Contemporary Issues in Colorectal Surgical Practice

Edited by Yik-Hong Ho

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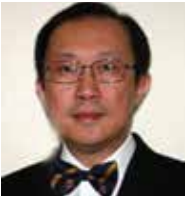
He is actively involved in colorectal surgical training as well as in academic supervision of postgraduate research doctorate degrees. His contributions to the medical literature include over 180 peer reviewed primary publications and 26 textbook chapters. He is associate editor for International Surgery and chairman of the editorial board for Techniques in Coloproctology, Yik-Hong is a member of several medical societies and is presently the World Corporate Secretary of the International College of Surgeons.

Contents

Preface

The practice of colorectal surgery is a rapidly evolving discipline which continually seeks to evaluate and incorporate new emerging technological advances and management concepts into routine day to day practice. This is necessary to achieve continued excellence in service delivery, particularly for patients with complex problems. When these techniques and concepts eventually withstand the robust testing of wide-spread routine surgical practice, they become assimilated into traditional textbooks. Nonetheless, there is a time lag because traditional textbooks require substantial time in production and readership distribution which is something that the on-line electronic medium overcomes, particularly when the latter is focused on selected key topics.

In recent years, significant progress in colorectal surgery has been made which includes laparoscopic techniques, pre-operative management, emergency colorectal surgery, fast track multimodal recovery, management of complex wound problems and colorectal cancer follow-up. "Contemporary Issues in Colorectal Surgical Practice" aims to bridge the gap between the journal article and the traditional textbook in these areas.

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Part 1

Perioperative Management

Preoperative Preparation in Colorectal Surgery

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1. Introduction

In august 1954 Robert J. Gosling Read said at the 59th Annual Convention of the National Medical Association, Washington, D.C: "…Through the personal knowledge of the patient's life history and interest he (*the good family physician*) has offered advice based on common sense rather than specialized training. This is the concept of accelerated recovery…"

This was the first time in the literature the concept was used. Interesting enough, several points of today's enhanced recovery are also common sense since all items are not evidence based. Evidence-based medicine is defined as the integration of best research evidence with clinical expertise and patient values to optimise clinical outcomes and quality of life.[1]

The concept returned in surgery in 1990. Krohn et al[2] published from Good Samaritan Hospital in Los Angeles a four days discharge from hospital after open-heart surgery. He called it rapid sustained recovery. This was the first paper on enhanced recovery after surgery (ERAS).

In 1994 Hartford Hospital and Baystate Medical Center[3] introduced the term "fast-track surgery" which included 1: preoperative education, 2: early extubation, 3: methyl-prednisolon sodium succinate before surgery followed by dexamethasone for 24 hours postoperatively, 4: prophylactic digitalization, metoclopramide HCL, docusate sodium, and ranitidine HAL, 5: accelerated rehabilitation, 6: early discharge, 7: a dedicated fast-track coordinator to perform both daily telephone contact and a 1-week postoperative examination and 8: a routine 1-month postoperative visit with a PA or MD. This showed a systematically control of all patients and a multimodal focus to enhance the recovery time. But all the interventions were not evidence based and the study was an observational study.

Why didn't the literature focus on recovery before1990?

One reason was that until the 1980´s the preoperative preparation was optimizing the organ function medically to tolerate the narcosis, bowel preparation to avoid anastigmatic leakage and infection and disinfection of the surgeons' hands and the patients' skin. There were no systematic antibiotics given, no thrombi-prophylaxis and no epidural anaesthetics.

Another reason was the lack of methodical trials and evidence based medicine on ancillary procedures. Variations in surgical procedures and peri-operative care have been recognised since the early 1980s and are generally interpreted as evidence of uncertainty among practitioners regarding optimal care.[4] How different surgeons or hospitals provided the procedures varied enormously, leading to and "expertise bias". They tended to be accepted

with little question and which, fore some surgeons, had become indispensible rituals. Most of the surgery was done the way you learned it from your mentor. He had his own meaning based on his experience and a standard saying was: "In our hospital we do it my way" or said by Edmund Burke: "custom reconciles us to everything."

Further, randomised trials to peri-operative care questions were often difficult or impractical to perform. A valid randomised controlled trial may also be impossible in many circumstances and may limit the generalisability of the results.

 In the 1990s there was a change. The main reason was the specialization. Earlier the surgeon did the anaesthetics themselves, but today we have specialists in this area, which make us treat patients. The securing of a safe anaesthesia during operations is more important than ever before, partly because of the mere number of operations, and partly because of the greater extent to which other operative risks — haemorrhage, shock and infection — have been overcome. The risk from the anaesthetic is now so very small that the joint aim of the surgeon and anaesthetist to abolish it altogether is not far from being accomplished.[5] The specialty of anaesthesia has seen major advances thanks to the development of safer anaesthetic agents, improved knowledge of pain physiology and pain management, and incorporation of a better understanding of peri-operative patho-physiology into peri-operative care. Concomitantly, development of minimally invasive surgery has further reduced stress responses and pain, thereby providing potential for enhanced recovery. However, an increasing proportion of elderly patients with organ dysfunction have led to demands for further reductions in postoperative complications and the costs of treating them.

The transition from inpatient surgery to ambulatory procedures has proceeded at a rate that was unthinkable a few decades ago, but could all surgical procedures ultimately be done on an outpatient basis?[6] The forthcoming years will, as before, pose several challenges for anaesthetists to improve peri-operative care and to take part in the multidisciplinary collaboration of fast-track surgery. Anaesthetists should consider the development of "peri-operative medicine" as a multidisciplinary effort that should not involve conflict between the anaesthetic and surgical specialities, but rather serve as a mutual platform for improvement of peri-operative care. All together there are more and more emphasis on the joint aim: peri-operative preparations and recovery.

Through the 1980´s and the 1990´s, evidence based medicine became the state of the art, but still it is troublesome to change the way of thinking.

2. ERAS

Kehlet et al gave some answers to these questions in 1997[7]: He focused on the improvements on the administration of opioid analgesics in new ways, such as continuous or on demand intravenous or epidural infusion. These methods allowed lower total opioid dosages, provided a more stable concentration of opioid and correspondingly better analgesic effects, and also fewer unwanted side effects. The introduction of rapid short acting volatile anaesthetics, opioids, and muscle relaxants also facilitated expansion of ambulatory surgery for minor to moderate procedures. The emphasis on ambulatory surgery and accelerated surgical stay programs, both with a focus on early recovery of organ function and provision of functional analgesia, provided an opportunity for a reappraisal of opioid use in these settings. However, the same techniques may be used to facilitate early recovery and

decreased need for prolonged monitoring and stay in recovery and high dependency wards after major procedures.

The key factors that keep a patient in hospital after uncomplicated abdominal surgery include the need of parenteral analgesia (persisting pain), intravenous fluid (persisting gut function), and bed rest (persisting lack of mobility).[8] ERAS change the way of thinking to minimal these factors.

Traditionally the complication rate in colorectal surgery is between 20-40%. The hospital stay is between one and two weeks.[9,10] Early clinical pathways had showed reduced length of stay in major surgery.[11] Kehlet published his first results[8,12,13] with a hospital stay of two days after colonic surgery. He established the concept accelerated recovery and started to compile an interest group, which later became the ERAS-group. Studies showed reduction in hospital stay, reducing ileus and cardiopulmonary complications.[10,13-23] Also in rectal cancer surgery the peri-operative "fast-track" multimodal rehabilitation program is effective and safe.[24,25] Randomised controlled trials (RCT) have showed the same results,[19,20,22,23,27-29] though Behrns patients were discharged on liquid diets.

Advances in peri-operative patho-physiology have indicated multi-factorial reasons for post-operative morbidity[30], length of stay and patient recovery. It is therefore required to deal with these causes by multifaceted interventions. First of all, the patient's medication must be optimized according to organ function like cardiac disease, chronic obstructive lung disease, diabetes mellitus etc. Further the patient must be evaluated according to malnutrition. Malnutrition can prolong the stress response and increase the likelihood of complications. Likewise, heavy drinkers and smokers should abstain from alcohol and smoking a month before surgery if possible. Otherwise they have higher incidence of complications. Thereafter the treatment should focus on pain relief, reducing stress response and reducing nausea and vomiting. Further on the patients should avoid hypothermia, immobilization and semi-starvation. Finally, the postoperative ileus should be minimized. There are reasons to believe that including as many ERAS elements as possible in a clinical pathway may result in a cumulative effect and contribute to enhanced recovery in patients.[31]

The major premise behind fast-track surgery is that patients regain function more rapidly and that this allows a reduction in the period during which the patient is unable to perform activities of daily living.[21]

Better adherence to the elements of the ERAS protocol is crucial to improve surgical outcome. Nearly all, preoperative and per-operative ERAS interventions, influenced postoperative outcomes beneficially.[32] Patients with high adherence to the ERAS protocol had a 25% lower risk of postoperative complications and nearly 50% lower risk of postoperative symptoms delaying discharge. They also had a higher tendency toward reaching length of stay within the target limits compared with patients operated on under less optimal ERAS protocol adherence. As the enhanced recovery field develops, certain interventions may turn out to be nonessential. However, before omitting specific components in the protocol, such a decision should be based on a closer understanding of the importance of each element in the program.

Many of the peri-operative interventions that have been widely adopted into clinical practice are supported by very limited evidence. For a number of interventions the data are either limited in quantity or quality, or are inconsistent. Systematic reviews should be

Elements	Guidelines
Preoperative information	Oral and written information to patients and relatives. Achieve patient management. Patient education before and after surgery.
Bowel preparation	No bowel preparation is necessary before colon surgery. Preparation still before rectal surgery.
Admission	The day before or operation day. Oral supplements given at home before admission.
Preoperative fasting	Fasting only 2 hours before surgery, food and milk rinks 6 hours before.
Carbohydrate loading	Drinks the evening before (800ml) and 2-3 hours before surgery (400ml)
Preoperative medication	Paracetamol (1g x 4) reduces postoperative pain, Alvimopan (12mg x2) reduces postoperative ileus
Preoperative anticoagulation	No-risk – no anticoagulation. Moderate-risk once a day at least 5 days. High-risk once a day 28 days
Preoperative antibiotics	Oral and intravenous or intravenous only. Cephalosporins (2g) or combination doxycycline (0,4g) and metronidazol (1,5g).
Preoperative epidural anaesthesia	Mid-thoracic EDA* during surgery (bolus and continous infusion) and EDA or PCA$ postoperatively for 2-3 days reduces PONV#, ileus, pain, and hospital stay.
PONV	Peroperative and early postoperative oxygen. On moderate-risk TIVA% or an antiemetic drug. In high-risk combination og TIVA and dexamethasone.
Surgical incisions	Less is better, laparoscopy even best.
Nasogastric tubes	Have no place routinely in elective colorectal surgery
Peroperative normothermia	Normothermia during surgery, reduces wound infections
Postoperative fluid management	Restricted, goal-directed fluid therapy is preferably
Drainage of the abdominal acity	No need in colon surgery. In rectal surgery still needed.
Urinary drainage	1 day after colon surgery and about 3 days after low-rectal surgery
Postoperative ileus	Complex aetiology with many contributors, but opioids exacerbate the ileus
Postoperative nutritional care	Oral intake 4 hours after surgery and normal food intake the day after.
Mobilization	Out of bed operation day and 6 hours the day after and thereafter

*EDA = epidural anaesthesia, $PCA = patient-controlled anaesthesia, #PONV = postoperative nausea and vomiting, %TIVA = total intravenous aenesthesia

Table 1. **Elements of ERAS (Enhanced Recovery After Surgery)**

conducted with the same methodological rigour expected for randomised controlled trials. Systematic reviews conducted under the auspices of Cochrane Collaboration have an established methodology and peer review process, and they may be less prone to bias than non-Cochrane systematic reviews.[1]

There is supportive evidence from studies that enhanced recovery programs should be considered as standard peri-operative care.[33] Still, there are controversies. Meta-analysis,[31,34,35] show reduction of complications, but not major complications. There may be a decrease, but it is not statistical significant. One reason may be the lack of robust RCT's. The reduction of hospital stay is real and the readmission rate does not increase. However, a Bayesian meta-analysis showed significant reduction in hospital stay, complications and no difference in readmission rates and mortality.[36] A Bayesian model has a number of advantages like full allowance for all parameter uncertainty, the ability to include other pertinent information that would otherwise be excluded, and the ability to extend the models to accommodate more complex, but frequent occurring, scenarios.[37]

The debate is still going and the conclusion is unclear, but ERAS should be considered the new standard. The markedly shortened hospital stay in fast-track rehabilitation should change the capacity of operative departments considerably. At the same time denotes the implementation of fast-track rehabilitation a paradigm shift away from invasive postoperative monitoring and regulation attempts of today's intensive care medicine to intensified pain therapy and reinforced physical rehabilitation.

Today the ERAS-group has consensus guidelines. They recommend as many elements as possible (for instance 17 out of 20), but as mentioned above – still several elements are highly debatable. We will therefore in this chapter discuss the elements mentioned in Table 1, to see if there are evidence today to change the way of preparing the patients and go into the next area: Optimize the preparation, peri-operative treatment, the logistics and the recovery.

But first, we will look at the concepts stress response and insulin resistance.

3. Stress response and insulin resistance

Surgical stress response is a major contributing factor to postoperative morbidity. Advances in surgical technique and peri-operative management the last years have allowed better control of the stress response intra-operatively and improved patient outcome.

Surgical stress response is mediated via neuro-endocrine mechanisms leading to alterations in protein homeostasis (increased catabolism), hyper-metabolism, altered carbohydrate metabolism (increased gluconeogenesis and insulin resistance) and increased lipolysis.[20]

The underlying hypothesis is that the reaction to a physical stress depends in part on the metabolic state at the onset of the stress. In many of its features, postoperative insulin resistance resembles type 2-diabetes mellitus. The reduction in insulin sensitivity develops after surgery in patients with and without type 2 diabetes.[38]

A state of insulin resistance has been confirmed in several different types of stress, including burn injury, accident trauma, and sepsis. During the 1990s studies of insulin resistance in elective surgery have been performed.[39] The degree of postoperative insulin resistance was

significantly correlated with the length of stay postoperatively. The duration of surgery was closely associated to the relative decrease in whole body insulin sensitivity. These findings suggest that the relative change in insulin sensitivity is related to the degree of surgical stress.[40]

4. Preoperative information

It is very important to inform both the patient and relatives days before the surgery. An effective implementation and a consequent huge rate of compliance are essential in terms of achieving uniformity of patient management. A thorough information orally and a written preadmission information describing what will happen during their hospital stay, what they have to expect, and what their role in their recovery, are essential.[8,41] The success relies on the patients understanding and appreciating their responsibilities.[42] Preoperative education may reduce anxiety and aid in coping, generally enhancing postoperative recovery with an earlier return of gastrointestinal motility after surgery.[43,44] Some patients require extensive education in issues relating to stoma care, self-monitoring for signs of dehydration, and sexual function. This education starts before operation and continues after the operation.[45]

It is well established that intensive preoperative patient information can facilitate postoperative recovery and pain relief, particularly in patients who exhibit most denial and the highest level of anxiety.[9] Teaching the patient to cope with pain and the importance of pain control and the expectation of some degree of nausea are important task to understand before surgery. Patients should also understand the importance of getting out of bed the evening of the operation or the envisioned discharge on the third or fourth postoperative day.

Further on an evaluation of the home environment is important beforehand. In that way it is easier to plan an early, realistic discharge day. Family or caregiver support is crucial to ensure a safe transition from hospital to home and to decrease the risk of readmission.

A cornerstone in the achievement is motivated surgeons, anaesthesiologists and study nurses.[9,46] Fast-track surgery requires a multidisciplinary, concentrated and coordinated effort, with nurses as essential to the success of these programs.[47,48] The dedicated and motivated team consists of anaesthesiologists, surgeons, residents, dieticians, physiotherapists, social workers, dieticians, and nursing team. The nurses should concentrate on individual tasks and spend much time on managing complications as they occur. They must challenge the traditional nursing practices and expend this role to avoid that patients become passive recipients of care. The nurses partner with the patient to achieve well-defined goals to improve patient's outcome.

Changes also need to be made to organisational strategies and the medical professionals involved in pre, intra and especially postoperative care require support, perhaps via continuing education.[47] A protocol is not enough and the importance of this collaboration has been widely described.[5,9,11,13,19,46,49-51]

- Orally and written information to reduce anxiety and postoperative pain
- Achieve patient management and avoid passive recipients of care

5. Bowel preparation

It was unquestionably a great convenience to the surgeon to operate on an empty bowel rather than on one loaded with faeces. It was also supposed through a century that operations on the bowel, especially those involving a suture line or an anatomises, were safer and less likely to be associated with gross contamination and sepsis if the intestine is in a relatively or completely empty condition.[52] The assumption, which formed the basis for the practice of mechanical bowel preparation prior to major colorectal surgery, was so widely accepted as sensible and logical, that nobody saw the need of any really stringent scrutiny. Until recently it was thought that vigorous preoperative mechanical cleansing of the bowel (mechanical bowel preparation), together with the use of oral antibiotics, reduced the risk of septic complications after non-emergency (elective) colorectal operations. Mechanical bowel preparation was performed routinely prior to colorectal surgery until 1972, when this procedure started to be questioned. Even though ES Hughes in 1972[53] concluded in a randomised clinical study that vigorous mechanical preparation was not necessary, most surgeons continued the bowel cleansing until late 1980s.

But in the late 1980s some started to question the necessity of bowel cleansing when using intravenous antibiotics.[54] The cleansing was time consuming and associated with discomfort. Even though Burke[55] stated that bowel preparation does not influence outcome after elective colorectal surgery and a review concluded with limited evidence in the literature to support the use of mechanical bowel preparation[56], still until late 1990s it was standard along with antibiotics preoperatively. The question wasn't answered until two well-designed randomized clinical trials were performed and printed in The Lancet and Br J Surg in 2007.[57,58]

Reviews and meta-analysis cannot show higher leakage rate with than without bowel preparation. Some studies and even meta-analysis have shown the opposite with higher frequencies after preparation,[59,60] but the evidence based answer today is that there are no differences and therefore it is not necessary with any preparations before colon surgery.[61] It is too early to conclude on rectal surgery, so still one may do the preparation before the surgery here. Further research on mechanical bowel preparation or enemas versus no preparation in patients submitted for elective rectal surgery and laparoscopic colorectal surgery is warranted.

There are also some controversies about what kind of preparation to use. No bowel preparation method meets the ideal criteria for bowel cleansing prior to surgery. The new generation of bowel purgatives include oral sodium phosphate preparations and polyethylene glycol-electrolyte lavage solutions. Both are well tolerated by the patients with the oral sodium phosphate preparation as the most preferred because of less fluid to drink for the patients and possibly more effective,[62,63] but there are still some safety issues without a clear solution. Both cleansing methods make some electrolyte disturbances even though it seems like the polyethylene glycol-electrolyte lavage solutions are less dangerous.[64] Therefore adequate hydration is important before, during, and after bowel preparation.[65]

Furthermore, in children and elderly, patients with kidney disease or decreased intravascular volume, and those using medicines that affect renal perfusion or function (diuretics, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and possibly non-steroidal anti-inflammatory drugs (NSAIDs)) should not use oral

sodium phosphate. There is a possibility to develop acute phosphate nephropathy. They should instead use polyethylene glycol-electrolyte lavage solutions.[66]

- No need for bowel preparation in colon surgery
- Still need in rectal surgery

6. Admission

Earlier the patients admitted to the hospital two days before surgery. On the admission day they were given a full liquid diet, and on the day before surgery, a clear liquid diet. Bowel cleansing was given the day before.

Today the history of the patient and co-morbidity are evaluated in an outpatient manner by the surgeon and the anaesthetist. The oral carbohydrate feeding and/or protein feeding are done home by the patient. It is a common view that nutritional support in the peri-operative phase is associated with decreased morbidity, particularly in severely nutritionally depleted patients.[9,67] Patients receiving oral nutritional supplements over an extended peri-operative period lost significantly less weight than those who received no supplements or postoperative supplements only. The incidence of minor complications was significantly lower than in those receiving no supplements or preoperative supplements only. The benefit of outcome occurred independently of nutritional status.[68]

The use of laxatives is still debatable, as the standard measure of return of bowel function would be the ability to tolerate oral feeding rather than just bowel movement.[31]

The patient, at home, may handle the injection of anti-coagulant, the evening before surgery. If the patient lives distant from the hospital, he can be admitted the day before surgery or stay at a hospital hotel.

- Admission the day before or operation day
- Patients receive and administrate oral nutrition supplements at home

7. Preoperative fasting and carbohydrate loading

The overnight fasting routine was first suggested in 1848 after Hannah Greener's death in Winlaton, as a result of the first reported death following general anesthesia.[69] Later the same century it was suggested that a better preparation for the patient was to allow a cup of tea or beef tea some hours before the operation.[70] In the early 1900s, reports of complications from aspirations resulted in the strict recommendation of nil by mouth.[66] General anaesthetic reduces reflexes that stop regurgitated gastric juices reaching the lungs. As this can be dangerous, people were often advised to have nothing to eat or drink from the midnight before surgery.

The main reason for questioning the nil by mouth rules was to improve patient's well being, by reducing thirst and for caffeine drinkers avoiding headaches from withdrawal symptoms. Norway was the first country to adopt new guidelines in 1993, the Norwegian Consensus Guidelines for preoperative fasting in elective surgery, and a national survey was performed three years later, which showed no increase in aspirations due to the new routines.[72] Fasting before general anaesthesia aims to reduce the volume and acidity of

stomach contents during surgery, thus reducing the risk of regurgitation-/aspiration.[73] Recent guidelines have recommended a shift in fasting policy from the standard 'nil by mouth from midnight' approach to more relaxed policies, which permit a period of restricted fluid intake up to 2 hours before surgery. Food or drinks containing milk make the emptying slower and need six hours.[74,75] Emptying of the stomach usually occurs within less than 90 minutes in elective patients after consumption of clear fluids, and after a 12,5% carbohydrate loaded drink 120 minutes.[76]

Practice has been slow to change. There was no evidence to suggest a shortened fluid fast results in an increased risk of aspiration, regurgitation or related morbidity compared with the standard 'nil by mouth from midnight' fasting policy. Permitting patients to drink water preoperatively resulted in significantly lower gastric volumes. Clinicians should be encouraged to appraise this evidence for themselves and when necessary adjust any remaining standard fasting policies (nil-by-mouth from midnight) for patients that are not considered 'at-risk' during anaesthesia. Some people are considered more likely to regurgitate under anaesthetic, including those who are pregnant, elderly, and obese or have stomach disorders. More research is needed to determine whether these people can also safely drink up to a few hours before surgery.[75]

Beverages including water, tea, coffee, or juices without fruit meat cannot be expected to cause any major changes in metabolism, and thus, even with the new and more liberal fasting guidelines, the patient will be operated in a metabolic state of fasting. Infusions of carbohydrates before elective abdominal surgery were shown to improve postoperative insulin sensitivity.[77] Carbohydrate feeding given shortly before elective colorectal surgery displayed less reduced insulin sensitivity (reduced insulin resistance) after surgery compared to patients who were operated after an overnight fast[40] and not associated with aspiration.[78]

The patients were given 800 ml 12,5% carbohydrate drink (malto-dextrin) the evening before the operation and another 400 ml about 2-3 hours before the operation. Insulin resistance has been shown to be an independent factor explaining the variation in length of stay.[79] This study showed that preparation with a carbohydrate-rich drink increased preoperative wellbeing compared with intake of placebo (water) or overnight fasting. These drinks lead to reduced anxiety and significantly reduced postoperative hospital stay, and a trend towards earlier return of gut function when compared with fasting or supplementary water.[8,32,38,80] This earlier return of bowel function may be a contributory factor for shorter hospital stay. Consumption of an appropriate potion composed of water, minerals and carbohydrates offers some protection against surgical trauma in terms of metabolic status, cardiac function and psychosomatic status.

- No fluid intake 2 hours before surgery, milk drinks and food until 6 hours before
- Carbohydrate drinks (>12,5%) the evening before and 2-3 hours before surgery

8. Preoperative medication

Patients should not receive pre-anaesthetic anxiolytic or analgesic medication.[8] Paracetamol used, as preoperative medication to reduce postoperative pain is well established. The use of diclofenac to strengthen the effect (postoperatively) has caused unwanted side effects both in animal studies and retrospective clinical studies.[81] This study showed significant

more anastomotic leakages. Therefore it is recommended to use other non-steroid anti-inflammatory drugs or opioid antagonists like Alvimopan.

Alvimopan is a novel, oral, peripherally acting antagonist, a μ-opioid receptor that has limited ability to cross the blood-brain barrier and is currently being evaluated for the management of postoperative ileus.[82] The use is 12 mg 2 hours before surgery and then twice daily beginning on first postoperative day until hospital discharge or for a maximum of 7 days of postoperative treatment. Alvimopan act within the gastrointestinal tract and does not affect the centrally mediated analgesia. Alvimopan significantly accelerate gastrointestinal recovery in bowel resection patients; reduce postoperative morbidity rates, hospital stay, and rates of hospital readmission[83] with a mean daily opioid consumption of 26 mg. However, opioids provide better pain control compared with other analgesics such as anti-inflammatory drugs.

Glucocorticoids (GCs) are well known for their analgesic, anti-inflammatory, immune-modulating, and antiemetic effects, although the mechanisms by which glucocorticoids exert their action are far from clarified.[84] Preoperative GCs decrease complications—including infectious complications specifically and length of stay after major abdominal surgery. Although inflammation is a necessary precursor for healing, it is the excessive amplitude of the inflammatory response after major abdominal surgery that is thought to contribute to postoperative morbidity and delay recovery. GCs do not seem to increase the risk of complications in colorectal surgery.[85] As an intervention; administration of GCs is inexpensive and simple allowing for clinical implementation without difficulty. Earlier there was not found a significant effect or no effect on postoperative nausea and vomiting and pain in studies. In the concept of enhanced recovery, the effects have been found[84] but Fukami et al found no effect in a randomized controlled trial[86] Another trial found that 8 mg dexamethasone preoperatively has no significant effect on reducing postoperative inflammatory response and also does not improve outcomes of colorectal surgery.[87]

The analgesic effects of GCs are provided through inhibition of the phospholipase enzyme and accordingly blockage of both the cyclooxygenase and the lipoxygenase pathway in the inflammatory chain reaction. The mechanism by which GCs alleviate nausea and vomiting is not fully understood, but the effects are probably centrally mediated via inhibition of prostaglandin synthesis or inhibition of the release of endogenous opioids.

Postoperative fatigue appears to be an important problem following only certain forms of surgery. Preoperative administration of dexamethasone resulted in a significant reduction in early postoperative fatigue, associated with an attenuated early peritoneal cytokine response. Peritoneal production of cytokines may therefore be important in postoperative recovery.[88] The reduction in fatigue was moderate and was associated with a diminished peritoneal pro-inflammatory cytokine reaction on day 1, supporting the hypothesis that peritoneal inflammation is an important contributor to fatigue after major abdominal surgery.

Because of divergence in the trials, we need larger randomised trials before we can recommend the use of GCs before surgery.

- Paracetamol given preoperatively reduce postoperative pain
- Alvimopan is an alternative to reduce postoperative ileus

9. Preoperative anticoagulation

Venous thrombo-embolism (VTE) is the most common preventable cause of death in surgical patients. Thrombo-prophylaxis, using mechanical methods to promote venous outflow from the legs and antithrombotic drugs, provides the most effective means of reducing morbidity and mortality in these patients. Despite the evidence supporting thrombo-prophylaxis, it remains underused. The reasons for its underuse are not fully understood, but those having abdominal surgery are often considered to be at a lower risk than orthopaedic patients. In addition, there are still concerns about an increased risk of bleeding complications.[89,90]

The overall incidence of venous trombo-embolism (VTE) without anticoagulation is 20-25% for patients more than 40 years old in general surgery. For patients having cancer, the incidence slightly rise to 30-40%.[89-93] Fatal embolism occurred in about 1%. After low molecular weight heparin (LMWH) the incidence of VTE is 6% and fatal embolism 0,01%.[92,94,95] Complication rates are low and should not prevent the use of prophylaxis in most patients.[91] Patients undergoing surgery of the large bowel and the rectum have a considerable risk of developing vascular complications expressed as venous thrombosis and/or thrombosis in the lungs (pulmonary embolism). These complications can lead to lifelong impaired venous function in the legs or occasionally sudden postoperative death. The clinical importance of asymptomatic proximal and distal deep vein thrombosis (DVT) remains uncertain and controversial. Unrecognised DVT may lead to long-term morbidity from post-phlebitic syndrome and predispose patients to recurrent VTE. Because VTE in hospitalized patients often is asymptomatic, it is inappropriate to rely on early diagnosis. Furthermore, non-invasive tests, such as compression ultrasonography, have limited sensitivity for a diagnosis of asymptomatic DVT. The high mortality rate in patients with asymptomatic proximal DVT underscores its clinical relevance and supports asymptomatic proximal DVT as an appropriate endpoint in clinical trials.[96,97] Thrombo-prophylaxis is, therefore, the most effective strategy to reduce morbidity and mortality from VTE in surgical patients. Low-dose unfractioned heparin (UFH) and LMWH appear to be equally effective and safe in this patient group, and either agent can be used. Because patients with underlying cancer are at higher risk, it is reasonable for them to use elastic stockings in conjunction with these agents.

The advantage of LMWH is that it can be administered once daily and it is less likely to cause heparin-induced thrombocytopenia and thrombosis than standard heparin preparations. Among the most important risk factors are a previous history of thrombotic disease, advanced age (risk levels increase above 40 years), prolonged immobility, and coexisting cancer and its treatment.[90]

In low-risk patients, who undergoing minor or relatively short operations, are less than 40 years old and with no additional risk factors, no prophylaxis is necessary except early and frequent mobilization.

In moderate-risk patients who are more than 40 years old and undergoing major surgery with no additional risk factors, LMWH given once daily (>3,400 anti-Xa Units) or graduated compression stockings used properly, is sufficient for at least 5 days.[98]

In high-risk patients more than 40 years old with additional risk factors, LMWH given once daily supplied with graduated compression stockings may be sufficient. But the length of anticoagulation has been discussed. A review demonstrates that this combined treatment also is effective within the high-risk group of patients undergoing surgery of the large bowel or rectum.[97]

In addition to ensuring optimal timing for the initiation of prophylaxis, it is also important to establish the duration of prophylaxis. A review suggests that prophylaxis should be administered for at least one month after surgery.[99] The ENOXACAN II study showed, at least in high-risk patients, a significant benefit of an extended 4-week prophylactic period compared with the standard 1-week regimen, with no increase in adverse effects, confirmed by a meta-analysis.[87,100,101] It is now some evidence that late thrombotic events can occur up to 6-7 weeks after operation.[90] Even if there are no difference in mortality, the patients with lower limb DVTs have almost 60% higher relative risk of suffering from post-thrombotic syndrome. Furthermore there are associations between higher 90 days mortality and asymptomatic proximal DVT, which explain the large number of fatal pulmonary emboli in autopsy series.

In laparoscopic surgery and fast-track surgery there are not any RCTs to tell if it is sufficient to give the prophylaxis for a shorter period. Until then one must carefully include selected high-risk patients, major cancer surgery or they who have previously had VTE, to continuing thrombo-prophylaxis after hospital discharge with LMWH for up to 28 days.

It should be emphasized that epidural analgesia per se reduces thrombo-embolic complications by 50% in lower body procedures, but this has not been demonstrated after abdominal procedures.[8]

- In low-risk patients no prophylaxis is necessary
- In moderate-risk patients LMWH once daily or compression stockings, 5 days
- In high-risk patients LMWH supplied with stockings recommended for up to 28 days

10. Preoperative antibiotics

Without any prophylactic antibiotics, one may consider more than 40% wound infections after colorectal surgery, or at least 27% found by Raahave et al[102] with extensive bowel cleansing. In that case it is unethical to operate without any coverage as pointed out in the first meta-analysis on the field.[103] The conclusions were that the chosen antibiotics were not the crucial point, but the timing, coverage and duration were the most important variables. The latest Cochrane Analysis confirms this.[104]

The antibiotics must cover the copious mixture of both anaerobic and aerobic species, which are in the large intestinum. [104] The optimal drug should be one that is not used as a first-line choice in the treatment of surgical infection. But the most common drug used worldwide is cephalosporin, which also is used in the treatment of infections. However, doxycycline, used in Scandinavians studies[105,106] and still used in Scandinavia, is not an antibiotic commonly used in the treatment of established surgical infection, nor is it prominently associated with causing C. difficile colitis, and it is not expensive. But to cover the anaerobic agents, doxycycline is given together with metronidazol with the same limitations as cephalosporin. Doxycycline has not been studied extensively in comparison to other established gold-

standard antibiotic recommendations, but perhaps it should be. According to timing it is well accepted that one hour before surgery is optimal and there is no need for a second dosage because of increased risk of resistant organisms and Clostridium difficile colitis. A combination of oral and intravenous antibiotics seemed to be better than intravenous only, but because of current recommendations before surgery; it should probably be given intravenously.

- Antibiotics given intravenously or a combination of oral and intravenous antibiotics
- Cephalosporin (2g) or Doxycycline (400mg) and Metronidazol (1,5g) preoperatively

11. Preoperative Epidural Anaesthesia (EDA)

Prevention and treatment of postoperative pain is the central goal of interdisciplinary anaesthetists and surgeons. The use of epidural anaesthesia is not for pain control only. Effective analgesia reduces the intensity of autonomous and somatic reflexes, but of importance is the blockade of afferent fibres from the surgical site in order to positively modulate posttraumatic stress reaction either by peripheral nerve blockade, spinal or epidural analgesia.[41] It leads to a modification of the endocrine metabolic action after major surgical procedures, whilst postoperative inflammation is not affected. Mid–thoracic epidural activated before the onset of surgery also blocks stress hormone release and attenuates postoperative insulin resistance.[8]

Both afferent pain fibres and sympathetic efferent fibres contribute to ileus. Because postoperative pain activates the autonomic system and indirectly causes adverse effects on various organ systems, blockage of these pain signals both intra-operatively and postoperatively with epidural anaesthesia and analgesia can blunt the stress response and minimize the effect of surgery on bowel motility.[107,108] There is experimental evidence that the sympathectomy produced by local anaesthetics is associated with increased gastrointestinal blood flow. Shortened duration of postoperative ileus after abdominal operations using these techniques may be translated into decreased length of stay and patient satisfaction.[109]

Regional anaesthesia and analgesia, particularly neural blockade, produce a host of benefits for surgical patients, accelerates recovery of organ function including gastrointestinal and pulmonary function, decreased cardiovascular demands, superior pain relief, reduce the amount of general anaesthetic used (allowing faster recovery), and allows intensified early mobilisation.[49,107,110] Administration of epidural local anaesthetics to patients undergoing laparotomy reduces gastrointestinal paralysis compared with systemic or epidural opioids, with comparable postoperative pain relief. Addition of opioid to epidural local anaesthetic may provide superior postoperative analgesia with activity compared with epidural local anaesthetics alone, and can be accomplished with less toxicity than either class of drug.[1,109-111] The activation of nociceptive afferent and sympathetic efferent nerves are believed to reduce pain and peri-operative opioid requirements, which may lead to reduced postoperative nausea and vomiting (PONV).

Most important may be the significant and prolonged response in the stress response when the epidural anaesthesia is continued postoperatively. To produce the benefit reliably, it appears that epidural analgesia with local anaesthetics should be instituted before the surgical stress and continued until postoperative ileus has resolved, typically 2-3 days later. This peri-operative analgesia may contribute to lower risk of death after surgery. The low risk of serious

adverse consequences suggest that many high-risk patients undergoing major intra-abdominal surgery will receive substantial benefit from combined general and epidural anaesthesia intra-operatively with continuing postoperatively epidural analgesia.[112,113] The effect of additional epidural opioid on gastrointestinal function is so far unsettled even if it is indicated that epidural local aesthetic/opioid provide the most superior treatment.[8,110]

The effect of using epidurals on the postoperative pain outcome was investigated in two studies using visual analogue score (VAS).[19,20] Improved postoperative pain relief is important for patient comfort and may decrease the hospital stay and lead to reduction in morbidity. Improved blood flow consequent on sympatholysis has additional potential benefits, including a reduction in thrombo-embolic complications.[1]

Some studies have shown that thoracic epidural analgesia with a mixture of local anaesthetics and opioids, in contrast with patient-controlled anaesthesia (PCA) IV opioids, provides superior pain relief and contributes to a faster restoration of bowel function.[49,108] However, other trials with patients on a fast-track care pathway with intravenous PCA analgesia did not get further benefits with use of a pre-emptive thoracic epidural.[111,114] In a Cochrane Database analysis,[110] although epidural administration of local anaesthetics was found to accelerate gastrointestinal recovery and reduce nausea after abdominal surgery compared with epidural or systemic opioids, it did not reduce length of stay compared with patient-controlled opioid analgesia.[83]

And therefore, research continues to find the optimum infusion (constituents, concentration and total volume) and the optimum timing and duration of infusion to find significant difference between mid-thoracic epidural analgesia peri-operatively and PCA on the length of stay, too.

A practical problem may evolve during operations. The blockade of these fibres leads to hypotension and the laparotomy intensifies low blood pressure. Then it is very tempting to fill up with intravenous fluid to achieve normal tension. But, as we will discuss later, the risk is intravenous fluid overload. Therefore remember, peroperative hypotension is safely treated with vasopressors.

- Mid-thoracic EDA during surgery and EDA or PCA postoperatively at least for 2-3 days, reduces PONV, postoperative ileus and pain and therefore reduces hospital stay
- Addition of opioid to epidural local anaesthetic provide superior analgesia

12. Preventing and treating postoperative nausea and vomiting

Postoperative nausea and vomiting and postoperative ileus are well-recognized syndromes that lead to significant morbidity and prolong hospitalization. Anaesthesia is given worldwide to more than 75 million surgical patients annually. Untreated, one third of surgical patients suffer from PONV.[115] Patients often rate PONV as worse than postoperative pain. Volatile anaesthetics, nitrous oxide and opioids appear to be the most important causes. Female gender, non-smoking and a history of motion sickness and PONV are the most important patient specific risk factors.[116] Vomiting increases the risk of aspiration and has been associated with suture dehiscence, oesophageal rupture, subcutaneous emphysema, and bilateral pneumothorax. Numerous patho-physiological mechanisms are known to cause nausea or vomiting but their role for postoperative nausea and vomiting is not quite clear.

Intra-operative and early postoperative supplemental oxygen may reduce nausea and vomiting after colonic surgery, and the effect may be as affective as odansetron.[5]

The use of short-acting volatile and intravenous anaesthetics can influence the postoperative course favourably and reduces the incidence of PONV markedly. At a moderate risk the use of total intravenous anaesthesia (TIVA) or an antiemetic is reasonable because PONV frequently delays discharge from post-anaesthesia care units. In very high-risk patients one may justify the combination of several prophylactic antiemetic interventions. The necessary doses are usually a quarter of those needed for treatment.[116] Management techniques such as TIVA cannot be used once PONV is established. A reasonable treatment strategy in high risk patients would be to use dexamethasone and total intravenous anaesthesia as first- and second-line prophylaxis for postoperative nausea and vomiting, leaving serotonin antagonists as a rescue treatment.[115] But dexamethasone, prevents PONV only when given in the beginning of surgery, probably due to reducing of surgery-induced inflammation. "Rescue" treatment, like serotonin antagonists, is ineffective when the same drug has already been used as prophylaxis. Prophylaxis may therefore be preferable to treatment of established PONV.

- Oxygen supplement intra-operative and early postoperative reduces PONV
- Moderate-risk patients may respond to TIVA or an antiemetic drug peroperative
- In high-risk patients a combination of TIVA and dexamethasone peroperative

13. Surgical incisions

To minimize the inflammatory process and pain, the incisions should be reduced to a minimum. Transverse incisions may cause less postoperative pain and better pulmonary function.[117] Therefore laparoscopic incisions may be even better.[118,119] Laparoscopic colon resections have showed advantages over conventional surgery. Blood loss is less; pain, treated with epidural or patient-controlled on demand analgesia, is less intense; time to return of bowel function is less, lung function is improved with reduced postoperative stay in hospital and improved quality of life in the first 30 days. The operation time is still longer with laparoscopic surgery than with conventional surgery. Re-operation is not more likely after laparoscopic surgery and general complications in the lungs, heart, urinary tract or deep vein thrombosis (DVT) were similar with the two surgery techniques. Wound infections were less in laparoscopic patients.[120-123]

Despite the minimally invasive nature of laparoscopy, host physiologic responses to stress are still variably activated. The sane gamut of metabolic, hormonal, inflammatory, and immune responses activated by open surgery are also induced by laparoscopy, but to a lesser degree and proportionate to the extent of surgical injury.[124]

- Small incisions give smaller inflammatory responses. Laparoscopy even better.

14. Nasogastric intubation

In 1933 Wangensteen and Paine[125] wrote: "It is now twenty-four years since Westermann first used the duodenal tube in the relief of postoperative distension of peritonitis. With the introduction of the smooth tipped duodenal tube for nasal intubation by Levin in 1921 and satisfactory demonstration of the source of gas in postoperative dissention by McIver and

his associates in 1926 as being largely swallowed air, the relief of postoperative distension through employment of the duodenal tube has become a matter of general practice." Thereafter the nasogastric tube was used routinely.

The practice was based largely on tradition and perception that nasogastric decompression protected patients from postoperative complications such as nausea, vomiting, aspiration, wound complications, anastomotic leak, and therefore allowed an earlier hospital discharge. Formerly, some used nasogastric tubes for 24 hours when using or more. Many of the early studies advocated nasogastric decompression allowing the patients ad libitum oral intake with the nasograstric tube in place, a practice that would not be advocated by most surgeons today.[126]

Routine nasogastric decompression was widely practiced after elective laparotomy. But the use of nasogastric tubes affect patients considerably. Studies have shown that nasogastric tube decompression does not shorten the duration of ileus and may, in some cases, contribute to postoperative complications such as nasal and pharyngeal injury, fever, atelectasis, increased gastric reflux, regurgitation, and pulmonary infections.[82,127] RCTs could not show any relevant benefit. Although patients may develop abdominal distension or vomiting without nasogastric tube, this is not associated with an increase in complications or length of stay.[126]

The beginning of modifications in practice came after a RCT by Olesen et al 1984,[128] which showed earlier passage of flatus without using tubes and no differences were found regarding duration of postoperative ileus, severity of postoperative paralysis, as measured by occurrence and duration of nausea and vomiting, postoperative per oral fluid intake, and time for defecation. And a meta-analysis showed that patients not having routine tube use had an earlier return of bowel function, a decrease in pulmonary complications and an insignificant trend toward increase in risk of wound infection. On the other hand routine use may decrease the risk of wound infection and subsequent ventral hernia.[127] Although abdominal distension and vomiting are increased without nasogastric decompression, nasogastric tube insertion is required in only 5% to 7% of selectively treated patients,[129] whereas nasogastric tube replacement postoperatively is required in 2% of routinely treated patients. Routine use of nasogastric decompression after elective operations is today not supported by the literature.[127]

- Nasogastric tubes have no place routinely in elective surgery today

15. Preventing intra-operative hypothermia

When compared with normothermic controls, the degree of mild hypothermia has been associated with a twofold to threefold increase in surgical wound infections.[5]

Maintenance of normothermia is critical for the surgical patient. Hypothermia has been shown to impair coagulation and increase the stress response and cardiovascular demands. Using forced-air warmer devices and providing adequate clothing and covering during surgery, can help to reduce postoperative wound infections, blood loss, untoward cardiac and overall rate of nitrogen excretion and catabolism.

- Maintenance of normothermia reduces wound infections

16. Peri-operative fluid management

Intravenous fluid and electrolytes are given to resuscitate the patient from losses sustained during surgery and to maintain homeostasis during periods when oral intake may not be possible. In major surgery, the need for intravenous fluid is greater. However, the optimum fluid replacement strategy remains controversial.

Avoidance of intravenous fluid overloading is an important element in many protocols. Current practice in fluid regimens has been based on 40-year old concepts.[130] It was postulated a decrease in functional extracellular fluid after surgery but this decrease has never been found.[27,131]

However, a study on dogs back in 1937, showed that a modest positive salt and water balance caused weight gain after elective colonic surgery and was associated with delayed recovery and gastrointestinal motility, increased complication rate and hospital stay.[132] The same was found in humans in 2002.[133] An excess of salt and water may lead to more complications than restriction of fluid.

Francis Moore first recommended restriction in fluid regimen.[134] He argued that the metabolic-endocrine response to trauma, (conservation of salt and water), required a fluid restriction. Shires' recommendations have led to 4-6 litres or more intravenous substitution during surgery and 24 hours after, despite minimal blood loss. In contrast, "dry" regimen has been considered beneficial in thoracic surgery.[135] Intravenous fluid overload or excess early sodium and fluid prescription during and after surgery have been shown to give adverse outcome like decrease in muscular oxygen tension and delayed recovery of gastrointestinal function after segmental colonic resection with moderate fluid restriction. Postoperative weight gains after intra-operative fluid overload have been associated with poor survival and complication.[27,136,137] The pattern peri-operative intravenous fluid administration has a major effect upon cardio-respiratory and anastomotic complications, and restricted peri-operative intravenous fluid management and a preoperative carbohydrate drink were found to be of specific importance for beneficial outcomes.[32]

Factors that allow successful use of restricted intra-operative fluid regimen include preventing the patient from coming to the theatre in a dehydrated state by avoiding bowel preparation or excessive duration of preoperative fasting. There was no apparent difference between the effects of fluid-restricted and standard or liberal fluid regimens on outcome in patients undergoing elective open abdominal surgery in a meta-analysis. However, patients managed in a state of fluid balance fared better than those managed in a state of fluid imbalance.[50,138] It is clear that restriction of intravenous fluid during and after operation is safe in well-hydrated patients undergoing major elective abdominal surgery[50] without finding any significant effect on postoperative gastrointestinal function or hospital stay between conservative intra-operative fluid control, and postoperative restriction of fluids and sodium. On the other hand, restricted postoperative IV fluid management, as performed in one trial, in patients undergoing major abdominal surgery, appears harmful as it is accompanied by an increased risk of major postoperative complications and a prolonged postoperative hospital stay.[139] But this study was not an ERAS protocol and had no multimodal approximation.

Some studies have used Doppler-guided fluid administration as goal-directed therapy. Oesophageal Doppler-guided fluid management may improve outcome following major intra-abdominal surgery. However, comparison with fluid restriction strategies, including a cost-effectiveness analysis is required.[139] Evidence regarding use of Doppler-guided fluid administration is limited by heterogeneity in trial design, and recent advances in surgical techniques and peri-operative care may largely offset the initial clinical benefits observed.[140]

All together when using standardized definitions, restricted rather than standard fluid amount according to current textbook opinion, and goal-directed fluid therapy rather than fluid therapy guided by conventional hemodynamic variables, reduce morbidity after colorectal resection.[141]

- Avoiding unnecessary bowel preparation or excessive duration of preoperative fasting
- Restricted, goal-directed fluid therapy seems to be the best regimen

17. Drainage of peritoneal cavity following colonic anastomosis

Drainage of chest empyema and ascites go back to the Hippocratic era. Ambroise Pare was the first to describe drainage of the abdominal cavity, but abdominal drainage had probably been used in practice earlier.[142] During the last 2 centuries, surgeons also used drains for prophylactic purposes. Prophylactic drains have been employed to remove intra-peritoneal collections such as ascites, blood, bile, chyle, and pancreatic or intestinal juice.[143] Another assumed potential function of prophylactic drains is their signal function to detect early complications, such as postoperative haemorrhage and leakage of enteric suture lines.

F. Manley Sims[144] was the first surgeon who used prophylactic drains after gynaecological operations in the end of 19th century. Since that time, surgeons have routinely used prophylactic drainage of the peritoneal cavity after abdominal surgery.[143] Many surgeons use prophylactic drainage after colorectal anastomoses worldwide to prevent anastomotic dehiscence by evacuating fluid collections. Previous authors have suggested that drainage is important to prevent accumulation of exudative fluid, but randomised trials that examined pelvic fluid accumulation in the presence and absence of a drain demonstrated no reduction in fluid accumulation despite the presence of a functioning drain.[145,146] And there is no evidence that fluid exuded from the pre-sacral fascia will remain in the pelvis rather than communicate with the free peritoneal cavity, and may therefore not be susceptible to capture by a pelvic drain. In addition, a drain will usually not serve to control an anastomotic leak as many surgeons expect. The fact is that only in very few instances leaks among drained patients in evaluated studies, pus or faeces emerging from the drain.[146,147]

These traditional practices can impede mobility and cause discomfort and thereof increased morbidity. The use should be selective and not used routinely. Many surgeons continue to place a prophylactic drain in the pelvis after completion of a colorectal anastomosis, despite considerable evidence that this practice may not be useful. If drainage tubes first have been inserted they are normally left in situ for several days until drainage ceases. During the last 3 decades, surgeons have made effort to investigate the value of prophylactic drainage after abdominal surgery in controlled randomised clinical trials. Despite evidence-based data questioning prophylactic drainage in many instances, most surgeons around the world continue to use them on a routine bases. A possible reason for the persistence of practice may be that the surgeons are not convinced by the negative results of the existing trials. The

relatively small sample size and the rarity of the outcomes in these studies limit their power to exclude a true benefit, should one exist.[142]

The large variability of drainage duration may indicate the need for future RCT focused on drainage duration, especially on short-term drainage (24-48 hours). But reviews and meta-analysis of the literature found no evidence that justifies routine drainage of colon and rectal anastomosis after uncomplicated surgery today.[143,147] They showed no difference in all outcome measures (mortality, clinical anastomotic dehiscence, radiological anastomotic dehiscence, wound infection, reoperation, length of hospital stay, extra-abdominal complications).[145,148]

However, due to the lack of statistical power after stratification to the level of the anastomosis, anastomosis in the pelvic still may need short-time drainage. Especially concerning the increase in the rate of neoadjuvant radiotherapy and the increase of Gy used, the reactive hyperaemia should indicate the need of drainage.

- No drainage after colon surgery is needed
- Because of increasing use of radiation, drainage may be used in pelvic surgery

18. Urinary drainage

Some prefer to leave the catheter in situ for several days after surgery, until the patient is fully mobilized. Others remove it the day after surgery on colonic resections, leaving the catheter for seven days after pelvic surgery. Few RCTs are available to define the optimal duration of such drainage, but patients require a shorter period of urinary catheterisation, are able to mobilise more quickly, and had an earlier return of gut function in optimized pathways.[5,20] One study recommend in major low-rectal operations, urinary bladder drainage to be limited to about 3 days and to 1 day after types of colonic surgery.[5]

- 1 day after colonic surgery, about 3 days after low-rectal operation

19. Prevention of postoperative ileus

The aetiology of postoperative ileus is complex, and major intrinsic contributing factors include surgical stress (i.e., from physical manipulation of the bowel), secretion of inflammatory mediators and endogenous opioids in the gastrointestinal tract, and changes in hormone levels and electrolyte and fluid balance, pharmacological agents such as inhalation anaesthetics, and use of opioids for postoperative analgesia implying that both stimulation of nociceptive afferent and sympathetic efferent nerve pathway initiate ileus.[82,108,113] Opioids are the most widely prescribed analgesics used to treat postoperative pain. However, opioids bind to μ-opioid receptors within the gut, exacerbating postoperative ileus.[83] The μ-opioid receptors have been the subject of investigative targets to block and thereby add a pharmacologic adjunct that has previously been lacking.[149]

Postoperative ileus is defined as a disruption of the normal peristaltic motion of the gut, resulting in failure to propel intestinal content through the gastrointestinal tract. Symptoms associated with postoperative ileus include abdominal distension and bloating, nausea and/or vomiting, lack of bowel sounds, gas and fluid accumulation in the bowel, delayed passage of flatus and stool, and inability to tolerate solid diet. Small bowel ileus resolves

within hours of manipulation, but gastric and colonic motor function does not return until 48 to 72 hours postoperatively.[23] It is due to inhibition of extrinsic motility regulation in the colon. The potential benefits from prompt resolution of postoperative ileus may include reduction in the incidence of bowel complications, the potential for more rapid return to normal bowel function, improved patient comfort, reduced length of stay, and reduced healthcare costs.[82]

Postoperative ileus has been shown reduced in fast-track groups[47] even though Lewis[67] found an increased risk of vomiting among patients fed early. This meta-analysis did not include patients in an ERAS protocol. And again, including many ERAS elements in a clinical pathway may result in a cumulative effect not found studying one at the time.

The greatest advance in limiting postoperative ileus to date has probably resulted from the expanded use of laparoscopic surgery and the advantage of limiting tissue trauma. Animal and clinical trials have demonstrated significant reductions in postoperative ileus after laparoscopic colectomy compared with open techniques, which translate into decreased hospital stay.[149]

Postoperative ileus is one of the most common causes of prolonged length of hospital stay. Furthermore, postoperative ileus may be a significant contributing factor for hospital readmission.

- Opioids exacerbating postoperative ileus, but the aetiology is very complex and many elements may contribute

20. Postoperative nutritional care

Standard before ERAS was no oral alimentation until flatus passed, and then progressive diet was initiated. Initially, clear fluids were given, followed by full liquids, and than a regular diet. On average, fluids were commenced on the third or fourth day, with discharge of the patient on the seventh or the eighth day following surgery. Intravenous fluid was administered until the patient was able to drink ad libitum. Until intestinal activity was demonstrated to have reasserted itself in a normal way, by the detection of vigorous peristaltic sounds on regular auscultation of the abdomen and the passage of flatus per rectum, normal diet was banned.

The immediate advantage of caloric intake could be a faster recovery with fewer complications. In the 1990s, early oral intake after elective abdominal colorectal surgery was found safe and was tolerated by the majority of the patients, though they were on a clear liquid diet on the first postoperative day, and advanced to a regular diet within the next 24-72 hours,[150,151] and there was a significant attenuation in gut mucosal permeability.[152] Early studies showed early feeding as a key factor in reducing acute hospital stay,[153,154] and later studies reduced infection rate and the length of stay, but did not significantly reduce mortality.[1] A recent meta-analyse by Lewis et al[155] concluded with reduced mortality, but increased vomiting. However, the trend was in the direction of reduced complication rate and hospital stay. There is no advantage keeping the patient "nil by mouth".

Reduction in complication rates may explain the shortened length of stay as might faster return of gastrointestinal function upon early commencement of enteral feeding.[78] Early

enteral feeding is predicated on radiologic and electro-physiologic studies that indicate a return of small bowel function in 4 to 8 hours post incision, right colon function by 24 hours and left colon function by 72 hours. Severity in duration of the atony can be attenuated by laparoscopy, reduction in opioid-based anaesthesia and analgesia, as well as blockade of the sympathetic reflex circuit through effective continuous thoracic EDA with local anaesthetics.

Early oral intake has become a routine feature in management after elective colonic surgery. And when is it appropriate to start? Patients should be encouraged to commence oral fluid intake 4 hours after surgery.[8]

- There is no advantage keeping the patient "nil by mouth".
- Patients should be encouraged to commence oral fluid intake 4 hours after surgery and normal food intake the day after surgery

21. Early mobilization

Previously, active movements were encouraged in bed after surgery. On the second or the third evening, the patient was usually helped out of bed for a few minutes whilst the bed was made. Thereafter the ambulation was gradually increased.

However, immobilization, over a longer period, can lead to organ dysfunction, loss of lean body mass, reduced muscle power and fatigue.[20] Bed rest not only increases insulin resistance but also decreases pulmonary function and tissue oxygenation and give an increased risk of thromboembolism.[8] To avoid pulmonary complications caused by reduced pulmonary function due to immobilization and reduced tissue oxygenation, mobilizing the patients as soon as possible is important. Mobilization starts on the day of surgery or on the first operative day.[107]

Patients should be nursed in an environment that encourage independence and mobilization. A care plan that facilitates patients being out of bed for up to 2 hours on the day of surgery and 6 hours thereafter is recommended.

To be considered fit for discharge patients had to be apyrexial, fully mobile, passing flatus or faeces, and using oral analgesics only for pain control.[50]

- Out of bed the operation day and 6 hours first operation day and thereafter

22. Economic consideration

In colorectal surgery, cost-analysis of enhanced recovery protocols is limited. Two early clinical pathway programmes proved useful in standardising patient care and reducing costs,[11,48] and were probably instrumental in the development of modern ERAS protocols.[156] None of these studies addressed the set-up costs of an ERAS protocol nor provided a detailed breakdown of where cost savings were achieved in the postoperative recovery phase. However, there has been a huge paradigm shift in postoperative care principles in colorectal surgery since that time, making the cost-analysis reported in those studies inapplicable to current programmes.

Cost-effective analysis has shown that an ERAS programme is a very cost-effective intervention in elective colonic surgery in the setting of an elective hospital.[156] Another case-

control study by King et al 2006[157] focussing on quality-of-life after colonic and rectal surgery, showed in hospital stay half as long as those receiving conventional care, with no increased morbidity, deterioration in quality of life or increased cost.

Evidence from the literature, supports the view that the ERAS pathway seems to reduce the overall healthcare cost.[114,158,159] The largest reduction was in expenses for nursing care, although significant reduction were recorded also in costs of laboratory tests, medications (pharmacy), medical service and other expenses.[114] From a health economics point of view, the data suggests that, with the decrease of complications and hospital stay and similar readmission rates, the cost of treatment per patient would be significant lower for those treated with an ERAS pathway than those receiving traditional care, despite the need for dedicated staff to implement the pathway.[33]

23. Implementation

Improved adherence to the standardized multimodal ERAS protocol is significantly associated with improved clinical outcomes following major colorectal cancer surgery, indicating a dose-response relationship.[32] In spite of a large evidence base for peri-operative care aiming to alleviate postoperative catabolism and organ dysfunction, surgical patients remain exposed to unnecessary starvation, suboptimal stress reduction, and fluid overload.[160]

Although the concept of multimodal postoperative rehabilitation seems rationale and simple, implementation in daily practice has been surprisingly slow so far. This can be partly explained by the need to break with longstanding traditions such as preoperative fasting, postoperative advancement of oral feeding and delayed mobilization.[47] Partly that the ERAS concept as such possibly appears elusive because the relative contribution of each intervention in the program remains uncertain. The most plausible explanation is that a successful multimodal rehabilitation program requires the reorganisation of peri-operative care, with increased collaboration between the patient, anaesthetist (acute pain service), surgical nurse and surgeon. Furthermore, major efforts must be made for educational programmes, with emphasis on peri-operative patho-physiology, as well as a revision of traditional postoperative care programmes with drains, gastrointestinal tubes, catheters, restrictions etc.[48]

The step from best evidence to best practice is simple. However, most of the time it is not, and we need various strategies targeting obstacles to change at different levels, which could even present conflicting values for individual practitioners. Therefore, changes in clinical practice are only partly within doctor's control. Obstacles to change are generally not only in the professional setting but also in the patient, the organisation of care processes, resources, leadership, or the political environment. The prevailing professional and organisational culture towards quality determines the outcome to a large extent.[161]

For instance, patients were not expecting to go home in less than seven days and surgeons were cautious with early discharge.[108] Patients made an early functional recovery, but discharge was generally 2 days later.[9] Strict discharge criteria were met approximately 1,5 days before actual discharge. Social factors, patient's needs, and physician care all influenced the actual discharge date or length of stay.[107]

Introducing ERAS protocols usually requires a major shift in clinical routines, and many units may have difficulties in making all these changes at once. The delay in integrating novel management strategies with routine practice may be ascribed to the time required to develop guidelines, the implementation process, the target group of professionals, the patients, the cultural and social setting, and the organizational and economic environment.[9] Much may be achieved simply by raising the quality of surgical care according to existing evidence. In many ways, this is far more difficult task than simply doing more research.[4]

Nevertheless, some of the elements in the ERAS program, such as omission of routine bowel preparation for colonic resections, no routine use of postoperative drains, early removal of nasogastric tubes, and early feeding and mobilization, have already been incorporated in traditional care. The effect of the different peri-operative ERAS interventions as well as the importance of adherence to the protocol in terms of clinical outcomes, such as postoperative symptoms, morbidity, and length of stay (LOS), remain unclear.[32]

If you would like to start tomorrow to change practice and implement evidence, prepare well: involve the relevant people; develop a proposal for change that is evidence based, feasible, and attractive; study the main difficulties in achieving the change, and select a set of strategies and measures at different levels linked to that problem; of course, within your budget and possibilities. Define indicators for measurement of success and monitor progress continuously or at regular intervals. And, finally, enjoy working on making patients' care more effective, efficient, safe, and friendly.[161]

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Postoperative Ileus in Elective Colorectal Surgery: Management Strategies

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1. Introduction

Postoperative ileus (POI) is a condition characterised by transient interruption of gut function following surgical intervention. Ileus develops due to impaired motility of the gastrointestinal tract in the absence of any mechanical bowel obstruction (Holte and Kehlet 2000). This results in disturbance of coordinated propulsive action leading to accumulation of luminal gas and fluid mainly within small bowel. Clinically it is manifested by abdominal distension, nausea, vomiting and diet intolerance (Lubawski and Saclarides 2008; Parvizi, et al. 2008).

Despite a number of advances in perioperative care and surgical techniques, POI remains one of the commonest challenges in surgery. Although most commonly seen following abdominal surgery, it is also associated with extra-abdominal operations such as cardiothoracic and orthopaedic procedures (Parvizi, et al. 2008; Stewart and Waxman 2010). Historically, POI has been regarded as an inevitable event after major abdominal surgery and it is considered the single largest factor prolonging the length of hospital stay (LOS) following gastrointestinal surgery (Lubawski and Saclarides 2008). It impacts greatly on patient's recovery even after uncomplicated abdominal surgery. Similarly, postoperative ileus is one of the commonest factors affecting healthcare costs in surgical patients. Furthermore, POI causes significant frustration amongst the patients and the surgeons alike (Asgeirsson, et al. 2010).

In recent years, some progress has been made in understanding of underlying causative mechanisms of POI. The multifaceted pathophysiology of POI includes neurogenic, hormonal, inflammatory and pharmacological factors which have been targeted to reduce the incidence and duration of POI. However, there is no definitive treatment to prevent this condition. Key principles in the prevention and management of POI pertain to minimising surgical trauma and preserving normal physiological functions, including gut function. Evidence suggests that this is best achieved by a multimodal approach involving a host of interventions in the perioperative period. Perhaps the most significant development in recent times is the formulation of enhanced recovery after surgery (ERAS) protocols. ERAS protocols provide a multimodal approach to optimising perioperative care and enhancing postoperative recovery. Likewise, minimally invasive surgery i.e. laparoscopic approach has been shown to provide benefits like reduction in length of stay in hospital. Similarly, newer pharmacological therapies (e.g. Mu-opioid receptor antagonist) have shown promising results, however, more scientific evidence is awaited in this area.

In this chapter, we give an account of pathophysiology, natural history, and classification of ileus. Different strategies to prevent and manage POI such as ERAS protocols, minimally invasive surgery and pharmacological approaches are discussed.

2. History and definitions of POI

Ileus is a Greek word which literally means "obstructed" however it is referred to as a functional impediment without mechanical obstruction. POI has been a recognised condition for more than two centuries. The exact definition of POI has been a topic for debate for over a century. It was suggested by Finney in 1906 to divide the phenomnon of ileus into pathophysiological, mechanical, septic or adynamic ileus (Finney 1906). One hundred years later in 2006, the '*Postoperative Ileus Management Council' (PIMC)* was formed by experts in the field of surgery and anaesthesia. The PIMC collected all scientific evidence and developed a consensus on the definition of POI. According to this panel POI is a:

"*transient cessation of coordinated bowel motility after surgical intervention, which prevents effective transit of intestinal contents or tolerance of oral intake"*.

The PIMC categorised POI into primary and secondary ileus. Primary POI develops in the absence of any precipitating factors (i.e. absence of any complications), while secondary POI develops in the presence of a complication such as wound infection, intra-abdominal collection, anastomotic leak, and sepsis etc. In addition, a further three types of POI were described based on the part of gastrointestinal tract (GIT) involved. Type–I POI involves all part of the GIT and thus called pan-intestinal ileus. Clinically it is manifested as nausea and vomiting along with absence of bowel movement or passage of flatus. Type–II POI affects only the upper GIT and manifests as nausea and vomiting. These patients are able to tolerate food but are unable to pass flatus. Type–III POI comprises of ileus of the lower GIT. The patients may be able to tolerate food but are unable to pass flatus or have a bowel motion (Delaney C 2006).

The duration of POI and the cardinal features of its resolution are important aspects which need careful consideration. The minimum time period following surgery before ileus develops is not well defined. Animal and human models have shown that return of gut function occurs first of all in small bowel (24 hours) followed by stomach (48 hours) and colon (48 to 72 hours) (Lubawski and Saclarides 2008). It has been suggested that the colon may take up to 120 hours to resume normal peristaltic activities postoperatively. (Miedema and Johnson 2003).

The return of gut function is historically assessed by either of the presence of bowel sounds, passage of flatus or stool, or tolerance to oral food. Passage of flatus or stool and/or presence of bowel sounds are considered as the benchmark criteria for the recovery of bowel function. However, concerns have been expressed about the validity and accuracy in recording these signs. For example, presence of bowel sounds does not necessarily indicate return of propulsive activities of the whole bowel as they may only represent small bowel activity without colonic peristalsis (Holte and Kehlet 2000). In addition, accuracy of recording these features is usually low. To record presence of bowel sounds requires frequent auscultation which is practically difficult. Similarly, passage of flatus is also not the ideal end point. Some patients are simply not comfortable to report it whereas others may not be able to recall passing flatus in the postoperative peroid. The passage of stool is also

considered to have low specificity. A patient might report having a bowel movement which would be representing distal bowel evacuation as opposed to global gastrointestinal tract function. Hence determination of the end of postoperative ileus is another contentious issue.

The combination of all three signs (i.e. presence of bowel sounds, passage of stool or flatus along with tolerance of oral feed) provides higher accuracy in confirming resolution of POI. Thus, based on the available evidence and PIMC consensus report the resolution of POI can be defined:

"the duration of POI is the time from the surgery until passage of stool or flatus and until oral feed that is tolerated and maintained during 24 hours".

However, it is important to appreciate that uncertainties in criteria for the resolution of POI have impact on the conclusions of various studies published in the literature (Boeckxstaens and de Jonge 2009).

3. Pathophysiology of post-operative ileus

3.1 Normal physiology

The normal motility of gut is maintained by the complex interaction among the central nervous system, enteric nervous system, and hormonal and local factors directly acting on the intestinal smooth muscle (Livingston and Passaro 1990; Mattei and Rombeau 2006). The autonomic nerve system consists of parasympathetic, sympathetic and enteric nervous systems. It has a profound effect on gut motility, ion transportation and is involved in secretory and absorptive processes within GIT. The parasympathetic part of the nervous system is provided by vagus (proximal GIT) and pelvic parasympathetic (distal GIT) nerves. These nerve fibres have a stimulating effect on GIT. The sympathetic innervation is provided by the splanchnic nerve. These post-ganglionic fibres run along the arteries and synapse with the myenteric plexus on the gut wall. The sympathetic nerve fibres have an inhibitory effect on gut which includes inhibition of secretions and motility, and constriction of sphincters and blood vessels. The animal models have shown the sympathetic control is dominant over parasympathetic (Livingston and Passaro 1990).

The enteric nervous system, which is also known as the intrinsic nervous system, consists of myenteric and submucosal plexuses. It makes an important contribution in controlling GI motility and coordinating relaxation and contraction of smooth muscle. The myenteric plexus mainly controls motility of the digestive tract, whilst the submucosal plexus mainly regulates the gastrointestinal blood flow and epithelial function. The enteric nervous system consists of sensory, motor and interneurons. Acetylcholine is the major neurotransmitter which is produced by enteric neurons. Although, the enteric nervous system has the ability to function independently, for normal digestive process it links with the central (extrinsic) nervous system. Due to these cross connections gut provides sensory information to the central nervous system and therefore it may recieve efferent signals from it (Boeckxstaens and de Jonge 2009; Luckey, et al. 2003; Wood 2008). In addition, various hormones and enzymes play an important role in gut function and its motility. The gastrointestinal tract is the largest endocrine organ, called enteric endocrine system, with endocrine glands diffusely scattered throughout the GIT. The hormones secreted by these glands work by a negative feedback mechanism. The enteric endocrine system and nervous systems (enteric and autonomic nervous systems) work in a coordinated way to maintain

the regular contractions of smooth muscle. It has two specific patterns: slow wave and spike potentials. The spike potentials are true action potentials which trigger the muscle contraction. The motility of stomach and small bowel varies according to fed and fasting states. Further, in fed state the number of contractions, their intensity and duration are based on the food ingested. During fasting state the migrating motor complex (MMC) dictates the pattern of bowel contraction (Luckey, et al. 2003). Due to MMC, the remnants of meal, bacterial and other debris are pushed into the large intestine. Hence they have housekeeping function and prevent bacterial overgrowth in the small intestine. Thus any imbalance in autonomic nerves system, enteric endocrine and the local environment may impair the normal gut motility and digestive process, and may lead to ileus.

3.2 Pathophysiology

Ileus is caused by temporary inhibition of extrinsic motility regulation and is more prominent in the colon, while paralytic ileus involves all or part of the GIT and is caused by the inhibition of local and intrinsic contractile systems along with extrinsic inhibition (Bauer and Boeckxstaens 2004). Hence each local factor, autonomic nervous system and hormonal effect has an independent role in the development of POI.

In the past, surgical stress was considered to cause POI by increasing serum catecholamine concentration which would inhibit the gut motility and augment sympathetic activity (Smith, et al. 1977). However, experiments on animal models have shown that although adrenalectomy reduces the level of catecholamine, it does not improve POI. In contrast, splanchnicectomy partially improves ileus (Dubois, et al. 1975). These findings support the hypothesis that the sympathetic nervous system is independent of adrenal activity in causing ileus (Livingston and Passaro 1990). Similarly, vasopressin inhibits intestinal motility (Mitchell and Collin 1985). It is released as a part of stress response following surgical trauma and after the use of opiates (Cochrane, et al. 1981); (Weiskopf, et al. 1987). The exact mechanism by which vasopressin mediates dysmotility is not clear. However, it is suggested that vasopressin is related to reduction in mesenteric blood flow which may subsequently cause impairment of gastrointestinal motility (Livingston and Passaro 1990).

Evidence suggests that three major mechanisms play important role in the development of POI, namely; neurogenic, inflammatory and pharmacological mechanisms. Either of these can cause ileus independently, as does their cumulative effect (Bauer and Boeckxstaens 2004).

3.2.1 Neurogenic mechanisms

In 1872, Golz suggested that intestinal contractility increases after division of the neural axis. This was one of the first observations suggesting the presence of inhibitory spinal reflexes (Bauer and Boeckxstaens 2004). Later evidence has shown that splanchnicectomy improves bowel contraction after laparotomy. It was further suggested that splanchnic afferents are largely involved during gastrointestinal surgery, rather than vagal afferents, leading to hypomotility after surgical intervention (Bauer and Boeckxstaens 2004).

Recent investigations found that different neural pathways are activated during abdominal surgery. Their pathways depend upon the part of GIT involved and the intensity of nociceptive stimulus. For instance, skin incision and laparotomy activate an adrenergic

inhibitory pathway, which is a low threshold spinal reflex and reduces gut motility (Boeckxstaens, et al. 1999). Strong stimuli, such as manipulation of the intestine, may activate an additional high-threshold supraspinal pathway (Barquist, et al. 1996). The corticotrophin-releasing factor (CRF) also plays a central role in this pathway. CRF antagonist has been shown to prevent gastric ileus (Bonaz and Tache 1997). Along with these there are non-adrenergic, vagally mediated, inhibitory pathways triggered by intense stimulation of splanchnic afferent fibres (Boeckxstaens, et al. 1999). Animal models have shown that nitric oxide (NO) is a most potent neurotransmitter in non-adrenergic pathways (Boeckxstaens, et al. 1999; De Winter, et al. 1997). Similarly, vasoactive intestinal peptide (VIP) acts as an inhibitory neurotransmitter during surgical stress (Boeckxstaens, et al. 2000; De Winter, et al. 1998).

Other studies have shown that μ-opioid receptor agonists (e.g morphine) prolong the duration of POI and k-opioid receptor agonists, such as fedotosine, resolve ileus through a peripheral action on non-vagal sensory afferent (Gue, et al. 1989). It is suggested that activation of k-opioid receptors on splanchnic afferent reduces POI by decreasing visceral nociception and inhibitory reflexes. The neural mechanism is primarily activated during the first few hours after surgery and cannot account of POI that lasts for days (Holte and Kehlet 2000; Reissman, et al. 1996).

3.2.2 Inflammatory mechanisms

The inflammatory response develops mainly at a local level and is associated directly with the development of POI (Bauer and Boeckxstaens 2004). For this local inflammatory response, muscularis externa provides a unique immunological compartment containing a rich network of macrophages (Faussone-Pellegrini, et al. 1990; Mikkelsen 1995). These macrophages secrete a number of inflammatory mediators such as cytokines, nitric oxide (NO), prostaglandins, and defensins (Cicalese, et al. 1996; Kagan, et al. 1994). Surgical manipulation of bowel activates the macrophages in muscularis externa stimulating release of above inflammaotory mediators (Kalff 1999; Schwarz, et al. 2001).

Intestinal manipulation also provokes the release of tumour necrosis factor-α (TNF-α), monocyte chemotactic protein-1, interleukin-1b and interleukin-6. These pro-inflammatory cytokines up-regulate adhesion molecules, such as intercellular adhesion molecule-1 (ICAM-1). This molecular response expands to cellular level and recruits more leucocytes (monocytes and neutropils) into the muscularis externa that further release NO, cytokines, reactive oxygen intermediates and proteases (Kalff, et al. 1999). The role of NO and prostaglandins in the development of POI has been shown in pharmacological and genetic studies ((Kalff 1999; Schwarz, et al. 2001). There is strong association between neural and inflammatory mechanisms as discussed below.

3.2.2.1 Inflammatory–neuronal interaction

It is well established that intestinal manipulation mediates local inflammation which causes inhibition of smooth muscle function. The manipulation of the small bowel not only causes ileus in the small bowel, it is also linked with delayed gastric emptying (de Jonge, et al. 2003). This raises the question as to whether there is any other mechanism which affects motility distant from the site of inflammation or manipulation? Bauer and Boeckxstaens (2004), suggested that:

"One possible mechanism could be an interaction between the inflammatory milieu of the postoperative muscularis and primary afferent neuronal activity, triggering the neural inhibitory pathways".

Animal models show that the delay in gastric emptying is induced by intestinal manipulation which occurs through an inhibitory adrenergic pathway. Up-regulation of cyclooxygenase-2 (COX-2) releases prostaglandins that participate in local inflammation and the development of POI (Schwarz, et al. 2001). A number of experimental studies have suggested that prostaglandins act as neuromodulators and their levels increase significantly following surgery. Animal models treated with selective COX-2 inhibitors show a reduction in incidence of ileus. Based on the findings of such studies Bauer and Boeckxstaens (2004) also concluded that:

"the intestinal inflammation in response to bowel manipulation results in primary afferent activation, initiating subsequent inhibitory motor reflexes to the gut, and leading to postoperative intestinal gut dysfunction, with prostaglandins playing a crucial role".

Furthermore, intestinal manipulation activates mast cells which play a vital role in the development of inflammation. During surgery even a gentle manipulation of intestine triggers the release of mast cell mediators. The activated mast cells release potent pro-inflammatory mediators such as TNF-α, protease and histamine which contribute to the inflammatory response. In addition, these mediators recruit more leucocytes and up-regulate adhesion molecules, all taking part in inflammatory process (Kubes and Kanwar 1994; Wershil, et al. 1996). The activated mast cells briefly increase intestinal permeability resulting in translocation of bacteria and consequently activation of resident macrophages in the muscularis externa. An inhibitory adrenergic neural pathway is also activated which impairs the neuromuscular function of the distant part of intestine, explaining the generalised features of ileus (Boeckxstaens and de Jonge 2009). Studies have demostrated that mast cell stabilizers improve gastric emptying and reduce inflammatory response (de Jonge, et al. 2003). Hence mast cells and resident macrophages are mainly responsible for activation of the innate immune system, leading to an inflammatory response after intestinal manipulation.

3.2.3 Pharmacological mechanisms

There are two types of opiates: endogenous and exogenous. Both play an important role in gastrointestinal dysmotility. Both are simliar and exert their actions through same opioid receptors (Prasad and Matthews 1999). Overall, opiates have an inhibitory effect which leads to impairment in gut motility, its secretions, and the transport of fluid and electrolytes across the gut wall. Understandibly, such actions lead to a delay in gastric emptying and inhibition of intestinal peristalsis and the development of POI (Kurz and Sessler 2003). This phenomenon has been proven in a number of studies on animal and human models which have shown that δ and μ opioid agonists diminish peristalsis (Bauer, et al. 1991; Bauer AJ 1991).

There are three different types of opoid receptors: δ (delta), μ (mu) and κ (kappa). Opiates have a receptor-specific effect on intestine and hence they mainly affect μ- receptors on GIT, while it has less effect on other organs receptors such as the brain or spinal cord. This is why morphine has more of a constipating effect than an analgesic effect. The requirement of morphine is four times more likely to increase to have an analgesic effect than constipating effect (4:1 ratio) (Holte and Kehlet 2000; Kalff, et al. 1998). Therefore, when opiates are used

repeatedly, patients develop a tolerance to analgesic effect but not to the side effects on GIT (Holte and Kehlet 2000). A prospective study performed by Cali and colleagues did not show any significant correlation between the length of incision and the dose of morphine taken. However, it suggested that the dose of morphine is directly related to the return of gut function (Cali, et al. 2000). Similarly, opiates bind to leucocytes and affect the immune system which slows down gut motility. They also facilitate NO synthesis which plays a significant part in the pathogenesis of POI. Release of various hormones also plays a role in the pathogenesis of ileus. For example, corticotrophin-releasing factor stimulates inflammatory mediators in the bowel (Tache, et al. 1993).

In summary, there are multiple factors which contribute to the pathogenesis of POI and major mechanisms include neurogenic, inflammatory, pharmacological and hormonal responses (figure 1).
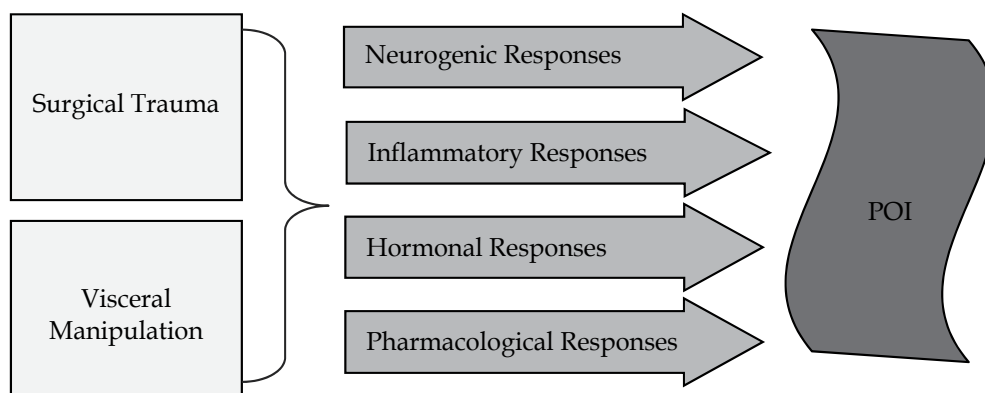
Fig. 1. Pathogenesis of post-operative ileus

4. Strategies to reduce POI

Over the past two decades, a number of strategies have been introduced to improve the quality of peroperative care. Most of those were primarily directed at reducing perioperative mortality, morbidity and LOS in hospital. All of those were aimed to prevent ileus by minimising the stress response and maintaining the normal body physiology during and after surgery. These include ERAS programmes, laparoscopic surgical approaches and the use of specific pharmaceutical agents. In this section, different strategies to prevent and manage POI are discussed.

4.1 Modalities to manage POI

4.1.1 Enhanced Recovery After Surgery (ERAS) protocols

ERAS protocols involve a series of measures taken pre-, per- and post-operatively which collectively ease the stress response to surgical trauma and enhance post-operative recovery. It has been shown that this 'multimodal rehabilitation' programme improves surgical outcome and patient satisfaction after elective surgery (Khoo, et al. 2007; Varadhan, et al. 2010; Wind, et al. 2006b). ERAS programme consists of a number of elements which are summarised in Figure- 2.
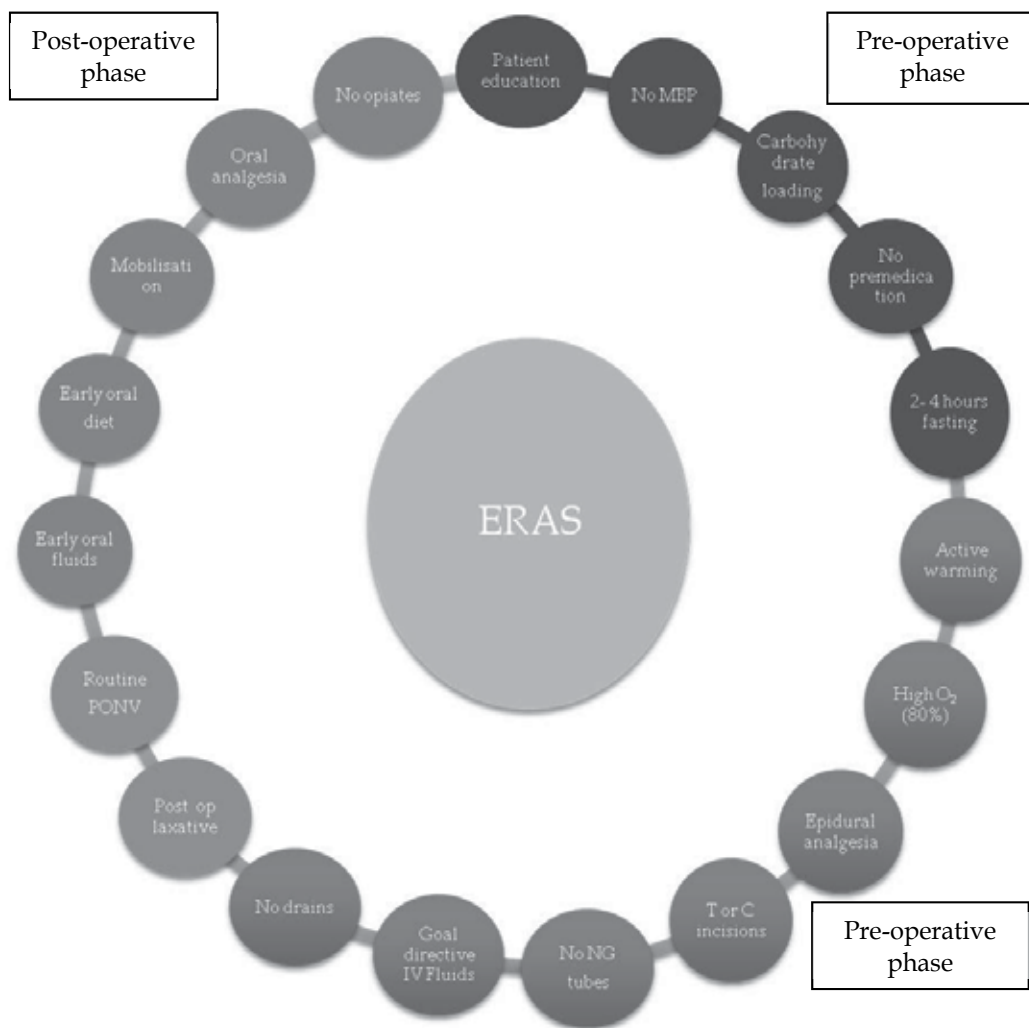
Fig. 2. MBP- Mechanical Bowel Preparation, T and C- Transverse and curve , NG- Nasogastric, PONV- prevention of nausea and vomiting. (Authors previously published this figure as Ahmed J et al, Colorectal Disease, 2011 Oct 11. doi: 10.1111/j.1463- 5 1318.2011.02856.x.)

4.1.2 Pre-operative components of ERAS protocols

Preoperative patient counselling and education prior to surgery is important aspect of ERAS protocols. Along with counselling, patients should also see other members of the multidisciplinary team such as dieticians, stoma care nurses and nutrition nurses. Recently, a number of centres have introduced a dedicated ERAS nurse who provides information regarding ERAS pathways and the various stages during and after surgery. An important component of preoperative phase is the ingestion of carbohydrate-rich drink the night before and on the morning of surgery. A short period of fasting and carbohydrate loading both help in maintaining patients' nitrogen balance and reducing post-operative insulin resistance (Soop, et al. 2004; Svanfeldt, et al. 2007).

Oral mechanical bowel preparation should be avoided in patients undergoing elective bowel surgery. A single phosphate enema can be used on the days of surgery to clear the rectum in patients undergoing left-sided anastomosis. A Cochrane review suggested that low molecular weight heparin (LMWH) and graduated compression thromboembolic deterrent stockings (TEDs) are the most effective anti-thrombotic prophylaxis (Wille-Jorgensen, et al. 2003). A single dose of broad spectrum antibiotics reduces the risk of wound infection and should be administered prior to skin incision.

4.1.3 Peri-operative components of ERAS protocols

High inspired oxygen concentrations (80%) should be administered during anaesthesia and in the early post-operative period (for a minimum of six hours). Oxygen molecules are required for the production of free radicals, which play an important role in the defence mechanism against pathogens to reduce surgical site infection, and in the synthesis of collagen for wound healing and angiogenensis (Allen, et al. 1997; Hopf, et al. 1997; Qadan, et al. 2009). In addition, high concentration of oxygen in the tissues during the immediate post-operative period improves perfusion at the anastomotic site and may also be associated with a reduction in post-operative nausea and vomiting (PONV) (Greif, et al. 1999; Orhan-Sungur, et al. 2008)**.**

The core temperature should be measured and monitored using an oesophageal probe. In patients undergoing prolonged surgery (i.e., more than one hour) warmed intravenous fluid should be administered (Lindwall, et al. 1998; Smith, et al. 1998).

Hypothermia (core temperature less than 36°C) causes tissue hypoxia due to peripheral vasoconstriction which increases the risk of coagulopathy, wound infections and cardiac complications (Frank, et al. 1997; Ozaki, et al. 1995; Schmied, et al. 1996). It is also linked to a change in immune response and an increase in catabolic response (Frank, et al. 1995). Prevention of hypothermia in the peri-operative phase has been shown to decrease blood loss, and cardiac and infective complications (Melling, et al. 2001; Wong, et al. 2007).

Goal directed intra-operative intravenous fluid administration has shown positive impact on early return of gut function and reduction in length of stay in hospital. Oesophageal Doppler or LiDCO plus™ and LiDCO rapid™ are minimally invasive methods used to measure the cardiac output and stroke volume. These devices enable the anaesthetist to tailor the fluid requirement (goal directed) according to changes in cardiac output per-operatively. Goal directed fluid therapy has been shown to result in early return of gastric motility, reduction in time to defecation and an improved tolerance to oral feed due to reduced gut oedema (Gan, et al. 2002; Lobo, et al. 2002; Nisanevich, et al. 2005) . Splanchnic hypoperfusion, which may remain unnoticed with traditional monitoring, results in delayed return of gut function. It may lead to bacterial translocation across the gut wall and sepsis (Mythen and Webb 1994). Similarly, an excessive amount of intravenous fluid during surgery may cause the development of gut oedema which may also result in the delay in return of gut function (Grocott, et al. 2005).

The concept of minimally invasive surgery is recommended which includes both open (small and appropriate incisions) as well as laparoscopic approach. In open approach, a transverse, limited midline, oblique or paramedian incision should be used whenever possible. Such small transverse or mini-laparotomy incisions may have positive impact on analgesic requirement, pulmonary complications, systemic inflammatory response and length of stay in hospital

(Nakagoe, et al. 2001; Nakagoe, et al. 2004; Takegami, et al. 2003; Werawatganon and Charuluxanun 2005). In ERAS protocol, routine use of nasogastric tubes and abdominal drains following GI surgery is not recommended. A Cochrane review (33 studies, 5240 patients) has suggested that there was an earlier return of gut function, reduction in pulmonary complications and an insignificant trend towards increased risk of wound infection in patients not having routine nasogastric tube. However, no difference in the rates of anastomotic dehiescence was demonstrated. Its use is also associated with pain and discomfort to patient and impedes post-operative mobility (Nelson, et al. 2007; Nelson, et al. 2005). Similarly, several randomised studies and meta-analyses have suggested that the routine use of drains does not confer any clinical advantage in the early detection of anastomotic leak or intra-abdominal collection (Jesus, et al. 2004; Karliczek, et al. 2006; Urbach, et al. 1999).

It is recommended that all patients undergoing open abdominal surgery should have high thoracic epidural analgesia. Patient should receive epidural analgesia for at least 12 hours to a maximum of 48 hours. Ideally weaning form epidural should start 12 hours after operation.

However, in laparoscopic colorectal surgery the benefits of epidural analgesia are not clear. It may be used depending upon the preference of the operating surgeon and anaesthetist. The epidural anaesthesia blocks sympathetic reflexes and afferent stimuli. This attenuates the post-operative stress and promotes early return of gut function which reduces incidence of PIO (Holte and Kehlet 2002; Marret, et al. 2007). It is important to note that epidural analgesia may cause hypotension due to vasodilatation which may have an adverse affect on the anastomosis. Early recognition of these patients and monitoring in the high dependency unit is therfore critical.

Recently, other modalities such as transversus abdominis plane (TAP) blocks and wound irrigation (PainBuster®) with local anaesthetic (0.2% ropivacaine®) have shown a reduction in use of opiates and improvement in patient mobilisation in the early post-operative period (Bamigboye and Hofmeyr 2009; Beaussier, et al. 2007).

4.1.4 Post-operative components of ERAS protocols

Opiates have a profound negative effect on the gut motility, consequently delaying return of gut function and prolonging the duration of POI. Regular use of Paracetamol and non-steroidal anti-inflammatory drugs (NSAIDS) is recommended unless contraindicated. NSAIDS help promote gut recovery by reducing local mucosal inflammation (Cali, et al. 2000). Prophylactic antiemetics should be prescribed to those patients receiving opiates.

It is emphasised that all patients be allowed oral fluid and diet soon after surgery. Intravenous fluid should be stopped as soon as the patient's oral intake is adequate. There is now evidence to support the view that early commencement of enteral feeding is beneficial and is safe to introduce within 24 hours of surgery (Andersen, et al. 2006; Lewis, et al. 2009). Similarly, early feeding facilitates gut motility and may help in the early return of gut function and reduce the ileus.

All patients should have an enforced and structured mobilisation plan during the post-operative period. A designated physiotherapist with a mobilisation plan tailored to the individual patient's need should work closely with the patient in order to achieve best outcome. Early mobilisation is paramount in preventing venous thromboembolism (VTE), respiratory complications and reduction in muscle strength (Schuster and Montie 2002). It is

noteworthy that early post-operative ambulation plays a little role in preventing or resolving POI. However, it has proven benefits in preventing atelectasis, pneumonia and VTE (Carroll and Alavi 2009) which may cause secondary POI.

A clinical management pathway, based on ERAS protocols, is proposed below which would be useful for colorectal surgeons in day-to-day management of surgical patients (Figure- 3).

A typical pathway for management of patients after colorectal surgery – Based on multimodal optimisation

Preoperative Phase

Patient counselling and education (both written and verbal)
Assessment by Anaesthetist and ERAS Nurse
Optimisation of nutritional status (MUST scoring) and co-morbidities
Stoma education and training (if required)

Preoperative assessment

Carbohydrate loading
Clear fluids till 2 hours prior to surgery
Bowel prep (if required)
VTE prophylaxis
No premedication

Day of admission

Peroperative Phase

Epidural analgesia
Goal directed IV fluids (Use Oesophageal Doppler)
No nasogastric tube or drains
Prophylactic antibiotics
Minimally invasive surgical approach (laparoscopic/ small / transverse incision)

In operating theatre

Postoperative Phase

Set of daily goals for postoperative care
Start oral fluids and diet as soon as patient tolerates
Regular paracetamol and NSAID if not contraindicated
Continue high energy drinks
Avoid regular Morphine and other opiates
Daily review by physio and active and enforced mobilisation
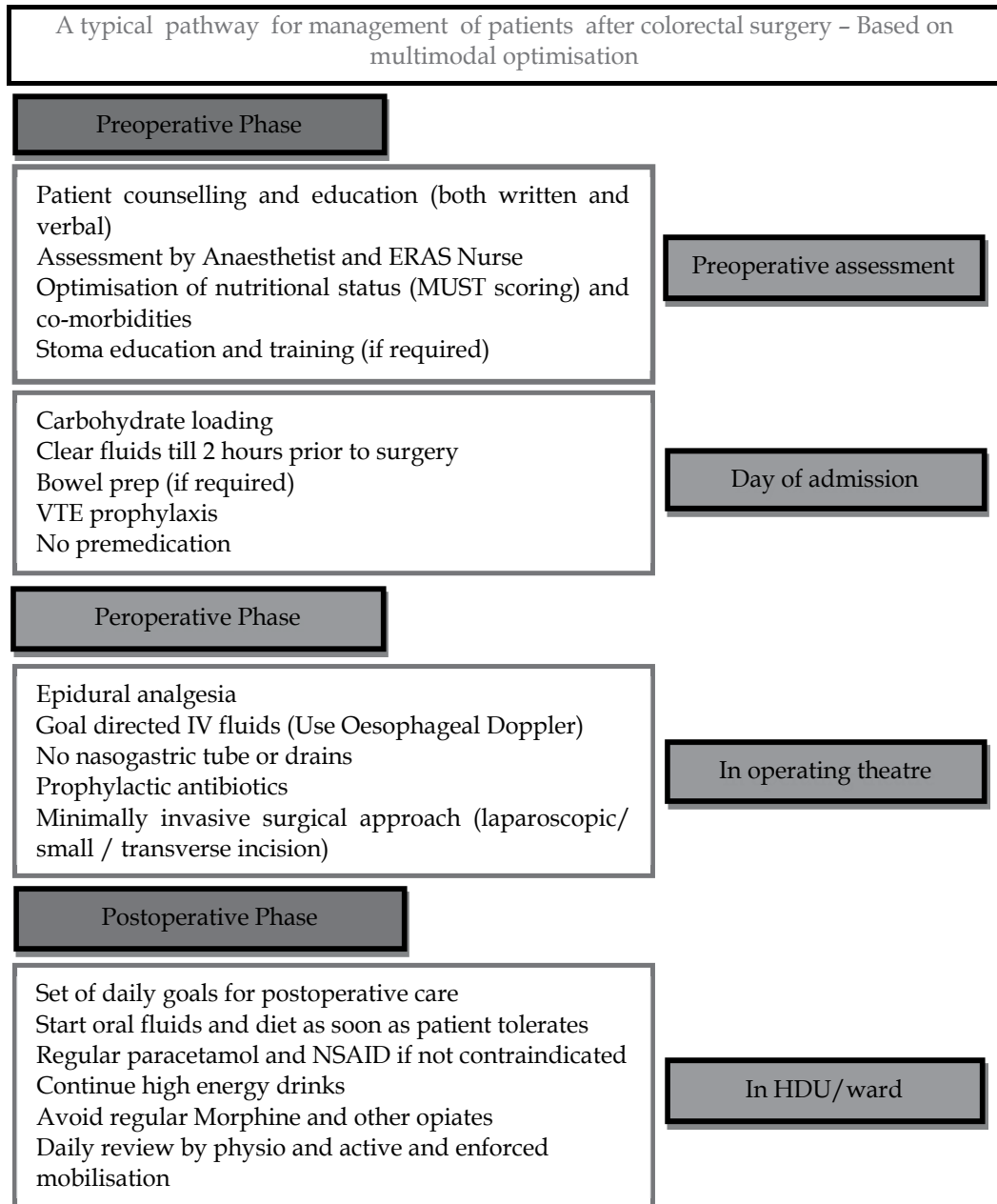
In HDU/ward

Fig. 3. Clinical management pathway based on ERAS protocols

4.2 Laparoscopic approach

Introduction of laparoscopic approach has significant imapct on surgical practice, for both the surgeons and patients alike. It is known that the laparoscopic techniques cause less surgical stress and trauma, and the patients recover faster (Bauer and Boeckxstaens 2004; Kalff, et al. 1998). Laparoscopic surgery involves less bowel manipulation and inflicts reduced tissue trauma compared with open approach. Similarly, reduced inflammatory and catabolic responses in laparoscopic approach may also result in early recovery after operation. Therefore, the return of gut function is faster compared to open surgery. Effective postoperative analgesia may be obtained with simple analgesics and use of opiates can easily be avoided. Understandably, laparoscopic technique is considered to reduce severity and duration of ileus resulting in shorther length of stay in hospital (Leung, et al. 2004).

Laparoscopic technique has attracted ethusiasm and application by most surgical specialities and has become standard approach for a number of surgical procedures. Its wide spread popularity is based on the short term benefits. Randomised studies have demonstrated that laparoscopic approach reduces duration of POI after abdominal surgery (Basse, et al. 2003; Lacy, et al. 1995; Milsom, et al. 1998). Similarly, laparoscopic colorectal resections have been shown to cause less post-operative pain, and early return of organ function and discharge from hospital when compared with conventional open surgery (Reza, et al. 2006).

Whereas individual trials demostrate short term benefits of laparoscopic approach especially in early postoperative period (Guillou, et al. 2005; Murray, et al. 2006; Veldkamp, et al. 2005), a Cochrane review found no difference in long term outcomes compared with open approach (Kuhry, et al. 2008). However, it is important to consider that most of above evidence is collected from studies lacking ERAS programme of perioperative optimisation. Recently, two trials investigated impact of laparoscopic approach within ERAS application (Basse, et al. 2005; King, et al. 2006). Unfortunately, the results of these two trials are not consistent. Basse et al. failed to show any advantage of laparoscopic approach in colonic resections, while King et al suggested benefits of laparoscopic approach compared with open techniques. However, latter trial was not blinded which might have impacted on the results of the study. Nevertheless, it is established that laparoscopic surgery, in general, is associated with reduced post operative pain and inflammatory response. Consequently, it may play a role in reducing the incidence of POI (Story and Chamberlain 2009). More work is underway in this area and evidence is eagerly awaited.

4.3 Pharmacological therapies

There are a number of pharmacological therapies which are part of ERAS protocols. For instance, carbohydrate loading, use of NSAID and prophylactic anti-emetics, epidural and/or regional analgesia are integral part of ERAS pathways. These therapeutic modalities have been shown to have significant impact on early return of gut function (Kehlet and Wilmore 2008). Moreover, it is possible to avoid opiates which have a profound effect on gut motility and cause ileus.

A number of new pharmacological agents are under investigation at different levels. For example, Alvimopan, a selective Mu-opioid receptor antagonist which acts peripherally, has

been shown to have positive effect on the ileus in phase III trail. It has been shown to have an association with early return of bowel function, reduced incidence of POI, and reduction in length of hospital stay (Ludwig, et al. 2010). Similarly, estimated hospital cost was reduced by $879 - $977 for patients who received alvimopan compared with placebo. Long-term safety, accurate indications and dosage are important issues which need addressing before its widespread use in future. However, it is unknown that if alvimopan is more cost effective than optimal use of laparoscopic approach and ERAS protocols, and further research is needed (Stewart and Waxman 2010).

Similarly, vagal stimulation by enteral administration of lipid-rich nutrition has shown early recovery of gut peristalsis (Lubbers, et al. 2010). Other agents such as peripheral opioid antagonist methylnaltrexone, motilin analogue atilmotin and Cisapride have been used with promising results (Livingston and Passaro 1990). Adrenergic blockers and parasympathetic agonists (e.g neostigmine) have also been investigated as potential options in treating POI. Unfortunately, these agents have serious side effects and hence not suitable for routine practice. Moreover, drugs such as Erythromycin and Metoclopramide have shown some favourable results in early gastric emptying, however, there is no quality data to support their routine use at a larger scale in daily practice (Sustic, et al. 2005; Yeo, et al. 1993). A recent review suggested that gum chewing in postoperative period is associated with reduction in POI, likely due to vagal stimulation of the gastrointestinal tract (Fitzgerald and Ahmed 2009).

The pharmacological management of POI is still evolving and has an important role in the management of POI. Further evidence is required to establish the summative effect of pharmacological therapies, laparoscopic surgery and ERAS pathways.

5. Conclusion

POI is a complex condition of multifactorial aetiology, most commonly seen following abdominal surgery. It causes significant frustration amongst health professionals and patients alike. It is one of the commonest causes of delay in patients' postoperative recovery and carries financial implications due to prolonged length of stay. It is estimated to cost $1.28 billion annually in United States (Senagore 2007).

In recent years, efforts have been made to address this issue albeit without any major progress. Nonetheless, our understanding of pathophysiology of ileus is better than before and a number of strategies to overcome the causative factors have been tried (Stewart and Waxman 2010; Story and Chamberlain 2009). Although such strategies help reduce the duration of ileus, they have limited role in preventing its onset (Lubawski and Saclarides 2008). Three major mechanisms – neurogenic, inflammatory and pharmacological – have been implicated in causing ileus (Augestad and Delaney 2010). The level of activation of these factors varies during a surgical procedure. Moreover, understanding of pharmacological mechanisms has opened new windows for research and interventions in this area.

Evidence has accumulated to suggest enhanced recovery after surgery protocol, laparoscopic approach, and pharmacological interventions all reduce the incidence of ileus. Figure 4 illustrates a suggested pathway for prevention and management of prolonged Ileus.

Post Operative Ileus
Prevention and clinical management pathway

Prevention of POI   Management of Prolonged POI

| Perioperative optimisation | Mechanical obstruction must be excluded with contrast studies |

| Implementation of ERAS protocols Nutritional support | watchful waiting and supportive treatment |

| Use of minimally invasive surgical approach

Consider use of pharmacological therapy | Nil per mouth

Consider nasogastric tube Intravenous fluids

Correct electrolytes imbalance |

| Prevention of complications such as chest infection, heart failure, urinary infection, intrabdominal sepsis | Treat underlying cause i.e. sepsis , reduce opiates use

Patient developing gut failure consider artificial nutrition through central line |
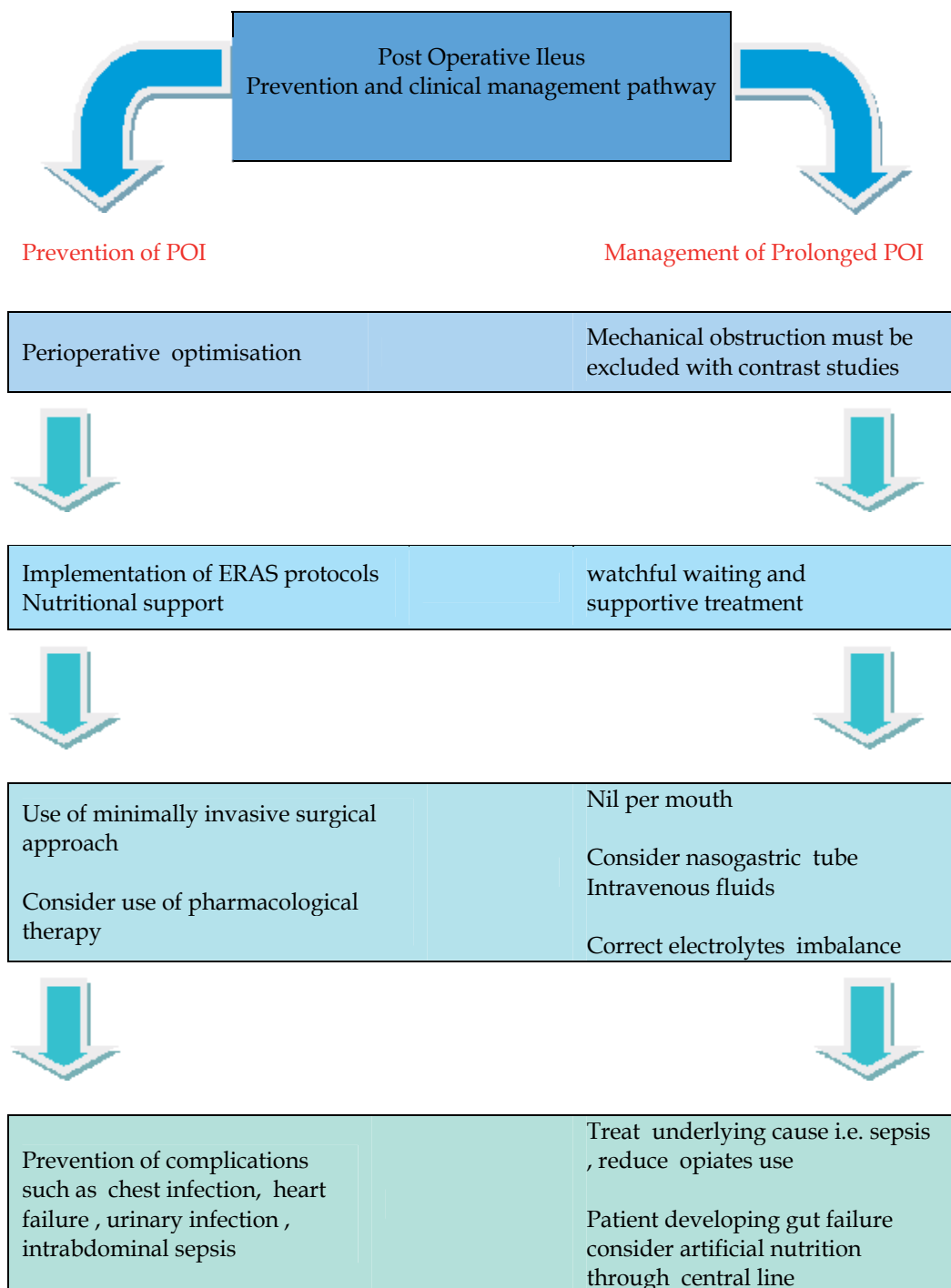
Fig. 4. Management pathway for Prolonged POI

Laparoscopic surgery produces better short term results compared with open approach (Guillou, et al. 2005; Hewett, et al. 2008). Short term morbidity, including incidence of ileus, is significantly low in patients treated with laparoscopic approach. It remains an area of significant reserach interest to investigate whether the combination of laparoscopic surgery and ERAS protocol will offer any further clinical benefit. The ongoing LAFA (Dutch) and EnRoL (UK) trials are desinged to answer above question when completed (Wind, et al. 2006a).

Of above, ERAS pathway was most extensively studied intervention over the last 15 years.The components of ERAS protocol are aimed at optimising patient care, reducing operative stress, and enhancing recovery after surgery by persevering normal physiology and early return of gastrointestinal function. Whereas POI has not been investigated as sole primary endpoint in studies comparing ERAS verusu conventional perioperative care, it has been studied as a part of morbidity rates in both as primary and secondary endpoints. There is now evidence that ERAS protocol of perioperative care is associated with significant reduction in incidence of POI, along with length of hospital stay, compared with conventional perioperative care.

Pharmacological interventions, as part of ERAS or outside ERAS, play key role in reduction of incidence of ileus. Such interventions with promising results include use of preoperative carbohydrate loading, NSAIDs, prophylactic anti-emetics, and epidural and/or regional analgesia. Avoidance of opiates and use of mu-opoid receptor antagonists are associated with early return of gut function.

The impact of ileus as an important health issue cannot be over emphasized:

"In patients who underwent colectomy surgery, postoperative ileus was associated with a 29% increase in hospital LOS and a 15% increase in hospitalization costs. Prevention of postoperative ileus could potentially yield benefits in reduction in hospital LOS and associated health care costs." (Lyer, et al. 2009)

POI is a challenging yet preventable event in surgical patients. It has a multifactorial pathophysiology that requires a multimodal approach in its management. Whereas there is no definitive treatment of ileus, strategies to prevent and manage ileus should be followed as discussed above. Essentially, prevention and management of POI centres on minimising perioperative stress and preserving normal physiological functions.

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Part 2

Laparoscopic Colorectal Surgery

Laparoscopic Surgery for Rectal Cancer: Approaches, Challenges and Outcome

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1. Introduction

Jacobs et al (1991) reported the first series of laparoscopic colonic resections in 20 patients. It took over a decade of debate and controversy to establish that laparoscopic colon surgery for cancer, when compared with open surgery, is associated with better short term outcomes while maintaining at least equivalent long-term outcomes (Lee, 2009). These improved short term outcomes include reduced postoperative pain, short hospital stay, decreased intra-operative blood loss, quicker return of gut function and faster return to normal activities (Lacey et al., 2002; Veldkamp et al. ; 2005, Guillou et al., 2005). However, the debate around laparoscopic rectal surgery is far from over.

Oncologic outcomes of rectal cancer patients have been shown to depend on the skills and techniques of the operating surgeon (Heald et al., 1998). It took the surgical community several years to accept and adopt the current modern concepts of rectal cancer surgery which involves the standardisation of surgical resection with total mesorectal excision (Heald et al; 1986) and adequate circumferential resection margin (Quirke et al., 1988). It seems that the surgical community has yet to go through another phase of development in the surgical management of rectal cancer to address the concerns whether the technical challenges of laparoscopy may further add to the complexity of the surgical technique that may result in variability in outcomes (Lee, 2009).

Even though there are several studies on the outcomes of laparoscopic rectal surgery, there is limited level 1 evidence in surgical literature (Kang et al., 2010). Safety and benefits associated with laparoscopic colon cancer surgery have been demonstrated in many prospective randomized trials. However the same benefits have not yet been clearly confirmed for laparoscopic rectal cancer surgery (Lee, 2009). The debate around laparoscopic rectal surgery has become even more complex with the slow, but steady, increase of the practice of robotic rectal surgery. To be universally accepted, minimally invasive approaches to rectal cancer need to demonstrate at least equivalent onlcologic & safety results to open surgery combined with evidence of improved short term outcomes. In addition, minimally invasive approach should be cost-effective (Champagne et al., 2007).

2. Conventional laparoscopic rectal surgery

2.1 Pros and cons of conventional laparoscopic rectal surgery

Laparoscopic surgery provides unique, unobstructed views of the rectal dissection not only for the operating surgeon but also to the entire surgical team. Magnification of the surgical field allows more precise dissection. The pneumoperitoneum assists in opening up the planes for mobilization of the mesorectum (Lee, 2009). Also, blood loss is minimised as meticulous haemostasis is essential to preserve the laparoscopic view. (Cecil et al., 2006).

However, there are many well documented limitations to conventional laparoscopic rectal surgery. These include tremor, assistant dependant unstable two-dimensional view, inability to perform high-precision suturing, poor ergonomics and fixed tips as well as limited dexitry of surgical instruments (Delaney et al., 2003; Choi et al., 2009; Abodeely et al, 2010). These limitations are particularly relevant for rectal cancer surgery. As the surgeon operates into the confines of the pelvis the dissection becomes more difficult due to a combination of factors. Retraction of the rectum may prove difficult as one approaches the retrorectal and Denovillier's fascias. Crowding and clashing of instruments can result in a poor view and an experienced assistant is essential. Diathermy or vapour fumes from energy sources in the confined spaces of the pelvis often results in fogging of the camera scope that could slow progress of the procedure (Cecil et al., 2006).

2.2 Challenges in conventional laparoscopic rectal surgery

There are many technical challenges that are associated with laparoscopic rectal cancer surgery. One of the main technical challenges is obtaining adequate exposure, tissue tension & retraction of the rectum by the currently available conventional laparoscopic instruments. In the absence of tactile feedback during laparoscopic surgery, intra-operative localisation of the tumour represents another challenge. Lesions during laparoscopic colon surgery are easily identifiable with or without tattoo marks. However, this is not easily possible with rectal cancers without tactile feedback. It is often difficult to determine the extent of distal rectal dissection that is needed to grantee adequate tumour clearance and to be sure that the stapler is applied at the appropriate level distal to the tumour (Lee, 2009).

There are well known limitations in the currently available laparoscopic distal rectal stapling devices. Most of the current laparoscopic staplers can only reticulate to a maximum of 65 degrees which makes horizontal division of the rectum difficult. For this reason, multiple firings are often required to complete distal rectal transection (Cecil et al., 2006). Division of the rectum in the presence of very low anterior and bulky lesions is particularly challenging (Champagne et al., 2011). Laparoscopic division of the distal rectum is not always technically feasible because of the limited angulation of the stapling device and the physical limitations of working in the bony confines of the pelvis. A virtual simulation demonstrated that the current design of staplers has to go through the iliac bone in order to achieve a 90° angle at the level of levator ani (Brannigan et al., 2006). Some surgeons overcome by this by the use of a conventional stapler through a small suprapubic incision (Shalli et al., 2009).

Identifying the correct surgical plane anterior to Denonvillier's fascia during conventional laparoscopic rectal surgery, adequate radial margin and maintaining meticulous

haemostasis are essential for high quality rectal cancer surgery. This can be challenging as without adequate retraction and tissue tension, surgical planes can be more ambiguous. Any bleeding will further obscure the appropriate anatomy (Champagne et al., 2011).

2.3 Outcomes of conventional laparoscopic rectal surgery

2.3.1 Evidence from early randomised controlled trials

The MRC CLASICC (**C**onventional vs. **L**aparoscopic- **A**ssisted **S**urgery in **C**olorectal **C**ancer) Trial was done between 1996 and 2002 in 27 UK centres. It randomised 794 patients with colon and rectal cancer into laparoscopic resection (n = 526) open resection (n = 268) with a ratio of 2:1. The CLASICC trial was the first RCT to include patients with rectal cancer. The study reported a 29% conversion rate. Patients who had conversion ended up with increased complication rates. Also, there was higher incidence of positive circumferential resection margin after laparoscopic anterior resection but this did not reach statistical significance. There was no difference in hospital mortality or quality of life at 2 weeks and 3 months postoperatively (Guillou et al., 2005).

A subset of 148 patients in the CLASICC trial was analyzed with regard to sexual and urinary function with the help of validated questionnaires. The perceived change in the overall level of sexual function was considerably higher in the laparoscopic group compared with the conventional group (41 vs 23%). These differences in sexual function reflected a clear trend, but were not significant at the 5% level.

Multivariate analysis revealed that conversion to open surgery was significantly correlated with postoperative male sexual dysfunction. In this study morbidity was an obvious issue in rectal surgery. Therefore, the authors concluded: *'laparoscopic resection for colon cancer is as effective as open surgery. However, impaired short-term outcomes after laparoscopic resection for rectal cancer do not yet justify its routine use. '* (Guillou et al., 2005).

2.3.2 Challenges in rectal surgery as identified from the clasicc trial

The outcomes of the MRC CLASICC trial should be interpreted with caution as in the study design, which was based on the best available data at that time (Simons et al., 1995), the surgeons' learning curve was set at 20 laparoscopic resections. Clearly this was an underestimation of the learning curve especially for rectal surgery (Leung et al., 2004; Good et al., 2011). This could explain the increased complication rate for laparoscopic rectal resections in the study and the authors' conclusion that laparoscopic rectal surgery was associated with increased morbidity. The reduction in the conversion rates for every year of the study is an indication that the learning curve was operative during the trial (Guillou et al, 2005). More recent studies set the learning curve at 55 cases for right-sided and 62 for left-sided laparoscopic colonic resections to achieve proficiency (Tekkis et al., 2005). However, there is little data on the numbers required to achieve proficiency in laparoscopic rectal cancer surgery (Good et al., 2011).

Despite the limitations of the MRC CLASICC trial, it helped to highlight the challenges of laparoscopic rectal surgery when compared to laparoscopic colon surgery. These findings were confirmed & debated in other publications (Quah et al., 2002; Scheidbach et al., 2002; Cecil et al., 2006). It became evident that laparoscopic rectal surgery has a longer learning

curve & higher conversion rate, increased circumferential margin involvement as well as poorer outcome of urinary and sexual function especially in men (Quah et al., 2002; Bretagnol et al., 2005).

Increased anastomotic leak rate was another challenge that was identified in laparoscopic rectal surgery. Multiple firings are often required to complete distal rectal transection as the current laparoscopic staplers can only reticulate to a maximum of 65 degrees and therefore horizontal division of the rectum difficult. This is even more challenging for low-lying lesions and may contribute to increased anastomotic leakage. There is a documented positive relationship between the number of linear endostapler firings and anastomotic leak rate (Ito et al., 2008; Kim et al., 2009). Reported leak rate of 17% if the anastomosis were located less than 12 cm from the anal verge and as high as 25% in those patients who were not diverted following laparoscopic rectal surgery (Morino et al., 2003). These leak rates are higher than those reported after open rectal resection (4–11%) (Enker et al., 1995; Heald et al. 1998). Refinements in the laparoscopic stapling devices may help addressing this problem in the future.

2.3.3 Evidence from more recent publications

More recent publications show much lower rate of circumferential resection margin (CRM) involvement following conventional laparoscopic rectal surgery between 2. 14%-4% (Ng K. H. et al., 2009; Lujan et al., 2009; Ng SS et al., 2009). On the other hand, anastomotic leak rate remains high for most of the studies in the range of 9 to 17% compared to 5% for open surgery (Champagne et al., 2007). However, some authors report anastomotic leak rate after conventional laparoscopic rectal surgery as low as 3. 8% (Good et al., 2011).

2.3.4 Evidence from meta-analysis and cochrane reviews

The CRM involvement was evaluated in a meta-analysis of 10 trials reported a mean positive radial margin of 5% for laparoscopic resections compared with 8% for open resections. However, this was not statistically significant. The distal margin positivity rates were also not different between laparoscopic and open rectal surgery (Anderson et al., 2008). However, it should be noted that a clear distal margin can be of an issue in laparoscopic resections of the lower third of the rectum, especially in male patients (Laurent et al., 2007).

A meta-analysis for 20 studies published between 1993 and 2004 looking at laparoscopic versus open surgery for rectal cancer showed that there was no significant difference in circumferential margin positivity or number of lymph nodes harvested. This confirmed that laparoscopic and open surgery were comparable in terms of their adequacy of oncological clearance (Aziz et al., 2006). Despite the known limitations of meta-analysis of nonrandomized data, the authors' conclusions are particularly useful because of the limited number of randomized data available for laparoscopic rectal cancer surgery (Champagne et al., 2007).

A Cochran systematic review for 48 studies comparing laparoscopic and open resection for rectal cancer concluded that laparoscopic TME surgery had clinically measurable short-term advantages in patients with primary resectable rectal cancer (Breukink et al., 2006).

2.3.5 Outcomes of conventional laparoscopic resection of extra-peritoneal rectal cancer in recent studies

The ongoing debate as to the exact length of the rectum makes it difficult to accurately assess the results of the various studies reporting the outcomes of laparoscopic rectal surgery. Despite these apparent discrepancies there is an agreement that rectal cancer consists of extra-peritoneal and intra-peritoneal lesions and those tumours at or below the peritoneal reflection ideally should be grouped together (Champagne et al., 2011) when discussing laparoscopic rectal cancer outcomes because those lesions represent the real challenge for conventional laparoscopic rectal surgery. There is only limited number of studies that specifically address short and long term outcomes of conventional laparoscopic resection of these lesions.

Short-term Outcomes:

COREAN Trial (*Comparison of O****pen versus laparoscopic surgery for mid and low RE****ctal cancer After N****eoadjuvant chemoradiotherapy)***

This randomised study by Kang et al. (2010) aimed to evaluate the safety and short-term efficacy of laparoscopic surgery for rectal cancer after preoperative chemoradiotherapy. It was done between 2006-2009 in three tertiary referral centres by teams who have extensive experience in open and laparoscopic rectal surgery. Short-term outcomes assessed were involvement of the circumferential resection margin, macroscopic quality of the total mesorectal excision specimen, number of harvested lymph nodes, recovery of bowel function, perioperative morbidity, postoperative pain, and quality of life. Patients were followed up to assess the 3-year disease-free survival.

Conversion rate was 1. 2%. Laparoscopic group had a longer operating time but less post-operative pain, decreased blood loss and better physical functioning score. There was no difference between the two groups in the involvement of the circumferential resection margin, macroscopic quality of the total mesorectal excision specimen, number of harvested lymph nodes, and peri-operative morbidity did not differ between the two groups. The authors concluded that '*Laparoscopic surgery after preoperative chemoradiotherapy for mid or low rectal cancer is safe and has short-term benefits compared with open surgery; the quality of oncological resection was equivalent*' (Kang et al., 2010).

Even though the COREAN study showed no statistical difference in the anastomotic leak rate between the open and laparoscopic groups, other recent studies have highlighted that laparoscopic resection of extraperitoneal rectal cancer is associated with increased anastomotic leak rate when compared to open surgery. Reported anastomotic leak rate following conventional laparoscopic low anterior resection is 9% (Morino et al., 2003; zhu et al., 2010) and up to 43% for an ultralow anterior resection (Choi et al., 2010).

Long-term Outcomes:

There is limited number of studies looking at the long-term prognosis following laparoscopic surgical resection of middle and lower rectal cancers. The long term outcomes in this subgroup of patients remain unclear because they are affected by anatomical factors as well as the complexity of the surgical procedures. Li et al. (2011) reported the outcome of 236 patients (laparoscopic, n = 113; open, n = 123) who underwent curative resection for middle and lower rectal cancer from 2000 to 2005. Surgery was performed by the same

surgical team with extensive experience in laparoscopic and open procedures. The mean follow-up time of all patients was 74. 8 months. There was no statistical differences in local recurrence, distant recurrence or the 5-year overall survival rates between the laparoscopic and open groups. The authors concluded that *'laparoscopic and open surgery for middle and lower rectal cancer offer similar long-term outcomes. The continued use of laparoscopic surgery in these patients can be supported'*.

3. Hybrid and hand-assisted laparoscopic rectal surgery

In an attempt to avoid compromising oncologic rectal dissection but at the same time maintain the benefits of laparoscopic surgery some have studies reported the use of hybrid procedures in which colonic portion of the surgery is completed by the laparoscopic approach but rectal dissection is completed through a limited low midline or Pfannenstiel incision (Vithiananthan et al., 2001; Shalli et al., 2009).

Similarly, hand-assisted laparoscopic techniques have been used for rectal cancer surgery. Rectal exposure and dissection can be either performed directly through the hand assisted port incision using the open approach following laparoscopic mobilisation of the colon or laparoscopically with manual assistance. The latter technique uses the benefits of the unmatched laparoscopic view and at the same time allow the completion of oncologically similar dissection under tension as in open surgery (Lee et al., 2007).

Hybrid laparoscopic surgery allows the preservation of tactile sensation; optimal traction and exposure of the surgical planes and at the same time helps tumour localization which is a well known challenge in purely laparoscopic approach. Outcomes with this technique have been reported to be favourable and it certainly has some advantages but many surgeons feel that it is not 'totally' laparoscopic rectal surgery and it should not be included in trials or case series for laparoscopic rectal resection. However, the published literature highlights its role and it is suggested that if this procedure continues to demonstrate favourable outcomes and has a shorter learning curve it may require its own procedure code in the future (Champagne et al., 2011).

4. Robotic assisted rectal surgery

The inherent limitations of conventional laparoscopic surgery; which include tremor, unstable two-dimensional view, and limited degree of freedom of the instruments, are particularly significant in patients undergoing rectal cancer surgery with total mesorectal excision (Ballantyne, 2002). Robotic surgery has the potential to address some of these limitations and the potential to offer technical abilities greater than those offered by open or conventional laparoscopic surgery. Robotic colorectal surgery was first reported in by Ballantyne et al. in 2001. The concept of robotic total mesorectal excision for rectal cancer was first reported by Pigazzi et al. in 2006.

4.1 Potential advantages of robotic surgery

Robotic systems can address many of the inherent limitations of conventional laparoscopic surgery. These include the fulcrum effect, poor depth perception, limited range of motion as wells as instrument tremor (Maeso et al., 2010). The use of robotic systems in rectal cancer

surgery has the potential to offer accurate dissection in the avascular 'holly' plane of the rectum without injury to the integrity of the mesorectum or autonomic pelvic nerves in the narrow pelvic cavity. Ultralow rectal dissection could be more easily performed by using precise movements of robotic arms (Kim & Kang, 2010).

Robotic system offers a camera system that is controlled by the operating surgeon combined with three dimensional ten-fold magnification vision thus allowing a perfectly still visibility of the operative field. (Ballantyne & Moll, 2003; Lanfranco et al., 2004; Baik, 2008). One of the main advantages of the use of robotic system in rectal surgery is that it gives the surgeon equal access to both right and left pelvis as if standing above the head of the patient (Hellan et al., 2007). The tips of the instruments of a robotic arm have an endowrist which has functions of seven degrees of freedom, one hundred and eighty degrees articulation and five hundred and forty degrees rotation (Baik, 2008). Also the availability of multi-articulated instruments allows for a range of angles to approach the rectum thus allowing sharp dissection around the rectum and mesorectum. The robotic handles transfer the hand movements of the surgeon to the tip of the instruments offering a comfortable, ergonomically ideal operating position (Stylopoulos & Rattner, 2003). Many studies highlighted that the operating surgeon experienced less physical strain with robotic assisted surgery (Stylopoulos & Rattner, 2003; Ballantyne et al., 2003; Hellan et al., 2007). In addition, robotic technology offers additional features such as motion scaling and remote telesurgical applications including tele-mentoring (Kim & Kang, 2010)

4.2 Limitations of the current robotic systems

The current robotic systems have some limitations which should be addressed in the future. There is lack of both tactile sensation and tensile feedback to the operating surgeon. Therefore, tissue damage can occur easily during traction by the robotic arm and during movement of the robotic instrument (Baik, 2008). Therefore, the surgeon must rely on visual cues to estimate the amount of tension exerted on the tissues (Hellan et al., 2007). Also, suture material can be cut during suturing because there is no tensile feedback to the robotic instrument (Baik, 2008). Therefore, great care must be taken to avoid traumatic injuries when handling bowel.

The system requires precise positioning of the robot for optimal operative outcome and to avoid robotic arm collision and the position of the patient cannot be changed without undocking the robotic arms (Hellan et al., 2007). The docking and separation procedure of a robotic cart from the patient is a time consuming procedure. Also, when using the robot to perform a surgical procedure in different compartments in the abdominal cavity, such as anterior resection, repeated docking and undocking of the robot is often needed and this is reflected on increased operating time. When immediate open conversion is necessary to deal with serious intra-operative bleeding delayed separation of the robotic cart can create a difficult situation (Baik, 2008).

High capital and running costs of the currently available robotic system made the taking up of this technology rather limited in many countries. The average price of one robotic system is more than U$2,000,000 and combining this with U$2,000 for the disposable instruments is a major issue when cost-effectiveness of robotic surgery is debated (Baik, 2008).

4.3 Approaches to robotic rectal surgery

There are several techniques for robotic rectal cancer surgery described in the surgical literature.

4.3.1 Multiple stages totally robotic technique

This is described as either a two-stage technique or a three-stage technique (D'Annibale et al., 2004). The number of stages mirrors the number of movements of the robotic cart. The need for frequent docking & undocking of the robotic system is reflected on increased operating time.

4.3.2 Hybrid technique

To eliminate the need for repositioning of the robot most surgeons choose conventional laparoscopic mobilization of the left colon and splenic flexure as well as division of the inferior mesenteric vessels and then use the robot for the TME part of the operation only. This hybrid approach saves the time for repetitive robotic setups. The actual TME is reported to take an average of 60 minutes (Hellan et al., 2007; Baik et al., 2008).

4.3.3 Single stage totally robotic

This approach has been recently reported by Kawak & Kim (2011). It eliminates the need for frequent docking & undocking of the robot but at the same time preserves the advantages of the use of the robotic approach for the whole procedure.

4.4 Advantages of totally robotic rectal surgery

Advocates of the totally robotic approach, whether multiple stage or single stage, believe that robotic dissection around the IMA pedicle is a fundamental step of the procedure to identify and preserve the periaortic nerves. They correctly consider that not only the pelvic nerves but also the periaortic nerves are important in sexual/bladder functions. They also feel that the use of robotics could also improve access and enable easier mobilization of the splenic flexure (Kawak & Kim, 2011).

4.5 Learning curve in robotic rectal surgery

The three-dimensional view and the ability of the robot to transfer the surgeon's hand movements to the tips of the surgical instruments makes the learning curve for robotic surgery much less steep than that for laparoscopic colorectal surgery. Therefore, an inexperienced laparoscopic surgeon is able to operate with the robot safely (Hellan et al, 2007). This is particularly evident for distal rectal cancers as the robot offers superior visualization and mobility during the pelvic dissection (Abodeely et al., 2010). Robotic surgery actually requires the same skill set used during open surgery and thus the learning curve at the console is relatively short (Giulianotti et al., 2003).

The learning curve of robotic assisted technology entails the surgeon's mastery of several unique skills to overcome the loss of tensile and tactile feedback by recognizing visual cues, conceptualize the spatial relationships of robotic instruments outside the active field of view

and mentally visualizing the spatial relationships of the robotic arms and cart while operating at the console (Bokhari et al., 2011).

Bokhari et al. (2011) believe that to facilitate the acquisition of robotic unique skills in a safe and stepwise manner, the surgeon should acquire expert laparoscopic skills before using the robotic approach. They divided the learning curve into three phases. Phase 1 to include 15 cases and it represents the initial part of the learning curve. Phase 2 includes an additional 10 cases to allow the consolidation of the additional experience once the initial learning curve has been completed. Phase 3 is the post-learning period when the surgeon can start offering robotic surgery for a more complex and challenging cases. The authors concluded that their data suggest that after a learning curve phase that involves of 15 to 25 cases, the surgeon may achieve a higher level of competence and consider using robotic surgery for patients presenting with more difficult cases safely.

4.6 Outcomes of robotic assisted rectal surgery

4.6.1 Evidence from case series reports & case-matched studies

Pigazzi et al. (2006) reported the first series of robotic-assisted low anterior resection with total mesorectal excision on six consecutive patients with rectal cancer. These cases were compared with six consecutive low anterior resections performed with conventional laparoscopic technique by the same surgeon. There were no conversions in either group. Operative and pathological data, complications, and hospital stay were similar in both groups. However, robotic operations appeared to cause less strain for the operating surgeon. The authors concluded that robotic-assisted laparoscopic low anterior resection for rectal cancer is feasible in experienced hands and the technique may facilitate minimally invasive radical rectal surgery. The same group published 2 further case-matched reports with bigger series (Hellan et al., 2007; Baek et al., 2011) confirming their conclusion from the initial study. They particularly highlighted the low conversion rate with robotic assisted rectal surgery.

Patriti et al. (2009) reported on the short and medium term outcome of robotic assisted and traditional laparoscopic rectal resection in a case matched study. They found that robot-assisted laparoscopic rectal resection results in shorter operative time when a total mesorectal excision is performed and significantly lowers conversion rate. Postoperative morbidity was comparable between both groups. Overall survival and disease-free survival were comparable between groups, even though a trend towards better disease-free survival in the robotic assisted group was observed.

Baik et al. (2009) compared the short-term results between robotic-assisted low anterior resection and standard laparoscopic low anterior resection in rectal cancer. Conversion rate and serious complication rate were significantly lower in the robotic surgery group. The specimen quality was acceptable in both groups with a significantly better quality of the mesorectum grading in the robotic group.

Biffi et al. (2011) investigated the estimated blood loss after full robotic low anterior resection in a case-matched model with conventional open approach. Estimated intra-operative blood loss was significantly higher in the open group. They also found that the robotic surgery group had significantly decreased length of hospital stay, increased number of harvested lymph nodes and extent of distal margin.

Pigazzi et al. (2010) reported a multicentre study on the role of robot-assisted tumour-specific rectal surgery (RTSRS) to verify, on a multicentre basis, the peri-operative and oncologic outcome of RTSRS. The study included 140 consecutive patients undergoing RTSR in three centres. Conversion rate was 4. 9%. The number of harvested nodes and margin status compared favourably with those of open series. The 3-year overall survival rate was 97% with no isolated local recurrences were found at mean follow-up of 17. 4 months. The authors concluded that RTSRS is a safe and feasible procedure and highlighted the need for randomized clinical trials and longer follow-up are needed to evaluate a possible influence of RTSRS on patient survival.

Park et al. (2011) compared the short-term outcomes in 263 patients (open group = 88 patients, laparoscopic group n = 123 & robot-assisted group n = 52). Patients from the laparoscopic & robotic assisted groups recovered significantly faster than did those from the open surgery group. The specimen quality, with a distal resection margin, harvested lymph nodes, and circumferential margin, did not differ among the three groups. The authors concluded that laparoscopic & robotic assisted surgery reproduce equivalent short-term results of standard open surgery while providing the advantages of minimal access. For experienced laparoscopic colorectal surgeon, the use of the da Vinci robot resulted in no significant short-term clinical benefit over the conventional laparoscopic approach.

4.6.2 Evidence from randomised controlled trials (RCT)

There is lack of evidence from RCT to support robotic assisted surgery for rectal cancer. The **RO**botic versus **LA**paroscopic **R**esection for **R**ectal cancer **(ROLARR)** is designed to address this issue. This is an international, multicentre, prospective, randomised, controlled, unblinded, parallel-group trial of robotic-assisted versus laparoscopic surgery for the curative treatment of rectal cancer.

The study will perform a rigorous evaluation of robotic-assisted rectal cancer surgery against conventional laparoscopic rectal cancer resection by means of a randomised, controlled trial. Key short-term outcomes will include assessment of technical ease of the operation and improved oncological outcome. Also, quality of life assessment and analysis of cost-effectiveness will be performed. Short-term outcomes will be analysed to provide a timely assessment of the new technology. Longer-term outcomes will focus on oncological aspects of the disease with analysis of disease-free and overall survival and local recurrence rates at 3-year follow-up (http://www. leeds. ac. uk/hsphr/research/AUHE/rolarr. html).

5. Extended resection techniques in laparoscopic rectal cancer surgery

In an attempt to decrease the risk of local recurrence following radical surgery for rectal cancer, techniques have been described which offer extended resection. These were originally described in open surgery, but more recently these extended resections have been also offered laparoscopically (Georgiou et al., 2009; Stelzner et al., 2011).

5.1 Laparoscopic extended lateral pelvic node dissection

Lateral pelvic lymph node involvement in rectal cancer has been well recognised for many years (Sauer et al., 1951). In Japan, lateral pelvic node dissection is performed to minimise

local recurrence and improve survival as they believe that total mesorectal excision does not clear the metastases in the lateral pelvic lymph nodes which has an overall incidence between 8. 6 to 27% (Fujita et al., 2003; Kim et al., 2008). However, evidence from meta-analysis confirms that extended lateral pelvic node dissection is associated with increased blood loss and urinary and sexual dysfunction without significant overall cancer-specific advantage (Georgiou et al., 2009). Therefore, preoperative radiotherapy or chemoradiotherapy followed by rectal resection with total mesorectal excision is the standard treatment in Western countries.

There is limited evidence in the literature on the outcomes of laparoscopic extended lateral pelvic node dissection with total meseorectal excision in patients with locally advanced rectal cancer. Advocates of the technique believe that laparoscopic approach has the potential to decrease the well known drawbacks of the open lateral pelvic wall dissection as the magnified views offer clear vision of the smallest structures in the narrow pelvis which make it easier to identify lymphatic tissue and protect the autonomic nerve plexus (Park et al., 2011). Some studies also suggest decreased blood loss and operative time with the laparoscopic approach (Fujita et al., 2003). Increasingly, robotic assisted approach has been used to perform extended lateral pelvic wall lymphadenectomy with remarks that dissection of the lymph nodes around major pelvic vessels is much easier (Park et al., 2011).

However, the currently available evidence is rather limited to make valid conclusions on the safety and outcomes of laparoscopic or robotic-assisted extended lateral pelvic node dissection in locally advanced rectal cancer.

5.2 Laparoscopic extended abdominoperineal resection for low rectal cancer

Standard abdominoperineal resection (APR) is well known to be associated with inferior oncological outcomes when compared to anterior resection for low rectal cancer (Stelzner et al., 2011). This is attributed to the relatively high incidence of intra-operative tumour or bowel perforation and positive circumferential resection margin due to the relative lack of the mesorectal fat around the lower rectum (Nagtegaal et al, 2005). This led to progressive development of an extended version of APR, now known as extended abdominoperineal resection (EAP), extralevator abdominoperineal excision (ELAP) or cylindrical abdominoperineal resection (Holm et al, 2007; Marecik et al, 2011). This technique aims at a wider circumferential resection margin at the level of the tumour bearing segment. Systematic reviews suggests that extended techniques of APR result in superior oncologic outcome in terms of lower incidence of tumour perforation and positive circumferential resection margin when compared to standard techniques (Stelzner et al., 2011).

However, extended abdominoperineal resection has been reported to be associated with higher incidence of perineal wound complications and hernia in comparison with the conventional APR. Also, lateral relatively blind excision of the levator muscles can put the neurovascular structures along the lateral pelvic wall at risk for injury which could increase the morbidity of the procedure. There are limited reports in the literature on laparoscopic and robotic assisted extended abdominoperineal resection (Marecik et al, 2011). However, the data so far are limited and more research is needed to assess the specific value of laparoscopic and robotic-assisted approach in relation to extended abdominoperineal resection.

6. Other approaches for laparoscopic rectal cancer surgery

There are few reports in the literature describing alternative approaches to rectal cancer surgey including single port access mesorectal excision (Gaujoux et al., 2011; Bulut et al., 2011; Lauritsen & Bulut, 2011), transanal or transvaginal retrieval of the specimen (Choi et al., 2009). However, the number of studies & cases are limited to make any valid conclusions. There is slow, but steadily increasing, interest in the application of completely natural orifice transluminal surgery (NOTES) in colorectal surgery (Sylla, 2010).

7. Conclusion

The debate over the optimal approach to the laparoscopic resection of rectal cancer is far from over. The short-term outcomes of conventional laparoscopic resections by experienced laparoscopic surgeons are better than those of open surgery and seem to be improving over time. The role of robotic assisted rectal surgery still needs to be better defined. There is limited evidence whether laparoscopic approach confers any long-term benefits for the patients. Also, further research is needed to establish if the different laparoscopic approaches can vary in their effect on the long term prognosis.

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Part 3

Emergency Colorectal Surgery

Emergency Surgery for Colorectal Cancer Complications: Obstruction, Perforation, Bleeding

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1. Introduction

Colorectal cancer represents the third most common cause of malignancy in men and the fourth most common cause of malignancy in women. Prevalence is estimated at 25 to 100,000 inhabitants (1).

Left colon cancer is more frequent than right colon cancer with half of colorectal cancers being situated at the level of the sigmoid colon.

There is a higher incidence of this form of malignancy in developed countries with higher living and is thought to be mainly due to environmental factors. An improvement in survival of the patients has been obtained thanks to national screening programs which enables diagnosis in the early stages which allows for treatment.

Despite current screening guidelines a large number of cases present to the surgical clinic as complications of colorectal cancer in the advanced, such as are tumoral obstruction, colon perforation, and lower GI hemorrhage.

The age of patients presenting with these complications is generally advanced, a factor which contributes to a high post-operative mortality of patients. Malignant processes evolve over a longer period in order for these complications to be produced, which is why patients are usually found to be in advanced stages of oncologic evolution with peritoneal carcinomatosis or distance metastasis. Despite this fact, radical treatment for the complicated colorectal cancer is recommended whenever possible.

2. Obstruction from colorectal cancer

The great majority of colorectal cancers have an asymptomatic or paucisymptomatic evolution over an extended period of time until they succeed in being clinically determined by a major complication. This is often a lower intestinal occlusion. Several cases have been cited whereby patients have beencompletely asymptomatic but have a sudden clinical onset. This was reported as a result of air flights, but without establishing a correlation between the flight and onset of disease (2).

Of the total colorectal cancers (CRC) 8-10% present as bowel occlusions, their variability being registered depending on the specificity of the surgical service. They do not tend to

have a favorable prognosis due to the increased age of patients, the advanced stage and the emergency nature of the surgical intervention (3).

Cancer represents the most frequent cause of large bowel obstruction, comprising 60% of the occlusions in elderly patients. Two thirds of colorectal cancers are situated at the left colon level and one third at right colon level (4).

Intestinal occlusion due to CRC has always raised problems regarding surgical treatment. Due to the fact that most of these patients are operated as an emergency, their metabolic state is insufficiently assessed and mechanically, the colon is not ready for surgical intervention. Surgical teams must make an ongoing choice between surgical treatments in one operative session and serialized surgical interventions. At present the most common choice is usually made for resection with primary anastomosis (5).

2.1 Presentation

Patients present to surgical clinic with abdominal colic pains, abdominal distension, altered mental status, and cessation of bowel transit of gas and feces. The patient is usually elderly, with altered general state, signs of neoplastic toxicity, and rich hyperseptic colon content.

As opposed to small bowel occlusions, colic-like pains are less frequent and less intense. Intestinal distension comprises solely the colic framework for a long period of time and only later does it extend to the small bowel. At this point, fecal vomiting occurs. The mechanism of vomiting is through a a reflex mechanism present in abdominal colic. On exam, distension of the abdomen on the colic frame shows dullness on percussion. In older occlusions, distension with dullness comprises the whole abdomen.

The abdomen is slightly sensitive spontaneously and to palpation. On auscultation, can be noted accentuated bowel sounds are detected. In older occlusive forms, the absence of sounds due to the presence of paralytic ileus.

At the per rectum examination, an empty rectal ampule is detected, without fecal matter. Quite often in lower rectal cancers, the tumor, which is completely stenotic, may be palpated by the exploratory finger.

Following fecal vomiting and abdominal fluid sequestration, the patient shows signs of dehydration and shock with cold, cyanotic, dried teguments and low blood pressure .

2.2 Diagnosis

Abdominal X-ray emphasizes few hydro-aeric levels situated in the colonic frame, and having a large diameter vertically. This investigation can therefore make a diagnosis of a large bowel obstruction. Abdominal ultrasound shows dilated intestinal loops with liquid content and bracing movements. It can also reveal free liquid in the peritoneal cavity, can highlight the mass formed at the colon level if it is of significant size and can also observe potential metastatic disseminations to other abdominal organs.

Abdominal CT diagnoses the obstruction and can detect the primary tumor with its potential secondary determinations with a greater precision than abdominal ultrasound.

When the general state of the patients enables, a colonoscopy can be performed, highlighting the colorectal cancer, taking a biopsy and also perform potential trans-tumoral drilling which can relieve the obstruction with the possibility of a delayed emergency surgical intervention.

A chest X Ray can also detect potential secondary pulmonary metastasis.

Due to the older age of patients and their multiple co-morbidities, an extensive pre-operative assessment is necessary, measuring creatinine, urea and electrolytes and arterial blood gases. Patients are usually dehydrated suffering from severe metabolic imbalances which must be treated at the preoperative stage.

The ECG is Compulsory part of the surgical preoperative protocol.

2.3 Differential diagnosis

A diagnosis of large bowel obstruction can be made with the aid of history taking, the objective examination, and also the additional investigations performed. However, a differential diagnosis is required mainly having to rule out small bowel obstructions with higher intestinal occlusions. These usually determine a more painful and prominent symptomatology, with more frequent and intense colicky pains, with frequent food vomiting and only later, in neglected obstructions, they become fecaloid. Abdominal X Ray highlights hydroaeric levels with central disposition, having a large diameter on the horizontal plane. Other causes must also be ruled out including intussusception, sigmoid volvulus, engagement of the colon in a hernia sac with strangulation, invasion of the colon in the framework of extension of a neoplastic process from proximity (stomach, genital, urinary, pancreas etc).

Once the tumoral cause of the obstruction is established, a differential diagnosis of causes of colonic tumors is necessary, namely stenosed vegetating benign tumors, phytobezoar etc. Often the decision for surgical treatment is made in an emergency and the final diagnosis is only made intra-operative.

2.4 Preoperative treatment

Preoperative assessment and treatment must be carefully and rapidly undertaken, in order to avoid delay of a surgical intervention in patients who may have altered mental status or unstable vital signs. Metabolic acidosis, hypo or hyperglycemia and electrolyte imbalances are corrected based on the previous investigations performed. Antibiotics are administered prophylactically at this stage and the choice is usually a second or third generation cephalosporin in conjuction with Metronizadole or Vancomycin. Also, prophylaxis of deep venous thrombosis prophylaxis is achieved with low molecular weight heparin. Symptomatic treatment may be given to relieve the distress and may includes, analgesics, antiemetics, gastric antisecretion drugs and anticholinergics (6).

Oral laxatives are contra indicated.

If there is a probability that the surgical intervention includes a colostomy, it is advisable to mark the pre-operated place of colostomy.

All other co-morbidities must be optimized whenever possible.

2.5 Treatment options

In the therapeutic strategy of obstructive colorectal cancer, application of palliative methods and other radical treatment methods are advised.. Whenever possible, treatment has to be radical.

Palliative treatment is recommended in patients with severely altered general health and advanced stage disease with hepatic non- resectable metastasis (7).

Palliative treatment can be carried out as follows: pneumatic dilation of the tumorally stenosed region with the help of a balloon or rechanneling with laser Nd-YAG which can be effective as a palliative method in 80-90% of patients.

Endoscopic setting of the auto expandable metallic prosthesis has been used more and more with greater success in the preparation of the radical or palliative surgery for a non-resectable obstructive cancer. If this procedure is performed by an experienced surgeon, the success rate is over 90% (8).

In the operable cases, the implanted stent allows the gastrointestinal transit to restart while resolving the obstruction at the same time. Subsequently, the patient's condition and biological parameters improve, also permitting the delivery of neoadjuvant therapy where needed (9).

The affected bowel reduces its dimensions, the edema disappears and blood perfusion to the bowel improves. All of these changes create the premise for a planned radical intervention to be performed. A study done by Tekkis (8) looked at two groups of patients with obstructive colon cancer and similar tumor stages. One group had an initial surgical treatment and the other group had the endoscopic prosthesis as a first step followed by a surgical intervention. In the group who received the stent prosthesis, there were 87% of cases who ended up having resection and anastomosis, compared to 41% of cases in the non-stented group.

The specific complications associated with stoma care have to be considered, as they potentially increase co-morbidities, hospital admission, and also the costs of the intervention. The post-operative evolution was better in the group of patients who received the endoscopic stent, and they also had a shorted hospital admission (8). Performing elective surgical interventions also proved to decrease post-operatory mortality.

Inserting expandable metallic stents is the intervention of choice for tumors in the advanced stages, with metastasis and peritoneal carcinomatosis.

A study done by Jeffrey H. Lee et al (10) showed that this method is safe and feasible. When it was performed by an experienced team, it had a success rate of 94%. Re-obstruction caused by the tumoral proliferation was noted in 7.3% cases. Death occurred due to specific complications related to the neoplastic process rather than surgical interventions.

Some of the disadvantages of the stenting process are related to the iatrogenic complications as a result of inserting the prosthesis in emergency conditions. Watt et al (11) noted that the rate of complications was of 27%. These include stent migration (11%), perforation (4.5%) and tumoral growth with stent obstruction (12%).

Radical treatment can be performed during a surgical intervention or during serialized interventions. In the course of history, the following were performed: at the end of the 19th century Paul-Mikulicz performed the intervention in one single operative session through externalizing the colon together with the tumor, which was resected postoperatively and an external anastomosis with a special clamp was performed. This operation was performed in one single intervention and has the advantage of lowering operative mortality by 70% compared to previous procedures, but also has the disadvantage of a high local recurrence. At the beginning of the 20th century the procedure used was one completed in three separate interventions:

1. colostomy which resolved the occlusion,
2. resection of the tumor and ultimately
3. restoring the intestinal transit. The advantage of this method is that it was performed on a mechanically stable colon but had the great disadvantage of a high morbidity rate of 30% (30% the morbidity rate) and mortality of 7% for each operative intervention In 1921, Hartmann proposed a procedure divided into two phases resection of the tumor with terminal colostomy subsequently followed by restoring of the intestinal transit. The advantage consists of rapid removal of the tumor and resolving the occlusion. The anastomosis is not performed on unfavorable terms, but the disadvantage is that of summation of mortality and morbidity indexes for each operative session, given that reintegration in transit is made through a new laparotomy.

The objective of analyzing the historical data was to avoid serialized operative disadvantages and surgical intervention in one operative session with primary anastomosis as the preferred option (12), (13).

2.6 Surgical options in obstructive colorectal cancers

Surgical attitude is different depending on the localization of tumor.

In right colon cancers the indicated operation is right hemicolectomy with primary ileotransverse anastomosis. In elderly patients with increasing age, a significantly altered general state or peritoneal carcinomatosis, the accepted operation is ileotransverse anastomosis with short circuiting of the tumoral obstacle.

In transverse colon cancers, the unanimously accepted surgical intervention is the single resection with a primary anastomosis. In special cases with very significant colon distension, elderly patients with multiple organic deficiencies, a very altered general state or peritoneal carcinomatosis, two phases are indicated for the intervention: colostomy immediately upwards from the tumor then followed by segmentary resection with colo-colonic anastomosis.

Cancers localized to the left colon level have the greatest number of controversies regarding operations in a single session or in two sessions. It is ideal to have a left hemicolectomy with primary colo-rectal anastomosis. If there is an insufficient preparation of the colon, there is a leakage at the hydro-pneumatic test, or anastomosis tension, a protection colostomy is recommended for execution or a provisional ileostomy. If there is severe distension of the colon, technical difficulties in resecting the tumor or ASA (American Society of Anesthesiologists) score >3 (high operative risk), a two step surgical intervention is recommended. The primary step consists of a colostomy, which frees the patient from occlusion, or Hartmann type operation, and resection with anastomosis, or anstomosis as secondary step, respectively. Due to the fact that many patients with left colon cancer are admitted for surgical intervention with an obstruction which evolves over a longer period and therefore there is marked distension of the entire colonic frame, in such cases subtotal colectomy with primary anastomosis was proposed. The advantages of the procedure consisted of removing potential synchronous cancers which were left undiagnosed at the preoperative stage due to the urgent nature of the surgical intervention. Also there is a small risk of fistula for the ileo-colonic anastomosis, similar to that of elective surgery,. The procedure eliminates the necessity for post operative follow-up colonoscopy. Disadvantages consist of extending the surgical intervention with a subsequent increase in operative risk

and in the presence of numerous stools postoperatively. There are still a multitude of controversies regarding the treatment of such lesions.

In rectal cancers surgical attitude is dictated by the patient's general state, localization and oncologic stage of the tumor. Either an anterior rectum resection of the tumor with primary anastomosis, a Hartmann operation or a simple colostomy can be performed.

2.7 Postoperative treatment

At the post operative stage, intensive rebalancing of the patient is continued, low molecular weight heparin is administered prophylactically to prevent thromboembolic complications and a further prophylactic dose of antibiotic is administered.

Drainage disturbances are monitored and suppressed as early as possible. Nutrition with liquid intake is restarted upon resolution of the ileus, followed by solid food once intestinal transit is restored.

Skin threads are suppressed 7 to 10 days post operatively.

The results of surgical treatment are less effective because they are performed in emergency situations and add multiple surgical risk factors. In 2005, Coco detected a 44% morbidity and a 4% mortality in emergency surgery of these tumors compared to 12% morbidity and 0% mortality in the elective surgery of the of tumors in the same locations (14).

Zhang MS and his collaborators (15) highlighted the fact that the prognosis of patients with occlusive neoplasms of the left colon and of the rectum depends on the TNM stage of the disease, the preoperative level of CEA, and the radical nature of the surgical intervention.

Localization of the occlusive tumor does not influence the prognosis (16).

2.8 Personal experience

In the Surgery Clinic No III from Cluj-Napoca, the treatment approach of occlusive colorectal cancers is surgical. In all situations where the disease is potentially treatable and the general and local state of the patient enables, resection is performed within oncologic safety limits as well as regional lymphadenectomy with reconstruction of continuity through primary anastomosis. If the bowel is highly distended and edematous, a Hartmann type intervention is performed or a resection with anastomosis and protective ileostomosis. In patients with severely altered general state, in those with a surgically surpassed disease, an upward colostomy or internal derivation is performed.

2.9 Conclusion

Occlusive colorectal cancers are severe forms of disease which represent a serious problem of therapeutic strategy, that is still intensely debated at present. Whenever possible, a radical surgical treatment is indicated with a single operative resection and primary anastomosis.

3. Perforated CRC

The incidence of perforated colorectal cancer is approximately 2.3-2.5% of the total number of surgically treated colorectal cancers (3). This is not a very common complication; however it is

very serious due to the severe peritonitis that results. Perforations of the colon have been documented in the literature after administration of bevacizumab for malignant tumors of the colon (17).

3.1 Introduction

Colorectal cancer can present emergently as a colonic perforation as a result of leakage of the hyperseptic content into the peritoneal cavity and subsequently causing localized or generalized peritonitis. The perforation can be produced in a juxtatumoral position or or at some distance from the tumor, the so-called diastatic perforation. It usually appears in large neoplasms which evolve over a longer period of time, being therefore advanced from a regional perspective. Diastatic perforation appears in left colon cancers which undergo complete stenosis and result in upwards colon distension. The vascularization of the cecum where the perforation occurs, results in the outflow of the hyperseptic stasis content into the peritoneal cavity with consecutive peritonitis. Juxtatumoral perforation appears most frequently in right colon cancers and causes an abscess which subsequently perforates into the free peritoneum.

Tumoral perforation appears in the advanced stages of the disease. In the study conducted by Masaichi Ogawa and his collaborators (18) it is shown that in 53% of cases the disease is in stage IV, while in 37% it is in stage IIIb and in 10% stage IIIa.

3.2 Presentation

Patients are referred to the hospital showing signs of an acute surgical abdomen. Abdominal pain is intense and diffused with low blood pressure, cold cyanotic teguments, and altered general health state. The history taking reveals colon distress manifested as diarrhea alternating with constipation, weight loss and stools with blood, mucus and pus.

On exam, patients can show signs of septic shock, with general abdominal muscular contraction and peritoneal irritation. In the later stages they can present with a distended abdomen without intestinal peristalsis with an intensely altered general state and signs of shock.

In the case of intra peritoneal abscess which has not yet opened into the entire peritoneal cavity, signs of peritonitis are localized at the tumor level which may be palpated on exam. If the perforation has led to the formation of a retroperitoneal abscess, the patient usually presents with a septic state associated to subcutaneous emphysema and abdominal wall cellulites.

3.3 Diagnosis

The diagnosis is mainly clinical and demands urgent surgical treatment.

Abdominal X-rays display pneumoperitoneum in the case of free perforation in the peritoneal cavity. Marked cecum distension can be discerned with diastatic perforation imminence even before its onset.

X-rays and abdominal CT scan show a consecutive intraperitoneal abscess in the blocked tumor perforation. Laboratory investigations reveal an important leukocytosis with potential signs of secondary renal failure from the emergent peritonitis.

3.4 Differential diagnosis

The juxtatumoral perforation of the cecum with consecutive abscess must be distinguished from a gangrenous and blocked appendicitis. This situation is especially due to the fact that this form of appendicitis can be seen in the elderly patients. In addition to cancer of the cecum may present in this manner. The ultimate diagnosis can often be established only after the histopathological examination of the surgical resection piece.

Perforated cancer of the sigmoid colon must be differentiated from perforated sigmoid diverticulitis with abscess, which often presents with a similar clinical picture. In this case too, the final diagnosis is histopathological.

Retroperitoneal abscess following perforation of left or right colon cancer must be differentiated from a retroperitoneal abscesses of renal origin. This differentiation can be performed following imaging explorations which reveal renal modifications.

3.5 Preoperatory preparation

The preoperative preparation needs to be short but thorough insofar as generalized peritonitis is concerned, so as not to delay the surgical intervention and miss the appropriate moment for surgical intervention. Shock therefore needs to be treatedand patients require a wide spectrum antibiotic prophylaxis, and finally basic preoperatory protocols (ECG, biochemistry, arterial blood gases, chest X-ray, etc).

3.6 Treatment

Due to the neoplastic background on which the hyperseptic peritonitis occurs, any large-scale surgical intervention resulting in anastomosis must be avoided as it is shown to have poor outcomes.

It is crucial for the treatment to be marked as high emergency. Together with the extended resections, this can improve the prognosis (19).

Treatment of the peritonitis mainly consists of abundant washing of the peritoneal cavity, multiple drains, and broad spectrum antibiotics.

The approach of the perforated tumor is different depending on the local situation. If it can be removedeasily, that can be done without an anastomosis, and instead through an upward terminal colostomy with closure of the remaining distal end (Hartmann type intervention) (20). If the tumor cannot be easily resected, a simple upwards derivative colostomy is performed or an ileostomy associated with the aforementioned peritonitis treatment. After the general condition of the patient improves, surgical intervention is performed and completed to remove the perforated tumor, if possible.

In case of diastatic perforation of the cecum, surgical treatment is a subtotal colectomy with ileostomy followed by the reconstruction of intestinal transit through an ileocolic or ileorectal anastomosis when the patient's condition improves.

3.7 Postoperative treatment

In the postoperatory stage, the antibiotic treatment of peritonitis continues, as well as the hydroelectrolythic and acid-base rebalancing as and venous thrombosis. Drains and colostomies are monitored and drains should be discontinued when deemed appropriate.

An improved survival rate at 5 years is associated with administration of postoperative chemotherapy, compared with patients who did not receive this following release from hospital (21).

3.8 Prognosis

Prognosis of this complication is linked to the evolution and stage of tumor and to the severity of the peritonitis. In general, this complication carries an unfavorable prognosis, especially in case of diastatic perforation (22).

Mortality reaches 30 to 40% in cases of tumor perforation. In cases of diastatic perforation, mortality is between 50% and 68% (23), (24). If cases of death are excluded shortly after the intervention, the prognosis of perforated colorectal cancers is similar to that of unperforated cancers in the same stage (25).

4. Colorectal haemorrhagic cancers

4.1 Introduction

Hemorrhagic cancers are those cancers of the rectum and colon which manifest as colorectal bleeding. This is usually presents as melena for those cancers situated at the right colon level or as rectorrhagia with fresh blood for those situated in more distal positions, especially those situated at the recto-sigmoid level (1). Cancers that present as severe hemorrhage are rare; but they usually manifest through rectorrhagia and are extremely critical (26). Such cases require emergency surgery due to hemorrhage and the immediate goal of the treatment is obtaining hemostasis. Radical treatment of colorectal cancer is encouraged whenever possible.

4.2 History

The patient is referred to a physician in order to determine the presence of blood in the stool, either as dark stool (melena), or as fresh blood. Symptoms usually appear in a patient with previous stool disturbances, with alternating diarrhea-constipation, weight loss over a couple of months and altered general condition. The patient also may have a history of abdominal pains often colicky-like. For recto-sigmoid cancers the patient can present with rectal tenesmus and pathological products in the stool (eg. mucus). Usually patients are pale and frail, showing signs of acute or chronic anemia. At the rectal examination, fecal occult blood may be detected.

4.3 Diagnosis

In the presence of lower gastro-intestinal hemorrhage, colonoscopy is performed and highlights the presence of colorectal cancer with localization of the hemorrhagic source. Biopsies are collected for the histopathological diagnosis. Abdominal ultrasound and CT scan establishes the lesional abdominal record by emphasizing the local and regional extension of the lesion. Pulmonary radiologic exploration detects any eventual pulmonary disseminations of the colorectal cancer.

The TC99 scintigraphy has a reliability of 100% and a sensitivity of 91% in establishing the source of hemorrhage (27).

Biochemical and hematological explorations are compulsory for the preoperatory inventory. Microcytic hypochromic anemia is usually detected, requiring preoperatory correction with blood transfusion.

4.4 Differential diagnosis

A differential diagnosis has to be made between lower and upper gastro-intestinal tract hemorrhage. Upper digestive hemorrhage originates above the ligament of Treitz and it is usually manifested through hematemesis and melena. If the hemorrhage is significant it can manifest itself as a rectorrhagia, but is usually associated with hematemesis. Emergency colonoscopy branches out the diagnosis. Apart from colorectal cancer there are other diseases which can evolve with rectorrhagia, for example ulcero-hemorrhagic rectocolitis, benign tumors which can cause bleeding, intestinal mesenteric infarct, intestinal invagination, etc. However, the clinical picture is different to that of colorectal cancer, as there can be present signs of peritonitis and shock (intestinal-mesenteric infarct) or of bowel obstruction (invagination). At the distal gastro-intestinal tract, the cause of rectorrhagia can be represented by hemorrhoids or anal fissure, which can be detected through anoscopy and rectal examination.

4.5 Preoperative treatment

The preoperative assessment and treatment is usually performed as an emergency in order not to delay surgical intervention. Correction of anemia is necessary through transfusion of packed red blood cells, often rh- because of the emergent nature.

Electrolytes should be monitored and corrected as appropriate.

4.6 Treatment

The objective is to remove the source of hemorrhage, i.e. the source of colorectal cancer. If possible, an intervention with radical aim is performed when the patient's general condition allows it.

Therefore, in right colon hemorrhagic cancers a right hemicolectomy is performed, while in left colon cancers a left hemicolectomy. In recto-sigmoid cancers a resection or rectum amputation is planned depending on the distance from the tumor to the anal margin.

There are situations when the cancer is in the advanced stages, making it impossible to be removed. In these cases a derivative process can be performed with anupward colostomy type or the colo-colonic or entero-colonic derivation thus putting the colon to rest in the hope that in the absence of local trauma represented by the fecal discharge, the hemorrhage will stop.

4.7 Postoperatory treatment

Resuscitation procedures initiated at the pre operatory stage are continued with whole blood transfusions or packed red blood cells and prophylactic antibiotics aiming to correct the hemorrhagic shock.

The stoma and the surgical trauma are appropriately treated.

4.8 Results and prognosis

These depend on the stage of evolution of the colorectal cancer and advanced forms with marked regional invasion have a poor prognosis.

5. Conclusions

Fortunately, complicated colorectal cancers with significant hemorrhage are rare. They usually present with occult bleeding and chronic signs of anemia.. The advanced regional forms with severe hemorrhage from the necrosed tumor unfortunately have little therapeutic options and results are poor.

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Part 4

Postoperative Follow-Up

Surveillance and Characteristics of Recurrence After Curative Resection for Colorectal Cancer

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1. Introduction

Cancer is the leading cause of death in economically developed countries and the second leading cause of death in developing countries.[1] In developed counties, colorectal cancer is the second leading cause of cancer death in men and the third leading cause of cancer death in women.[2] In developing countries, colorectal cancer is the fifth leading cause of cancer death in men and the sixth in women. Worldwide, colorectal cancer is the fourth leading cause of cancer death in men and the third in women.[2]

The most promising treatment for colorectal cancer is curative surgery. However, some patients recur after curative resection.[3] In order to detect and treat recurrent tumors earlier, a post-operative surveillance after curative resection for colorectal cancer is in clinical use, although an optimal surveillance system for patients with curative resection for colorectal cancer is still uncertain.

In this chapter, we describe some topics concerning surveillance and characteristics of recurrence after curative resection for colorectal cancer as follows:

i.   historical review of surveillance
ii. characteristics of recurrence
iii. surveillance tools
iv. recommended surveillance from European Society for Medical Oncology (ESMO), American Society of Clinical Oncology (ASCO), and Japanese Society for Cancer of the Colon and Rectum (JSCCR)

2. Historical review of surveillance after curative resection for colorectal cancer

2.1 Randomized controlled study

The consensus on the optimal surveillance schedule after curative resection for colorectal cancer has not been established. Six randomized controlled trials (RCT) were reported to validate the usefulness of intensive surveillance after curative resection for colorectal cancer (Table 1).[4-9] In all RCTs, there were no differences in recurrence rate between patients with

and without intensive follow-up. There was a description of time to recurrence after curative resection for colorectal cancer in three RCTs.[4,5,7] Intensive surveillance led to earlier detection of recurrence in all three RCTs. As for curative resection rates of recurrent tumor, in three RCTs, intensive surveillance led to more frequent curative resection for recurrent tumor.[4,7,9] On the other hand, in two RCTs, there were no differences in resection rates of recurrent tumor.[5,6] Two RCTs disclosed the better survival in the intensive group,[7,9] although the majority of RCTs failed to show a survival benefit of intensive surveillance after curative resection for colorectal cancer.[4-6,8]

2.2 Meta-analysis

Although six RCTs have been conducted, all trials were underpowered or unsatisfactory. Therefore, three meta-analyses using the data of these RCTs evaluated the usefulness of intensive surveillance.[10-12] There was no significant difference in recurrence rate between patients with intensive surveillance and those with non-intensive one. Renehan et al. reported that intensive surveillance led to earlier detection of recurrence after curative resection for colorectal cancer.[12] Jeffery et al. clarified that intensive surveillance led to higher resection rate of recurrent tumor.[11] In all meta-analyses, intensive surveillance improved survival after curative resection for colorectal cancer.

3. Characteristics of recurrence after curative resection for colorectal cancer

The Japanese Society for Cancer of the Colon and Rectum (JSCCR) organized the study group on post-surgical surveillance after curative resection for colorectal cancer in 2003. The data were collected from 14 institutions which were the members of JSCCR. The recurrence rate after curative resection for colorectal cancer was investigated according to the TNM stage and the recurrence site.[3] The data of 5,230 patients who underwent curative resection for colorectal cancer from 1991 to 1996 were collected. Among 5,230 patients, 3,583 had colon cancer and 1,647 had rectal cancer. Among these, 906 patients (17.3%) developed a recurrence during the median surveillance of 6.6 years. The characteristics of patients are shown in Table 2. The recurrence rate was significantly higher in patients with rectal cancer (24.3%) than in those with colon cancer (14.1%, p<0.0001).

3.1 Recurrence by TNM stage

The recurrence rate in each stage was 3.7% in stage I, 13.3% in stage II, and 30.8% in stage III, respectively (p<0.0001). In each stage, the recurrence rate in patients with rectal cancer was higher than that in patients with colon cancer. The recurrence rates after curative resection for stage I, II, and III colon cancer were 2.7%, 12.1%, and 24.3%, respectively. Those after curative resection for stage I, II, and III rectal cancer were 5.7%, 16.7%, and 43.2%, respectively. The speed of recurrence in patients with stage I cancer was slow and constant (Figure 1a). On the other hand, the recurrence appeared rapidly within 3 years after curative resection for stage II and III colorectal cancer (Figure 1b and 1c). The cumulative appearance rates of recurrence at 3 years for stage I, II, and III were 68.6%, 76.9%, and 87.0%, respectively. Those at 5 years were 96.1%, 92.9%, and 97.8%, respectively. Recurrence after 5 years was rare for all three stages: 0.14% (2/1367), 0.94% (18/1912), and 0.67% (13/1951), respectively.

Author	Year	Number of patients	Study design	Recurrence rate	Time to detection of recurrence	Resection rate of recurrent tumor	Prognosis
Kjeldsen et al. [4]	1997	597	RCT	26% : 26% (NS)	18 months : 27 months (p<0.01)	20% : 7% (p<0.01)	5-year survival rate 70% : 68% (NS)
Makela et al. [5]	1995	106	RCT	42% : 39% (NS)	10 months : 15 months (p = 0.002)	22% : 14% (NS)	5-year survival rate 59% : 54% (NS)
Ohlsson et al. [6]	1995	107	RCT	32% : 33% (NS)	–	29% : 17% (NS)	5-year survival rate 75% : 67% (NS)
Pietra et al. [7]	1998	207	RCT	Local recurrence 25% : 19% (NS)	Local recurrence 10 months : 20 months (p<0.0003)	Local recurrence 65% : 10% (p<0.01)	5-year survival rate 73% : 58% (NS)
Schoemaker et al. [8]	1998	325	RCT	34%, 41% (NS)	–	–	5-year survival rate 76% : 70% (NS)
Secco et al. [9]	2002	358	RCT	53% : 57%	–	31% : 16% (p<0.05)	5-year survival rate in high risk group 50% : 32% (p<0.05) 5-year survival rate in low risk group 80% : 60% (p<0.01)
Figueredo et al. [10]	2003	1679	Meta-analysis	NS	–	–	Hazard ratio in intensive group 0.80 (p = 0.0008)
Jeffery et al. [11]	2002	1342	Meta-analysis	Odds ratio 0.91 (NS)	–	24% : 9%	Hazard ratio in intensive group 0.73 (p = 0.007)
Renehan et al. [12]	2002	1342	Meta-analysis	32% : 33% (NS)	8.5 months earlier in intensive group (p<0.001)	–	Hazard ratio in intensive group 0.81 (p = 0.007)

Table 1. Trials concerning surveillance after curative resection for colorectal cancer

		Patients with relapse (%)	Patients without relapse (%)	Total	P value*
Number of patients		906 (17.3)	4324 (82.7)	5230	
Age		62 ± 11	63 ± 11	63 ± 11	NS**
Gender					
	Male	559 (18.0)	2546 (82.0)	3105	NS***
	Female	347 (16.3)	1778 (83.7)	2125	
Primary tumor site					
	Colon	506 (14.1)	3077 (85.9)	3583	p<0.0001***
	Rectum	400 (24.3)	1247 (75.7)	1647	
TNM stage					
	Stage I	51 (3.7)	1316 (96.3)	1367	
	Stage II	255 (13.3)	1657 (86.7)	1912	p<0.0001***
	Stage III	600 (30.8)	1351 (69.2)	1951	
Median follow-up peric		3.5 ± 2.9	7.1 ± 3.1	6.6 ± 3.1	p<0.0001**

* Characteristics of patients with relapse compared to those without relapse, **Man-Whitney U test, ***chi-square test.

Table 2. Characteristics of patients
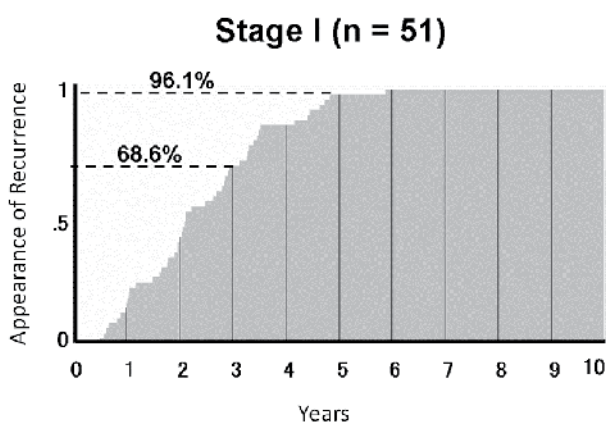
Fig. 1a. The cumulative appearance rate of recurrence after curative resection for stage I (a), stage II (b), and stage III (c) colorectal cancer.
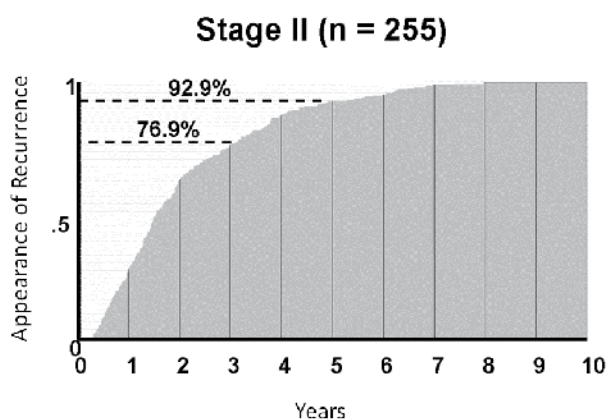
Fig. 1b. The cumulative appearance rate of recurrence after curative resection for stage I (a), stage II (b), and stage III (c) colorectal cancer.
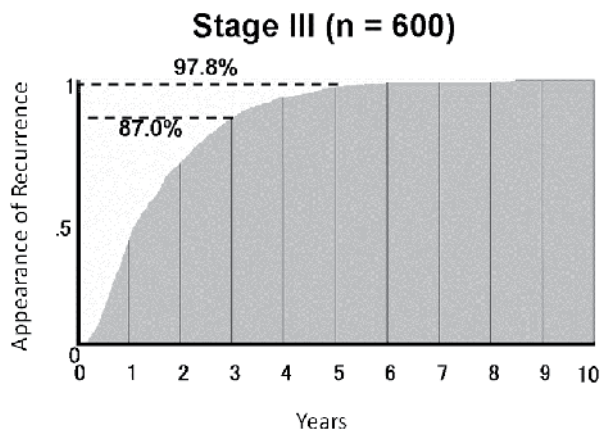
Fig. 1c. The cumulative appearance rate of recurrence after curative resection for stage I (a), stage II (b), and stage III (c) colorectal cancer.

An intensive surveillance program could be adopted in stage II and III patients for the first 3 years and less intensive program for the next 2 years. Patients with stage I colorectal cancer could be followed less intensively.

3.2 First recurrence site

A study using autopsy reported that the most frequent metastatic site from colorectal cancer was the liver followed by the lung.[13] This was consistent with our study (Table 3).[3] The liver was the most frequent recurrent site after curative resection for colon cancer (7.0%). The second was the lung (3.5%). The local recurrence was most frequent after curative resection for rectal cancer (8.8%). The lung and the liver were the second and the third frequent metastatic sites. There was no difference in hepatic recurrence rate between patients with colon cancer and those with rectal cancer, while the pulmonary, local and anastomotic recurrence rates after curative resection for rectal cancer were significantly higher than those for colon cancer. In each recurrent site, approximately 80 to 90% of recurrence developed within 3 years (Figure 2). More than 95% of anastomotic recurrence was found within 3 years after curative resection for colorectal cancer (Figure 2d). In 5 years after curative resection for colorectal cancer, more than 95% of recurrence was found in each recurrent site (Table 4).

In this study, there was no patient with preoperative radiotherapy for rectal cancer. At present, the standard therapy for rectal cancer is total mesorectal excision with preoperative chemoradiotherapy in many countries.[14-18] Six percent of the patients with preoperative combined modality therapy for rectal cancer followed by total mesorectal excision developed a recurrence over 5 years.[19] In their study, of the 67 patients who developed recurrent disease, 4 (6%) had recurrent disease documented greater than 5 years following surgery. Three of these 4 patients had a distant recurrence, and 1 had both a local and distant recurrence. The recurrences were documented 61, 71, 76, and 96 months following curative rectal resection.

Therefore, the surveillance after 5 years might be necessary if patients receive radiotherapy or adjuvant chemotherapy.

		Colon	(%)	Rectum	(%)		P value*
		Patients with relapse		Patients with relapse			
Number of patients							
		506/3583	(14.1)	400/1647	(24.3)		p<0.0001**
Gender							
	Male	306/2066	(14.8)	253/1039	(24.4)		p<0.0001**
	Female	200/1517	(13.2)	147/608	(24.2)		p<0.0001**
TNM stage							
	Stage I	24/891	(2.7)	27/476	(5.7)		p = 0.0056**
	Stage II	171/1410	(12.1)	84/502	(16.7)		p = 0.0091**
	Stage III	311/1282	(24.3)	289/669	(43.2)		p<0.0001**
First recurrence site							
	Liver	252/3853	(7.0)	121/1647	(7.3)		NS**
	Lung	126/3583	(3.5)	124/1647	(7.5)		p<0.0001**
	Local	64/3583	(1.8)	145/1647	(8.8)		p<0.0001**
	Anastomotic	9/3583	(0.3)	13/1647	(0.8)		p = 0.0052**
	Others	130/3583	(3.6)	69/1647	(4.2)		NS**

* Recurrence rates in patients with colon cancer compared to those with rectal cancer, ** chi-square test, *** Mann-Whitney U test

Table 3. Comparison of recurrence rates between patients with colon cancer and those with rectal cancer

First recurrence site	% recurrence (observed recurrences /5230)	Cumulative appearance rate of recurrence (%)		
		within 3 years	within 4 years	within 5 years
Liver	7.1 (373)	87.9	94.1	98.7
Lung	4.8 (250)	77.7	88.8	94.8
Local	4.0 (209)	81.1	90.3	96.1
Anastomotic	0.4 (22)	95.5	95.5	95.5
Others	3.8 (199)	79.8	91.4	95.5

Table 4. Recurrence rates by the initial recurrence site

Liver (n = 373)
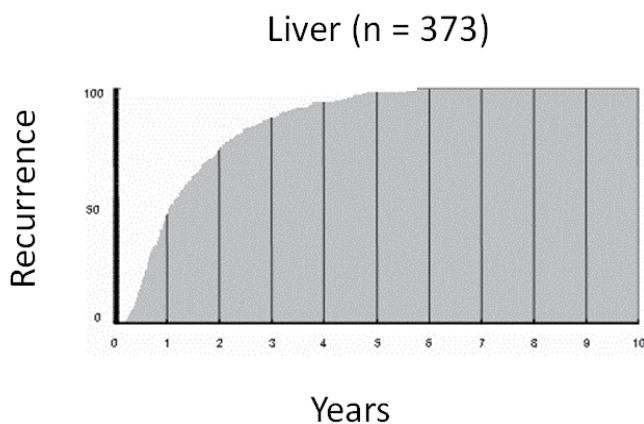

Fig. 2a. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).
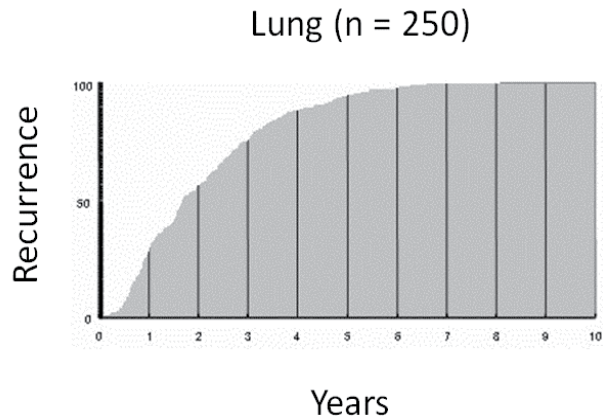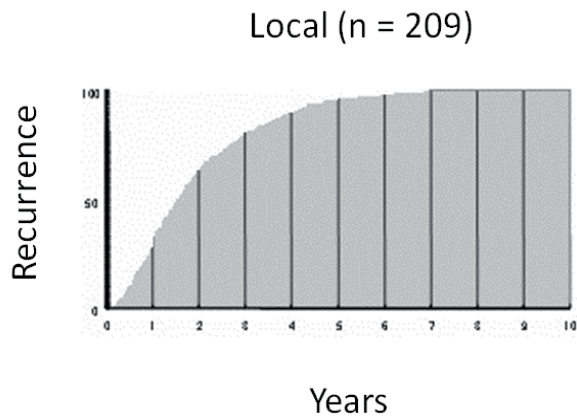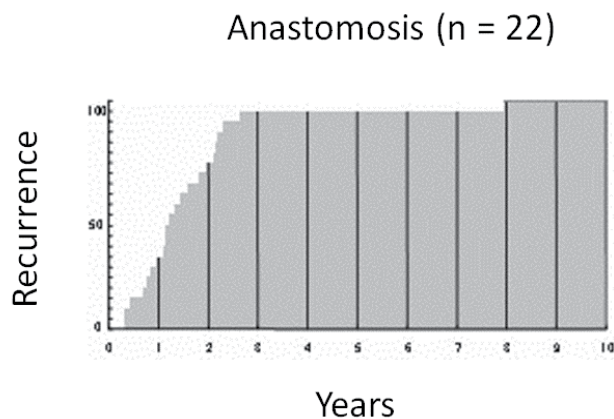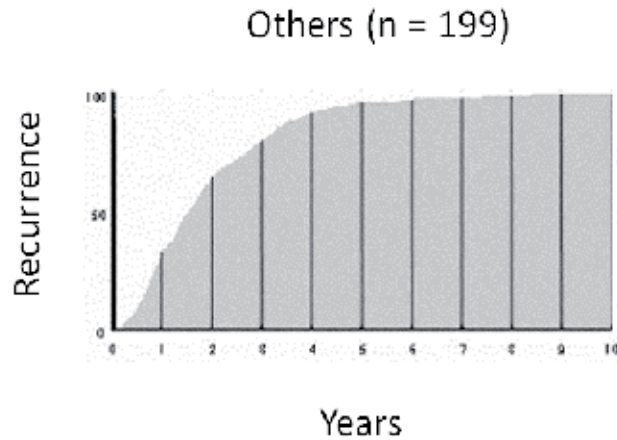
Lung (n = 250)

Fig. 2b. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

Local (n = 209)

Fig. 2c. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

Anastomosis (n = 22)

Fig. 2d. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

Others (n = 199)

Fig. 2e. The cumulative appearance rate of recurrence in liver (a), lung (b), local (c), anastomosis (d), and others (e).

3.3 Survival

According to the Japanese data, the 5-year overall survival rates in patients with stage I, II, and III colon cancer were 92.8%, 85.5%, and 76.2%, respectively (Figure 3a). Those in patients with stage I, II, and III rectal cancer were 92.2%, 84.6%, and 62.0%, respectively (Figure 3b).[3] These outcomes seem to be better than those of the patients in the Surveillance, Epidemiology, and End Results (SEER) population-based data from 1992 to 2004. According to the SEER data, the 5-year survival rates in patients with stage I, T3N0, and T4N0 colon cancer were 76.3%, 66.7%, and 55.0%, respectively.[20] Those in patients with stage III colon cancer varied from 73.7% (T1-2N1a) to 12.9% (T4bN2b).
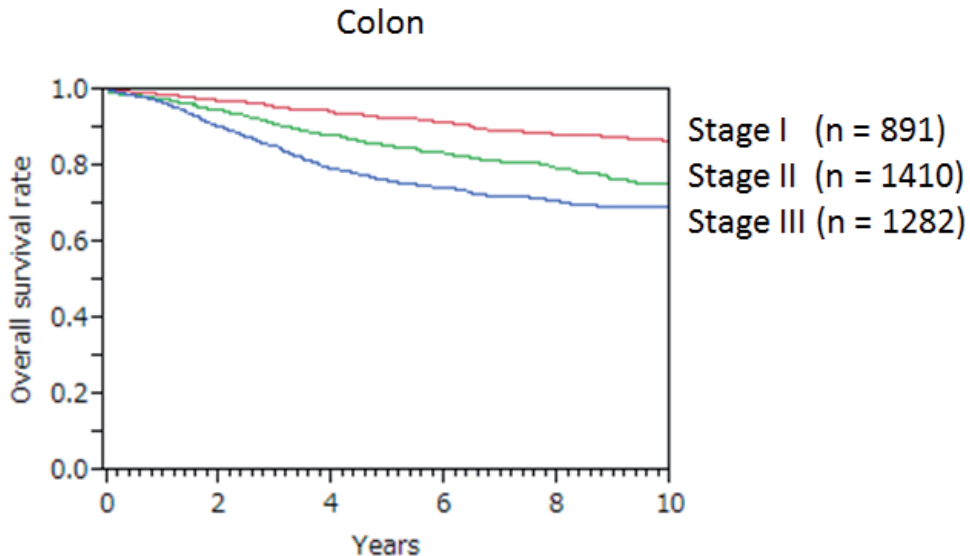
Colon

Fig. 3a. The overall survival curve after curative resection for cancer of the colon (a) and rectum (b).
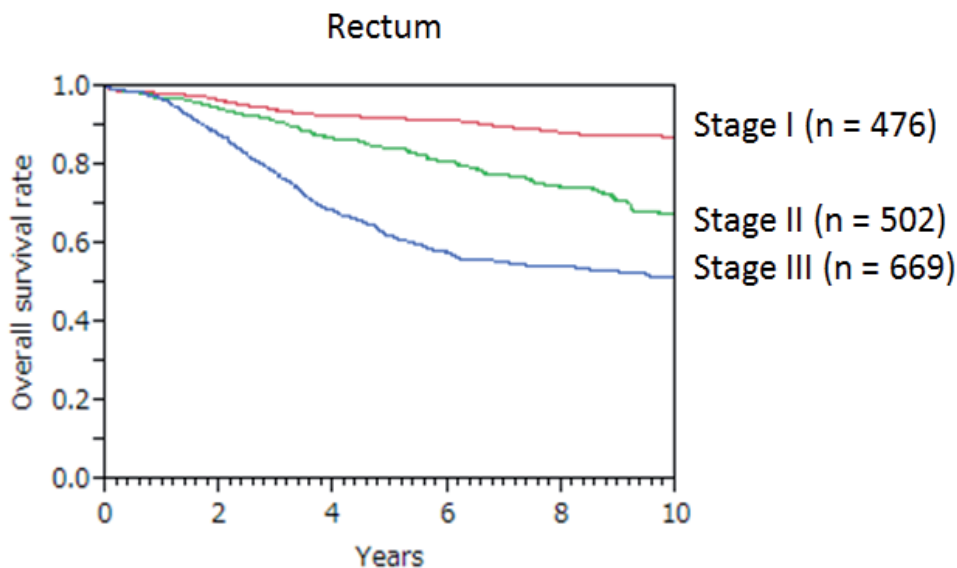
Fig. 3b. The overall survival curve after curative resection for cancer of the colon (a) and rectum (b).

In terms of rectal cancer, the 5-year overall survival rates in Japanese patients with stage I, II, and III rectal cancer were 92.2%, 84.6%, and 62.0%, respectively. According to the SEER data, the 5-year observed survival rates in patients with stage I, T3N0, and T4N0 rectal cancer were 77.6%, 64.0%, and 50.5%, respectively.[21] As for stage III rectal cancer, the 5-year observed survival rates varied from 75.7% (T1N1a) to 12.3% (T4bN2b).

In each stage, the prognosis of the Japanese patients with colorectal cancer was better than that of US patients. One of the possible reasons might be the difference of surveillance system after curative resection for colorectal cancer. The Japanese patients with curative resection for colorectal cancer usually receive more intensive surveillance to detect recurrence than the American patients. Another possible reason might be the difference of surgical technique. The Japanese surgeons usually perform central vascular ligation to dissect regional lymph node. Some European institutions adopt the similar technique called complete mesocolic excision with central ligation. Hohenberger et al. presented an excellent outcome of patients who underwent complete mesocolic excision with central ligation.[22] However, most institutions in the Western countries do not adopt this technique.[23]

3.4 Resection for recurrence

In our study, among the 906 patients with recurrence after curative resection for colorectal cancer, 379 (41.8&) underwent resection for recurrence with curative intent.[3] The prognoses of patients with resection for recurrence were better than those without resection. The 5-year survival rates after initial colorectal surgery in patients with and without resection for hepatic, pulmonary, local, and anastomotic recurrence were 55% and 11% (p<0.0001), 68% and 13% (p<0.0001), 48% and 22% (P = 0.0002), and 53% and 0% (p = 0.0003), respectively (Figure 4). The 5-year survival rates after resection for hepatic, pulmonary, local, and anastomotic recurrence were 45%, 48%, 27%, and 33%, respectively.

Liver (n = 373)

Overall Survival

55%

resection n = 172

p < .0001

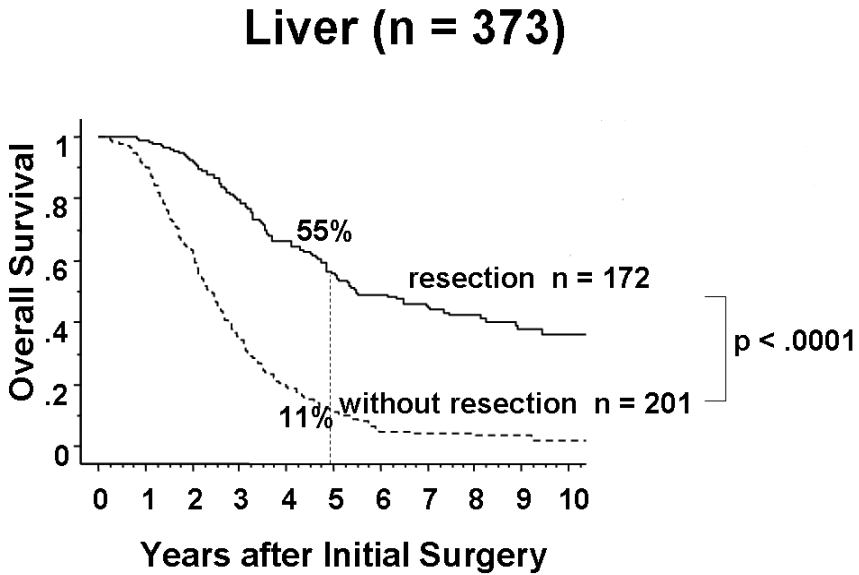11% without resection n = 201

Years after Initial Surgery

Fig. 4a. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).
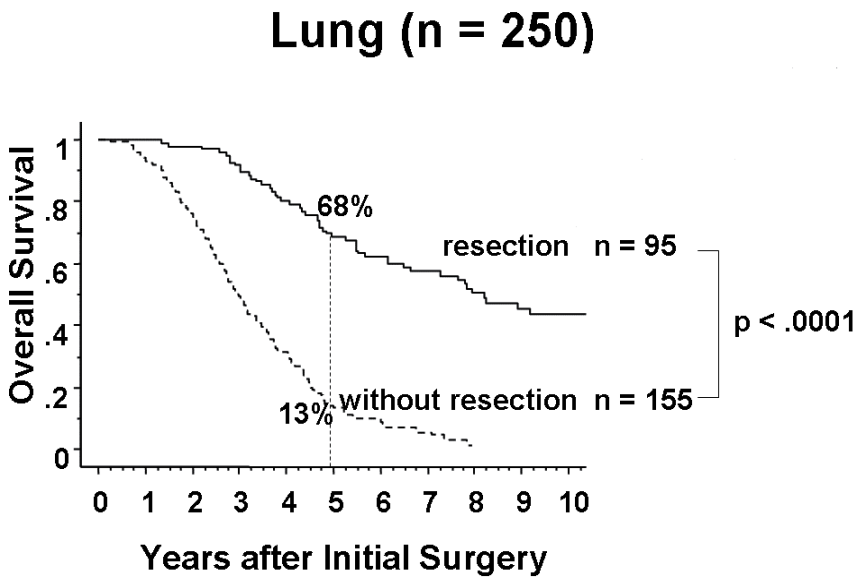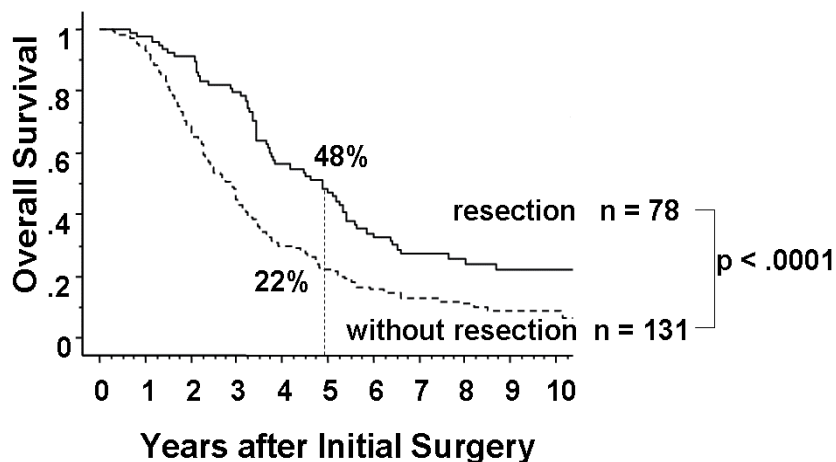
Lung (n = 250)

Overall Survival

68%

resection   n = 95

p < .0001

13% without resection n = 155

Years after Initial Surgery

Fig. 4b. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).

Local recurrence (n = 209)

Fig. 4c. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).
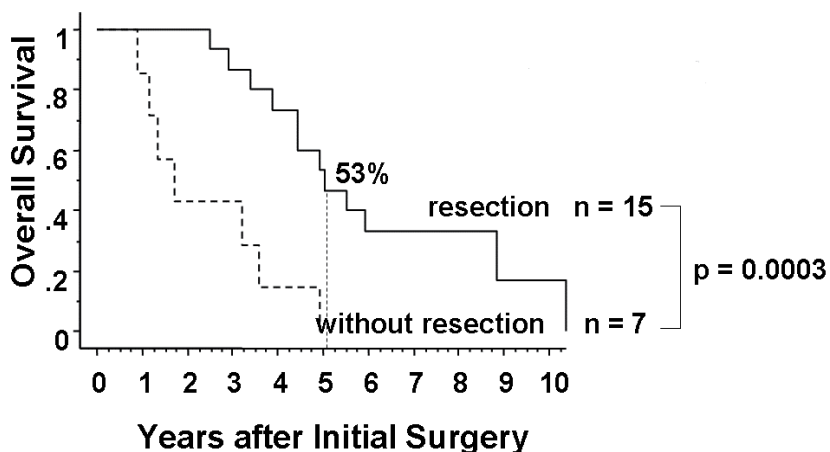
Anastomosis (n = 22)

Fig. 4d. The outcomes after initial colorectal surgery in patients with and without resection for recurrence of liver (A), lung (B), local (C), and anastomosis (D).

3.5 Timing of recurrence

Patients were classified into three groups according to the timing of recurrence (TR): TR≤1 year, 1<TR≤3 years, 3 years<TR. The earlier the hepatic, pulmonary, and local recurrence, the poorer the survival after initial colorectal surgery (Figure 5).[24] If patients had resection for recurrence, there was no difference in survival after recurrence according to the timing of recurrence (Figure 6).
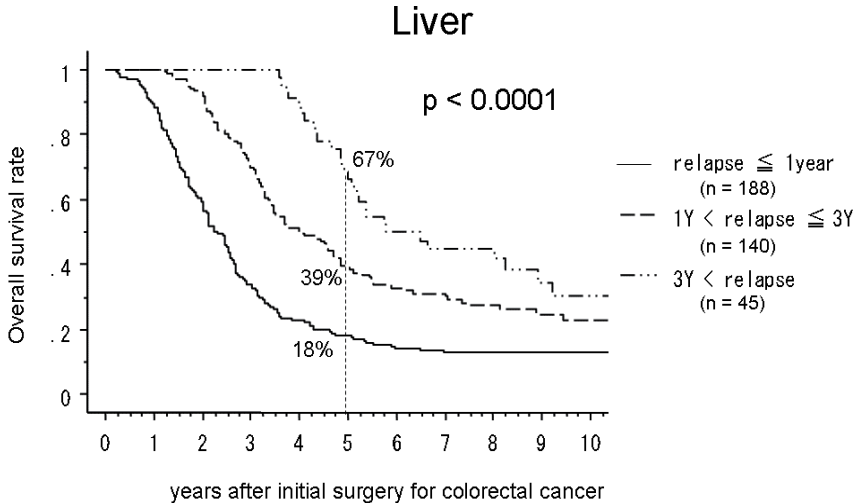
Liver

Fig. 5a. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.

Lung

Fig. 5b. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.
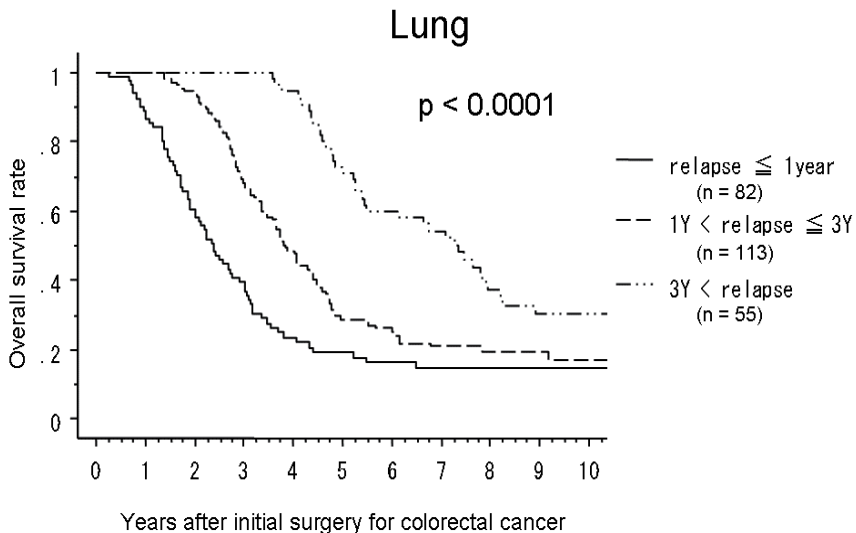
Local

Fig. 5c. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.

Anastomosis

Fig. 5d. The overall survival curve after initial colorectal surgery according to the timing of recurrence. The later recurrence in liver (a), lung (b), and local (c) leads to the better survival.
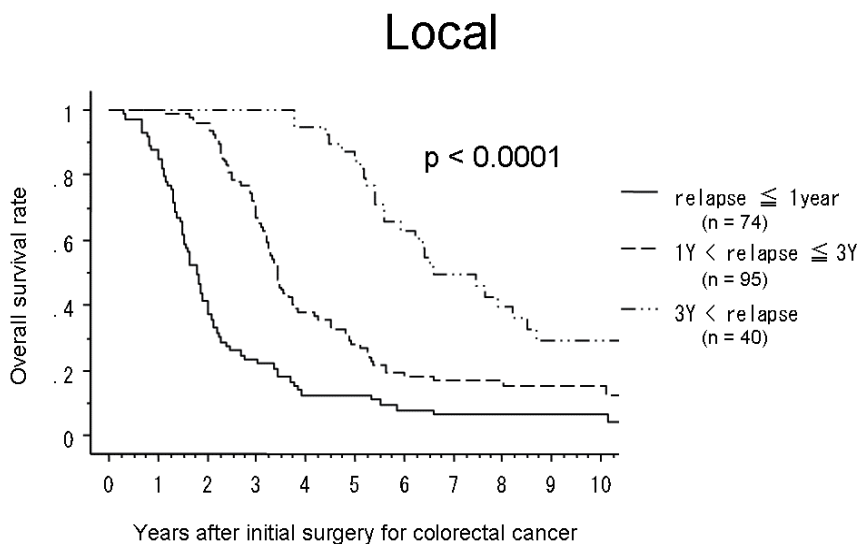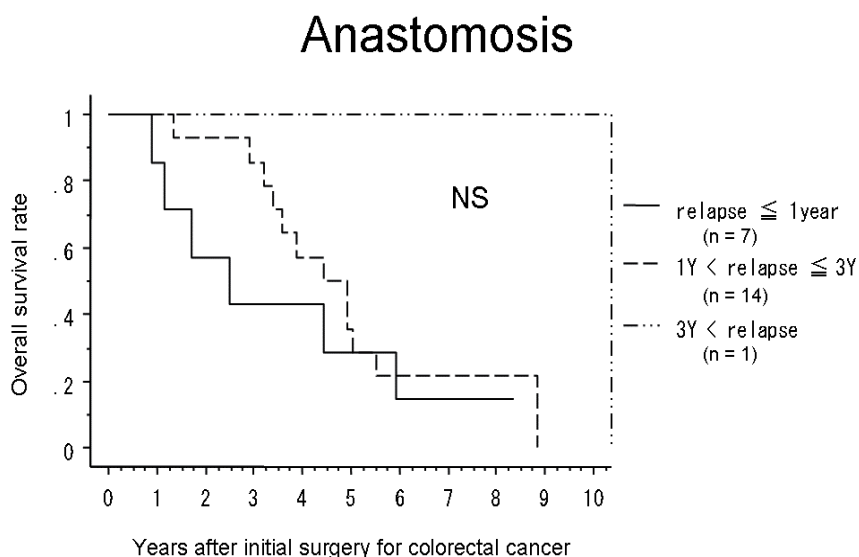
Liver

Fig. 6a. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.

Lung

Fig. 6b. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.

Local
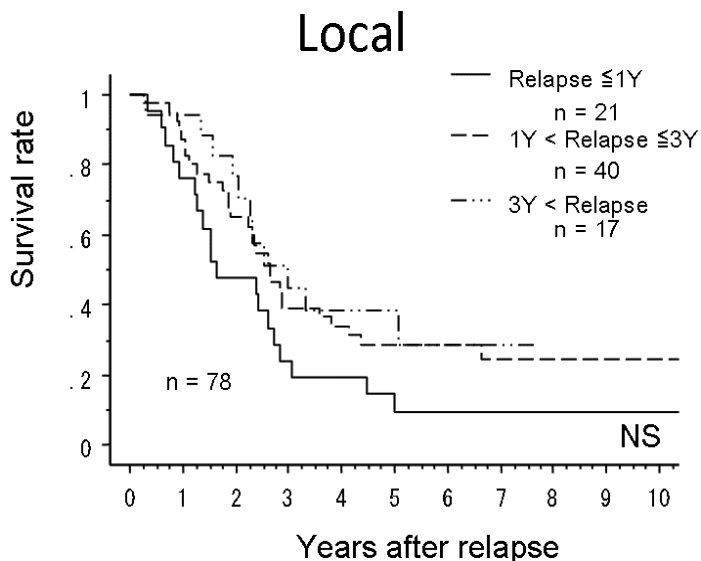
Fig. 6c. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.

Anastomosis
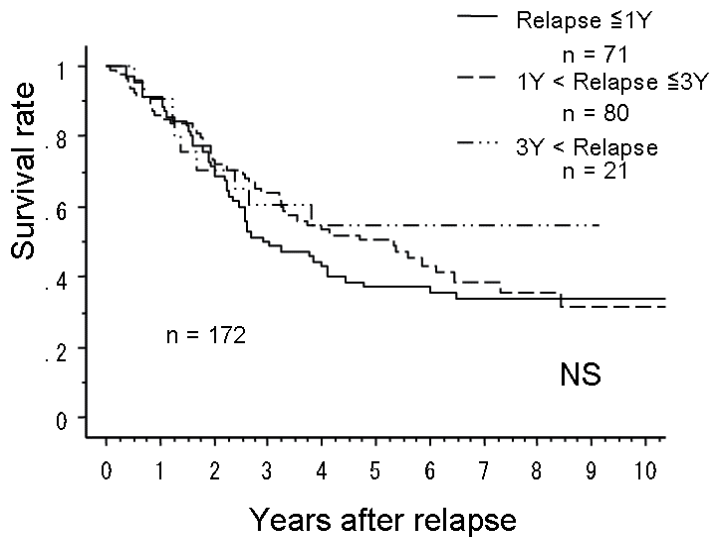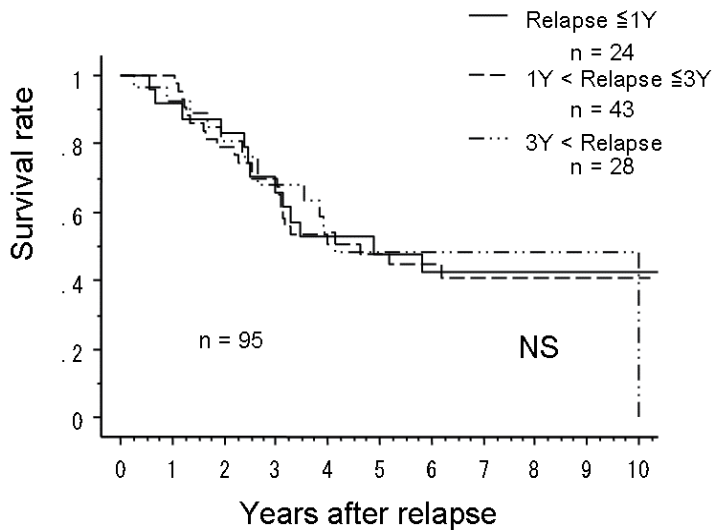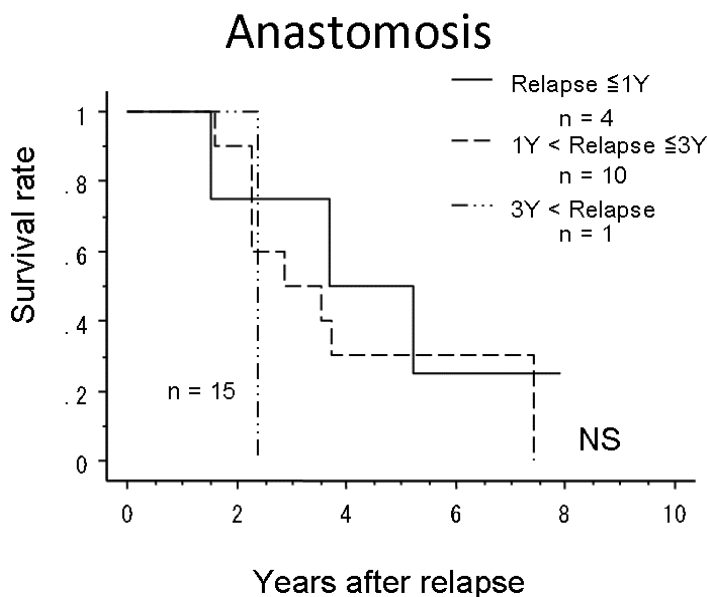

Fig. 6d. If the patients underwent curative resection for recurrence, the outcomes after recurrence were irrespective of the timing of recurrence.

4. Surveillance tools after curative resection for colorectal cancer

In our study, the combination of symptoms, physical examination, and tumor marker detected the majority of recurrence in all sites except for lung (Table 5).[3] In this section, the evidence for usefulness of each surveillance tool is discussed.

First recurrence site	Liver (n = 373) Rate of FI* (%)	Lung (n = 250) Rate of FI* (%)	Local (n = 209) Rate of FI* (%)	Anastomotic (n = 22) Rate of FI* (%)	Others (n = 199) Rate of FI* (%)
A: Symptoms**	3.2	6.8	27.2	13.6	19.6
B: Physical examination	1.6	1.6	20.6	36.4	8.5
C: Tumor marker	46.6	26.4	23.4	18.2	41.7
A + B + C	51.5	34.8	71.3	68.2	69.8
Liver imaging	43.4				
Chest x-ray	1.3	48.4			
CT		10.4	18.2	18.2	18.6
CS***			6.7	9.1	
Others		2.8	2.9		5.5
Unknown	3.8	3.6	1	4.5	6

*FI: First indicator
**Symptoms include anal pain, anal bleeding, abdominal pain, and so on
***CS: Colonoscopy

Table 5. Rate of first indicator for recurrence

4.1 History and physical examination

It is not rare that patients have a symptom at the time of recurrence after curative resection for colorectal cancer. According to the result of RCTs, 16% to 66% of patients had some sort of symptom.[4,5] Therefore, periodical clinical visits seem to be important to detect a recurrence after curative resection for colorectal cancer. On the other hand, Ohlsson et al. reported that it was rare to detect a resectable recurrent tumor only history and physical examination.[6]

4.2 CEA

Carcinoembryonic antigen (CEA) is most widely used as tumor marker for colorectal cancer. The serum CEA level was high in the majority of patients with recurrence after curative resection for colorectal cancer.[25] Especially, 80% of patients with hepatic recurrence from colorectal cancer had higher serum CEA levels.[25] Graham et al. reported that serum CEA measurement was the most useful and economical surveillance tool to detect recurrence after curative resection for colorectal cancer.[26] Therefore, serum CEA test was recommended as a surveillance tool after curative resection for colorectal cancer.[10]

4.3 Chest X-ray

It is controversial to use chest x-ray as a surveillance tool to detect recurrence after curative resection for colorectal cancer. Since chest x-ray can detect resectable pulmonary metastasis with probability of 1%,[26,27] it is not recommended to use chest x-ray as a surveillance tool in many institutions. On the other hand, Ike et al. reported the good outcomes of 42 patients with curative resection for pulmonary recurrence which was detected by the combination of serum CEA test of every 2 months and chest x-ray of every 6 months.[28] The 5-year survival rate after curative resection for pulmonary recurrence was 63.7%.

4.4 CT scans

Howell et al. reported that annual computed tomography (CT) scan could detect 87.5% of liver metastases at an asymptomatic stage,[29] whereas, in total, only 2 cases out of 157 (1.3%) underwent curative resection for liver metastases. An RCT conducted by Schoemaker et al. clarified that abdominal CT scan increased the detection rate of liver metastases, although there was no difference in resection rate between the groups with and without CT scan.[8] On the other hand, the UK group reported the usefulness of serum CEA measurement and CT scan in the surveillance of patients after adjuvant chemotherapy for colorectal cancer.[30] In their study, among 530 patients with stage II and III colorectal cancer, 154 had recurrence after adjuvant chemotherapy. Recurrences were detected by symptoms (n = 65), CEA (n = 45), CT (n = 49), and others (n = 9). The CT-detected group had a better survival compared with the symptomatic group (P =.0046).

Intensive surveillance after curative resection for colorectal cancer was not adopted in Western countries.[31,32] However, since the results of meta-analyses revealed that intensive surveillance after curative resection for colorectal cancer contributed to better outcomes, routine use of CT scans has been recommended.[33,34]

4.5 PET scans

The usefulness of positron-emission tomography (PET) in the detection of recurrence after curative resection for colorectal cancer is uncertain. Sobhani et al. reported a clinical trial that randomly assigned 130 patients with curative resection for colorectal cancer to the conventional surveillance group (periodic serum tumor marker, ultrasound, chest x-ray, and CT scans) and the PET-additional group.[35] The PET scans were performed in 9 and 15 months after surgery. Recurrences were detected after a shorter time (12.1 vs 15.4 months) in the PET group. Moreover, recurrences were more frequently cured by surgery (R0) in the PET group. The usefulness of PET scans in the detection of recurrence after curative resection for colorectal cancer should be clarified in a large-scale study.

4.6 Colonoscopy

Since the anastomotic recurrence rate after colectomy is low, the usefulness of periodical colonoscopy to detect anastomotic recurrence is skeptical.[36] On the other hand, since the anastomotic recurrence rate after resection for rectal cancer is higher than that after resection for colon cancer, several studies reported the adequacy of periodical colonoscopy to detect anastomotic recurrence after surgery.[31,37] At the same time, colonoscopy can find metachronous adenoma and cancer in the colon and rectum. Metachronous lesions develop in 1.5 to 3% of patients in the first 5 years after colorectal surgery.[8,27,38-42] In Japan, the colonoscopy is usually performed one year after colorectal surgery and thereafter every two years. If total colonoscopy cannot be performed preoperatively because of the stenosis, it is recommended that the first colonoscopy should be performed three to six months after colorectal surgery.

5. Recommended surveillance after curative resection for colorectal cancer from ESMO, ASCO, and JSCCR

Both previous and present guidelines for surveillance after curative resection for colorectal cancer from ASCO and ESMO are shown in Table 6.[31,33,34,43] Previously, neither ASCO nor ESMO recommended the intensive surveillance after curative resection for colorectal cancer, because most RCTs failed to show the prognostic significance of intensive surveillance.[4-8] However, since three meta-analyses showed the effectiveness of intensive surveillance, these guidelines changed their attitude toward surveillance after curative resection for colorectal cancer. At present, both societies recommend periodical serum CEA measurement and CT. Periodical colonoscopy to detect metachronous adenoma and cancer is also recommended.

In Japan, JSCCR published the first edition of guidelines for the treatment of colorectal cancer in 2005 and the second edition in 2009. The Japanese institutions adopted more intensive surveillance to detect recurrence after curative resection for colorectal cancer. The recommended surveillance schedule in the Japanese guidelines is shown in the Table 7.

On the other hand, the optimal schedule and modality to detect recurrence after curative resection for colorectal cancer are still uncertain. These issues should be clarified by RCTs in future.

	ASCO Previous	ASCO Present	ESMO Previous	ESMO Present
History and physical examination	Every 3 to 6 months for the first 3 years and annually thereafter	Every 3 to 6 months for the first 3 years, every 6 months during years 4 and 5, and subsequently at the discretion of the physician	Every 6 months for 2 years	Every 3 to 6 months for the first 3 years, every 6 months during years 4 and 5
Carcinoembryonic antigen	If resection of liver metastases would be clinically indicated, it is recommended that postoperative serum CEA testing be performed every 2 to 3 months in patients with stage II or III disease for ≥ 2 years after diagnosis.	Every 3 months postoperatively for at least 3 years after diagnosis, if the patient is a candidate for surgery or systemic therapy	Restricted to patients with suspicious symptoms	Every 3–6 months for 3 years and every 6–12 months in years 4 and 5 after surgery if initially elevated
Chest x-ray	May be ordered to diagnose abnormalities prompted by elevated CEA levels or for patients who have symptoms suggestive of a pulmonary metastasis	Not recommended	Restricted to patients with suspicious symptoms	Can be considered every year for 5 years
Chest computed tomography	–	Annually for 3 years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for curative-intent surgery	Restricted to patients with suspicious symptoms	Can be considered for 3 years in patients who are at higher risk for recurrence
Abdominal ultrasonography	Not recommended	–	Annually for 3 years	Every 6 months for 3 years and after 4 and 5 years
Abdominal computed tomography	Not recommended	Annually for 3 years after primary therapy for patients who are at higher risk of recurrence and who could be candidates for curative-intent surgery	Restricted to patients with suspicious symptoms	Can be considered for 3 years in patients who are at higher risk for recurrence
Pelvic computed tomography	Not recommended	For rectal cancer surveillance, especially for patients with several poor prognostic factors, including those who have not been treated with radiation	Not recommended	Restricted to patients with suspicious symptoms
Colonoscopy	Every 3 to 5 years to detect new cancers and polyps	At 3 years after operative treatment, and, if results are normal, every 5 years thereafter; flexible proctosigmoidoscopy every 6 months for 5 years for rectal cancer patients who have not been treated with pelvic radiation	Every 5 years	At 1 year and thereafter every 3–5 years to look for metachronous adenoma and cancers

Table 6. Recommended guidelines from ASCO and ESMO

	Monthes after surgery																			
	3	6	9	12	15	18	21	24	27	30	33	36	39	42	45	48	51	54	57	60
Colon cancer																				
Clinical visit	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
CEA and CA19–9	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
Chest CT		•		•		•		•		•		•		○		•		○		•
Abdominal CT		•		•		•		•		•		•		○		•		○		•
Colonoscopy				•								•								
Rectal cancer																				
Clinical visit	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
CEA and CA19–9	•	•	•	•	•	•	•	•	•	•	•	•		•		•		•		•
Digital examination		•		•		•		•		•		•								
Chest CT		•		•		•		•		•		•		○		•		○		•
Abdominal and pelvic CT		•		•		•		•		•		•		○		•		○		•
Colonoscopy				•				•				•								

•Stage I – Stage III
°Omissible in Stage I and Stage II

Table 7. Surveillance schedule recommended by JSCCR

6. Summary

i. The most frequent site of recurrence after curative resection for colon cancer is the liver. The second is the lung.

ii. The most frequent site of hematogenous recurrence after curative resection for rectal cancer is the lung. The second is the liver.

iii. The recurrence rate in rectal cancer is higher than in colon cancer.

iv. Approximately 80 to 90% of recurrence after curative resection for colorectal cancer developed within 3 years.

v. In any recurrent sites, the prognosis of patients with curative resection for recurrence was better than that of patients without curative resection for recurrence.

vi. The later the recurrence, the better the survival.

vii. If patients undergo curative resection for recurrence, the prognosis after resection for recurrence is irrespective of timing of recurrence.

viii. Although the optimal surveillance tools and schedule are uncertain, the intensive surveillance leads to better survival after curative resection for colorectal cancer compared to the non-intensive one.

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Difficult Infected Wound After Colorectal Surgery

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1. Introduction

Surgical site infection (SSI) is a well known and commonly encountered scenario following major colorectal resection and has been documented as being a potentially morbid and costly complication.

Surgical wounds in normal, healthy individuals heal through an orderly sequence of physiologic events that include inflammation, epithelialisation, fibroplasia, and maturation. Mechanical failure or failure of wound healing at the surgical site can lead to disruption of the closure leading to seroma, hematoma, wound dehiscence or hernia. Other complications include surgical site infection and nerve injury.

For this reason, of late, emphasis has been placed on more efficient management of these patients including early recognition, and prompt treatment with a view to improve patient outcomes which are measured both in terms of postoperative morbidity, prolonged hospital stay and by extension an increased demand on finite hospital resources[1].

However, there has been wide discrepancy in the reported incidence of incisional SSI following colorectal surgery, ranging from 3 to 30%[(1)]. Additionally, there has been no clear consensus on the risk factors contributing to SSI following colorectal surgery, which has limited the data's value to surgeons involved in quality improvement programs hoping to address specific variables that could reduce this risk.

In this era of managed care organizations where patients expect short hospital stay and one-stage resections are becoming more frequent, peri operative assessment of risk factors for wound infection should be intensified for the patient.

Surgical site infections (SSI) are the third most common hospital-acquired infection and account for 14% to 16% of all such infections. However, in surgical patients, SSI is the leading cause of hospital-acquired infection[2,3]. Similar incidence of SSI has been documented by various studies in patients after colorectal surgery.

The National Nosocomial Infection Surveillance system surveys all colorectal surgeries together, without differentiating the type of colorectal surgery performed. The outcome of their survey showed rectal surgery may have a higher risk for SSI, and identifying risk factors that are more specific to this procedure would be a better indicator to predict the possibility of SSI.

Several reports have described the substantial cost of these infections in terms of attributable mortality,[3] increased morbidity measured as increased postoperative hospital length of stay, and increased hospital costs.

2. Risk factors

Various studies have identified multiple risk factors and other associations which have a direct bearing on the incidence of these infections.

a. **Type of surgery:** Timing of the surgical procedure does not significantly predispose or preclude wound infections as it occurs in patients who have undergone both emergency surgery as well as those that had an elective procedure.

b. **Patient related risk factors for surgical site infection**[4] *(Table 1)*: This group of risk factors have a significant impact on the incidence of surgical site infection. Included in this group are pre-existing conditions like diabetes and cardiovascular disease. Patients nutritional status – both malnutrition and obesity and life style habits like smoking can cause significant impact on post-operative wound. Prior medical history of surgery, irradiation or cancer also adversely effect wound healing.

1.   Diabetes
2.   Obesity
3.   Immunosuppression
4.   Cardiovascular disease
5.   Smoking
6.   Cancer
7.   Previous surgery
8.   Malnutrition and
9.   Prior irradiation

Table 1. Patient Related Risk Factors for Surgical Site Infection [4]

c. **Technique related risk factors for surgical site infection**[4] *(Table 2)*: Various surgical related factors affect wound healing differently. This includes both pre surgical patient preparation and post operative care. Intra operative procedures including the surgical techniques like excessive use of electrocautery, poor haemostasis and tissue trauma can adversely affect wound healing as can the length of the surgery. Insertion and duration of intra abdominal drains remains a controversial point.

1. Use of electrocautery	9. Operating room ventilation
2. Closure of subcutaneous tissue	10. Inadequate sterilisation of
3. Duration of surgical scrub	instruments
4. Skin antisepsis	11. Foreign material in the surgical site
5. Preoperative shaving	12. Surgical drains
6. Preoperative skin prep	13. Poor haemostasis
7. Duration of operation	14. Failure to obliterate dead space
8. Antimicrobial prophylaxis	15. Tissue trauma

Table 2. Technique Related Risk Factors For Surgical Site Infection [4]

d. **Factors associated with increased risk of fascial disruption[5]** *(Table 3)*: Multiple factors can increase the changes of loss of integrity of the fascia and largely relate to patient factors including patients' premorbid and associated medical conditions as does patient demographics.

1. Age > 65 years	8. Shock
2. Emergency surgery	9. Poor nutrition: albumin <3.5 g/dL
3. Anemia: hemotocrit <30 percent	10. Infection
4. Obesity: body mass index >30 kg/m²	11. Immunosuppressive therapy, glucocorticoids, antineoplastic agents
5. Ascites	
6. Diabetes mellitus	
7. Pulmonary disease, COPD, chronic cough	12. Jaundice
	13. Male gender

Table 3. Factors associated with increased risk of fascial disruption

3. Classification of abdominal wound infection

Surgical wound infection can be classified into different types based on various criteria[6].

a. Based on the depth and the site of the surgical wound infection, the three types are:
   1. **Superficial incisional surgical site infection**: Involves skin and subcutaneous fat (Image 1).
   2. **Deep incisional surgical site infection**: Involves rectus sheath and preperitoneal space (Image 2).
   3. **Organ / space surgical site infection**: Involves intraperitoneal compartment and intra abdominal organs (Image 3).
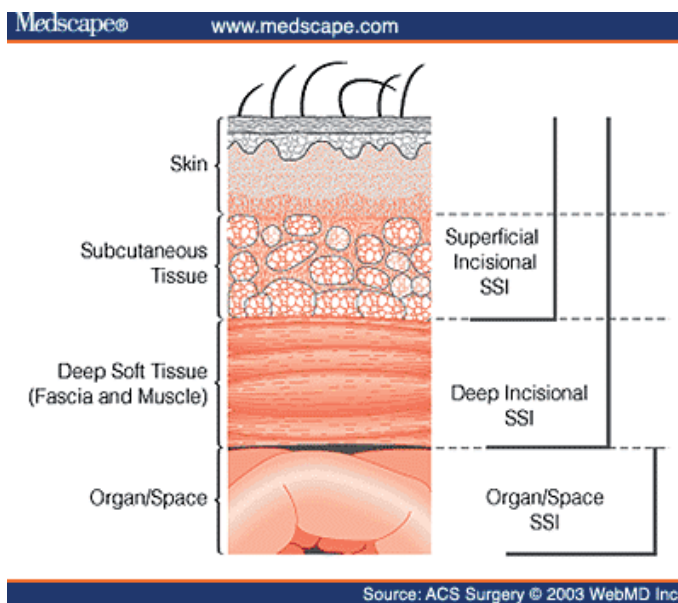

Fig. 1.

b. Based on the type of wound they are classified as:
    1. **Clean**
    2. **Clean contaminated**
    3. **Contaminated**
    4. **Dirty**

Studies have shown an association between the type of wound and the incidence of surgical site infection (Table 4):

Classification	Examples	Incidence of SSI (%)
Clean	Elective surgery without violation of the gut or infected spaces	< 2
Clean contaminated	Elective bowel surgery (prepared bowel, mechanical and antibiotic)	5-15
Contaminated	Emergent bowel surgery (unprepared bowel, minor spillage), drainage of infected spaces	15-30
Dirty	Grossly contaminated traumatic wounds, significant intestinal spillage, grossly infected and devitalized tissue (necrotizing infection)	>30

Table 4. Wound Classification and Risk for Surgical Site Infection

4. Clinical manifestation and diagnosis

As with infection anywhere, surgical site infections present with localized erythema, induration, warmth, and pain at the incision site. Purulent wound drainage and separation of the wound may occur.

Some patients will have systemic evidence of their infection such as fever and leukocytosis.

Image 1. Superficial incisional surgical site infection showing skin and subcutaneous fat involvement.

Image 2. Deep incisional surgical site infection involving rectus sheath and preperitoneal space.

Image 3. Organ surgical site infection shown as an open abdomen with Involvement of the peritoneal cavity and omentum managed by mesh placement.

Diagnosis of surgical site infection is largely clinical.

Role of imaging is limited to those patients in whom there is a clinical suspicion of deep space infections or collections. Of the imaging modalities, Computed Tomography is the preferred modality for assessment.

Ultrasound may have a limited role in assessing deep space infections but can evaluate collections related to superficial wounds, particularly, if the clinical evaluation is difficult or inconclusive.

5. Complication of SSI

In addition to the complications related directly to the wound, patients with SSI can have other complications based on their pre surgical risk factors and co morbidities that can adversely affect their long term outcome and prolong their convalescence.

These complications have been well documented and researched and include long hospital stay, increasing morbidity,   SIRS – Sepsis – MOF and even death.

5.1 Management

Recent studies have shown the strong influence of the various risk factors that results in an increase in the incidence of surgical site infection. Thus, there has been a shift in the approach to the management of these patients with emphasis being placed on prophylaxis.

5.1.1 Prophylaxis

- Adequately identifying and correcting the various systemic co-morbidities thus optimising the pre-operative status and reducing the pre-operative risk for SSI.
- This has shown to be as important as post-operative and intra-operative care. It includes ensuring adequate control of diabetes and assessment and correction of cardiovascular problems pre-operatively.
- Studies have shown that cessation of smoking at least a week prior to surgery reduces the risk of SSI.
- Both reduction of weight in obese patients and improvement of nutrition in cachectic patients have shown to favourably improve surgical outcome.
- Optimising surgical techniques at various levels starting with adequate patient preparation for surgery which include antibacterial shower on the day of surgery, shaving of the site on table.
- Adequate antimicrobial prophylaxis which is continued intra operatively at 4 hourly intervals.
- Mass closure of the abdominal wound incorporating all layers of the rectus sheath taking wide tissue bites of more than 1cm and with short stitch interval (less than 1cm) using suture length to wound length ratio of 4 to 1.
- Reducing tissue trauma during surgery by gentle dissection of tissue, cautious use of electrocautery and saline wash-out of the wound has shown a lower incidence of SSI. Reducing operative time and appropriate use of intrabdominal drains also reduces the risk.
- **Best practices for preventing surgical site infections [7] :**

Evidence category IA - Well designed studies

1. Cancel elective surgery if the patient has an infection at or remote from the surgical site
2. Achieve maximal subcutaneous concentration of peri operative antibiotics
3. Maintain prophylactic antibiotics for only a few hours after closing incisions
4. If it is necessary to remove hair, use clippers, not shaving, immediately before operation

Evidence category IB - Good evidence and expert consensus

1. Control glucose levels in diabetic patients and avoid peri operative hyperglycemia

2. Encourage patients who use tobacco products to quit using or to abstain for 30 days prior to surgery
3. Have the patient shower or bathe with an antiseptic agent on at least the night before surgery
4. Follow strict standards for sterilizing instruments, disinfecting operating room, and air circulation
5. Do not routinely use vancomycin for prophylaxis if other agents are appropriate
6. Do not use UV radiation in the operating room for infection prophylaxis
7. Surgical staff who have draining skin lesions are excluded from duty
8. Surgical staff should wear sterile clothing and gloves
9. Surgical team hand hygiene to include keeping fingernails short, scrubbing with antiseptic to elbows for 2-5 min, using sterile towels
10. Use appropriate topical microbicides during surgery
11. Use proper surgical technique
12. Apply sterile dressing to incision for 24-48 hours postoperatively and wash hands before contact with surgical site
13. Perform hospital surveillance for surgical site infection

5.1.2 Definitive management

Definitive management of SSI depends on the type of infection.

5.1.2.1 Superficial incisional surgical site infection

Infected wounds are opened, explored, drained, irrigated, débrided and dressed open.

If fascial disruption is suspected, drainage should be performed in the operating room.

The severity of the infection determines the need for antibiotic therapy. Once the infection has cleared and granulation tissue is apparent, the wound can be closed secondarily.

5.1.2.2 Deep incisional surgical site infection

Fascial dehiscence:

Fascial disruption is due to abdominal wall tension overcoming tissue or suture strength, or knot security as a result of infection or collection. It can occur either early or late in the postoperative period and can involve a portion of the incision (i.e, partial dehiscence) or the entire incision (i.e, complete fascial dehiscence).

The incidence of fascial disruption ranges from 0.4 to 3.5 % depending upon the type of surgery performed. Despite improved perioperative care and stronger suture materials, the incidence and morbidity of fascial dehiscence is largely unchanged.

When fascial disruption is suspected, wound exploration should be performed in the operating room. Complete fascial dehiscence is associated with a mortality rate of 10% and is a surgical emergency. At the bedside, a moist dressing is placed over the wound and a binder placed around the patient's abdomen to prevent evisceration on the way to the operating room.

Once opened, the wound is thoroughly debrided. Treatment options include either using VAC dressing or mass closure. Mass closure done with continuous or retention non-

absorbable sutures is an option only if the intra-abdominal pressure and tissue oedema intraoperatively is not high. In such cases VAC dressing is the preferred treatment.

Prevention

Meta-analyses related to abdominal fascial closure suggest an optimal technique for closure of abdominal surgical wounds includes[8,9]:

- Use of a simple running technique
- Use of #1 or #2 delayed absorbable monofilament suture
- Use of mass closure to incorporate all layers of the abdominal wall (except skin)
- Taking wide tissue bites (≥1 cm)
- Use of a short stitch interval (≤1 cm)
- Use of a suture length to wound length ratio of 4 to 1
- Use of non-strangulating tension on the suture.

5.1.2.3 Organ/Space surgical site infection

One of the critical decisions in the surgical treatment of patients with severe peritonitis is whether to use an open-abdomen or a closed-abdomen technique.

Closed abdomen technique

The goal of the closed-abdomen technique is to provide definitive surgical treatment at the initial operation which saves the patient from repetitive trauma of anaesthesia and surgery.

Opting for this technique should be judicious in an unstable patient.

Open abdomen technique

VAC dressing and temporary closure with sponge or mesh are types of open abdomen techniques which are valuable tools for the management of patients with acidosis, hypothermia and coagulopathy. This is a very resource-intensive decision.

The goal of the open-abdomen technique is to provide easy, direct access to the affected area. Source control is achieved through repeated reoperations or through open packing of the abdomen. This technique may be well suited for initial damage control in extensive peritonitis.

The open-abdomen technique should also be considered in patients who are   at high risk for the development of abdominal compartment syndrome (eg, patients with intestinal distension, extensive abdominal wall and intra-abdominal organ edema), because attempts to perform primary fascial closure under significant tension in these circumstances are associated with an increased incidence of multiple organ failure (eg, renal, respiratory), necrotizing abdominal wall infections, anastomotic leak, entero-cutaneous fistula and mortality.

Temporary closure of the abdomen to prevent herniation and contamination can be achieved by using various materials (Table 5):

1. Self-adhesive impermeable membrane dressings using sponge and opsite. Though it is in inexpensive and easy to apply, the major disadvantage is difficulty in maintaining wound seal. In addition, there is loss of large volumes of extracellular fluid.
2. Mesh like Vicryl and Dexon made of absorbable material can be directly applied over bowel, but the drawbacks are loss of strength in the presence of infection and higher incidence of ventral hernia development.

Closure Technique	Description	Advantages	Disadvantages
Self-adhesive impermeable membranes	Abdominal dressing with gauze and coverage of the entire wound with impermeable membrane with and without placement of drains between the layers	Inexpensive Easy application	Difficult to maintain seal Potentially large volume losses Fistula formation
Vicryl or Dexon mesh	Suturing of the mesh to the fascial edges; different options for dressing	Can be applied directly over bowel Allows for drainage of peritoneal fluid	Rapid loss of tensile strength (in the setting of infection) Potentially large volume losses Higher incidence of later ventral hernia development No reopen-and-close option Fistula formation
Polypropylene mesh	Suturing of the mesh to the fascial edges; different options for dressing	Good tensile strength Allows for drainage of peritoneal fluid	Risk of intestinal erosion when applied directly over bowel Potentially large volume losses High risk of mesh infection Fistula formation
GORE-TEX mesh	Suturing of the mesh to the fascial edges; different options for dressing	Good tensile strength Reopen and close option	Potential fluid accumulation underneath the mesh Limited tissue integration and granulation tissue formation over the mesh Risk of mesh infection Fistula formation
Human acellular dermis	Suturing of the mesh to the fascial edges	Good tensile strength	Expensive Needs 10 minutes of rehydration
Vacuum-assisted closure device	Sponges applied over mesh and attached to controlled, low-level suction	Controlled drainage of secretions Accelerated granulation tissue formation Wound debridement Can remain in place for longer than 48 hours	Cost Risk of intestinal erosion when applied directly over bowel Fistula formation
Wittmann patch	Suturing of artificial burr (ie, Velcro) to fascia, staged abdom-inal closure by application of controlled tension	Good tensile strength Allows for easy re exploration and eventual primary fascial closure	Fistula formation

Table 5. Temporary closure materials.

3. Non absorbable mesh like GORE-TEX and polypropylene can be used for closure with or without zipper. These materials have good tensile strength and provide additional option of repeated surgeries. The disadvantage, however, is mesh erosion into the bowel wall forming fistula and subsequent high risk of mesh infection.

4.   Vacuum assisted closure device has the advantage of controlled drainage of secretions. It can also be left in situ for more than 48 hours which is adequate time for the patient to recover from systemic conditions like coagulopathy or metabolic acidosis (Damage control surgery). Increased cost is a major limiting factor against widespread use.
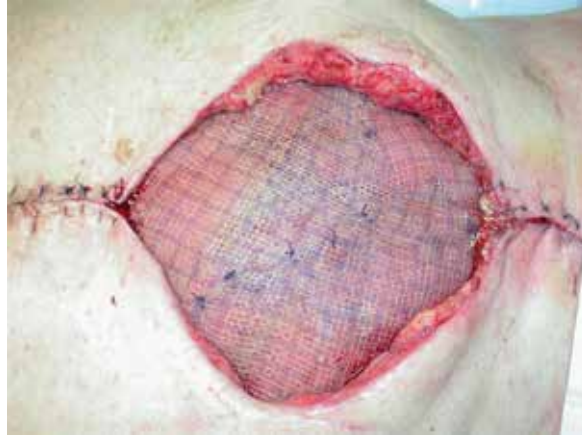

Image 4. Open abdomen technique (mesh)

6. Emerging new techniques for management of open abdomen

6.1 Abdominal vacuum-assisted closure (V.A.C.) systems[10,11]

The V.A.C.® Abdominal Dressing System is a specialty dressing indicated for temporary bridging of the open abdomen where primary closure is not possible and/or repeat abdominal entries are necessary.

The V.A.C. Abdominal Dressing System can be used to assist in the management of an open abdomen due to Abdominal Compartment Syndrome, trauma requiring damage control or staged abdominal repair, and other complex abdominal pathologies.

V.A.C systems are intended to create an environment that promotes wound healing by secondary or delayed primary intention by preparing the wound for closure, reducing edema, promoting granulation tissue formation and perfusion and by removing exudative and infectious material.

These systems are indicated for patients with open abdomen and dehisced wounds, partial-thickness burns, chromic ulcers (such as diabetic, pressure or venous insufficiency).

The V.A.C. GranuFoam™ Silver Dressing is an effective barrier to bacterial penetration and may help reduce infection in the above wound types.

Placement of V.A.C systems directly in contact with exposed blood vessels, anastomotic sites, organs, or nerves is contraindicated. V.A.C. Therapy is also contraindicated for patients with malignancy in the wound, untreated osteomyelitis, non-enteric and unexplored fistulas and necrotic tissue with eschar present.

However, after debridement of necrotic tissue and complete removal of eschar, V.A.C. Therapy may be used.

Following initiation of V.A.C Therapy, the wound can be re evaluated after 72 hours. This can either be done at the bed-side under sedation or under anaesthesia in the theatre. If the wound continues to be infected or dirty, the V.A.C system is reapplied. On the other hand, if the wound is clean, then the decision to proceed to secondary closure of the abdomen can be made.

(a)   (b)

Image 5. a,b: V.A.C Therapy for open abdomen

6.2 Mist therapy [12]

MIST Therapy® is a painless, noncontact, low frequency ultrasound delivered through a saline mist to the wound bed.These gentle sound waves stimulate the cells within and below the wound bed to promote healing.

The result of these gentle sound waves pushing against the tissue include:

- Cell stimulation
- Reduced inflammation
- Reduced bacteria and bio burden
- Increased blood flow

7. Summary

Surgical site infection (SSI) is a well known and commonly encountered scenario following major colorectal resection and has been documented as being a potentially morbid and costly complication.

Risk factors for surgical site infection include: smoking, diabetes, malnutrition, cancer, obesity, immunosuppression, cardiovascular disease and prior incision or irradiation at the surgical site. Meticulous surgical technique that avoids excessive tissue injury and ischemia while providing adequate hemostasis are important for preventing infection.

Surgeons can modify rates of infection with preventive measures that include antibiotic prophylaxis, proper skin preparation and maintenance of sterile conditions intra operatively. Proper surgical technique with gentle tissue handling and a secure closure that does not cause tissue ischemia are also important.

Infected wounds are opened, explored, drained, irrigated, débrided and dressed open. If fascial disruption is suspected, drainage should be performed in the operating room. The severity of the infection determines the need for antibiotic therapy. Once the infection has cleared and granulation tissue is apparent, the wound can be closed secondarily.

Fascial disruption is due to abdominal wall tension overcoming tissue or suture strength, or knot security. It can occur early or late in the postoperative period. With early fascial dehiscence, the skin closure may be intact depending upon the method of closure (ie, staples, sutures); the patient, nevertheless, is at risk for evisceration. Early postoperative fascial dehiscence is a surgical emergency. The late complication of fascial disruption is incisional hernia which can lead to bowel obstruction, ischemia and even death.

Management of the deep incisional surgical site and organ/space surgical site infection includes open abdomen technique using various types of dressings and mesh. Occasionally, single stage closure of the abdomen is used.

Of late, V.A.C dressings are the preferred choice for open abdomen management. However, the most recent development is the MIST therapy using low frequency ultrasound.

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In recent years, significant progress in colorectal surgery has been made which includes laparoscopic techniques, pre-operative management, emergency colorectal surgery, fast track multimodal recovery, management of complex wound problems and colorectal cancer follow-up. "Contemporary Issues in Colorectal Surgical Practice" aims to bridge the gap between the journal article and the traditional textbook in these areas.

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