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TOPIC HIGHLIGHT

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Improving the outcomes in oncological colorectal surgery

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Abstract

During the last several decades, colorectal cancer surgery has experienced some major perioperative improvements. Preoperative risk-assessment of nutrition, frailty, and sarcopenia followed by interventions for patient optimization or an adapted surgical strategy, contributed to improved postoperative outcomes. Enhanced recovery programs or fast-track surgery also resulted in reduced length of hospital stay and overall complications without affecting patient safety. After an initially indecisive start due to uncertainty about oncological safety, the most significant improvement in intraoperative care was the introduction of laparoscopy. Laparoscopic surgery for colon and rectal cancer is associated with better short-term outcomes, whereas long-term outcomes regarding survival and recurrence rates are comparable. Nevertheless, long-term results in rectal surgery remain to be seen. Early recognition of anastomotic leakage remains a challenge, though multiple improvements have allowed better management of this complication.

Key words: Laparoscopic surgery; Colorectal surgery; Anastomotic leakage; Frailty; Nutritional status; Sarcopenia; Enhanced recovery after surgery; Audits

Core tip: Laparoscopic surgery is a fundamental improvement in oncological colorectal surgery, associated with better short-term outcomes. However, anastomotic leakage still presents a major challenge in the postoperative course. Future research should therefore aim at the prevention, timely recognition and treatment of this complication. Correction of nutritional compromise, frailty and muscle loss, optimization of fluid and microcirculatory status, implementation of clinical and laboratory diagnostic markers, and the use of clinical audits may all contribute to a reduction of anastomotic leakage.

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INTRODUCTION

Colorectal cancer is one of the predominant types of cancer and the fourth leading cause of cancer-associated deaths worldwide[1]. In numbers, 600000 patients died of colorectal cancer in 2008, and disability-adjusted life-years lost from colorectal cancer were 300 per 100000

Table 1 Items of the short nutritional assessment questionnaire and malnutrition universal screening tool

Tool	Item	Score
SNAQ	Weight loss	
	> 6 kg in the last 6 mo	3
	> 3 kg in the last month	2
	The experience of a decreased appetite over the last month	1
	The use supplemental drinks or tube feeding over the last month	1
MUST	BMI kg/m^2	
	> 20	0
	18.5-20	1
	< 18.5	2
	Unplanned weight loss in past 3-6 mo	
	< 5%	0
	5%-10%	1
	> 10%	2

Adapted from Kruizenga *et al*[17] (interpretation: 2 = moderate malnutrition, 3 = severe malnutrition) and Lomivorotov *et al*[18] (interpretation: 0 = low risk of malnutrition, 1 = medium risk of malnutrition, ⩾ 2 = high risk of malnutrition). SNAQ: Short nutritional assessment questionnaire; MUST: Malnutrition universal screening tool.

patients, which was estimated to be 7% of the total cancer burden worldwide[2]. Although treatment of colorectal cancer is multidisciplinary nowadays, optimal surgery remains the cornerstone of improved survival[3,4]. Sixty-six percent of patients with colorectal cancer will undergo at least one major surgical resection[5]. The perioperative course of colorectal surgery for malignancy is crucial for the clinical outcome of treatment, in terms of mortality, tolerance, efficacy, and functional recovery, and has a considerable impact on health care resources[6,7]. In the past decades, perioperative care improved largely due to advances in anesthetic and analgesic approaches, minimally invasive operative techniques, and the introduction of fast-track protocols[8,9]. However, complications are still observed after oncological colorectal surgery, leading to prolonged hospital stay and high readmission rates with concurrent health care costs[10]. Early recognition and adequate intervention of complications will attenuate severity and may prevent mortality.

Anastomotic leakage is among the most prevalent and detrimental complications of colorectal surgery. Of 10017 registered resections for colorectal cancer in the Netherlands in 2012, 691 (6.9%) were complicated by anastomotic leakage requiring re-intervention (Dutch Surgical Colorectal Audit 2012)[11], making anastomotic leakage the primary complication requiring re-intervention. Anastomotic leakage is associated with high morbidity[12], mortality[11], reoperation[7], and duration of hospitalization[13]. In cancer, anastomotic leakage is related to diminished disease-specific survival and higher recurrence rates[7,14,15]. It is therefore imperative to keep searching for strategies to prevent, diagnose and treat anastomotic leakage.

This review article describes pre-, intra- en postoperative advancements in oncological colorectal surgery and highlights the opportunities for further improvement, particularly aiming at laparoscopy and the prevention and recognition of anastomotic leakage.

ADVANCES IN PREOPERATIVE CARE

Risk factors for anastomotic leakage are numerous and already widely described[16]. Therefore, describing risk factors is beyond the scope of this review article. The focus is on preoperative patient assessment and optimization.

Nutritional status

A powerful and easily obtainable tool to assess the patient's physical and/or mental condition is the use of questionnaires. Various questionnaires have been developed to evaluate nutritional status. A poor nutritional condition correlates well with impaired quality of life and physical functioning[17]. The short nutritional assessment questionnaire (SNAQ) and malnutrition universal screening tool (MUST) (Table 1) scores are commonly used nutritional screening tools in surgical patients. These questionnaires accurately detect malnutrition, and the MUST score predicts postoperative complications in cardiac surgery[18]. Evidence for the value of nutritional screening tools to predict postoperative outcome in colorectal surgery is lacking. As one in five patients undergoing colorectal surgery is malnourished[19], the detection of nutritional depletion is of great importance, especially with neo-adjuvant therapies compromising the nutritional and metabolic status. A disbalance between energy expenditure and nutritional supplementation is the fundamental physiologic derangement leading to cancer-induced weight loss. Both malnourishment and weight loss are associated with poor clinical outcome after surgery[20,21].

Although nutritional supplementation strategies in oncological colorectal surgery can improve handgrip strength, pulmonary function and insulin resistance[22], nutritional support has not been proven unequivocally effective to reduce length of hospital stay and anastomotic leakage rates[23,24]. It may be concluded that only severely malnourished patients benefit from nutritional support[25]. Nutritional status questionnaires may however not only be used to identify malnourished patients for nutritional support. As a tool for accurate prediction of postoperative complications, SNAQ and MUST scores could lead the way to other treatment options, for example surgery without a primary anastomosis or protection of the anastomosis using a diverting stoma. The predictive value of these scores for postoperative complications remains yet to be determined.

Contradictory to malnourishment, also obesity, particularly abdominal visceral obesity measured by computed tomography (CT)-based fat volumetry, is considered a predictor of postoperative complications, prolonged hospital stay and higher intraoperative conversion (from laparoscopic to conventional surgery) rates in colon surgery[26,27]. The effect on anastomotic leakage particularly is not known yet. Obviously, the presence of (visceral)

Figure 1 Computed tomography image at the third lumbar vertebral level. The following skeletal muscles are outlined in red: psoas, paraspinal, transverse abdominal, external oblique, internal oblique and rectus abdominis muscles. This female sarcopenia patient had an L3 (third lumbar spine) muscle index of 34.3 cm²/m².

obesity does not necessarily equal a sufficient nutritional status.

Frailty and sarcopenia

Advanced age is associated with an increased incidence of cancer[28]. The number of elderly cancer patients is concomitantly increasing. Fifty percent of patients with colorectal cancer is above the age of 70[11]. While survival of all cancer types is increasing, improvement of cancer outcome has been relatively limited in older patients[29]. Higher age is an independent predictor of disease-specific perioperative mortality in patients undergoing surgery for colorectal cancer[30,31]. Especially in older patients, weight loss, cachexia and nutritional compromise are associated with impaired response to chemotherapy and decreased survival[32,33].

Frail elderly undergoing colorectal surgery have a 4-fold increased risk of major postoperative complications[34]. Frailty is a state of increased vulnerability towards stressors in older individuals, leading to an increased risk of developing adverse health outcomes[35]. The definitions and biological characteristics of frailty are subject of debate. Weight loss, decreased muscle strength, reduced physical activity, exhaustion, and reduced walking speed are symptoms of a physical definition of frailty[34,36], whereas comorbidity, polypharmacy, decreased physical functioning, impaired nutritional and cognitive status, depression and social support are components of a more multidimensional description of frailty[37]. A simple screening instrument for frailty is the groningen frailty index, based on physical, cognitive, social and emotional items[38]. Skeletal muscle depletion or sarcopenia is an element of frailty in both definitions. Sarcopenia, mostly assessed by measurement of muscle area at the level of the third lumbar spine at CT-scan (Figure 1), is associated with prolonged hospital stay, infectious complications and decreased recurrence and survival rates following colorectal and liver surgery[39,40]. Moreover, sarcopenia frequently occurs in obese patients too and the combination of sarcopenia and obesity (sarcopenic obesity) may result in even a worse outcome in terms of physical ability and survival[41]. However, a specific effect of sarcopenia on the anastomotic leakage rate has not yet been established.

Currently, with increasing age and incidence of colorectal malignancies, new research should aim at frailty and sarcopenia as risk factors for anastomotic leakage. Moreover, new options for preoperative treatment of frailty and sarcopenia should be investigated. Both nutritional and muscle exercise interventions have been proposed to counteract sarcopenia, with the best effects when both strategies are combined, which elicits the greatest anabolic response[42]. Effectiveness of such a dual approach on postoperative outcomes has not been investigated thus far.

Enhanced recovery after surgery

Several meta-analyses have shown that enhanced recovery after surgery (ERAS) programs result in reduced length of hospital stay and overall complications without affecting patient safety[9,43,44]. Although strong evidence exists for many recommendations, such as antibiotic prophylaxis and preoperative bowel preparation, controversies remain around perioperative fluid therapy, oxygen supplementation and use of non-steroidal anti-inflammatory drugs (NSAIDs)[45,46].

Furthermore, the effect of thoracic epidural anesthesia on splanchnic blood flow and anastomotic healing remains uncertain and demands future research[47,48]. After all, adequate tissue perfusion and oxygenation is imperative for anastomotic healing[49-52]. Major surgery accompanied by systemic hypotension and blood loss is thought to lead to redistribution of blood to preserve the vital organs (brain and heart) at the expense of the splanchnic circulation[53,54]. Indeed, intraoperative hypotension and blood loss are associated with an increased risk of anastomotic leakage in patients undergoing colorectal surgery[55]. Nevertheless, alterations in the microcirculation have been observed although systemic hemodynamic parameters, such as blood pressure, may be within an acceptable range[56]. Compromised visceral circulation, due to atherosclerosis of the visceral (celiac and superior/inferior mesenteric) or iliac arteries, is not associated with anastomotic leakage[57]. These findings imply that not the macroscopic circulation, but the microvascular flow at site of the anastomosis is of uppermost importance for anastomotic healing and that the microcirculation can be considered as a separate entity. Hence, the role in anastomotic healing and potential therapeutic targets for optimization of the gastrointestinal microcirculation remain to be clarified.

To reduce cardiopulmonary complications, restrictive fluid regimens seem superior to liberal fluid treatment[58]. Liberal and restrictive fluid therapies may induce hypoperfusion of the anastomosis by causing local edema or hypovolemia, which could be avoided by individualized, goal-directed fluid therapy. Individualized fluid therapy based on cardiac output measurement has been proposed as the ideal treatment strategy regarding complications, mortality and length of hospital stay[59]. However,

a recent randomized controlled trial (RCT) using esophageal Doppler monitoring for cardiac output measurement could not prove a reduction in postoperative complications[60]. The effect of goal-directed fluid therapy on intestinal (microvascular) perfusion, damage and healing therefore needs further exploration.

Although an inspired oxygen concentration of over 80% during surgery and in the first two hours after surgery has been shown to reduce surgical-site infections[61], little is known about the effect on anastomotic oxygenation and healing. Only a small randomized trial describes a decrease in anastomotic leakage prevalence when administering 80% oxygen during surgery and in the first six hours following surgery[62]. Supplementation of high inspired oxygen concentration seems beneficial for anastomotic healing and should be evaluated in more patients and on the intestinal oxygenation level to draw definite conclusions.

Several studies have indicated that the use of NSAIDs is markedly correlated with anastomotic leakage following colorectal surgery[63-65]. The ERAS guidelines state that sufficient evidence is lacking to stop using NSAIDs as a component of multimodal analgesia[45]. The mechanisms by which NSAIDs exert their detrimental effects on colonic surgical wound healing are not known, which deserves further investigation.

ADVANCES IN INTRA-OPERATIVE CARE: LAPAROSCOPIC COLORECTAL SURGERY

Although strong evidence exists that a diverting stoma significantly reduces anastomotic leakage in rectal surgery[66,67], other measurements, such as omentoplasty, prophylactically leaving intra-abdominal drains, and application of a sealant (*i.e.*, fibrin glue) around the anastomosis, seem obsolete in preventing anastomotic leakage[68-70]. Moreover, stapled anastomoses and hand-sewn techniques have comparable effects[71]. The most significant improvement in intraoperative care last decades, was the introduction of laparoscopy. Large incisions are avoided and surgical trauma is minimized.

Laparoscopic colon cancer surgery

Following the successful introduction of laparoscopic cholecystectomy and appendectomy, laparoscopic colon resection was first described by Jacobs and colleagues in 1991[72]. However, skepticism about its safety and feasibility rose, since early reports described high port or wound site cancer recurrence rates[73]. Consequently, laparoscopic colectomies were performed decreasingly and surgical societies summoned to only perform these under the auspices of randomized trials. Therefore, one single-center and three multi-center phase 3 randomized clinical trials were initialized to compare oncological outcomes between laparoscopic and conventional open colectomy for cancer: the Barcelona trial[74] and the clinical outcomes of surgical therapy (COST)[75], conventional *vs* laparoscopic-assisted surgery in colorectal cancer (CLASICC)[76] and colon cancer laparoscopic or open resection (COLOR)[77] trials, respectively.

Short-term benefits of laparoscopic colon cancer surgery

The early reports of these trials described similar[75-77] or even lower[74] postoperative complication rates for laparoscopic surgery compared with open surgery. Thirty-day mortality rates were not significantly different[74-77]. On the one hand, operative time was longer for laparoscopy in all studies. On the other hand, patients in the laparoscopic arm had significantly less blood loss[74,77], earlier return of bowel function[74,76,77], earlier resumption of fluid intake and regular diet[76,77], shorter use of oral and parenteral analgesics[75] and shorter hospital stay[74-77]. Radicality of resection, reflected by resection margins and the number of lymph nodes in the resected specimen, did not differ significantly[74-77]. Equivalence of the number of harvested lymph nodes was later confirmed in a meta-analysis[78].

The four exploring randomized trials were followed by multiple others. These trials also found short-term benefits in laparoscopic compared with open surgery[79-82] and confirmed similar postoperative complication and 30-d or in-hospital mortality rates for either operative modality[79-83]. Since the laparoscopic surgical technique is more similar to the conventional approach for right colectomies compared with other colorectal procedures, benefits seem less significant for this laparoscopic procedure[84]. Both long- and short-term health-related quality of life are higher in laparoscopic compared with open colon cancer surgery[85-87].

Hence, laparoscopic colon cancer surgery is associated with multiple short-term benefits compared with conventional surgery. Although these benefits might be clinically less important, laparoscopy seems more comfortable for the patient.

Laparoscopic colon cancer surgery and its oncological safety

Primary endpoints of the four pioneering trials mostly consisted of oncological parameters, since oncological safety was the main concern in early years. The Barcelona trial aimed to compare cancer-related survival after laparoscopic and open colon cancer resection. After a median follow-up of 43 mo, cancer-related survival was significantly higher after laparoscopic surgery[74]. Updated results with a median follow-up of 95 mo showed a tendency of higher cancer-related survival and overall survival for the laparoscopic group. Moreover, laparoscopic surgery was independently associated with a reduced risk of tumor recurrence[88]. This superiority of laparoscopy was mainly caused by the results in patients with stage Ⅲ disease. This led to the hypothesis that the effect of surgery on the immune system is reduced in laparoscopy[89].

Time to tumor recurrence was the primary endpoint of the non-inferiority COST trial. Concerning this, it showed laparoscopic surgery to be non-inferior to open

surgery. Moreover, no significant differences were found in cumulative incidence of recurrence, overall-survival, and disease-free survival. Tumor recurrence in surgical wounds was rare in both treatments groups (less than 1%) and did not differ between groups[75]. The 5-year results of the COST trial confirmed non-inferiority of laparoscopic surgery in terms of disease-free 5-year survival, overall 5-year survival, overall recurrence rates and recurrence distribution[90].

The CLASICC trial was initiated to investigate oncological safety regarding overall and disease-free survival and recurrence rates. No significant differences were found for either endpoint after three years[91]. Moreover, 5-year analysis of the data showed similar (local and distant) recurrence, and overall and disease-free survival rates for both study arms[92].

Primary outcome of the COLOR non-inferiority trial was 3-year disease-free survival, which differed 2% (95%CI: 3.2-7.2); 74.2% in the laparoscopic group and 76.2% in the open surgery group (P = 0.70), when all stages of disease combined were analyzed. Despite exceeding the predetermined non-inferiority boundary of 7% of the upper 95%CI, the authors concluded that this difference was clinically acceptable and that laparoscopy could safely be implemented into daily practice. After all, a per-protocol analysis showed laparoscopic surgery to be non-inferior to open surgery. The combined 3-year overall-survival did not significantly differ[93].

To enhance power, the transatlantic laparoscopically assisted *vs* open colectomy trials study group conducted a meta-analysis including the individual databases of the four mentioned trials (3-year results of the CLASICC and COLOR trial were not yet published at that moment). It showed similar 3-year disease-free and overall survival rates for all stages of disease in the two study arms. Furthermore, recurrence rates and patterns were comparable[94]. Later performed trials reproduced comparable long-term oncological results for both treatment groups[79,80,95]. Moreover, equivalence in long-term oncological outcomes was confirmed in multiple meta-analyses including high-quality RCTs[96-98].

In conclusion, early concerns regarding oncological safety have been invalidated nowadays. Particularly wound or port site recurrence rates are comparable in trials specifically reporting its incidence[74,80,90,93]. Laparoscopic surgery for curative colon malignancies is proven feasible, safe and non-inferior compared with conventional open surgery with multiple short-term advantages in patients with disease stages Ⅰ-Ⅲ on basis of solid level Ⅰ evidence.

Laparoscopic rectal surgery

The CLASICC study was the first randomized trial also comparing oncological outcomes in laparoscopic and open surgery for rectal cancer. Laparoscopic rectal resection was considered technically more demanding than laparoscopic colon resection, as a high conversion rate (34%) and longer operation time were reported[76]. Feasibility and safety of laparoscopic rectal cancer surgery were questioned since. Nevertheless, successful total mesorectal excision was more frequently performed in laparoscopic procedures[76]. The suggested better practicability of this technique in laparoscopic surgery is essential, since complete resection of the mesorectum (with preservation of pelvic autonomic nerves) has shown to improve survival and recurrence rates[99]. Reacting on the CLASICC trial results, a research group from Hong Kong performed an updated subgroup analysis on rectal cancer[100] of their prospective randomized trial on laparoscopic resection of rectosigmoid carcinomas. This analysis showed faster recovery after and similar survival and disease-free survival rates in laparoscopic surgery compared with open surgery[101]. Due to these controversies, additional high-quality trials investigating oncological safety of laparoscopic rectal resection were required.

Short-term benefits of laparoscopic rectal cancer surgery

This need was fulfilled by the performance of multiple RCTs with both short- and long-term parameters as primary outcome. Several benefits of laparoscopic over open rectal surgery have been identified, which are almost identical to those in colon surgery. Laparoscopy is associated with significantly less blood loss or a trend towards significance[102-107]. This resulted in fewer blood transfusions, known as a risk factor for anastomotic leakage, in one trial reporting on this outcome[102]. Postoperative recovery was enhanced in laparoscopy, reflected by faster bowel recovery (shorter time to first postoperative peristalsis[76,105-108], flatus[103,106], stool[103,108], or resumption of normal diet[76,103,105,106]), and less analgesic use[103,105-107]. Moreover, length of hospital stay was shorter in the laparoscopic group, reaching significance in three single-center studies with short-term recovery as its primary outcome[102,106,107]. A wide range in postoperative complication rates is reported. Nonetheless, a meta-analysis reported significantly less postoperative complications after laparoscopic surgery[109]. On the other hand, like in colon cancer surgery, significantly longer operative time or a trend towards significance in laparoscopy is reported in most trials[76,102-108]. This issue would be of decreasing importance nowadays, since experience is growing.

In contrast to colon cancer surgery, higher health-related quality of life in laparoscopic compared with open rectal cancer surgery was only reported on the short-term (one week postoperatively) in a prospective study[110], whereas no difference was found on the long-term in the COLOR Ⅱ cohort (one year postoperatively)[111].

Laparoscopic rectal cancer surgery and its oncological safety

No significant differences were found for both short- and long-term oncological outcomes in terms of proximal, distal and radial resection margins, number of lymph nodes harvested, three- or five-year overall-, cancer-related- or disease-free survival, and local recurrence rates in patients undergoing both sphincter-sparing (low

anterior) resection for mid or high and abdominoperineal resection (APR) for low rectal carcinoma[102-104,106,108,112]. Since these studies incorporated relatively small patient numbers, consequently lacking power, and were mostly conducted in a single-center setting by one team or even one surgeon, a phase 3 non-inferiority multicenter trial including 1103 participants undergoing LAR or APR was conducted comparing oncological outcomes (COLOR Ⅱ trial). Locoregional recurrence was its primary endpoint. Like the COLOR trial for colon cancer, the COLOR Ⅱ trial showed that postoperative recovery was improved after laparoscopy, whereas radicality of resection, intra- and postoperative complications, and 30-d mortality were comparable in both groups. Moreover, laparoscopic rectal cancer surgery was considered feasible with a conversion rate of 16%. However, it should be noted that these findings are not applicable to all rectal cancer patients, since T3 tumors within 2 mm from the endopelvic fascia and T4 tumors were not included in the trial[113].

Meanwhile, long-term results of the CLASICC trial have been reported. Although higher positive resection margin rates were reported in the early results[76], 3-year results showed no differences in (local) recurrence and mortality rates. Moreover, similar results for APR and LAR were reported[91]. Multiple meta-analyses confirmed comparable short- and long-term oncological outcomes in laparoscopic and open surgery[114,115]. The Hong Kong study group reported equal overall survival, cancer-related survival, disease-free survival, and local and distant recurrence rates after ten years in patients with stage I -IV upper rectal cancer undergoing LAR[105]. Results for locoregional recurrence of the COLOR Ⅱ trial are expected at the end of 2013[113].

In conclusion, rectal cancer surgery has short-term advantages over conventional open surgery and seems oncological safe. Nevertheless, recurrence and long-term survival rates of the COLOR Ⅱ trial need to be awaited before laparoscopic resection of rectal cancer is indisputably proven to be oncological safe.

Surgical feasibility of laparoscopic colorectal surgery

Intraoperative conversion is considered an important measure of feasibility of a laparoscopic procedure. Due to the non-selective design of RCTs and the inability of researches to adequately choose patients eligible to be randomized to either surgical approach, high conversion rates were reported in early trials. In the CLASICC trial up to 25% of colon and 34% of rectal cancer patients underwent conversion[76]. However, no uniform definition of conversion was used in different trials. Conversion rates of the CLASICC trial improved each year, from 38% in the first year to 16% in the sixth year of the study[76]. Furthermore, low conversion rates of 2.8% to 14.6% were reported in later performed RCTs (allowing surgeons to be more experienced) and single-center studies with a specialized laparoscopic surgical team[74,79-81]. This demonstrates its function of the learning curve.

The COLOR case volume study demonstrated that high volume centers (> 10 cases per year) had fewer complications, greater lymph node harvest and shorter hospital stay compared with medium (5-10 cases per year) and low volume (< 5 cases per year) centers[116], again addressing the learning curve of laparoscopic surgery. Moreover, operative time was significantly shorter in high volume centers[116]. Hence, laparoscopic experience is a major factor in outcome. Higher costs for laparoscopy, despite the shorter mean hospital stay, may be reduced in high volume centers. After all, the main cause for higher costs are operative expenses[117].

Patient-tailored strategies

Although conversion rates were high in the firstly performed multicenter RCTs, laparoscopic colon surgery is considered standard of care in many countries nowadays. Intraoperative conversion was associated with higher complication rates and prolonged hospital stay[76,118]. Moreover, cases converted were associated with a worse overall[92] or 5-year disease-free[81] survival compared with laparoscopically completed or open surgery. The most common reasons for conversion in the early performed RCTs were tumor fixation and advanced disease, uncertainty of tumor clearance, and obesity[76]. As intraoperative conversion is nowadays mainly needed due to unfavorable tumor characteristics instead of inexperience of surgeons, these cases have a worse outcome. Moreover, laparoscopic surgery is currently regarded safe and suitable for obese patients also[119].

Besides surgical experience, a patient-tailored treatment strategy with optimal selection of patients eligible for laparoscopic surgery seems essential to optimize results. Adequate patient selection leads to lower conversion rates as shown in the LAPKON Ⅱ trial[83]. Patients with rectal cancer were randomized after initial diagnostic laparoscopy to assess feasibility of laparoscopic resection. Hence, conversion should not be considered as surgical failure, but as a judicious decision. Nevertheless, appropriate selection should preferably be performed preoperatively. Feasibility and safety of laparoscopic surgery in elderly colorectal cancer patients for instance, have been underlined in a recent randomized study[120]. Another possible vulnerable population suitable for laparoscopy could be malnourished patients, since malnourishment and weight loss are associated with impaired clinical outcome[20,21].

Laparoscopic colorectal surgery in the light of enhanced recovery programs

As previously described, another major improvement in colorectal cancer surgery has been the introduction of fast-track or enhanced recovery programs. However, only one trial described in this review was performed within such a program. The LAFA trial, a multicenter randomized trial comparing laparoscopic and open surgery plus or minus a fast track program in segmental (right and left-sided) colectomy, concluded that the best perioperative treatment is laparoscopy combined with fast track surgery regarding total hospital stay. Secondary outcomes

(postoperative hospital stay, morbidity, reoperation rate, readmission rate, in-hospital mortality, quality of life at two and four weeks, patient satisfaction and in-hospital costs) did not significantly differ between the four treatment groups[82]. Currently, a multicenter randomized trial is performed to investigate the hypothesis that laparoscopic surgery is superior compared with conventional surgery even when both treatments are optimized within the ERAS program[121].

ADVANCES IN POSTOPERATIVE CARE: DETECTION OF ANASTOMOTIC LEAKAGE

The clinical presentation of anastomotic leakage is heterogeneous and may be nonspecific. Anastomotic leakage is frequently diagnosed late due to a low index of suspicion based on clinical and conventional laboratory findings[122]. Moreover, abdominal CT-scan with intraluminal contrast undoubtedly has a role in timely recognition of anastomotic leakage, but yields low sensitivity (68%), which may delay the diagnosis and appropriate treatment[123]. Intervening weekends may further delay diagnosis and re-interventions[124]. Delay in recognizing and consequently treating anastomotic leakage after colorectal surgery is associated with increased mortality[125,126].

Clinical signs for accurate and early detection of anastomotic leakage have been widely investigated. den Dulk *et al*[127] standardized postoperative monitoring and developed a leakage-score, consisting of general, local physical examination, laboratory investigation and dietary items. The use of this score resulted in a significantly shorter delay in the diagnosis of anastomotic leakage.

Accurate diagnostic markers are needed to detect anastomotic leakage early after colorectal surgery. Various biomarkers have been investigated, although none has been validated clinically and studies are difficult to compare, mainly due to different definitions of anastomotic leakage[128]. C-reactive protein (CRP) has been widely proposed as an early indicator to diagnose anastomotic leakage on postoperative day 2-4[129]. However, the test characteristics are not convincingly robust, with approximately 70%-80% sensitivity and specificity[129]. Currently, the PRECIOUS trial investigates a step-up approach in major abdominal surgery combining CRP and CT imaging of the abdomen to diagnose severe complications, including anastomotic leakage[98]. Furthermore, specific plasma markers for intestinal cell damage and inflammation may provide better accuracy.

Finally, intraperitoneal microdialysis measuring intraperitoneal cytokines after rectal surgery has sometimes been used for early detection of anastomotic leakage. Lactate/ pyruvate ratio and interleukin (IL)-6, IL-10 and tumor necrosis factor-α were increased before clinical signs were detected in patients with anastomotic leakage[130,131]. Moreover, higher levels of intraperitoneal cytokines compared with systemic cytokines suggest the gastrointestinal tract to be the origin of the postoperative inflammatory response after colorectal surgery[132]. However, it should be noted that intraperitoneal microdialysis is an invasive method, with two catheters left behind intra-abdominally, that could involve complications. When a drain is left after surgery, measuring biomarkers in the peritoneal fluid, such as cytokines and metalloproteinases, could attribute to early detection of anastomotic leakage[133,134]. Also, a polymerase chain reaction for *Enterococcus faecalis* in drain fluids could be used as a screening test for anastomotic leakage[135]. Nevertheless, drains should not be used routinely, microdialysis is an invasive method, and the value of these markers in the absence of other clinical signs is limited.

ADVANCES IN ORGANIZATION OF CARE: AUDITS

Clinical auditing has been initiated in several countries and is considered an important tool for quality assessment and the identification of factors needing improvement. Furthermore, clinical audits provide a unique dataset for research as well. Starting in 2009, a nationwide audit for colorectal surgery has been initiated in the netherlands, the dutch surgical colorectal audit (DSCA)[136]. Later adopted as a quality indicator for the health care inspectorate, the DSCA has become a performance index for colorectal surgeons. Postoperative mortality and anastomotic leakage rates indeed decreased between 2010 and 2012[11,137]. This is in line with audits in other countries, including the United States, Belgium, Germany, United Kingdom, Spain, Italy, Denmark, Norway, and Sweden[138,139]. Whether these improvements are directly related to the introduction of the audit has to be determined. Yet, it can at least be stated that the DSCA has effectuated increased awareness of and insight in aspects of improvement.

Clinical audits have revealed several interesting findings with respect to postoperative complications. Hospitals with higher mortality rates had only slightly higher incidences of postoperative complications. However, the ability to let patients with a serious complication survive was significantly lower in high-mortality centers[136]. This phenomenon is addressed as failure to rescue and was previously described for other gastro-intestinal operations[140]. Data from the American College of Surgeons National Surgical Quality Improvement Program showed that although complication incidences did not vary between hospitals, mortality rates, largely contributed to death after major complications, significantly varied, indicating that timely recognition and treatment of complications deserves greater attention[141]. Future research should aim at identifying and improving the fundamental aspects causing failure to rescue. Another important finding was that anastomotic leakage rate variation between hospitals was mainly due to treatment-associated factors, such as blood loss or transfusion and operation time, than population characteristics, as was the case

with postoperative mortality[142]. Therefore, anastomotic leakage is proposed as an accurate read-out for quality of care, underlining the importance of anastomotic leakage rate reduction in colorectal surgery. In conclusion, clinical audits provide unique insight in aspects associated with health care quality and more studies have to be done to find in-hospital factors correlated with anastomotic leakage for further improvement.

CONCLUSION

During the last several decades, colorectal cancer surgery has experienced some major perioperative improvements. Preoperative risk-assessment of nutrition, frailty, and sarcopenia followed by interventions for patient optimization or an adapted surgical strategy, contributed to improved postoperative outcomes. Enhanced recovery programs or fast-track surgery also resulted in reduced length of hospital stay and overall complications without affecting patient safety. After an initially indecisive start due to uncertainty about oncological safety, the most significant improvement in intraoperative care was the introduction of laparoscopy. Laparoscopic surgery for colon and rectal cancer is associated with better short-term outcomes, whereas long-term outcomes regarding survival and recurrence rates are comparable. Nevertheless, long-term results in rectal surgery remain to be seen. Early recognition of anastomotic leakage remains a challenge, though multiple improvements have allowed better management of this complication.

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