Review Article | Palliative Medicine and Palliative Care for Serious or Advanced Diseases

Potential of prehabilitation in hepatocellular carcinoma: a narrative review of available evidence

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Background and Objective: Hepatocellular carcinoma (HCC) is a leading cause of cancer deaths. Patients with HCC are often significantly affected by sarcopenia and cancer cachexia. Prehabilitation, a multimodal pre-operative exercise and nutritional intervention, has been implemented with varying degrees of success in enhancing outcomes among other gastrointestinal (GI) malignancies. However, remarkably little is described how prehabilitation may be beneficial in improving outcomes among those with HCC. Thus, a narrative review is warranted to examine previously developed prehabilitation models and determine how interventions affected sarcopenia as a prognosticator in HCC and other GI malignancies. This article seeks to offer guidance on how prehabilitation may be implemented for those with HCC based on available data published on other GI malignancies and serve as a call for additional research specific to the value of prehabilitation in HCC.

Methods: Independent key-term searches were conducted by all authors of various databases (PubMed, ScienceDirect, Google Scholar) for relevant articles examining role, safety, and efficacy of prehabilitation in HCC and/or other GI malignancies. Relevant articles pertaining to sarcopenia, Enhanced Recovery After Surgery (ERAS) guidelines, and prehabilitation models were collected and analyzed. Review authors held multiple meetings to ensure coherence of narrative review process and final product.

Key Content and Findings: Patients with HCC often suffer from sarcopenia and/or cachexia, which are known to be associated with poorer outcomes. The benefits of a prehab program in patients with HCC are not well described in current literature, but in referencing the benefits of prehab programs in other GI malignancies and ERAS protocols on patients undergoing liver resection and liver transplant, there is potential for a similar multimodal program to yield similar benefits and healthcare cost-savings. However, further investigation is needed as HCC has multiple etiologies and affects a wide variety of people.

Conclusions: A multimodal prehabilitation program emphasizing regular aerobic and resistance exercise, nutritional optimization, lifestyle modifications, mental health and wellness practices, with a nurse and rehabilitation physician's oversight may improve outcomes in patients undergoing treatment for HCC. However further investigation into specific exercise models, optimal nutrition regimens and benefit/cost analysis of a multimodal prehabilitation program within this complex patient population is needed.

Keywords: Hepatocellular carcinoma (HCC); prehabilitation; exercise; nutrition; sarcopenia

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Introduction

Background

Hepatocellular carcinoma (HCC) is the 3rd leading cause of worldwide mortality among solid organ tumors, developing from liver cirrhosis in >90% of cases (1). With increasing rates of non-alcoholic fatty liver disease (NAFLD) in the United States, incidence of cirrhosis and HCC are expected to rise substantially over the course of the next decade (2). One of the most important negative prognosticators of morbidity and mortality in HCC is sarcopenia, defined by the National Cancer Institute as the loss of muscle mass, strength, and function along with gains in fat mass and abdominal circumference, specifically due to normal aging processes (3). Importantly, this is distinguished from cachexia, which is a multifactorial syndrome characterized by severe muscle wasting, fat loss, and weight loss secondary to an underlying illness, such as malignancy (3). Studies have found sarcopenia to be an independent risk factor for all-cause mortality in people with HCC and a poor indicator relating to tumor recurrence and overall complications after treatment (1). Another study by Meza-Junco *et al.* determined sarcopenia to be a significant risk factor for mortality in HCC patients who were being evaluated for liver transplantation (4).

Cancer rehabilitation ("CR") is medical care that, ideally, is integrated into a cancer patient's total care from the moment of diagnosis through the entire oncology care continuum. CR should be delivered by trained rehabilitation professionals whose scope of practice includes the diagnosis and treatment of patients' physical, psychological, and cognitive impairments, to decrease disability, maintain or restore function, reduce symptom burden, maximize independence, and improve quality of life (5). "Prehabilitation", a subset of CR also known as "prehab", is the concept by which a multimodal pre-treatment exercise program combined with nutritional and psychosocial support seeks to optimize a cancer patient's health and functional reserve prior to beginning cancer treatment to best prepare for the potentially disabling effects of treatment (*Figure 1*). Such preparation can help reduce or even prevent anticipated treatment-related impairments (such as sarcopenia and cachexia), reduce treatment-related morbidity and mortality, decrease length of stay, reduce emergency department (ED) visits and readmissions, and potentially improve outcomes by increasing available treatment options or the ability to return to intended oncologic treatment (RIOT). Multimodal prehabilitation programs include tailored aerobic and resistance exercise programs, nutrition guidance, support and possible medical management for smoking/alcohol cessation, and behavioral health support.

Rationale and knowledge gap

Much of the evidence examining impacts of prehabilitation has come from studies of other solid organ cancers. A comprehensive review of prehab in colorectal cancer (CRC) found that studies overwhelmingly demonstrated improvement in physical function of patients that underwent prehab prior to treatment (6). Ngo-Huang *et al.* at MD Anderson Cancer Center found that an exercise program prior to pancreatectomy in patients with pancreatic cancer improved physical function and health related quality of life (7). However, HCC is more complex. There are multiple causes and multiple treatment options are available, especially if diagnosed early on. As liver transplantation, locoregional treatments, and systemic immunotherapy are all potential treatment strategies, studies looking into specific prehabilitation models in HCC are necessary. However, in this malignancy, there are a paucity of studies, particularly large randomized controlled trials, that definitively demonstrate the effect of a pre-treatment program on outcomes after surgical and non-surgical treatments.

Objective

We attempt to examine existing literature exploring the impacts of a multimodal prehabilitation program on outcomes of similar intra-abdominal solid tumors as a framework for developing future hypotheses for prehabilitation programs for patients with HCC and raising a call for further investigation. We present this article in accordance with the Narrative Review reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-23-175/rc).

Methods

A pre-planning meeting of all authors was held to discuss review outline and divide assigned sections of the article. A literature review was then conducted independently by all authors utilizing database key-term searches of PubMed, ScienceDirect, and Google Scholar. Key-terms utilized included: hepatocellular carcinoma, rehab, prehab,

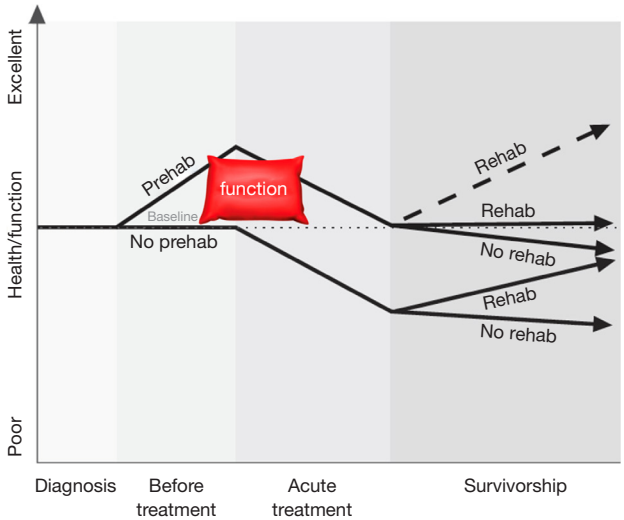

Figure 1 The goal of prehabilitation (or prehab) is to build a functional "cushion" prior to beginning cancer treatment in an effort to soften the potentially disabling effects of treatment. Screen capture of "Pre-habilitation in HCC" presentation given by Dr. Brian Fricke at the San Antonio Liver Cancer Symposium in 2021. HCC, hepatocellular carcinoma.

prehabilitation, sarcopenia, oncology, nutrition, diet, quality of life, exercise, and cancer in various combination through PubMed and ScienceDirect, and ERAS surgery, ERAS outcomes, ERAS colorectal, ERAS implementation, Rising cost of health care USA, and Health care spending through Google Scholar. Each author then independently reviewed English-language abstracts of search results from within the last 15 years to determine relevance for inclusion within their assigned section. A second meeting was held to discuss search results and finalize section assignments, outline, writing goals, and timeline. Authors focused on studies that established links between sarcopenia and outcomes, studies outlining ERAS guidelines as a potential foundation for prehabilitation, and studies examining multimodal prehabilitation programs in HCC and other gastrointestinal (GI) malignancies. Articles with reproducible models and were deemed to be practical within the U.S. healthcare model were included and analyzed. Individual sections were then submitted to the senior author who compiled sections together into manuscript form and edited to maintain stylistic consistency and grammatical correctness. A draft version was then distributed to each author for independent and collective review during a last meeting prior to final submission (*Table 1*).

Table 1 The search strategy summary

Items	Specification
Date of search	Nov 11, 2022
Databases and other sources searched	PubMed, ScienceDirect, Google Scholar
Search terms used*	Hepatocellular carcinoma, rehab, prehab, prehabilitation, sarcopenia, oncology, nutrition, diet, quality of life, exercise, and cancer in various combination for PubMed and ScienceDirect, ERAS surgery, ERAS outcomes, ERAS colorectal, ERAS implementation, Rising cost of health care USA, and Health care spending for Google Scholar
Timeframe	Within last 15 years
Inclusion and exclusion criteria	Any article type included
	Titles and abstracts were reviewed to screen for relevance
	Human only (non-human research excluded)
	English language or available English translation included
Selection process	Independent abstract and literature review by each author to determine relevance for inclusion within their assigned section
	Several meetings held to ensure coherence and consistency maintained throughout search process and article production

*, filters used included human studies within last 15 years. ERAS, Enhanced Recovery After Surgery.

Narrative

Sarcopenia and cachexia

Sarcopenia is a term first coined in the context of frailty syndrome seen in elderly individuals, but has since been described in patients with cancer, pulmonary and cardiac disease, and other chronic illnesses. The definition has been frequently updated as new measurement techniques have become available, but the classic definition is comprised of loss of skeletal muscle mass, strength and function and can be associated with normal aging (8). Importantly, normal aging is also associated with an increase in fat mass. Sarcopenic obesity, defined as sarcopenia in individuals

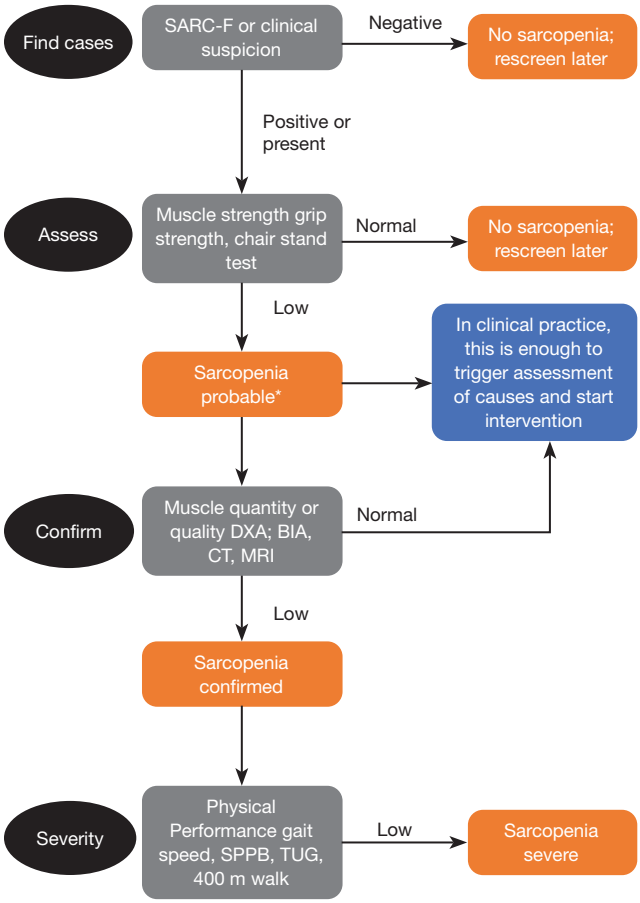

Figure 2 Sarcopenia: EWGSOP2 algorithm for case-finding, making a diagnosis and quantifying severity in practice. The steps of the pathway are represented as Find-Assess-Confirm-Severity or F-A-C-S. *, consider other reasons for low muscle strength (e.g., depression, stroke, balance disorders, peripheral vascular disorders) (11). SARC-F, strength, assistance with walking, rising from chair, climbing stairs, falls; DXA, dual-energy X-ray absorptiometry; BIA, bioelectrical impedance analysis; CT, computed tomography; MRI, magnetic resonance imaging; SPPB, Short Physical Performance Battery; TUG, timed up-and-go.

with a body mass index (BMI) >25 kg/m^2, has become more prevalent as correlated with the increase in overweight and obese populations (9). The European Working Group on Sarcopenia in Older People published a report in 2010 and revised in 2019 classifying sarcopenia by using three variables: mass, strength, and function (10). Mass is quantified using available imaging techniques [computed tomography (CT), magnetic resonance imaging (MRI) or dual-energy X-ray absorptiometry (DXA)], while strength was measured by hand grip strength, knee flexion/extension force, and peak expiratory flow. Using tests like gait speed and timed up-and-go (TUG), an objective measure of muscle performance could also be obtained. Many studies used in this report defined a muscle mass greater than two standard deviations below the mean of young adults or in the 20th percentile of the study population as sarcopenia (8). The report also used a gait speed <0.8 m/s as the cutoff functional performance measure for sarcopenia (*Figure 2*).

Cachexia is distinct from sarcopenia as it is an abnormal process secondary to an underlying illness (3). Although both processes result in loss of skeletal muscle, cachexia also results in significant loss of fat mass and body weight due inflammatory cytokines that put the body under severe catabolic stress (3). Cachexia is a strong predictor of mortality and very difficult to treat with exercise and nutrition alone (3). The aging population, with higher rates of immobility and malnutrition, can be particularly susceptible to cachexia in the setting of a chronic illness, such as cancer (3). Thus, sarcopenia and cachexia both need to be addressed in malignancies to help avoid adverse outcomes.

Sarcopenia is quite prevalent among those with solid organ malignancies; for example, as high as 57% in a study of patients with gastric cancer (11) met criteria for sarcopenia. In the setting of solid organ malignancy, sarcopenia has been found to be an independent risk factor for decreased overall survival (12,13). Kazemi-Bajestani *et al.* reviewed studies that used abdominal CT scans at the L3 vertebral body level to measure the cross-sectional area of the rectus abdominus, psoas and paraspinal muscles (14). Using these measurements, along with intra-abdominal fat, a skeletal muscle index (SMI) and visceral adipose fat index were generated in patients with non-hematological malignancies to objectively quantify severity of sarcopenia. Higher levels of sarcopenia were not only found to be a risk factor for poorer overall survival but were also associated with chemotherapy toxicity and increased post-operative complications (15). Because of this, sarcopenia has begun to be considered as an important clinical factor when diagnosing and treating cancer. Using an existing axial CT scan of the abdomen at the level of L3, SMI, visceral adipose fat index, subcutaneous fat index and muscle attenuation can all be calculated and tracked with interventions over time (16). As CT scans are relatively cheap and often part of the original oncological work up, sarcopenia can be used as an objective and precise prognosticator when developing a pre-treatment plan with prehabilitation.

One of the challenges seen among studies examining the role of sarcopenia in cancer outcomes is the poor consensus in defining and tracking sarcopenia. As described above, early definitions of sarcopenia focused on muscle loss while other studies have described the importance of muscle quality and strength, especially as a person ages (17). Similarly, there are no standardized, age and gender normalized values to objectively diagnose sarcopenia when it comes to measurements of SMI, adipose fat index, or muscle attenuation. Such scales would require stratification by age, sex, race and possibly cancer type as general muscularity and fat content will vary widely amongst these different populations. There are studies analyzing these variables, but larger population-based normal values are necessary for better accuracy and external validity.

Multidisciplinary prehab program

A significant factor contributing to the difficulty in establishing a causal relationship between prehabilitation and outcomes has been a lack consensus on the components of an ideal program, resulting in significant heterogeneity among prehabilitation studies. Obviously, there is not expected to be a "one-size fits all" prehabilitation program as oncology and specifically HCC patient populations are incredibly complex and vary broadly. However, determining the impacts of choosing a unimodal *vs.* multimodal prehabilitation program as well as studying impacts of different exercise programs related to frequency, intensity, type, duration, and timing would all be especially relevant to optimizing the potential for a statistically and clinically significant positive impact on outcomes. A unimodal program is characterized by pre-operative exercise alone, while a multimodal program would include other components such as nutrition, physical therapy (PT) to oversee and guide progression of the exercise program, case management and/or social work to assist with social determinants and goal setting, and a nurse to periodically check-in on patients for adherence to their program and triage any injuries sustained during prehab. A multimodal program such as this would address other crucial factors that affect patient outcomes but would require more resources to implement. A 1-month pilot study in CRC patients demonstrated that a multimodal prehab program could result in increased functional capacity as well as improvements in self-reported physical activity and health related quality of life (18).

Exercise

As a cornerstone of prehabilitation programs, exercise programs of varying types, intensities, lengths, and frequencies have been studied. For example, VO_2max at anaerobic threshold (AT) has been studied with lower values shown to be associated with higher morbidity, higher mortality, and longer hospital lengths of stay (19,20). Dunne *et al.*, one of the first major studies to examine the effectiveness of a prehabilitation program in liver resection, used a 4-week exercise program performed three times a week and consisting of a warm-up, thirty minutes of aerobic cycle training alternating between moderate and vigorous intensity, and cool down (21). Monitoring VO_2max at AT as the primary outcome measure for effectiveness of the exercise intervention, this exercise program led to a statistically significant increase of VO_2max that decreased the number of patients considered high-risk prior to liver resection (21). Wang *et al.*, in contrast used a 2–4-week program that consisted of deep breathing exercises four times a day along with a lower body strengthening program and aerobic walking activity for thirty minutes five times per week (22). With the primary goal of examining the effect on clinical outcomes, the study found a statistically significant lower number of post-operative complications along with decreased hospital length of stay in the prehab group (22). The American College of Sports Medicine (ACSM) multidisciplinary roundtable in 2018 generated a variety of exercise recommendations for cancer survivors based on randomized clinical trials that could provide a great foundation for the exercise component of prehab programs. The strong evidence-based recommendations prescribed 60–80% of max heart rate for aerobic exercise totaling at least 90-min per week and 60–80% of one-rep max intensity for resistance training with different number of repetitions, frequencies, durations and lengths at least twice a week but based on exercise goals and different cancer populations (23). Future studies could include two prehab groups with differences in types, frequencies, duration, and/or intensities of exercise to determine differential effects on change in VO_2max at AT along with other functional outcome measures like the 6-min walk test, TUG test, grip strength, body composition changes, and several patient-reported outcome measures.

Nutrition

There are very few interventional studies examining nutritional therapy and its effect on long-term outcomes

in HCC. There are a few retrospective studies with small sample sizes showing nutritional supplementation with branched chain amino acids (BCAA) perioperatively resulting in a 3-year mortality benefit, lower rates of ascites, and higher albumin levels (24). However, they showed no improvement on 1-year mortality or rates of HCC recurrence. A systematic review by Beaudart *et al.* looked at the effect of varying types of nutritional supplementation in the context of sarcopenia (25). Thirty-seven randomized controlled trials were included that sought to determine if nutritional supplementation and exercise compared to exercise alone impacted muscle size and/or performance (25). The findings varied significantly between studies due to the heterogeneity of types of exercise and varying nutritional regimens, making it difficult to draw any conclusions, thus highlighting the need for well-designed and well-conducted studies in future (25). There is a strong need for interventional studies examining the effect of protein, BCAA and vitamin supplementation on outcomes in HCC. Challenging though it may be due to the complexity of nutritional programs, studies should aim to ascertain optimal dietary supplementation that could help reduce the functional impact of HCC treatment.

Psychosocial

Similar to the trimodal approach used in CRC patients, Wang *et al*. developed a prehabilitation program administered prior to liver resection that included a case manager as an integral member of the multidisciplinary team (22). Their role included explaining post-operative expectations, identifying the social support plan and addressing any financial issues prior to the operation. Albeit in a small sample size (n=104), there was a significant difference (P=0.03) of increased social issues that delayed discharge encountered by patients in the control group *vs.* the prehab group (22). Of the 70 patients in the prehab group, there were no significant social issues encountered (22). A larger scale study could help illustrate a clearer picture of the types and frequencies of social issues encountered during and after HCC treatment. Using established and feasible patient reported outcome measure tools, like the SF36 and PROMIS (26), future studies could track patient well-being, perceptions and satisfaction through the prehab program.

A proposed multidisciplinary prehabilitation model would coordinate between medical and surgical oncology and CR in risk-stratifying HCC patients by establishing fall risk, calculating frailty index, measuring body composition with CT abdomen/pelvis, and screening medical comorbidities. Oncology and CR would then be able to determine which patients are appropriate for prehabilitation. For patients included in the program, CR would provide additional medical support to reduce potential medical barriers, such as treating cancer pain and medical comorbidities that would limit patients' ability to participate in prehab. CR would then oversee and support a team consisting of PT to assist with exercise counseling and measure progress through functional outcome measure and patient-reported outcome measures, a dietician to provide nutrition patient-specific nutrition counseling and optimize protein intake, a nurse to contact patients regularly to ensure adherence to the program and triage any adverse events, and a counselor/social worker to help manage stress/anxiety and address potential social obstacles that would prevent optimal treatment outcomes (*Figure 3*).

Enhanced recovery after surgery (ERAS)

Concepts similar to CR, and its prehab subset, have been successfully applied in the surgical context. These concepts have been implemented by many surgical facilities, using the widely accepted, evidenced-based ERAS. The ERAS pathway can in many ways be considered a quality improvement tool that has been shown to reduce postoperative morbidity, decrease hospital length of stay and cost, and achieve early recovery for patients undergoing major surgical procedures (27). It is a multimodal, perioperative care pathway that encompasses the interval prior to surgery to the day of discharge using an interdisciplinary team approach (28). Originally, the ERAS pathway focused on achieving the above-stated goals by reducing the invasiveness of surgery, but the contributory impact of other care components, such as preoperative nutrition, exercise, and psychosocial support, could not be overlooked. As a result, ERAS care professional teams now work together to address approximately 20 evidence-based care elements to mitigate surgical stress and postoperative catabolism (29).

Similar to CR models, ERAS employs a multidisciplinary approach for early patient and family engagement and education. Both models employ a care team consisting of multidisciplinary specialized professionals, including physician team members, specialized nurses, nurse educators, pharmacists, case managers, social workers, dieticians, and administrative and project managers, all of whom are trained in the ERAS protocol. The ERAS model

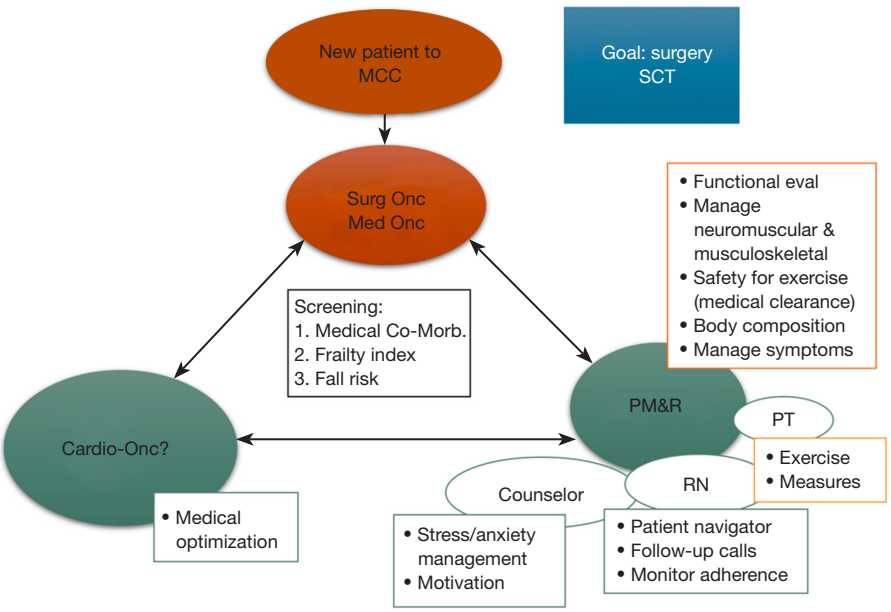

Figure 3 Proposed Multidisciplinary Prehab Model including potential third major arm to include cardio-oncology. Screen capture of "Prehabilitation in HCC" presentation given by Dr. Brian Fricke at the San Antonio Liver Cancer Symposium in 2021. MCC, Mays Cancer Center; SCT, stem cell transplant; PM&R, physical medicine & rehabilitation; PT, physical therapy; RN, registered nurse; Onc, oncology; Morb., morbidity; HCC, hepatocellular carcinoma.

can also be divided into phases of a continuum of care, namely, the preoperative phase, the intraoperative phase, and the postoperative phase (28), which run parallel to the pretreatment, treatment, and survivorship or end-of-life phases in the CR model continuum of care.

The ERAS model provides a standardized, multidisciplinary set of guidelines to address a specific diagnosis or procedure. In the preoperative phase, the goal is pre-procedure optimization of the patient's health and functional reserve. An initial clinic visit may include patient and family counseling to increase engagement, provision of education on expectations, an assessment of behavioral and psychosocial factors, and discussion about and provision of referrals for appropriate consultations. ERAS protocols have established detailed guidelines relative to optimized oral intake prior to anesthesia, modification of bowel preparation recommendations, and the importance of medical optimization (27). With respect to preoperative optimization, risk factors such as age, lifestyle, comorbidities, type of procedure, cardiorespiratory fitness, nutritional status, and anesthesia are addressed (30). Potentially modifiable risk factors include: health status, lifestyle (with focus on smoking cessation and elimination of use of alcohol prior to procedure and activity), BMI, nutritional status, assessment of appropriate medications, and interventions for reducing current and anticipated symptom burden related to pain, dyspnea, anxiety, and nausea (28). Intraoperatively, ERAS has established guidelines with respect to individualized goal-directed fluid therapy, use of multimodal anesthesia, intraoperative antibiotic recommendations, medication recommendations, anesthesia recommendations, and the use of lung protective ventilation strategies (28). Postoperatively, ERAS strongly encourages early mobilization on postoperative day one. A single-center study of 168 consecutive patients demonstrated less reduction of muscle strength and lung function ($P<0.05$) in an enhanced recovery group following ERAS compared to the traditional, non-ERAS group (31). ERAS protocols also encourage early oral intake, the use of multimodal pain regimens, and early resumption of activities and discharge to home (28).

In summary, ERAS programs ultimately aim to decrease the stress reaction of the body that occurs because of surgery with the goal of achieving fewer post-operative complications, shorter hospital lengths of stay, and quicker overall recovery with the lowest amount of cost to the

healthcare system (32). Initial thoughts were geared towards decreasing the invasiveness of surgery, but other components have examined the impact of preoperative nutrition, exercise, and psychosocial support. Current ERAS protocols specific to liver resection and liver transplantation strongly recommend preoperative nutritional assessment in all cases with objective criteria (10–15% weight loss in previous 6 months, BMI <18.5 kg/m^2, albumin <30 g/L) that would warrant a delay in surgery (32). However, although mentioned in the preoperative considerations and with some studies showing decreased lung and thrombotic complications, there were no specific recommendations for specific preoperative exercises (32). Given the similarity of phases and goals in the ERAS and CR programs, it is reasonable to propose that further investigation is needed to focus on specific care elements employed in ERAS models that may translate to CR models and may be implemented to the benefit of cancer populations.

Value of care

It is essential that those delivering care recognize that health care costs are increasing year after year. According to a study published in *JAMA*, the following five factors contribute to the increased healthcare costs in the United States: (I) increasing population; (II) aging population; (III) changes in disease prevalence or incidence; (IV) increases in how often people use health care services; and (V) increases in the price and intensity of services (33). In April of 2022, the American Hospital Association (AHA) warned that the current trajectory for hospital costs is unsustainable. Quality improvement protocols, such as ERAS have been shown to standardize care, result in better patient outcomes, and reduce health care costs.

Advantages of ERAS protocols in colorectal surgery are well documented in literature. Randomized controlled trials have been performed that confirm the safety of the ERAS protocol (34). An observational study involving five European centers demonstrated an average reduction of three days in length of stay with use of ERAS protocols (29). Another single-center study demonstrated a reduced number of postoperative complications in colorectal surgery patients and reduced length of stay with use of ERAS protocols. While that study also saw an increase in readmission rates, total hospital days were still lower for the ERAS group (31).

Perioperative care accounts for most expenses related to hospital admissions, much of which is attributable to postoperative morbidity and complications, with an average cost of $12,000 per event. One community hospital implemented an enhanced recovery program that within the first 9 months resulted in reduced hospital lengths of stay by at least 50% and a variable reduction in direct cost of $4,357 per surgical case (30). These numbers support further development of other standardized, multidisciplinary pathways.

Successful implementation of any protocol requires a dedicated team of champions to represent each area involved in the patient's care. This team of champions will be responsible for implementation of the protocol. The team will collaborate to design the protocol based on evidence in the literature, provide education to care team members, continually track adherence to the protocol and assess outcomes, and meet regularly to make ongoing improvements to the process. Pędziwiatr *et al.* found that implementation of an ERAS protocol was a gradual process, taking a minimum of thirty patients and six months to achieve a compliance rate of 80% (34). Continual education for patients and involved professionals was a factor found to be important in maintaining success and program compliance (30).

Johns Hopkins University Hospital initially implemented an evidence-based ERAS pathway for colorectal surgery and, following its success, expanded use of the ERAS pathway to liver resection, radical mastectomy, gynecologic oncology, and pediatric surgery (35). In similar fashion, cancer programs could begin implementation of a prehabilitation protocol by piloting with one specific cancer subgroup, such as HCC. While ERAS focuses on optimizing patients for surgical intervention, the prospective HCC prehabilitation programs can use the similar tenets of the ERAS model to functionally optimize HCC patients for the variety of different oncologic treatments available. Careful tracking and well-documented data of a limited cohort of patients as a pilot study may provide the results to further engage support from hospital administration with the goal of expansion for other cancer populations.

Strengths and limitations

As discussed intermittently as above, the evidence supporting ERAS programs is quite strong and extensive and includes description of objective healthcare dollars saved through broad implementation. Utilizing this may provide sufficient basis for support in expanding prehabilitation programs focused on improving the outcomes of cancer patients. However, the relative scarcity of literature

specifically investigating the benefits of an ERAS/prehab approach within the HCC population significantly limits the ability of the authors to make any assertions as to the positive impacts on HCC outcomes or similarly rates of sarcopenia and cachexia in patients battling HCC.

Conclusions

When considering the implementation of a prehabilitation program to support patients with HCC and possibly improve outcomes, there are several crucial components of an evidence-based successful prehab program. Similar to ERAS protocols, pre-operative intervention with a multimodal approach to emphasize the importance of regular physical activity, nutrition, lifestyle modification, mental health and wellness practices, and frequent check-ins to monitor for adherence and complications are critical. Review of some of the ERAS literature pertaining to liver resection and liver transplant demonstrate positive outcomes and overall reduction in healthcare costs. However, the additional complexity of the patient with HCC and its strong association with independent risk factors for poorer outcomes of sarcopenia and cachexia make it difficult to directly translate these findings to the HCC population. While we could postulate suggestions for successful HCC prehabilitation program based on studies in other GI malignancies, it would be difficult to make data-driven conclusions based on the current availability of research. Limitations of previous studies within HCC include lack of consistency with components of multimodal prehabilitation models as well as in measuring and tracking sarcopenia. It will be important in future studies to compare different exercise models and nutritional programs and their effect on sarcopenia to ascertain the optimal interventions within a prehab program. Many of the current studies also did not comment on whether certain patients were unable to tolerate prehabilitation or if certain populations were found to be poor candidates for the program. Further investigation looking into the risks/benefits/costs of implementing a multimodal prehab program for patients with HCC who are undergoing neoadjuvant chemotherapy prior to anticipated surgical resection is needed. As HCC cancer pain is a unique treatment challenge, further studies should also investigate which pain management strategies in a prehabilitation model, whether medication or procedure-based, would facilitate the best clinical outcomes (36). Future studies may also take into consideration patients with HCC who simultaneously meet the criteria for sarcopenia and/or cachexia.

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Footnote

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