Review

Patient optimization for gastrointestinal cancer surgery

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Background: Although surgical resection remains the central element in curative treatment of gastrointestinal cancer, increasing emphasis and resource has been focused on neoadjuvant or adjuvant therapy. Developments in these modalities have improved outcomes, but far less attention has been paid to improving oncological outcomes through optimization of perioperative care.

Methods: A narrative review is presented based on available and updated literature in English and the authors’ experience with enhanced recovery research.

Results: A range of perioperative factors (such as lifestyle, co-morbidity, anaemia, sarcopenia, medications, regional analgesia and minimal access surgery) are modifiable, and can be optimized to reduce short- and long-term morbidity and mortality, improve functional capacity and quality of life, and possibly improve oncological outcome. The effect on cancer-free and overall survival may be of equal magnitude to that achieved by many adjuvant oncological regimens. Modulation of core factors, such as nutritional status, systemic inflammation, and surgical and disease-mediated stress, probably influences the host’s immune surveillance and defence status both directly and through reduced postoperative morbidity.

Conclusion: A wider view on long-term effects of expanded or targeted enhanced recovery protocols is warranted.

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Introduction

Resection of the primary tumour remains the principal element of treatment and potential cure for the majority of solid epithelial malignancies. However, surgery itself is only one component of a complex series of assessments and interventions that make up the patient’s cancer journey. Beyond a histological diagnosis and radiological staging, patients may undergo neoadjuvant chemotherapy, resection of the primary lesion, adjuvant chemotherapy, surgical metastasectomy, palliative chemotherapy, palliative surgery and then be entered into phase I drug trials. Not all will pass down this complex route, particularly those with early-stage disease for whom surgical cure is readily achieved. For those with significant co-morbidity or advanced disease, the complexities and toxicities of their treatments mean that at various critical time points, without due attention to optimizing overall physiology, the opportunity to achieve the best oncological outcome may be compromised.

Most patients with cancer are managed by multi-professional and multidisciplinary teams (MDTs) involving surgeons, pathologists, radiologists, medical and clinical oncologists, cancer nurse specialists and audit support. Despite this, treatment plans will sometimes be agreed before a patient is assessed fully and discussions do not always consider the patient’s specific co-morbidities, nutritional status or cardiopulmonary reserve. A pragmatic view might be that the cancer treatment is necessary and that, beyond gross impairment, patients will survive. On the other hand, variation in outcomes suggests that variables outside routine MDT decision-making may be important and worthy of consideration. For example, there are surgeon and institution league tables that show considerable variation in 30-day morbidity and mortality for
standard cancer surgery\(^1\), and international comparisons of long-term cancer outcomes show considerable variation between countries\(^2\). The main discussion at a MDT meeting may focus on the small but significant benefit of adjuvant or neoadjuvant chemotherapy or radiotherapy. However, it is relevant to consider that effects of the same magnitude on long-term cancer recurrence and survival may result from postoperative morbidity, for example an anastomotic leak\(^3,4\) or a complication that delays significantly the start of adjuvant chemotherapy\(^5\). Equally, being elderly and undergoing an oesophagectomy is associated with reduced use of adjuvant therapy, increased 30-day mortality, reduced overall 5-year survival and reduced 5-year cancer-free survival\(^6\). It is against this background that the issue of patient optimization for cancer surgery needs to be considered.

The likelihood of metastatic spread depends on the balance between the metastatic potential of the tumour and host defences, of which cell-mediated immunity and natural killer cell function are particularly influential. These components provide immune surveillance, and are influenced by factors including nutritional status and systemic inflammation. This has led to a focus on modifiable perioperative factors that may tip the balance in favour of reduced cancer spread and recurrence.

Over the past 10 years there has been a revolution in the nature of perioperative care with the introduction of enhanced recovery after surgery (ERAS) protocols. These place particular emphasis on diminishing the stress response while maintaining homeostasis. Although it is clear that ERAS is safe and reduces complications\(^7\), there has been no systematic review that identifies specific elements of an ERAS pathway that positively and independently influence long-term cancer outcomes.

Short-term issues such as 30-day morbidity and mortality and the longer-term cancer-specific outcomes (local and systemic recurrence, disease-free survival) are important to both clinicians and patients. The purpose of this review is to explore how these two domains interact during the perioperative period, to determine when the surgeon and anaesthetist should influence one to improve the other, and suggest methods whereby this might be achieved.

Assessing the impact of disease and treatment

The disease

The spectrum of clinical presentation of malignant disease can range from small tumours that produce neither symptoms nor physiological dysfunction to disseminated disease precipitating anaemia, malnutrition and cachexia and the need for palliative surgical intervention. As such, disseminated cancer constitutes a risk factor for morbidity and mortality following surgery\(^8\).

Some tumours, even when still at a curable stage, may cause physiological derangements and malnutrition, increasing risk of complications and death. Usually, these are tumours obstructing the upper gastrointestinal (GI) or biliary tracts. Conversely, the effects of obstruction on local tissues that influence healing and the risk of anastomotic leak can be quite different. Grossly dilated large bowel caused by a obstructing tumour is a risk factor for anastomotic leak\(^9\), whereas an obstructed and dilated duct in an atrophic and chronically inflamed pancreatic gland is favourable in terms of risk of fistula formation or anastomotic breakdown\(^10\).

Neoadjuvant treatments

In some GI cancers, at a locoregional level, neoadjuvant chemotherapy (and/or radiotherapy) affects outcome by reducing tumour size, improving ease of resection and the likelihood of positive margins. Still, preoperative oncological therapy per se, or the choice of agent or radiation doses, may increase short-term morbidity or even mortality and in generating morbidity may adversely alter long-term outcome. These risks must be considered carefully for each patient. Apart from the consequences following bone marrow depression or gut mucosal sloughing, some organ-specific side-effects are well described. Rectal resections are associated with a higher risk of short-term morbidity following preoperative radiation therapy\(^11\), and oesophageal radiation induces local tissue healing problems\(^12\), as well as being toxic to the heart and lungs\(^13\). Preoperative chemotherapy for colorectal liver metastasis, mainly with irinotecan and oxaliplatin, may cause damage to the liver parenchyma, increasing both complication rates and critical volume for the future liver remnant\(^14\). Neoadjuvant chemotherapy for oesophageal cancer is associated with significant loss of skeletal muscle mass\(^15\), a reduction in quality of life and impaired physical activity levels\(^16\). Trials evaluating perioperative chemotherapy for resectable gastric adenocarcinomas have not identified an increase in postoperative complications\(^17\).

Surgical treatment

The nature and extent of surgery is often determined by the perceived stage of disease and frequently follows a standardized approach. However, it is important to recognize situations in which modifications are needed.
owing to deranged physiology that cannot be corrected promptly or because of unexpectedly severe side-effects following preoperative oncological treatments. Based on large databases, various case-mix or prognostic tools rank abdominal operations according to the magnitude of surgical trauma and hence complication risks\textsuperscript{18–20}. For abdominal cancer surgery, the risks are highest in oesophageal resection, major pancreatic and hepatic resection, and abdominoperineal resection\textsuperscript{18,20}.

Tools have been developed to take into account the factors above and the state of the patient’s resilience to trauma (see below). These tools, such as the Portsmouth modification of the Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity (P-POSSUM) and the modified form of Estimation of Physiologic Ability and Surgical Stress (mE-PASS)\textsuperscript{19,20}, attempt to encompass the disease, the planned oncological and surgical treatment, as well as patient factors. Although validated repeatedly against large outcome registries, such tools have yet to gain wide adoption for individuals. They are useful as case-mix calculators to allow comparison between larger groups treated differently or by different centres, to ensure comparable baseline risk.

Assessing the patient

General

Socioeconomic status, health literacy and ethnicity are associated with significant disparities in cancer-related outcome\textsuperscript{21,22}, and age is probably an independent risk factor\textsuperscript{23}. Daily smokers and abusers of alcohol have an increased risk of postoperative complications\textsuperscript{24,25}, and in both situations outcome has been improved following preoperative abstinence\textsuperscript{26–29}. Obesity is linked to ethnicity and socioeconomic status\textsuperscript{30,31}, but its role as an independent risk factor for surgical morbidity is not clear\textsuperscript{32–36}. Obesity is associated with increased conversion rate, operating time and postoperative morbidity in some laparoscopic colorectal surgery series, but does not affect surgical safety or oncological margins\textsuperscript{37}.

Co-morbidity

Ageing is characterized by changes in pulmonary and cardiovascular systems, metabolic disorders and reduced muscle mass. Co-morbidities associated with ageing include hypertension, hypercholesterolaemia, chronic obstructive airway disease and diabetes. Age per se is not an exclusion criterion for cancer surgery. The presence of coexisting diseases has a greater impact on postoperative morbidity and mortality than age alone.

In the context of traditional perioperative care, reduced total body protein mass (mainly skeletal muscle) has been linked to adverse surgical outcome\textsuperscript{38}. In an ERAS setting, when the stress of surgery is minimized, low body mass index (BMI) does not appear to be an independent risk factor for complications or prolonged length of stay, suggesting that baseline nutritional status may not be as critical in this setting as in more traditional perioperative care\textsuperscript{39}. The epidemic of obesity in Western societies means that the average BMI of patients is often in the overweight or obese range and this may hide underlying muscle wasting. A recent study has demonstrated that the presence of low muscle mass is predictive of complications and length of stay following colorectal surgery\textsuperscript{40}. Whether such muscle wasting relates to pre-existing co-morbidity or cancer-associated muscle loss is not known. Obesity is often present in patients with cancer, and the associated metabolic syndrome with insulin resistance leads to a constellation of pathological changes that in turn can impair recovery.

Pulmonary dysfunction such as chronic obstructive pulmonary disease has been associated with postoperative pulmonary complications in oesophageal cancer resection\textsuperscript{41}. Similarly, cardiac diseases and abnormalities of cardiac rhythm can influence the course of postoperative events\textsuperscript{42}. Anxiety and depression are common features in patients with cancer, and result in poorer postoperative healing and recovery\textsuperscript{43}.

Optimization

Patient information and counselling

Personal counselling addressing core items of the perioperative pathway may reduce discomfort and anxiety and improve recovery\textsuperscript{44,45}, and is generally recommended in ERAS protocols\textsuperscript{46,47}.

Obstructive jaundice

Jaundice is associated with immunosuppression and gut mucosal dysfunction. A high bilirubin level in combination with low albumin and raised creatinine concentrations is strongly predictive of adverse outcome following major biliary tract surgery\textsuperscript{48}. Although researched extensively\textsuperscript{49–53}, the effects of preoperative biliary drainage on outcome have been inconsistent, suggesting neither harm nor benefit. The most recent of the large randomized trials concluded that patients with serum bilirubin concentrations below 250 µmol/l should not undergo routine preoperative biliary drainage\textsuperscript{54}.
Anaemia

Anaemia is generally considered a risk factor for surgery, associated with more advanced disease stage, higher mortality and morbidity rates, and longer hospital stay. Although extensive blood loss during surgery must be replaced, transfusion of allogeneic red blood cells is associated with earlier cancer recurrence and poorer long-term survival. Establishing a causal relationship is impossible from observational studies alone, as intraoperative difficulties and postoperative complications are confounders. The concept of an immunosuppressive effect (such as a reduction in T helper cell and natural killer cell count, and a reduction in cytokine production including interferon γ) from blood transfusion affecting the host’s immunological surveillance is well accepted. Interestingly, transfusions may have a greater adverse effect when given after surgery than when given during the operation, and neither autologous transfusion (self-donation) nor leucocyte reduction of transfused blood changes recurrence rates or survival.

The consequence of preoperative correction of malignant or iron-deficiency anaemia is uncertain. For patients with colorectal cancer, preoperative oral iron therapy has been submitted to randomized study, reducing transfusion requirements and increasing haemoglobin and ferritin levels. More evidence is needed to establish a role for intravenous iron therapy and/or erythropoietin in the preoperative and perioperative setting.

Cardiovascular and respiratory insufficiency

Cardiac complications are a major source of intraoperative and postoperative morbidity and mortality. The literature on cardiac adverse events has evolved from prediction to optimization through intervention. Careful risk stratification is fundamental. In general, risk factors include age, congestive cardiac failure, BMI greater than 30 kg/m², cardiovascular disease, hypertension, emergency surgery, duration of surgery and units of blood transfused. More specific clinical risk indices exist that have high capability for discriminating patients at risk of major cardiac events and assist in decision-making with preoperative optimization.

Pre-emptive beta-blockade has received much attention. Although repeatedly shown to reduce the risk of perioperative cardiac complications, the risk of serious stroke was increased significantly in some trials. Well regulated preoperative beta-blockade has been advocated to be safer than perioperative initiation. Careful selection and dosage is crucial to achieve a net reduction in postoperative complications. Beta-blockers should not be used routinely for perioperative treatment of patients undergoing non-cardiac surgery unless they are being taken for clinically indicated reasons, such as heart failure, coronary artery disease or previous myocardial infarction.

Statin use has been associated with a decreased mortality rate after non-cardiac surgery, probably owing to anti-inflammatory and plaque-stabilizing effects.

Aspirin therapy for the purposes of primary and secondary prevention of cardiovascular disease should be continued during the perioperative period in all patients with coronary artery, cerebrovascular or peripheral vascular disease.

Assessment of pulmonary function is a valid indicator of postoperative pulmonary complications. A forced expiratory volume in 1 s of less than 70 per cent of predicted value requires assessment and treatment. Preoperative respiratory muscle training in patients undergoing thoracic surgery has been shown to prevent postoperative pulmonary complications by increasing inspiratory and expiratory muscle strength.

Renal failure

Chronic kidney disease, even in relatively early stages, is associated with an increased rate of postoperative infection. Patients should be kept adequately hydrated, and further hazards to renal function (such as antibiotics or analgesics) assessed and modified.

Cirrhosis and liver failure

The liver hosts the largest resident macrophage population (Kupffer cells) in the body and liver failure is associated with systemic immunosuppression. Cirrhosis in non-hepatic surgery is associated with increased complications and mortality. This risk increases significantly in both major surgery and emergency surgery, and in the presence of portal hypertension. Morbidity and mortality rates correlate with the degree of cirrhosis as measured by standard models, including the preoperative Model for End-stage Liver Disease (MELD) and Child–Turcotte–Pugh (CTP) grade. On the other hand, the majority of minor and intermediate procedures can be undertaken relatively safely in patients with low MELD score or CTP grade. The overall benefit of preoperative transjugular intrahepatic portosystemic shunt in patients with portal hypertension remains unclear.

Diabetes

Pre-existing diabetes mellitus confers an increased risk of postoperative morbidity and mortality in colorectal
surgery\textsuperscript{81,82}. Although anastomotic leak rates are not increased, mortality rates after a leak are substantially increased in diabetics\textsuperscript{81}. There appears to be an association between morbidity and preoperative hyperglycaemia\textsuperscript{81}, indicating that these patients require careful assessment. The effect of rigid glycaemic control before surgery is, however, less clear\textsuperscript{81,82}.

### Malnutrition and cachexia/sarcopenia

Poor nutritional status is associated with worse outcome after major surgery. Traditionally, patients with gross cancer cachexia requiring surgery have received 10–14 days of preoperative parenteral or enteral nutrition\textsuperscript{83}. It is relevant to consider that patients with gross cachexia may have more advanced disease than previously assumed and should be restaged carefully as heroic attempts at resection of their primary disease may be unsuccessful. A more conservative approach (such as luminal stenting) may provide a better overall outcome.

### Medications

#### Morphine

Recent epidemiological studies have examined the impact of perioperative anaesthetic or analgesic agents on long-term survival after surgery for various types of malignancy including rectal\textsuperscript{84} and prostate\textsuperscript{85} cancer. Some studies suggest a reduced recurrence with regional anaesthesia/reduced use of opioids\textsuperscript{84,85}, whereas others do not\textsuperscript{86}. Potential mechanisms include reduced stress response–immunosuppression with regional anaesthesia or a direct effect of opioids on tumour growth and metastasis. The effect of morphine on tumour growth is controversial, with both growth-promoting and growth-inhibiting effects being observed. Evidence suggests that morphine can affect proliferation and migration of tumour cells as well as angiogenesis. Various signalling pathways are implicated, including co-activation of the epidermal growth factor receptor by the \(\mu\)-opioid receptor\textsuperscript{87} and overexpression of the \(\mu\)-opioid receptor in lung cancer promoting Akt and mTOR activation, tumour growth and metastasis\textsuperscript{88}. The potential for suppression of the immune system by morphine is an additional issue.

#### Anticoagulants

A number of basic science and clinical studies have suggested that oral anticoagulants may improve the survival of patients with cancer through an antitumour effect in addition to their antithrombotic effect. Existing evidence does not, however, support a mortality benefit from oral anticoagulation in patients with cancer. There is an increased risk of bleeding\textsuperscript{89}.

### Non-steroidal anti-inflammatory drugs

Prostanoids have long been recognized as potential tumour autocrine growth factors. There is increasing epidemiological evidence that aspirin can reduce cancer prevalence and recurrence\textsuperscript{90}. There is evidence from animal models that a single perioperative dose of the cyclo-oxygenase 2 inhibitor celecoxib can inhibit chronic morphine-induced promotion of angiogenesis, tumour growth, metastasis and mortality\textsuperscript{91}. The influence of perioperative use of non-steroidal anti-inflammatory drugs on long-term outcomes of patients with cancer is not known.

### Improving functional reserve

#### Physical prehabilitation

Subpopulations of patients with cancer with pre-existing dementia, low preoperative albumin level, poor exercise tolerance and frailty remain especially vulnerable to postoperative complications. Cognitive impairment delays return to baseline performance. A decline in physical activity as a result of ageing and cancer represents a significant risk that can be attenuated by physical exercise as a preventative intervention. Poor preoperative fitness scores are associated with increased mortality, longer postoperative hospital stay and increased complications\textsuperscript{92,93}. Most physiotherapy and dietary interventions aimed to promote recovery are carried out after surgery (rehabilitation) when patients are fatigued and emotionally vulnerable, and thus unable to comply with intense recovery programmes. It seems plausible that optimal physical functioning before surgery (prehabilitation) might result in better postoperative outcome.

Aerobic and muscular strength training in elderly patients has been shown to increase endurance capacity, reduce weight gain, and improve muscle strength and range of motion in a number of joints\textsuperscript{94}. Although constraints to proceeding with surgery limit the time for initiation of preoperative physical activity, 3 weeks may be sufficient to obtain a moderate gain in aerobic and muscle strength reserve. Studies on prehabilitation before thoracic and GI cancer surgery showed an increase in postoperative functional exercise capacity, decreased postoperative complications and shorter hospital stay\textsuperscript{95,96}. It appears that patients who are deconditioned require only moderate physical training to obtain an increase in functional capacity\textsuperscript{97,98}. The addition of nutritional supplements to
physical training has been shown to enhance further physiological reserve and impacts positively on postoperative functional exercise capacity.

Whether such preoperative regimens produce long-term benefits is untested. However, in the post-treatment phase, an increase in physical activity has been associated with improved disease-specific and overall survival, regardless of prediagnosis activity levels.

Nutritional therapy

For adequately nourished patients submitted to routine surgery within an ERAS programme there should be no requirement for artificial nutritional support as return of GI function is a key priority, and the patient should be able to eat and drink within 24 h of (non-oesophageal) surgery with a low risk of prolonged gut dysfunction. It has been shown that combining preoperative oral carbohydrate treatment, epidural analgesia and early enteral nutrition balances nitrogen equilibrium with almost complete abrogation of the metabolic response to injury. For patients who are at significant risk of malnutrition (for example those undergoing oesophagectomy), the use of cancer-specific enteral feeds may be justified to maintain lean body mass.

Immunotherapy/immunonutrition

Different combinations of diets containing components aimed to enhance immune function in surgical patients have been studied. These diets, often termed ‘immunonutrition’, usually contain combinations of arginine, glutamine, omega-3 fatty acids and nucleotides. Several meta-analyses have been published on their clinical effectiveness. Most studies have shown clinical benefit by reducing complications and shortening length of stay in the context of traditional perioperative care, but the results are heterogeneous. There is evidence to suggest that such treatment is most effective in malnourished patients, but there are no trials in an ERAS setting when stress is minimized.

Carbohydrate loading

To avoid patients undergoing surgery in an unfed state, complex carbohydrates can safely be administered orally 2–3 h before induction of anaesthesia. Carbohydrate treatment like this has been shown to attenuate protein and nitrogen loss, and decrease postoperative insulin resistance. It reduces the sense of hunger, thirst and anxiety. Gut function immediately after colorectal surgery may be improved, as well as preservation of skeletal muscle mass. Results are not uniform, however, and further data are needed, especially in diabetic patients.

Modifying the immunological effects of cancer and surgery

Abnormal postoperative immune function increases risks of postoperative infection and metastasis of tumour cells. Therefore, maintaining normal immune function, particularly cell-mediated immunity, in the perioperative period may affect long-term oncological results. Compared with traditional open surgery, laparoscopic operations have been shown to decrease the stress response, to result in lower levels of interleukin (IL) 6 and C-reactive protein, and to be associated with better preservation of immune competence as measured by human leucocyte antigen expression on monocytes. Whether minimizing the effect on cell-mediated immunity produces true oncological advantage has yet to be proven, although extrapolations have been made from studies in which a survival advantage was identified in stage III colorectal cancer treated in the laparoscopic arm. No other randomized trials have identified a similar survival advantage with laparoscopy and critics have raised concerns that a disparity in adjuvant therapy use may have produced apparent advantage in the laparoscopic arm. However, others suggest that the transition to adjuvant chemotherapy was facilitated by more prompt recovery in the laparoscopic arm. There are no additional data that provide a clear explanation.

It is also relevant to consider the effect of postoperative morbidity on immune function and outcome, and the potential systemic immunosuppressive effect of sepsis and inflammation. Infectious complications are associated with an excessive and persisting synthesis and release of proinflammatory cytokines. Persisting high levels of IL-6 may decrease the number, maturation and activity of cytotoxic T lymphocytes, natural killer and other immunocompetent circulating cells, such as dendritic antigen-presenting cells. Low plasma levels of these cells and high levels of IL-6 in the late postoperative period are correlated with poor prognosis in colorectal cancer.

It is clear that all efforts should be made to reduce morbidity to an absolute minimum, and a combination of protocol-driven perioperative care and minimally invasive surgery may permit this. Further studies are needed to determine the relative contributions of both minor (such as wound infection) and major (for example reoperation, anastomotic leak and unplanned admission to the intensive care unit) morbidities on cancer-specific, disease-free and overall survival.
Attenuating the challenge to the patient

Surgical access

Laparoscopy attenuates the stress response, causes less tissue damage and fewer adhesions, reduces pain and produces a shorter time to functional recovery, compared with open surgery. The role of laparoscopy has been scrutinized most closely in colorectal cancer surgery, although its application for other GI malignancies is evolving.

The safety and advantages of laparoscopic colectomy for cancer have been much debated and several randomized clinical trials have clarified these issues. When performed by surgeons with adequate experience and training, it is clear that laparoscopic colorectal surgery dramatically improves functional outcome following bowel resection. However, open abdominal surgery with modern enhanced recovery pathways has also produced remarkable reductions in time to functional recovery and length of stay. Nevertheless, there is still a significant difference between open and laparoscopic surgery, and this is evident in both observational series and more recent randomized trials. Failure to identify differences within ERAS care between open and laparoscopic colorectal resection in earlier comparative studies is likely to relate to the steep learning curve associated with laparoscopic resection and a broad variation in what has been regarded as ‘laparoscopic’.

The recent LAparoscopy and/or FAst track multimodal management versus standard care (LAFA) trial included 400 patients from nine hospitals. The study randomized patients between laparoscopic or open surgery, and also between ERAS and ‘standard’ care. It demonstrated that laparoscopy was the only predictive factor with an effect on hospital stay and morbidity. Within the non-ERAS group six of the predefined 15 ERAS elements were applied routinely, as it was felt unethical to leave these out.

The role of laparoscopy in the management of rectal cancer has been assessed in the COlorectal cancer Laparoscopic or Open Resection (CoLOR) II trial, with 2:1 randomization to laparoscopy or open surgery. Although operating times were longer, blood loss, hospital stay and time to first bowel movement were significantly improved in the laparoscopic group, with no difference in the anastomotic leak rate, overall morbidity or mortality. Similar studies are being conducted in the US (American College of Surgeons Oncology Group (ACOSOG) Z6051) and in Japan (Japan Clinical Oncology Group (JCOG) 0404 trial). Trials that include thousands of patients are likely to be required to determine the long-term oncological effects of laparoscopy–ERAS.

Enhanced recovery pathways

ERAS protocols designate a multimodal and evidence-based protocol-driven approach to perioperative care that aims to attenuate the surgical stress response and in consequence reduce rates of complications, enhance recovery and reduce length of stay. As a by-product, cost savings from successful protocols are substantial. A number of such protocols have been published, varying in comprehensiveness, numbers of elements employed routinely and the degree of validation. Until recently, the surgical community largely ignored this evidence, although ERAS protocols are being used increasingly.

The benefits of introducing ERAS programmes have been demonstrated consistently, particularly in colorectal surgery, but the impact on outcomes other than time to recovery has been modest. It should be noted that measuring direct improvements after successful protocol implementation is notoriously difficult. For observational cohort series, bias is introduced from the Hawthorne effect (patients in trials do better). For experimentation, finding a truly ‘pure’ control group, which has received no part of an enhanced recovery protocol as standard care, is practically impossible. It is likely that, if such a group existed, ethical concerns would preclude their inclusion in an experimental design. The true effect of these comprehensive protocols must be shown as benefits from each and every protocol item (where feasible) or from large, multi-institutional and consecutive registries where compliance and outcome are carefully recorded.

Although conventional ERAS–laparoscopic pathways have focused on optimizing short-term recovery, it is now evident that current elements of ERAS may need to be modified and expanded to take account of the growing literature that identifies the many factors that may influence long-term oncological outcomes. The challenge will be to design and conduct trials with sufficient sample size to prove the value of each intervention.

Disclosure

The authors declare no conflict of interest.

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