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Discussion

The Role of Prehabilitation in Oncology Patients Undergoing Complex Systemic Anticancer Therapy

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ABSTRACT

Objectives: To review the recent literature around the role of patient-centric prehabilitation for oncology patients undergoing complex systemic anticancer therapy (SACT) and the nurse's role in this area.
Method: A narrative review of recent peer-reviewed literature, national guidance, and government strategy for prehabilitation in oncology patients undergoing complex SACT.
Results/Conclusion: Prehabilitation interventions in people receiving complex SACT are feasible and benefit patient outcomes. These results must still be viewed with caution; however, as of now, there are only small-scale studies in this area, although larger-scale studies are now being done. The role of the nurse is key here (as part of the interdisciplinary team) through the establishment of the therapeutic relationship underpinning patient screening, assessment, intervention implementation, and patient reassessment, ensuring care is dynamic, consistent, and tailored to patient needs.
Implications for Nursing Practice: The review has discussed the beneficial patient outcomes from prehabilitation in patients receiving complex SACT, but more research is warranted in the form of larger multisite trials to increase the validity of the prehabilitation interventions. The review advocates for the role of the nurse in the provision of prehabilitation in SACT oncology patients through the provision of personalized patient care.

In England, the NHS's standard contract and priorities for 2023/2024[1] endorse the implementation of early screening, risk assessment, and health optimization for all patients awaiting inpatient surgery through the provision of personalized care. By using prehabilitation interventions, patients are enabled to prepare for cancer treatment through personalized and multimodal prehabilitation prescriptions, based on exercise, nutrition, psychological support, and medical optimization. [2]

Prehabilitation has been principally investigated in the presurgical or perisurgical pathway,[3] where there is a sufficient window of time for patients to undergo prehabilitation interventions before surgery [4] in contrast to complex systemic anticancer therapy (SACT), including novel therapies, where the timing of beginning SACT treatment may be very close to diagnosis and therefore not give sufficient time to begin a prehabilitation intervention.[4] However, cancer is often treated with multiple lines of therapy, each with its effects and challenges to patients and caregivers [2,5] where prehabilitation can be applied, such as complex SACT and stem cell transplants.[6] Over the last 6 years, emergent research, principally in Western Europe and North America,[7] around uni/multimodal prehabilitation delivered before and during complex SACT regimens including novel therapies has given promising results and patient benefits.[5] Hence, justifying a narrative review of this research to inform future research on the benefits of prehabilitation in complex SACT patients and shape future clinical practice.

SACT encompasses all types of drug treatment used to control and treat cancer. These drug types include cytotoxic chemotherapy (both neoadjuvant and adjuvant), endocrine therapy, targeted therapies (monoclonal antibodies, small molecule inhibitors, and anticancer immunotherapy). The majority of SACT is given as combination therapy in complex multiagent treatment regimens, which include novel SACT.[8]

Due to the advent and frequency of novel therapies, personalization and tailoring of treatments and complex patient pathways, and increased management and monitoring of increased patient toxicities, SACT provision is a complex process.[9,10] Complex SACT combination regimens include both chemotherapy and biological therapies in multiple lines of treatment, such as sequential cytotoxic combination therapy followed by more cytotoxic therapy and yet more immunotherapy, in complex care pathways that require multiple health disciplines to manage their different aspects and stages.

The author uses the term "complex SACT" in the following discussion to encapsulate the increased complexity of managing patients who are treated with multiple types and courses of treatment that

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Layperson Summary

What we investigated and why

Research has found that preparing patients for surgery, by improving their physical and mental health, can help them through their cancer journey and to get better. This is called prehabilitation. Most research has been carried out with patients at the time of their operation. I investigated if prehabilitation helped patients who were taking anticancer drugs (systemic anticancer therapy [SACT]) and how nurses can help in this process.

How the research was done

We accessed and reviewed research that has been written about this topic.

What was found

Prehabilitation can help patients who are having SACT, which includes different anticancer therapies, including newer therapies, by improving their physical and mental health before, during, and after their treatment has finished. However, more research with larger trials must be carried out in this area. The chemotherapy nurses and clinical nurse specialists are well placed to give patients prehabilitation advice, assess/reassess them, and connect them with other health care professionals as needed.

What it means

It is shown that prehabilitation can help patients with complex SACT, but more research is needed to be done in this area with larger trials.

include novel SACT, requiring multiple clinical teams to manage patients on these complex SACT treatment pathways.

The author presents current evidence in a narrative review addressing the efficacy and benefits of prehabilitation interventions in oncology patients who are undergoing complex novel SACT regimens and the role of the nurse within this.

Methodology

MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL) complete, Psychological and Behavioural Sciences Collection, Cochrane Database of Systematic Reviews, and EMBASE were searched for published and ongoing peer-reviewed studies through November 19, 2024, excluding book reviews, commentaries, conference abstracts, and editorial articles.

Search terms were selected to identify studies pertinent to the area of research. Since prehabilitation can encompass dietary, exercise and psychological interventions as both uni and multimodal- the search terms were selected to keep the search as broad as possible. The search strategy included combinations of the following terms: cancer, oncology, anti-cancer therapy, SACT, novel, complex, chemotherapy, neo adjuvant, adjuvant, immunotherapy, targeted, endocrine, cytotoxic, prehabilitation, uni modal, multimodal, diet, exercise, nutrition, psychosocial support, and psychological support.

Evidence for Prehabilitation

Prehabilitation enables patients to prepare for cancer treatment, through personalized, evidence-based approaches involving multimodal prehabilitation prescriptions, based on exercise, nutrition, psychological support, and incorporation of key health promotion messages (eg, smoking cessation).[2,6] Through these measures, improvements can be seen involving long-term behavioral change.[3] Detailed screening and assessment within the prehabilitation process support the optimization of existing chronic health conditions (eg, diabetes or anemia) and personalization of the rehabilitation intervention.[11,12]

These activities have the potential to provide complementary benefits by improving cancer outcomes,[3,13] improving physiological function[14] and resilience to cancer treatment through fortification of the body's response,[15] empowering patients by fostering a sense of control and thus improving psychological function and enhancing the overall treatment experience,[16] and spurring long-term behavioral change.[16]

From a service provider perspective, prehabilitation optimizes capacity by improving patient flow, releasing critical care beds, reducing hospital stays,[17] and reducing unplanned hospital readmissions. Recent evaluations have shown significant improvements in patient outcomes and health system efficiency following prehabilitation interventions in various surgical settings.[3,6]

Timing of Prehabilitation Intervention in Patients Undergoing Complex SACT

Perhaps this is best illustrated in the cancer continuum (Fig 1), which advocates beginning prehabilitation at diagnosis, or any early treatment stage, preparing for primary treatment, and moving through recovery to the next stage of treatment through the cancer journey alongside effective rehabilitation.[2,17,18]

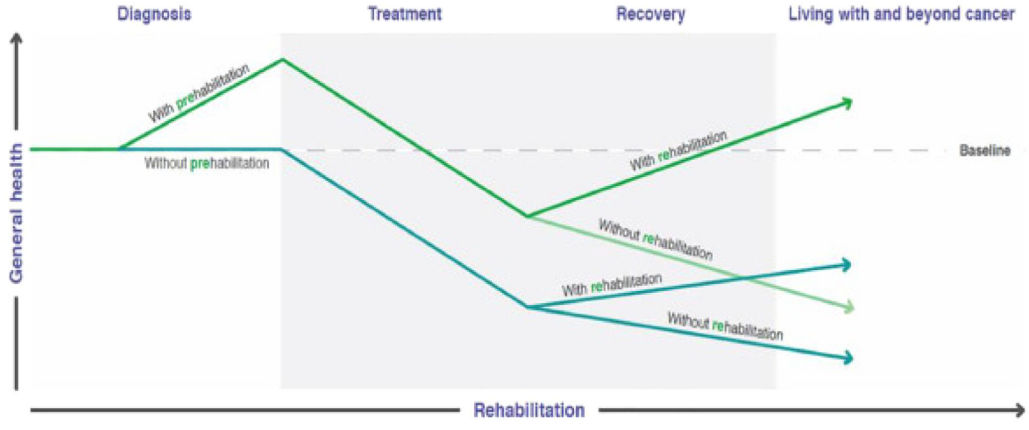

Fig 1. Cancer continuum: relationship between prehabilitation and rehabilitation and proposed difference in outcomes.[18]

The timing of the prehabilitation intervention and the patient pathway in complex SACT is illustrated in Fig 2, which also highlights the nurse's role (discussed later).

Prehabilitation Interventions in Immunotherapy and Targeted Therapies

Traditionally, cytotoxic chemotherapy has provided the blueprint for medical treatment of cancer. However, cytotoxic chemotherapy has an extensive toxicity profile as it targets all rapidly dividing cells, including both normal tissues and cancer cells.[19]

The treatment intent of targeted therapies is to inhibit cancer growth and the development of metastatic disease, but the mechanism of action of these drugs is cytostatic rather than cytotoxic.[19] Targeted therapies can inhibit specific molecular targets implicated in cancer or single oncogenic drivers. These drugs have transformed cancer care, leading to the personalization of treatment plans, improving cancer outcomes, and tailoring treatment to an individual patient's tumor. Further, rather than a disease-specific approach used in traditional cytotoxic chemotherapy, these novel therapies may be used to treat multiple cancer types.[19]

Although targeted therapies are found to have a lower profile of side effects than cytotoxic chemotherapy by patients, they can be associated with inhibitory effects on the biological function of the targets in healthy tissue resulting in specific treatment-related side effects, requiring specialist multidisciplinary management and representing an increasing burden for health economics.[19]

Immunotherapy harnesses the body's immune system to act against cancer cells, leading to a transformation of the treatment of hematological and solid malignancies. However, immunotherapies have a unique toxicity profile dependent on their mechanism of action, related to the upregulation of immune activity with side effects ranging from mild to life-threatening, such as lung, gastric, and cardiovascular toxicities.[20]

The evidence for multimodal prehabilitation in both targeted therapy and immunotherapy is scarce. However, there is evidence for the value of a unimodal exercise prehabilitation intervention for both treatment types.

Recent research in hematology patients has suggested a positive relationship between exercise and the effectiveness of monoclonal antibodies by augmenting cellular cytotoxicity, phagocytosis, and direct delivery of cytotoxic agents.[21] Further research is needed in this area around feasibility and adjuvant exercise, timing, type, and dose of exercise.[21] A small pilot study was undertaken in patients with non-small cell lung cancer receiving targeted therapy, which found an exercise intervention of 8 weeks of training improved physical exercise capacity and alleviated some cancer-related symptoms.[22] Further research is being undertaken in oral targeted therapies to relieve symptoms of fatigue in metastatic cancer patients, which is a frequently reported severe side effect. The QUALIOR trial is a two-part study that aims to evaluate the feasibility of home-based supervised exercise for patients with metastatic cancer receiving a first- or second-line treatment and the efficacy of this home-based program on patient's fatigue and quality of life.[23] Recent reports from this study suggest the feasibility of the intervention has been established with further efficiency analysis ongoing.[23]

Immunotherapy experimental evidence, largely from murine studies, suggests a role for exercise in augmenting immunological response and subsequent tumor regression through the modulation of multiple cytokines, influencing transcriptional pathways, and reprogramming certain metabolic processes, ultimately promoting antitumor immunity and enhancing the efficacy of immune checkpoint inhibitors in cancer patients.[24-28] This presents a promising therapeutic avenue for cancer treatment through the synergistic combination of exercise and immunotherapy.

Currently, the applicability of this research to a human population is limited. However, further clinical trials are indicated to examine different cancer types, host immune status, exercise frequency, intensity, time, and type of exercise,[28] thus addressing the feasibility and role of exercise on local and systemic antitumor immune response in different cancer types.

Hearteningly, this research is now beginning to emerge, although in small pilot and feasibility studies, where exercise and multimodal prehabilitation interventions are feasible associated with a decrease in patient symptoms (eg, fatigue) and a positive effect on the well-being and quality of life in patients who are undergoing immunotherapy.[29,30] Further studies are also in process: the ERICA trial examines the feasibility of an acute exercise intervention before immunotherapy infusion in non–small cell lung patients as well as the changes regarding immune and inflammatory biomarkers in their blood samples[31]; the larger HI-AIM randomized control trial, which investigates if high-intensity exercise can mobilize and increase infiltration of immune cells in the tumor environment in patients with lung cancer[32]; the IMOVE pilot randomized trial to assess the effect of a 12-week supervised exercise program on fatigue in advanced melanoma patients before receiving immunotherapy[33]; and a larger study to evaluate an exercise program for individuals preparing for chimeric antigen receptor (CAR) T-cell immunotherapy for hematological malignancies that examines both feasibility and acceptability of the intervention plus physical fitness levels, skeletal muscle mass, and health-related outcome measures.[34] These studies are presented in Table 1.

Sustained efforts and investment will be essential to drive progress in this field to achieve valuable insight into the interactions between multimodal prehabilitation and immunotherapy, looking at

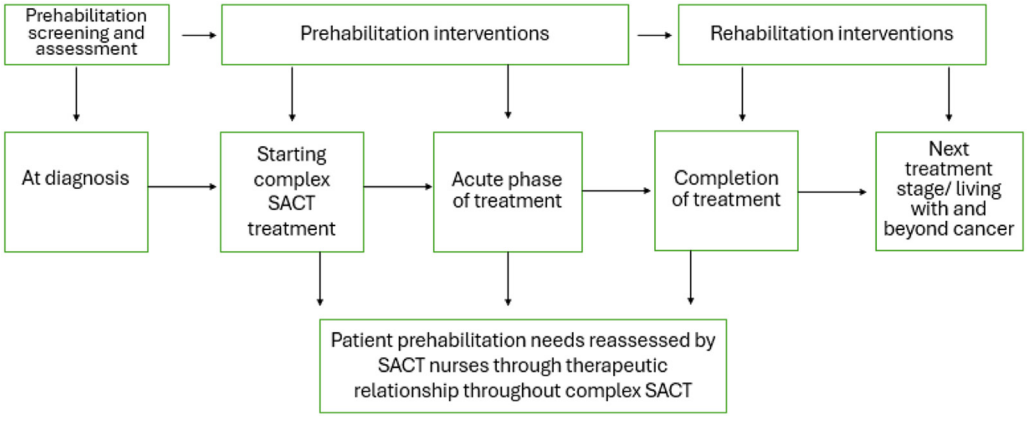

Fig 2. Timing of prehabilitation intervention in patients who are undergoing complex SACT.

Table 1
Protocols of Studies in Process on Prehabilitation and Complex SACT

Study Name	Study Type	Country	Prehabilitation Intervention	Timing of Intervention	Patient Population	Primary Outcomes	Secondary Outcomes
ERICA trial[31]	Feasibility	France	Acute exercise intervention/walking program (3 months)	Immediately before immunotherapy infusion/runs alongside immunotherapy	Lung cancer patients	Feasibility of intervention	Changes in immune and inflammatory blood markers
HI-AIM[32]	RCT	Denmark	6-week exercise program	Runs alongside course of immunotherapy	Lung cancer patients	Circulating immune cells	Inflammatory markers, QOL, physical activity levels, clinical outcomes
IMOVE[33]	Feasibility	Australia	Face-to-face and telephone exercise program, 12 weeks	Runs alongside course of immunotherapy	Melanoma patients	Feasibility	Qualitative data around intervention
CAR-T[34]	Feasibility	US	Exercise program 4 weeks	4 weeks before starting CAR-T	Older adults (age $\geq$ 65) preparing for CAR-T	Feasibility	Functional fitness, HRQOL, and muscle maintenance
PRIME-DC[35]	Feasibility	Germany	Multimodal prehabilitation: mind-body medicine, exercise therapy, nutrition therapy, naturopathic counseling	8 weeks during neoadjuvant SACT	Adult patients with cancer, with a primary tumor in the abdomen or the breast requiring a neoadjuvant treatment	Feasibility	Physical assessment and quality of life, a structured assessment of neoadjuvant treatment–associated side effects
PREOPtimize[36]	RCT	Spain	Nordic walking and resistance exercises	2 weekly sessions conducted between the fourth month of treatment and surgery	Breast cancer patients receiving neoadjuvant treatment	Functional capacity Adherence to the intervention in prehabilitation	Physical activity levels and health-related quality of life
Multimodal prehab breast cancer patients[37]	Feasibility	Australia	Multimodal supportive care program including exercise and complementary therapies	Runs alongside neoadjuvant therapy	Breast cancer patients receiving neoadjuvant treatment	Recruitment rate, retention rate, adherence, and acceptability	Patient-reported outcome measures, surgical outcomes, length of stay, satisfaction with surgery, chemotherapy completion rates, changes in metabolic markers, and adverse events

both biological makers, patient survival rates, and patient-related outcome measures and bringing about a better quality of life and treatment outcomes for patients.[26]

Prehabilitation Interventions in Neoadjuvant Chemotherapy

Neoadjuvant chemotherapy (NACT) treatment induces tumor regression leading to simpler surgery through tumor downstaging and increasing overall patient survival.[38,39] However, NACT has a broad side effect profile that increases risk associated with major surgery and can result in a poor patient experience.[40] Although NACT treatment scheduling is not considered as a novel treatment, some NACT regimens include novel agents in combination with chemotherapy; the use of this is expanding.[41]

NACT induces nausea, vomiting, and anorexia so compromises preoperative nutritional status and increased rates of sarcopenia[5,42] and persistent fatigue relating to a suboptimal health-related quality of life.[43] Therefore, reducing objectively measured physical function, a known risk factor for increased postoperative complications, hospital and critical care length of stay, and poor patient experience.[44] Accompanying this is the psychological stress and mental fatigue of a recent cancer diagnosis and treatment, increasing preoperative depression scores, therefore hampering the rehabilitation program, delaying return to preoperative functional capacity, quality of life, and psychological well-being.[2]

A scoping review of the benefits of prehabilitation in NACT patients was conducted by Renouf and Martin,[5] principally finding prehabilitation both feasible and beneficial to NACT patients. Of the 24 studies chosen for review, benefits for patients were shown in improvements in treatment responses, mitigation of cardiorespiratory conditioning and improvements in fitness levels, improvements in levels of sarcopenia, and improvements in patient experience and well-being. Reductions were also seen in postoperative complications, postoperative length of stay, and unplanned admissions.[5] These findings also correlated with surrounding literature not included on the review.[6,13,45,46] However, the reviewed studies were found to be mainly feasibility and pilot studies conducted in a single site with a small sample size predominantly focusing on unimodal prehabilitation interventions (principally exercise).[5]

Since our publication, more research has been carried out in this area. Multimodal prehabilitation and unimodal exercise interventions have been found to improve rates of completion of NACT without dose reduction in gastric-esophageal cancer patients, improved quality of life,[47,48] with improvements in cardiorespiratory fitness, overall functional capacity,[49] improved preoperative functional capacity, nutritional status, and enhanced tumor regression.[50,51]

Preliminary studies with ovarian cancer patients have shown multimodal prehabilitation during NACT improves nutritional status and postoperative recovery,[52] improves frailty, and is viewed positively by patients.[53] Further, in hematological patients who are receiving high-dose chemotherapy before stem cell transplant, multimodal prehabilitation was found to improve functional exercise capacity, lower limb strength and function, grip strength, physical activity, and patients' symptoms of fatigue and dyspnea.[54] Recent randomized controlled trials and meta-analyses in breast cancer patients have shown improvements in the pathological response to treatment and treatment completion rates, improvements in muscle mass and prevention of the loss of cardiorespiratory fitness,[55] with patients reporting better quality of life, less fatigue, and improved physical activity levels.[56] However, these results must be viewed with caution as small sample sizes mean only low to moderate certainty of evidence.[56,55] Further, a randomized controlled

implementation of a structured multimodal prehabilitation program in hepatopancreatobiliary patients showed patient benefit in improvements in patients' frailty scores and chemotherapy toxicity.[57]

Further studies are now being carried out in this fast-moving area in multiple tumor groups[35-37] with an indication to move toward larger, multicenter randomized trials needed for higher evidence certainty.

Prehabilitation Interventions in Adjuvant Chemotherapy

Adjuvant chemotherapy is often introduced following primary therapy and is crucial to patient survival. Patients who undergo adjuvant chemotherapy are often deconditioned following multiple primary lines of therapy and may benefit from both effective rehabilitation to improve and restore physical condition while helping to alleviate nutritional deficits and prehabilitation to prevent the damaging psychological/physiological effects of chemotherapy.[2,58]

Prehabilitation (before commencement of treatment), alongside effective rehabilitation (after commencement of treatment), addresses impairments caused by earlier treatment and helps to protect patients from the harmful effects of adjuvant chemotherapy.[2,58]

However, the evidence base in this patient group is scarce and warrants further research, with only one published study in this area. This study found that prehabilitation was feasible in adjuvant chemotherapy, associated with improved fitness levels and quality of life in colon cancer patients.[59]

Role of the Nurse in Prehabilitation in Patients Who Are Receiving Complex SACT

A key recommendation in the provision of a prehabilitation intervention for maximum patient benefit is that it is personalized to patient needs, empowering patients with cancer to play an active role in managing their disease.[60] This is fundamental in co-designed prehabilitation interventions and shared decision-making.[6,15]

Central to multimodal prehabilitation is the role of the nursing workforce, which is integral to the provision of joined-up, personalized, patient-centric care in prehabilitation[2,61] as part of the interdisciplinary team required to deliver complex SACT. The nurse underpins the whole process of patient screening and onward referral to prehabilitation programs, assessment, implementation of the intervention, and patient reassessment, ensuring care is dynamic and tailored to patient need through the close patient relationship.[2]

This is of particular importance for patients who are receiving complex SACT regimens, including novel SACT. Oncology patients will often undergo SACT treatment in multiple rounds, which may have a cumulative effect, contributing to functional decline and amplifying deficits, hence indicating the need for reassessment throughout treatment.[62] SACT nurses have been found to be the healthcare professionals with whom patients will spend the most face-to-face time during their cancer journey,[63] where SACT nurses establish a patient-focused therapeutic relationship with patients who they see regularly throughout multiple rounds of treatment and are key to this reassessment. This leads to modification of the intervention and re-referral to appropriate members of the prehabilitation team, ensuring care is proactive, dynamic, and constantly tailored to the patient's needs.[2]

Clinical nurse specialists (CNSs) (the patient's key worker) are also key to the prehabilitation intervention, where they will often see patients at the start of their complex SACT journey to provide patient education and start the assessment and referral process of the prehabilitation intervention as part of the interdisciplinary team.[15] The two roles will often overlap and link with SACT nurses regularly referring or signposting back to CNSs, as they see the patient throughout their complex SACT treatment.[64]

These roles are also constantly evolving in the era of the introduction of novel SACT medications, all of which may introduce increased patient toxicities, require complex patient pathways, and increase demand capacity and workforce pressures on SACT units and clinical teams by extending patient life expectancy and often requiring complex administration.[10,64] Therefore, requiring SACT nurses to not only reassess/assess their patients' complex health needs in SACT units, which are often pushed for capacity and time, but also ensure they are constantly updating their knowledge and clinical skills so they can provide safe patient care and provide the increasing support needed in patients who are receiving complex, novel SACT.[64] Recent research highlights that this therapeutic patient relationship is under threat. While SACT nurses value this relationship and their opportunities to provide patient support, it can be deprioritized in favor of ensuring SACT is delivered safely due to the escalating demands on unit capacity and workforce[64] exacerbated by the delivery of complex and novel SACT. In order to support SACT nurses to maintain their therapeutic relationships with patients, provision of prehabilitation interventions, and assessments, greater research needs to be undertaken to explore strategies to support nurses in their roles and release both SACT unit and workforce capacity.[64] Work in this area is now being undertaken nationally by Bopa, UKONS, and the Royal College of Radiologists.[8,10,65] Further, the provision of an educational evidence-based, accessible, and tailored educational program for CNSs and SACT nurses is warranted to lead to improved skills and confidence, equipping health professionals with a multimodal prehabilitation toolbox and thus improving care.[2,15]

Conclusion

Prehabilitation interventions in people receiving complex SACT have been found to be feasible and benefit patients through a variety of outcomes including treatment response, fitness levels, quality of life, frailty scoring, and reduced treatment toxicity. However, these results must be viewed with caution as, so far, there are only small-scale studies in this area. More research in this field is warranted, although larger scale studies are now in process in this fast-moving field. Nevertheless, prehabilitation has been found to be safe and feasible in this patient group and the beneficial effects of prehabilitation in people receiving complex SACT treatments are now emerging from the research. In future service planning, after the publication of larger studies, this would point towards the incorporation of patients receiving complex SACT in prehabilitation services to ensure equity across all groups of patients.[2,6] This review has also discussed the key role that SACT nurses and clinical nurse specialists play in this area through the establishment of a therapeutic relationship providing personalized care underpinning patient screening, assessment, intervention implementation, and patient reassessment, ensuring care is dynamic and tailored to patient need and highlighting their role in prehabilitation provision to this patient group.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Tessa Renouf: Writing – original draft, Methodology, Conceptualization.

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