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Improving Outcomes in Oncological Colorectal Surgery by Prehabilitation

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Introduction: The cornerstone in the treatment of colorectal cancer is surgery. A surgical event poses a significant risk of decreased functional decline and impaired health-related quality of life. Prehabilitation is defined as the multimodal preoperative enhancement of a patient's condition. It may serve as a strategy to improve postoperative outcomes. Prehabilitation requires a multidisciplinary effort of medical health care professionals and a behavioral change of the patient.

Methods: The goal of prehabilitation is threefold: (1) to reduce postoperative complications, (2) to enhance and accelerate the recovery of the patient, and (3) to improve overall quality of life. In this article, we introduce the FIT model illustrating a possible framework toward the implementation of both evidence-based and tailor-made prehabilitation for patients undergoing surgery for colorectal cancer.

Results: The model is composed of three pillars: "facts" (how to screen patients and evidence on what content to prescribe), "integration" (data of own questionnaires assessing motivation of patients and specialists), and finally "tools" (which outcome measurements to use).

Discussion: Developing implementable methods and defining standardized outcome instruments will help establish a solid base for patient-centered prehabilitation programs. Any party introducing prehabilitation requiring multidisciplinary teamwork and behavioral change can potentially use this framework.

Key Words: Prehabilitation, Colorectal Cancer, Surgery

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Colorectal cancer is the third most common type of cancer in men and the second most common in women, with more than 1.3 million new cases diagnosed annually worldwide. More than 80% of these patients are older than 60 yrs.[1] Currently, surgery remains the cornerstone of treatment. However, the physical stress associated with surgery brings significant morbidity and mortality, especially in patients with diminished physical reserves.[2,3]

The rate of complications is considerably increased (up to 50%) in vulnerable patients.[4] These vary from minor wound infections to more severe adverse events such as prolonged ileus and anastomotic leakage.[5] On the short term, these complications impede early mobilization and discharge his original residency. Moreover, on the long term, they pose a risk to the patient's survival and quality of life on the long term. Recent studies have identified several modifiable risk factors for complications in patients undergoing colorectal surgery (such as malnutrition, poor functional capacity, cigarette smoking, anemia, and anxiety).[6–9] The preoperative period can serve as a window of opportunity to enhance the condition of high-risk patients and consequently decrease surgery-associated morbidity and mortality.[10,11]

This preoperative enhancement has been coined prehabilitation and can consist of any form of patient optimization before surgery.[12] The research group of Carli et al.[13] has proposed a model illustrated in Figure 1, demonstrating the potential benefit of prehabilitation. The Enhanced Recovery After Surgery program has significantly accelerated recovery and made patients less care dependent on high-level care after surgery.[14,15] However, Enhanced Recovery After Surgery specifically focuses on the postoperative period and only starts 48 hrs before operation. Prehabilitation can shift the classic "waiting period" to a time frame in which patients can influence their own treatment outcomes. The waiting period before surgery is a salient time for patients to improve their lifestyle choices. The patient's functional capacity may thereby be improved before surgery, leading to a smaller decline of function during the postoperative period and possibly even faster recovery (Fig. 1).[13]

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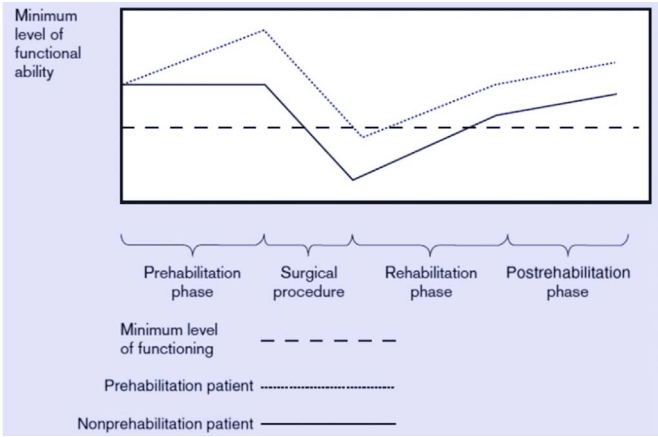

FIGURE 1. Prehabilitation model according to Carli.[13]

life. To date, research has been performed on single modal programs mostly focusing on nutritional status or exercise training as is also demonstrated in our previous systematic review on physical prehabiliation.[16] However, taking into account the multifactorial origins of a patient's vulnerability, a multimodal approach combining nutritional support, exercise training, psychological support, smoking cessation, and anemia correction, might be more effective, as is hinted in pilot studies of Chia and Gillis and several larger studies of which protocols have been published.[17–19]

Prehabilitation requires the multidisciplinary collaboration of medical experts and to support behavioral changes of a patient. Optimal implementation will be indispensable to ensure optimal compliance among patients. This narrative review introduces the FIT model (*facts*, *integration*, *tools*) to assess the current screening methods, prehabilitation contents, user assessment, and outcome measurement of prehabilitation in patients undergoing surgery for colorectal cancer (Fig. 2). In *facts*, we describe the need for triage and the different components considered essential in a multimodal prehabilitation program. In *integration,* we present questionnaires, which we used to assess the motivation of patients and specialists regarding prehabilitation. In *tools*, we describe the available outcomes measurements (Fig. 2).

FACTS: PREHABILITATION SCREENING AND CONTENTS

Based on the prehabilitation hypothesis, patients with poor overall well-being may benefit most from a prehabilitation program. In some cases, surgical intervention should be reconsidered, or surgery should be postponed to substantially improve the patients' functional capacity. Currently, five modifiable risk factors have been described in colorectal cancer surgery: poor functional capacity, malnutrition, cigarette smoking, anemia, and anxiety.[6–9] Although there are more modifiable risk factors such as social economic state, support system, we would like to focus on the five key elements mentioned previously since they have a great impact within a short timeframe. Furthermore, a synergistic effect is to be expected that will also have a domino effect on other risk factors (e.g., better physical condition will facilitate patient to increase activity radius, which can possibly lead to more social interaction).

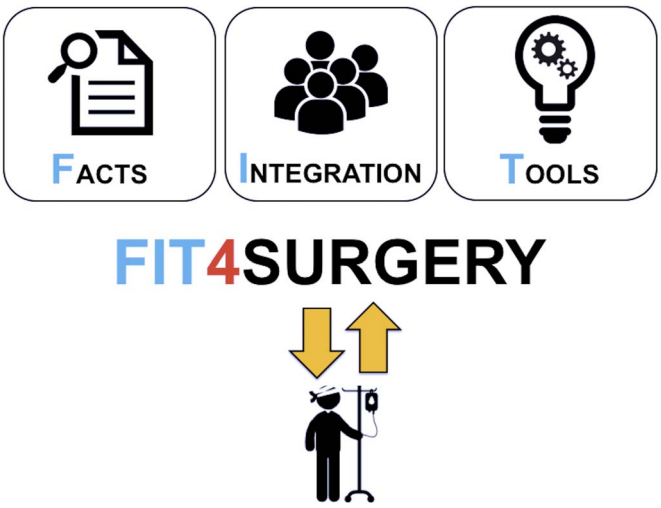

FIGURE 2. The FIT model.

Physical Condition

Screening

Declined preoperative functional capacity is an independent risk factor for postoperative complications and delayed recovery in patients undergoing colorectal surgery.[20,21] Impaired functional capacity (decreased muscle performance, poor cardiorespiratory state) leads to impaired functional performance. Especially older patients are at an increased risk for adverse outcome due to comorbidities, sarcopenia, and functional impairment.[22] Physical performance can be assessed in multiple ways, ranging from questionnaires (e.g., KATZ-ADL) to physical tests (grip strength, cardiopulmonary exercise testing, 6-min walk test).

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Preoperative exercise interventions can increase physical performance in patients with colorectal cancer.[23,24] Current physical programs vary from a complete training program involving both cardiorespiratory exercises combined with strength training in a sports facility to at-home exercise programs.[25–27] Because physically frail patients are often not used to exercise on a daily basis, researchers should strive to construct a feasible but exerting workout.[28] Even though a research setting often demands a standardized intervention, it should be the aim of investigators to develop methods in which it is possible to adapt the training to the patient's baseline condition.[28]

Nutrition

Screening

Approximately 55% of all patients and 25% to 40% of surgical patients are undernourished on admission to the hospital.[29–31] Moreover, malnutrition is further intensified during hospitalization especially in patients undergoing major surgery.[32] Malnutrition has been recognized as an independent risk factor for perioperative morbidity and severe postoperative complications.[33,34] Nutritional support is therefore recommended, sometimes even in seemingly well-nourished patients to target relative deficiencies (e.g., protein).[35–37]

There are various screening instruments to assess nutritional state of which the Patient-Generated Subjective Global Assessment Short Form is an example of a screening tool that can be used to identify malnutrition. It is an internationally validated instrument that identifies malnutrition in oncologic patients by assessing weight loss, comorbidity, and metabolic stress combined with a physical examination.[38,39] The Short Nutritional Assessment Questionnaire is another validated instrument to identify patients at risk for postoperative complications due to a poor nutritional state (also in non-oncological patients).[40] The Short Nutritional Assessment Questionnaire score consists of three questions assessing weight loss, appetite, and need for supplemental nutrition such as parental or tube feeding. A recent study showed that a score of higher than 3 is specifically associated with postoperative complications in patients undergoing surgery for colorectal cancer.[9]

More specifically in the case of patients with colorectal cancer, it should be noted that impaired nutritional status can also refer to a state of relative protein deficiency, which manifests itself as sarcopenia or loss in lean body mass.[41] Sarcopenia is defined as a combination of loss of muscle mass and muscle strength.[22] Importantly, it is often not detected with standard malnutrition screening tools that measure low body mass index (BMI) or recent weight loss, because many patients with sarcopenic colorectal cancer are overweight or obese.[42] Various methods to screen for sarcopenia have been described by the European Working Group of Sarcopenia in Old People including measurement of psoas density on computed tomography scan, hand grip strength measurement, etc.[22]

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It is not only challenging to measure the contents of a patient's diet but also challenging to interfere with it. Diets are notoriously difficult to adhere to, and each patient will likely require tailor-made optimization. Regarding protein intake, the European Society of Enteral and Parenteral Nutrition advices a total of 1.5 g/kg per day in cancer patients.[43] Recent studies aim for a total protein intake of 1.5 to 1.8 g/kg per day.[17] The daily estimated habitual protein intake can be estimated and a dietary specialist can provide patients with a tailored dietary advice aiming at a total intake of two portions of 20–40 g/protein a day. Because patients with colorectal cancer are often able to eat normally, severe cachexia requiring tube or parenteral feeding is not frequently encountered.

At the level of micronutrients, vitamin D is associated with muscle mass and muscle strength.[44] Vitamin D will be supplied daily immediately after cancer diagnosis according to guidelines of the World Health Organization (10 μg for men <70 yrs and for women aged 50–69 yrs or for women <50 yrs with colored skin or little sun exposure, and 20 μg for women and men aged 70 yrs and older). Many elderly patients may have other micronutrient deficiencies or ingest vitamins and minerals below recommended doses before and after surgery.[45] Therefore, it may be recommended to provide the patients with a multivitamin/mineral supplement.

Smoking

Screening

Cigarette smoking is a well-known risk factor for postoperative complications.[46] Smoking has a transient effect on the tissue microenvironment and a prolonged effect on inflammatory and reparative cell functions leading to delayed healing and complication.[47] Wound contraction and collagen metabolism are also affected by a smoking-induced alteration in vitamin C turnover and by a change in inflammatory cell response.[46] Evidence has shown that preoperative smoking cessation interventions reduce postoperative morbidity.[48]

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A period of 4 to 8-wk smoking cessation before surgery has already been shown to significantly reduce postoperative complications and morbidity.[48] Patients may be referred to institutes that can help them stop smoking. Successful smoking cessation may be achieved in just a few weeks as long as the patient is offered a combination of intensive counseling and nicotine replacement therapy.[49]

Anemia

Screening

Preoperative iron deficiency anemia is associated with increased morbidity and mortality.[50,51] Furthermore, anemia is associated with overall fatigue and impaired physical performance.[52] As the most common cause of anemia in patients with colorectal cancer in case of iron deficiency anemia, low hemoglobin levels (men <8 g/dl, women <7.5 g/dl) should be assessed in combination with low ferritin (<10 ug/l) and low transferrin saturation (<16%) levels.[53]

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Patients should be preoperatively screened to identify insufficient hemoglobin levels. In case of iron insufficiency, optimization of hemoglobin levels using iron injections is preferable. Oral iron supplementation has low compliancy and more adverse effects, whereas red blood cell transfusions are associated with higher perioperative morbidity and inferior long-term oncological outcomes.[54,55] The specific dose is calculated according to the severity of anemia and the weight of the patient.[52,53,56] By using iron injections, anemia may be corrected in a relatively short timeframe. To first achieve sufficient hemoglobin levels, postponing surgery may also be considered. Importantly, an optimal hemoglobin level may enhance patients' fitness levels, thereby also allowing for optimal exercise training.

Anxiety and Mood Disorders

Screening

Psychological status (mood, motivation, knowledge) may also play an important role in surgical recovery. It is well documented that patients awaiting major surgery experience anxiety concerning their upcoming operation, its outcome, and their course of healing and recovery.[57,58] They may also feel depressed, hold unrealistic expectations (overly optimistic or pessimistic) about their health status, and possess inadequate strategies for coping in the preoperative and postoperative periods. Any of these factors may influence pain and interfere with postoperative functioning.[59] Furthermore, high levels of cortisol induced by anxiety might have a negative effect in muscle strengthening.[60] Various instruments have been developed to assess mood and anxiety state. The Generalized Anxiety Disorder 7 questionnaire for anxiety, the Patient Health Questionnaire 9 for depression and the Hospital and Depression Scale combining both are examples of international validated questionnaires. The Generalized Anxiety Disorder 7 is a valid and efficient tool for screening for generalized anxiety disorder and assessing its severity in clinical practice and research.[61] The Patient Health Questionnaire 9 including nine questions is half the length of many other depression measures, has comparable sensitivity and specificity, and consists of the actual nine criteria on which the diagnosis of DSM-IV depressive disorders is based.[62] The Hospital and Depression Scale is a 14-question measure with seven items each for depression and anxiety.[63] It generates separate scores for anxiety and depression as well as a combined score of psychological distress, has been shown to have good psychometric properties for factor structure, homogeneity, and internal consistency, and has been used in studies of patients with a variety of healthcare problems.[64]

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Patients can experience stress and anxiety before and after surgery. Cognitive training in the form of psychological counseling, meditation, or yoga can reduce anxiety and stress perioperatively.[59] Furthermore, providing the patient with detailed information of the upcoming treatment and course of hospitalization and the opportunity to contact former patients with colorectal cancer can reduce preoperative anxiety.[65]

A summary of all screening methods and interventions is provided in Table 1.

INTEGRATION: IMPLEMENTATION IN THE FIELD

To achieve successful integration and implementation of a prehabilitation program, behavioral change is required in both patients and those providing the care. Therefore, we investigated the attitude of patients and surgeons toward prehabilitation.

Patients

In 2016–2017, a prehabilitation pilot study in patients undergoing colorectal surgery for cancer took place in Maxima Medical Center, Veldhoven/Eindhoven, the Netherlands (NL54547.015.15, submitted data). This pilot study was initiated to test the feasibility and safety of a multimodal prehabilitation program at both patient and organizational level.

Fifty patients were assigned to intervention (n = 20) or control group (n = 30). They participated in a multimodal prehabilitation of 4 wks in hospital physical training (high-intensity endurance and strength training, 3× per week), tailored dietary advice and supplements (total protein intake of 1.5 to 1.8 g/kg per day, 0.4 g/kg per day after strength training and daily before sleep, 50% of recommended daily allowance for multivitamins, and extra vitamin D), a smoking cessation program (including intensive counseling and any nicotine replacement therapy), and psychological support (one session at the psychologist providing strategies to cope with stress and anxiety). Perioperative care and rehabilitation were given according to the Enhanced Recovery After Surgery Guidelines.[66] Four weeks after surgery, patients were asked to give feedback on the prehabilitation program.

Evaluation of the program showed high patient appreciation. The attendance rate to the weekly training sessions by the physiotherapist was 88% and patient satisfaction was high (4 on a scale of 1–5). Reasons for joining the prehabilitation program were the motivation to optimally prepare for surgery (90%), distraction from the disease in the period before surgery (70%), and to be able to self-manage and change the condition (90%). Overall, these results suggest that prehabilitation could be of additional value to patients undergoing colorectal cancer surgery. A full description of the pilot study is provided in the original article.

Colorectal Surgeons

In 2016, a questionnaire was distributed to explore colorectal surgeons' intentions to cooperate in prehabilitation programs. Dutch colorectal surgeons were contacted via e-mail to respond to an online questionnaire (Supplementary Table 1,

TABLE 1. Prehabilitation content elements

Content	Measurement	Intervention	Compliance
Exercise			
Cardiovascular	6MWT, CPET, TUG	3×/wk HIT 30-min bicycle	Activity tracker (e.g., actigraph) (Digital) diary
Strength	Muscle mass, hand grip strength	Strength 10–15-min arms (flex/ext), trunk (chair rise), legs (knee raising, heel raises), 6–10 reps, 1–2 reps	
Functional	KATZ-ADL		
Nutrition			
Protein intake micronutrients	MNA, SNAQ, PG-SGA Diary	2× day snack/supplement containing 40 g protein, 1.5–1.8 g/kg/protein/d multivitamin supplement	(Digital) diary product registration
Psychological			
Anxiety	GAD-7, HADS	Psychological counseling, meditation, yoga	Daily logging of mood
Depression	PHQ-9, HADS	Information sessions, former patient contact	
Knowledge	Patient interview		
Social	Anamnesis		
Smoking	Anamnesis	Personalized counseling	(Digital) diary intoxication screening
Anemia	Hemoglobin Transferrin saturation	Diet optimalisation iron supplementation	Medication accountability tracking

6MWT, six 6-min walking test [72]; CPET, cardiopulmonary exercise test [73]; GAD-7, Generalized Anxiety Disorder Assessment [67]; HADS, Hospital and Depression Scale [70]; HIT, high-intensity interval training [75]; KATZ-ADL, questionnaire about daily living dependency [21]; MNA, Mini Nutritional Assessment [76]; PG-SGA, Patient-Generated Short Global Assessment [42]; PHQ-9, Patient Health Questionnaire [68]; SNAQ, Short Nutritional Assessment Questionnaire [43]; TUG, Timed Up and Go [74].

Supplemental Digital Content 1, http://links.lww.com/PHM/A663). A link to the survey was also distributed via the online newsletter of the Dutch Colorectal Cancer Group. The questionnaire contained items related to the surgeons' attitudes concerning the content, the design, and the delivery of prehabilitation programs. Descriptive statistics were used to analyze these data. A total of 29 colorectal surgeons responded (27% response rate). Prehabilitation was considered an essential part of optimal care by 93% of the surgeons. Aerobic training (97%), optimization of medication (79%), and improved nutrition (79%) were the most popular forms of prehabilitation. A total of 86% were willing to postpone the operation to optimize the patient. Seventy-six percent considered a period of 2–4 wks sufficient, and 93% agreed that insurance companies should cover the costs of prehabilitation. A prehabilitation program was available in 15 (52%) of the 29 responding hospitals and consisted most often of optimization of medication (80%), smoking cessation (60%), and/or psychosocial support (60%). A total of 90% of the surgeons was willing to participate in research on prehabilitation. Seven hospitals (24%) were already performing research (Fig. 3).

Networks

In 2016, the Fit4Surgery project group was founded in the Netherlands with the aim of creating the first online platform bringing together scientific evidence, clinical expertise, and evidence/data from all other stakeholders (ranging from personal trainers to supermarkets). The merging of clinical, scientific, and personal data will result in the design of an optimal multimodal prehabilitation program for each individual patient facing surgery. The current state of the healthcare system is characterized by divided coordination and the lack of overview for the individual patient. The Fit4Surgery platform aims to be a wisely accessible platform, providing all knowledge and tools required to participate in prehabilitation. The Fit4Surgery platform focuses on patients' interests and the empowerment of caretakers, thereby exceeding organizational, political, and financial incentives.

Future prehabilitation may not take place within the hospital. To achieve sustainability in healthcare, it is in the interest of all to aim for more cost-effective quality, prevention of disease, and the introduction scalable healthcare solutions. Although the targets seem clear and do fit the prehabilitation concept completely, there is still a gap toward clinical practice. To facilitate these changes, a new collaboration has to be created between the different parties, such as hospitals, patient organizations, health insurance companies, technical developers for patient monitoring devices, and business developers to support the financial plans and business model. In this way, we may achieve a prehabilitation concept, which may improve sustainability in treatment for a large number of patients.

TOOLS: OUTCOME MEASUREMENT

The goal of prehabilitation is threefold: (1) to reduce postoperative complications, (2) to enhance and speed up recovery, and (3) to improve overall quality of life. The chosen instruments to measure outcome should reflect these three dimensions. Furthermore, measuring compliance to the prehabilitation program is vital to ensure its effect. Based on previous literature on prehabilitation, we propose validated and frequently used measurement instruments in each domain.

Compliance

Because prehabilitation is a behavioral intervention, adherence and correct implementation of the intervention might

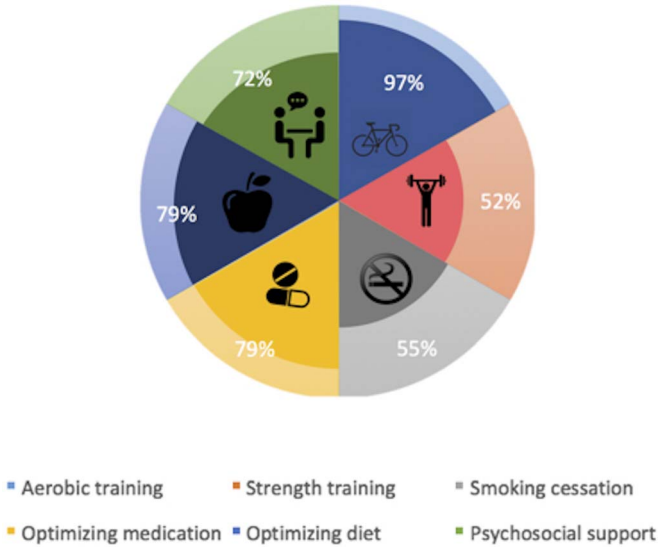

FIGURE 3. Prehabilitation contents according to questionnaire performed among Dutch colorectal surgeons.

be a challenge. It is therefore recommended that research groups objectify adherence to specific prehabilitation contents.[67] Compliance can be defined as the percentage of attendance to the prehabilitation program (e.g., attendance to training sessions or exercise modalities, compliance to protein intake). Besides compliance, a sufficient quality of execution or so-called fidelity will be essential for the program to be successful.[67] Furthermore, measuring compliance for scientific purposes is important, but it should be noted that a prehabilitation program is also largely based on the patient's intrinsic motivation. An overly present paternalistic approach with police-like compliance measurement can be potentially harmful.

Regarding the different components of prehabilitation, both active and passive ways to register compliance and fidelity remain scarce. Physical activity can be easily quantified by wearables with sensors. However, adequate methods to monitor nutritional intake, smoking cessation, and adherence to a psychological program without too much interference with the patient's daily life remain to be a field of pioneering research for the years to come.[68,69]

Reduction of Postoperative Complications

Considering the use of postoperative complications as a measurement tool, it should be noted that the definitions for complications are extremely heterogeneous between studies. For example, one of the most serious complications of colorectal surgery is anastomotic leakage and currently no consensus on the definition exists.[70] Therefore, it might be of more use to implement the Comprehensive Complication Index, which calculates the sum of morbidity and mortality presented on the Clavien-Dindo scale.[71] Because the Comprehensive Complication Index assesses the resulting action that was undertaken to treat a complication, interference due to heterogeneity of definitions is diminished.

Enhancement of Recovery

At minimum, the goal after surgery is to return the patient to his original level of functioning before diagnosis. Cardiopulmonary exercise testing serves as a criterion standard in measuring physical performance. It provides an objective assessment of the integrative exercise responses involving the pulmonary, cardiovascular, and skeletal muscle systems, which are not adequately reflected through the measurement of individual organ system function.[72] Overall recovery is currently expressed in standardized tests such as the 6-min walk test, which has been proven to be strongly correlated with postoperative outcomes in colorectal surgery.[73,74]

However, it remains a major challenge to develop a validated outcome instrument that allows patients to track their progress according to their own baseline rather than a population-based mean. Previous literature has introduced the concept of "time to return to normal activities," in which normal activities (e.g., getting dressed, cycling, shopping for groceries) are defined by a comprehensive item bank (Supplementary Table 2, Supplemental Digital Content 2, http://links.lww.com/PHM/A664) reflecting physical performance based on information from validated patient-reported outcomes measurements.[75,76] Ideally, information regarding functional performance could be registered by activity diaries or passively by using sensors and mobile devices.

Increasing Quality of Life

Questionnaires remain to be the most frequently used and validated way to assess quality of life in patients. In colorectal surgery, the EORTC-QLQ-CR29/C30, including physical, emotional, and social functioning and mobility and overall well-being, is most commonly used.[77] Overall quality of life can be measured by the Short-Form Health Survey questionnaire.[78]

CONCLUSIONS

The preoperative period maintains a window of opportunity to address modifiable risk factors such as nutrition, functional capacity, anemia, cigarette smoking, and mood/anxiety and to optimize a patient's condition before surgery. This can be achieved by implementing a prehabilitation program, defined as the multimodal preoperative enhancement of a patient's

condition. The goals are to reduce postoperative complications, to enhance recovery, and to improve overall quality of life. This review offers an integrative FIT model (facts, integration, tools) to successfully investigate and implement prehabilitation in the coming years. Facts comprises all the evidence that has been gathered in scientific research and by platforms on which patients can track their progress. Integration includes efforts to establish a continuous dialogue between patients and medical experts to identify potential bottlenecks and deal with them in an agile way. Furthermore, integration involves the development of online platforms that gather facts and feedback and can offer both an overview of all the available evidence and a tailor-made program for every patient. Lastly, *tools* refer to the development of all instruments and methods to create evidence and implement prehabilitation. These can vary from research methods to measure progress to devices that allow the patient to perform prehabilitation at home. The basis of the current prehabilitation method should focus adjusting modifiable risk factors such as malnutrition, poor physical state, smoking, anemia, and poor cognitive state. However, a standard prehabilitation program should only serve as a starting point. A tailored approach focusing on specific individual risk factors of each patient could potentially be more effective. Future research should focus on the value of prehabilitation as optimal preparation for colorectal surgery and other abdominal surgical procedures. Developing implementable methods and defining standardized outcome instruments will help establish a solid base for patient-centered prehabilitation programs.

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