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Peri-operative patient optimization for oesophageal cancer surgery – From prehabilitation to enhanced recover

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Prehabilitation

"By failing to prepare, you are preparing to fail."

Benjamin Franklin

Delivery of care for patients with oesophageal cancer is no longer the preserve of single modality surgical intervention but has become a multifactorial 'aggregation of marginal gains' in multidisciplinary practice. This review aims to explore the benefits of exercise prehabilitation in oesophageal cancer treatment.

Keywords:

Oesophageal cancer

Surgery

Prehabilitation

Enhanced Recovery after Surgery

Background

The physiological impact of having an oesophagectomy is often likened to that of running a marathon. Whilst nobody would consider starting a marathon without months of dedicated preparation, the majority of patients scheduled for surgery undergo little or no physical training in the lead up to their operation.

In recent years, Enhanced Recovery After Surgery Programs (ERAS/ERP) have resulted in improved short-term outcomes after surgery (1) and have widely been integrated into surgical-oncology pathways as best practice. Yet, increasing the expectations on patients recovering from high-risk surgery without preparing them physically makes little sense. In some disciplines, where pre-operative exercise programs have been introduced to optimise physical function in patients before surgery, a positive benefit on post-operative functional capacity and return to activities of daily living has been seen in the short-term(2). Physical or

multimodal prehabilitation of patients before cardiovascular, abdominal and colorectal cancer surgery has resulted in improved pre-and post-operative functional capacity (3–5). However, the focus in these programs has been in the peri-operative period. The opportunity for extended prehabilitation from the time of diagnosis, through neo-adjuvant oncological therapy, is the subject of a number of on-going clinical trials. (Table 1)

Current status in oesophago-gastric cancer

In patients diagnosed with locally advanced oesophago-gastric cancers, neo-adjuvant chemotherapy (NAC) or chemo-radiotherapy (NACRT) followed by surgery remains the treatment of choice (6,7). Introduction of neo-adjuvant oncological therapies has resulted in improved overall and disease-free survival (8,9). However, the effects of neo-adjuvant chemotherapy result in physiological deconditioning. In a study using cardiopulmonary exercise (CPEX) testing before and after NAC, Jack et al recorded a 15% decline in oxygen uptake at estimated lactate threshold in patients due to undergo oesophago-gastric surgery (10).

Improvements in surgical techniques, including minimally invasive and robotic surgery, and centralisation of surgery to specialist centres have improved safety. As a result, the 30 day post-operative mortality has reduced from 10.3% to 1.9% in the UK national audit (11,12). ERAS programs have resulted in reduced length of stay and readmissions to hospital after surgery(1). However, whilst mortality rates have fallen, reported post-operative morbidity rates of 36 – 59% (13–15) and resolution of quality of life remain a significant challenge - both of which may conceivably be improved by prehabilitation.

The demographic of patients being diagnosed with potentially ‘curable’ oesophageal cancer is also a changing landscape. With the ageing population, older patients on poly-pharmacy regimens are presenting with tumours that are

technically surgically resectable but who are of borderline fitness for high-risk and physiologically demanding surgery. Profoundly unfit patients with comorbidities relating to sedentary lifestyles are also being seen with a cancer diagnosis at a young age.

The health benefits of exercise are well established (16). These include lower mortality and morbidity rates (17,18), improved cardiovascular function, strength and muscle mass, postural stability and psychological function, improvements in depressive symptoms and sleep disorders(19) and better overall quality of life (20). With the safety and benefits of exercise during cancer treatment being accepted as a principle(21,22) and encouraged by cancer support organisations (23), the focus of attention in oesophageal cancer has turned to prehabilitation before surgery, specifically encompassing the neo-adjuvant treatment period.

Heldens et al. (24) reported on the feasibility of a structured exercise program during neo-adjuvant chemo-radiotherapy in patients diagnosed with rectal cancer. They concluded that an outpatient prehabilitation program was largely feasible and safe, and not only prevented the reduction in physical fitness decline associated with NACRT but improved functional exercise capacity by 9.0% and leg muscle strength by 39.2%.

Pre-operative programs, focusing mainly on respiratory function, have shown mixed results across a variety of surgical disciplines, including cancer(25). Dettling et al. reported on the benefits of Inspiratory Muscle Training (IMT) as significantly improving respiratory muscle function but with no benefit on post-operative pneumonia following oesophagectomy (26). However Boden et al. reported a 50% reduction in postoperative pulmonary complications after major upper abdominal surgery following a single preoperative physiotherapy session (27). An increase in inspiratory muscle function but no increase in peripheral muscle strength or aerobic capacity using IMT, was reported by Valkenet et al.

who suggested that the limited benefits were partly due to a short interval between screening and surgery.(28)

In a trial, which included pre-operative aerobic and resistance training versus rehabilitation in colorectal cancer patients, Gillis et al. reported similar hospital length of stay and post-operative outcomes (29). However, there was an improvement in 6-min walk test (6MWT) in the prehabilitation group at 8 weeks after surgery when compared to the rehabilitation group, suggesting a better maintained physical capacity and/or accelerated recovery post-surgery following prehabilitation.

Prehabilitation in surgery

Tew et al.(30), in their 'Clinical guidelines and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery', graphically represent the physical trajectory of prehabilitation before surgery with the anticipated post-surgery improvement in functional capacity, versus that of the non-optimised surgical patient (Figure 1).

Figure 1 The prehabilitation concept. Following major surgical intervention all patients experience and acute drop in physiological reserve/functional capacity followed by a recovery and rehabilitation phase (A). A low physiological reserve/functional capacity may increase the risk of peri-operative complications and lead to slower, sometimes incomplete recovery (B). A prehabilitated patient may possess greater physiological reserve/functional capacity at the time of surgery, facilitating a more rapid and complete recovery (C). Crucially, in the event of a complicated recovery, prehabilitated patients may be better placed to retain their functional independence and quality of life in the longer term (D).(30)

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A summary of their key recommendations on peri-operative exercise include:

- Priority of patient selection, especially those identified with a higher risk of peri-operative complications
- Multimodal interventions including: smoking cessation; reduction in alcohol intake; and treatment of anaemia
- Presentation of the exercise program as pre-operative optimisation rather than as an optional extra
- Initial patient assessment, including comorbidity optimisation, risk evaluation and education on the benefits of exercise
- Objective functional evaluation and quality of life assessment
- Ongoing 'response to training' functional assessments
- Sufficient time for intervention, commencing as early in the surgical pathway as possible, ideally with a minimum of 4 weeks before surgery
- A combination of aerobic training, resistance training and inspiratory muscle training, tailored to each patient
- Supervised programs by trained individuals. Self-managed programs may be suitable in selected individuals.

In an elective surgical patient group, these are valuable and important recommendations. However, there are challenges in following these guidelines within a cancer treatment pathway. Patient selection after a diagnosis of cancer is based largely on tumour-stage and patient fitness. With 'time-to-treat' targets and established cancer treatment pathway guidelines, there is little time for optimization of modifiable comorbidities and lifestyle factors particularly if these interventions are constrained to the narrow window between diagnosis and start of NAC. Patient fitness, in the majority of these patients, is already compromised. Cramer et al. found that, on average, colorectal cancer patients had a baseline VO₂ peak of 23% below that of general population, age-matched controls (31). To compound this, patients frequently develop induced complication toxicities from

chemotherapeutic agents. Anthracyclines and anti-angiogenic targeted therapies, commonly used in the neo-adjuvant pathway, lead to increased exercise intolerance in cancer patients (32). In the UK MRC OE05 chemotherapy trial, 12% of patients stopped chemotherapy early due to toxicities and 11 % of patients did not proceed to surgery. Of these, 15% developed significant comorbidities that precluded surgery. The mortality from combined Epirubicin, Cisplatin and Capecitabine (ECX) chemotherapy was 1.8%, equivalent to the post-operative mortality seen in the trial (33).

Therefore, a diagnosis of cancer, and especially oesophageal cancer, results in a unique group of patients requiring an individualised or tailored approach to prehabilitation. This mandates a fundamental understanding of the treatments they receive and an appreciation that the exercise intervention may differ at the various stages of the treatment pathway.

Prehabilitation in cancer

Silver and Baima describe *cancer prehabilitation* as “a process on the cancer continuum of care that occurs between the time of cancer diagnosis and the beginning of acute treatment, includes physical and psychological assessments that establish a baseline function level, identifies impairments, and provides targeted interventions that improve a patient’s health to reduce the incidence and the severity of current and future impairments” (34).

Table 1 represents the current landscape of registered clinical trials of pre-operative exercise interventions in oesophageal cancer, focusing on those during NAC. They are limited to relatively small, prospective studies with numerous primary end-points and large variations in how physical function is measured.

Each study has been evaluated according to Silver’s definition of prehabilitation in cancer (34). The few studies that have reported results mainly include exercise

interventions focusing on pre-operative respiratory muscle training with the aim of reducing post-operative pulmonary complications.

The awaited results will help to inform and shape the future of UGI cancer prehabilitation.

A number of important points are highlighted from the Silver's description that present challenges that need to be met in any attempt to successfully deliver prehabilitation in cancer patients:

1. A process on the cancer continuum of care

A continuum is 'A continuous sequence in which adjacent elements are not perceptibly different from each other, but the extremes are quite distinct.' (35)

In the context of the cancer patient, the investigative and treatment pathways may feel like a continuum. However, in reality, there are distinct needs during each element from diagnosis, through chemotherapy, surgery and into the recovery period.

The exercise advice given to a treatment-naïve patient will differ from that of a patient during active chemotherapy treatment especially in the first days following chemotherapy infusions. In the 'washout period' after NAC, as the effects of chemotherapy toxicities subside, activity may be designed to increase in intensity in preparation for surgery. Nutritional and psychological support, will likewise adjust to each phase of treatment. In-hospital physiotherapy teams will oversee early post-operative recovery, but following discharge, any exercise program clearly needs to be sympathetic to the resultant physical deficiencies incurred by the surgery.

2. Between the time of diagnosis and the beginning of acute treatment

The timing of introducing prehabilitation programs poses a significant challenge with regards to imposed 'time-to-treat' treatment pathways. Once staging has been completed, patients may be required to attend the hospital multiple times for additional investigations including renal and cardiac function, and nutritional optimization prior to starting neo-adjuvant chemotherapy. Patients also take time to process the diagnosis of cancer and the impact it will have on their lives and that of their families (36). Initiating exercise training during this period is challenging. Opportunities for exercise training need to be accessible and preferably provided on-site to avoid additional travel for patients (37).

Prehabilitation during NAC aims to reduce physical deconditioning, increase pre-operative activity levels and as a result, optimise fitness and improved mental and emotional health ahead of demanding surgery. Much of the reported research in exercise training has focused on the 2 – 6 weeks before surgery. In Figure 2, Jack et al. present the CPEX results of VO₂peak before and after NAC showing decline of physical function in patients during treatment (10). This study highlights that exercise interventions, in patients undergoing neo-adjuvant treatments, need to be introduced from the time of diagnosis rather than waiting to begin prehabilitation in the pre-surgery period.

Figure 2 A ladder plot of oxygen uptake at estimated lactate threshold pre-and-post-neoadjuvant chemotherapy (NAC) (10)

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3. *Physical and psychological assessments that establish a baseline function level*

There is general consensus (30,38) that patients undergoing prehabilitation in cancer should undergo baseline assessment of physical and psychological function. Cancer treatment is physically, emotionally and psychologically stressful(39,40) . Each patient will have unique comorbidities and physical capabilities. As a result, physical training needs to be individualized to those specific needs, measured against a baseline assessment and with subsequent monitoring and guidance during training (30) .

In clinical trials, baseline assessments vary and may include: 6-minute walk test, muscle function/strength tests (*i.e.* leg press and chest press), VO₂max as measured by Cardiopulmonary Exercise Test (CPEX) or estimated from a sub-maximal test, grip strength, Forced Expiratory Volumes (FEV), in addition to measures of insulin resistance, haemoglobin, white cell and blood albumin levels.

Cardiopulmonary exercise testing (CPEX) is a holistic measure of cardiorespiratory capacity and oxygen delivery within an individual, including that of skeletal muscle function(41). It is a useful tool in risk stratifying patients, may predict post-operative morbidity and can guide exercise prehabilitation programs (42). Early mobilization of patients is a key aspect of ERAS programs for good reason, given that the pulmonary and systemic circulation, and peripheral muscle function are all activated through ambulation of patients post-operatively.

Some of the 'softer' physical measures, for example, 6MWT, grip strength and Forced Expiration Volume (FEV) used in studies are restricted in how they measure overall physical function. However these limitations need to be weighed against advantages such as ease of access, cost and time taken to perform the test.

Validated psychological and well-being measures are readily available for use in cancer patients (43–45). Baseline measures will serve to inform the clinical team of a patient's current status, may highlight important areas where intervention may be required and also provide valuable context during the survivorship period.

4. Identifies impairments

Whilst surgery is still considered to be the cornerstone of curative treatment, discussion with the patient involves identifying limiting factors prior to treatment selection. Pre-existing comorbidities and specific cancer-related risk factors need to be considered in relation to the toxicities resulting from chemotherapy and chemo-radiation treatments. Renal, cardiac and pulmonary function, in addition to smoking status, synchronous cancers, morbid obesity and mental health are all considerable risk factors for patients. The need for single lung ventilation during oesophagectomy needs to be considered at the outset in relation to patient fitness for surgery.

The Eastern Cooperative Oncology Group (ECOG) Performance Status (46) is a standard used by oncologists to establish how the patient's disease affects their daily living abilities and to determine appropriate treatment. Furthermore, personal goals and patient wishes should be considered. An understanding of the benefits of physical exercise will have a significant influence on the patient's compliance when enrolling in exercise programs. The concept of "teachable moments" where patients are receptive to, and may act upon, health advice is particularly relevant to prehabilitation. Nadler et al. discuss some of the barriers relating to exercise during cancer treatment including, poor knowledge, lack of time and safety concerns (47). Advice from oncology care providers may be important in addressing these concerns. In addition, tailored exercise programs, targeted to the needs and preferences of the patient, combined with the use of group activities including family and friends, and regular monitoring with feedback, are some of a number of ways to improve motivation and adherence.

A number of strategies are emerging to adequately assess elderly and more complex patients prior to surgery. These include dedicated, high-risk, anaesthetic clinics and specific services overseen by Geriatricians e.g. POPS - 'Proactive care of older persons undergoing surgery' services. These services assist in identifying modifiable impairments which, if not addressed, would pose increased risk of post-operative problems in older, or less fit, surgical patients(48). Once identified, these impairments may be optimized through prehabilitation. Carli et al. described mitigation of the post-operative stresses of surgery using an integrated multi-disciplinary approach of prehabilitation in the pre-operative period, highlighting especially the benefits in the older patient (49). Of note, physical activity levels and physical capacity in the general population falls significantly with age. In the UK population, 43% of 55 to 64 year olds are inactive (less than 30 minutes of physical activity per week), rising to 68% inactive in the 75+ years age group. Accordingly, prehabilitation to improve physical capacity is of greater importance in older patients and likely to become increasingly important as activity levels in the general population continues to fall (50)

5. *Provide interventions to promote the physical and psychological health of the patient that reduce the incidence and severity of future impairments*

Macmillan Cancer Support (51) encourage the World Health Organisation guideline of Activity in Healthy Adults (52). The recommendation is for “150 minutes/week of moderate intensity or 75 minutes of high intensity activity. Adults (aged 19 – 65+) should also aim to undertake activity to improve muscle strength and balance training sessions twice per week”. The advice for patients with cancer is to aim to achieve the WHO guidelines but to adjust activity according to their physical symptoms and treatment status (51).

In a study of physical activity guideline compliance in U.S. adults, Tucker et al.(53) reported that fewer than 9.6% met the WHO guideline for physical activity when objectively monitored on accelerometer. In contrast, the self-reported level of compliance was 63%. In a Sport and Physical Activity: Special Eurobarometer Report (2013), 29% of EU adults claimed to undertake vigorous activity for 1-3 days per week. 25% of adults reported participating in moderate activity, 4-7 days per week (54).

Physical training interventions in past studies described a range of exercises for pre-operative optimization. Some suggested exercise of selected muscle groups to reduce post-op complications e.g. Inspiratory Muscle Training, to selectively attempt to reduce post-operative pneumonia (25-27). The majority of current trials include a combination of aerobic and resistance training programs. (Table1). A meta-analysis by Marzolini et al. reported improved body composition, strength and cardiovascular fitness, and ‘probably quality of life as well’, in combined aerobic and resistance training versus resistance training alone(55). Furthermore, they concluded that in stroke patients, aerobic training may be reduced by up to 40%, but with similar improvements in mobility and VO₂peak, if combined with resistance training (56).

Psychological health of the patient is also important in cancer prehabilitation. The advantageous outcomes of exercise on psychological health during cancer rehabilitation have been reported by Smith et al. (56) and Losito et al. (57,58). These include improved quality of life and cancer-related fatigue. 'Living with and beyond cancer' and 'survivorship' are terms frequently being used in post-treatment cancer patient groups. Physical exercise before, during and after cancer treatment improves physical status and quality of life (58).

Prehabilitation, cancer and immunity

The effect of exercise prehabilitation in cancer may also impact on tumour control through immune system regulation. In a review of patients who undertook monitored exercise following a diagnosis of cancer, there was a lower relative risk of cancer recurrence and cancer-related mortality compared to patients who did little or no exercise. Furthermore, the same patients experienced fewer or less severe treatment side effects (59). Patients who experience complications after surgery have higher rates of cancer recurrence independent of tumour stage (60). This implies an immunological component to cancer recurrence. Terra et al. (61) described inherent activation of the immune response cascade through exercise, eliciting a pro-inflammatory response during moderate intensity exercise. However, during high intensity exercise an anti-inflammatory response was noted. Hojman (62) further described the effects of exercise on the control of immune cell function, modulation of inflammatory signaling and regulation of systemic inflammation linking these regulatory effects to lowered tumour incidence and disease progression. Pederson et al. linked exercise to reduced tumour growth and through increased infiltration of natural killer (NK) cells in exercised mice (63). The mechanism of increased mobilization of NK cells is speculated to be through increased release of Interleukine-6 (IL-6) myokines in response to muscle contraction.(64) Exercise-induced IL-6 is described as having a pro-inflammatory effect on bacterial infections and contrasting anti-inflammatory inhibiting effect on Tumour Necrosis Factor-alpha (65). Research programs in clinical practice aim to provide evidence that exercise reduces the

risk of complications and may also have immunological benefits on tumour control and recurrent disease.

Summary and clinical implications

Mortality rates after oesophagectomy have fallen, however morbidity rates remain high. The introduction of ERAS programs provided a consolidated framework for improvements of care in the peri-operative period and has reduced length of hospital stay. The introduction of prehabilitation programs, in order to optimise patients physically and psychologically for surgery, have proved to be beneficial in some tumour groups. The health benefits, safety and biological benefits on tumour control following exercise have also shown positive results. A number of questions remain in regards to prehabilitation in oesophageal cancer. These include the timing and accessibility of the intervention, how to improve compliance, the optimal makeup of training programmes, how to measure physical performance and, the cost-effective implementation of prehabilitation into standard practice.

With a coordinated, multidisciplinary approach to introducing a holistic prehabilitation program in cancer care, there is realistic potential to change the current status quo and improve surgical outcomes, physical health, psychological well-being and long-term survival in these patients.

Conclusion

‘Living with and beyond cancer’ begins at the time of cancer diagnosis - so too should prehabilitation.

Dr Nick Cavill, a health promotion consultant said: “If exercise were a pill, it would be one of the most cost-effective drugs ever invented”. Therefore, the challenge to those making clinical decisions in cancer care is to develop a greater

understanding of exercise prehabilitation and its active promotion as an integral part of the treatment pathway.

Much is said about empowering patients with long-term conditions and joint clinical decision-making with patients. ERAS provided an excellent matrix for a coordinated, multi-disciplinary approach to peri-operative improvements in patient care. Prehabilitation, or 'Pre-ERAS', is the opportunity to broaden the benefits of ERAS to include engagement of the patient in their care from the time of diagnosis.

Practice Points

- Exercise during cancer treatment is safe and advisable
- Prehabilitation in cancer should commence at diagnosis
- Benefits of prehabilitation extend beyond physical optimisation and include general health, well-being, psychological improvements and immune function support
- Prehabilitation should form the starting point of Enhanced Recovery After Surgery Programs

Future research agenda

- To define the timing and accessibility of the exercise prehabilitation intervention in order to optimise compliance
- To identify the optimal structure of the exercise program during the treatment pathway
- To achieve consensus on how best to measure baseline function and monitor physical performance changes during prehabilitation.

Conflict of Interest: None

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Acknowledgements

Figure 1. Reprinted from *Anaesthesia*, January 2018, Vol 73, Issue 6 , Authors: Tew GA, Ayyash R, Durrand J, Danjouw GR , Clinical guideline and recommendations on pre-operative exercise training in patients awaiting major non-cardiac surgery, Pages 750-768, Copyright (2018), with permission from Journal of the Association of Anaesthetists of Great Britain and Ireland. Copyright © 2018 The Association of Anaesthetists of Great Britain and Ireland.

Figure 2. Reprinted from *European Journal of Surgical Oncology*, Vol 40/Issue 10, October 2014, Authors: Jack S, West MA, Raw D, Marwood S, Ambler G, Cope TM, et al, The effect of neoadjuvant chemotherapy on physical fitness and survival in patients undergoing oesophagogastric cancer surgery, Pages 1313-1320. Copyright © 2014 Elsevier Ltd. All rights reserved

Table 1 Registered Clinical Prehabilitation Trials

Trial Registration	Author	Trial Design	Study Title	Participants	Intervention/Exercise Regimen	Outcomes	Target/ current status (intervention: control groups)	Adenocarcinoma/Squamous Cell Carcinoma	NAC/NACRT	Intervention during neo-adjuvant oncological treatment and surgery (continuum of care)	Intervention before start of acute oncological treatment	Baseline measures: 1. Physical, 2. Psychological	Cardiopulmonary exercise testing	Intervention to promote physical, psychological health and reduce future impairments
ClinicalTrials.gov Identifier: NCT03418298	Piroux; Gilles	Single group assignment	Prehabilitation in Patients With Esophageal or Gastric Cancers	Esophageal and Gastric cancer; Post NAC, >2 weeks pre-surgery	Preoperative internet-based program including aerobic and resistance training three sessions per week; IMT	Retention; Adherence; Patient satisfaction; adverse events	20/recruiting	Not specified	Not specified	Mixed	Mixed	Mixed		
ClinicalTrials.gov Identifier: NCT02962219	Lamy; Hart	Randomised; Parallel assignment	Exercise Prior to Oesophagectomy (ExPO)	Oesophageal adenocarcinoma; 3-4 months before surgery; NAC + surgery	1) Behavioural change techniques (BCTs), 2) home inspiratory muscle training (IMT), 3) a home exercise programme (HEP) - which is also current standard care, 4) a 4 week hospital-supervised aerobic and muscle strengthening programme (Hos-PEP).	Feasibility data on whether PEP is acceptable, adhered to and safe, and whether it improves patient fitness above standard care.	32/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02780921	Lacarin; Le Roy	Randomised; Parallel assignment	Effect of Prehabilitation in Gastroesophageal Adenocarcinoma: Study Protocol of a Multicentric, Randomised Control Trial	Oesophageal and Gastric cancer; pre-chemo (NAC) + surgery	1 hour of supervised exercise for at least 3 days per week, for a total of 18 cycles, alternating between aerobic and resistance training	% Patients completing oncological treatment as determined by MDT	120/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02722785	Christensen	Non-randomised; Parallel assignment	Perioperative Study of Exercise Training in Patients With Operable Cancer of the Gastroesophageal Junction (PRESET)	Operable gastro-oesophageal junction; pre-surgery but during NAC not specified	After a light warm-up, patients will perform 20-30 min of aerobic interval training of stationary bicycle. Resistance training comprises 4 exercises for the major muscle groups: chest press, leg press, lateral pull, and knee extension with 3-4 sets of 8 to 15 repetitions	Safety and Feasibility of pre-and-post-op exercise - incidence of adverse events; Adherence to program	40/active, not recruiting	OAC	Not specified			✓		✓
ClinicalTrials.gov Identifier: NCT02680990	Hershey; Cooper	Randomised; Parallel assignment	Resilience and Exercise in Advanced Cancer Treatment (REACT)	Operable Oesophageal, Gastric and Pancreatic Cancer; during NAC	Sessions completed 3 times/week: 3 sets of 6 exercises: 1. chair stands, 2. chest press, 3. shoulder press, 4. arm curls, 5. pulls, and 6. calf raises. In addition, Band Together participants will be asked to work up to a walking goal of 10,000 additional steps per week	Feasibility: Adherence and Contamination	60/14 - closed	OAC	NAC/NACRT	✓	✓	✓		✓
ClinicalTrials.gov Identifier: NCT01952210	Xu; Chen	Randomised; Parallel assignment	Effectiveness of a Nutritional Consultation and Exercise Program in Esophageal Cancer Patient: Walk and eat	Neo-adjuvant chemoradiotherapy in oesophageal cancer (SCC)	Upper extremity muscle training and walking exercise at 45%-65% of maximal heart rate reserve, 3 times per week, 20-30 minutes per session.	6MWT; hand grip strength; lean muscle mass; body weight change; Nutritional status	56/50 - completed; published	OAC/SCC/NET	NAC/NACRT	✓	✓	✓		
ClinicalTrials.gov Identifier: NCT01666158	Carli	Randomised; Parallel assignment	Prehabilitation for Esophageal Resection Surgery	Oesophageal cancer surgery; 4 weeks before elective surgery	20 min of general exercise training, 3 days per week, alternating between aerobic and resistance training	Enhance Postoperative Functional Capacity Following Esophageal Resection; 6MWT	68/68	Not specified	Not specified			✓		✓
ClinicalTrials.gov Identifier: NCT02950324	Allen; Sultan	Randomised; Parallel assignment	Does Prehabilitation Improve Exercise Performance and Insulin Resistance After Surgery for Oesophago-gastric Cancer?	Oesophago-gastric cancer; 17 weeks before surgery	Multimodal programme that involves 15 weeks of exercise	Improved performance on CPEX; reduced insulin resistance; HRQL	50/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT03626610	Zylstra; Davies	Non-randomised; Parallel assignment	Pre-EMPT: Prehabilitation in oEsophageal Malignancies on a Perioperative Treatment pathway including neo-adjuvant chemotherapy	Operable oesophago-gastric adenocarcinoma; during neo-adjuvant chemotherapy and pre-surgery	WHO guidelines for exercise in adults as minimum; 10,000 steps/day (measured using wearable device); Strength, core and relaxation exercise training commencing before NAC	Cardiopulmonary fitness; LOS & Post-op complications; Commencement of recommended adjuvant treatment; HRQL; DFS	66/recruiting	OAC	NAC	✓	✓	✓	✓	✓
ClinicalTrials.gov Identifier: NCT02478996	Pfirschmann; Gockel	Randomised; Parallel assignment	Internet-based Perioperative Exercise Program in Patients With Barrett's Carcinoma Scheduled for Esophagectomy (iPEP)	Barrett's carcinoma scheduled for surgery; 8-12 weeks before and after surgery	Internet-based perioperative exercise program (iPEP), including daily endurance, resistance and ventilation training	Peak oxygen uptake (VO2peak)	80/recruiting	OAC	Not specified			✓	✓	
ACTRN12613000664741	Boden et al. (2018)	Randomised; Parallel assignment	LIPPSMack POP trial - Lung Infection Prevention Post Surgery (Major Abdominal) with Pre-Operative Physiotherapy education	Upper abdominal surgery; 2 weeks before surgery; NAC not specified	Interview and breathing exercise instructions	Pulmonary Complications	377/441; completed; published	Not specified - mixed tumour groups	Not specified					
Unknown	Detting et al. (2012)	Non-randomised controlled trial	Feasibility and Effectiveness of Pre-operative Inspiratory Muscle Training in Patients Undergoing Oesophagectomy: A Pilot Study	Oesophageal cancer; NAC not standard care	Lung Function test	Post-operative pneumonia	90/48:42	Not specified	Not specified			✓		
ClinicalTrials.gov Identifier: NCT01893008	Valkenet et al. (2018)	Randomised; Parallel assignment	PREPARE: Pre-operative Inspiratory Muscle Training in patients undergoing oesophageal resection	Oesophageal resection - at least 2 weeks before surgery	Inspiratory Muscle Training using flow-resistance; 1 physiotherapy-lead training session	Decreased pulmonary complications after esophageal resection	245/120:121; completed; published	Not specified	NACRT			✓		

Enhanced Recovery

Introduction

Since the enhanced recovery after surgery (ERAS) study group published the first guidelines advocating the importance of multidisciplinary team collaboration to advance the recovery of patients after surgery this approach has been embraced across a range of surgical disciplines. A number of centers have established standardized care pathways for management of patients undergoing oesophagectomy (Table 1). In the absence of formal ERAS guidelines for oesophagectomy, these pathways have been drawn from other examples within surgical oncology. Variation in the design and implementation of care pathways within different institutions continues to be a limiting factor when seeking to derive summative evidence for wider implementation. Notwithstanding there have been reports that standardization of care can be associated with improvement in important outcomes in patients undergoing oesophagectomy, including anastomotic leak and length of hospital stay (1). An overview of major studies in ERAS in oesophagectomy patients is presented in Table 2.

The purpose of this review is to discuss the core elements of an enhanced recovery program for oesophagectomy that is applicable to both malignant and benign disease. For convenience this review has been divided between interventions that are most applicable to intra-, and post-operative periods. Although pre-operative identification of potential barriers to successful enhanced recovery is a core component of any successful ERAS program, a commentary on these interventions as part of prehabilitation was provided earlier within this chapter.

Table 1. Example of institutional standardized clinical pathway for oesophagectomy from Virginia Mason Medical Center

Initial Contact	Initial Assessment / Staging	Pre-op Arrangement /Restaging	Surgery	POD 0 PPICU "step-down unit"	POD 1 Surgical ward	POD 2-3 Surgical ward	POD 4-5 Surgical ward	POD 6-7 Surgical ward / DC
<p>Phone interview Within 24 hr of referral – PMH – Current Symptoms – Assess Dysphagia and weight loss – Current Investigations – Travel Arrangements</p> <p>Ensure previous notes, investigations, films, pathology are available</p> <p>Preparation of tailored patient schedule ≥ physiologic and staging investigations completed in 48 hr</p>	<p>Consultations – Medical Oncology – Radiation Oncology – Cardiology – Thoracic Surgery – Gastroenterology</p> <p>Investigations – CT – PET/CT – EGD, EGD-US – Path review – PFT – Selective objective cardiac testing</p> <p>Nutritional Assessment</p> <p>Thoracic Tumour Board Within 7 days of consult Communicate results following day to patient and referring physician.</p> <p>Initiate Neoadjuvant Therapy Appropriate patients with cT2-4, N1-4, Mx</p>	<p>Restaging 2-4 Weeks Following neoadjuvant therapy – CT – EGD + US – Tumour Board</p> <p>Surgical Approach Tailored according to – Tumour / Barrett characteristics – Patient Physiology – Previous Surgery – Conduit Availability</p>	<p>Thoracic epidural placed preoperatively – Bupivacaine 0.05% – Hydromorphone 10µg/ml</p>	<p>• Antiemetic Protocol • Continue Beta Blocker, and ASA • IV PPI – Monitor gastric pH</p>	<p>• Continue Beta Blocker + ASA • Selective start routine meds down J-tube • IV PPI (esomeprazole)</p>	<p>• Consider – Dulcolax sup – Lasix • Start oral crushed PPI when NGT removed</p>	<p>• Consider Erythromycin if delayed gastric emptying • Continue oral PPI • Transition all meds to J-tube</p>	<p>• Oral PPI • All routine meds and analgesics given liquid or crushed via J-tube</p>
			<p>Single dose 2nd Generation Cephalosporin</p>	<p>• PCEA ± PCA • Avoid bolus adjustment • Consider – IV Acetaminophen</p>	<p>• PCEA ± PCA • Consider Ketorolac</p>	<p>• PCEA ± PCA • Consider Ketorolac</p>	<p>• Transition from PCEA • J-tube scheduled oxycodone ± NSAID</p>	<p>• Provide prescriptions 24-48 hrs prior Discharge</p>
			<p>Selective SQ Heparin</p>	<p>• Keep HOB>45° • Compress Stocking • Chair 4-6/hr postop • 100ft walk 12-14/hr post-op</p>	<p>• Keep HOB>45° • Compress Stocking • 200ft walk x 2 in PPICU • Transfer to ward</p>	<p>• Keep HOB >45° • Compress Stocking • In chair 2-3 hr/day • 200ft walks 6-8/day</p>	<p>• Keep HOB > 45° • Compress Stocking • Chair 80% of day • Independent Activity</p>	<p>• Keep HOB >45° • Chair 80% of day • Independent Activity • Discharge Planning</p>
			<p>Minimize blood loss / transfusion</p>	<p>• Avoid CPAP • Maintain MAP>70mmHG Treat MAP<70mmHg • Decrease epidural rate/no bolus • Epinephrine Drip • Infuse up to 2l crystalloid</p>	<p>• Maintain MAP>70mmHG • Avoid CPAP</p>	<p>• Reinitialize CPAP if needed</p>	<p>• Routine Vital Signs</p>	<p>• Routine Vital signs</p>
			<p>No routine central venous catheter</p>	<p>• Recovery room post-op CXR</p>	<p>• CXR (2 view)</p>	<p>• CXR (2 view) • Witnessed UGI POD 3-4</p>	<p>• CXR (2 view)</p>	<p>• CXR (2 view) for clinical issues only</p>
			<p>Restrictive fluid administration intra-operatively Target <4l crystalloids</p>	<p>• CD to 20 cm suction • NGT – low cont. wall suction • Foley Catheter</p>	<p>• D/C apical CD if no air leak & low output • CD water seal</p>	<p>• May D/C 2nd CD (except Ivor Lewis) • F/U CXR in 4hr • Ivor Lewis: CD till oral intake</p>	<p>• D/C NGT when contrast study shows good gastric emptying (target day 3-4) • In IL D/C 2.CD when oral intake</p>	<p>• Advance oral protocol • J-tube teaching for patient and family</p>
			<p>Immediate Extubation</p>	<p>• IV Fluid basal rate 70cc/hr D5½NS • MAP<70 consider fluid bolus (max 2L)</p>	<p>• IV Basal rate 50cc/hr D5½NS • J-tube 10ml/hr and selective meds.</p>	<p>• J-tube 30cc/hr advance to goal • No oral intake • D/C IV fluids</p>	<p>• J-tube target rate & transition to nocturnal feed • Start oral protocol* when no gastric emptying delay on UGI</p>	<p>• Dietary – Nutritional oral & J-tube protocol over next 4-6 weeks</p>
			<p>On table epidurogram to verify correct epidural placement</p>	<p>• Pain service • PSY elderly patients • Selective RT • PT mobilization</p>	<p>• Dietary</p>	<p>• Dietary 1-2 days prior to D/C • Social work – PRN • ± Rehab • Home Health Care Services for J-tube</p>		
<p>1. Description Surgery & Pathway</p>	<p>2. Description Surgery & Pathway</p>	<p>3. Description Surgery & Pathway</p>	<p>Critical Measurable Goals</p>	<p>Immediate Extubation Maintain MAP >70 mmHG Mobilize Day of Surgery</p>	<p>Transfer to Ward Initiate Enteric Feeding Mobilize 2-4 Walks</p>	<p>J-Tube Feeding to Goal Assess Gastric Emptying Remove NG & Chest Drain</p>	<p>Independent Mobility Start Oral Intake</p>	<p>Discharge Day 6-7</p>

* Oral Protocol: Ward nurse direct advancement of liquid oral intake from 15cc/hr $\geq$ $\frac{2}{3}$ Cup/hr

PMH past medical history, CT computed tomography, PET/CT positron emission tomography w CT, EGD gastroscopy, US ultrasound, PFT pulmonary function test, PPICU post procedural intensive care unit, PCEA percutaneous epidural analgesia, PCA patient controlled analgesia, POD post-operative day, HOB head of the bed, MAP middle arterial pressure, CXR chest x ray, CD chest drain, NGT nasogastric tube, PSY psychiatric consult, RT respiratory therapy, PT physical therapy, IV intravenous, PPI proton pump inhibitor, J-tube jejunostomy, NSAID non steroid anti-inflammatory drug, D/C discharge, F/U follow up

Routine post discharge goals

- Represent at MTB (recommendations to referring and primary care MD's)
- J-tube removed 4-12 weeks post discharge
- Q.O.L and patient satisfaction assessment
 - Commit to 3 years follow-up

ACCEPTED MANUSCRIPT

Table 1. ERAS studies in oesophagectomy

Author	Year	Country	Design	Patient No. (total/ERAS)	Outcome	Ref
Benton	2018	Australia	Retrospective	33/17	ERAS was associated with no difference in hospital stay	(2)
Blom	2013	Netherlands	Prospective	181/103	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(3)
Cao	2013	China	Retrospective	112/55	ERAS was associated with reduced hospital stay and postoperative morbidity	(4)
Chen	2016	China	Prospective	260/128	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(5)
Findlay	2015	UK	Retrospective	132/55	ERAS was associated with no difference in hospital stay and postoperative morbidity	(6)
Ford	2014	UK	Prospective	116/75	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(7)
Giacopuzzi	2017	Italy	Prospective/retrospective	29/22	ERAS was associated with no difference in hospital stay and postoperative morbidity	(8)
Li	2012	Canada	Prospective	106/59	ERAS was associated with reduced hospital stay and postoperative morbidity	(9)
Li	2017	China	Prospective	110/55	ERAS was associated with reduced hospital stay and postoperative morbidity	(10)
Markar	2014	USA	Prospective	275/183	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(11)
Munitiz	2015	Spain	Retrospective	148/74	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(12)
Preston	2013	UK	Prospective	24./12	ERAS was associated with reduced hospital stay and postoperative morbidity	(13)
Shewale	2015	USA	Retrospective	708/386	ERAS was associated with reduced hospital stay and postoperative morbidity	(14)
Tang	2013	UK	Prospective/retrospective	63/36	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(15)
Tomaszek	2010	USA	Retrospective	386/110	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity*	(16)
Zehr	1998	USA	Prospective/retrospective	152/96	ERAS was associated with reduced hospital stay	(17)
Zhao	2014	China	Prospective	68/34	ERAS was associated with reduced hospital stay but equivalent postoperative morbidity	(18)

*Lower rates of anastomotic leak observed

Multidisciplinary engagement

The multidisciplinary engagement, often in the form of a formal tumour board, has become an established part of the management of patients with oesophageal cancer. In addition to oncological consideration, other important determinants of patients care including: comorbidities, physiological reserve and nutrition often feature as a component of tumour board discussions. The tumour board should actively seek engagement from the full spectrum of the multidisciplinary team including the patient, who should remain the central focus and be kept informed of recommendations. The needs of patient populations, who do not traditionally receive the benefit of formal multidisciplinary discussion, such as those with benign or emergency indications of for oesophagectomy, should not be forgotten.

Operative components

Timing of surgery

For patients receiving neoadjuvant chemoradiotherapy the competing pressures of allowing adequate time to recover from therapeutic toxicities in the presence of ongoing tumour regressive effects versus the risk of new tumour progression and evolving fibrosis of surgical tissue planes must be carefully balanced. Current recommendations are for an interval of 6-10 weeks after neoadjuvant chemoradiotherapy and 6-8 weeks after neoadjuvant chemotherapy before oesophagectomy (19-21).

Surgical technique

Surgical approach: Recently published data from a collaboration of 24 high volume centers in 14 countries indicate that approximately half (48%) of all oesophagectomies are currently performed by a minimally invasive approach. This trend is reflective of a desire to reduce the magnitude of surgical trauma that is associated with this operation. Questions however remain as to the safety and efficacy of both open and minimally invasive techniques. There have been eleven meta-analyses comparing the outcomes of open versus minimally invasive oesophagectomy (22-32). Taken together their findings suggest the minimally

invasive techniques are associated with lower overall postoperative morbidity, early mortality and length of hospital stay. Minimally invasive procedures were more often associated with longer operative time but equivalent lymph node harvest (26, 29, 30). Overall survival was either equivalent (23, 24) or superior (26) in the minimally invasive cohort.

Lymphadenectomy: The extent of the lymphadenectomy performed during oesophagectomy for oesophageal cancer remains a contentious subject. Proponents of radical lymphadenectomy cite evidence that it reduces local recurrences rates and improves long-term survival as well as supporting more accurate pathological staging (33-36). In comparison those in favor of a more conservative approach would contend that such an approach increases perioperative morbidity with inconclusive evidence supporting improved survival. Current recommendations are that the extent of lymphadenectomy should reflect the location of the tumour within the esophagus in addition to its histological stage (33-35, 37).

Oesophageal reconstruction: Several factors should be considered when selecting the most appropriate method of oesophageal reconstruction: the type of conduit, the route of the conduit to the site of anastomosis and the method of anastomosis. In the majority of cases a conduit formed from the tubularized stomach is favored, both because of the accessibility of the gastric remnant and the requirement for a single anastomosis. Alternative conduits such as the colon and jejunum, may be used in certain circumstances, including: significant invasion of the proximal stomach by tumour and in cases where there has been a history of prior gastric resection or compromise of a previous gastric conduit.

Anastomosis: Evidence supporting an optimal method of anastomosis formation is lacking. Meta-analysis of studies that compared anastomotic technique in oesophagectomy found that linearly stapled hybrid anastomoses (38) was associated with a reduced leak rate compared to hand-sewn anastomosis (39). The same was not however true for circular stapled techniques whose leak rates were comparable to hand sewn anastomosis (39). In the absence of strong

evidence for or against a particular form of anastomosis, surgeons are recommended to develop confidence in one or a number of techniques that may be adapted to difference clinical scenarios should a need present itself.

Surgical drains

The long held convention of placing surgical drains at the time of oesophagectomy is a practice that occurs largely in the absence of evidence-based guidelines. Whilst chest drains are often favored for their ability to drain air and fluid from the thoracic cavity potentially heralding clinically significant anastomotic or chylous leak, they may be associated with pain and reduced mobility (40). Whilst many surgeons may exercise caution when removing chest drains after oesophagectomy, opting to wait for daily draining levels to fall below 100-150ml, higher output volumes have been proposed as safe by other studies albeit after pulmonary resections (41-43). Likewise in pulmonary surgery use of a single, centrally placed, drain is considered as effective as two drains with the added effect of having less associated pain (44, 45). The use of active drainage was also not found to confer and added benefit in patients after oesophagectomy (46). There is currently insignificant evidence to support the use of either cervical or thoracic peri-anastomotic drains.

Nasogastric tube placement

Since the widespread adoption of ERAS program within gastrointestinal surgery the routine used of nasogastric tubes for postoperative gastric decompression has been virtually eradicated from clinical practice. In the case of oesophagectomy justification of their use has often centered on the requirement for conduit decompression that may in turn prevent aspiration pneumonia and anastomotic leak. A recently published meta-analysis found that peroperative or early (day 2) nasogastric tube removal did not result in increased morbidity or mortality (47). Furthermore early removal was associated with shorter hospital stay. Current recommendations are for nasogastric tube decompression following oesophagectomy with early removal considered on postoperative day two in the absence of any contraindications.

Anesthetic management

Intraoperative actions and events have the potential to significantly impact on postoperative outcomes. The aims should be to minimize local (pulmonary) and systemic inflammatory responses associated with oesophagectomy and to facilitate early extubation.

Interventions that may facilitate early extubation after oesophagectomy include use of bispectral index to monitor the depth of anesthesia (48) and use of short or intermediate acting neuromuscular blockers at appropriate doses (49).

Frequent requirement for periods of single lung ventilation during oesophagectomy serves as an additional challenge when defining anesthetic and ventilator strategy. Whilst there is limited evidence from studies in patients undergoing oesophagectomy the adoption of lung protective ventilator strategies during both double and single lung ventilation has been advocated. Lung protective ventilation is acknowledged to reduce both the local and systemic inflammatory response facilitating early extubation with a lower risk of re-intubation. There is emerging evidence that driving pressures is the principal mediator of lung injury during ventilation (50). Accordingly minimization of driving pressure as well as limiting the duration of one lung ventilation should be clear objectives in preventing lung injury during oesophagectomy.

Higher rates of respiratory complications and delayed extubation are recognized sequelae of increased intravenous fluid administration during oesophagectomy (51-53). Conversely overly restrictive fluid usage may be responsible for end organ damage through hypoperfusion (54). Current guidance support balanced fluid therapy with zero weight gain. Current recommendations are for the use of balanced crystalloids solution as opposed to 0.9% saline and colloids (55, 56).

Hypotension in the presence of normovolaemia is a common occurrence after oesophagectomy and is often a consequence of the vasodilatory effects of epidural analgesia. In such circumstances vasopressors may be required to maintain of mean artery pressure at a target of 70 mmHg and urine output >0.5ml/Kg/hr

without further provision of intravenous fluids. Lower urine output in patients without risk factors for acute kidney injury may also be tolerated (57).

Post oesophagectomy nutrition

Risk of aspiration pneumonia and anastomotic disruption are often cited as the main reasons for a delay in the initiation of oral intake after oesophagectomy. Whilst parenteral nutrition has been described in this setting, current evidence favors feeding via an enteral route wherever possible (58, 59). Utilization of the intestinal tract over parental routes has the added advantage of suppressing the surgical stress response as well as helping to maintain gastrointestinal health through preservation of its immune and barrier functions.

The preferential route for establishing early enteral feeding after oesophagectomy is via a feeding jejunostomy placed at the time of surgery. Complications of jejunal feeding tubes are acknowledged but are most often minor events such as tube dislocation, occlusion, leakage, entry site infection and gastrointestinal disturbance (60). Major tube related complications including death (0-0.5%) and reoperation (0-2.9%) are reported in a small number of patients (60). Feeding via either a nasojejunal or nasoduodenal tube offers an alternative and potentially safer route for enteral feeding, however patient acceptability and high rates of dislocation limit their use (60). Several studies have examined the feasibility and safety of early oral feeding after oesophagectomy in an effort to subvert the widely held dogma against this practice. When compared to patient whose oral intake was delayed until postoperative day five following oesophagectomy, early oral feeding on postoperative day one was not associated with higher rates of complications (60, 61) and intensive care and hospital stay were significantly shorter (62).

Once a route of providing enteral nutrition has been established full caloric requirements should be targeted by postoperative day 3-6 (60). There is no clear evidence supporting the use of pharmaconutrition, over traditional enteral feeding solutions, as such their use is not currently supported (63).

Postoperative components

Care level

Owing to the magnitude of the operation and historical practice of prolonged elective intubation after oesophagectomy, it has historically been a requirement that patients were cared for within an intensive care unit during the immediate postoperative period. In the absence of a specific clinical indication the practice of prolonged mechanical ventilation and sedation after oesophagectomy should be avoided. This practice results in continued exposure of the lungs to an injurious stimulus, hemodynamic instability that can precipitate fluid overload and a delay in the ability to initiate physical rehabilitation through early mobilization.

In the majority of cases patients can be extubated immediately after oesophagectomy, thereafter they should be transferred to a clinical environment that is able to provide the required level of physiological and physical support at each stage of recovery. Initially this may involve the intensive care unit, but in some hospitals may include other facilities such as high dependency, step down or progressive care units. Prior to hospital discharge patients would be expected to transfer to a general surgical ward.

Pain control

Adequate control of postoperative pain is vitally important in facilitating patients' ability to comply with fundamental aspects of an ERAS program, including early mobilization and respiratory exercises. Inadequate pain control is associated with pulmonary complications, venous thrombosis and prolongation of the surgical stress response (64). The physiological and psychological implications of inadequate pain control may contribute to higher opioid usage and associated side effects. Choice of analgesia should reflect a multimodal approach that encompasses local and regional anesthetic techniques and seeks to minimize the opioid usage.

For open surgery thoracic epidural analgesia may offer the optimal method of ensuring analgesia. Concern for motor and sympathetic blockade that can result

in unwanted side effects of epidural analgesia may be mitigated through use of dilute local anesthetic and opioid infusions and avoidance of bolusing. By ensuring normovolemia and the cautious use of vasopressors in selected patients, the risks of hypotension can be further reduced.

Use of paravertebral block that can be placed under direct vision has emerged as an alternative to thoracic epidural, with several publications demonstrating equivalent analgesia without the unwanted side effects (65-67). Use of paravertebral blocks may be particularly useful where the abdominal component of oesophagectomy has been completed laparoscopically.

Additional analgesic agents that should form part of the multimodal management of oesophagectomy patients include: acetaminophen, non-steroidal anti-inflammatory drugs (NSAIDs), gabapentinoids and ketamine. The use and titration of these and other agents should ideally be overseen by a specialized anesthesia pain service.

Mobilization

Early postoperative mobilization is a central tenet of almost all ERAS programs as it serves to prevent the well-documented detrimental effects of bed rest. In the absence of any contraindication it is reasonable to target patient mobilization on the day of surgery. Following this mobilization should continue with a daily incremental increase in expected activity. Independent mobilization is typically a targeted pathway goal prior to discharge.

Pharmacological prophylaxis

Consideration for the use of one of a number of pharmacological agents to prevent adverse outcomes after oesophagectomy should be considered in all patients. For the most part evidence for the use of pharmacological prophylaxis in patients who have undergone oesophagectomy is extrapolated from studies in general surgical populations. A summary of recommended prophylactic drugs and indications for their use is presented in Table 3.

In addition to these prophylactic drugs special consideration should be given to the use of pharmacological agents for glycemic control and treatment of common complications including arrhythmias and infections. Whilst there is limited evidence regarding the optimal approach to managing these complications, including the choice of pharmacological agents, individual centers should take steps to develop algorithms for their early detection and treatment. Engagement of the wider multidisciplinary teams including specialists in internal medicine, infectious disease and microbiology is recommended.

Table 3. Pharmacological prophylaxis in patients undergoing oesophagectomy

Class	Intention	Indications
Cardiovascular	Thromboprophylaxis	All patients in the absence of a specific contraindication should receive LMWH or equivalent
	Beta-blockade	Beta blockade should be considered in patients who are long-term users of beta-blockers and high risk beta-blocker naive patients with coronary artery disease
Antiemetics	Prevention of PONV	Patients with identifiable risk factors should be considered for combination therapy including two or more antiemetic agents one of which should be a 5-HT ₃ antagonist (e.g. ondansetron)
Antibiotics	Prevention of surgical site infection	All patients should receive a short course (<24hrs) of intravenous antibiotics with initial dose given prior to surgical incision
Bowel stimulation	Prevention of postoperative ileus	Use of simple intestinal stimulants including oral laxatives, glycerine suppositories and chewing gum should be considered in all patients

LMWH, low molecular weight heparin. 5-HT₃, 5-hydroxytryptamine receptor

Audit

To ultimately be successful in improving patient care, individual centers must develop a detailed understanding of their own practice and how this impacts upon outcomes. The introduction of any change in care should be preceded by an assessment of practice in the form of a clinical audit. Once completed this audit will serve as a benchmark against which all subsequent iterations of care can be measured. In addition to assessing outcomes such audits serve as a valuable method of evaluating compliance with guidelines. The ERAS society, amongst others, has demonstrated that regular audit can improve guideline compliance and a persistent reduction in perioperative morbidity, length of stay and economic cost of care (68-71). There is emerging evidence that compliance with ERAS guidelines is associated with improved long-term survival after cancer surgery (72). It follows that failure to commit to a process of regular audit can result in a decline in adherence to guidelines and outcomes (73).

Future Perspective: the role of ERAS in maintaining oesophagectomies position in the treatment of oesophageal cancer

Oesophagectomy has historically been identified as the 'Gold Standard' treatment for oesophageal cancer. This is in spite of the realization that the operation has higher levels of Morbidity and Mortality than virtually any other oncologic operation. A recent comprehensive review of the short term contemporary outcomes of oesophageal resection have demonstrated that even in High volume centers; 59% of patients will have complications and 90 day mortality remains 4.5% (74).

Definitive and Neoadjuvant Chemoradiotherapy has demonstrated the ability to eliminate regional disease in a significant component of patients with adenocarcinoma and squamous cell cancer. Many centers are citing current levels of morbidity and mortality associated with the surgical treatment of oesophageal cancer to question its 'Gold Standard' designation. In addition, current

randomized studies in Europe specifically the SANO and ESOSTRATE trials are reviewing the potential to apply a 'surgery as needed' approach to patients with clinical complete responses.

Surgeons must look to improve outcomes associated with oesophagectomy to a point where mortality is rare and complications occur less frequently. The best infrastructure for this to occur is for oesophageal resections to be centralized to high volume centers. These centers should all initiate a standardized ERAS program and monitor its successful application and acceptance by the multidisciplinary team.

Clinical practice points:

- Oesophagectomy is a complex surgical procedure associated with high rates of morbidity and mortality
- Adoption of standardized ERAS guidelines in oesophageal surgery, but have the potential to improve clinical outcomes
- Such guidelines should reflect standard issues related to enhanced recovery as well as those unique to oesophageal resection
- The importance of a multidisciplinary team approach should be emphasized
- Regular audit of practice and outcomes is recommended

Research agenda:

- Further high quality clinical studies are however needed to clarify the specific role of ERAS guidelines within oesophagectomy and oesophageal surgery

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