SUMMARY, GENERAL DISCUSSION & FUTURE PERSPECTIVES

This thesis focuses on several aspects of the treatment of colorectal cancer, its effects on patients undergoing colorectal cancer surgery and how to diminish its complications. Colorectal cancer surgery is a developing field even though it has been performed for a long time. Where it started with laparotomies, significant mortality rates and high chances of locoregional recurrence it has evolved into a minimally invasive, safe and in many cases curative field of surgery.

To get there several important steps had to be taken. As stated before, rectal cancer surgery started as mutilating amputative surgery with high recurrence and mortality rates. The introduction of a new sharp dissection technique in the nineteen eighties referred to as total mesorectal excision (TME), instead of conventional blunt dissection, transformed rectal surgery into a restorative and curative procedure. Overall survival (from 48% to >60%) as well as local recurrence rates (from >20% to <10%) improved. Moreover, higher incidence of sphincter preservation and less blood loss and autonomic nerve damage was observed. Hereafter radiotherapy was added as neo-adjuvant therapy, where both the Swedish rectal cancer trial and the Dutch TME trial showed half the amount of local recurrences with the addition of preoperative radiotherapy compared to TME surgery alone. Complete mesorectal excision and tumor resection proved necessary to achieve these results, as involvement of the circumferential resection margin (CRM) still resulted in high local recurrence rates. Introduction of minimally invasive surgery in colorectal cancer at the end of the twentieth century predicted less surgical trauma with equal oncologic results. To evaluate these expectations, multiple studies have been initiated. Several large randomized controlled trials showed the safety of laparoscopic surgery in colon cancer (CLASICC trial, COLOR trial, Barcelona trial), which opened the door for studies evaluating laparoscopic surgery in the technically more challenging field of rectal cancer.

Chapter 2 discusses the short-term results of the COLOR II trial, which was conducted to compare laparoscopic and open surgery in patients with rectal cancer and was the largest RCT of its kind, since 1044 patients who were eligible for analysis were included in 30 centers in 8 countries. Results were similar to data obtained in trials in laparoscopic colon cancer surgery. Less blood loss, and faster return of bowel function was observed. Moreover, hospital stay was shorter in the laparoscopic group. Operating time was however longer in the laparoscopic group, while completeness of resection, positive CRM, morbidity and mortality did not differ between groups. Other comparable RCTs were performed, including the CLASICC trial, COREAN trial, ACOSOG Z6051 trial and the ALaCaRT
All showed longer operating times and less blood loss for laparoscopy, with comparable intraoperative morbidity. Hospital stay was shorter in the COREAN and CLASICC trials, while no difference was found in the ACOSOG Z6051 and ALaCaRT trials. Bowel recovery was faster in the ACOSOG Z6051 and CLASICC trials, whereas no difference was found in the ALaCaRT trial. The COREAN trial did not report these values. Overall, results in favor of laparoscopic rectal resection were reported.

Oncologic endpoints are of most importance when evaluating a new technique in cancer surgery. Chapter 3 discusses the primary endpoint of the COLOR II trial, which was locoregional recurrence at 3 years after surgery. This was 5% for both laparoscopic and open surgery groups with a confidence interval (CI) of -2.6% to 2.6%. The COREAN trial (n=340) used a non-inferiority margin of 15%. Its primary endpoint was 3-year disease-free survival, which was 72.5% for the open surgery group and 79.2% for the laparoscopic group, with a CI for the difference of -15.8 to 2.4%. In 2015, the safety of laparoscopic rectal resection was questioned by two large randomized controlled trials from the US and Australia, the ACOSOG Z6051 and the ALaCaRT trials respectively. Both trials were unable to establish non-inferiority of the laparoscopic approach as a result of inadequate surgical resection due to higher distal and circumferential margin involvement. No real explanations were given for these inadequate resections, although the ACOSOG Z6051 mentioned the challenging nature of rectal cancer surgery at baseline and the constraints of rigid laparoscopic instruments in a narrow pelvis. Nonetheless, these same problems were encountered by the COLOR II and COREAN trials, which did show non-inferiority for laparoscopic resection compared to open resection. When evaluating these trials very wide confidence intervals were observed in both the ACOSOG Z6051 and the ALaCaRT trial around the difference of the primary endpoint (-12.4 to ∞ and -10.8 to ∞, respectively). Since the confidence interval represents the range around the study’s result in which we expect the true value to lie, a wide confidence interval diminishes the high quality evidence of RCTs. Possible factors that could have contributed to the wide confidence intervals of these two trials are that numbers randomized were too small (486 patients for ACOSOG Z6051 and 475 for ALaCaRT), that a surrogate endpoint was used or that the laparoscopic technique was not completely standardized. As stated before the best ways to confirm non-inferiority are oncological outcome on survival and recurrence. Both the ALaCaRT and the ACOSOG Z6051 trials reported their two-year oncological follow-up only recently. The ACOSOG Z6051 trial reported two-year disease free survival for laparoscopic surgery of 79.5% (95% CI 74.4-84.9) and for open surgery 83.2% (95% CI 78.3-88.3) with locoregional recurrence rates of 4.6% in the laparoscopic group and 4.5% in the open group respectively. The ALaCaRT trial described a two-year disease free survival for laparoscopic surgery of 80% and for
open surgery 82% (difference 2.0%; 95% CI, -9.3% to 5.4%) with locoregional recurrence rates of 5.4% in the laparoscopic group and 3.1% in the open group respectively (difference 2.3%; 95% CI -1.5% to 6.1%).\textsuperscript{19} Recently a meta-analysis on the non-inferiority of laparoscopic rectal cancer surgery which included data from all these before mentioned trials has been performed and these outcomes further support the non-inferiority of laparoscopic rectal cancer surgery found by the COLOR II and COREAN trial.\textsuperscript{20} The COLOR II trial is the largest randomized trial conducted on the subject. Due to the large number of patients, narrow confidence interval regarding the primary endpoint and the very high follow-up rate of 99% it can be considered as high quality evidence. Several learning points can be taken from the study design for planning future studies to further increase quality of the data. First, a standardized imaging modality to determine the location of the tumor and central storage of the complete surgical videos would be preferable. Second, pathological evaluation of the resected specimen with central revision by independent professionals would improve standardization in future studies. The same applies to some form of surgical quality assurance by way of storage and central access of the operation videos. In the COLOR III trial, in which transanal TME (TaTME) is compared with laparoscopic TME, learning points that were observed in the COLOR II trial have been incorporated in the study protocol. Because all data are collected digitally, including imaging and operation videos, it is unique in its design and extensive quality assurance.\textsuperscript{21} While rectal cancer surgery emerged as a minimally invasive operation with excellent results on survival and recurrence of disease, other patient related outcomes also became more important. Chapter 4 discusses the health related quality of life after rectal cancer surgery in the COLOR II trial and most importantly the effects on urinary dysfunction and sexual dysfunction.\textsuperscript{22} Sexual problems after surgery for rectal cancer are common, multifactorial, inadequately discussed, and undertreated.\textsuperscript{23} Sexual and urinary functions are dependent on dual autonomic (sympathetic and parasympathetic) innervation. The most important structures are the superior hypogastric plexus, hypogastric nerves, pelvic splanchnic nerves and the inferior hypogastric plexus. Damage of the superior hypogastric plexus and the hypogastric nerves causes bladder instability (loss of relaxation) and retrograde ejaculation or loss of ejaculation, whereas damage of the inferior hypogastric plexus and sacral branches leads to difficulties in bladder emptying (loss of contraction) and impotence. In women, the increased blood flow to the vagina and vulva, causing vaginal lubrication and swelling of the labia and clitoris, is also under the predominant control of these parasympathetic nerves and injury results loss of these functions in women.
During neoadjuvant therapy, especially radiotherapy, nerve pathways as well as microvasculature are damaged. Subsequent rectal surgery only aggravates this damage.24–26

In the COLOR II trial both female and male genitourinary function was impaired by surgery, with no differences between open and laparoscopic surgery. Micturition problems were less affected than sexual function and mostly recovered to preoperative levels within six months after surgery. Male sexual function was affected in approximately 80% of patients in both groups four weeks after surgery. Male sexual function slightly improved but remained worse than index levels at one year after surgery for both groups. In literature sexual function remains an undervalued and underexplored field, especially lacking high quality evidence. Several systematic reviews have been performed that in line with our study, did not show differences between laparoscopic or open approach concerning sexual function.27,28 Concerning sexual function and robotic surgery versus laparoscopy, there is only one prospective randomized study and several non-randomized studies, all with very small samples, and thus far no convincing differences have been found.29 Radiotherapy increases the rate of sexual dysfunction but is rarely the only causative factor.30 To obtain higher-level evidence on this subject, it is very important that all high quality studies use the same validated questionnaires. Furthermore, healthcare professionals should always ask about these functions pre- and postoperatively in men and women alike.

Interesting novel treatment developments for rectal cancer are currently underway. The main cornerstone remains radical surgical treatment, but since rectal cancer surgery is associated with significant morbidity and decrease in quality of life there has been a shift to different treatment strategies to preserve function and quality of life without hampering oncological outcome. Because of screening programs more early stage cancer is detected, leading to more trials and possibilities for local therapies and organ preservation. One example is the TESAR trial, comparing radical TME surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancers.31 It is expected that the latter will result in comparable oncological results with less morbidity and increased quality of life, including sexual and urinary function. Another example is the STARTREC trial, which investigates rectal preserving strategies after neoadjuvant therapy. The rectal preserving group consists of two arms of which one arm receives short course 5x5Gy radiotherapy, whereas the other arm will receive chemoradiotherapy (Capecitabine and long-course radiotherapy) according to current protocols. Subsequent treatment will be decided based on the response of the tumor to the neo-adjuvant treatment regimens. Non-responders will undergo low-anterior resection, partial responders will undergo TEM and complete responders will have a ‘wait and see’ policy with intensive follow-up.32 This nonoperative ‘wait and see’ approach in case of complete remission after neoadjuvant
therapy is being investigated more in recent years.\textsuperscript{33-36} Evidence suggests that this a safe strategy in an adequately selected population and should be offered to patients in a controlled trial setting to increase the available level of evidence. More clarity on the exact role of radiotherapy on sexual/bladder dysfunction and incontinence is expected from the long-term follow-up of patients undergoing watch and wait approach after complete response following radiotherapy.

Another way to improve patient outcome is the reduction of complications in the postoperative phase. Infectious complications affect 20 to 40 percent of patients undergoing surgery for colorectal cancer\textsuperscript{28}, while anastomotic leakage, the most severe complication of colorectal surgery, has an incidence ranging from 5\% to 15\%\textsuperscript{37} and a mortality rate of 6\% to 30\%.\textsuperscript{38} The patient’s own microbiome seems to play an important role in the etiology of these complications.\textsuperscript{39} Alterations to the patients’ microbiome might be a way to decrease these serious complications and improve outcome. One way to influence the microbiome is with selective decontamination of the digestive tract (SDD). This mixture of oral nonabsorbable antibiotics, mostly consisting of oral colistin, tobramycin and amphotericin B, is designed to minimize the impact of infections by potentially pathogenic microorganisms that are endogenous to the patient.\textsuperscript{40} These microorganisms colonize the digestive tract and consist predominantly of aerobic Gram-negative bacteria, \textit{Staphylococcus aureus} and fungi against which SDD is effective. SDD has been safely introduced in the intensive care unit (ICU) setting after it reduced mortality in ventilated ICU patients.\textsuperscript{41}

In \textit{chapter 5} we provide an overview on the use of SDD in digestive surgery.\textsuperscript{42} The review discusses five randomized controlled trials and one cohort study on SDD in esophageal, gastric and colorectal surgery. These studies reported a positive effect of SDD on infectious complications and in some studies on anastomotic leakage rates, especially in colorectal surgery. Available literature was however performed in heterogeneous populations, underpowered for anastomotic leakage and additional proof for the benefit of SDD in colorectal surgery was needed.

We therefore initiated a study for a large multicenter randomized clinical trial in six hospitals in the Netherlands to evaluate the role of SDD in colorectal cancer surgery (SELECT trial). The study protocol is presented in \textit{chapter 6}.\textsuperscript{43} The primary aim of this trial was to investigate the role of SDD on anastomotic leakage in colorectal cancer surgery patients. The clinical anastomotic leakage rate was the primary endpoint of this study. Secondary endpoints included infectious complications, disease-free survival, overall survival, costs, and quality of life. Patients with a colorectal carcinoma without evidence of metastases at imaging who were candidates for elective curative surgery with a primary
anastomosis were eligible for inclusion. Oral colistin, tobramycin and amphotericin B were administered to the SDD group to decontaminate the digestive tract. Both groups received cefazoline and metronidazole as pre-operative prophylaxis. Decontamination by SDD was verified by the presence of potential pathogenic microorganisms in the gut by microbial analysis by Interspace-profiling technique (IS-pro) on rectal swabs of patients. To our knowledge this was the first large multicenter RCT with SDD in patients undergoing only colorectal cancer surgery.

Chapter 7 highlights the primary outcome results of the SELECT trial. Patients were recruited from May 2013 until March 2017. A total of 485 patients was included of which 455 were eligible for analysis with 228 patients randomly assigned to the intervention (SDD) group and 227 patients to the control group. Anastomotic leakage was observed in 6.1% of the patients in the SDD group and in 9.6% of the patients in the control group with an odds ratio (OR) of 0.610 and a 95% confidence interval (CI) of 0.304 to 1.224. In the SDD group, fewer patients had one or more infectious complications compared to the control group (14.9% versus 26.9%, OR 0.477 and CI of 0.299 to 0.761. No differences between study arms were observed in thirty-day mortality, median days until first intake, median days until first defecation, median hospital stay in days, readmissions within 30 days or ICU admissions. Adequate decontamination in the SDD group was confirmed by IS-pro analysis (see Chapter 8) and no infections with resistant microorganisms occurred.44

Unfortunately the trial was stopped prematurely when the interim-analysis indicated that superiority was no longer attainable for anastomotic leakage. We were unable to show a significant decrease in anastomotic leak rate. Nonetheless, the robust reduction of over 50% of the infectious complications advocates the standard use of perioperative SDD in all colorectal cancer surgery to prevent infectious complications. As previously stated SDD is based on the administration of oral nonabsorbable antibiotics to minimize the impact of endogenous infections by potentially pathogenic microorganisms. Oral antibiotics and bowelprep are mostly used in the United States for the reduction of SSIs and seem to have a comparable effect on SSI rate as the described effect by SDD in our study.45,46 Concerning the use of bowl prep and oral antibiotics however, varying levels of evidence for this effect are presented. Performed studies are mostly not randomized or underpowered. Additionally, oral antibiotics are not specified or substantial selection bias cannot be ruled out. Besides that, no substantial evidence on possible antibiotic resistance occurrence is available when oral antibiotics are given for only one day prior to surgery. SDD is also a form of oral antibiotics, but with a standardized and reproducible protocol. No antibiotic resistance occurrence by SDD was shown in several very large randomized
trials in an ICU setting,\textsuperscript{47,48} as well as in our study. Furthermore, SDD had a substantial effect on the total number of infectious complications in our study including pulmonary and urinary tract infections in addition to a reduction of 75\% on SSIs. We therefore recommend SDD over “any” oral antibiotics and bowel prep for the reduction of infectious complications.

Little is known about the effect of SDD on composition of the gut microbiota. Until recently, all research on gut microbiota was culture-based. The vast majority of gut microbiota however, is uncultivable and therefore these studies give biased results. In addition, previous studies on the effect of SDD with molecular techniques were based on small and heterogeneous groups and have mainly evaluated gut microbiota composition with techniques targeted at specific species.\textsuperscript{49,50} These studies consisted of mostly ICU patients who are patients with different comorbidities and confounding factors, which may influence the gut microbiota composition, such as feeding through a nasogastric tube and the use of multiple additional antibiotics.\textsuperscript{51}

\textbf{Chapter 8} focuses on the effect of SDD on overall gut microbiota composition. In this accessory study to the SELECT trial rectal swabs of 118 patients were analyzed (56 SDD vs 62 control) with the IS-pro technique. With IS-pro, bacterial species are discriminated based on the length of the 16S-23S rDNA interspace region.\textsuperscript{52} SDD samples showed different microbial signatures compared to control samples. \textit{Escherichia coli}, \textit{Sutterella} spp., \textit{Faecalibacterium prausnitzii} and \textit{Streptococcus} spp. were the most discriminatory species. The SDD group showed clustering into two subgroups. In one subgroup a decrease in Proteobacteria was observed, whereas the other subgroup showed a shift in Proteobacteria, which was characterized by a decrease in \textit{E. coli} and \textit{Sutterella} spp. and an increase in \textit{Desulfovibrio} spp. and \textit{Hafnia alvei}.

This contrasting effect of SDD, dividing the SDD group into two subgroups, has never been shown in previous studies. These results also provide a first indication that it might be feasible to predict in which patients SDD will exert its desired effect. SDD also leads, however, to a nonselective change in gut microbiota composition and more research to study this effect is needed.
FUTURE PERSPECTIVES

Several interesting topics for further research have surfaced from this thesis and should be explored. Patient reported outcome measures (PROMS) on sexual and urinary function should be included in the standard workup of rectal cancer patients. In this era of organ sparing rectal cancer surgery and with long-term results from a watch-and-wait (W&W) approach after (chemo-) radiotherapy (CRT) for rectal cancer quality of life becomes even more important. Several studies to provide higher-grade evidence on the W&W approach are currently underway and should give a clearer answer on the safety and limits of this approach. Most evidence thus far suggests that the W&W approach and organ preserving surgery give better results on PROMS compared to TME surgery. Preferentially future high quality surgical studies should be performed through international collaboration to decrease the time in which a high number of patients can be accrued. Hopefully in that way the interval between commencement of a trial and reporting of long term outcomes can be shortened to several years instead of a decade as most previous large trials.

I believe that the treatment of rectal cancer has to be tailored to each specific patient in the future. Patients who show partial response to CRT should be closely monitored in a surveillance program and allowed longer time to achieve the best possible reduction in tumor load as it may take more than 12 weeks to achieve complete response for some tumors. Patients who do not respond are however unlikely to benefit from longer waiting periods and should be operated sooner when a safe and successful procedure is still feasible. Rectal cancer surgery should always be performed minimally invasive when possible and expertise is available as shown in this thesis. However, as in most rectal cancer trials T4 tumors are excluded these results cannot be extrapolated to this subgroup. Therefore, in large and invasive tumors there is still a role for open rectal cancer surgery.

When evaluating mid and low rectal tumors, TaTME or robotic-assisted laparoscopic surgery could become the standard treatment instead of laparoscopic low anterior resection (LAR). Thus far however, no high level evidence of the superiority of either of these techniques has been published.

TaTME is a single port transanal technique while adhering to TME principles and has potential benefits: better specimen quality with better radicality, less morbidity due to better anastomotic techniques and more sphincter saving procedures. Thus far results from several cohorts are promising, since specimen quality proves equal or better, the number of harvested lymph nodes is higher and quality of life seems comparable to laparoscopic TME. Before adaptation of TaTME as standard surgical therapy, a well-designed randomized study is however imperative to demonstrate its efficacy and safety.
This led to the initiation of the COLOR III trial. Until the COLOR III trial provides evidence for similar recurrence and survival rates as laparoscopic resection alone, it cannot be fully implemented for mid and low rectal tumors.

One of the largest randomized trials investigating robotic rectal cancer surgery has been the Robotic versus Laparoscopic Resection for Rectal cancer (ROLARR) trial. This trial randomized 237 versus 234 patients for robotic or laparoscopic resection respectively, in 29 hospitals in 10 countries. It showed similar outcomes in both groups regarding quality of TME, CRM involvement, conversion to open surgery, intraoperative complications, 30-day mortality, bladder dysfunction, and sexual dysfunction and was therefore not able to show superiority of robotic rectal cancer surgery.\(^{57}\) Since robotic surgery has several drawback such as lack of tactile feedback, high costs and large size of the systems, the role of robotic surgery in rectal cancer surgery remains under debate.

Besides several other factors that could influence infectious complications and anastomotic leakage, the key to reducing infectious complications, anastomotic leakage and possibly even the development of colorectal cancer could very well lie in the patients’ microbiome.\(^{58-60}\)

As shown in this thesis, gut microbiota manipulation can lead to beneficial effects on postoperative outcomes. Interestingly, not all patients responded equally to SDD treatment. Evaluating which patients did not respond to SDD with the desired effect and why, and determining whether they had different outcomes than classic responders to SDD is crucial to get more insight in the effects and underlying mechanism of the treatment. SDD should be implemented to decrease infectious complications. Simultaneously, more studies should be performed to better understand the influence of the patients’ microbiome on outcome after surgery. In the future, fecal sampling and microbial profiling of every patient before colorectal surgery could well be part of the preoperative workup in order to assess the microbiome and regulate potential deleterious effects. Although we were not able to proof it in the SELECT Trial due to lack of statistical power, I believe a decreasing effect on anastomotic leakage will be observed with larger numbers of patients treated with SDD. We observed a trend in the SELECT Trial of minus 3.5 percent leakage rate for SDD-treated patients, and the large number of patients needed to provide statistical evidence for a smaller decrease in anastomotic leakage rate of a couple percent.

Through new molecular techniques, a more complete understanding of “a healthy microbiome” is emerging as well as what constitutes a pathological disturbance in the microbiome.\(^{61}\) Such dysbiosis in microbial community membership can consist of a loss of specific beneficial bacteria or a critical loss of diversity among the beneficial bacteria, which results in a pathobiome.\(^{62}\)
It is plausible that higher levels of pathogens are present in the microbiome of patients who are more at risk for SSIs and anastomotic leakage, such as those with lengthy operations, increased blood loss, reoperative surgery in the same wound site, poor nutritional status and smokers. Normally these pathogens remain contained by the abundance and diversity of the microbiota. But during surgery, low abundance pathogens can become unleashed by the very process of preparing and treating the patient, beginning with nil per os after midnight, application of broad spectrum antibiotics, and physiologic stress among others. Several pathogens are linked to the development of anastomotic leakage, infectious complications and even the development of colorectal cancer. Pathogens, such as P. aeruginosa, E. faecalis and Serratia marcescens can proliferate when the microbiota becomes depleted in the perioperative period. These pathogens can produce collagenase and elicit intestinal inflammation leading to anastomotic leakage.

To correct the pathobiome perioperatively should be a topic for further research. This could be through e.g. nutritional advice, probiotics, antibiotics or even a bowel prep solution containing both nutrients and antivirulence agents that promote the proliferation of beneficial bacteria, restores the balance in the gut and preserves or enhances the normal microbiota.

To get as much insight on this as possible, the microbiome of colorectal cancer patients should be analyzed by molecular diagnostics, preferably pre-, per- and postoperatively. In this way, large databases with colorectal cancer patients and their microbiome constitution, fluctuation and repopulation will become available to find pathogens and compositions that can be linked to colorectal cancer as well as anastomotic leakage and other complications. This could lead to a further decrease in infectious complications, anastomotic leakage rates and therefore a more favorable oncological outcome.
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