General discussion and future perspectives

The aim of this thesis is to further improve the multimodality treatment for rectal cancer, locally advanced rectal cancer and locally recurrent rectal cancer. Further development of the multidisciplinary approach and 'tailor made' treatment strategies is ongoing and has rapidly improved since the early 90's with neoadjuvant/induction therapy and perioperative improvements.(1) Current research may cause a shift towards even more conservative therapies after preoperative treatment such as rectal sparing surgery or non-operative treatment with watchful waiting.(2) Although this is not the aim of this thesis, these new insights in future treatment of rectal cancer will also be discussed in this chapter. In the current thesis, the focus lies on different aspects and outcomes of treatment for primary rectal cancer, locally advanced rectal cancer and locally recurrent rectal cancer.

The first part of this thesis focuses on treatment of rectal cancer and mainly on short- and long-term outcomes associated with hospital volumes in rectal cancer surgery. This association is still a subject of debate. Since 2012 a minimal hospital volume of 20 rectal cancer resections annually per hospital is mandatory in the Netherlands, irrespective of tumour stage.(3) Centralization is recommended for patients with advanced stages of rectal cancer in specialized colorectal cancer hospitals. In the first Snapshot database study of this thesis, including 2095 patients treated in 71 Dutch hospitals in 2011, annual hospital volume was not significantly associated with any outcome measure after rectal cancer surgery in low (<20 resections/year), medium (20-50 resections) or high (>50 resections) volume hospitals, regardless of tumour stage. The differences that were observed among volume groups were related to clinical nodal staging and the use of minimally invasive surgery and diverting stoma. Overall complications seemed to be lower in low volume hospitals, although reintervention rates did not differ significantly. Three-year overall survival rates were similar for low (75.9%), medium (79.1%) and high volume (80.3%) hospitals. We did not find a significant difference between CRM-positivity rates, in contrast with a study of Gietelink et al.(4), where a significant higher incidence of CRM positivity was found in low-volume hospitals in 2011 and 2012 using DSCA data of all 94 Dutch hospitals.(4) This underlines the difficulty in interpretation of hospital volume as a single discriminator, because specific low-volume hospitals may actually be high performing.(5) In 2011, centralization for treatment of advanced stages was already recommended and it seems likely that a certain volume is needed to manage this complex care. Patients with cT4 tumours are potentially more accurately assessed in experienced multidisciplinary tumour board (MDT) meetings and treated by specialized surgeons for 'beyond TME' surgery in centres for locally advanced disease. These centres may not necessarily be high-volume, because of their focus on referred patients with less use of their capacity for patients with cT1-3 tumours. These results suggest that hospital volume, as a single discriminator should be used with caution, although a certain unspecified volume is likely needed to gain and retain expertise in rectal cancer care with increasing complexity.

Treatment of rectal cancer is dependent on tumour stage. A majority of patients will present with early stage rectal cancer (cT1-cT3) and may be treated with standard TME-surgery. Less patients will present with advanced rectal cancer (cT4) and a more multidisciplinary approach with preoperative (chemo-) radiotherapy and extensive resections beyond the standard TME-plane are mandatory. A recent population-based study revealed no differences in 5-year survival rates between hospital volumes for patients with colorectal cancer, but outcomes were not stratified for rectal cancer, nor for tumour stage.(6) Therefore, stratification for clinical tumour stage according to hospital volumes is important. Our study showed that patients with locally advanced (cT4) rectal cancer treated in high volume hospitals (≥ 10 resections/year) had a significantly improved 5-year overall survival of 63% compared to 53% in low volume (1 – 4 resections) and 54% in medium volume cT4 hospitals (5 - 9 resections), when corrected for patient and tumour related confounders. This difference disappeared after adjustment for neoadjuvant therapy, but the omission of neoadjuvant treatment in cT4 rectal cancer may also reflect lower quality of care. This survival difference related to hospital volume was not found in cT1-3 rectal cancer. Further centralization of cT4 rectal cancer seems warranted to improve outcome for this difficult group of patients. Several studies in other malignancies, such as oesophagus, pancreas and bladder cancer have reported survival differences according to hospital volume in complex surgical procedures.(7-9) The hypothesis of this survival benefit is that more exposure and experience in the multimodality treatment (staging, induction therapy and surgical expertise) of these relatively rare malignancies results in an improved long-term outcome.(7-9) As described previously in an experienced MDT, cT4 tumours are potentially more accurately assessed and this may lead to superior selection for preoperative therapy and surgical treatment, which eventually results in better outcomes. CRM involvement did not differ significantly for cT4 tumours according to hospital volume, but even in an experienced high volume hospital radical resection of cT4 tumours is challenging. Referral of the most difficult cases to high volume hospitals may offer an explanation for similar CRM involvement in different volume hospitals for cT4 rectal cancer.

In line with association between long-term oncological outcomes, short-term perioperative outcomes may be dependent on hospital volume and tumour stage. In our nationwide analysis, perioperative outcomes of cT1-3 rectal cancer surgery were not superior in high volume hospitals as compared to medium or low volume hospitals, so there appears no benefit for centralization regarding perioperative complications. With regard to cT4 rectal cancer, high volume hospitals performed more extensive surgical treatment with similar perioperative results. Pathologic examination revealed more frequently pT4 in high volume hospitals, while R0 rates were similar between low, medium and high volume hospitals. In a sub-analysis of pT4 patients, the rate of irradical resection was significantly increased in low volume hospitals. Gietelink and colleagues(4) did show that a low hospital volume de-

fined as < 20 rectal cancer resections per year, regardless of tumour stage, was associated with a higher risk of CRM involvement.(4) Unfortunately, they did not perform sub-analysis for different tumour stages, and results are not directly comparable to our study. However, these results indicate that centralization for advanced stage rectal cancer (cT4) may be beneficial regarding perioperative and oncological outcomes, and this beneficial effect may not apply to lower stage rectal cancer (cT1-cT3).

Lymphatic drainage in the lower rectum is partly by inguinal lymph nodes.(10) Currently, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual considers inguinal lymph node metastases (ILNM) from rectal cancer as a systemic disease.(11) ILNM caused by rectal cancer should not necessarily be considered as an incurable disease, especially in case of primary rectal cancer and the absence of other systemic metastases. In our study a median overall survival of 74 months with 1- and 5-year estimated overall survival rates of 83% and 52%, respectively, was reached for patients with solitary ILNM. Prognosis for patients with additional systemic metastases is worse and the benefit of surgery is unclear. Obviously, patients with ILNM have a worse prognosis than patients without ILNM, but even in patients with ILNM and lung or liver metastases curative treatment is sometimes considered.(12) Although, resection of ILNM may not be curative in these patients, it could still be beneficial. Currently, the ORCHESTRA-trial(13) is being performed in patients with multi-organ colorectal cancer metastases, to compare the added value of a combination of chemotherapy and maximal tumour debulking versus chemotherapy alone.(13) The morbidity of surgical treatment in patients with curative or palliative resection of ILNM should not be underestimated, since most of these patients experience lymphedema. On the other hand, most patients who did not undergo resection of ILNM experienced severe groin pain.

For distal rectal cancer, surgical options are often resection by low anterior resection (LAR) or an abdominoperineal resection (APR). Abdominoperineal resection for low rectal cancer still carries a significant risk of perineal wound problems.(14) This is likely related to the contaminated operative field and dead space formation with fluid accumulation, and may be further increased by extended resections and compromised perfusion after preoperative radiotherapy. A recent randomised controlled trial on perineal wound closure after APR reported an incidence of complicated perineal wound healing of 34-37% at 30 days postoperative and complications of primary perineal closure within one year up to 48%. (15) In the long-term patients may experience persisting perineal pain, or develop a chronic perineal sinus or perineal hernia. (16-18) Several techniques are used to improve perineal wound healing, including reconstruction with mesh, using a V-Y fasciocutaneous flap, a vertical rectus abdominis myocutaneous (VRAM) flap, a gluteal or a gracilis flap.(15, 19-21) There are potential disadvantages to these techniques. These include the need for a plastic surgeon, increased theatre time and the potential for donor site and recipient site compli-

cations, while often sacrificing the benefits of laparoscopy (22, 23). In our pilot study the feasibility of a new gluteal turnover flap (GT-flap) for routine perineal reconstruction after APR for (recurrent) rectal cancer was determined. The GT-flap was technically feasible with midline closure in all patients, except for one patient in whom more perineal skin had to be excised for oncological reasons. The flap added only limited additional theatre time, the majority of patients had uncomplicated perineal wound healing at 30 days postoperatively without any flap failure. A recent publication by Chasapi et al.(24) reported on a similar reconstructive procedure in 14 patients undergoing APR for anorectal cancer.(24) The type of flap used differed from the technique described in this thesis. The flap was detached from the gluteal fascia with one remaining perforator for blood supply. These findings support that in selected patients, adjacent gluteal skin and subcutaneous fat can be relatively easily used for perineal closure after APR, with the potential advantages of reduced perineal morbidity by filling the space of the resected anal sphincter complex. The GT-flap seems a technically feasible and safe method for perineal wound closure after APR if no additional perineal skin has to be sacrificed. The procedure is relatively quick and easily applicable, and seems associated with no apparent donor site morbidity or scarring. Currently, the use of the GT-flap is investigated in a randomized controlled trial, the BIOPEX-2 study.(25)

Another procedure intended to improve perineal wound healing is the use of a pedicled omentoplasty (OP).(26) The omental flap serves to obliterate the non-collapsible defect in the smaller pelvis with healthy and well-perfused tissue. This has been associated with reduced abscess formation and improved perineal wound healing.(27) The omentum is supposedly an ideal option to prevent dead space formation after APR. It has a rich blood supply, expresses anti-inflammatory cytokines, often provides for abundant bulk and appears relatively easy to release.(28, 29) Many surgeons therefore perform an OP as part of the APR procedure. In a recent nationwide study with variability in practice of applying OP, no improvement in perineal wound healing was observed, and the OP seemed to increase the risk of perineal herniation.(17) In line with these results, our systematic review and meta-analysis found no evidence to support the use of an OP for reducing pelviperineal morbidity. Omentoplasty did not reduce pelviperineal abscess formation, nor enhanced perineal wound healing or reduced the risk of small bowel obstruction. Similarly, no beneficial effect of OP was found in a planned subgroup analysis of patients that underwent APR with primary perineal closure for non-locally advanced cancer. Furthermore, OP appears to be associated with the long-term likelihood of developing perineal hernia. Two systematic reviews on the value of OP after APR have been published previously, both in contradiction with the current meta-analysis.(30, 31) Reviews of Killeen et al.(30) and Nilsson et al.(31) concern studies with a small sample size and diverse patient population and surgical methods, with only few comparative series. However, in studies included in our systematic review there also was a certain degree of selection bias. The use of OP was sometimes

based on surgeon's preference and surgical procedures where different, leading to larger or smaller defects and in some cases combined with muscle flaps. Therefore, results should be interpreted with care, but the standard use of OP may not be necessary after abdominoperineal resection. Studies directly comparing muscle flaps and OP are scarce. Tissue transfer seems to have the greatest potential, but high quality studies comparing muscle flap closure to other methods of perineal wound closure are warranted. Although VRAM flap closure has been effectively used in selective populations, there remains the issue of donor and recipient site morbidity.(20) A smaller flap without donor site problems such as the earlier described GT-flap may have potential to reduce perineal morbidity in selected patients.

Treatment of locally recurrent rectal cancer remains a challenge. The cornerstone of curative treatment and the long-term outcome of surgical treatment mainly depends on the ability to achieve a clear resection margin.(32, 33) In a large cohort of LRRC patients, treated surgically and non-surgically, we have demonstrated that R0- and R1-resections result in a 5-year overall survival rate of 51% and 34%, respectively. These survival rates are significantly prolonged compared to non-surgical palliative treatment. Although numbers were too small to implicate prognostic significance, R2-resections did not result in a 5-year overall survival benefit compared to non-surgical treatment with a rate of 10% vs. 4%. Moreover, the median survival may be poorer for surgically treated patients with a R2-resection compared to optimal palliatively treated patients. Patients with a high chance of a R2-resection could be offered palliative treatment, without local resection. On the other hand, untreated LRRC can cause severe impairment in quality of life mainly due to severe pain, but also fistula, obstruction or bleeding.(34, 35) There may be a role for palliative surgery in these patients to reduce pain, and relief symptoms of obstruction by stenting or a diverting stoma as reported by others.(36, 37) However, surgery is accompanied by high morbidity and mortality rates, occurring mainly perioperative or in the first 3 months after surgical treatment. This impairment in quality of life persists until one year after surgery. Thereafter, surgically treated patients tends to have a better quality of life.(38) This fact and the lack of a survival benefit of R2-resections suggest that debulking surgery for LRRC resulting in planned R2-resections should be abandoned.

A promising strategy to improve resectability of LRRC is induction chemotherapy. However, improved resectability does not always equal a survival benefit. Other factors, such as tumour behaviour, appear to have impact on overall survival as well. In our study few patients received induction chemotherapy, but a retrospective cohort study by van Zoggel et al.(39) compared outcomes of resection of LRRC in patients with induction chemotherapy followed by chemoradiotherapy to patients who received chemoradiotherapy alone. The R0-resection rate did not differ significantly, but a higher rate of pathologic

complete response was found in patients with combined treatment. Van Zoggel et al.(39) suggested that response rate to induction chemotherapy may be used as guidance to avoid overtreatment in patients with progressive disease under induction chemotherapy. In contrast with this study, our institute showed a lower response to chemotherapy of the local recurrence compared to the response of distant metastases in a small cohort of previously irradiated rectal cancer patients.(40) Because that study focussed on palliative patients this may reflect selection of patients with poor tumour biology. Careful evaluation of these patients individually in a MDT is mandatory to evaluate best possible outcome and treatment, whether to perform surgery or provide best non-surgical treatment.

For both primary rectal cancer and recurrent rectal cancer, achievement of a clear resection margin is described as an important prognostic factor for overall survival and local control. (33, 41-44) This emphasizes the importance of a radical resection margin with surgery. Standard abdominoperineal resection (APR) and low anterior resection (LAR) for rectal cancer often achieve radical resection margins, but if there is invasion of adjacent organs, such as bladder, ureters or male and female reproductive organs, a more radical approach is indicated, such as total pelvic exenteration.(45) Our book chapter outlines the surgical procedure of total pelvic exenteration for locally advanced rectal cancer or recurrent rectal cancer with invasion of the anterior compartment.

Five-year-survival rates after pelvic exenteration for locally advanced rectal cancer range between 22% to 66% and for locally recurrent rectal cancer between 0% to 37%.(33, 43). Achievement of clear resection margins in pelvic exenteration for locally advanced or locally recurrent rectal cancer leads to a significant increase in overall and disease free survival compared to positive resection margins as described by Simillis et al.(44) in a recent systematic review. Perioperative 30-day mortality rates are reported in a range of 0% - 10%.(33, 43, 46) Especially in frail and elderly patients high perioperative mortality rates have been reported; up to 14%.(47) The overall morbidity rate has been described to be anywhere between 32-100%. (33, 43, 48) Patients often have common complications such as (peroperative) bleeding, wound infection, pneumonia and (pelvic) abscesses, and the removal of adjacent organs is associated with other complications than normally encountered in colorectal surgery. Pelvic exenteration may be unavoidable to achieve clear resection margins in advanced rectal cancer, but this type of surgery does have a profound impact on the quality of life.(49, 50) On the other hand, the prognosis of patients with locally advanced or recurrent rectal cancer without treatment is poor and is associated with severe symptoms such as pain, incontinence, fistula and unmanageable wounds. Quyn et al.(51) showed that patients who underwent pelvic exenteration had a sharp decline in quality of life directly after surgery. However, their quality of life improved quickly after surgery and after three months, patients who had undergone pelvic exenteration reported

a higher quality of life than patients who did not have surgery. Thereafter, quality of life in the surgery group continued to improve, whereas quality of life in patients who did not undergo surgery deteriorated.(51) Therefore, patients should not be denied exenterative surgery based on perceived poor quality of life.

As previously described, total pelvic exenteration is an invasive procedure with considerable mortality and morbidity, especially in elderly patients. Although it is generally known that elderly patients often present with more comorbidities and that surgical outcomes are worse than in younger patients, there is controversy whether the cancer specific survival is also worse in elderly patients.(47, 52) The discussion remains whether patients should be withheld from surgery based on age. Our study showed that pelvic exenteration should not be withheld from the elderly patient. There is no significant difference in oncological outcome between younger (< 70 years) and elderly patients (≥ 70 years), but perioperative mortality is higher among elderly patients during the first 30 days after surgery. In line with our results Rutten et al. (47) described a significantly higher mortality rate (14%) in elderly patients (age ≥ 75 years) until six months after surgery for rectal cancer compared to younger patients (4%). In our study, the mortality rate was only significantly different at 30-days after surgery, and the significant difference disappeared after 30 days. Overall survival and disease specific survival did not differ significantly, but this cohort suggests that elderly patients have a better 5-year disease specific survival rate of 67% in elderly compared to 49% in younger patients. When patients are assessed in a MDT whether they are eligible for total pelvic exenteration, the MDT board is more reluctant to select elderly patients unless good clinical outcome is expected considering their comorbidities. This may be a bias. Nevertheless, Careful patient selection is needed to reduce perioperative mortality in elderly patients by better patient selection and/or improving patient's performance status prior to surgery.

If total pelvic exenteration with a complete cystectomy is performed, patients require a urinary diversion. Historically there are several urinary diversion techniques, but in current practice, the most common urinary diversion is an ileal conduit (i.e. Bricker). The colon conduit technique was described by several authors, but is less well known.(53, 54) Both surgical procedures slightly differ due to the use of different bowel segments. An ileal conduit requires an ileo-ileal anastomosis, whereas in colon conduits an extra anastomosis is usually not required because the terminal segment of the descending colon can be used in patients receiving an end colostomy anyway. In our pooled retrospective cohort of 259 patients undergoing total pelvic exenteration with urinary diversion for LARC and LRRC few differences in surgical and urological complications between a colon conduit and an ileal conduit were found. However, the formation of a colon conduit avoids the risk of ileo-ileal anastomotic leakage, which was 4% in this cohort. In addition, an ileal conduit

appears to be associated with a higher postoperative ileus rate. Prolonged duration of ileus is a known complication after formation of an ileal conduit and may lead to a prolonged hospitalization.(55, 56) Several studies reported on outcomes after multivisceral surgery with cystectomy and the formation of a urinary diversion for all types of pelvic cancer. A recent study by Bolmstrand and colleagues in colorectal and anal cancer patients, who underwent partial or complete cystectomy, reported a rate of 35% major complications (Clavien-Dindo≥3), comparable with the 39% in our cohort. The rate of overall intestinal anastomotic leakage was 9% in their series compared to 7% in our cohort.(57) Teixeira et al.(58) compared several outcomes in 74 patients who received an ileal or a colon conduit for all types of pelvic malignancies. Their study did not find significant differences for complications assessed separately, but a significantly higher incidence of complications in patients with an ileal conduit compared to a colon conduit was found if all complications were combined.(58) In line with the results found in this thesis, the colon conduit may be a feasible alternative for an ileal conduit in patients receiving an end colostomy.

FUTURE PERSPECTIVES

The multidisciplinary treatment of (recurrent) rectal cancer has evolved over the past decades and is still evolving in a high pace. Innovation in diagnostics and treatment may have a significant impact on current practice. The current standard diagnostics for (recurrent) rectal cancer staging are endoscopy, MRI-scan of the pelvic area and a CT-scan of the thorax and abdomen to search for signs of disseminated disease. This is also the standard for restaging after neoadjuvant therapy, to evaluate tumour response and in follow up to detect local or distant recurrence.

A promising new technique as a predictive or prognostic value to measure tumour response or detect tumour recurrence is the use of liquid biopsies.(59) Circulating tumour DNA (ctDNA) is a promising biomarker considered to be an important diagnostic tool for the detection of minimal residual disease with liquid biopsies.(60-62) CtDNA is part of the total amount of small fragments of DNA in the blood, called cell-free DNA. These fragments are shed into the bloodstream from dying cells during cellular turnover or other forms of cell death.(60-62) Several studies demonstrated that mutations found in ctDNA correspond to mutations found in tumour tissue. Therefore, ctDNA can potentially be used for early detection of minimal residual disease or response to local or systemic therapy. The detection limit of ctDNA analysis approaches to detect tumour DNA in the total amount of cell-free DNA is below 0.05%.(60, 61) This very sensitive technique still has a specificity of >99.99%. In colorectal cancer, the majority of patients have detectable ctDNA in their blood when the primary tumour is in situ (±78%) and in the metastatic setting (100%).(60,

62) CtDNA has a short half-life of approximately 2 hours, detection several days after surgical resection of the primary tumour is indicative for presence of minimal residual disease. Therefore, ctDNA analysis seems an accurate and reliable test to use in clinical practice and can be particularly useful in diagnosis, treatment and monitoring of rectal cancer patients.

As minimal residual disease is undetectable by imaging techniques, but may still be present after surgery in rectal cancer patients, they might have a high risk of recurrence. Tie and colleagues(63) studied ctDNA in colorectal cancer. They found a recurrence rate of 79% in stage II colon cancer patients with detectable ctDNA compared to 10% recurrence rate in patients without detectable ctDNA after surgery.(63) In locally advanced rectal cancer patients, 58% of the patients with detectable ctDNA had a recurrence within 2 years, in contrast to 8.6% in negative ctDNA patients.(64) These results show that postoperative ctDNA analysis stratifies patients with LARC into very high and low risk groups for recurrence.

In high-risk colorectal cancer patients, the positive effect of adjuvant chemotherapy is well established. In rectal cancer patients, the role of adjuvant chemotherapy is still under debate and it is not the standard of care in the Netherlands.(65-68) Several trials and reviews present contradicting results and could not demonstrate a beneficial role for adjuvant chemotherapy in rectal cancer. The EORTC-2291-(69), I-CTR-RT-(70), PROCTOR-SCRIPT-(67) and CHRONICLE-trial(71), showed no benefit of adjuvant chemotherapy on overall survival and disease free survival. The QUASAR-trial(72) and a Cochrane review(65) did demonstrated benefit of adjuvant chemotherapy on overall survival and disease free survival. A more recent meta-analysis by Bujko et al.(66) and Breugom et al.(73) demonstrated no improvement with adjuvant chemotherapy. None of the trials and meta-analyses could identify a specific group at high risk for recurrence who may benefit from adjuvant chemotherapy, which is the fact for high-risk colon cancer.(74, 75) In the study of Tie et al.(64) some patients received adjuvant chemotherapy and post-operative ctDNA detection was predictive of recurrence irrespective of administration of adjuvant chemotherapy. The negative impact of ctDNA seems more pronounced in patients without adjuvant chemotherapy. CtDNA may be a promising biomarker to predict tumour response and may identify patients at high risk for recurrence. Possibly the use of ctDNA can provide guidance in clinical decision making to treat rectal cancer patients with a high risk on recurrence with adjuvant chemotherapy. Besides identifying patients at high risk for recurrence, there also may be a role for ctDNA in measurement of tumour response after neoadjuvant therapy. These patients may be withheld from radical surgery in case of a ctDNA response and treated by local excision or even watchful waiting.(76) Implementing ctDNA as a predictive and prognostic marker in clinical practice is promising and may lead to better patient

selection and treatment, but the use of this new biomarker in clinical practice needs to be demonstrated.

Implementation of a more 'tailor made' treatment for rectal cancer and improved neo-adjuvant therapy have led to interesting research regarding organ preserving surgery and a 'watch and wait (or watchful waiting)' strategy. The role of chemoradiotherapy was previously limited to facilitating tumour shrinkage to perform radical surgery in advanced rectal cancer. In some patients, a pathologic complete response was observed after surgery. Even in lower stage rectal cancer, there may be a potential beneficial effect of chemoradiotherapy to achieve a complete response and this may lead to less invasive and rectal sparing or surgery can even be omitted in selected patients. Rectal cancer patients with a pathologic complete response after neoadjuvant chemoradiotherapy have a significantly better outcome.(77, 78) To assess whether a patient has a complete pathological response with 100% certainty a surgical resection is required. Already in 2004, Habr-Gama and colleagues(79) were one of the firsts to omit surgery in patients with stage 0 distal rectal cancer and compared results of this strategy with operative treatment. They showed that both treatment strategies had good long-term outcomes, and the omission of surgery prevents patients from unnecessary morbidity and mortality.(79) Radical surgery by total mesorectal excision is associated with a perioperative mortality rate of 2-5%, anastomotic leakage in 3-11%, permanent colostomy in 10-30% and long-term bowel, bladder and sexual dysfunction.(80). Rectal cancer patients may be spared from this extensive radical surgery by organ sparing therapy (i.e. transanal endoscopic microsurgery) or even no surgery, thus watch and wait. A recent systematic review by Dossa et al.(81) with multiple series following the pioneering research of Habr-Gama and colleagues showed promising results with this new strategy. They found no significant difference in overall survival between complete responders after a watch and wait strategy compared to surgical treatment for different stages of rectal cancer.(81) An international pooled cohort with individual patient data also described similar results and recurrence mostly occurred within 2 years, which emphasizes the need for close surveillance, but the vast majority of patients could still undergo salvage surgery.(82) In case of a partial response, patients can still possibly undergo organ sparing transanal endoscopic microsurgery (TEM), as shown in the CARTS study.(83) Appelt et al.(84) performed a prospective observational trial to assess the feasibility of high dose chemoradiotherapy and watchful waiting for rectal cancer and concluded that this might be a safe alternative to abdominoperineal TME-surgery. On the other hand, some patients with lower stage rectal cancer will receive chemoradiotherapy with possible morbidity not leading to a complete response. The current available literature seems promising for a watch and wait strategy or organ preserving surgery, but randomized trials need to be performed for further research as the results mainly depends on retrospective outcomes. (85, 86) Currently, the STAR-TREC study(87) is open for enrolment, which is a random-

ized comparison of standard radical surgery versus organ saving treatment using either short course radiotherapy or chemoradiotherapy with selective use of TEM based upon a radiotherapy response assessment. (87) This study may provide evidence in the future for this new treatment strategy.

The Prognosis of locally recurrent rectal cancer is still poor with a 5-year overall survival of 30-40% in optimally surgically treated patients.(88, 89) In the vast majority of patients with LRRC who did not and could not undergo surgery prognosis is worse with a 5-year survival of 4%, as described in chapter 8 of this thesis. Achievement of a radical resection margin is an important prognostic factor.(32, 33) This is challenging, because patients have often received previous radiotherapy and surgery in the TME-plane, and recurrent rectal cancer may invade other structures within the pelvic area. Tumour shrinkage preoperatively may achieve a higher rate of radical resections. Reirradiation with Capecitabine as radiosensitizer in LRRC is proven to be safe and effective.(90) Despite this treatment radical resections are only achieved in 60% of patients with LRRC.(89) Induction chemotherapy is widely used in several types of (primary) cancer or metastatic disease such as colorectal liver metastases, to induce tumour shrinkage and improve resectability. In LRRC, the role of induction chemotherapy is still limited. Few retrospective studies have been published on this topic. Kusters et al.(91) described a small cohort of patients with lateral node recurrences treated with induction chemotherapy follow by chemoradiotherapy and resection. This regimen resulted in an improved R0-resection rate of 85%.(91) A study by van Zoggel et al.(39) retrospectively compared a cohort of patients receiving induction chemotherapy with chemoradiotherapy versus matched patients who received chemoradiotherapy alone. They found a high complete pathological response rate of 17% compared to 4% in chemoradiotherapy alone group. Surprisingly, radical resection rates were similar.(39) Currently, a new study by Voogt and Burger et al. is being introduced to compare induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer. A recent retrospective study by Voogt et al.(92) compared the effect and potential benefit of induction chemotherapy for LRRC in patients from 2010 and 2018. They found a 3-year overall survival of 92% in patients with a complete pathological response after induction chemotherapy. They also found a similar pathological complete response rate compared to van Zoggel et al.(39) A radical resection margin was achieved in 63% of all patients treated with induction chemotherapy. In unpublished data, they observed a trend in higher R0-resection rates with increasing administration of induction chemotherapy overtime. These (preliminary) results seem promising to achieve a higher rate of pathologic complete response and maybe a higher rate of radical resections. Currently there is no hard evidence for the use of induction chemotherapy, but this new randomized controlled trial might give the answer and

alter standard treatment for LRRC in the future. This PelvEx-2 study has recently received funding and is expected to start accrual in the fall of 2020.

In summary, the goal of this thesis was to focus on several aspects of treatment and further improve treatment of primary rectal cancer, locally advanced rectal cancer and locally recurrent rectal cancer. For cT4 rectal cancer, centralization in high volume hospitals seems to improve outcome. In patients with ILNM from primary rectal cancer cure by surgical resection is still an option. The proposed gluteal turnover flap seem promising to reduce perineal morbidity after abdominoperineal resection but needs further clinical research and the standard use of an omentoplasty after APR may not be necessary. In patients with LRRC, achievement of a radical resection margin is important, patients with a high chance on R2-resection should maybe be withheld from surgery and receive non–surgical palliative treatment. Patients with LARC and LRRC undergoing total pelvic exenteration experience considerable morbidity but quality of life increases after surgery, and elderly should not be withheld from total pelvic exenteration on age only. In patients undergoing total pelvic exenteration, a colon conduit avoids the risk of ileo-ileal leakage and may be a feasible alternative for an ileal conduit in patients receiving an end colostomy. Future and current studies regarding organ preserving therapy and watchful waiting are promising as less invasive treatment strategies. In addition, the use of induction chemotherapy in LRRC may be important to achieve a higher rate pathologic complete response and R0-resections. The use of liquid biopsy and ctDNA as a predictive or prognostic marker may be of great value in the near future, but further research is warranted.

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