abuse, smoking); v) medical optimization (e.g., assessing/treating anemia; medication corrections); and vi) behavioural counseling to support intervention initiation and adherence in the pre-treatment setting and establish self-management skills for long-term health behaviour maintenance.17–19 Recent qualitative inquiry in a study of exercise-only prehabilitation prior to breast cancer surgery by our group (unpublished) found that participants were extremely interested in and felt they needed dietetic and stress management support. These findings are corroborated by data from a clinical prehabilitation program including lung and colorectal cancer patients, which suggest that having comprehensive support via complementary modalities within the prehabilitation intervention was especially important and well received by participants.20

Multimodal prehabilitation is a complex intervention that necessitates the involvement of an interprofessional team working collaboratively to ensure optimal delivery and uptake, and to maximize patient benefit. Importantly, in the interest of engaging patients towards self-managed behaviours, co-design of prehabilitation interventions by healthcare practitioners and patient (and family/caregivers as appropriate) is recommended to cultivate a sense of purpose and responsibility towards managing one’s health *with,* rather than *by,* the healthcare team. Drawing from the oncology rehabilitation and palliative care literature, an interprofessional approach allows for the delivery of patient- and family-centered care to improve health outcomes and reduce treatment burden.21, 22 Care plans are developed via a symptom-driven approach, which takes into account the physical, social, psychological, and medical components of treatment and enables individualization and appropriate intervention delivery (summarized in Figure 1).

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Figure 1. Prehabilitation within the Cancer Continuum

**Prehabilitation Prior to Surgery and Other Primary Treatments**

Despite the breadth of anti-tumour approaches and their distinct consequences to the patient, research on multimodal prehabilitation has almost exclusively focused on surgical oncology. The pre-surgical focus may be explained by the opportunity that wait-times afford for investing in peri- and post-treatment health and potential economic advantages of reduced surgical complications, postoperative morbidity, and length of stay. Addressing modifiable surgical risk factors (such as exercise intolerance, malnutrition, anemia, smoking, and medication usage) have demonstrated a profound effect not only on postoperative HRQoL, but also morbidity, mortality, and the need for further care.23–25 Consequently, surgical prehabilitation has often been thoughtfully tailored to specific target risk factors. For example, surgical prehabilitation commonly includes training to improve cardiorespiratory fitness to prepare the patient for the impending surgical stress response that invariably increases cardiac output and oxygen consumption26, 27 and because of its established relationship with post-operative morbidity, mortality, and hospital length of stay.28, 29 As a result, cardiorespiratory fitness is often used as a physiological indicator of intervention efficacy.

Systematic reviews of surgical prehabilitation in people with cancer20–22,62,63,66–69 conclude that it improves physical fitness and functional capacity, with lesser, yet still compelling, data to suggest potential improvements in hospital length-of-stay, post-surgical complication rates, post-operative recovery and HRQoL when compared to usual care or post-operative rehabilitation alone.9–12 The state of evidence is challenged by modest methodological quality that has yielded only a weak recommendation for integration into contemporary perioperative care pathways (e.g., Enhanced Recovery After Surgery; ERAS).30 Moreover, given that many studies fail to appropriately describe safety or adverse events, and higher-risk participants have often been excluded, the actual risk or benefit of prehabilitating patients who may need it most is still uncertain. Advancement towards clinical adoption will benefit from the findings of large, ongoing phase III clinical trials,31–33 as well as improved reporting of safety outcomes, inclusion of higher-risk study populations, well described implementation strategies, and comparisons of multimodal to unimodal strategies that attempt to delineate modality-specific benefit.

Beyond surgery, prehabilitation prior to stem cell transplant (SCT) has received growing research attention given that SCT is a cornerstone haematological cancer management that often follows high-dose chemotherapy or whole-body radiation. The ‘dual hit’ of treatment leaves patients severely deconditioned, where impairment is more apparent in those with poor physical function prior to transplant.34 While interventions delivered after SCT attempt to remediate deconditioning and dysfunction are more widely studied, researchers have also examined prehabilitation exclusively prior to SCT35–37 or in combination with post-transplant interventions.38–40 Pre- and peri-SCT studies have featured a combination of supervised and self-administered multimodal interventions, comprised of low-to-moderate intensity endurance and resistance training, stress management and relaxation, as well as dietary guidance. The available evidence suggests that prehabilitation interventions that precede SCT are feasible and may offer favourable changes in physical fitness, psychosocial distress, fatigue, HRQoL and hospital length of stay, but lack high quality data for definitive risk and benefit assertions.39 In light of the often markedly poor and often changing health status of SCT candidates, more research on the feasibility and effects of prehabilitation in this setting is warranted.

While the surgical and SCT settings currently form the evidence-base for multimodal prehabilitation for primary therapy, comparable preparatory interventions for primary radiation or chemotherapy (among others) remain largely unexplored. It is worth highlighting that the iatrogenic consequences of radiation and chemotherapy may have a more gradual onset than the more abrupt insult of surgery and SCT that can change the metrics of success. For example, although complications may be similar, the outcomes of interest in non-surgical contexts may further include treatment dose tolerance, modifications to treatment course, and markers of health over the entire treatment period that may be sensitive to prehabilitation.

**Prehabilitation During or After Neoadjuvant Therapy**

Neoadjuvant chemo- and/ or radio-therapy (NACRT)-related toxicities manifest, in part, as reduced cardiorespiratory and musculoskeletal fitness stemming from underlying tissue, organ, and cellular dysfunction.41–43 Early evidence indicates that this cardiorespiratory deconditioning is associated with an increased risk of surgical complications and peri- and post-operative morbidity and mortality.42, 43 Importantly, cardiorespiratory fitness does not naturally recover between the end of NACRT and surgery,44 but rather, continues to decline without intervention.45 In addition to impaired cardiorespiratory fitness, compromised nutritional status resulting from NACRT is common and can worsen physiological dysfunction46 and affect surgical eligibility.47 Ultimately, NACRT creates a more frail, nutritionally compromised surgical candidate that is more likely to have a worse surgical experience. The benefits of prehabilitation in this setting may include mitigated NACRT-induced deconditioning that may consequently promote an earlier and fuller recovery prior to surgery. One practical consideration for prehabilitation in this context, is that NACRT is often initiated shortly after diagnosis, when it may be pragmatically impossible to routinely intervene prior to its initiation. While initiating prehabilitation prior to NACRT may be ideal, there is a growing body of evidence highlighting the health benefits of exercise, enhanced nutrition, and psychology during and after radiation and chemotherapy.48, 49 Collectively, the data suggest that starting prehabilitation during this period with targeted outcomes for both neoadjuvant and primary treatments are advisable.

Interventions aimed at mitigating or preventing associated physiological and psychosocial deconditioning related to NACRT have not consistently been described as ‘prehabilitation’, making it difficult to synthesize the relevant literature, but are increasingly recognized as such.50 To our knowledge, exercise prehabilitation delivered concurrently with NACRT has been examined in five studies with small samples sizes and variable methodological quality.51–55 Early findings suggest that supervised exercise prehabilitation during NACRT is safe, feasible, and may maintain or improve cardiorespiratory fitness over the intervention period. Recently, West and colleagues45 have examined the role of prehabilitation exclusively in the post-NACRT/pre-surgical setting in 22 rectal cancer surgery patients who participated in six weeks of facility-based, high-intensity interval training and were compared to 17 usual care participants in a non-randomized trial. Those who participated in prehabilitation recovered cardiorespiratory fitness to baseline levels prior to surgery, whereas usual care participants exhibited suppressed aerobic capacity. Additionally, several prospective studies have reported that omega-3 supplementation at a wide range of doses during chemotherapy correlates with positive outcomes, including decreased frequency of chemotherapy-induced mucosal toxicities and tolerability of chemotherapeutic drugs.56–59 The preliminary evidence is promising and it is likely not surprising that prehabilitation during or after NACRT appears to be the most rapidly developing area of the field given the relatively quick deconditioning NACRT induces, making patients more vulnerable to poorer surgical outcomes.41–43

**Prehabilitation Prior to Adjuvant Treatment**

Commencement of early rehabilitation following primary therapy with synchronous or sequential prehabilitation for adjuvant therapy is likely to have both distinct yet complementary functions as shown in Figure 2. The initiation of adjuvant therapy is commonly contingent upon the recovery and functional status following primary therapy60, 61 which is important because delayed adjuvant therapy can affect survival.62 It is essential to highlight that re- and prehabilitation in-between primary and adjuvant therapy, are not mutually exclusive nor are they synonymous because they each have distinctive health objectives. For example, rehabilitation following resective surgery may be required to restore localized mobility and strength, whereas prehabilitation for adjuvant chemotherapy may focus on optimizing cardiorespiratory function to protect against chemotherapy-induced cardiotoxicity. Given that cardiotoxicity also has shown to have implications on tumour control due to reduced dosage amidst concerns of deteriorating cardiac function,63 improving preoperative cardiac resilience appears to be an important strategy demonstrated in a small, but growing body of pre-clinical research.64–68 Proof-of-concept in humans has recently been demonstrated in a small randomized controlled trial in women with breast cancer which found that a single acute bout of vigorous-intensity exercise prior to anthracycline administration attenuated cardiac damage.69 To our knowledge, no studies have specifically examined prehabilitation prior to adjuvant therapy.



Figure 2. Example of coordinated rehabilitation and prehabilitation between two treatments

Prehabilitation for adjuvant treatment may be particularly beneficial given the compounded deconditioning associated with multiple lines of therapy; and, as a result, these interventions might provide the opportunity to mitigate the catabolic losses and associated consequences of anti-cancer treatments. Martin et al.70 found that in a cohort of 1473 lung and gastrointestinal cancer patients exhibiting weight loss, low muscle mass, and low muscle density, survival was just 8.4 months, compared with 28.4 months in patients who had none of these characteristics. While treatment effects are often comparable to those experienced during neoadjuvant treatment prior to surgery, the prehabilitation window between primary and adjuvant treatments may be more amenable for intervention. Evidence in this setting is limited, but preclinical studies suggest biological plausibility of benefit against chemotherapy-induced cardiotoxicity,64–66 howeer, human clinical trials are needed for confirmation.

**Multiphasic Prehabilitation: A Conceptual Framework**

Multiphasic prehabilitation, as a novel conceptual framework for the field shown in the panels of Figure 1, incorporates and extends both the initial model described by Carli and Zavorsky71 and the cancer-specific definition by Silver and colleagues72 to provide an evidence and theory-informed application of prehabilitation across the entire cancer continuum.  This framework is intended to guide future research by connecting the burgeoning data that show the benefit of healthier patients at the beginning of different treatments with the body of evidence on modifiable risk factors for adverse treatment- and health-related outcomes. The framework captures an evolving body of literature that increasingly supports multimodal and interprofessional care that is tailored to the variability in cancer journeys.



Figure 1. Multiphasic Prehabilitation Conceptual Framework

Core to the multiphasic concept is that prehabilitation may be considered as a health optimizing strategy that can occur multiple times following an initial cancer diagnosis. Multiphasic prehabilitation is an innovation to initial conceptualizations that has yet to be empirically tested as a cohesive sequence of preparatory measures across treatment exposures. Nevertheless, it is intended to provoke investigation of proactive interventions that focus on periods of relative health where the ‘maximum tolerable dose’ for a health intervention can be pursued more readily in the absence of active treatments that often smother functional capacity, dwindle appetite, and erode mental health and motivation. Aggressively preparing for repeated challenges across the trajectory of survivorship with multiphasic prehabilitation can be compared to contemporary models of high-performance athletic training. Multiphasic prehabilitation requires nuance and tailoring to the current and anticipated patient experiences at each phase of the cancer journey to minimize treatment-related side effects and subsequent delays due to these side effects thereby maximizing health and wellbeing and potentially prognosis over the long term.

Inherently, the delivery of multimodal cancer prehabilitation is expected to incorporate multiple health practitioners that include the oncology physicians (e.g., surgeons, anesthesiologists, medical oncologists, radiation oncologists) overseeing tumour management (via referral, clearance, or other support) as well as the professions specific to delivery of each modality, including general and loco-regional exercise (e.g., physiotherapist, kinesiologist or exercise physiologist, occupational therapist), nutrition (e.g., dietitian, nutritionist), psychosocial and behavioural counseling (e.g., psychologist, psychiatrist, social work), and other medical professionals as necessary (e.g., family physicians, medical specialists, nurses). Furthermore, at the heart of person-centered care is engagement of the person with cancer which represents an essential element of appropriately co-designed interventions and shared decision making. While the aforementioned may constitute the typical prehabilitation team, it may often fail to encompass other healthcare roles that comprise care delivered in the advanced care setting, where prehabilitation needs may relate to spiritual and financial issues. Furthermore, persons outside of the tertiary care setting may be best suited to address the needs of the non-patient cancer survivors (i.e., friends and family) to prehabilitate for physical or psychological conditioning to support caregiving, bereavement preparation, and/or estate management. Finally, seeking integration of prehabilitation into an existing health system, pathway, or care plan (e.g., survivorship care plans, ERAS), administration, patient-advocates, and policy advisors will likely provide key contributions to system-level initiatives.

For multimodal prehabilitation, proof-of-concept and efficacy among select health markers has been best demonstrated in the surgical setting and, while modest or correlational in other settings, has plausibility for benefit that justifies rigorous examination. In particular, the field is likely to benefit from greater adoption of intensive methodologies that assess complex interventions, such as process evaluations as highlighted by the Medical Research Council.73 These mixed approaches will permit greater understanding of biological, psychological, social and behavioural (‘biopsychosociobehavioural’) factors that drive participation, adherence, and health outcomes in complex health interventions, such as prehabilitation through the cancer care continuum.  In addition to the completion of ongoing high-quality clinical trials of prehabilitation prior to surgery, the field will further benefit from innovative investigations of feasibility, efficacy, and mechanistic properties across treatment settings to inform health systems decision-making regarding integration into care models. Considerations for priority research areas in prehabilitation are presented in Table 1.

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| Table 1. Future Directions for Prehabilitation Research |
| * Prehabilitation prior to non-surgical treatments
* Multiphasic prehabilitation
* Prehabilitation for high-risk patient groups
* Usability and efficacy of technology to capture and promote pre-, peri-, and post-treatment health behaviours (e.g., activity trackers, virtual reality)
* Cost-benefit of prehabilitation implementation
* Delivery and implementation strategies (e.g., home versus facility-based prehabilitation; integration into established models of care, such as ERAS);
* Maximum tolerable dose, minimum clinically important dose, and dose-response of prehabilitation;
* Prehabilitation of the caregiver to support their needs people with cancer;
* Impact of delaying treatment for prehabilitation;
* Biopsychosociobehavioural determinants of adherence and efficacy;
* Identify responders versus non-responders to prehabilitation;
* Comparison of unimodal vs multimodal prehabilitation
 |

**Conclusion**

The concept of prehabilitation has rapidly ascended into the common lexicon of survivorship care with research across cancer types, treatments, and modalities. The proposed conceptual framework for prehabilitation aims to guide further investigation of the viability and impact of repeated, pre-treatment interventions that target improved health outcomes throughout the entire cancer continuum.

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