General introduction and outline of this thesis

INTRODUCTION

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.(1) 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.(2) Despite these stabilizing numbers, the burden of rectal cancer is high and treatment remains a challenge. In most rectal cancer cases, the local tumour growth is limited within the layers of the rectal wall and has not spread to local lymph nodes. 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.(3, 4) 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 structurers within the pelvic area in approximately 5-10% of the patients. These patients have locally recurrent rectal cancer (LRRC).(3-5)

Surgery remains the cornerstone of treatment in (recurrent) rectal cancer patients. Many studies over the last decades described a clear resection margin as the single most important prognostic factor for overall survival and local control in rectal cancer surgery.(3, 6-9) This emphasizes the importance of a radical resection margin with surgery. Achievement of a clear resection margin in lower stages of rectal cancer by standard total mesorectal excision surgery may be more straightforward than in advanced stages of rectal cancer. To achieve a clear resection margin in patients with LARC and LRRC a multimodality treatment with a more complex surgical dissection is required. These procedures, such as extralevatory abdominoperineal resections and partial or total pelvic exenteration, require a surgical dissection beyond the standard total mesorectal excision plane.(10)

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, and intraoperative radiation therapy (IORT) which improved overall survival and local control after treatment.(3, 11-15) Optimal treatment of rectal cancer is dependent on local tumour stage and the presence of locoregional or distant metastases. Neoadjuvant chemo- and radiotherapy leads to tumour shrinkage, thereby facilitating complete resections and a decrease in local recurrence rate.(12, 14-16) In more advanced stages of rectal cancer chemo- and radiotherapy is an essential part of the treatment.(3) Several years ago the effect of neoadjuvant therapy in early stages of rectal cancer was limited, but nowadays may play an important role in case of organ preserving treatment, as described by Habr-Gama and colleagues and as currently investigated in the multicentre

STAR-TREC study.(17-19) These new treatment strategies will not be discussed in this thesis, but will be outlined in the future perspectives.

The introduction of standardized total mesorectal excision (TME) combined with neoadjuvant therapies has led to improved oncological results after surgery for rectal cancer. Adjustment of radiotherapy regimens and time to surgery, as presented in the Stockholm trial, also reduced perioperative complications and improved outcomes.(3, 14, 15, 20) During surgery, patients can be treated with IORT to reduce local recurrence rates or even improve overall survival, when there is a known pre-operative or possible per-operative risk of a microscopically involved resection margin.(13, 21, 22).

The current multimodality treatment with surgery beyond the standard TME-plane for LARC and LRRC brings new challenges in terms of morbidity and mortality, especially with an incidence of rectal cancer increasing with age.(23) The improved oncological outcomes over the past decades are encouraging, but this multimodality treatment of rectal cancer and especially LARC and LRRC may have a major impact on quality of life.(24, 25) Despite all improvements, the treatment of rectal cancer remains a challenge.

GENERAL AIM OF THIS THESIS

The aim of this thesis is to further improve the multimodality treatment for rectal cancer, locally advanced rectal cancer and locally recurrent rectal cancer. Currently investigated modern treatment strategies such as organ preserving treatment and 'watchful waiting' will not be discussed in this thesis.

OUTLINE OF THIS THESIS

In Part I of this thesis the first chapters focus on the association between hospital volumes and outcomes in rectal cancer surgery on a population-based level. The impact of hospital volume on surgical outcomes after rectal cancer surgery are still under debate. The Dutch Foundation for Oncological Collaboration defined standards for cancer treatment and included a minimum volume of 20 rectal cancer resections annually per hospital in their first report in 2012, irrespective of the tumour stage. Until then, rectal cancer surgery was performed in every Dutch hospital with a few specialized centres treating locally advanced and recurrent rectal cancer, to which referral was recommended in the Dutch colorectal cancer guideline.(26) These guidelines recommend centralization of care for patients with advanced stages of rectal cancer in specialized colorectal cancer hospitals. A recent

population-based study revealed no differences in 5-year survival rates between hospital volumes for patients with colorectal cancer; however, outcomes were not stratified for rectal cancer, nor for tumour stage.(27)

In **chapter 2** of this thesis we aim to investigate the influence of hospital volume on long-term oncological outcome after rectal cancer surgery in the Netherlands in 2011, based on population-based data provided by the Dutch Snapshot Research Group.(28) The purpose of this study was to assess the impact of hospital volume on short- and long-term outcomes of rectal cancer surgery in the Netherlands in 2011 stratified for hospital volume.

Clinically staged T1-3 rectal cancer (cT1-3) is generally treated by TME-surgery with or without neoadjuvant therapy and sometimes requires beyond TME-surgery, whereas cT4 rectal cancer often requires both. Due to the more complex treatment of the advanced stages of rectal cancer, a personalized 'tailor made' multimodality treatment is needed. Moreover, cT4 rectal cancer is relatively rare and multivisceral surgery is technically demanding with higher amounts of blood loss, operation time and increased morbidity and mortality.(10) We hypothesize that hospital volumes may be more important in cT4 rectal cancer than in patients with cT1-3 rectal cancer. In **chapter 3,** we analyse 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.

Quality of rectal cancer surgery with respect to short-term outcomes is being monitored by the Dutch Surgical Colorectal Audit (DSCA) since 2009. Although not uniformly reported, hospital volume has been associated with operative mortality and morbidity.(29) In **chapter 4**, the purpose of the study was to investigate the impact of hospital volume on perioperative outcomes of rectal cancer stratified for cT1-3 and cT4 rectal cancer from population-based data provided by the DSCA.(30)

The following chapter focusses on treatment of locoregional lymph node metastases of rectal cancer. Rectal cancer is associated with locoregional pelvic lymph node metastases in and outside the mesorectum. In some cases inguinal lymph node metastases (ILNM) may occur, particularly in lower rectal cancer, due to the lymphatic drainage by inguinal lymph nodes.(31) The American Joint Committee on Cancer (AJCC) Cancer Staging Manual considers ILNM from rectal cancer as a systemic disease.(32) Obviously, patients with ILNM have a worse prognosis than patients without ILNM, but even patients with lung or liver metastases are not always restrained from curative treatment.(33) **Chapter 5** describes the outcome for patients treated with both curative inguinal lymph node dissection and palliative treatment for ILNM from rectal cancer.

The last two chapters of part I of this thesis concentrates on perineal wound morbidity after abdominoperineal resection for rectal cancer. The pelvic wound bed after abdominoperineal resection (APR) carries a high risk of morbidity.(34, 35) 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 post-radiotherapy. A randomized controlled trial showed that perineal complications within one year after APR with primary perineal closure may occur in up to 48%.(36) Patients frequently develop perineal wound dehiscence and infection, and often endure delayed healing. Secondary wound healing can take several months and may eventually result in perineal pain, sitting problems, a chronic perineal sinus and a perineal hernia.(37-39) There is no consensus on the optimal method for perineal wound closure after APR. Several techniques are used to improve perineal wound healing, including reconstruction using a V-Y fasciocutaneous flap, a vertical rectus abdominis myocutaneous (VRAM) flap, a gluteal or a gracilis flap, use of biological mesh and tissue flaps, such as a pedicled omentoplasty to fill the dead space. (36, 40-42) In **Chapter 6,** a feasibility study of a novel gluteal turnover flap without additional scarring or donor site morbidity is described.

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.(43) However, in a recent nationwide study of omentoplasty no improvement in perineal wound healing was observed and an omentoplasty seemed to increase the risk of perineal herniation.(38) 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.

Part II of this thesis focusses on several aspects of the multimodality treatment for both LARC and LRRC. LRRC has a major impact on quality of life, mostly by the occurrence of severe pain, bleeding and fistulation.(24) Since most patients presenting with LRRC present with extensive metastatic disease or an unresectable local recurrence, only a minority are suitable candidates for surgery.(44-47) These patients can be offered non-surgical treatment, consisting of external beam radiotherapy, chemotherapy, a combination of both or comfort care.(48) The only potential curative option for LRRC is surgical resection and the long-term outcome of surgical treatment mainly depends on the ability to achieve a clear resection margin.(6, 8, 47, 49) Management of LRRC remains a challenge for both curative surgical treatment and non-surgical treatment. 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.

If rectal cancer invades adjacent organs, such as bladder, ureters or male and female reproductive organs a more radical approach such as pelvic exenteration is required. Pelvic exenteration for advanced pelvic malignancies was first described in 1948 by Brunschwig et al.(50) as a palliative treatment of gynaecological cancer. Over time pelvic exenteration developed as a surgical technique for curative treatment of rectal cancer. **Chapter 9** provides an overview of pelvic exenteration for rectal cancer invading the male and female urogenitary tract.

Total pelvic exenteration is radical surgery with considerable morbidity and mortality.(6, 51, 52) Although it is generally known that elderly patients often present with more co-morbidities and surgical outcomes are worse than in younger patients, there is controversy whether the cancer specific survival is also worse in elderly patients.(53-55) The question remains, with an increasing elderly population with rectal cancer, whether it is justified to withhold extensive surgery from the elderly patient because of high mortality and morbidity. **Chapter 10** aims to compare mortality, morbidity, surgical and oncological outcomes between elderly and younger patients who underwent total pelvic exenteration for LARC or LRRC. When total pelvic exenteration including cystectomy is performed patients require a urinary deviation.(56, 57) Historically there are several urinary deviations, but in the current practice, the most common urinary deviation after complete bladder resection is an ileal conduit (i.e. Bricker) and more recently followed by a colon conduit.(58-60) Both procedures are associated with general surgical and urological complications, but also conduit specific complications may occur, such as metabolic changes or intra-abdominal complications of the loop diversion.(58, 61-63) 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.

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