Review Article

Prehabilitation for esophagectomy

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Abstract: Esophagectomy remains the mainstay treatment of esophageal cancer (EC). Combined with neoadjuvant therapies, the management of EC has deleterious effects on body composition, functional capacity and psychological well-being. Preoperative patient optimisation known as prehabilitation is a novel intervention aimed at reducing morbidity and mortality associated with the trajectory of EC care. There is emerging evidence to suggest that prehabilitation is safe, feasible and efficacious. In addition, there is strong data to infer that prehabilitation has a positive effect on functional capacity through exercise. Nutritional and psychological interventions are less well evaluated. Furthermore, no convincing relationship between prehabilitation and oncological outcomes has been demonstrated. Early studies evaluating prehabilitation are promising however further large scale research is required in order to assess the clinical effectiveness.

Keywords: Prehabilitation; exercise; nutrition; preoperative optimization

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Introduction

Esophagectomy retains an important role in the management of locally advanced esophageal cancer (EC) and remains the mainstay of potentially curative treatment. EC surgery carries significant morbidity and mortality, with 90-day mortality at 3.2% and 1-year survival rates varying between 76% and 78% with morbidity between 20% and 70% (1).

The association between esophagectomy and mortality/morbidity is multifactorial. EC surgery represents complex operations associated with significant weight loss and malnutrition. The implementation of pre-operative chemotherapy and combination chemoradiotherapy, in addition to surgery, has come at a cost on body composition and functional status (2). In addition, patients with EC are typically 'high-risk' because they tend to be frail and elderly. These patients are also susceptible to adverse outcomes due to diminished physiological reserve as a direct consequence of cancer-associated malnutrition (cachexia) (3). As a result patients are at high risk for pulmonary, cardiac and infective complications as well as prolonged hospital stay associated with increased surgery costs and poor postoperative quality of life (QOL) (4).

The incidence of EC increases with age which means that a higher proportion of elderly patients are being diagnosed with EC and are being considered for curative multimodal therapy. Current statistics show that 30% of patients are over the age of 75 at the time of diagnosis, with a median age of 68–70 (5). This is where the challenge arises as ageing is accompanied with frailty, comorbidities, polypharmacy and invariably a reduction in functional reserve (6). The basic tenet of frailty is that it confers vulnerability to stress, higher risk of treatment toxicities and complications. The perioperative period is when patients are at most risk of developing cardiopulmonary complications with an operative mortality rate of 13.4% in those who are between 70–79 years old and 19.9% in those over the age of 80 (7,8).

Frailty is multi-faceted and accompanied with a deterioration across several physiological domains. Fried *et al.* proposed that frailty is present in the presence of low grip strength, low energy, slowed walking speed, low physical activity, and/or unintentional weight loss. Some, or all of these are common findings in patients diagnosed with EC and exacerbated by neoadjuvant therapies and/or surgery (9).

There is strong evidence to suggest that baseline frailty infers a greater risk of postoperative complications especially in those with severe frailty (moderate frailty: OR =2.06, 95% CI: 1.18–3.6; severe frailty: OR =2.54, 95% CI: 1.12–5.77). Furthermore, 65–89% of patients with severe frailty had a protracted hospital admissions compared to 44–53% of patients with moderate frailty (10). It is plausible that this is a reflection of decline in cardiorespiratory fitness which accompanies age and previously shown to be linked with postsurgical mortality and morbidity. When clinical outcomes were evaluated, Snowden *et al.* demonstrated that patients over the age of 75 with concomitant poor cardiorespiratory fitness (as reflected by a low anaerobic threshold) spent a median of 11 days longer in hospital (23 *vs.* 12; P<0.0001) and 2 days longer in critical care (2.9 *vs.* 0.9; P<0.00001) (11).

A cause for concern in elderly frail patients with EC is malnutrition. Not only does inadequate nutrition adversely affect QOL it also reduces response to treatment and therefore impacts survival. A reduction in weight of more than 15% off baseline was shown to correlate with higher rates of mortality and morbidity when compared to patients with less weight loss (62% *vs.* 38% respectively). In addition, poor baseline nutrition was a presage of early death in elderly patients who underwent neoadjuvant therapies (12).

The aetiology of malnutrition stems from a combination of either inadequate intake, increased metabolic demands or inflammatory dysregulation that alter nutrient utilization resulting in cachexia and manifesting as a decline in physical fitness and reduced metabolic reserve (13). Cachexia is a pervasive feature of EC resulting in weight loss by reducing both lean and fat mass. EC is among the diseases with the highest known association with cachexia. Luminal obstruction from tumor incursion, toxicity associated with neoadjuvant therapies, and surgical resection, further exacerbates malnutrition (14,15). A recognised phenotypic feature of cachexia is sarcopenia. Sarcopenia is a multifactorial syndrome linked with loss of functional performance and characterized by loss of muscle mass with either low strength or low performance (16). Up to 75% of patients with EC are sarcopenic at diagnosis with associated dose-limiting toxicity (DLT) during neoadjuvant treatments, disease progression and adverse postoperative outcomes (17). Sarcopenic patients on average have been shown to have a reduced overall survival compared to non-sarcopenic patients (8 *vs.* 26 months). The body composition of cancer patients is highly variable with respect to features of muscle and fat mass as well as the distribution of fat in the abdominal and subcutaneous regions. As a result, sarcopenia should not be limited to patients who outwardly appear thin, and can be found in patients who are overweight or obese; a common finding in patients with adenocarcinoma of the oesophagus (18).

The implementation of neoadjuvant therapies has led to additional oncological and survival benefits, however these have come at a cost to functional capacity when it is needed the most. The relationship between neoadjuvant therapy and their detrimental effects on physiologic and functional capacity is well recognized. Neoadjuvant therapy has been shown to reduce skeletal muscle mass and strength, resulting in a significant increase in the prevalence of sarcopenia from 16% at diagnosis to 31% post-treatment, with an accompanying deterioration in performance status (19). Further studies support this showing that an increase in the prevalence of sarcopenia in patients undergoing neoadjuvant chemotherapy (NAC) has adverse effects on parameters of body composition, such as lean body mass and fat mass, which contribute to morbidity. Body composition, in particular skeletal muscle depletion, has been associated with excess toxicity during neoadjuvant therapy with a recent study demonstrating that DLT was present in 41.6% of patients undergoing NAC, and that sarcopenia was a key contributor to this (20-22).

The risk of toxicity associated with NAC directly influences surgical morbidity. Systemic toxicity results from proteolysis leading to skeletal muscle wasting, oxidative stress and mitochondrial death. Following major surgery, oxygen consumption increases and greater physiological reserve is demanded to allow patients to better withstand the metabolic burden (23). Elderly frail patients tend to have a low baseline level of fitness and in the context of NAC, Jack *et al.* demonstrated reduced one-year survival (3). Physical fitness has been shown to be an important determinant of perioperative outcomes, with less fit patients having higher incidences of morbidity and mortality. Inadequate physical performance is a reflection of reduced exercise capacity, and one method of measuring this is by the VO_2 max (mL/kg/min), which is the measure of a person's individual aerobic capacity. It has been postulated that this measure predicts morbidity, and that increased complications are associated with a VO_2 max <16 mL/kg/min (24). The stress of NAC and surgery are important contributors to a reduction in aerobic capacity and therefore poor pre-operative physical performance is linked with all-cause mortality, post-operative complications, length of hospital stay and hospital costs. It is becoming clearer that neoadjuvant treatments are causing harm to physical fitness, which in turn translates into adverse clinical outcomes (25).

Anxiety and depression are not uncommon findings in patients with newly diagnosed EC and inadvertently influences functional capacity during the pre- and postoperative periods due to low adherence. In addition, there is a significant deterioration in postoperative QOL which impacts recovery following surgery (23).

This has led to the introduction of multimodal interventions in the period preceding surgery aimed at optimizing patients and improving post-operative outcomes in EC resectional surgery.

Prehabilitation

In recent years there has been a shift towards the centralization of cancer surgery, adoption of minimally invasive techniques and widespread uptake of multidisciplinary perioperative care programmes such as enhanced recovery after surgery (ERAS). In combination, these have led to substantial improvements in post-operative outcomes.

Currently ERAS is a well-established component in the trajectory of surgical care but place little emphasis on pre-operative patient optimization. Despite the implementation of ERAS, complications following elective major abdominal surgery are still between 25–55% (23,25).

Prehabilitation is the process of providing patients with a reserve to withstand the stress of major cancer surgery. The principle is to extend beyond just pre-operative physiological and co-morbidity optimization to improvement in functional capacity, nutritional status and psychological well-being in preparation for major surgery (26).

Presurgical exercise

With frailty and ill-health comes a lack of physical activity which can exacerbate perioperative morbidity (27). Exercise as part of a prehabilitation programme has been proposed to counteract functional decline and enhance patient performance as well as attenuating sarcopenia and limiting deconditioning associated with disease burden (28). Traditionally, the notion of bed rest was advocated in anticipation for surgery but we now know that sedentary behaviour is associated with loss of lean muscle mass, reduced physical function and aerobic capacity and insulin resistance (29).

This is why emphasis must be placed on aerobic and muscular training to increase endurance, manage weight and build strength. Research highlights that in order to achieve this 3 weeks of exercise may be adequate (30). Several studies on prehabilitation in patients undergoing thoracic and gastrointestinal (GI) cancer resection have demonstrated an increase in preoperative physical fitness, physical activity and decreased postoperative complications with shorter hospital stay (31). In addition, feasibility and safety following neoadjuvant therapies, as well as improvements in long-term physical activity and QOL have also been demonstrated (30,31). Exercise includes consistent physical activity delivered through a structured programme to improve physical fitness. For exercise to be effective it needs to be prescribed at a certain 'dose' and adapted to meet the needs and requirements of the patient in order to achieve the desired outcomes (23,32). The prescription and dose of exercise requires consideration of frequency, intensity, time and type (FITT) of exercise. Although a lower dose of physical activity has clear health benefits, higher doses of exercise will result in greater improvements (33). Several pilot studies in rectal and breast cancer have shown improvements in fitness after supervised interval training and several reviews on exercise as part of a prehabilitation programme have demonstrated similar beneficial effects in patients undergoing major abdominal surgery (34-36). In a review looking at prehabilitation and postoperative clinical outcomes, Moran *et al.* established that aerobic and resistance training reduced the occurrence of complications in patients undergoing abdominal surgery (37). In support of this, one study showed that prehabilitation reduced the incidence of postoperative pulmonary complications [OR 0.27, 95% confidence interval (CI): 0.13–0.57] (13). Several studies have highlighted the positive impact of exercise on measures of functional capacity. West *et al.* reported that VO_2 increased by an average of 2.1 $mL\cdot kg^{-1}\cdot min^{-1}$ after 6 weeks of exercise (P<0.001) and further studies have supported this showing a significant increase in VO_2 and peak VO_2 (pVO_2) within exercise groups (38). In addition, several studies looking at postoperative outcomes showed that preoperative exercise reduced the length of hospital stay. Cho *et al.* reported a reduction in length of admission (9 *vs.* 10 days; P=0.038) as well as reduced intra-abdominal postoperative complications

(OR 0.12, 95% CI: 0.00–0.89, P=0.033) (39). In a review by Vermillion *et al.*, patients who underwent preoperative exercise training were more likely to return to their baseline fitness after surgical resection. In addition, a combination of aerobic exercise training with resistance training was effective in reversing sarcopenia in elderly individuals with a reduction in postoperative pulmonary complications. As well as enhancing cardiopulmonary fitness, exercise was also proposed to reduce fatigue and have desirable outcomes on QOL (28).

Nutrition

Malnourished surgical patients are known to have higher postoperative morbidity and mortality, and the risk of malnutrition is most severe immediately before surgery (13). EC patients are chronically malnourished and require nutritional prehabilitation in order to replenish nutrient stores and build a metabolic reserve to buffer the catabolic response to cancer, neoadjuvant therapies and surgery. Early patient engagement is paramount and tailored nutritional goals should be delivered in a pre-emptive rather than reactive method (40). A well-recognized phenomenon in critical illness and surgery is protein catabolism. Protein requirements are elevated in stressed states and therefore it is of paramount importance that provisions of protein are addressed as part of nutritional prehabilitation to maintain lean muscle mass and reduce subsequent risk of sarcopenia and frailty (41). The importance of perioperative nutrition and its influence on prognosis was recently discussed in the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines. Patients who were nutritionally deplete and had significant weight loss were more likely to have a protracted hospital admission, higher readmission rates and experience morbidity/mortality (42). It is essential that cachectic individuals are identified via early pre-assessment by a specialist dietitian and receive tailored, monitored and ongoing nutritional intervention up to the day of surgery. RCTs and meta-analyses have supported this and have shown that preoperative nutrition in malnourished patients prior to major abdominal surgery reduced postoperative morbidity by 20% (43). Diets aimed at enhancing immune function are called immunonutrition (IN). Several meta-analyses have been published on the clinical effectiveness of preoperative IN showing it to reduce the incidence of postoperative infectious complications and length of hospitalization (44). This is true of patients undergoing surgery for gastrointestinal malignancy and has been advocated as part of preoperative nutritional optimization. In the context of esophageal surgery however, results are heterogeneous. Current evidence is insufficient to recommend enteral IN in patients undergoing esophagectomy and/or chemoradiotherapy for EC (45).

Psychological

In the context of major life altering surgery, anxiety and depression is common, and has a negative impact on postoperative pain control, leads to prolonged hospital admission/readmissions and causes functional limitations with poor compliance to exercise (46). Prehabilitation encompasses psychological distress, and addressing anxiety and depression as part of this programme will have a positive influence on adhering to prescribed exercise and in turn promoting psychological well-being.

A number of trials have shown prehabilitation to improve QOL, reduce anxiety and depression as well as pain severity and fatigue (23).

In addition, prehabilitation has been shown to improve functional behaviors such as the ability to perform ambulation and rehabilitation tasks which are key for postoperative recovery. This also has a positive effect on subsequent QOL and the psychological wellbeing of the patient. There is new evidence that patients with distress and low self-confidence experience poorer QOL trajectories in the recovery period (47). Thus interventions to address distress and improve self-efficacy are likely to improve post-operative recovery

Discussion

There is substantial data which highlights the clear benefits of preoperative exercise and nutritional optimization, at the same time recognizing that psychological wellbeing is a critical aspect of perioperative care. However, the majority of data published on prehabilitation in GI cancer comes from colorectal cancer surgery and at present evidence that prehabilitation works in EC surgery is limited. Soares *et al.* investigated the effects of preoperative physical therapy on pulmonary function and physical performance before and after upper abdominal surgery. In a RCT of 32 participants the authors demonstrated that patients who received physical therapy had higher inspiratory strength and respiratory muscle endurance. Furthermore, patients who were randomly assigned to physical therapy achieved betters results in the 6-minute walk distance

(6MWD) than compared to control group. There was also a significant difference between postoperative pulmonary complications with the intervention group being less likely to develop a pulmonary complication (P=0.03) (48). In a similar RCT Xu *et al.* observed the effect of a 'walk-and-eat' intervention during neoadjuvant chemoradiotherapy on functional walking capacity and nutritional status. The intervention consisted of weekly supervised walking and nutrition advice. The study demonstrated that the intervention group had significantly less decline in 6MWD during neoadjuvant therapy. Similarly, there was less decline in hand-grip strength, weight and lean muscle mass. There was no difference observed in outcomes (49). More recently Minnella *et al.* looked at the effect of prehabilitation on functional status in patients undergoing EC resection. The authors showed that patients who underwent prehabilitation had improved functional capacity (absolute change in 6MWD) both before surgery and after surgery. However, there was no statistical difference between groups in terms of number and severity of complications, length of hospital stay, and readmission rates (50). A plausible explanation for this is the study being underpowered to detect an association between physical fitness and complications. Although Soares *et al.* did show a reduction in postoperative pulmonary complications, the study was also underpowered.

In line with recently published studies there are a number of ongoing trials centred around prehabilitation in EC. The PREPARE for surgery prehabilitation programme is an ongoing quality improvement project which delivers a personalized, home-based programme consisting of preoperative exercise, nutritional optimization and addressing psychological domains such as anxiety and depression as well as key aspects of QOL. Current data (unpublished) from the PREPARE programme has demonstrated a significant improvement in functional capacity as assessed by VO_2 $mL{\cdot}kg^{-1}{\cdot}min^{-1}$ as well as reduced postoperative complications including a reduction in Clavien-Dindo score of >2 (80% to 35%), postoperative pneumonia (70% to 29%) and median length of hospital stay (14 to 11) (26). Further details of trials on prehabilitation in EC can be found at http://clinicaltrials.gov. Some of these studies are still in the recruitment process, ongoing or completed and awaiting publication. Majority are RCTs and the focus lies with determining the impact of multimodal prehabilitation on functional exercise capacity, functional recovery both during and after neoadjuvant therapies and following surgery. Some of the studies are also aiming to address key important areas such as postoperative complications which is currently lacking in the literature. This will be eagerly anticipated as the evidence for the relationship between prehabilitation and postoperative outcomes is limited and where research is available it is not adequately powered.

Conclusions

Although a novel area of research in EC there is clear evidence that prehabilitation improves functional capacity and supports the patient through nutritional and psychological counselling. However further work is required to determine its effects on overall oncologic outcomes.

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Footnote

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