

Prehabilitation as an extra approach to usual care for cancer patients

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Prehabilitation seems to be an important issue in oncology. The main purpose of prehabilitation is to improve a patient's physical and psychological condition at the beginning of and during cancer treatment. Prehabilitation also reduces the risk of potential complications, average length of stay at hospital, stress and risk of depression, and improves quality of life. Prehabilitation activities should be individualized. Multimodal prehabilitation is more recommended and it can include a spectrum of interventions like: general conditioning exercise, targeted exercise, nutritional interventions, psychological interventions, smoking cessation and education. There is a lack of clinical trials concerning prehabilitation. Therefore new studies are still needed to standardize protocols for different types of cancer and clinical situations, and to estimate the efficacy of prehabilitation programs.

Key words: prehabilitation, cancer, exercise, psychological interventions

Introduction

Cancer diagnosis is a difficult and stressful time for a patient. The cancer patient undergoes aggressive diagnostic procedures followed by severe, strenuous, prolonged treatment (surgery, chemotherapy, radiotherapy, immunotherapy, hormone therapy) depending on the cancer type, localization, and clinical stage. Cancer treatment affects the patient's physical, emotional, and nutritional status due to medical and psychological complications [1]. The cancer itself and oncological treatments are associated with a loss of appetite, weight loss, weakness, loss of muscle mass and muscle function [2]. Cancer treatment complications may delay or preclude further treatment, reduce patients' quality of life and generate increased costs for the health service. The unawareness of patients may increase the rate of psychological distress. Cancer rehabilitation is well established. It is well-known that exercise programs

during and after therapy can improve quality of life and reduce depression in cancer patients [3]. However, special person-centered care seems to be necessary for cancer patients to support their physical, emotional, informational, spiritual, and social needs from the point of diagnosis, during treatment, and to follow-up [4].

Proper perioperative care was recognized as an important component of comprehensive surgical treatment back in the 1990s. The first perioperative care protocol to improve surgical outcomes was done for colorectal surgery (Enhanced Recovery After Surgery – ERAS) [5]. This protocol has been revised, improved, and adapted for surgery in other locations [6]. It includes, among other things, nutritional interventions, smoking and alcohol cessation, encouragement of physical activity and relaxation, anemia management, and detailed patient information about various aspects of treatment. ERAS

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recommends implementation of preparations for surgery from the first visit to the surgical outpatient clinic and optimal use of time to surgery to improve the patient's general condition.

Prehabilitation is a relatively new method in medicine, but it seems to be an important issue particularly in oncology. The first research concerning prehabilitation among cancer patients was published since about 10 years ago. Cancer prehabilitation is defined as "a process on the continuum care that occurs between the time of cancer diagnosis and the beginning of acute treatment and includes physical and psychological assessments that establish a baseline functional level, identifies impairments, and provides targeted interventions that improve a patient's health to reduce the incidence and severity of current and future impairments" [7]. The main purpose of prehabilitation is to improve the patient's physical and psychological condition at the beginning and during cancer treatment. Effects of prehabilitation were determined in some studies. The authors identified the influence of prehabilitation on physical activity levels, muscle strength, muscle and bone mass, total muscle/fat ratio, BMI, mental well-being, quality of life, postoperative complications, morbidity, average length of stay at hospital, disease-free survival, and reducing costs [8–20]. Cancer diagnosis can affect patients to carry out critical behavior modifications (e.g., exercise, smoking cessation). People often rethink their lives and are open for lifestyle changes [21]. It also seems that there is a need for education, providing more information because patients often have problems with processing the information and making decisions at the time of diagnosis [22]. Certainly, prehabilitation should make patients feel cared for and guided by a schedule. But on the other hand Giles and Cummins [23] claimed that patients are too upset and worried with their diagnosis to take part in training and they are not psychologically able to modify their lifestyle. A program conducted improperly may even occasionally worsen the psychological condition. The authors suggested that prehabilitation may increase the social inequalities in cancer survival due to less involvement of lower social classes [23]. It might be considered that additional activities could be an extra stress for patients. The question arises as to what interventions to introduce into patient's care: diet and/or exercises and/or smoking cessation and/or psychological consultations. Patients who receive too many recommendations and are unable to fulfill them may have a poorer quality of life. However, accurate informing of patients at the time of diagnosis seems to play a main role. Patients should not feel pressured, they should learn the purpose and potential effects of prehabilitation to avoid disappointment or blame for treatment failure due to noncompliance with the prehabilitation program.

Prehabilitation is also a challenge in practice due to the limited time from diagnosis to treatment and the need to organize effective activities based on patient compliance.

Because of the limited time available for prehabilitation prior to oncological treatment, primarily surgery, patients need to be quickly included into a prehabilitation program and be motivated to adhere to it quickly and effectively.

There is a lack of clinical trials concerning prehabilitation. In many countries the health care system is unable to provide the prehabilitation programs as a routine practice due to financial and organizational constraints [24]. It is difficult to introduce quickly and provide prehabilitation interventions in a short interval between diagnosis and the start of therapy since there are no standardized methods. Moreover, it is challenging to establish a prehabilitation scheme that will have an effect, especially in the short term.

Types of prehabilitation

Prehabilitation may involve single or multiple interventions. Generally physical exercise is a crucial factor in multidisciplinary cancer care [25]. But the implementation of a nutritional and psychological intervention into a prehabilitation program may impact clinical outcomes [26–28]. Multimodal prehabilitation can include a broad spectrum of interventions like: general conditioning exercises, targeted exercises, nutritional interventions, psychological interventions, smoking cessation, and education [18]. There are some data that multimodal prehabilitation programs including psychological, nutritional, and physical intervention are associated with better functional outcomes when compared with single interventions. Patients better tolerate exercise programs together with dietary supplementation [29]. Psychological interventions could reinforce patient's motivation for physical and nutritional interventions, while physical exercise could reduce anxiety and depression [30].

Individualized prehabilitation should be provided. It seems to be important to educate and engage patients about the prehabilitation program.

Physical intervention

There are recommendations to combine exercises with standard oncological treatments to improve physical and psychological well-being for all types of cancer [16]. Physical interventions include general conditioning exercises or targeted exercises and could also be used as prehabilitation. General conditioning exercises and cardiovascular fitness are useful for strengthening and increasing tolerance to cancer treatment, as well as reducing postoperative complications. Exercise interventions may also include aerobic, yoga, Qi-gong, and Tai-Chi [31]. Targeted exercises concerning body region which could be related with dysfunction after treatment, for example bladder exercises to prevent post-operative urinary incontinence.

Patients may undergo physical training to improve therapy outcomes and health-related quality of life [11]. Better post-operative results and shorter length of hospital stay were associated with physical activities before surgery [10, 17]. Women

with breast cancer, physically active before surgery, have 85% greater chance of returning to a baseline physical condition 3 weeks after surgery than inactive patients [32]. Targeted exercises would be associated with a reduction in absences from work [33]. Rao et al. [14] showed lower anxiety among women with breast cancer who partook in yoga prior to surgery.

Prehabilitation training may improve the 6-minute walk test (6MWT), which is used to measure functional capacity. The results of 6MWT was associated with post-operative morbidity and complications [34]. Cavalheri et al. [35] showed that non-small cell lung cancer patients who exercised before surgery demonstrated greater 6MWT than inactive patients; they had decreased risk of pulmonary complications by 67%, shorter time with an intercostal catheter, and a reduced hospital stay. Morano et al. [36] also showed that preoperative exercise training among lung cancer patients significantly decreases the time of hospitalization, time of need for a chest tube, and pulmonary complications. Exercise intervention before operations reduced complications after abdominal surgery [37]. Significantly higher heart rate, oxygen uptake, peak power output were reported in the group of colorectal cancer patients who had undergone a 4-week course of aerobic exercise prehabilitation before surgery in comparison to patients who did not receive exercise training [38]. Physical prehabilitation may improve muscular strength and reduce the frequency of sarcopenia. Prehabilitation could change body composition. Analysis of body composition demonstrated that in a case of esophageal cancer, patients' exercise interventions reduced overall fat mass and reduced fat-to-muscle ratio [39]. It could influence the hospital stay, postoperative complications, the risk of infection, and the need for assisted ventilation related to additional medical costs and rate of readmission [8, 9].

Meta-analysis showed that aerobic high-intensity interval training (HIIT) in prehabilitation programs is effective, safe and feasible among cancer patients. HIIT is defined as a discontinuous endurance exercise characterized by a relatively short time of high-intensity exercises between periods of rest or low-intensity activity during recovery [40]. This method significantly improved cardiovascular fitness, measured by peak oxygen uptake in comparison to usual care. HIIT has been shown to have beneficial effects on quality of life, mood, emotional and pain state, as well as cognitive health [41–42].

VO₂ peak is an independent predictor for surgical complications and the survival of non-small cell lung cancer patients [43]. Recent studies showed that intervention combined with moderate- and high-intensive training (maximum heart rate 70–80%) is an optimal exercise program to improve 6-minutes walk distant (6MWT) and clinical outcomes of cancer surgery patients [44, 45]. High-intensity training is more effective to increase cardiorespiratory function in a limited time from diagnosis to operation [46].

However, there are no established schedule of exercises (type, duration, frequency, composition of activities) [47].

Nutritional intervention

It is recommended to assess nutritional status before major surgery. Perioperative nutritional support therapy is indicated in patients with malnutrition and those at nutritional risk. Patients with severe nutritional risk shall receive nutritional therapy prior to major surgery in a period of 7 to 14 days. Severe nutritional risk has been defined according to the ESPEN working group as the presence of at least one of the following criteria: weight loss >10% within 6 months, BMI <18.5 kg/m², SGA (subjective global assessment) grade C or NRS (nutritional risk screening) >5, serum albumin <30 g/l [48]. ESPEN recommend that the total energy expenditure of cancer patients is similar to healthy subjects and generally ranging between 25 and 30 kcal/kg/day [49]. According to ESPEN guidelines, protein intake should be above 1 g/kg/day and, if possible up to 1.5 g/kg/day [49].

Nutritional supplementation in cancer patients is mainly aimed at increasing protein for higher efficiency of exercise and functional capacity [19]. Preoperative protein supplementation has a positive impact on outcomes, including bone mass increase and 6MWT improvement [19–20, 50].

Nutritional prehabilitation alone and in combination with exercise significantly shortens the length of hospital stay after colorectal surgery [51]. Results of randomized clinical trial and meta-analysis showed that among malnourished patients who received nutritional intervention before a gastrointestinal operation, complications after surgery were reduced by 20% [52]. Kabata et al. [53] conducted a prospective study among patients who underwent abdominal cancer surgery. Patients who partook in a nutritional intervention for 14 days prior to the operation had significantly less number and severity of complications in comparison to patients without nutritional intervention; their level of protein was stable after surgery.

Psychological intervention

Cancer diagnosis naturally influences the emotional well-being of patients. Patients often experience anxiety and shock at the time of diagnosis. Existential questions, self-blame, fears for the future, and loss of control usually accompanies cancer patients thoughts at this time. Distress during the wait for surgery may have an adverse effect on recovery and cause higher risk of mortality [54–55]. Psychological intervention provided immediately after cancer diagnosis could help patients to adjust to the current situation. The standard of care in US includes distress screening to assess the psychological functioning of patients [56]. It was reported that stress management training before surgery among women with breast cancer reduced depression, tiredness, and anxiety [14, 15]. Stress management includes relaxation techniques such as meditation, breathing, yoga, muscle relaxation and strategies for coping with stress and problem solving [57]. Distress connected with cancer surgery is correlated with education levels, family support, and preoperative education.

Depression, anxiety, and fear can have adverse impacts on recovery, with complications among patients who have abdominal surgery [58–59]. Patients with breast cancer, who partook in yoga or supportive care before treatment and continued after surgery and during radiotherapy and chemotherapy, experienced less anxiety [14].

Psychological prehabilitation programs based on stress management, relaxation methods delivered in at least four 45–60 minutes sessions appear to improve quality of life after surgery among cancer patients [60].

Changes in lifestyle

Smoking cessation is recommended after cancer diagnosis to reduce postoperative complications, infection, disease recurrence, and even mortality [61, 62]. It was noted that patients who stopped smoking before surgery demonstrated lower risk of complications and better functional status and well-being after operation [63]. Smoking cessation among breast cancer patients may improve adherence to adjuvant chemotherapy [64]. Female smokers after breast cancer resection with reconstruction showed a greater risk of complications, infection, and failure of reconstruction [65–67]. Smoking is noted as a predictive factor of distress [68].

Prehabilitation interventions in different cancer localizations

Prehabilitation research focuses on patients undergoing surgery for colorectal cancer, prostate cancer, and less often breast cancer, lung cancer, and bladder cancer patients. Mainly the prehabilitation program is introduced before surgery, but there are also some studies relate to radiotherapy and chemotherapy.

Colorectal cancer

Trimodal prehabilitation (exercise, nutritional and psychosocial counseling) used before colorectal cancer resection significantly improves functional capacity, physical fitness, and 6MWT [69, 70]. The results of randomized control trials in colorectal cancer patients treated by operation showed that physical fitness as measured by the 6-min walking test was significantly higher in patients with 4-weeks prehabilitation than in the group of patients who underwent rehabilitation first after operation [69]. In an international multi-center, prospective, randomized trial, the positive impact of 4 weeks multimodal prehabilitation (an individualized exercise programs, breathing techniques, dietician consultation, protein supplementation, smoking cessation program, psychological intervention after screening for anxiety and depression) on a group of 714 colorectal surgery cancer patients was established. Dimeo et al. [71] showed that 86% of patients with prehabilitation in comparison to 40% of patients without prehabilitation recovered to baseline function 4 weeks after operation ($p < 0.01$). By strengthening the functional capacity (6MWT) and postoperative complications, quality of life and survival may be improved [13]. But

in other randomized clinical trials, the impact of multimodal prehabilitation (exercise, nutritional and psychological interventions) on postoperative complications among colorectal cancer patients was not confirmed [69, 72].

Targeted prehabilitation among colorectal cancer patients may influence strengthening functional capacity and result in better outcomes by reducing delays in beginning the adjuvant therapy [73]. Trépanier et al. [12] showed that 4 weeks trimodal prehabilitation (exercise, nutritional and psychosocial counseling) improved 5-year disease-free survival in patients with stage III colorectal cancer at ($p = 0.044$). Aerobic exercise seems to be an independent predictor of disease recurrence and mortality among colon cancer patients [74].

In the case of colorectal cancer surgery, patients who underwent any prehabilitation intervention had significantly shorter hospital stays [51].

Prostate cancer

Patients who were offered pelvic floor muscle training prior to a prostatectomy had significantly higher urinary continence one and three months after the operation, in comparison to patients who received usual care [75–77]. Continence-related quality of life was significantly improved at one and three months after the operation [76]. Patients who underwent physical therapy and a pelvic floor exercise program before and after a prostatectomy, and continued this program at home twice a day after surgery, were more likely to regain continence earlier than control group at 12 weeks post operation [75].

Burgio et al. [78] among patients using preoperative behavioral training prior to prostatectomy showed the significant decrease in time to achieve continence ($p = 0.03$) and a reduction in the number of patients with leakage at endpoint 6 months after operation ($p = 0.04$) in comparison to patients who started training first after operation. The impact on return to work and usual activities or quality of life was not reported. The preoperative biofeedback combined with a postoperative program of perineal physiotherapy improved recovery of continence [76]. Prehabilitation also had an impact on anxiety among prostate cancer patients [79].

Breast cancer

Rehabilitation for breast cancer patients undergoing operation and radiotherapy is most commonly introduced after oncological treatment. It is focused on restoring the function of the shoulder and upper limb using mobility and flexibility exercises. The systematic review demonstrated that an exercise program conducted before breast cancer surgery may improve the shoulder's range of motion, grip strength, function recovery and reduce pain, but postoperative rehabilitation should be continued to aid recovery [80].

General conditioning exercises are also very important for well-being among breast cancer patients. Rao et al. [14]

showed that yoga, prior to breast operation, lower states and traits of anxiety. In Canada, Brahmhatt et al. [81] carried out a study among 22 women who underwent breast cancer surgery, receiving individualized exercise (aerobic exercise and upper quadrant-specific resistance training) before breast operation. All participants subjectively noted beneficial effects and did not consider discontinuation from exercises and rather planned to continue the training program. Participants also claimed that they would recommend it to other patients before surgery. The 6MWT significantly increased from baseline to the preoperative assessment, there was a small decrease in 6MWT in the 6-week postoperative assessment and this again significantly increased 3 months after surgery. There are suggestions that psychological screening and intervention immediately after breast cancer diagnosis can help improve psychological and social status [82]. Breast cancer patients, who received stress management training before operations, experienced a reduction in depression and fatigue shortly after surgery [83].

A cardioprotective effect was observed in animals that underwent exercises in the prechemotherapy period. Kirkham et al. [84] showed that breast cancer patients who did aerobic exercise 24 hours before doxorubicin, experienced a less severe decline in cardiac function after chemotherapy.

In general, multimodal prehabilitation for breast cancer treatment (general conditioning and targeted exercise, nutritional optimization, stress reduction, smoking cessation) may reduce postoperative complications, enhance the effect of adjuvant therapy, enhance usual activities, facilitate a return to work, and mitigate psychological and physiological reactions to surgery [85–87].

Lung cancer

The results of a randomized controlled trial conducted by Liu et al. [88] showed that a 2-week multimodal prehabilitation program before surgery in lung cancer patients (aerobic and resistance exercises, respiratory training, nutrition counseling with protein supplementation, psychological guidance) was associated with higher perioperative functional capacity (as measured by 6MWT). But there were no differences in lung function, postoperative complications, and length of stay in hospital. Lai et al. [89] showed that pre-operative short-term (one week) comprehensive pulmonary rehabilitation training can improve the pulmonary resistance of patients with mild to moderate chronic obstructive pulmonary disease and accelerate rapid recovery of patients after surgery. Moreover, in a study published by Stefanelli et al. [90], high-intensity prehabilitation (3 weeks) improved the physical performance of patients with chronic obstructive pulmonary disease and non-small-cell lung cancer (NSCLC) undergoing surgical resection. Coast et al. [91] demonstrated significant improvements in the depression score among lung cancer patients after the prehabilitation program. However, most authors did

not notice changes in the quality of life [89, 92, 93]. Significant quality of life improvements was observed only by Huang et al. [94] and Peddle et al. [92]. In the systemic review and meta-analysis from 2019, including 676 participants at stage I–IV NSCLC from 10 studies [95], significant positive results were found in functional capacity (6MWT, VO_2 peak, dyspnoea) and pulmonary complications among lung cancer patients who have undergone prehabilitation (moderate intensity aerobic, resistance, inspiratory muscle training). There were improvements regarding mental wellness, but the results were not statistically significant. The systematic review conducted by Garcia et al. [96] reported that preoperative exercise training in lung cancer patients significantly enhanced pulmonary function. Another systematic review [97] showed that moderate and intense preoperative exercise therapy among patients qualified to lung surgery had a beneficial impact, not only on physical fitness, but also on quality of life (not significant). Prehabilitation in lung cancer patients undergoing surgery may reduce postoperative complications [95–97]. Exercise training in lung cancer patients leads to a lower risk of pulmonary complication by 67% in comparison with the control group, improved 6MWT, and a shorter time of intercostal catheter need [98]. Among advanced lung cancer patients, physical capacity, anxiety and well-being, and quality of life were improved [99–100]. Prehabilitation for lung cancer patients decreased the length of hospital stay after surgery [96–97].

Other cancers

Minnella et al. [101], in a randomized clinical trial, showed that multimodal prehabilitation statistically improved perioperative functional capacity (as measured by 6MWT) in esophagogastric cancer patients. Patients got individualized home-based exercise training programs and aerobic exercise, food-based dietary advice was provided, and protein supplements were prescribed. Patients after prehabilitation more often experienced an improvement in their condition before operation in comparison to patients without prehabilitation (62% vs. 4%) as well as after surgery (52% vs. 6%). There were no statistically significant differences in complication rates and length of hospital stay.

In the case of head and neck cancer patients, prehabilitation includes some specific exercises: general stretching, motion exercises and specific swallowing exercises. Some trials showed positive functional outcomes, while other studies did not confirm that [102]. It seems that exercise should begin as soon as head and neck cancer is diagnosed, and should take place before surgery and continue after the operation [102].

There was no significant benefits for bladder cancer patients treated with radical cystectomy of peri-operative exercise [103]. However analysis from 2020 [104] showed a trend toward improved physical condition and psychological well-being with the use of prehabilitation in bladder cancer patients before radical cystectomy.

Prehabilitation vs. rehabilitation

Meta-analysis carried out by Treanor et al. [105], comparing prehabilitation with standard care for cancer patients, found that preoperative interventions significantly improved physical well-being, quality of life, mood, and immune function in prostate cancer patients, while reducing the length of hospital stay and post-operative complications among lung cancer patients. In breast cancer patients who underwent prehabilitation with psychosocial intervention, there was a significantly lower level of distress, anxiety, depression (3 months after surgery) and less distress related to losing the breast, the partner's response and worries one year after surgery were also reported [105].

Conclusions

There is growing evidence that multimodal prehabilitation (exercises, nutritional consultation with protein supplementation, psychological support and smoking cessation) may improve the treatment outcomes for cancer patients, especially surgery. The systemic reviews showed that use of prehabilitation programs is more effective than standard care for cancer patients before the start of cancer therapy [25, 41, 60, 105]. Prehabilitation is important not only in improving the patient's overall physical condition before cancer treatment, but also for reducing the risk of potential complications, stress and risk of depression, and improving the quality of life (tab. I). A structured prehabilitation program for cancer patients, implemented early on from diagnosis, allows patients to actively participate in preparing for treatment, gives them a sense of empowerment, increases motivation and helps them feel cared for. Prehabilitation is feasible and safe – no adverse effects of prehabilitation were noted [91]. However, there are no standardized prehabilitation guidelines. There is a huge heterogeneity in type, intensity, duration, timing, and supervision of prehabilitation programs. Multimodal prehabilitation is more recommended, but it seems that prehabilitation activities should be individualized.

Table I. Prehabilitation benefits

Benefits for patients	Benefits for health care system
improving general condition	fewer complications
improving nutritional status	reduction in length of hospital stay
reducing stress, anxiety	reducing the risk of re-hospitalization
shorter hospital stay	
fewer treatment complications	
shortening the time to adjuvant treatment	
improvement of quality of life	
a faster return to work	

New studies are still needed to standardize protocols in different cancer types and clinical situations and to estimate the efficacy of prehabilitation programs.

Conflict of interest: none declared

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