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Summary

Colorectal cancer is the third most common malignancy in the Western world and rectal cancer accounts for approximately one third of the colorectal cancer patients. In 2018, almost 4,000 patients were newly diagnosed with rectal cancer in the Netherlands and this number is stable over the last four years. Despite these stabilizing numbers, the burden of rectal cancer is high and treatment remains a challenge. At the time of diagnosis of primary rectal cancer, in approximately 10% of the rectal cancer patients, the tumour is close to the mesorectal fascia and may invade surrounding organs such as the bladder or male and female reproductive organs. These patients have locally advanced rectal cancer (LARC). After treatment for primary rectal cancer, the tumour may recur locally in the rectum or in surrounding structures within the pelvic area in approximately 5-10% of the patients. These patients have locally recurrent rectal cancer (LRRC). Over the past decades treatment of rectal cancer has evolved into a "tailor made" multidisciplinary approach including neoadjuvant chemo- and radiotherapy, total mesorectal excision surgery, sometimes with surgery beyond the TME-plane, and intraoperative radiation therapy (IORT). The aim of this thesis is to further improve the multimodality treatment for rectal cancer, locally advanced rectal cancer and locally recurrent rectal cancer.

Chapter 1 describes a general introduction and outline of this thesis.

In **chapter 2**, the impact of hospital volume on short- and long-term outcomes of rectal cancer surgery was assessed in a population-based study of a Dutch cohort in 2011 provided by the Dutch Snapshot Research Group. According to the Dutch National Guidelines, hospitals require a minimum number of rectal cancer resections a year. In this study no impact of hospital volume on outcome after rectal cancer surgery could be demonstrated between hospitals with low volume (<20 resections/year), medium volume (20-50 resections/year) or high volume (>50 resections/year) hospitals.

In **chapter 3**, we analysed the long-term results of cT1-3 and cT4 rectal cancer according to hospital volume in the Netherlands between 2005 and 2013 from data of the National Cancer Registry, stratified by tumour stage. Hospital volume was not associated with overall survival after surgery for cT1-3 rectal cancer. The treatment of cT4 rectal cancer in high volume cT4 hospitals was associated with an improved survival compared to low volume cT4 hospitals when corrected for patient and tumour related confounders. This association was no longer statistically significant after correction for neoadjuvant treatment. Further centralization of cT4 rectal cancer may further improve outcome for this difficult group of patients.

Chapter 4 evaluates the impact of hospital volume on surgical resection and perioperative outcomes of cT1-3 rectal cancer and cT4 rectal cancer using data from a national registry.

Patients with early stage rectal cancer (cT1-cT3) may be treated with standard TME-surgery. For patients with advanced rectal cancer (cT4) a more multidisciplinary approach with pre-operative (chemo-) radiotherapy and extensive resections beyond the standard TME-plane are mandatory. This study demonstrates that 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. 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).

In **chapter 5**, a cohort of patients with inguinal lymph node metastasis (ILNM) from rectal cancer is presented. Currently, the American Joint Committee on Cancer (AJCC) Cancer Staging Manual considers ILNM from rectal cancer as a systemic disease. Obviously, patients with ILNM have a worse prognosis compared to patients without ILNM, but surgery may not be withheld in some patients. Our study demonstrated a 5-year survival rate of 52% after surgical treatment of patients with primary rectal cancer and isolated ILNM. Prognosis for patients with additional systemic metastases is worse and the benefit of surgery is unclear. Inguinal lymph node metastases should not be considered as an incurable disease, especially in patients with primary rectal cancer and solitary ILNM.

In **chapter 6**, results of the BIOPEX II pilot study are presented. Abdominoperineal resection (APR) carries a high risk of perineal wound morbidity. In this study, the feasibility of a novel gluteal turnover flap (GT-flap) was assessed in a small cohort. 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. The GT-flap seems a technically feasible and safe method for perineal wound closure. 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.

In **chapter 7** a systematic review and meta-analysis of the effects of omentoplasty on pelviperineal morbidity following abdominoperineal resection (APR) in mostly rectal patients is presented. Our study 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 un-

derwent 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. Studies included in our systematic review had a certain degree of selection bias, therefore, results should be interpreted with care, but the standard use of OP may not be necessary after abdominoperineal resection.

In **chapter 8**, the long-term outcomes of a large cohort of patients with LRRC who underwent curative surgical treatment or non-surgical treatment are evaluated. In LRRC patients treated surgically and non-surgically R0- and R1-resections resulted 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. This study suggest that debulking surgery for LRRC resulting in planned R2-resections should be abandoned.

In **chapter 9**, a book chapter is presented which outlines the surgical procedure and outcomes of pelvic exenteration for locally advanced rectal cancer or recurrent rectal cancer with invasion of the anterior compartment.

In **chapter 10**, a study is presented aiming to compare mortality, morbidity, surgical and oncological outcomes between elderly and younger patients who underwent total pelvic exenteration for LARC or LRRC. 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. Careful patient selection is needed to reduce perioperative mortality in elderly patients by better patient selection and/or improving patients' performance status prior to surgery.

In **Chapter 11**, short- and long-term complications of an ileal and colon conduit after surgery for LARC or LRRC are presented in cohort of two large tertiary referral hospitals. Our study demonstrated similar urological complications after the formation of an ileal or colon conduit. However, the formation of a colon conduit rules out ileo-ileal anastomotic leakage, which was 4% in this cohort. In addition, an ileus was more frequently seen after the formation of an ileal conduit in this study. Therefore, the colon conduit may be a feasible alternative for an ileal conduit in patients receiving an end colostomy.