Review

Contemporary perioperative care strategies

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Background: **Historically, the preoperative and postoperative care of patients with gastrointestinal cancer was provided by surgeons. Contemporary perioperative care is a truly multidisciplinary endeavour with implications for cancer-specific outcomes.**

Methods: **A literature review was performed querying PubMed and the Cochrane Library for articles published between 1966 to 2012 on specific perioperative interventions with the potential to improve the outcomes of surgical oncology patients. Keywords used were: fast-track, enhanced recovery, accelerated rehabilitation, multimodal and perioperative care. Specific interventions included normothermia, hyperoxygenation, surgical-site infection, skin preparation, transfusion, non-steroidal anti-inflammatory drugs, thromboembolism and antibiotic prophylaxis, laparoscopy, radiotherapy, perioperative steroids and monoclonal antibodies. Included articles had to be randomized controlled trials, prospective or nationwide series, or systematic reviews/meta-analyses, published in English, French or German.**

Results: **Important elements of modern perioperative care that improve recovery of patients and outcomes in surgical oncology include accelerated recovery pathways, thromboembolism and antibiotic prophylaxis, hyperoxygenation, maintenance of normothermia, avoidance of blood transfusion and cautious use of non-steroidal anti-inflammatory drugs, promotion of laparoscopic surgery, chlorhexidine–alcohol skin preparation and multidisciplinary meetings to determine multimodal therapy.**

Conclusion: **Multidisciplinary management of perioperative patient care has improved outcomes.**

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Introduction

Significant efforts to improve the outcomes of patients with gastrointestinal cancer have produced impressive results with higher survival statistics now than ever[1,2]. Contemporary treatment strategies rely on multidisciplinary care teams, channelling individual expertise through a unified healthcare process. Similarly, perioperative care has evolved from a surgical and nursing team to a broad interdisciplinary cooperative endeavour. Prompt recovery is in the interest of patients with cancer, whether they require completion of adjuvant therapy, are returning to work, or have a short life expectancy. In this context, surgical leadership has proven invaluable in establishing perioperative care standards.

The purpose of this review is to report on current advances in perioperative care, to assess whether they translate into improved outcomes, and to discuss their relative contribution. This is particularly important in an era of enhanced scrutiny of healthcare practice, constrained resources and rising medical needs. This article has a focus on gastrointestinal cancer, as this is by far the most studied disease entity in the field.

Methods

The literature search for this narrative review was based on a synthesis of the many specific perioperative interventions and care strategies retrieved by using systematic reviews where appropriate, rather than multiple references of original works. In addition, the Cochrane Library and MEDLINE/PubMed were searched (January 1966 to March 2012) using the following keywords: fast-track, enhanced recovery, accelerated rehabilitation, multimodal

and perioperative care. Specific interventions were queried, including normothermia, hyperoxygenation, surgical-site infection (SSI), skin preparation, transfusion, non-steroidal anti-inflammatory drugs (NSAIDs), thromboembolism and antibiotic prophylaxis, laparoscopy, radiotherapy, perioperative steroids and monoclonal antibodies.

Priority was given to pragmatic perioperative interventions that have the potential to improve the outcomes of oncology patients under the care of surgeons, as opposed to unproven trends. Furthermore, a selection of topics was made owing to length limitations. Major themes, such as perioperative nutrition, that may warrant a dedicated review were not included.

Inclusion criteria were randomized controlled trials (RCTs), prospective or nationwide series, and systematic reviews/meta-analyses. Exclusion criteria were retrospective series, papers published in languages other than English, French or German, and papers excluding cancer.

Accelerated recovery protocols

A recent meta-analysis[3], including six RCTs, found that enhanced recovery pathways halved 30-day morbidity and reduced length of hospital stay by 2 days. These results were demonstrated across different healthcare systems, including Switzerland[4], the UK[5–7], the Czech Republic[8], the Netherlands[9] and the USA[10]. Colorectal resection was the commonest procedure studied because it is associated with a quarter of all complications[11,12]. Encouraging results were observed for other surgical procedures, together with improved patient satisfaction and effectiveness of care[3,13]. Nonetheless, the uptake of standardized care has been low, with less than one-third of institutions implementing such programmes in Europe and North America[14–16]. Meanwhile, there is increasing pressure on healthcare providers and institutions owing to a shortage of qualified personnel and resources, compounded by rising costs and demand. In this context, specific protocols may provide some relief by optimizing resources[3]. The implementation of diagnosis-related group compensation schemes and withholding of payments for excessive complications may encourage standardized perioperative care in some countries[17–19].

Information about the care process

Continuous information about the care process is paramount, starting in the preoperative clinic and extending to postdischarge management[20–23]. Written information about the planned procedure, the care process and the related expectations should be provided in plain language, including preset discharge criteria and postdischarge contact/follow-up arrangements. Appropriate discharge planning starts at the preoperative clinic where patient-specific needs that may delay discharge are identified and accounted for (for example, preoperative stoma education). Typical standardized discharge criteria include: the ability to tolerate three meals in a row, satisfactory oral analgesia (pain score of less than 4 on a visual analogue scale), passage of flatus or stool, and a patient agreeable to discharge with adequate social support. Ultimately, the patient, relatives and all healthcare providers involved in an episode of care should share a common understanding of the expected care pathway.

Preservation of gastrointestinal function

Preservation of gastrointestinal function is crucial to early recovery. Liquids are safe up to 2 h before surgery, including tea or coffee with milk, but solid food should be avoided for 6 h before elective surgery. These European guidelines also apply to obese or diabetic patients, and to pregnant women not in labour[24,25]. Administration of a carbohydrate solution the evening before surgery and for up to 2 h before surgery may reduce postoperative insulin resistance and catabolism[26–28], although the specific type (or constituents) may not matter. Prevention of postoperative nausea and vomiting can be achieved effectively by a multimodal strategy, including propofol-based total intravenous anaesthesia and a combination of antiemetic drugs acting at different receptor sites (dexamethasone, antidopaminergic drugs and serotonin receptor antagonists)[29,30]. Hence, liquids can be offered immediately after surgery without restriction on progression to diet. Early enteral feeding has been shown in meta-analysis to be effective in hastening recovery of gastrointestinal function and in reducing catabolism and morbidity[31–33].

Postoperative ileus is a physiological response to major surgery resulting in discomfort, morbidity and protracted hospital stay. It was estimated that in 2000 ileus in the USA was responsible for direct healthcare costs exceeding US $1 billion[34,35]. Several randomized trials have shown that the following techniques reduce the duration of ileus: avoidance of routine nasogastric intubation, prevention of fluid excess, laparoscopy instead of open surgery, thoracic epidural analgesia, intravenous and incisional local anaesthetics, peripheral opioid antagonists, laxatives and chewing gum[36]. Adherence to these techniques reduced the duration of ileus following colorectal resection to 24–48 h in over 90 per cent of patients, compared with 96–120 h in traditional care[7,22,37]. Of the many drugs tried (metoclopramide, erythromycin, neostigmine, propanolol,

cisapride, methylnaltrexone), a peripheral opioid antagonist (alvimopan) was found to be cost-effective in the presence of an intestinal anastomosis[38–41].

Fluids and electrolytes

Minimization of fluid and electrolyte imbalance maintains homeostasis and promotes recovery. Unnecessary fluid and electrolyte shifts may be prevented by avoiding bowel preparation. A number of RCTs and meta-analyses including up to 5805 patients concluded that orally delivered mechanical bowel preparation (MBP) had no influence on the rate of wound infection (9·6 per cent *versus* 8·5 per cent with no MBP; odds ratio (OR) 1·16, 95 per cent confidence interval (c.i.) 0·95 to 1·42), leak of colonic anastomosis (3·0 per cent *versus* 3·5 per cent with no MBP; OR 0·85, 0·58 to 1·26) and leak of low rectal anastomosis (8·8 per cent *versus* 10·3 per cent with no MBP; OR 0·88, 0·55 to 1·40)[42]. Similar results were reported when MBP was compared with enema. Moreover, replacement of fluid and electrolyte losses suffered during MBP contributes to intraoperative fluid overload. Preoperative tattooing of small intraluminal lesions may minimize the need for intraoperative colonoscopy, whereas the ease of bowel handling desired by many laparoscopic surgeons may be obtained with an enema.

Meta-analysis demonstrated that prevention of fluid excess reduced the morbidity of major abdominal surgery by up to two-thirds and consequently hospital length of stay[43–46]. Current UK and US recommendations for intraoperative goal-directed administration of fluid boluses using transoesophageal monitoring of the cardiac stroke volume may be outdated[47,48]. Recently, RCTs have found that maximization of stroke volume (as opposed to optimization) added no additional benefits[49], whereas goal-directed fluid therapy using crystalloid instead of colloid boluses necessitated reduced total intravenous fluid and was associated with less morbidity[50]. For practical purposes, restriction of perioperative fluids with or without monitored or goal-directed administration aiming at zero weight gain reduces postoperative morbidity[4,51].

Proactive analgesia

Active pain control and sound collaboration with the anaesthetist are key to postoperative care. Options include thoracic epidurals[52–55], wound catheters, local anaesthetics, total intravenous anaesthesia, short-acting volatile anaesthetics, opioids and muscle relaxants. For laparoscopic cases, patient-controlled analgesia is as effective as an epidural, with no additional side-effects when replaced by oral analgesia within 72 h[56–59]. Although there appears to be some physiological benefit to a transverse abdominal incision compared with a midline incision, meta-analyses and large randomized trials have provided no clear support in favour of a particular incision[60,61]. Conversely, meta-analyses of RCTs have established consistent benefits for a laparoscopic approach compared with laparotomy: earlier resumption of a normal diet, reduced blood loss[62,63], halved short- and long-term morbidity[36,64–69], and decreased postoperative pain and opioid use. Those benefits translated into a reduction of hospital stay of about 2 days, 30 per cent less skilled nursing facility utilization[70], and improved quality of life and recovery[62,71–74]. Oncological outcomes for gastric, colonic and rectal cancer surgery did not differ[68,75–80].

Pre-emptive multimodal non-opioid analgesia may be initiated with paracetamol/acetaminophen[52] and gabapentin[81]; the latter may reduce opioid consumption and related adverse effects (nausea/vomiting, urinary retention) at the cost of increased sedation and dizziness.

NSAIDs should be used with caution, owing to a possible association with an increased risk of anastomotic leak[82]. Perioperative administration of intravenous lidocaine, dexamethasone or ketamine reduces pain scores and opioid consumption, time to return of bowel function and nausea/vomiting[29,30,83,84]. Recently, transversus abdominis plane/rectus sheath local anaesthetic blocks have been proposed as a further component to multimodal analgesia: a meta-analysis[85] and subsequent randomized trials[86–91] showed a consistent improvement in postoperative pain scores and a reduction in opioid requirements at 24 and 48 h, translating into less postoperative sedation[88,91]. A further randomized trial[90] suggested equivalent pain control when an epidural infusion was compared with transversus abdominis plane block bolusing. Finally, two randomized trials showed transversus abdominis plane blocks to be superior to patient-controlled analgesia in terms of pain control for open surgery[87,88].

Patient mobility and independence

Efforts to promote the patient's autonomy are crucial, including avoidance or early removal of intravenous lines, drains and urinary catheter. Enforced mobilization, breathing exercises and preservation of the sleep pattern with night-time sedation as needed are important.

Routine use of abdominal drainage[92,93] and nasogastric tubes[94] increases gastrointestinal and infectious morbidity, with no benefit for the patient. Abdominal drains are used in the presence of an abscess or gross intra-abdominal contamination, or selectively for low colorectal anastomosis

if needed. Importantly, the presence of an epidural does not prevent removal of a urinary catheter on the first postoperative day after abdominal or thoracic procedures. Recatheterization rates of 10 per cent were found consistently in randomized trials investigating early removal of bladder catheters, whereas urinary tract infections and length of stay were significantly reduced[95,96]. Suprapubic bladder drainage is an often forgotten means of reducing infectious morbidity[97].

Example of a standardized protocol

Starting on the first postoperative day, meals are taken with free access to non-carbonated drinks, and five walks outside the patient's room are requested. Promotion of autonomy saved a mean of 83 min per day of nursing time over a typical 5-day stay after open colectomy for cancer (*Fig. 1*). Others have reported similar findings[22,98], with early restoration of organ function translating into improved autonomy, quicker recovery and faster discharge without a major impact on readmissions[99–103], the burden on relatives, or referrals to a skilled nursing facility[104]. Interestingly, patients discharged earlier seem to have fewer readmissions than those who stay longer[105–107], whereas non-adherence to standardized protocols may be associated with increased readmissions[99]. Overall, however, complications requiring readmission had similar outcomes and duration as those identified in hospital[99,106].

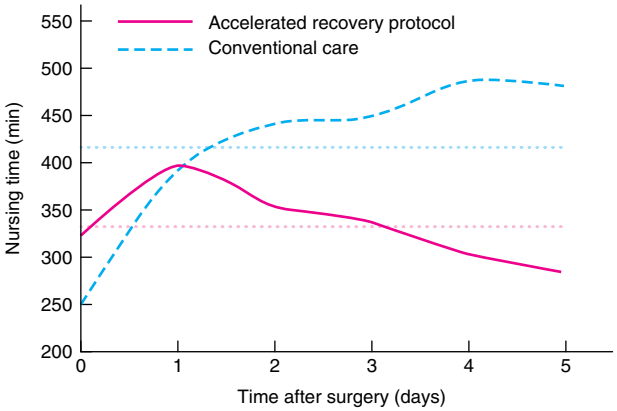

Fig. 1 Cumulative patient care-related nursing activities measured in minutes per day per patient for 172 consecutive patients undergoing open colectomy in a single institution (Kantonsspital St. Gallen, St. Gallen, Switzerland). Nursing activities in both the accelerated recovery protocol and conventional care were measured prospectively: mobility, personal care, clothing, nutritional support, toilet care, monitoring/support of vital parameters, administration, communication support, medication, venepuncture, reporting/interprofessional, personal support and nursing care. The dotted lines show the mean nursing time per patient per day: 333·3 min for the accelerated recovery protocol and 416·1 min for conventional care. Thus, adherence to the protocol saved 83 min of nursing time per day over a typical 5-day hospital stay for colectomy, while patient satisfaction ratings remained high and readmission rates low (T. Clerici *et al.*, unpublished results)

Laparoscopic surgery

Laparoscopic excision of colorectal cancer has comparable oncological outcomes, with improved perioperative recovery, quality of life, adhesion and incisional hernia risk, whereas societal costs are equal or improved, in comparison with open resection. This was demonstrated in the context of conventional care by multicentre randomized trials, nationwide cohort series and meta-analysis[3,68–70,76,77,80,108–115]. The combination of laparoscopy and standardized perioperative protocols has been investigated in three randomized and three controlled trials[3]. The larger trials, in particular a multicentre randomized Dutch trial, showed a 2-day reduction in hospital stay with accelerated programmes whether the procedure was open or laparoscopic. On multivariable analysis, laparoscopy was the single independent factor to reduce both morbidity and hospital stay[9]. Physiological studies showed faster recovery of colonic transit time with optimized care and/or laparoscopy, whereas gastric emptying time remained unchanged[116]. Lastly, a detailed investigation of which protocol elements were independently associated with early recovery found that female sex, laparoscopy, a normal diet and enforced mobilization on postoperative days 1–3 determined earlier recovery[32].

Thromboembolism prophylaxis

Venous thromboembolism (VTE) represents one of the most common preventable causes of death in patients with cancer undergoing surgery[117]. The incidence of VTE increases to nearly 10 per cent within 2 years of a cancer diagnosis, with recent surgery, advanced malignancy, chemotherapy and hospital admission being additional risk factors. The risk of recurrent VTE and readmission is also threefold higher than in the absence of malignancy[118]. Most institutions support in-hospital VTE prophylaxis based on updated evidence-based guidelines[118–120]. These guidelines also address perioperative bridging for patients receiving vitamin K antagonist or antiplatelet therapy, taking into account renal function and refining risk stratification. An important point emerging in a 2009 Cochrane review[117], and included in the current guidelines of the European Society for Medical Oncology[118], proposes

extended VTE prophylaxis with low molecular weight heparin for 30 days, that is beyond hospital discharge. Adherence to this recommendation may decrease the 3-month rate of VTE (14·3 *versus* 6·1 per cent; OR 0·41, 95 per cent c.i. 0·26 to 0·63), with no increase in the risk of bleeding at a comparatively low number needed to treat of 12. The evidence in favour of outpatient VTE prophylaxis beyond 30 days is weaker. A marginal survival benefit at 2 years (risk reduction 0·92, 95 per cent c.i. 0·88 to 0·97) was found. The risk of VTE remained halved, and no increase in minor or major bleeding was found in meta-analysis[121].

Antibiotic prophylaxis and skin preparation

SSIs are the second most common cause of nosocomial infections, as about 20 per cent of patients undergoing abdominal operations develop a SSI[122]. Adherence to recommended antibiotic prophylaxis reduces the rate of SSI by more than two-thirds in clean-contaminated surgery (relative risk 0·3, 95 per cent c.i. 0·22 to 0·41)[123]. For bowel surgery, cephalosporins and metronidazole are used widely against commensal aerobes and anaerobes, ciprofloxacin being a common alternative to cephalosporin if a history of severe allergy to penicillin is present. Antibiotics should be administered 30–60 min before incision for a bactericidal concentration to be reached when the skin barrier is breached. Just missing the appropriate antibiotic administration window may double the rate of SSI[124]. As distractions are common during this opportunity window, inclusion of timely antibiotic administration has been added to surgical checklists. Redosing of antibiotic prophylaxis in procedures longer than 4 h to reflect pharmacological half-life or when major blood loss occurs is recommended. Conversely, multiple doses of prophylactic antibiotics following procedure completion may not be useful and may risk pseudomembranous colitis[123]. In the context of colorectal surgery, the combination of oral and intravenous antibiotic prophylaxis may be more effective than intravenous antibiotics alone (risk reduction 0·55, 95 per cent c.i. 0·41 to 0·74)[123].

Use of hair clippers instead of shavers to remove body hair shortly before skin incision[125], as well as a preference for alcohol rubs rather than aqueous scrubbing, are further established means to reduce SSI[126]. A multicentre randomized trial demonstrated the superiority of chlorhexidine–alcohol over skin cleansing with povidone–iodine by halving the rate of superficial and deep incisional infections[127]. If this is true, the cost-effectiveness would be substantial[128]. Alcohol-based skin preparations, however, carry a risk of fire when used in conjunction with electrodissection close to a source of high oxygen concentration.

Perioperative oxygen supplementation

Preclinical studies have shown that high oxygen tension in subcutaneous tissue enhances the oxidative killing of pathogens by neutrophils[129] and promotes wound healing in animals[130]. Although antibiotic prophylaxis, perioperative normothermia, normoxia and normoglycaemia have proved to be effective strategies in reducing SSIs, the role of perioperative hyperoxygenation (defined as a perioperative oxygen concentration of 80 per cent) remains controversial in human studies[131–134]. Several randomized trials of hyperoxygenation have shown a significant reduction in the incidence of SSI in colorectal surgery[135–137], but these results have not been confirmed in other studies, mostly including the whole range of surgical procedures[138–141]. A recent meta-analysis of five randomized trials including a total of 3001 patients undergoing abdominal procedures showed a relative risk reduction of 25·3 (95 per cent c.i. 8·1 to 40·1) per cent and an absolute risk reduction of 3 (1·1 to 5·3) per cent for a number needed to treat of 33[142]. No adverse effects of perioperative oxygen supplementation were reported. The beneficial effect of hyperoxygenation was maximized in patients with colorectal cancer, and was confirmed in a second meta-analysis which showed a halving of SSI in these patients (OR 0·48, 95 per cent c.i. 0·32 to 0·71)[143]. Therefore, perioperative supplemental oxygen therapy should be used routinely as a non-invasive and inexpensive intervention, particularly in clean-contaminated and colorectal surgery, where intraoperative exposure to a significant bacterial load is the rule.

Perioperative normothermia

Hypothermia in surgical patients remains a common problem despite recognition of its deleterious physiological effects and the availability of straightforward techniques to reduce its occurrence. Both general and epidural/neuraxial anaesthesia impair thermoregulation in patients exposed to cold air and who are unable to counterbalance core heat loss[144]. Mild hypothermia (34–36°) occurs in about 30–70 per cent of surgical patients[145,146], accounting for increased morbidity, hospital length of stay and costs[147]. Coagulopathy induced by hypothermia leads to impairment of thrombocyte activity[148] and inactivation of coagulation factors[149], all of which increase blood loss and thus the requirement for allogeneic blood transfusion (ABT)[150]. Of note, most routine coagulation tests obtained during surgery are performed at 37°C, irrespective of

the patient's actual core temperature; their results may thus not reflect the ongoing coagulopathy. A meta-analysis including 24 randomized trials concluded that mild hypothermia significantly increased blood loss by an estimated 16 (95 per cent c.i. 4 to 26) per cent and the relative risk for transfusion by 22 (3 to 37) per cent. This detrimental effect was observed at a median core temperature of 35·6°C, about a single degree less than that of normothermic patients; hypothermia in this meta-analysis was thus of a magnitude typical for unwarmed surgical patients[150].

Beyond blood loss, hypothermia promotes the development of SSI[132,151]. Hypothermia-induced vasoconstriction occurs during operation in more than 75 per cent of patients. Vasoconstriction, in turn, reduces oxygen tension and impairs the oxidative activity of neutrophils. In addition, collagen deposition in the surgical wound is decreased and cell proliferation is impaired, compromising wound healing. Many randomized trials reported a significantly higher rate of SSI in hypothermic patients[131,132,152,153]. For instance, a randomized trial conducted in 200 colorectal patients showed a threefold increase in the rate of SSI in the hypothermic group (19 per cent SSI, $34{\cdot}7 \pm 0{\cdot}6$°C) in comparison with normothermic patients (6 per cent SSI, $36{\cdot}6 \pm 0{\cdot}5$°C)[128].

By simply maintaining intraoperative normothermia with inexpensive methods such as a warm blanket, warm intravenous fluids and a high room temperature, the rate of SSI can be decreased greatly. In this context, maintenance of perioperative normothermia has recently been linked to hospital reimbursement for the institutions participating to the US Surgical Care Improvement Project.

Are blood transfusions bad?

Anaemia is a common finding in patients undergoing surgery for cancer. Gantt[154] first suggested that immunomodulation induced by ABT may be implicated in tumour recurrence after curative surgery. Multiple trials have since been conducted to confirm this hypothesis and to improve our understanding of the impact of transfusion-related immunomodulation (TRIM) on the immune system. Despite a large number of experimental publications, the mechanism of TRIM remains poorly understood, with multiple mediators and mechanisms acting in combination to downregulate the immune system of recipients[155–159]. Many trials suggested a role for leucoreduction in minimizing transfusion-related lung injury[160], including a reduction in short-term mortality after cardiac surgery using extracorporeal bypass circulation[161]. However, a systematic review of more than 100 studies on cancer recurrence and SSI found no support for routine leucoreduction[162]. Nevertheless, patients undergoing surgery for cancer and receiving ABT remain prone to worse outcomes in terms of tumour growth and recurrence, with decreased long-term survival[163–173]. Hence, a Cochrane review focusing on colorectal cancer demonstrated a dose-dependent increase in tumour recurrence in patients receiving perioperative ABT[174]. Finally, the negative impact of TRIM in terms of SSI was confirmed in two large prospective observational studies published recently[175,176].

Meticulous and gentle technique, including electrosurgical dissection and laparoscopy, and acute haemodilution are effective in reducing the need for ABT[177]. Conversely, intraoperative blood salvage remained controversial, owing to a possible infusion of cancer cells shed during tumour resection. However, a recent meta-analysis suggested that cancer outcomes were not inferior to ABT when blood cells lost during surgery were transfused back[178]. The authors recommended cell salvage in all cases where estimated blood loss was above 1000 ml, including use of leucodepletion. Indeed, a National Institute for Health and Clinical Excellence guideline now recommends intraoperative cell salvage with leucodepletion for radical prostatectomy and cystectomy. Of note, the use of cell salvage during liver transplantation for hepatocellular carcinoma was found to be both safe and cost-effective[179,180], in spite of the requirement for postoperative lifelong immunosuppression.

In the case of anaemia requiring treatment, autologous transfusion and recombinant erythropoietin were proposed to reduce the need for ABT. Although autologous transfusion may not entirely prevent TRIM, adverse reactions including negative cancer outcomes may be minimized[181,182]. Trials investigating the use of recombinant erythropoietin to stimulate erythropoiesis before surgery demonstrated a significant reduction in the number of units transfused in cardiac[183], orthopaedic[184], and head and neck cancer surgery[185]. Conversely, a Cochrane review including four randomized trials in colorectal cancer did not demonstrate any difference in transfusion requirements or morbidity in favour of perioperative administration of erythropoietin[186]. A further Cochrane review investigating the use of erythropoietin in medical oncology suggested a marginally decreased overall survival[187], whereas a 2012 systematic review published in the *British Journal of Cancer* concluded that current clinical data do not support a significant effect of erythropoietin on disease progression[188]. Overall, recombinant erythropoietin may have a marginal role in the perioperative context, owing to its delayed effect, contrasting with the acute need of surgical patients when unplanned major blood loss occurs.

Perioperative steroids

Perioperative stress-dose steroids are administered routinely to patients presenting with adrenal insufficiency, most frequently as a consequence of long-course steroid therapy for autoimmune diseases or transplant, or less commonly from metastatic disease to both adrenal glands. Adrenal insufficiency is postulated in patients taking prednisone at a dose greater than 20 mg/day for 3 weeks or more. Perioperative dexamethasone has also gained wide clinical acceptance for the prevention of nausea and vomiting[29]. A meta-analysis of 24 RCTs including 2571 patients suggested further benefits: a single administration of dexamethasone at doses between 0·11 and 0·2 mg/kg reduced postoperative pain, opioid consumption and length of stay, particularly when administered before surgery. Wound healing was unaffected, as were rates of SSI[30]. Hence, dexamethasone may be propagated as an useful adjunct to perioperative care.

In a different setting, two meta-analyses of up to 21 RCTs suggested that prompt initiation of low-dose intravenous corticosteroid therapy in patients with severe septic shock (defined as a persisting systolic blood pressure of less than 90 mmHg despite adequate volume resuscitation and vasopressor support) decreased the mortality rate (absolute risk reduction of 6 per cent). The benefit of steroids was correlated to the severity of illness, with a detrimental effect in less severely ill patients[189,190].

Non-steroidal anti-inflammatory drugs and anastomotic leak

NSAIDs provide effective pain relief, thereby reducing perioperative opioid requirements. They exert anti-inflammatory and analgesic effects by inhibition of cyclo-oxygenase (COX)-dependent prostaglandin synthesis. Unfortunately, production of proinflammatory mediators involved in anastomotic healing is also affected[191,192]. Anastomotic leakage has significant implications, being associated with increased morbidity, mortality, length of stay and costs, and worse oncological outcomes[193,194]. If the theoretical risk of impaired anastomotic healing were to translate into clinically apparent leaks, this would severely limit the utility of NSAIDs in surgery. Several animal studies showed a negative impact of NSAIDs on anastomotic healing[195–197], whereas other preclinical studies were inconclusive[198,199]. To date, there have been no randomized trials investigating this relationship in patients. A small number of retrospective studies suggested a negative effect of NSAIDs on leak rates. Holte and colleagues[200] studied the rate of leakage before and after introduction of celecoxib for pain management (28 patients), and found a significantly higher incidence of anastomotic leakage in patients using this selective COX-2 inhibitor. Klein and co-workers[201] obtained similar results in a retrospective case–control study based on 75 consecutive patients undergoing laparoscopic colorectal resection. The largest published study is a retrospective analysis of 795 colorectal patients in which NSAIDs were associated with a nearly twofold increased anastomotic leak rate (13·2 *versus* 7·6 per cent; OR 1·84, 95 per cent c.i. 1·13 to 2·98). This effect was due mainly to the non-selective NSAID diclofenac (OR 2·13, 1·24 to 3·65), as the association with the selective COX-2 inhibitor celecoxib or meloxicam was not significant (OR 1·16, 0·49 to 2·75). Interestingly, a dose-dependent risk was apparent with each additional day on NSAIDs, increasing the risk of leakage by 24 (1·08 to 1·43) per cent[82]. Thus, increasing evidence may indicate a higher anastomotic leak rate when NSAIDs are used in colorectal surgery. A large multicentre randomized trial is needed urgently to answer definitively whether NSAIDs increase the risk of anastomotic leak in abdominal surgery (in contrast to current recommendations[202]).

Multidisciplinary team meetings

An increasing number of national guidelines make regular multidisciplinary team (MDT) meetings a prerequisite to certification as a cancer centre or simply to the practice of oncological surgery. Indeed, a prospective Dutch series of nearly 300 patients at an academic medical centre found that management plans were altered in over a third of patients with upper gastrointestinal malignancy discussed at the MDT meeting. A similar effect was observed in North American studies of pancreatic and urological cancers[203,204], and an interventional cohort study of 13 722 Scottish women suggested improved breast cancer survival and reduced regional variation in cancer outcomes when MDT meetings were attended[205].

Rectal cancer is a prime example of the benefits that MDT meetings may provide by reviewing complex multimodal therapy options and tailoring those to the needs of an individual patient. Neoadjuvant radiochemotherapy is recommended for some stage II/III rectal cancers, followed by surgery within 10 days (short course) or after 6–8 weeks (long course). Neoadjuvant therapy has a higher completion rate than its postoperative counterpart, owing to surgical morbidity and delayed recovery after surgery[206]. Tumour downstaging, some complete pathological responses, better local control and a better disease-free survival (but not overall survival) are further advantages of neoadjuvant chemoradiotherapy in comparison with

adjuvant radiochemotherapy[207–209]. The addition of sensitizing chemotherapy to neoadjuvant radiotherapy nearly doubles the acute toxicity of neoadjuvant therapy to nearly 14 per cent[210,211]. The benefit of multimodal therapy in terms of tumour response (threatened circumferential or distal margins) and local recurrence rates may, however, justify its side-effects, whereas postoperative complications, including anastomotic leak, are unchanged[209].

The absence of a significant difference in perioperative morbidity between three radiotherapy regimens (short-course radiotherapy followed by immediate surgery, short-course radiotherapy followed by surgery after 4–8 weeks, or long-course radiotherapy) was confirmed recently by the Stockholm III trial[212]. On the other hand, radiation toxicity is responsible for most of the lasting morbidity of rectal cancer treatment, including damage to bowel, sexual and urinary functions[209]. Growing evidence suggests that waiting a longer interval between neoadjuvant radiotherapy and total mesorectal excision increases clinical responses, including complete pathological responses[213–217]. Sphincter preservation, when in doubt, is best achieved by external-beam neoadjuvant radiation with dose escalation and endocavity contact radiotherapy[218,219] – neoadjuvant radiochemotherapy is less effective in this respect.

Impact of monoclonal antibodies

Monoclonal antibodies are playing an increasingly important role in oncology. Therefore, surgeons should be familiar with complications associated with their use. Side-effects of the angiogenesis inhibitors bevacizumab and pazopanib include delayed wound and anastomotic healing, bowel ischaemia and perforation, bleeding, thromboembolism, hypertension and proteinuria. Previous radiotherapy and anastomotic leak increase the likelihood of antibody-related complications[220,221]. Waiting at least a month before undertaking major surgery is recommended following administration of angiogenesis inhibitors. To date in colorectal surgery, no survival benefit has been found by adding monoclonal antibodies to adjuvant therapy[222,223], in contrast to their use in the neoadjuvant setting (as in synchronous colorectal liver metastasis) where there is proven benefit.

Table 1 Perioperative care strategies in patients with gastrointestinal cancer

Venous thromboembolism prophylaxis
Timely perioperative antibiotic prophylaxis
Appropriate antisepsis and asepsis standards
Perioperative oxygen supplementation
Perioperative normothermia maintenance
Laparoscopic surgery
Minimization of perioperative blood loss and transfusion requirements
Standardized recovery protocols
Multidisciplinary team meetings for cancer care

Discussion

The present review has addressed important factors in the care of surgical oncology patients (*Table 1*). Although they are not all directly effective against cancer *per se*, they do make a difference in clinical outcomes when applied. Perioperative care strategies include elements as diverse as adherence to perioperative protocols, thromboembolism and antibiotic prophylaxis, normothermia and hyperoxygenation, use of laparoscopic surgery, minimal blood transfusion, postoperative pain control, perioperative steroids, and whether to advocate in favour of or against radiotherapy. Many of these elements belong to clinical routine and may be influenced by tradition as much as by the current evidence available.

Uptake of innovations and compliance to recommendations may lag many years behind published evidence, sometimes requiring a nationwide initiative to get rid of a trusted but deleterious companion, like the routine use of a nasogastric tube[3,224]. Indeed, dissemination of innovation in healthcare can be a daunting task. Failure to use available science is harmful and costly. Interventions as simple as administering antibiotic prophylaxis in the correct time window may halve the rate of SSI[120]. Maintaining core body temperature above 36°C with warmed air and fluids has the same magnitude of effect[128]. Yet, these simple, inexpensive and effective targets may remain elusive. Although many clinicians are aware of an association between SSI and worse oncological outcomes, or between hypothermia and blood loss, fluid overload and perioperative recovery, surgical morbidity and delayed chemotherapy, compromises in the care delivered are frequently made that may not serve well the quality one strives to achieve. Indeed, in order to implement even small changes in clinical routine, many members of the care team have to be convinced and motivated.

Incentives and authority may differ when addressing nursing staff, residents or hospital staff. Surgical leadership is crucial to change management, with efforts ultimately paying off. The implementation of standardized perioperative protocols[3] or the adoption of laparoscopic resection outside of expert centres[225] or in training programmes[226] follows a learning curve. Surgeons are familiar with this concept and know what it takes to overcome initial clumsiness, although institutions have a much slower learning pace than does an individual. At the heart of disseminating

new approaches lies first the perception of innovation before contextual factors involving communication, incentives and management skills[227]. Surgeons are seasoned leaders by their everyday accomplishments in the duty of care to patients. The present review should help to reinforce the perception of the little changes in daily practice that collectively do make a difference to patients with gastrointestinal cancer.

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