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Concept Paper

Improving Outcomes in Elderly Patients with Ovarian and Pancreatic Cancer through Multimodal Prehabilitation

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Abstract

Elderly patients with ovarian and pancreatic cancer frequently experience malnutrition and sarcopenia, which negatively impact treatment tolerance, functional outcomes, and survival. The increasing use of neoadjuvant chemotherapy in this population necessitates structured interventions to mitigate these challenges. While prehabilitation has shown promise in enhancing treatment tolerance and quality of life, its role during chemotherapy remains underexplored. This prospective study evaluates the feasibility and impact of a multimodal prehabilitation program for elderly patients (≥65 years) with ovarian or pancreatic cancer undergoing neoadjuvant chemotherapy. The intervention consists of a 9-week structured program incorporating supervised aerobic and resistance exercises, individualized nutritional support (protein supplementation and dietary counseling), and psychosocial interventions (counseling and stress management strategies). Feasibility will be assessed through recruitment rates, adherence levels, and patient-reported satisfaction scores. Secondary outcomes include changes in physical function (6-minute walk test, grip strength, chair stand test), body composition (CT-derived muscle mass and sarcopenia markers), perioperative and

chemotherapy-related complications (dose reductions, hospitalizations, and adverse events), and patient-reported outcomes (quality of life, fatigue, anxiety, and depression scores). We hypothesize that patients completing the prehabilitation program will demonstrate improved functional capacity, reduced treatment-related toxicities, and enhanced chemotherapy tolerance compared to baseline. Additionally, we anticipate that prehabilitation will lead to preserved muscle mass, decreasing rates of chemotherapy dose modifications, and improved post-treatment recovery. This study will provide critical insights into the feasibility of integrating multimodal prehabilitation into routine oncology care. It will serve as a foundation for future randomized controlled trials to optimize outcomes in this high-risk population.

Keywords
Sarcopenia; frailty; exercise oncology; prehabilitation; geriatric oncology

1. Introduction

Cancer incidence among older adults is a growing concern as advanced age is a well-established risk factor for cancer, characterized by markedly higher incidence and mortality rates in older individuals. In the 60–69 age group, the likelihood is almost fourfold higher than that in the 49 and below age group, and it increased to nearly tenfold for individuals aged 70 years and above [1]. Elderly patients with cancer often face higher rates of morbidity and mortality due to the advanced stage of disease at diagnosis, comorbidities, and age-related vulnerabilities. Furthermore, elderly patients tend to receive less aggressive treatments due to the perceived risks of toxicity and complications, and they are generally underrepresented in clinical trials. Thus, comprehensive and personalized cancer care is essential to ensure optimal treatment outcomes for elderly patients.

In this review, we discuss the challenges faced by elderly patients with cancer, and we review existing evidence on strategies to mitigate the effects of sarcopenia. We present our clinical study aimed at evaluating the safety and feasibility of a multimodal prehabilitation program for elderly patients with ovarian or pancreatic cancer undergoing neoadjuvant chemotherapy.

2. Challenges in the Oncologic Care of Elderly Patients

The oncologic care of elderly patients with advanced malignancies presents numerous clinical challenges due to physiological factors, immunologic factors, metabolic alterations, and psychosocial and cognitive issues. Age-related changes, such as the decline in renal function, decreased bone marrow reserve, anemia, poor nutrition, and gastrointestinal alterations, significantly affect drug pharmacokinetics and other physiological processes [2]. To address these complexities, the American Society of Clinical Oncology (ASCO) recommends using geriatric assessments to evaluate functional status, physical performance, fall risk, comorbid conditions, social support, nutritional status, and cognition [3].

Cancer often leads to weight loss and muscle loss, while aging is associated with a gradual decline in strength and body weight. Frailty, characterized by heightened vulnerability due to age-related decreases across various physiological systems, includes five critical domains: weight loss, exhaustion, weakness, reduced walking speed, and diminished physical activity [4]. This condition is

common among elderly patients and is strongly linked to a higher likelihood of developing disabilities, which further increases the risks associated with cancer treatments [4].

Malnutrition is highly prevalent in the elderly population and is linked to severe postoperative complications, intensive care unit admissions, non-home discharge, and reduced survival [5]. Sarcopenia, defined as progressive loss of skeletal muscle mass, strength, and function associated with aging, can occur before or during cancer treatment. It significantly impacts treatment outcomes by compromising physical function, treatment tolerance, and overall quality of life [6]. The loss of muscle mass and strength results in decreased mobility and limits activities of daily living, making it challenging for elderly patients with cancer to cope with treatment. Sarcopenia is associated with an increased risk of falls and fractures, further complicating the ability to undergo aggressive cancer treatments or recover from treatment-related complications.

Additionally, elderly patients with cancer are generally more prone to hospitalization, which is associated with further declines in functional capacity and muscle strength and higher rates of hospital-acquired infections [3, 7]. They are also more likely to be discharged to nursing homes and less likely to return home, increasing the risk of muscle strength loss and dependence on walking aids [3]. Cancer and its treatment, including surgery, systemic therapy, and radiation, can exacerbate these vulnerabilities, leading to more significant physical decline and reduced treatment tolerance. Therefore, caring for elderly patients with cancer requires a multidisciplinary approach centered on geriatric assessment principles and comprehensive supportive care, which should include psychological support, nutritional guidance, and palliative care.

3. The Pathophysiology of Sarcopenia

Sarcopenia is an acute or chronic syndrome characterized by decreased skeletal muscle mass, reduced muscle strength, and impaired physical function [8]. It is primarily caused by decreased type II (fast-twitch fibers) and reduced muscle use, leading to motor neuron loss, muscle denervation, and neuromuscular junction instability [6]. Sarcopenia can be classified as primary or secondary. Primary sarcopenia is associated with age-related factors such as reductions in motor neurons, skeletal muscle alterations, mitochondrial dysfunction, and increased pro-inflammatory cytokines [3]. Secondary sarcopenia is attributed to external factors, such as lack of physical activity and chronic medical conditions, which can exacerbate primary sarcopenia [3].

Several factors contribute to the development of sarcopenia, including increased inflammatory cytokine release due to chronic inflammation associated with aging, increased visceral fat accumulation, and declines in anabolic hormones such as testosterone [9]. Malignancy contributes to sarcopenia through chronic inflammation, elevating pro-inflammatory markers such as tumor necrosis factor-alpha (TNF-alpha), interleukin-6 and -1, and interferon-gamma significantly contribute to cancer cachexia [10]. TNF-alpha promotes skeletal muscle wasting and anorexia via the NF-kB pathway. The overall impact of cancer cachexia can be severe, accounting for up to 30% of all cancer deaths. Therefore, targeted interventions are essential to mitigate the effects of sarcopenia and cancer cachexia and improve patient outcomes.

4. The Intersection of Malnutrition, Cachexia, and Sarcopenia

Malnutrition, cachexia, and sarcopenia are distinct clinical conditions that are frequently intertwined among cancer patients, particularly the elderly. Although frailty, sarcopenia, and

cachexia share overlapping characteristics and often co-occur, they are not interchangeable. All three conditions lead to accelerated age-related loss of lean body mass, strength, and functionality, a phenomenon known as malnutrition-sarcopenia syndrome [3]. While sarcopenia and cachexia both involve muscle wasting, they have distinct clinical characteristics and impacts.

Patients with sarcopenia often experience more severe disease progression and reduced responses to cancer therapies. A review of 30 meta-analyses on sarcopenia and adverse outcomes revealed that sarcopenia is associated with poorer prognosis across 12 cancer types, including gastric, hepatocellular, urothelial, head and neck, hematological malignancies, pancreatic, breast, colorectal, lung, esophageal, and ovarian cancers [6]. Sarcopenia is also associated with higher postoperative complications, such as infections, higher readmission rates, and more extended hospital stays.

The impact of sarcopenia extends beyond surgical settings to cancer treatment outcomes. For instance, patients with pancreatic ductal adenocarcinoma (PDAC) and sarcopenia showed worse overall survival [11]. Similarly, sarcopenic obesity has been linked to more severe hematologic toxicities in patients undergoing palliative chemotherapy [11]. These findings highlight the critical role of muscle mass preservation in optimizing cancer treatment tolerance and patient outcomes.

Cachexia is defined as "a multifactorial syndrome driving skeletal muscle wasting, with or without loss of fat mass, that cannot be fully reversed by conventional nutritional support and leads to progressive functional impairment." It is prevalent in up to 80% of cancer patients and can occur even in individuals with a standard or elevated BMI. The prevalence of cancer cachexia depends on the cancer type, with pancreatic cancer estimated to have up to a 70% prevalence [12]. Cachexia often remains undiagnosed and untreated, which can negatively impact patient outcomes. On the other hand, malnutrition encompasses a broader range of nutritional deficiencies that contribute to poor health outcomes. A study investigating the prevalence of malnutrition, cachexia, and sarcopenia among elderly patients found that up to 83% had one or more of these conditions, with a third diagnosed with all three [3]. These conditions are often overlooked, underplayed, and accepted as inevitable consequences of aging and disease.

The economic burden of malnutrition and sarcopenia is significant. A study of hospitalized, malnourished patients showed daily expenses of $228 compared to $138 for well-nourished patients [3]. Similarly, a US-based research estimated that malnutrition generates $18.5 billion in direct health expenditures annually [3]. Given the high prevalence and impact of malnutrition, cachexia, and sarcopenia among elderly patients with cancer, addressing these conditions through early screening and intervention is crucial in improving patient outcomes and reducing healthcare costs.

5. Assessment of Sarcopenia

The assessment of sarcopenia involves various methods to evaluate muscle mass, strength, and function. The most common assessment method is computed tomography (CT), which uses the third lumbar vertebra as a standard bony landmark. CT scans provide high-resolution, three-dimensional reconstructions of muscle mass and density, with cutoff points of ≤38.5 cm^2/m^2 in women and ≤52.4 cm^2/m^2 in men, to define sarcopenia [13].

Bioimpedance analysis is another method used to assess sarcopenia. However, it is sensitive to hydration status and dependent on the instrument used, which can be limited in clinical settings,

especially for patients with cirrhosis and volume overload [13]. Dual-energy X-ray absorptiometry (DXA) can also differentiate fat, bone, and muscle, comprehensively assessing body composition [14]. Anthropometric assessments of lean body mass, including skinfold thickness measurements, calf circumference, and mid-upper arm circumference, can predict overall muscle mass. However, these measurements are prone to human error and can be affected by changes in skin elasticity and body mass associated with aging [14].

Standard muscle strength measurements include handgrip strength and the chair stand test. Handgrip strength is measured with a dynamometer in the dominant hand, with the base resting in the palm. The chair stand test measures the time needed to rise from a seated position five times, assessing lower body strength and function [14].

Laboratory biomarkers have been investigated for their potential to assess muscle mass and function. One such biomarker is serum creatinine, derived from creatine phosphate, a significant product of muscle cells excreted as creatinine via the kidneys. Serum creatinine levels can serve as biomarkers for muscle and kidney function; however, this dual role means that muscle mass estimates based on serum creatinine can be confounded by kidney function [15]. Cystatin C, a protein expressed in all tissues and freely filtered by the kidneys, provides an alternative marker not directly influenced by muscle mass. Given its ubiquitous expression and constant generation and clearance rates, cystatin C has been considered alongside serum creatinine to form the serum creatinine to cystatin C ratio [15]. This ratio has been proposed as a potential biomarker for assessing relative muscle mass and function.

6. Evidence-Based Strategies to Mitigate Sarcopenia

Sarcopenia in cancer patients has been linked to poorer overall survival rates [16-19]. Furthermore, Shah et al. investigated chemotherapy dosing in patients receiving neoadjuvant chemotherapy for advanced epithelial ovarian cancer [20]. They found that those with sarcopenia were unable to complete all six cycles of chemotherapy [20]. Several interventions have been suggested to alleviate muscle loss and the consequences of sarcopenia in the general population [16-19]. Physical exercise counterbalances the effects of muscle catabolism by chronic systemic inflammation and protein turnover, preserves muscle satellite cells, and maintains mitochondrial biogenesis and function. Resistance training has been shown to mitigate the effects of progressive skeletal muscle loss across all ages. Muscle hypertrophy associated with resistance training increases muscle protein synthesis and can counter muscle degradation. Resistance training interventions lasting 10-18 weeks, with a frequency of 2-3 days per week, have been shown to increase muscle size and restore strength in the elderly [21].

Adams et al. conducted a three-arm randomized controlled trial comparing aerobic exercise, resistance exercise, and usual care among cervical cancer patients. Their findings revealed that resistance exercise was significantly more effective in reversing sarcopenia than aerobic exercise or usual care. The study also noted that sarcopenia was associated with a lower quality of life among breast cancer patients on adjuvant chemotherapy, and its reversal led to clinically meaningful improvements in quality of life [22]. These findings were further supported by a systematic review and meta-analysis that examined the efficacy of resistance training in preventing sarcopenia among breast cancer patients undergoing chemotherapy [23]. The findings revealed significant positive effects of resistance training on multiple key outcomes, including reduced body fat, increased lean

body mass, enhanced handgrip strength, improved leg press strength, and better overall physical performance [23]. These results suggest that resistance training is an effective intervention for mitigating chemotherapy-induced sarcopenia in breast cancer patients [23].

Combining aerobic training with resistance training has also demonstrated efficacy in mitigating the adverse effects of aging and sarcopenia. Adelaine et al. [24] investigated the effects of aerobic exercise and resistance on physical ability in elderly patients with cancer. They demonstrated a significant increase in grip strength, lean weight, and a 6-minute walking test. Moreover, Liang et al. conducted a study with 60 patients who underwent a 12-week balance and resistance exercise program compared to resistance-only training among patients with sarcopenia in a post-acute care unit [25]. This study revealed a significant benefit for the mixed exercise program compared to resistance-only training in decreasing the frequency of falls [25].

Nutritional interventions are also critical in managing patients with sarcopenia by improving muscle growth and repair. Adequate protein intake (>1.2 g/kg/day), emphasizing the amino acid leucine, which plays a central role in skeletal muscle anabolism, is essential [26]. Aredes et al. found that cervical cancer patients who were highly compliant (over 80%) with fatty acid supplements experienced lower SMI loss (-2.76 cm^2) compared to the total intervention group (-3.43 cm^2) [27].

Several studies have investigated the effects of protein supplementation on muscle mass with variable results. A study in colorectal cancer patients undergoing chemotherapy showed improved sarcopenia indices and nutritional status with whey protein supplementation. However, a meta-analysis of eight randomized trials with 557 older adults found no significant positive effects of protein or amino acid supplementation on muscle mass or strength [6]. Managing medications that affect muscle mass, such as corticosteroids, is also vital. Overall, a diet rich in protein and essential nutrients, combined with regular exercise, may be highly effective in preserving muscle mass and function in individuals with sarcopenia [19].

Novel pharmacologic interventions designed to combat sarcopenia are under investigation. These include myostatin antibodies, activin receptor agonists, exercise mimetics, and selective androgen receptor modulators [28]. Inhibiting the myostatin/activin A pathway has shown promise, with studies on agents like LY2495655, a myostatin-targeting antibody, demonstrating improvements in appendicular lean mass and physical performance in older adults [28]. However, results from randomized controlled trials remain mixed, with some failing to meet primary outcomes [28]. Additionally, the efficacy of IGF-1 mimetics, growth hormone, and ghrelin secretagogues in sarcopenic patients is unclear, with conflicting findings and epidemiological data raising questions about their benefits in improving muscle mass and function [28]. Furthermore, anabolic hormones, such as testosterone, have been widely studied for their positive impact on muscle mass and function, but results have been inconsistent. Further research is needed to clarify the potential of these treatments in the management of sarcopenia.

No FDA-approved therapeutic agents for sarcopenia exist [6, 29], and the evidence for using medications to treat or prevent it is insufficient. Therefore, the primary recommendation is multidomain lifestyle interventions, especially exercise training focused on muscle strength and power and protein-rich diets.

7. Exercise and Cancer Treatment

Exercise during cancer treatment has been associated with improvements in cardiorespiratory fitness, strength, fatigue, and other patient-reported outcomes [26, 27]. In patients with lung cancer, exercise can also lead to shorter hospital stays and fewer complications. However, most research on exercise in oncology focuses on common cancers, such as breast, lung, and prostate cancer, which highlights a gap in research on the role of exercise across a broader range of cancer types and stages. The American Cancer Society recommends that cancer patients engage in activity, including aerobic exercise, resistance training, or a combination of both [30]. This is further reinforced by the guidelines from ASCO, which also recommends regular aerobic and resistance exercise [31].

The consensus statement from the 2018 American College of Sports Medicine (ACSM) International Multidisciplinary Roundtable on Physical Activity and Cancer Prevention and Control asserts that the evidence is sufficient to recommend exercise prescriptions for managing treatment-related side effects, including anxiety, depression, physical function, and lymphedema [32]. Specifically, they recommend aerobic exercise three days a week for 20 to 40 minutes per session at an intensity that elicits a heart rate of 60-85% of the maximal heart rate. Additionally, resistance training is advised two to three times a week, performing two sets of 8 to 12 repetitions for each major muscle group at 60-75% of the one-repetition maximum [32].

An evidence-based resource utilizing the Frequency Intensity Time Type (FITT Rx) format has been developed to facilitate exercise prescriptions with improvement in overall health demonstrated [32]. The ACSM and ASCO also outline that cancer survivors should receive a comprehensive assessment, including cardiorespiratory fitness, muscle strength and endurance, body composition, and flexibility [31, 32].

However, there is limited evidence in ovarian and pancreatic cancer to guide recommendations for exercise. Preliminary evidence suggests that exercise during cancer treatment may improve treatment tolerance and response, although current evidence is insufficient to make definitive recommendations [33, 34]. A multimodal prehabilitation program, including supervised exercise, nutritional optimization, and psychological preparation, was evaluated for feasibility and postoperative impact in patients with advanced ovarian cancer (AOC) undergoing cytoreductive surgery [34]. In this single-center, before-and-after intervention pilot study, 15 patients received prehabilitation, while 19 served as controls. Adherence to the program was high (80%), with notable improvements in postoperative outcomes. The prehabilitation cohort had a significantly shorter hospital stay (median 5 vs. 7 days, $p = 0.04$) and a reduced time to chemotherapy initiation (median 25 vs. 35 days, $p = 0.03$) [34]. While postoperative complications did not differ significantly, the findings suggest that prehabilitation is feasible and may enhance recovery in AOC patients [34].

Elderly patients with epithelial ovarian cancer and pancreatic ductal adenocarcinoma undergoing neoadjuvant chemotherapy comprise a unique population likely to benefit from multimodal interventions. Patients undergoing neoadjuvant treatment have been found to lose muscle mass and is associated with worse overall survival [17]. A targeted program consisting of structured exercise, nutritional assessment and supplementation, and psychosocial interventions in elderly patients with ovarian carcinoma and pancreatic ductal adenocarcinoma undergoing neoadjuvant chemotherapy is predicted to improve functional, perioperative outcomes, and quality of life. However, evidence to date on the benefit of this intervention has been limited.

8. The Concept of Prehabilitation

Prehabilitation is a multidisciplinary process broadly designed to enhance functional capacity before surgery by incorporating structured exercise, nutritional support, and psychological assessment into preoperative care. Prehabilitation may be crucial in modifying postoperative outcomes and improving overall "fitness" for surgery by decreasing the surgical stress response and enhancing patients' preparedness for the planned surgical procedure. Structured exercises to strengthen inspiratory, limb, back, and abdominal muscles can improve overall physiological capacity and strength [35, 36]. A cost-effectiveness analysis evaluated the impact of prehabilitation in medically frail women undergoing surgery for EOC [37]. Using institutional inpatient charges, nursing facility costs, and complication rates from the literature, a model estimated cost savings and effectiveness [37]. In a cohort of 4,415 women, prehabilitation reduced overall healthcare costs from $404.9 million to $371.1 million, saving $33.8 million annually [37]. The cost per patient was lower with prehabilitation ($84,053 vs. $91,713 for usual care), and prehabilitation was found to be both cost-saving and more effective. These findings suggest that prehabilitation can optimize healthcare efficiency by reducing complications and the need for post-discharge care, warranting further prospective studies [37].

The evidence for prehabilitation in oncology has been established in patients with breast cancer, gastrointestinal cancer, lung cancer, and hematologic malignancies. Furthermore, structured prehabilitation programs have been effectively applied to patients with cancer undergoing abdominal and thoracic surgery, demonstrating significant benefits in improving perioperative outcomes. These programs have improved walking capacity, as measured by the 6-minute walk test, particularly in colorectal or upper abdominal surgery [37, 38]. Patients who participated in a prehabilitation program experienced shorter median hospital stays, were more likely to be discharged to their homes, and incurred lower costs associated with Medicare surgical episodes, home health services, and skilled nursing facility stays [39]. In lung cancer, prehabilitation is especially beneficial for high-risk or poor surgical candidates. It has demonstrated improvements in pulmonary function and walking tolerance, enhancing patients' performance and making them better equipped to tolerate surgery and adjuvant therapy [40]. Incorporating nutritional supplementation into prehabilitation programs has shown further benefits such as improved length of stay, quality of life, and reduced healthcare costs [41].

In contrast, the application of prehabilitation during chemotherapy has not been as extensively studied and is currently being investigated in the settings of neoadjuvant and adjuvant chemotherapy. While the principles of incorporating structured exercise, nutritional support, and psychological assessment remain the same, the specific benefits and outcomes in the chemotherapy setting are not well-defined. Prehabilitation for cancer patients undergoing chemotherapy shows promising results, but evidence remains limited. A 2023 study on esophageal cancer patients found that prehabilitation significantly improved chemotherapy completion rates (93.6% vs 77.7%, $p = 0.03$) [42]. Prehabilitation during neoadjuvant therapy has been shown to preserve cardiorespiratory fitness and may improve treatment tolerance across different protocols [40, 42]. Despite these challenges, prehabilitation’s potential benefits extend beyond surgery to various cancer treatments, including stem cell transplantation and neoadjuvant therapy [43]. Future research should focus on larger, randomized controlled trials with standardized interventions to establish prehabilitation’s efficacy and optimize its implementation in cancer care [42, 43].

Concerns about patients' ability to comply with or tolerate exercise interventions during treatment are often raised. Thus, comprehensive studies are needed to explore the potential advantages of prehabilitation during chemotherapy, particularly regarding treatment tolerance, quality of life, and overall health outcomes. Understanding these differences is crucial for developing tailored prehabilitation programs that address the unique needs of patients in both preoperative and chemotherapy settings [40].

9. Proposed Study

To address the need for a structured approach to integrating exercise and physical activity into oncology care, we propose a prospective clinical study to implement a multidisciplinary prehabilitation program for patients aged 65 and older with epithelial ovarian cancer or pancreatic ductal adenocarcinoma undergoing neoadjuvant chemotherapy. Eligible patients are individuals aged 65 and older with a diagnosis of advanced (Stage III or IV) epithelial ovarian, fallopian tube, or EOC or Stage I–III pancreatic adenocarcinoma, who are all undergoing neoadjuvant chemotherapy. The enrollment and screening would occur before the start of Cycle 2 of chemotherapy.

Patients will be enrolled in a 9-week multimodal prehabilitation program, incorporating a structured exercise regimen, nutritional support, and psychosocial interventions. The primary objective of this study is to assess the feasibility and acceptability of multimodal prehabilitation during neoadjuvant chemotherapy, which will be determined by recruitment rates, adherence to interventions, and attrition rates. Acceptability will be measured through patient-reported satisfaction surveys and adherence patterns. Secondary objectives include evaluating the effect of 9 weeks of prehabilitation on physical function (pre- and post-intervention), body composition (sarcopenia measures), nutritional status, patient-reported outcomes (including quality of life, anxiety, and depression), and chemotherapy tolerance.

The 9-week duration was selected based on several key factors. First, it aligns with standard neoadjuvant chemotherapy regimens for ovarian and pancreatic cancers, which typically span 9 to 12 weeks, ensuring that prehabilitation can be implemented without disrupting treatment schedules. Second, existing pre-rehabilitation literature suggests that an 8- to 12-week timeframe is optimal for improving muscle mass, physical function, and treatment tolerance while remaining feasible in an oncology setting [41, 44]. Third, a 9-week intervention allows for sufficient physiological adaptation, as neuromuscular improvements, aerobic capacity gains, and sarcopenia mitigation, as observed in structured exercise programs of this duration. Finally, this timeframe was chosen to balance effectiveness with feasibility, ensuring that patients can complete the intervention while minimizing burden and attrition, particularly in an older population with comorbidities.

Patients will undergo a comprehensive geriatrics assessment in addition to baseline assessments to evaluate their functional status, frailty (using the Fried Frailty Index), pre-existing comorbidities, and nutritional status. Laboratory tests, including measurements of albumin, prealbumin, and inflammatory markers, will be conducted to assess muscle mass and the severity of sarcopenia, along with CT scans.

Patients will be classified based on their frailty status, sarcopenia severity, and ECOG performance status, allowing for the development of personalized intervention plans. Comprehensive assessments will consist of physical function tests (6-minute walk test, grip strength assessment, and

sit-to-stand test), body composition analyses using contrast-enhanced CT scans, geriatric assessments, frailty assessments, and patient-reported outcomes. Additionally, chemotherapy-related adverse events will be monitored and recorded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

The intervention phase will span 9 weeks, with structured exercise sessions scheduled three days per week following the FITT (Frequency, Intensity, Timing, and Type) principle. Aerobic exercises will include walking, cycling, or treadmill use at moderate intensity, targeting 50–70% of heart rate reserve for two days. At the same time, resistance training will focus on major muscle groups using body weight, resistance bands, or light weights, with progressive intensity adjustments based on patient tolerance. Training exercise physiologists will initially supervise exercise sessions, with home-based adaptations available for patients with mobility limitations or travel constraints. For frail patients, modifications such as chair-based exercises or lower-intensity activities will be incorporated to promote engagement while ensuring safety.

The nutritional intervention will consist of personalized consultations with a dietitian and high-protein oral nutritional supplements (ONS) tailored to meet each patient's needs. This approach aims to optimize nutritional status and support muscle preservation. A comprehensive nutritional assessment will be conducted at baseline (before chemotherapy) and on Day 1 of each subsequent chemotherapy cycle. This assessment will evaluate dietary intake, malnutrition risk, and weight trends.

Patients will receive 1 to 2 bottles of high-protein ONS daily, supplied by the study team at Screening and on Day 1 of each chemotherapy cycle. This will ensure that their protein needs are consistently met. Protein intake will be adjusted based on body weight, targeting a range of 1.2 to 1.5 grams of protein per kilogram of body weight per day. Adherence will be monitored through patient checklists at each study visit.

Additionally, patients will receive standardized educational materials from the Cleveland Clinic Foundation (CCF) or the Eat Right Oncology Dietetic Practice Group (ONC DPG) as needed. Dietitian follow-ups will occur at baseline and during each chemotherapy cycle to ensure ongoing monitoring and to adapt nutritional strategies to optimize patient outcomes.

Patients will have access to oncologic Patient Support Services, which provide psychosocial interventions, including individual counseling, structured peer support groups, guided mindfulness practices, and stress reduction techniques. Additional free supportive care services from the Cancer Institute will be available, including yoga, mindfulness practices, art therapy, and music therapy. At each study visit, patients will be asked about their participation in these support services, and responses will be documented in the EPIC note. Anxiety and depression will be assessed using validated tools, including the Hospital Anxiety and Depression Scale (HADS) and the Edmonton Symptom Assessment System (ESAS), to monitor psychological well-being and intervention effectiveness.

Patient adherence to exercise, nutrition, and psychosocial interventions will be monitored through self-reported adherence questionnaires. A limitation of this study is the lack of wearable technology, which may lead to less accurate adherence estimates. To better understand the barriers to adherence, structured patient interviews will be conducted to document reasons for dropout or non-compliance. Additionally, the impact of travel burdens, financial considerations, and staff resource utilization will be assessed by collecting patient data regarding transportation difficulties,

scheduling conflicts, and costs associated with participation. Furthermore, patients will be compensated and receive vouchers to cover their travel expenses.

We hypothesize that a 9-week multimodal prehabilitation program will be feasible and acceptable for elderly patients with ovarian and pancreatic cancer and will result in improvements in physical function, body composition, and quality of life, ultimately enhancing chemotherapy tolerance and clinical outcomes.

10. Addressing Research Gaps in Chemotherapy-Related Prehabilitation

While prehabilitation has demonstrated benefits in improving perioperative outcomes across various malignancies, its role in the context of chemotherapy remains underexplored. Most existing prehabilitation studies have focused on surgical oncology, particularly in colorectal, lung, and gastrointestinal cancers, where structured interventions have improved functional capacity, reduced postoperative complications, and enhanced recovery [45, 46]. However, data on prehabilitation in patients undergoing chemotherapy, particularly in neoadjuvant settings, remains scarce [45, 47].

Several critical research gaps exist in this area. First, there is a lack of large-scale, randomized controlled trials evaluating the impact of prehabilitation on chemotherapy tolerance, functional decline, and quality of life in non-surgical oncology patients. Second, existing studies are often limited by small sample sizes, heterogeneous intervention protocols, and a lack of standardized outcome measures, making it difficult to generalize findings across different cancer types and treatment regimens. Third, the interplay between sarcopenia, systemic inflammation, and chemotherapy-related toxicities remains poorly understood, highlighting the need for targeted interventions that address these metabolic and physiological challenges [17].

Our study seeks to address these gaps by systematically evaluating a multimodal prehabilitation program in elderly patients undergoing neoadjuvant chemotherapy for ovarian and pancreatic cancer. By incorporating structured aerobic and resistance exercise, individualized nutritional supplementation, and psychosocial interventions, we aim to determine the feasibility and impact of prehabilitation on functional outcomes, chemotherapy-related complications, and patient-reported outcomes. Additionally, pre- and post-treatment CT scans will provide objective measures of muscle mass changes, offering valuable insights into the effects of prehabilitation on sarcopenia progression.

Given the increasing use of neoadjuvant chemotherapy in elderly patients, understanding the role of prehabilitation in this setting is critical. This study's findings will contribute to the growing body of evidence supporting integrated supportive care interventions in oncology and serve as a foundation for future randomized trials to optimize cancer treatment outcomes in this high-risk population.

11. Conclusion

Sarcopenia is often overlooked and underdiagnosed in clinical practice despite its profound implications. Elderly patients with cancer, particularly those with ovarian cancer and pancreatic cancer undergoing neoadjuvant chemotherapy, face unique challenges due to age-related declines in physiological function and the high prevalence of conditions such as sarcopenia and malnutrition.

These conditions can significantly impact treatment outcomes, functional status, and overall quality of life.

This concept study underscores the critical need for a comprehensive approach to managing elderly patients with cancer. Multimodal prehabilitation, which includes structured aerobic and resistance exercises, nutritional protein supplementation, and psychosocial support services, offers a promising strategy to mitigate the adverse effects of cancer treatment in this vulnerable population. These interventions aim to prepare elderly patients for the challenges of cancer treatment, ultimately enhancing their ability to tolerate treatment and improving survival outcomes. This research will be a foundation for future large-scale randomized controlled trials comparing prehabilitation to standard care. It will also establish a practical framework for incorporating exercise and nutrition interventions into routine oncology care, utilizing wearable devices for closer and more accurate monitoring.

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Author Contributions

Jasmin Hundal: Conceptualization, writing – original draft, writing – review and editing. Mariam AlHilli: Conceptualization, critical revision, and editing of the manuscript. All authors have read and approved the published version of the manuscript.

Competing Interests

The authors have declared that no competing interests exist.

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