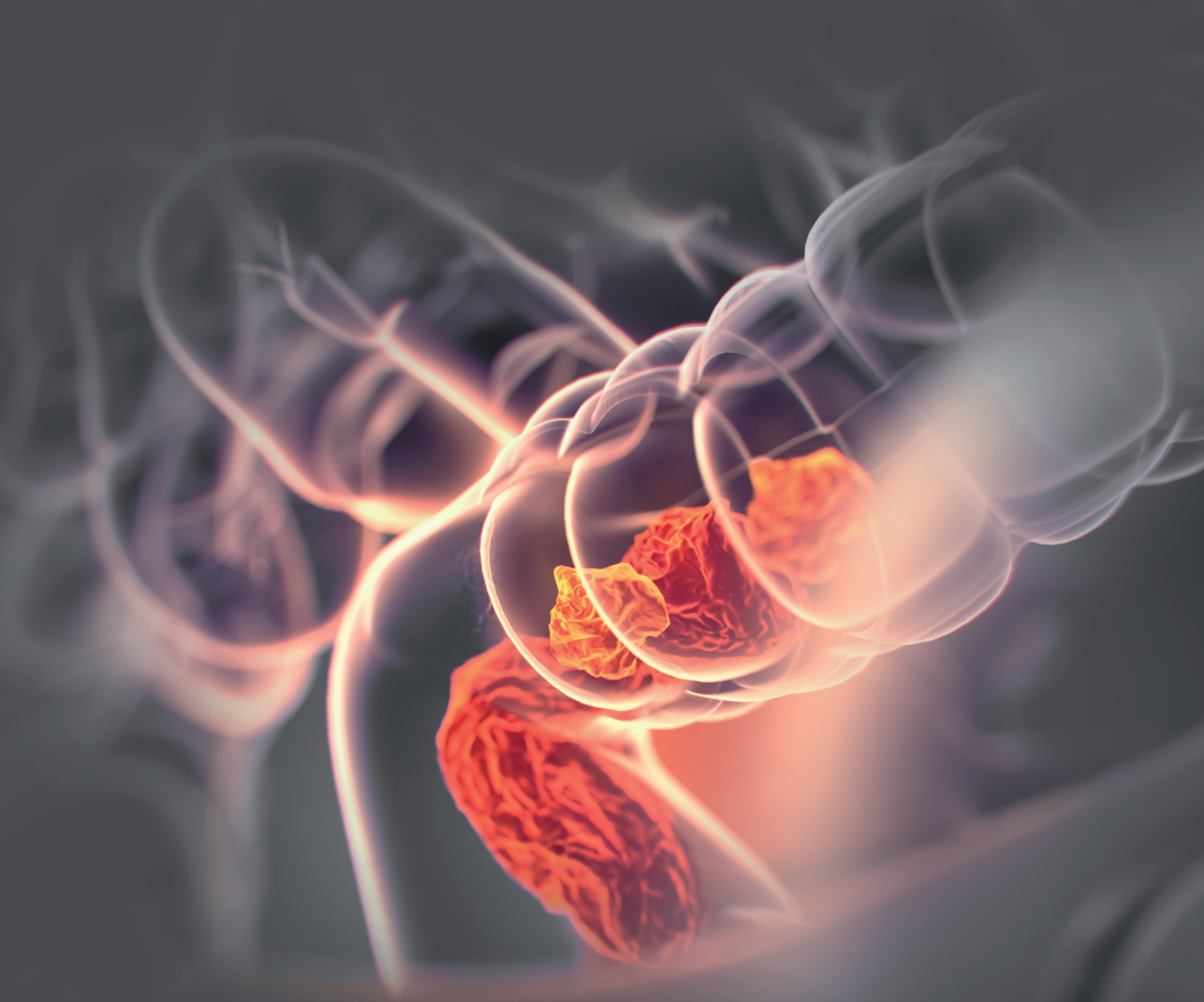

The Multimodality Treatment of Rectal Cancer

Jan A.W. Hagemans

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J.A.W. Hagemans

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Chapter 1

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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PART I

PRIMARY RECTAL CANCER

Chapter 2

The influence of hospital volume on long-term oncological outcome after rectal cancer surgery

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ABSTRACT

Introduction

The association between hospital volume and outcome in rectal cancer surgery is still subject of debate. The purpose of this study was to assess the impact of hospital volume on rectal cancer surgery in the Netherlands in 2011.

Methods

In this collaborative research with a cross-sectional study design, patients who underwent rectal cancer resection in 71 Dutch hospitals in 2011 were included. Annual hospital volume was stratified as low (< 20), medium (20-50) and high (≥ 50).

Results

Of 2095 patients, 258 patients (12.3%) were treated in 23 low-volume hospitals, 1329 (63.4%) in 40 medium volume hospitals, and 508 (24.2%) in 8 high-volume hospitals. Median length of follow-up was 41 months. Clinical tumour stage, neoadjuvant therapy, extended resections, circumferential resection margin (CRM) positivity, and 30- day or in-hospital mortality did not differ significantly between volume groups. Significantly, more laparoscopic procedures were performed in low-volume hospitals, and more diverting stomas in high-volume hospitals. Three year disease-free survival for low-, medium-, and high volume hospitals was 75.0%, 74.8%, and 76.8% (p = 0.682). Corresponding 3-year overall survival rates were 75.9%, 79.1%, and 80.3% (p = 0.344). In multivariate analysis, hospital volume was not associated with long-term risk of mortality.

Conclusions

No significant impact of hospital volume on rectal cancer surgery outcome could be observed among 71 Dutch hospitals after implementation of a national audit, with the majority of patients being treated at medium-volume hospitals.

INTRODUCTION

The association between hospital volume and outcome in rectal cancer surgery is still subject of debate, because current literature is difficult to interpret given the variety in volume definitions and outcome indicators. Furthermore, studies on this topic come from different health care systems, and hospitals may substantially differ in case mix and specialization level regardless volume. Although not uniformly reported, hospital volume has been associated with operative mortality.(1) More sphincter-saving surgery and lower permanent colostomy rates are more consistently reported outcomes for high-volume hospitals.(2,3) The association with long-term risk of recurrence or survival has almost never been observed.(4,5)

The Dutch Foundation for Oncological Collaboration (www.soncos.nl) defines standards for cancer treatment and included a minimum volume of 20 rectal cancer resections annually per hospital in their first report in 2012. 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. These recommend centralization of care for patients with advanced stages of rectal cancer in specialized colorectal cancer hospitals. Quality of rectal cancer surgery with respect to short-term outcome is being monitored by the Dutch Surgical Colorectal Audit (DSCA) since 2009, and participation by each hospital is mandatory by the National Inspectorate of Health Care.

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.

METHODS

Study design and data collection

All 94 hospitals that registered in the Dutch Surgical Colorectal Audit (DSCA) in 2011 were asked to participate in a resident-led collaborative research project in 2015. A total of 71 hospitals agreed to participate. Registered rectal cancer resections that were performed in these hospitals in 2011 were identified from the DSCA.(6) In the second half of 2015, additional procedural data and long-term surgical and oncological outcomes were retrospectively added to the perioperative DSCA data using a specifically developed web-based and privacy controlled data-entry tool for this purpose. Data-entry in this cross-sectional study was performed by one or two surgical residents supervised by a consultant surgeon. Medical ethics committee of the Academic Medical Centre, Amsterdam, the Netherlands

decided that approval was not required for this study as all data were anonymized and no there was no additional burden for the patient. Details of this Snapshot study cohort have been published previously.(7)

Hospital volume

Annual hospital volume was defined as the total number of rectal cancer resections performed in 2011. This volume was classified as low (< 20), medium (20-50) or high (> 50). Patient characteristics, stage distribution, type of treatment, postoperative outcome, and disease-free and overall survival were calculated for the three categories of annual hospital volume.

Data analysis

Missing data were not defaulted to negative and denominators reflect only actual reported cases. Nominal variables were compared between the three groups using the Chi-square test, and continuous variables using the Student's ***t*** test. Kaplan Meier survival analysis with log rank test was used to compare disease-free and overall survival rates at 3 years between volume groups. Multivariable Cox regression analysis was performed to determine independent predictors of long-term mortality. Hospital volume was included in this model besides all variables that were significant in univariable analysis ($p < 0.05$). SPSS 22 was utilized for the analyses, and a p value < 0.05 was considered significant. The STROBE guidelines were used to ensure the reporting of this observational study.(8)

RESULTS

Baseline characteristics

A total of 2095 patients with rectal cancer were included, of which 258 patients (12.3%) were treated in 23 low-volume hospitals, 1329 (63.4%) in 40 medium-volume hospitals, and 508 (24.2%) in 8 high-volume hospitals. Baseline characteristics are displayed in Table 1, stratified for annual hospital volume. Demographics, medical history, clinical tumour stage, distance of the tumour to the anorectal junction, type of surgical procedure, and extended resection for cT4 did not differ significantly between different volume groups. Overall, approximately 90% of patients underwent neoadjuvant therapy, while there were small in differences in neoadjuvant regimes between different volume groups (Table 1). High volume hospitals diagnosed significantly more often a clinical node-positive status compared to low and medium volume hospitals ($p < 0.001$), mainly as cN2-stage. A laparoscopic approach was more frequently used in low-volume hospitals compared to medium and high volume (59.8% vs. 44.8% and 45.7, $p < 0.001$). In patients undergoing low

anterior resection, the anastomosis was more frequently diverted in high-volume hospitals compared to low and medium-volume hospitals (80.3% vs. 65.5% and 68.5%, p = 0.001).

Table 1. Baseline and operative characteristics of rectal cancer patients stratified for hospital volume

	Low volume (<20) N= 258 (12.3%)	Medium volume (20-50) N= 1329 (63.4%)	High volume (>50) N=508 (24.2%)	P value
Age (year)	66.0 ±12.3	66.9 ±11.1	66.7 ±11.2	0.448
Male gender	153 (59.3%)	855 (64.4%)	309 (60.8%)	0.164
Medical history				
Cardiac	58 (31.4%)	295 (33.4%)	107 (30.2%)	0.380
Vascular	91 (49.5%)	441 (49.9%)	174 (49.2%)	0.862
Pulmonal	36 (19.5%)	147 (16.6%)	59 (16.7%)	0.790
Diabetes	37 (20.0%)	170 (19.2%)	66 (18.6%)	0.960
Neurologic	24 (13.0%)	153 (17.3%)	60 (16.9%)	0.622
ASA class 3/4	39 (15.7%)	223 (17.2%)	81 (16.3%)	0.796
Multidisciplinary tumour board meeting	241 (98.4%)	1243 (95.8%)	481 (96.6%)	0.130
Neoadjuvant therapy	232 (89.9%)	1187 (89.3%)	457 (90.0%)	0.901
Short-course (5x5 Gy)	116 (45.0%)	620 (46.7%)	219 (43.1%)	
Long-course	8 (3.1%)	53 (4.0%)	8 (1.6%)	
Chemoradiotherapy	91 (35.3%)	465 (35.0%)	155 (30.5%)	
Different regimen	17 (6.6%)	49 (3.7%)	75 (14.8%)	<0.001
cT stage				
cT1	6 (2.8%)	56 (4.8%)	18 (4.2%)	
cT2	55 (25.9%)	289 (25.0%)	129 (30.0%)	
cT3	128 (60.4%)	709 (61.2%)	230 (53.5%)	
cT4	23 (10.8%)	104 (9.0%)	53 (12.3%)	0.070
cN stage				
cN0	89 (45.4%)	517 (45.9%)	146 (35.3%)	
cN1	76 (38.8%)	440 (39.1%)	167 (40.3%)	
cN2	31 (15.8%)	169 (15.0%)	101 (24.4%)	<0.001
cM1	19 (8.3%)	90 (7.1%)	30 (6.8%)	0.777
Distance to anal verge (cm)	5.6 ±3.6	5.9 ±3.9	6.2 ±4.0	0.152
Operative characteristics				
LAR	113 (43.8%)	635 (47.8%)	250 (49.2%)	
APR	79 (30.6%)	401 (30.2%)	159 (31.3%)	
Low Hartmann	53 (20.5%)	261 (19.6%)	88 (17.3%)	
Different	13 (5.0%)	32 (2.4%)	11 (2.2%)	0.142
Deviating stoma (in LAR)	76 (65.5%)	440 (68.5%)	204 (80.3%)	0.001
Laparoscopic	149 (59.8%)	582 (44.8%)	227 (45.7%)	<0.001

Table 1. Baseline and operative characteristics of rectal cancer patients stratified for hospital volume (continued)

	Low volume (<20) N= 258 (12.3%)	Medium volume (20-50) N= 1329 (63.4%)	High volume (>50) N=508 (24.2%)	P value
Additional resection	18 (7.2%)	94 (7.2%)	42 (8.4%)	0.676
Partial vaginectomy	13 (5.0%)	29 (2.2%)	12 (2.4%)	0.028
Uterus resection	2 (0.8%)	20 (1.5%)	7 (1.4%)	0.656
Ovariectomy	1 (0.4%)	18 (1.4%)	11 (2.2%)	0.136
Vesicula seminalis resection	2 (0.8%)	10 (0.8%)	10 (2.0%)	0.066
Partial prostatectomy	2 (0.8%)	18 (1.4%)	5 (1.0%)	0.649
Partial bladder resection	1 (0.4%)	9 (0.7%)	4 (0.8%)	0.812
Total exenteration	2 (0.8%)	12 (0.9%)	4 (0.8%)	0.960

ASA: American Society of Anaesthesiologists

LAR: low anterior resection; APR: abdominoperineal resection; low Hartmann: total mesorectal excision with end-colostomy.

Different included proctocolectomy or local excision followed by rectal resection.

Table 2. Pathologic and short-term outcome of rectal cancer patients stratified for hospital volume

	Low volume (<20) N= 258 (12.3%)	Medium volume (20-50) N= 1329 (63.4%)	High volume (>50) N=508 (24.2%)	P value
Pathologic tumour stage				
(y)pT0	28 (11.3%)	86 (6.8%)	19 (4.0%)	
(y)pT1	21 (8.5%	94 (7.4%)	41 (8.6%)	
(y)pT2	81 (32.8%)	413 (32.7%)	164 (34.3%)	
(y)pT3	103 (41.7%)	610 (48.3%)	225 (47.1%)	
(y)pT4	14 (5.7%)	61 (4.8%)	29 (6.1%)	0.027
Pathologic lymph node stage				
(y)pN0	163 (66.8%)	787 (62.5%)	328 (66.3%)	
(y)pN1	63 (25.8%)	331 (26.3%)	126 (25.5%)	
(y)pN2	18 (7.4%)	142 (11.3%)	41 (8.3%)	0.172
CRM involvement [a]	17 (8.9%)	96 (9.2%)	35 (9.2%)	0.993
Postoperative outcomes				
Overall complication	81 (32.5%)	506 (39.2%)	186 (37.7%)	0.004
Reintervention	30 (14.1%)	186 (17.2%)	53 (13.6%)	0.184
30-day or in-hospital mortality	7 (2.8%)	34 (2.6%)	14 (2.8%)	0.970

[a] CRM (circumferential resection margin) involvement: if the smallest non-peritoneal resection margin to the tumour was ≤ 1mm at pathologic examination.

Postoperative outcomes

Pathological tumour stage slightly differed among the volume groups with more complete response (y) pT0 (11.3% vs. 6.8% and 4.0%) and less (y) pT3 stage (41.7% vs. 48.1% and 47.3%, p = 0.027) in low-volume compared to medium and high-volume hospitals. The overall higher cN stage in high-volume hospitals did not translate into high (y)pN stage (p = 0.172). Circumferential resection margin involvement was found in approximately 9% and did not differ among volume groups (Table 2; p = 0.993). Overall complication rate was lower in low-volume hospitals compared to medium and high-volume hospitals, with non-significantly different reintervention rates. The 30-day or in-hospital mortality rate was 2.8% in low volume hospitals as compared to 2.6% and 2.8% in medium and high-volume hospitals, respectively (p = 0.970).

Long-term oncological outcomes

Median length of follow-up was 41 months (interquartile range 30 - 52 months). Disease-free survival at 3 years was 75.0% for patients operated in low-volume hospitals, compared to 74.8% and 76.8% in medium and high-volume hospitals (Figure 1, p = 0.682).

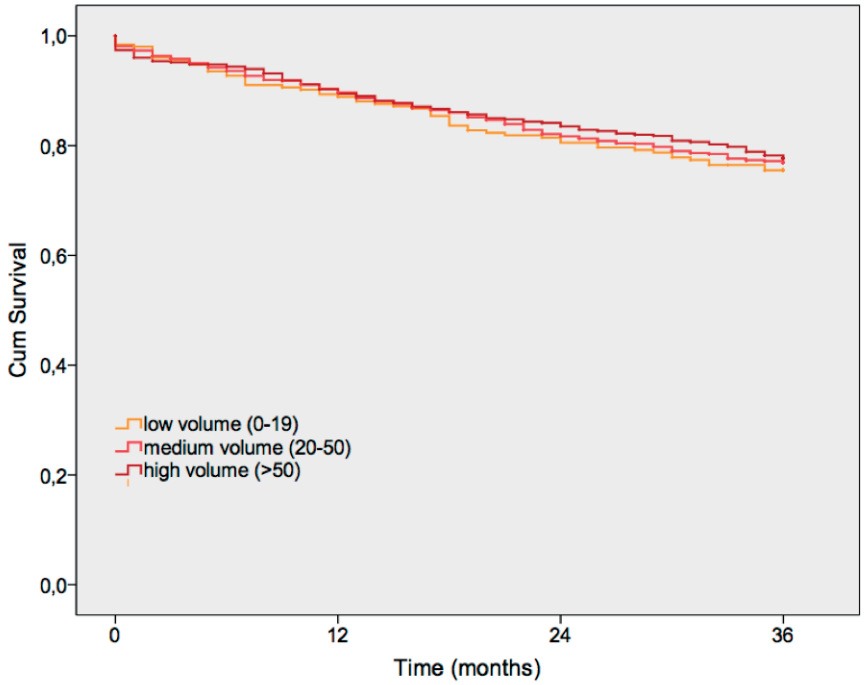

Figure 1. Disease-free survival after rectal cancer surgery, stratified for hospital volume. Disease-free survival at 3 years was 75.0% for patients operated in low-volume hospitals, compared to 74.8% in and 76.8% in medium and high-volume hospitals (p = 0.682).

Three-year overall survival was 75.9% for patients operated in low-volume hospitals, compared to 79.1% in and 80.3% in medium and high-volume hospitals (Figure 2, p = 0.344).

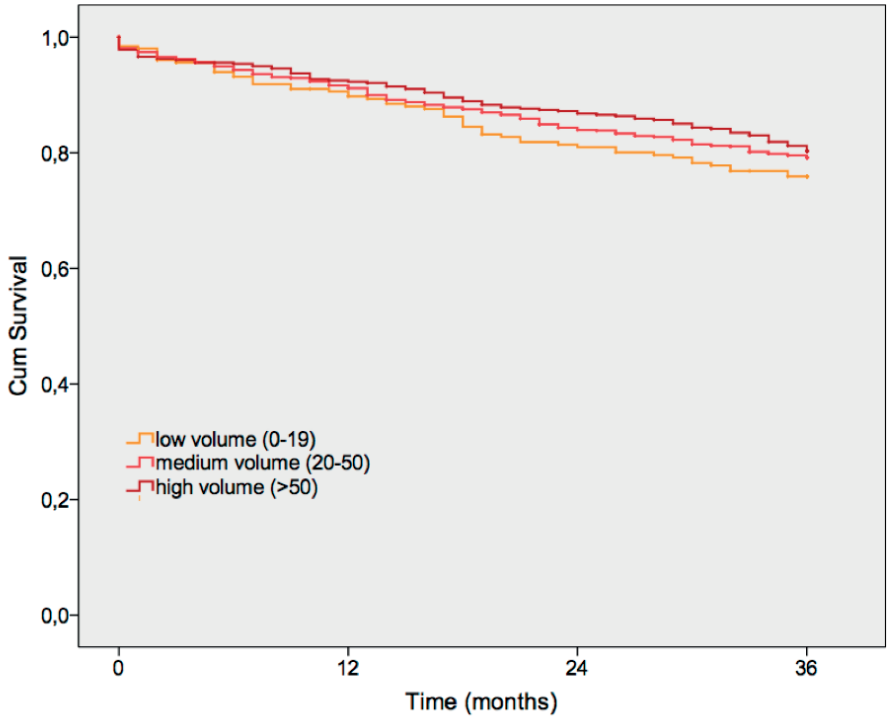

Figure 2. Overall survival after rectal cancer surgery, stratified for hospital volume. The overall survival rate at 3 years was 75.9% for patients operated in low-volume hospitals, compared to 79.1% in and 80.3% in medium and high-volume hospitals (p = 0.344).

Independent predictors of long-term mortality in Cox regression analysis were age above 70 years, ASA class 3 or 4, pathological tumour and nodal stage, synchronous metastasis, extended resection because of suspected tumour involvement, and circumferential resection margin (CRM) involvement (Table 3). After adjustment for these factors, annual hospital volume was not significantly associated with a long-term risk of mortality.

Table 3. Multivariate cox regression analysis of predictors of long-term mortality after rectal cancer surgery

Variable	Odds ratio	95% CI	p value
Age > 70	2.28	1.84-2.82	<0.001
Female gender	0.84	0.67-1.04	0.114
ASA class 3/4	2.08	1.65-2.63	<0.001
Neoadjuvant therapy	0.85	0.62-1.17	0.320
Laparoscopic	1.02	0.82-1.26	0.883
Pathologic tumour stage			
pT0	1.00	-	-
pT1	0.37	0.16-0.83	0.016
pT2	0.60	0.33-1.08	0.089
pT3	1.07	0.61-1.88	0.815
pT4	1.01	0.52-1.94	0.979
Pathologic nodal stage			
N1/N2	1.15	1.05-1.26	0.003
Synchronous metastasis	2.71	2.08-3.52	<0.001
Additional resection	2.07	1.49-2.89	<0.001
CRM involvement	1.78	1.34-2.34	<0.001
Hospital volume [a]			
Low volume (0-19)	1.00	-	-
Medium volume (20-50)	0.93	0.68-1.27	0.635
High volume (>50)	0.93	0.65-1.32	0.676

[a] Low volume was used as reference category

DISCUSSION

In this Snapshot study, including 2095 patients treated in 71 Dutch hospitals, annual hospital volume was not significantly associated with any outcome measure after rectal cancer surgery. The only differences that were observed among volume groups were related to clinical nodal staging and the surgical treatment, regarding the use of minimally invasive surgery and diverting stoma. Treatment of locally advanced disease did not seem to be related to annual hospital volume.

This cross-sectional study design enabled evaluation of a much debated volume-outcome relationship within the context of most recently provided rectal cancer care in the Netherlands. Since the TME trial in the late 1990s, rectal cancer care has increasingly been provided by dedicated multidisciplinary teams in the Netherlands, with rectal resections almost exclusively performed by specialized surgeons in recent years. The Association of

Surgeons of the Netherlands initiated a colorectal audit in 2009. The first report revealed substantial inter-hospital variability in process and outcome indicators. Regularly updated feedback and quality improvement projects led to substantial improvements in the next few years.(6) This probably explains the overall high performance independent of hospital volume as observed in the present snapshot of 2011.

Limitations of the present study are related to potential incompleteness and validity of the data. The hospital volume was based on the number of cases originally registered in the DSCA and data are self-reported. However, validation of the DSCA against the Dutch National Cancer Registry showed high accuracy and completeness of the data.(9) Furthermore, it should be noted that participation in this snapshot study was voluntary, while registration in the DSCA is mandatory. Some small non-teaching regional hospitals that did not participate in this resident-led research project could have influenced the results. In contrast to a similar CRM positivity among volume groups in the current study, a significant higher CRM positivity was found among volume groups in the current study, a significant higher CRM positivity was found in low-volume hospitals in 2011 and 2012 using DSCA data of all 94 Dutch hospitals.(10) This underlines the difficulty in interpretation of hospital volume as a single discriminator, while some low-volume hospitals might be high-performing hospitals.(11)

Treatment of rectal cancer has become more and more complicated considering several clinically relevant subgroups of patients regarding clinical condition, clinical staging, and types of neoadjuvant therapy, different surgical approaches, pathological and molecular assessment, and an increasing number of systemic therapy options. It seems likely that a certain volume is needed to manage this increasing complexity of care. In the Netherlands, centralization of rectal cancer has been recently initiated through a minimum volume of 20 rectal resections annually, with involvement of patient societies and insurance companies besides the relevant national medical societies. Hospitals that did not reach the minimum of 20 resections a year were encouraged to stop performing rectal surgery since 2012, which resulted in collaboration initiatives with concentration of specific patient groups. It may well be that specific subgroups do benefit from centralized care in high-volume centres. However, our patient cohort might not be able to show this because of already implemented quality improvement measures, and because the sample size is still relatively small to show subtle differences between subgroups.

Data from previous studies regarding hospital volume and rectal cancer care are conflicting, and definitions of high and low volume vary considerably. According to the Californian Office of State-wide Health planning and Development database(12) and the Swedish Rectal Cancer Registry(13), short-term mortality rates after rectal cancer surgery were

significantly lower in medium and high-volume hospitals (0.9% - 2.2%) as compared to low-volume centres (2.1% - 3.6%). Noteworthy is the definition of low volume in the Californian study, being 30 procedures or less during a six-year study period, corresponding to an annual volume of 5 or less. A recent analysis from the Rectal Cancer Project of the Spanish Society of Surgeons of 9809 consecutive patients showed an overall postoperative mortality rate of 1.8%, which varied significantly among hospitals, but this could not be attributed to the hospital volume.(14) The same authors could not demonstrate a significant influence of hospital volume on the anastomotic leakage rate after LAR in another study.(15) PROCARE investigators recently found some volume effects in the quality of care in the treatment of rectal cancer, but concluded that their effect size was limited.(4) The authors underline that PROCARE is a voluntary registry, which cannot be extrapolated to the Belgian population.

Regarding the effects of hospital volume on long-term survival after rectal cancer surgery, data is limited. Overall survival rates after 5 years appear not to be associated with hospital volume.(3,13,16,17) Only two studies including patients treated between 1992 and 1997 found a slightly better survival rate after 2 years for high-volume hospitals.(2,18) However, the validity of these historical data for modern rectal cancer management are questionable. In the present study, overall survival rates slightly differed with higher probabilities in high-volume hospitals. However, this did not reach statistical significance and multivariate analysis confirmed that there was no impact of hospital volume on survival. Combining these findings and the previously reported results in the literature, the influence of overall hospital volume on long-term outcomes after rectal cancer resection appears to be limited, if it exists at all.

Care for patients with locally advanced tumours was already centralized in the Netherlands before 2011. If exenterative procedures, sacral resection or intraoperative radiotherapy are indicated, the previous Dutch guideline from 2008 already recommended referral to specialized centres.(19) The similar percentages of extended resections and ypT4 stage among the different volume groups suggest that treatment of locally advanced disease is not related to volume, but more related to availability of expertise and treatment modalities. Patients with cT4 tumours are potentially more accurately assessed in experienced multidisciplinary tumour board 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.

In conclusion, no impact of hospital volume on outcome after rectal cancer surgery could be demonstrated among 71 Dutch hospitals at the time already significant improvements in rectal cancer care were achieved. 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.

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Chapter 3

Hospital volume and outcome in rectal cancer patients; results of a population-based study in the Netherlands

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ABSTRACT

Background

Clinically staged T1-3 rectal cancer (cT1-3) is generally treated by total mesorectal excision (TME) with or without neoadjuvant therapy and sometimes requires beyond TME-surgery, whereas cT4 rectal cancer often requires both. This study evaluates the outcome of cT1-3 and cT4 rectal cancer according to hospital volume.

Methods

Patients undergoing rectal cancer surgery between 2005 and 2013 in the Netherlands were included from the National Cancer Registry. Hospitals were divided into low (1 - 20), medium (21 - 50) and high (> 50 resections/year) volume for cT1-3 and low (1- 4), medium (5- 9) and high (≥ 10 resections/year) volume for cT4 rectal cancer. Cox-proportional hazards model was used for multivariable analysis of overall survival (OS).

Results

A total of 14.050 confirmed cT1-3 patients and 2.104 cT4 patients underwent surgery. In cT1-3 rectal cancer, there was no significant difference in 5-year OS related to high, medium and low hospital volume (70% vs. 69% vs. 69%). In cT4 rectal cancer, treatment in a high volume cT4 hospital was associated with a survival benefit compared to low volume cT4 hospitals (HR 0.81 95% CI 0.67 - 0.98) adjusted for non-treatment related confounders, but this was not significant after adjustment for neoadjuvant treatment. Patients with cT4-tumours treated in high volume hospitals had a significantly lower age, more synchronous metastases, more patients treated with neoadjuvant therapy and a higher pT-stage.

Conclusions

Hospital volume was not associated with survival in cT1-3 rectal cancer. In cT4 rectal cancer, treatment in high volume cT4 hospitals was associated with improved survival compared to low volume cT4 hospitals, although this association lost statistical significance after correction for neoadjuvant treatment.

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) Outcome of rectal cancer has improved over the last two decades, mainly due to the introduction of improved imaging modalities, total mesorectal excision (TME) and neoadjuvant (chemo-) radiotherapy.(2-6)

Optimal treatment of rectal cancer is dependent on local tumour stage and the presence of distant metastases. In lower stages of rectal cancer, the effectiveness of neoadjuvant (chemo-)radiotherapy is limited, whereas in more advanced stages of rectal cancer (chemo-) radiotherapy is an essential part of the treatment.(7) It leads to tumour shrinkage, thereby facilitating complete resections and a decrease in local recurrence rate.(3, 8)

Local tumour stage is also important to determine the optimal surgical treatment. Lower stages of rectal cancer can be treated by standard TME procedures or even rectal sparing surgery in selected patients.(9) Advanced stages of rectal cancer with tumours invading the mesorectal fascia often require a more radical surgical approach to achieve a complete resection. These procedures, such as extralevatory abdominoperineal resections and partial or total exenterations, require a surgical dissection beyond the standard TME plane.(10)

To improve the outcome of rectal cancer, the current Dutch standard indicates a minimum of 20 surgical resections of rectal cancer per year per hospital and advises centralization of care for patients with advanced stages of rectal cancer (i.e. clinically staged T4 and locally recurrent rectal cancer) in specialized colorectal cancer hospitals.(11) 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.(12) We hypothesize that hospital volumes may be more important in cT4 rectal cancer than in patients with cT1-3 rectal cancer. This study analyses the long-term results of cT1-3 and cT4 rectal cancer according to hospital volume in the Netherlands.

PATIENTS AND METHODS

Data collection

Data of all rectal cancer patients diagnosed between 2005 and 2013 in the Netherlands were retrieved from the nationwide population-based Netherlands Cancer Registry (NCR). Registration is mainly based on notification by the automated pathological archive (PALGA) and the National Registry of Hospital Discharge Diagnosis. Trained registrars of the NCR collected data from the medical records of the different hospitals. The population based NCR database has a 95% completeness of cancer registrations.(13) Information concerning the cause of death was not available. No ethical approval was required for this study.

Study population

All patients undergoing surgery for rectal cancer were included. The following patient/tumour related variables were available: year of diagnosis, age, gender, clinical and pathological TNM stage, histopathology and the presence of synchronous distant metastases. Available treatment related variables were: neoadjuvant treatment, adjuvant treatment, hospital volume based on number of rectal cancer resections per year, type of surgical procedure (low anterior resection, abdominoperineal resection or proctocolectomy). Involvement of circumferential resection margin (CRM) was available from 2008 onwards.

Clinically staged T1-3 and T4 rectal cancer were analysed separately. Patients with an unknown cT-stage were excluded from analysis, but were included in the determination of rectal cancer hospital volume. For cT1-3 rectal cancer, hospitals were divided into low volume hospitals (1 - 20 resections), medium volume hospitals (21 - 50 resections) and high volume hospitals (> 50 resections), based on the total number of rectal cancer resections performed annually in one hospital. For cT4 rectal cancer, hospitals were divided into low (1 - 4 resections), medium (5 - 9 resections) and high (≥ 10 resections) volume based on cT4 rectal cancer resections performed annually in one hospital.

The TNM-classification was used according to the edition valid at the time of cancer diagnosis (6^{th} edition for 2005-2009 and 7^{th} edition for 2010-2013). The 7^{th} edition included a distinction between cT4a (tumour penetrates the surface of the visceral peritoneum) and cT4b tumours (tumour invades or is adherent to surrounding organs or structures).

Endpoints

The primary endpoint was overall survival according to the total hospital volume for cT1-3 and cT4 rectal cancer.

Follow up

Vital status of patients was retrieved by linkage of the NCR to the nationwide municipal population registries network.

Statistical analysis

Data were reported as median (interquartile range) or mean (standard deviation) as appropriate. Categorical data were reported as count (percentage). The Chi-square was used for comparison of groups. For comparison of the proportion of patients treated per volume category over time the Chi-square test for linear trend was used. For survival analysis, follow-up time was calculated from date of diagnosis until date of death or end of follow-up. Patients who were alive at the end of follow-up were censored. Three and five-year survival rates were calculated by Kaplan-Meier analysis and comparisons between groups were made using log-rank tests. Multivariable Cox's proportional hazards analysis was performed to analyse differences in overall survival according to hospital volume. Variables with p-values < 0.10 in the univariate analysis were included in the multivariable analysis. Only variables available for the whole study period were included in the multivariable analysis. Two sided p-values < 0.05 were considered statistically significant.

RESULTS

16.154 patients underwent rectal cancer surgery and had a confirmed clinical T-stage, while in 6394 patients the cT-stage was unknown. The number of patients with an unknown cT-stage was especially high in the first years and this decreased over the study period (55% in 2005 and 7% in 2013). Of those patients with a known cT-stage, 14.050 patients (87%) had a cT1-3 tumour and 2.104 patients (13%) had a cT4 tumour.

cT1-3 rectal cancer

The baseline characteristics of the 14.050 patients with cT1-3 rectal cancer are outlined in Table 1. The majority of these patients underwent surgery in medium volume hospitals (62%), followed by high volume hospitals (21%) and low volume hospitals (17%). An increase was seen in patients treated in high volume hospitals (2005-2007: 13% vs. 2011-2013: 23%, p < 0.001). Neoadjuvant chemoradiotherapy was administered more often to patients in high volume hospitals compared to medium volume and low volume hospitals (43% vs. 37% and 32%, p < 0.001). High volume hospitals performed less abdominoperineal resections (31% vs. 34% vs. 35%, p = 0.002) and had a higher percentage of ypT0 stage (9% vs. 7% vs. 8%, P = 0.010). There was no difference in nodal stage and CRM-involvement. Patients treated in low volume hospitals received adjuvant chemotherapy less often (11% in high and medium volume hospitals compared to 8% in low volume hospitals, p < 0.001).

Table 1. Baseline characteristics cT1-3 rectal cancer patients

	Low volume hospitals 1-20/year	Medium volume hospitals 20-50/year	High volume hospitals ≥50/year	P-value
Total patients	2452	8708	2890	
Gender				
Male	1526 (62)	5573 (64)	1824 (63)	0.25
Female	926 (38)	3135 (36)	1066 (37)	
Median age	67	67	67	0.10
Year of diagnosis *				
2005-2007	685 (24)	1791 (63)	380 (13)	< 0.001
2008-2010	780 (16)	2985 (62)	1017 (21)	
2011-2013	987 (15)	3932 (61)	1493 (23)	
Neo-adjuvant treatment				
None	252 (10)	1007 (12)	280 (9)	< 0.001
Radiotherapy	1408 (57)	4448 (51)	1359 (47)	
Chemotherapy	7 (1)	48 (1)	16 (1)	
Chemoradiotherapy	785 (32)	3205 (37)	1235 (43)	
Type of surgery				
LAR/Hartmann	1569 (64)	5575 (64)	1952 (68)	0.002
APR	854 (35)	2980 (34)	892 (31)	
Proctocolectomy	12 (1)	65 (1)	27 (1)	
Not otherwise specified	17 (1)	88 (1)	19 (1)	
Pathological tumour stage				0.01
T0	190 (8)	648 (7)	269 (9)	
T1	183 (7)	627 (7)	209 (7)	
T2	824 (34)	2788 (32)	929 (32)	
T3	1174 (48)	4270 (49)	1384 (48)	
T4	50 (2)	191 (2)	57 (2)	
TX	31 (1)	184 (2)	42 (1)	
Pathological nodal stage				
N0	1592 (65)	5519 (63)	1863 (64)	0.17
N+	835 (34)	3087 (36)	993 (35)	
NX	25 (1)	102 (1)	34 (1)	
Pathological distant metastases				
M0	2381 (97)	8317 (96)	2767 (96)	0.002
M+	71 (3)	391 (4)	123 (4)	
Tumour grade				
Well differentiated	70 (3)	259 (3)	168 (2)	< 0.001
Moderately differentiated	1009 (41)	3466 (40)	1040 (36)	

Table 1. Baseline characteristics cT1-3 rectal cancer patients (continued)

	Low volume hospitals 1-20/year	Medium volume hospitals 20-50/year	High volume hospitals ≥50/year	P-value
Total patients	2452	8708	2890	
Poorly differentiated/ undifferentiated	161 (7)	532 (6)	159 (6)	
Unknown	1212 (49)	4451 (51)	1623 (56)	
CRM-involvement #				
Involved	125 (7)	477 (7)	180 (7)	0.50
Not involved	1292 (73)	4967 (72)	1779 (71)	
Unknown	349 (20)	1470 (21)	551 (22)	
Adjuvant chemotherapy	201 (8)	980 (11)	326 (11)	< 0.001

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis. #, CRM was reported in the database starting from 2008*

Outcomes

The median follow up was 31 months (IQR 15 – 54 months). The estimated 5-year survival rates of patients with cT1-3 rectal cancer who were treated in low, medium or high volume hospitals were similar (70%, 69%, 69% respectively; p = 0.88). Survival curves are shown in Figure 1. Univariate Cox regression analysis showed no significant difference in survival between different hospital volumes. Univariate hazard ratios for survival of medium and high volume hospitals compared to low volume hospitals were 1.01 (95% CI: 0.92 – 1.11) and 1.03 (95% CI: 0.92 – 1.16), respectively.

cT4 rectal cancer

The baseline characteristics of 2.104 patients with cT4 rectal cancer are depicted in Table 2. The majority of patients (60%) underwent surgery in low volume cT4 hospitals (1 - 4 resections/year), followed by 25% in high volume hospitals (≥ 10 resections/year) and 15% in medium volume hospitals (5 - 9 resections/year). Eight hospitals performed less than one surgical procedure for cT4 rectal cancer per year on average (2005 - 2013). An increase was seen in patients treated in high volume hospitals (2005 - 2007: 21% vs. 2011 - 2013: 28%, p = 0.03). There was an increase in referral of cT4 rectal cancer patients for resection to any other hospital from 23% in 2005 to 38% in 2013 (p = 0.003) (Figure 2a). CT4 patients were most often referred by low volume hospitals, followed by medium and high

volume hospitals (Figure 2b) and most often referred to high volume hospitals, but also to medium volume hospitals and even to other low volume hospitals (Figure 2c).

Patients treated in high volume cT4 hospitals had a significantly lower age compared to medium and low volume hospitals ($p < 0.001$). The number of synchronously metastasized patients was significantly higher in high volume hospitals compared to low volume cT4 hospitals (11% vs. 7%, $p = 0.001$) and was similar in medium cT4 hospitals (11% vs. 10%, $p = 0.66$). The percentage of patients who received neoadjuvant therapy was higher in high volume cT4 hospitals (98%) than in medium and low volume cT4 hospitals (respectively 91% and 88%, $p < 0.001$). In high volume cT4 hospitals, 83% of the patients received chemoradiotherapy, compared to 70% in medium volume cT4 hospitals and 62% in low volume cT4 hospitals. The proportion of patients with a pathological T4-stage was higher in high volume hospitals compared to low volume hospitals (28% vs. 23%, $p = 0.02$). Low volume hospitals had the highest proportion of node positive patients: 41% compared to 34% in both medium volume and high volume hospitals ($p=0.04$).

In a subgroup analysis of the cT4 patients diagnosed between 2010 and 2013, more patients were staged cT4b in high volume hospitals compared to medium volume hospitals (82% vs. 70%, $p = 0.007$) and low volume hospitals (82% vs. 68% $p < 0.001$). However, there was no significant difference between the proportion of patients with pT4b stage in high volume hospitals compared to medium volume (20% vs. 22%, $p = 0.86$) or low volume hospitals, (20% vs 26%, $p = 0.48$). In the period 2008 - 2013, there was no

Table 2. Baseline characteristics of cT4 rectal cancer patients

	Low volume hospitals 1-4/year	Medium volume hospitals 5-9/year	High volume hospitals ≥10/year	P-value
Total patients	1.256	328	520	
Gender				
Male	622 (50)	175 (53)	294 (57)	0.02
Female	634 (50)	153 (47)	226 (43)	
Median age	67	65	63	<0.001
Year of diagnosis *				
2005-2007	433 (64)	102 (15)	142 (21)	0.03
2008-2010	442 (59)	120 (16)	188 (25)	
2011-2013	381 (56)	106 (16)	190 (28)	
Neo-adjuvant treatment				
None	156 (12)	29 (9)	13 (2)	<0.001

Table 2. Baseline characteristics of cT4 rectal cancer patients (continued)

	Low volume hospitals 1-4/year	Medium volume hospitals 5-9/year	High volume hospitals ≥10/year	P-value
Radiotherapy	308 (25)	53 (16)	58 (11)	
Chemotherapy	10 (1)	16 (5)	15 (3)	
Chemoradiotherapy	782 (62)	230 (70)	434 (83)	
Type of surgery				<0.001
LAR/Hartmann	528 (42)	103 (31)	138 (27)	
APR	590 (47)	157 (48)	259 (50)	
Proctocolectomy	121 (10)	63 (19)	114 (22)	
Not otherwise specified	17 (1)	5 (2)	9 (2)	
Pathological tumour stage				
T0	87 (7)	23 (7)	47 (9)	0.02
T1	26 (2)	10 (3)	19 (4)	
T2	198 (16)	43 (13)	59 (11)	
T3	610 (49)	142 (43)	239 (46)	
T4	287 (23)	95 (29)	143 (28)	
TX	48 (4)	15 (5)	13 (3)	
Pathological nodal stage				
N0	710 (57)	204 (62)	330 (64)	0.04
N+	512 (41)	113 (34)	179 (34)	
NX	34 (3)	11 (3)	11 (2)	
Pathological distant metastases				
M0	1,174 (93)	294 (90)	461 (89)	0.001
M+	82 (7)	34 (10)	59 (11)	
Tumour grade				
Well differentiated	34 (3)	6 (2)	18 (3)	<0.001
Moderately differentiated	455 (36)	87 (27)	147 (28)	
Poorly differentiated/ undifferentiated	116 (9)	25 (8)	38 (7)	
Unknown	651 (52)	210 (64)	317 (61)	
CRM-involvement #				
Involved	160 (19)	45 (20)	63 (17)	0.58
Not involved	466 (57)	131 (58)	213 (56)	
Unknown	197 (24)	50 (22)	102 (27)	
Adjuvant chemotherapy	172 (14)	52 (16)	54 (10)	0.05

*LAR; Low anterior resection, APR, Abdominal perineal resection, CRM; Circumferential resection margin, *, percentages are calculated within years of diagnosis.* #, CRM was reported in the database starting from 2008

significant difference in CRM-involvement between high, medium and low volume cT4 hospitals (respectively 19%, 20%, 17%, p = 0.58).

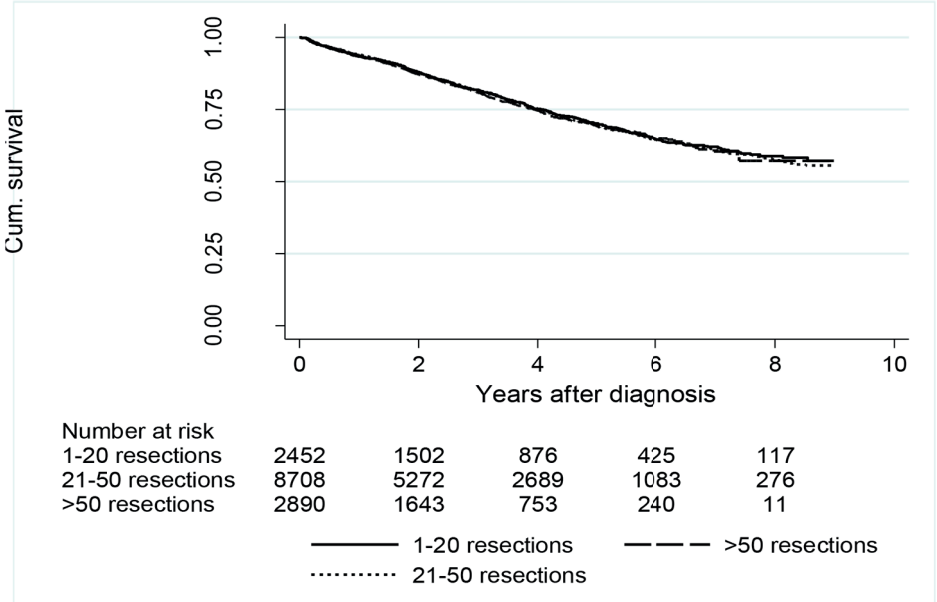

Figure 1. Overall survival in cT1-3 patients, according to hospital volume.

Outcomes

There was no difference in 30-days mortality and 90-days mortality according to hospital volume. Patients were followed with a median of 33 (IQR 16 - 60) months. The estimated overall survival of cT4 patients treated in high volume cT4 hospitals was significantly longer than in medium and low volume cT4 hospitals (p =0 .001). The estimated 3-year survival rate was 76%, 71% and 67% respectively and the 5-year survival rate was 63%, 53% and 54% respectively (Figure 3). Multivariable analysis demonstrated that resection in high volume cT4 hospitals was independently associated with a better overall survival compared to low volume cT4 hospitals (HR 0.81, 95% CI 0.67-0.98), after adjusting for patient/tumour related confounders (age, pTNM-stage and tumour differentiation) (Table 3). When treatment related confounders were included in the multivariate analysis, neoadjuvant chemoradiotherapy was associated with improved survival. Adjustment for neoadjuvant therapy resulted in the disappearance of a significant difference between high, medium and low volume hospitals.

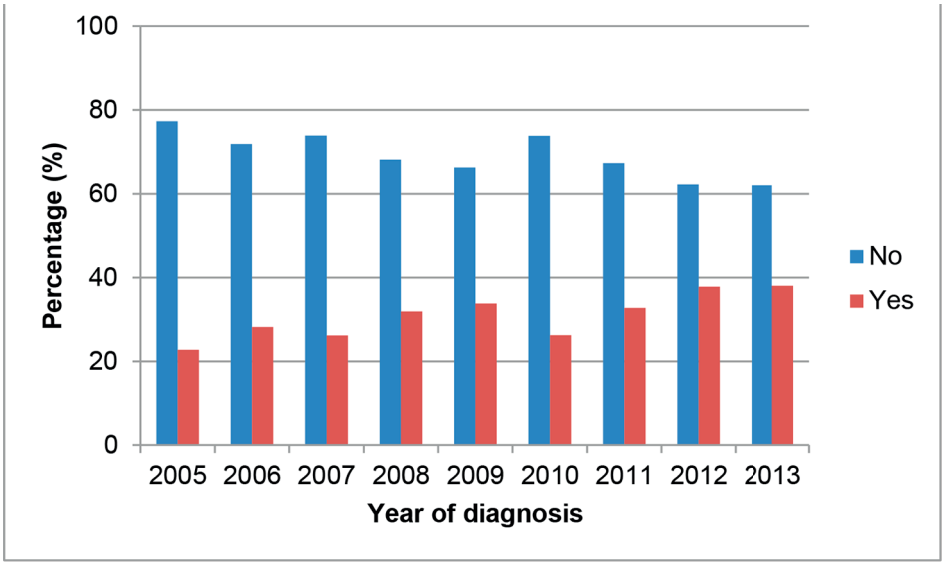

Figure 2a. Referral of cT4 rectal cancer patients for resection

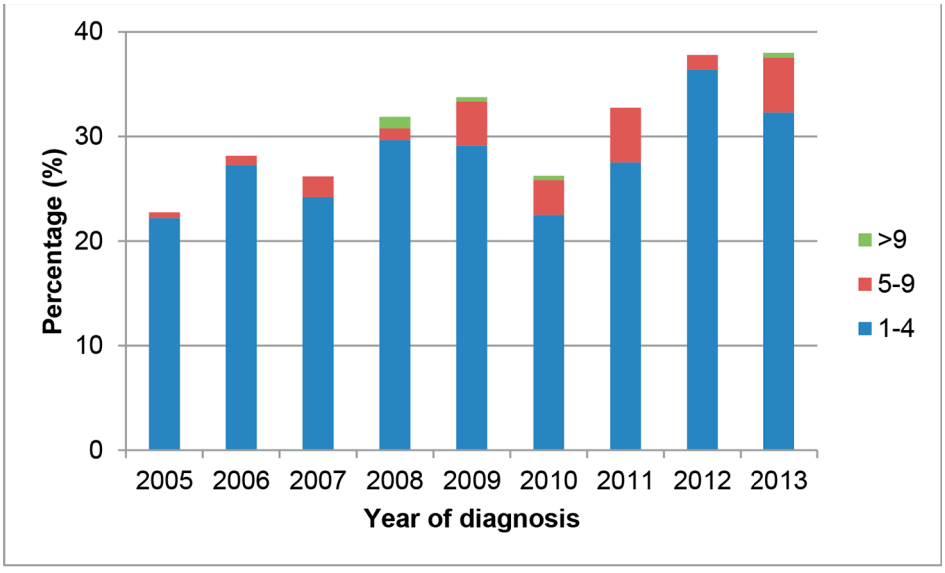

Figure 2b. Volume of hospital of diagnosis of the referred patients

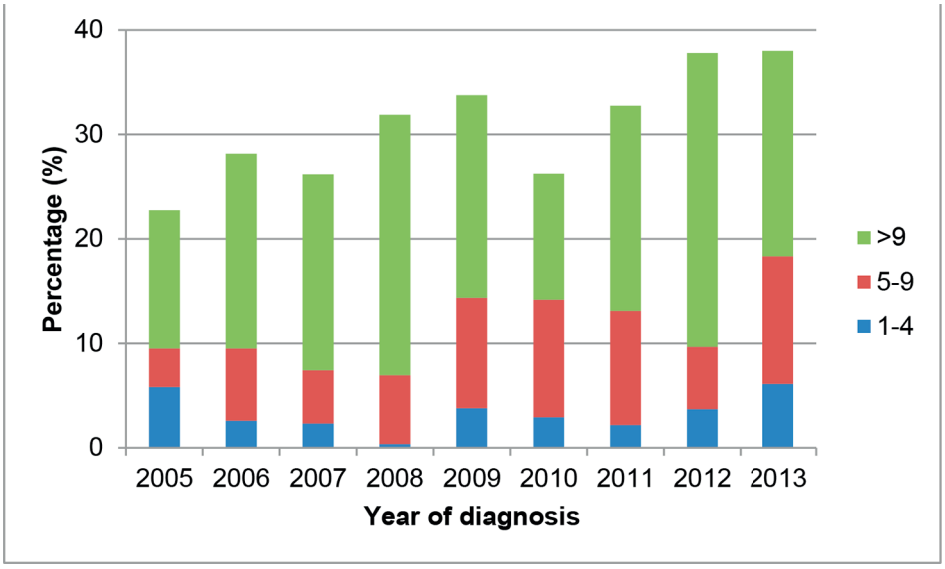

Figure 2c. Volume of hospital of resection of the referred patients

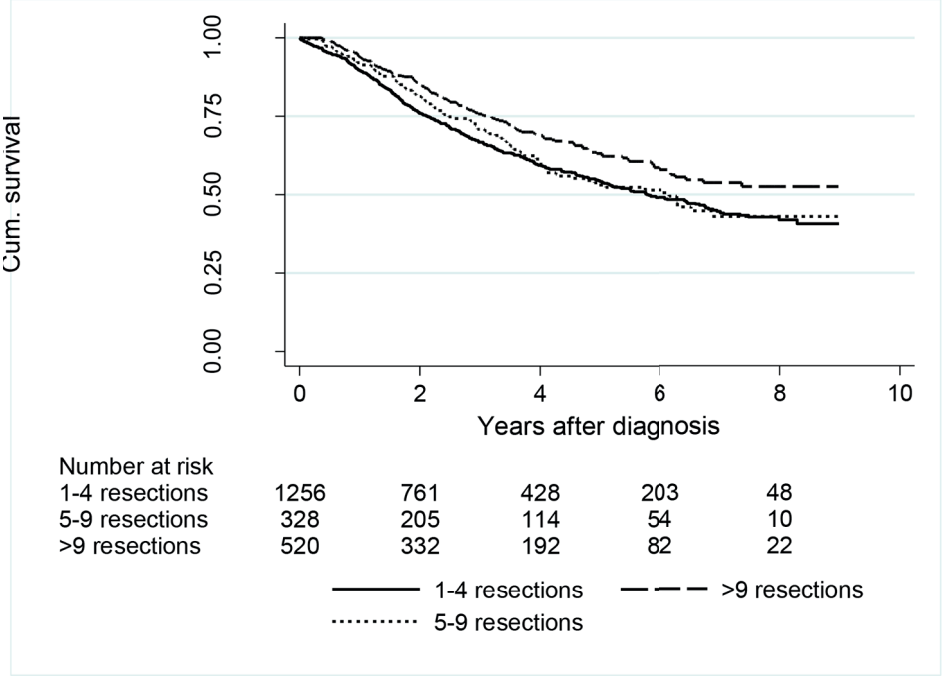

Figure 3. Overall survival of cT4 rectal cancer according to the cT4 hospital volume

Table 3. Univariate and multivariable survival analysis for overall survival of cT4 tumours with and without treatment related confounders

	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI) without treatment related confounders	Multivariable Hazard ratio (95%CI) with treatment related confounders
Hospital volume (procedure per year)		<0.001		
1-4	1		1	1
5-9	0.93 (0.76-1.14)		0.97 (0.79-1.19)	0.99 (0.81-1.22)
≥10	0.71 (0.59-0.85)		0.81 (0.67-0.98)	0.87 (0.71-1.05)
Gender		0.98		
Male	1		-	-
Female	1.00 (0.87-1.15)		-	-
Age	1.03 (1.02-1.04)	<0.001	1.03 (1.03-1.04)	1.03 (1.02-1.04)
Year of diagnosis	0.98 (0.95-1.02)	0.32		
Neo-adjuvant therapy		<0.001		
None	1		-	
Radiotherapy	0.58 (0.46-0.73)		-	0.70 (0.54-0.88)
Chemotherapy	0.59 (0.35-0.97)		-	0.69 (0.41-1.17)
Chemoradiotherapy	0.32 (0.26-0.39)		-	0.53 (0.42-0.68)
Type of surgery		0.02		
LAR/Hartmann	1		-	1
APR	0.81 (0.69-0.95)		-	0.99 (0.84-1.17)
Proctocolectomy	0.95 (0.78-1.16)		-	0.95 (0.77-1.18)
Not otherwise specified	1.42 (0.83-2.43)		-	1.47 (0.85-2.53)
Pathological tumour stage				
T0	1	<0.001	1	1
T1	0.89 (0.35-2.24)		0.92 (0.37-2.32)	0.87 (0.35-2.21)
T2	2.02 (1.20-3.39)		1.84 (1.09-3.10)	1.75 (1.04-2.94)
T3	3.57 (2.22-5.72)		2.73 (1.69-4.41)	2.53 (1.56-4.09)
T4	5.89 (3.65-9.50)		4.30 (2.65-6.99)	3.89 (2.38 (6.37)
TX	2.64 (1.46-4.78)		2.50 (1.38-4.56)	2.42 (1.33-4.41)
Pathological nodal stage		<0.001		
N0	1		1	1
N1	1.64 (1.38-1.95)		1.34 (1.12-1.61)	1.32 (1.10-1.58)
N2	2.74 (2.29-3.28)		2.06 (1.71-2.49)	1.95 (1.61-2.36)
NX	2.31 (1.62=3.30)		2.06 (1.43-2.97)	2.11 (1.46-3.04)

Table 3. Univariate and multivariable survival analysis for overall survival of cT4 tumours with and without treatment related confounders (continued)

	Univariate Hazard ratio (95%CI)	p-value	Multivariable Hazard ratio (95%CI) without treatment related confounders	Multivariable Hazard ratio (95%CI) with treatment related confounders
Pathological distant metastases				
M0/X	1	<0.001	1	1
M+	2.14 (1.71-2.67)		2.12 (1.68-2.69)	1.99 (1.56-2.52)
Tumour grade		<0.001		
Well differentiated	0.93 (0.62-1.42)		1.04 (0.69-1.60)	1.11 (0.73-1.69)
Moderately differentiated	1		1	1
Poorly differentiated/ undifferentiated	1.66 (1.32-2.09)		1.49 (1.18-1.88)	1.47 (1.16-1.86
Unknown	0.83 (0.71-0.97)		1.01 (0.86-1.19)	1.14 (0.96-1.35)
Adjuvant chemotherapy				
No	1		-	-
Yes	1.06 (0.87-1.30)	0.54	-	*

LAR; Low anterior resection, APR, Abdominal perineal resection.

DISCUSSION

The current population-based study found an overall survival benefit for cT4 rectal cancer patients treated in high volume cT4 hospitals compared to low volume cT4 hospitals. This overall survival difference related to hospital volume was not found in cT1-3 rectal cancer. 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, but this difference disappeared after adjustment for neoadjuvant therapy. The referral of cT4 tumours to high volume hospitals has increased during the study period, but in the period 2011-2013, the majority of patients (56%) were still treated in a low volume cT4 hospital.

Patients with cT1-3 rectal cancer are suitable candidates for a standard TME procedure, although beyond TME surgery is sometimes required if the mesorectal fascia is involved. Standard TME in patients with close tumour contact to the mesorectal fascia (cT4 or cT3MRF+/) often leads to incomplete resections (R1/2-resections).(14) Incomplete resections are deleterious for oncological outcome and all efforts should be aimed at avoiding R1/2-resections.(15) The advanced stages of rectal cancer have the greatest benefit of

multimodality treatment, including neoadjuvant chemoradiotherapy, which potentially leads to tumour shrinkage, more complete resections and reduces local recurrence rates. (3, 8) Accurate staging of the rectal tumour is essential in selecting patients who should be treated with neoadjuvant therapy, and to differentiate between those who can be treated by a standard TME procedure and those who require beyond TME surgery. The quality of this assessment may be enhanced by multidisciplinary tumour board meetings (MDT), including dedicated radiologists, radiation oncologists, medical oncologists and surgeons. Nowadays, almost all rectal cancer patients in the Netherlands undergo MRI staging of the primary tumour and are discussed in an MDT.(2) In an experienced MDT, cT4 tumours are potentially more accurately assessed and a more appropriate neoadjuvant and surgical strategy may be selected. This may explain why more patients in low volume hospitals did not receive chemoradiotherapy despite the clear indication for chemoradiotherapy. Furthermore, in experienced MDTs, standardized care for patients with advanced stages of rectal cancer may result in an improved long-term outcome. Other legitimate reasons for refraining from chemoradiotherapy in low or medium volume centres including patient factors, such as comorbidities, age or patient preference, cannot be retrieved form the NCR.

Several studies have reported survival differences according to hospital volume in complex surgical procedures in other malignancies, such as oesophagus, pancreas and bladder cancer.(16-18) 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.(16-18) In line with the findings of studies in other malignancies, the current study showed a survival benefit in the treatment of cT4 rectal cancer in high volume cT4 hospitals, but not in the more common cT1-3 rectal tumours. A previously published Dutch population based study in a smaller cohort described no differences in long-term oncological outcomes for rectal cancer (cT1-4) based on hospital volume, but no separate analysis for cT4 rectal cancers were performed.(19)

Presumably, the overall survival benefit of cT4 rectal cancer in high volume cT4 hospitals is caused by multiple factors. Optimal staging, neoadjuvant therapy, surgical treatment differences and experience of the MDT may lead to superior selection, treatment and results when optimally combined. Optimal staging may result in the selection of appropriate neoadjuvant treatment. Experience with extensive rectal resections in high volume hospitals may contribute, but did not lead to a lower percentage of CRM-involvement in high volume cT4 hospital compared to medium and low volume cT4 hospital in the years evaluated. This may partly be explained by referral of patients with more advanced tumours to high volume cT4 hospitals, which explains the higher pathological stage (pT4)

in high volume cT4 hospitals compared to low volume hospitals, regardless of the higher percentage of neoadjuvant therapy administered. In a subgroup analysis the proportion of pT4b tumours was higher in high volume hospitals compared to medium and low volume hospitals (26% vs. 22% vs 20%), but not significantly so. Even in an experienced high volume hospital, radical resection of cT4b tumours is challenging and referral of these patients to high volume hospitals could offer an explanation for similar CRM involvement in different volume hospitals. Our data cannot prove this referral pattern. Moreover, a difficult resection does not automatically translate in a pT4b stage, especially since most patients undergo neoadjuvant chemoradiotherapy. The number of multivisceral resections per hospital may also provide an indication of the complexity and difficulty of the procedures performed in different volume hospitals. The NCR, however, started gathering data on multivisceral resections since 2010 only. Secondly, multivisceral resections were not registered as such in the Dutch registry of surgical procedures resulting in a large amount of missing data with regard to this variable. In addition, the availability of intraoperative radiotherapy (IORT) may have contributed to the survival benefit is. High volume cT4 hospitals in the Netherlands have the ability to apply an extra radiation dose during surgery. IORT may eradicate remaining tumour cells and this may lead to a survival benefit.(20, 21) Unfortunately, IORT was not comprehensively registered in the NCR making further evaluation of the role of IORT impossible.

The relatively high CRM-involvement (17%) in cT4 rectal cancer patients treated in high volume hospitals in our study suggests that even in high volume hospitals there is room for improvement. A more recent cohort by Jonker et al. (22) on perioperative outcomes for cT1-3 and cT4 rectal cancer by hospital volumes did find a significantly higher rate of irradical resections for cT4 rectal cancer in low volume hospitals compared to medium and high volume hospitals, and therefore advocates that centralization may be beneficial for cT4 patients. Further centralization leading to an increase in the number of patients treated in high volume hospitals could further improve treatment in these centres, and eventually result in a higher percentage of clear margins, a decrease in local recurrence rates and an increase in overall survival. The total number of cT4 rectal cancer diagnosed annually in the Netherlands (approximately 250) is limited. The appointment of 4 or 5 cT4 rectal cancer centres would seem appropriate and result in an adequate number of patients in specialized centres. Excluding cT4 rectal cancer from the required total number of rectal cancer procedures per hospital may eliminate the stimulus to treat these patients in hospitals without T4 rectal cancer experience.

Due to its retrospective nature, this study has limitations. Patients referred to high volume centres for extensive surgery were younger, and probably in a relatively good clinical condition. Both may improve their survival. On the other hand, the pathological T-stage and

the number of metastasized patients was higher in high volume cT4 hospitals, suggesting that advanced stages of disease were referred to high volume cT4 hospitals, which would decrease overall survival in these patients. This type of discussion on the profile of patient groups in different hospitals is often referred to as the 'case mix' discussion. Unfortunately, for reasons described earlier, we cannot conclude whether 'case mix' is the driver behind the differences that we did and did not find.

In conclusion, 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, but the omission of neoadjuvant treatment in cT4 rectal cancer may also reflect lower quality of care. There was a small increase in referral of cT4 rectal cancer to high volume cT4 hospitals, but further centralization of cT4 rectal cancer seems warranted to further improve outcome for this difficult group of patients.

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Chapter 4

The impact of hospital volume on perioperative outcomes of rectal cancer

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ABSTRACT

Introduction

The purpose of this study was to investigate the impact of hospital volume on perioperative outcomes of clinical tumour stage (cT)1-3 rectal and cT4 rectal cancer.

Methods

16.162 patients operated for rectal cancer enrolled in the Dutch Surgical Colorectal Audit were included. Hospitals were divided into low (< 20 cases/year), medium (21-50 cases/year) and high (> 50 cases/year) volume for cT1-3 rectal cancer, and for cT4 rectal cancer into low (1-4 cases/year), medium (5-9 cases/year) and high (≥ 10 cases/year) volume. The influence of hospital volume on perioperative outcomes was investigated.

Results

With regards to cT1-3 tumours, low volume hospitals had lower rates of complications (33.8% vs. 36.6% and 38.1%, p = 0.009), anastomotic leakage (5.4% vs. 8.1% and 8.6%), and reintervention (11.5% vs. 12.6% and 14.8%, p = 0.002) as compared to medium and high volume hospitals. Thirty-day mortality and R0 rates were comparable between groups.

In high cT4 volume hospitals, rates of extensive resection of tumour involvement (49.4% vs. 25.4% and 15.5%, p < 0.001) and additional resection of metastasis (17.5% vs. 14.4% and 3.0%, p < 0.001) were increased as compared to medium and low volume hospitals. Thirty-day mortality and R0 rates were comparable between groups. In a sub-analysis of pathologic tumour stage 4 patients, irradical resections were increased in low volume hospitals (33.8% vs. 22.5% and 20.8% in medium and high volume hospitals, p = 0.031).

Conclusions

For cT4 rectal cancer, high volume hospitals may offer a better multimodality treatment, while for cT-3 rectal cancer there appears no benefit for centralization.

INTRODUCTION

The introduction of standardized total mesorectal excision (TME) and neoadjuvant therapies has led to improved oncological results after low anterior resection (LAR) for rectal cancer.(1, 2) The primary goal of surgical treatment of rectal cancer is to achieve a radical resection (R0) since a positive circumferential resection margin (CRM) is a poor prognostic factor, associated with local recurrence, distant metastasis, and inferior survival after rectal cancer surgery.(3, 4) Generally, neoadjuvant (chemo) radiotherapy is administered for the more advanced stages of rectal cancer, to induce tumour shrinkage to facilitate complete resections and reduce local recurrence rates.(5, 6) Neoadjuvant treatment is usually not necessary for lower stages of rectal cancer, which can be treated by standard TME procedures or even rectal sparing surgery in selected patients.(5, 6, 7) The most advanced stage of rectal cancer, including clinically staged 4 tumours (cT4) invading the mesorectal fascia and/or surrounding organs, often require an induction treatment for tumour downsizing and a more radical surgical approach to achieve a complete resection. These procedures, such as extralevatory abdominoperineal resections (APR) and exenterative procedures, require a more complex surgical dissection beyond the standard TME plane.(8)

In order to further improve the outcome of rectal cancer, the current Dutch standard indicates an overall minimum of 20 rectal resections annually per hospital, irrespective of the tumour stage. In addition, the Dutch guideline recommends centralization of care for patients with advanced stages of rectal cancer in specialized colorectal cancer hospitals.(9) The impact of hospital volume on surgical outcomes after rectal cancer surgery are under debate. 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.(10) Little is known regarding the exact effects of hospital volume on different cT1-T4 stages of rectal cancer. The purpose of this study was to evaluate 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.

METHODS

DSCA

All patients undergoing resection of colorectal cancer in the Netherlands are since 2009 registered in the Dutch Surgical Colorectal Audit (DSCA). The DSCA was initiated by the Dutch Surgical Society to monitor and improve the quality of oncological care in colorectal cancer patients on a national level.(11) Nowadays, all 92 Dutch hospitals participate in the DSCA and its data shows a nearly 100% concordance on validation against the Na-

tional Cancer Registry dataset.(12) Data on patient and tumour characteristics, diagnostics, treatment and short term outcome were collected. Medical ethics committee approval was not required for this study as all patients and hospital information in the DSCA was de-identified. Individual patient data were collected in the treating hospital and transferred in encrypted form to the DSCA database.

Patient selection

All patients operated for rectal cancer, defined as a tumour within 15 cm of the anal verge, enrolled in the DSCA between January 2009 and December 2015 were included. Overall, 19.354 patients with presumed rectal cancer were enrolled in the DSCA. After excluding tumours > 15 cm of the anal verge, those with unknown distance between tumour and anal verge, unknown procedures, or other procedures than rectal cancer surgery (i.e. left-sided colectomy), 17.477 patients remained. After excluding tumours with unknown clinical tumour stage, 16.162 patients remained.

Patients with cT1-3 tumours were stratified based on median annual cT1-3 hospital volume, which was defined as low volume (0-19 cases/year), medium volume (20-50 cases/year) or high volume (> 50 cases/year). In addition, cT4 tumours were stratified based on median annual cT4 hospital volume, which was defined as low volume (0-4 cases/year), medium volume (5-9 cases/year), or high volume (> 9 cases/year). Subsequently, baseline and operative characteristics, pathologic and postoperative outcomes were compared between cT1-3 hospital volume groups, and cT4 hospital volume groups.

Data analysis

Missing data were not defaulted to negative and denominators reflect only actual reported cases. Nominal variables were compared between groups using the Chi-square test, continuous variables using the One-Way ANOVA test. Multivariable regression analysis was performed to investigate independent effects of hospital volume on a complicated course after resection of cT4 rectal cancer. Hospital volume and variables that were significant in univariable analysis ($p < 0.05$), were included in a multivariable logistic regression model to determine independent associations with this endpoint. SPSS 22 was utilized for the analyses, and a P value < 0.05 was considered significant. The STROBE guidelines were used to ensure the reporting of this observational study.(13)

RESULTS

Overall, 14.651 patients (90.7%) had clinical tumour stage 1, 2 or 3, of which 3.210 (21.9%) were operated in 39 low volume hospitals; 8730 (59.6%) were operated in 44

medium volume hospitals, and 2.711 patients (18.5%) were operated in 8 high volume hospitals. In addition, there were 1.511 (9.3%) patients with clinical tumour stage 4 (cT4), of which 759 (50.2%) were operated in 72 low volume hospitals; 336 (22.2%) were operated in 8 medium volume hospitals, and 416 (27.5%) were operated in 3 high volume hospitals.

Clinical tumour stage 1-3

Baseline and operative characteristics

Fewer cT1-3 patients underwent neoadjuvant therapy in high volume hospitals (72.7% vs. approximately 75% in medium and high volume hospitals, p = 0.026). Clinical tumour stage 3 was more common in medium volume hospitals, while clinical nodal stage 0 was more frequently seen in low volume hospitals (p < 0.001). An abdominoperineal resection was more often performed in medium (28.1%) and high volume hospitals (27.8%) as compared to low volume hospitals (26.4%, p < 0.001). A laparoscopic approach was slightly more common in low volume hospitals, while resection of synchronous metastases was more frequently performed in medium volume hospitals (Table 1).

Postoperative outcomes

In high volume hospitals, pathologic tumour stage 3 was more often found. A radical resection was achieved in 96.7% and did not differ significantly between the three volume groups (Table 2). A complicated course was more often seen in high volume hospitals (38.1% vs. 33.8% and 36.6% in low and medium volume hospitals, respectively, p = 0.009). Reintervention including (re)laparotomy were more frequently performed in high volume hospitals (14.8% vs, 11.5% and 12.6% in low and medium hospitals (p = 0.002). Anastomotic leakage after LAR was lower in low volume hospitals (5.4% vs. 8.1% and 8.6% in medium and high volume hospitals, respectively, p = 0.001). The overall 30-day mortality rate was 1.9% and did not differ significantly between groups, while the median length of stay was one day longer in high volume hospitals (Table 2).

Clinical tumour stage 4

Baseline and operative characteristics

Mean age of cT4 patients was lower in high volume hospitals and these were less frequently classified as ASA 3 or 4, but more often discussed in multidisciplinary tumour board (MDT) meetings preoperatively (Table 3). Overall, neoadjuvant therapies were less frequently offered in high volume hospitals, while cT4 patients did receive more often chemoradiotherapy in these clinics (69.2% vs. 66.4% and 65.0% in low and medium

Table 1. Baseline and operative characteristics of cT1-3 rectal cancer patients

	Low volume (0-19) N=3210 (21.9%)	**Medium volume (20-50) N=8730 (59.6%)**	**High volume (>50) N=2711 (18.5%)**	P value
Age (y)	68.1±10.7	67.1±10.7	67.5±10.4	<0.001
Male gender	2030 (63.3%)	5674 (65.0%)	1740 (64.2%)	0.195
BMI	26.3±4.1	26.3±4.1	26.2±4.1	0.673
Medical history				
Cardiac	719 (31.1%)	1934 (32.0%)	597 (30.6%)	0.633
Vascular	1153 (51.4%)	3153 (52.1%)	1010 (51.7%)	0.832
Pulmonal	409 (18.3%)	1017 (16.9%)	341 (17.5%)	0.125
Diabetes	446 (20.0%)	1197 (19.8%)	358 (18.3%)	0.159
Neurologic	340 (15.2%)	1011 (16.8%)	325 (16.6%)	0.222
ASA class 3 or 4	584 (18.4%)	1366 (15.7%)	459 (16.9%)	0.001
MDT meeting preoperative	3080 (96.0%)	8464 (97.1%)	2631 (97.1%)	<0.001
Neoadjuvant therapy	2392 (75.3%)	6555 (75.2%)	1964 (72.7%)	0.026
Short-course (5x5 Gy)	1468 (46.2%)	3433 (39.6%)	1169 (43.3%)	
Long-course	107 (3.4%)	261 (3.0%)	46 (1.7%)	
Chemoradiotherapy	816 (25.7%)	2803 (32.4%)	746 (27.7%)	<0.001
cT stage				
cT1	160 (5.0%)	475 (5.4%)	173 (6.4%)	
cT2	965 (30.1%)	2226 (25.5%)	908 (33.5%)	
cT3	2085 (65.0%)	6029 (69.1%)	1630 (60.1%)	<0.001
cN stage				
cN0	1585 (51.9%)	3889 (46.6%)	1180 (44.7%)	
cN1	1043 (34.2%)	2784 (33.3%)	961 (36.4%)	
cN2	426 (13.9%)	1677 (20.1%)	498 (18.9%)	<0.001
cM1	102 (3.8%)	624 (7.2%)	156 (5.8%)	<0.001
Distance to anal verge (cm)	7.5±4.1	7.3±4.2	7.4±4.2	0.079
Operative characteristics				
LAR	1701 (53.1%)	4436 (50.8%)	1399 (51.6%)	
Low Hartmann	604 (18.8%)	1504 (17.2%)	445 (16.4%)	
APR	847 (26.4%)	2453 (28.1%)	753 (27.8%)	
Different	54 (1.7%)	332 (3.8%)	114 (4.2%)	<0.001
Elective resection	3132 (97.6%)	8610 (98.7%)	2674 (98.7%)	<0.001
Laparoscopic	2018 (63.1%)	5171 (59.3%)	8891 (60.8%)	<0.001
Additional resection metastasis	23 (0.7%)	265 (3.1%)	43 (1.7%)	<0.001
Blood transfusion needed	297 (9.6%)	921 (11.0%)	200 (7.7%)	<0.001

BMI: body mass index; ***ASA***: American Society of Anaesthesiologists; ***MDT*** meeting: multidisciplinary tumour board meeting; ***LAR***: low anterior resection; ***low Hartmann***: LAR with end-colostomy; ***APR***: abdominoperineal resection. ***Different*** surgical procedures included local resection procedures and proctocolectomy.

Table 2. Postoperative outcomes of cT1-3 rectal cancer patients

	Low volume (0-19) N=3210 (21.9%)	Medium volume (20-50) N=8730 (59.6%)	High volume (>50) N=2711 (18.5%)	P value
Pathologic tumour stage				
pT0	198 (6.3%)	576 (6.8%)	139 (5.3%)	
pT1	297 (9.5%)	930 (10.9%)	275 (10.5%)	
pT2	1124 (36.0%)	2811 (33.0%)	893 (34.0%)	
pT3	1446 (46.3%)	3989 (46.9%)	1265 (48.2%)	
pT4	61 (2.0%)	206 (2.4%)	53 (2.0%)	0.007
Pathologic lymph node stage				
pN0	2112 (67.4%)	5471 (65.7%)	1706 (66.0%)	
pN1	727 (23.2%)	1931 (23.2%)	601 (23.3%)	
pN2	293 (9.4%)	927 (11.1%)	276 (10.7%)	0.099
R0 resection	3025 (96.6%)	8063 (96.6%)	2463 (97.0%)	
Irradical resection[a]	107 (3.4%)	283 (3.4%)	77 (3.0%)	0.647
Any complication	1079 (33.8%)	3141 (36.6%)	1018 (38.1%)	0.009
Respiratory complication	116 (4.0%)	349 (4.4%)	110 (4.5%)	0.547
Cardiac complication	81 (2.1%)	217 (2.8%)	66 (2.7%)	0.985
Reintervention[b]	308 (11.5%)	886 (12.6%)	315 (14.8%)	0.002
(re)laparotomy	170 (7.0%)	420 (6.6%)	168 (8.6%)	0.001
Anastomotic leakage	78 (5.4%)	300 (8.1%)	96 (8.6%)	0.001
Other intra-abdominal abscess	59 (2.2%)	141 (2.0%)	55 (2.6%)	0.257
Ileus	44 (1.6%)	117 (1.7%)	22 (1.0%)	0.110
30-day or in-hospital mortality	62 (1.9%)	173 (2.0%)	49 (1.8%)	0.107
Length of stay (d)	8 (IR 7)	8 (IR 7)	7 (IR 8)	<0.001

[a] ***Irradical resection*** includes both R1 and R2 resections (microscopically and macroscopically positive resection margins).
[b] ***Reintervention*** includes both radiologic as surgical reintervention.

volume hospitals, $p < 0.001$). Clinical nodal stage 0 was more frequently seen in low volume hospitals, while synchronous metastasis was less common (Table 3).

An abdominoperineal resection was less frequently performed in low volume hospitals, while laparoscopic resection of cT4 rectal cancer was more common in these centres (52.2% vs. 32.7% and 0.2% in medium and high volume hospitals, respectively, $p < 0.001$). Additional extensive resection of suspected tumour involvement of cT4 rectal cancer was performed in 49.4% in high volume hospitals, as compared to 25.4% in medium volume hospitals and 15.5% in low volume hospitals ($p < 0.001$). Additional resection of metastasis was more frequently performed as well in high volume hospitals (17.5% vs. 14.4% and 3.0% in medium and low volume hospitals, respectively, $p < 0.001$). Intra-operative radiotherapy was used more often as well for cT4 patients in high volume hospitals (Table 3).

Table 3. Baseline and operative characteristics of cT4 rectal cancer patients

	Low volume (0-4) N=759 (50.2%)	Medium volume (5-9) N=336 (22.2%)	High volume (>9) N=416 (27.5%)	P value
Age (y)	67.1±11.0	65.2±12.0	63.3±11.1	<0.001
Male gender	376 (49.5%)	179 (53.3%)	231 (55.5%)	0.126
BMI	25.6±4.6	25.1±4.2	25.2±4.5	0.076
Medical history				
Cardiac	117 (22.8%)	51 (22.0%)	62 (23.8%)	0.885
Vascular	272 (52.7%)	112 (47.7%)	130 (49.8%)	0.290
Pulmonal	97 (18.9%)	43 (18.6%)	43 (16.5%)	0.802
Diabetes	117 (22.8%)	49 (21.2%)	57 (21.9%)	0.889
Neurologic	92 (17.9%)	36 (15.6%)	29 (11.1%)	0.048
ASA class 3 or 4	149 (19.8%)	58 (17.3%)	58 (13.9%)	0.042
MDT meeting preoperative	734 (96.7%)	329 (97.9%)	414 (99.5%)	0.033
Neoadjuvant therapy	674 (89.4%)	294 (88.0%)	349 (84.3%)	0.040
Short-course (5x5 Gy)	127 (17.1%)	52 (15.8%)	31 (7.5%)	
Long-course	43 (5.8%)	23 (7.0%)	31 (7.5%)	
Chemoradiotherapy	494 (66.4%)	214 (65.0%)	285 (69.2%)	<0.001
Tumour characteristics				
cN0	202 (28.8%)	46 (14.5%)	73 (18.0%)	
cN1	278 (39.7%)	83 (26.2%)	135 (33.3%)	
cN2	221 (31.5%)	188 (59.3%)	197 (48.6%)	<0.001
cM1	89 (11.8%)	57 (17.4%)	76 (18.4%)	<0.001
Distance to anal verge (cm)	6.1±4.7	5.7±4.6	6.2±4.6	0.268
Surgical procedures				
LAR	223 (29.4%)	68 (20.3%)	118 (28.4%)	
Low Hartmann	176 (23.2%)	66 (19.7%)	48 (11.5%)	
APR	355 (46.8%)	197 (58.8%)	247 (59.4%)	
Different	5 (0.7%)	4 (1.2%)	3 (0.7%)	<0.001
Laparoscopic	396 (52.2%)	109 (32.7%)	1 (0.2%)	<0.001
Intraoperative radiotherapy	0 (0.0%)	4 (1.4%)	56 (24.9%)	<0.001
Additional resection tumour involvement[a]				<0.001
None	523 (71.0%)	195 (58.2%)	138 (34.0%)	
Limited resection	100 (13.6%)	55 (16.4%)	62 (15.7%)	
Extensive resection	114 (15.5%)	85 (25.4%)	195 (49.4%)	<0.001
Additional resection metastasis	23 (3.0%)	48 (14.4%)	73 (17.5%)	<0.001
Blood transfusion needed	111 (14.8%)	87 (26.6%)	212 (51.0%)	<0.001

BMI: body mass index; ***ASA***: American Society of Anaesthesiologists; ***MDT*** meeting: multidisciplinary tumour board meeting; ***LAR***: low anterior resection; ***low Hartmann***: LAR with end-colostomy; ***APR***: abdominoperineal resection. ***Different*** surgical procedures included local resection procedures and proctocolectomy.

[a] Extensive additional resection of tumour involvement included typically total or partial exenterative procedures, while limited additional resection usually included partial resection of adjacent tissue outside of the mesorectal fascia.

Postoperative outcomes

Pathologic tumour stage 4 was more often found in high volume hospitals (32.6% vs. 21.3% and 25.9% in low and medium hospitals, respectively, p < 0.001), while the overall rate of a radical resection did not differ between groups (Table 4). In a sub-analysis of pT4 patients, irradical resections were seen in 33.8% in low volume hospitals, as compared to 22.5% and 20.8% in medium and high volume hospitals (p = 0.031).

A complicated course after resection of cT4 rectal cancer occurred in 50.8% in high volume hospitals, as compared to 44.9% in medium volume hospitals and 21.3% in low

Table 4. Postoperative outcomes of cT4 rectal cancer patients

	Low volume (0-4) N=759 (50.2%)	**Medium volume (5-9) N=336 (22.2%)**	**High volume (>9) N=416 (27.5%)**	P value
Pathologic tumour stage				
pT0	66 (9.0%)	24 (7.4%)	35 (8.6%)	
pT1	29 (4.0%)	8 (2.5%)	10 (2.5%)	
pT2	159 (21.7%)	58 (17.9%)	43 (10.6%)	
pT3	323 (44.1%)	150 (46.3%)	185 (45.7%)	
pT4	156 (21.3%)	84 (25.9%)	132 (32.6%)	<0.001
Pathologic lymph node stage				
pN0	480 (65.3%)	196 (60.3%)	936 (64.0%)	
pN1	160 (21.8%)	77 (23.7%)	99 (24.6%)	
pN2	95 (12.9%)	52 (16.0%)	44 (10.9%)	0.243
pM1	94 (13.3%)	57 (18.2%)	76 (19.6%)	0.014
Overall R0 resection	659 (89.1%)	292 (89.3%)	365 (88.4%)	
Overall irradical resection[a]	81 (10.9%)	35 (10.7%)	48 (11.6%)	0.912
pT4 R0 resection	100 (66.2%)	62 (77.5%)	103 (79.2%)	
pT4 irradical resection	51 (33.8%)	18 (22.5%)	27 (20.8%)	0.031
Any complication	294 (38.9%)	151 (44.9%)	211 (50.8%)	0.002
Respiratory complication	42 (6.0%)	10 (3.4%)	32 (8.5%)	0.026
Cardiac complication	12 (1.7%)	10 (3.4%)	15 (4.0%)	0.068
Reintervention[b]	88 (14.1%)	26 (10.5%)	41 (13.4%)	0.364
(re)laparotomy	39 (7.1%)	15 (7.1%)	22 (9.0%)	0.492
Anastomotic leakage	12 (6.6%)	1 (1.9%)	3 (3.2%)	0.258
Other intra-abdominal abscess	31 (5.0%)	7 (2.8%)	14 (4.6%)	0.378
Ileus	10 (1.6%)	4 (1.6%)	1 (0.3%)	0.230
30-day or in-hospital mortality	12 (1.6%)	2 (0.6%)	9 (2.2%)	0.214
Length of stay (d)	8 (IR 8)	9 (IR 8)	10 (IR 8)	<0.001

[a] ***Irradical resection*** includes both R1 and R2 resections (microscopically and macroscopically positive resection margins).

[b] ***Reintervention*** includes both radiologic as surgical reintervention.

volume hospitals (p = 0.002). The 30-day mortality rate was 1.6% in low volume hospitals, 0.6% in medium volume hospitals and 2.2% in high volume hospitals (p = 0.214), and reintervention did not differ significantly between groups as well.

In multivariate analysis, ASA class 3 or 4, extensive resection of tumour involvement, and abdominoperineal resection were associated with increased risks of complications, while female gender was associated with lower risk of complications. Hospital volume did not significantly affect the risk of complications (Table 5).

Table 5. Predictors of a complicated course after resection of cT4 rectal cancer in multivariate analysis

Variable	Odds ratio	95%CI	P value
Female gender	0.60	0.46-0.79	<0.001
Cardiac co-morbidity	1.31	0.95-1.82	0.105
ASA class 3 or 4	1.47	1.07-2.02	0.019
pT4	1.36	0.98-1.88	0.070
Laparoscopic approach	0.92	0.67-1.27	0.598
APR[a]	1.40	1.07-1.84	0.015
Extensive resection of tumour involvement	1.60	1.14-2.26	0.007
Additional resection metastasis	1.31	0.82-2.08	0.253
Hospital volume[b]			
Low volume (0-19)	1.00	-	-
Medium volume (20-50)	1.09	0.77-1.54	0.618
High volume (>51)	1.30	0.89-1.90	0.169

ASA: American Society of Anaesthesiologists.
[a] ***APR***: abdominoperineal resection; low anterior resection or low Hartmann procedure was used as reference category.
[b] Low hospital volume was used as reference category.

DISCUSSION

In this 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. With regards to cT4 rectal cancer, high volume hospitals performed more extensive surgical treatment of primary tumour and metastases, with similar perioperative outcomes. In case of pT4 rectal cancer, low volume was associated with increased rates of irradical resection.

Approximately 90% of rectal cancer resections in the Netherlands were performed for cT1-3 tumours, which usually can be treated by standard TME procedures or even local excision in selected cases.(7) Risks of complications, anastomotic leakage, and reintervention were slightly decreased in lower volume hospitals after surgery for cT1-3 rectal cancer, while

the rate of irradical resection and 30-day mortality were similar for the different volume groups. Therefore, it appears that further centralizing the care by increasing the minimal numbers to treat per centre may not be needed for patients without locally advanced disease in case of proper protocols, MDT meetings and regional networks.

In patients with tumour invasion through the mesorectal fascia (cT4), more radical procedures than standard TME surgery is needed in order to achieve R0-resections. These surgical procedures beyond the TME planes are less straightforward and more technically demanding compared to cT1-3 rectal cancer.(8) In addition, the advanced stages of rectal cancer have the greatest benefit of a multimodality treatment, including neoadjuvant chemoradiotherapy, to facilitate complete resections and reduce local recurrence rates.(5, 6) Accurate staging of the rectal tumour by a dedicated MDT is essential to select those patients who should be treated with neoadjuvant therapy, and to assess what kind of surgical approach is needed.

We observed that in high cT4 volume hospitals, patients were more often discussed preoperatively in a MDT meeting and rates of neoadjuvant chemoradiotherapy were higher. It remains unclear why preoperative chemoradiotherapy was less frequently adopted for cT4 rectal cancer in low and medium volume hospitals, possibly this was related to inadequate preoperative staging. Generally, in order to facilitate adequate preoperative staging and optimal neoadjuvant treatment, all rectal cancer patients should be discussed preoperatively in a MDT meeting. Patients in medium or high cT4 volume hospitals underwent more abdominoperineal resections, and additional resection of tumour involvement outside of the mesorectal fascia was more often needed, as compared to low volume hospitals. Intraoperative radiotherapy and resection of metastasis were performed more frequently as well. High volume hospitals performed less laparoscopic cT4 resections, which may suggest more advanced tumour stages in these hospitals. 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 (34%). To our knowledge, this is the first study evaluating pathologic outcomes stratified for hospital volume and tumour stage. Gietelink and collagues(14) did show that a low overall hospital volume defined as < 20 rectal cancer resections per year, was associated with a higher risk of CRM involvement, but they did not perform sub-analysis for different tumour stages.(14)

The extensive surgical treatment offered for cT4 rectal cancer in high volume hospitals was associated with increased rates of overall postoperative complications. However, after adjusting for confounding factors in multivariable analysis, including the type of surgery (APR) and extensive additional resection, hospital volume did not significantly affect the

complication rate anymore. Postoperative mortality rates were similar for low, medium and high volume hospitals as well. These findings may suggest that for true cT4 rectal cancer, high volume hospitals may offer a better multimodality treatment, eventually resulting in lower positive resection margins.

Obviously, data regarding overall and local recurrence-free survival, stratified for hospital volume, is needed in order to assess if centralized care for locally advanced rectal cancer translates in a better long-term outcome. Unfortunately, the DSCA registry only contains data regarding perioperative outcomes. Regarding long-term outcomes of colorectal cancer, there appears to be a volume-outcome relationship as suggested in a Cochrane review; however, this was not stratified for tumour stage.(15) Most individual studies suggest similar overall survival rates at 5 years after cT1-4 rectal cancer surgery for low, medium and high volume hospitals.(10, 16-18) Hodgson and colleagues(19) did demonstrate higher survival 2 years after surgery in high volume hospitals (84%) as compared to low volume hospitals (77%), however, their study did not differentiate either between cT1-3 and cT4 rectal cancer. In addition, patients were operated between 1994 and 1997 and neoadjuvant treatment has improved considerably since then.(19)

Since positive circumferential resection margins are associated with increased local recurrence rates and poorer survival in the literature, long-term outcomes of (true) cT4 patients operated in low volume hospitals may be inferior as compared to medium or high cT4 volume hospitals.(3, 4) Future research should investigate whether higher hospital volume does indeed lead to improved survival, in order to confirm if centralized care for locally advanced rectal cancer is warranted.

Large population-based cohort studies, such as the present data from the DSCA, provide proper insights regarding the influence of hospital volume on perioperative outcomes of rectal cancer. However, limitations of the present study design should be taken into account, such as incompleteness of data. The hospital volume was based on the number of cases enrolled, which could theoretically differ from the actual hospital volume. Furthermore, we did not have details regarding exact additional resections performed for tumour involvement. Although registration bias cannot be excluded fully since data are self-reported, recent validation of the DSCA against the Dutch National Cancer Registry showed high accuracy and completeness of the data.(12) In addition, patient of more advanced stages of rectal cancer may have caused some bias in the present evaluation. Finally, long-term outcomes were not available for this evaluation, which are essential for determining whether centralized care is needed for cT1-3 and cT4 rectal cancer.

In conclusion, 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. With regards to cT4 rectal cancer, high volume hospitals performed more extensive surgical treatment with similar perioperative results. In case of pT4 rectal cancer, low hospital volume was associated with increased rates of irradical resection. For true cT4 rectal cancer, high volume hospitals may offer better multimodality treatment; however, long-term oncologic outcomes of rectal cancer surgery stratified for hospital volume and tumour stage are needed.

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Chapter 5

Treatment of inguinal lymph node metastases in patients with rectal adenocarcinoma

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ABSTRACT

Background

Inguinal lymph node metastases (ILNM) from rectal adenocarcinoma are rare and staged as systemic disease. The aim of this study is to provide insight into the treatment and prognosis of ILNM from rectal adenocarcinoma.

Methods

All patients with a diagnosis of synchronous or metachronous ILNM from rectal adenocarcinoma between January 2005 and March 2017 were retrospectively reviewed.

Results

The study identified 27 patients with ILNM (15 with synchronous and 12 with metachronous disease). After discussion by a multidisciplinary tumour board, 19 patients were treated with curative intent, 17 of whom underwent inguinal lymph node dissection. Of the 17 patients, 12 had locally advanced rectal cancer (LARC) with isolated ILNM, 3 had LARC and metastases elsewhere and 2 had locally recurrent rectal cancer (LRRC). The median overall survival (OS) for all the patients treated with curative intent was 27 months [95% confidence interval (CI) 11.6 - 42.4], with a 5-year OS rate of 34%. The median OS for the patients with LARC and isolated ILNM (n = 12) was 74 months [95% CI 18.0 - 130.0], with a 5-year OS rate of 52%. All the patients with metastases elsewhere (n = 3) or LRRC (n = 2) experienced recurrent systemic disease. Eight patients were treated with palliative intent. The median OS for this group was 13 months [95% CI 1.9 - 24.1] with a 3-year OS rate of 0%.

Conclusions

Clinicians should not consider ILNM as an incurable systemic disease. Patients with primary rectal cancer and solitary ILNM who are eligible for curative surgical treatment had a 5-year survival rate of 52%. The prognosis for patients with additional systemic metastases or LRRC is worse and the benefit of surgery is unclear.

INTRODUCTION

Locally advanced rectal cancer is associated with pelvic lymph node metastases inside and sometimes outside the mesorectum. Besides these locoregional lymph node metastases, inguinal lymph node metastases (ILNM) may occur, particularly in lower rectal cancer, due to the lymphatic drainage by inguinal lymph nodes.(1) These ILNMs are relatively rare and the number of patients described in the literature is low.(2-7) The American Joint Committee on Cancer (AJCC) Cancer Staging Manual considers ILNM from rectal cancer as a systemic disease.(8) Whether ILNM should be treated with palliative or curative intent is unclear.(9-11) 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.(12) The evidence in literature whether patients with ILNM from rectal adenocarcinoma can possibly be cured is scarce and few studies described treatment for ILNM of rectal cancer.(2,4-6) At our hospital, ILNM has been treated by inguinal lymph node dissection (ILND), with and without neoadjuvant chemotherapy, in case there were no other metastases, or when limited metastases were present elsewhere. This report presents the results for patients treated with both curative and palliative intent for ILNM from rectal cancer.

METHODS

All consecutive patients with ILNM from rectal adenocarcinoma treated at the Erasmus MC Cancer Institute, a tertiary referral centre in the Netherlands, between January 2005 and March 2017, were retrospectively identified by a search in the local pathology and rectal cancer database. All patients with synchronous or metachronous ILNM were included. Patients with deep/iliac groin nodes were not included.

Patient characteristics, collected from medical records, included tumour characteristics, treatment, surgical variables, short- and long-term outcomes and postoperative mortality and morbidity. All the patients were followed up in our institution, and the last update of follow-up was 24 April 2018. Approval for this study was granted by the local medical ethics committee (Registration No. MEC-2017-448).

Synchronous ILNMs were defined as all ILNMs diagnosed before surgery for the primary rectal tumour. Metachronous ILNMs were defined as all ILNMs diagnosed after surgery. All the patients with suspicious ILNMs during physical examination or on imaging [computed tomography (CT) of the abdomen or magnetic resonance imaging (MRI) of the pelvis] underwent lymph node biopsy. All the patients were screened for disseminated disease

by CT of the thorax and abdomen. All the patients were discussed by a multidisciplinary tumour board before treatment and were assessed for eligibility to receive treatment with curative or palliative intent.

Neoadjuvant (chemo)radiotherapy usually comprised a cumulative dose of 50 Gy for primary rectal cancer and a cumulative dose of 30 Gy for LRRC in fractions of 1.8 - 2 Gy, both with concomitant oral chemotherapy (Capecitabine 825 - 1000 mg/m2 for 5-7 days a week). The target volume (95% of the radiation dose) mainly was the rectum, but inguinal nodes often received a substantial percentage (~ 30-50%) of the radiation dose. Neoadjuvant induction chemotherapy for ILNM was incidentally given.

For the patients with synchronous ILNM who underwent surgical treatment, an inguinal lymph node dissection (ILND) was performed either simultaneously with surgery for the rectal tumour or upfront before the start of neoadjuvant treatment for the rectal tumour. In case of metachronous metastases, an ILND was performed, in some cases simultaneously with surgical removal of a local recurrence. Notably, only superficial groin dissections were performed.

Statistical analysis

Data are reported as median [interquartile range (IQR) or 95% confidence interval] or mean ± standard deviation as appropriate. Categorical data were reported as count (%). The Kaplan-Meier method was used for survival analysis and a log rank test was performed for comparison. The median follow up was calculated with the reversed Kaplan-Meier method. Overall survival was calculated from the day ILNM was diagnosed until death or the date of last follow up visit. Statistical analysis was performed using IBM SPSS Statistics version 24.0.0 for Windows (IBM Corp, Armonk, New York, USA).

RESULTS

A flowchart of study patients is shown in Figure 1. Patient and primary tumour characteristics are listed in Table 1. The characteristics of ILNM and follow up evaluation are shown in Table 2. The study identified 27 patients with ILNM from rectal adenocarcinoma. The majority of the ILNMs were from low rectal cancer (82%). The median age at diagnosis of ILNM was 63 years (IQR 44 – 69 years). The median interval between diagnosis of the primary tumour and diagnosis of ILNM was 6 months (IQR 1 – 30 months). All the patients were discussed by a multidisciplinary tumour board, after which 19 patients were treated with curative intent and 8 patients with palliative intent.

Curative intent

For 10 of the 19 patients treated with curative intent, neoadjuvant chemotherapy for ILNM was administered, and all the patients received (chemo) radiotherapy for the rectal tumour. For two patients, the target volume included the ILNM. In all the remaining patients, the inguinal nodes received a lower percentage (30-50%) of the total radiation dose. Two patients with primary rectal cancer had progression of disease during neoadjuvant chemotherapy and were then treated palliatively, as depicted in Figure 1. Subsequently, ILND was performed for 17 patients, of these 17 patients, 12 had primary locally advanced rectal cancer and solitary ILNM, 3 patients had metastases elsewhere (liver, n = 2; peritoneal, n = 1) and 2 patients had locally recurrent rectal cancer.

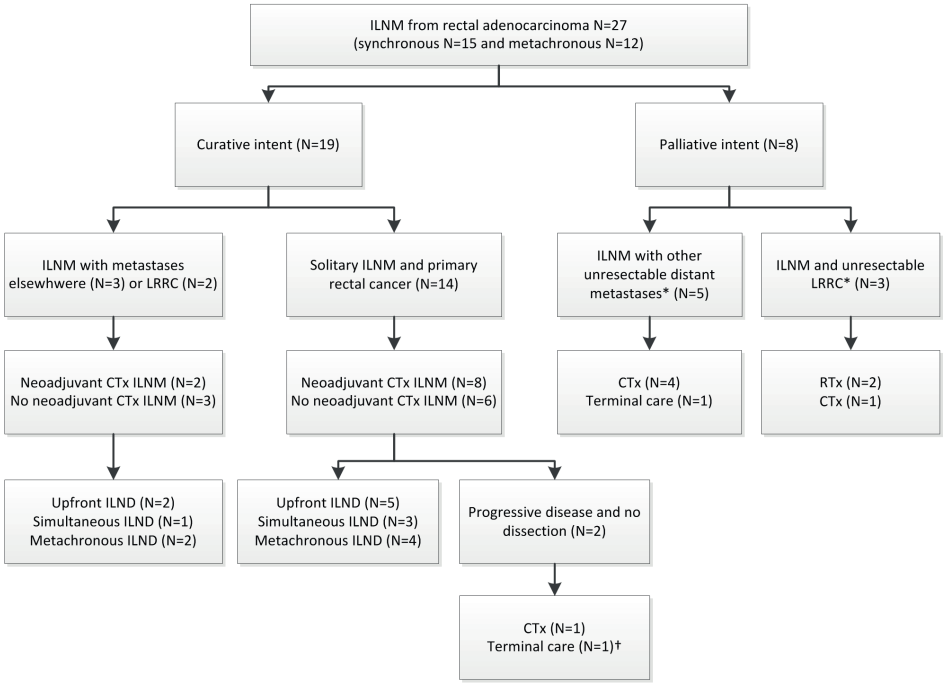

Figure 1. Flowchart included patients
*ILNM = Inguinal lymph node metastases; ILND = Inguinal lymph node dissection; LRRC = Locally recurrent rectal cancer; CTx = Chemotherapy; RTx = Radiotherapy; Upfront = upfront dissection before resection of rectal tumour; Simultaneous = simultaneous resection with rectal tumour; Metachronous = resection during follow up rectal tumour; * Reason palliative treatment; †Died of respiratory failure before treatment*

Palliative intent

Eight patients were treated with palliative intent for disseminated disease or unresectable LRRC using either chemotherapy, radiotherapy or terminal care, as displayed in Figure 1. Five of these patients had received neoadjuvant radiotherapy for the rectal tumour, and

the ILNMs were outside the target volume but still received a lower percentage (30-50%) of the total radiation dose. Two patients had received palliative radiotherapy with ILNM receiving the target volume, with a dose of 32 and 45 Gy, respectively.

Table 1. Patient and primary tumour characteristics

		Total	**Curative intent**	**Palliative intent**
		N = 27 N (%)	**N=19 N (%)**	**N=8 N (%)**
Gender	Male	12 (44%)	7 (73%)	3 (38%)
	Female	15 (56%)	12 (63%)	5 (63%)
Age at diagnosis ILNM	Median (IQR)	63 (44-69)	60 (40-69)	64 (57-67)
ASA	ASA I-II	25 (93%)	18 (95%)	7 (78%)
	ASA > II	2 (7%)	1 (5%)	1 (13%)
Rectal tumour at diagnosis ILNM	Primary	21 (78%)	17 (90%)	4 (50%)
	LRRC	6 (22%)	2 (11%)	4 (50%)
Distance from anal verge (cm)	Median (IQR)	2 (1-3)	1 (0-7)	2 (1-3)
Location of rectal tumour	Low rectal (<5 cm)	22 (82%)	14 (74%)	8 (100%)
	Mid rectal (5-10 cm)	3 (11%)	3 (16%)	0 (0%)
	High rectal (>10 cm)	2 (7%)	2 (11%)	0 (0%)
Neoadjuvant therapy rectal tumour	CTxRTx	18 (67%)	14 (74%)	4 (50%)
	RTx	4 (15%)	3 (11%)	1 (13%)
	CTx	0 (0.0%)	0 (0%)	0 (0%)
	No neoadjuvant therapy	5 (19%)	2 (11%)	3 (38%)
Surgical procedure primary tumour	No resection†	2 (5%)	2 (11%)	0 (0%)
	LAR	7 (26%)	4 (21%)	3 (38%)
	APR	9 (33%)	5 (26%)	4 (50%)
	APR with HIPEC	1 (4%)	1 (5%)	0 (0%)
	Posterior pelvic exenteration	4 (15%)	3 (16%)	1 (13%)
	Total pelvic exenteration	4 (15%)	4 (21%)	0 (0%)
Tumour stage primary tumour	No resection	2 (8%)	2 (11%)	0 (0%)
	T2	3 (11%)	2 (11%)	1 (13%)
	T3	11 (41%)	7 (37%)	4 (50%)
	T4	11 (41%)	8 (42%)	3 (38%)

Table 1. Patient and primary tumour characteristics (continued)

		Total	Curative intent	Palliative intent
		N = 27 N (%)	N=19 N (%)	N=8 N (%)
Nodal stage primary tumour	No resection	2 (7%)	2 (11%)	0 (0%)
	N0	10 (37%)	5 (26%)	5 (63%)
	N1	8 (30%)	6 (32%)	2 (25%)
	N2	7 (26%)	6 (32%)	1 (13%)

ILNM = Inguinal lymph node metastases; LRRC = Locally recurrent rectal cancer; CTxRTx = Chemoradiotherapy; CTx = Chemotherapy; RTx = Radiotherapy; LAR = Low anterior resection; APR = Abdominoperineal resection; HIPEC = Hyperthermic intraperitoneal chemotherapy; † No resection due to progressive disease
Numbers do not add up due to rounding

MORTALITY AND MORBIDITY

Curative intent

None of the patients died within 30 days of surgery, and 6 (35%) of the 17 patients experienced postoperative complications. Four patients experienced inguinal seroma despite the standard use of postoperative suction drainage, which required percutaneous drainage in all cases. Two patients used antibiotics to treat superficial wound infections. Two patients experienced lymphedema during follow-up period and required elastic compression garments. Of all patients with inguinal complications, one patient had received neoadjuvant radiotherapy specifically on the inguinal nodes, in all the remaining patients inguinal nodes were outside the target area but still partly inside the radiotherapy field.

Palliative intent

Half of the patients who received palliative treatment had ILNM-related morbidity. Four patients experienced severe pain requiring intravenous pain medication and three of these patients also had lymphedema. One patient experienced lymphedema without complaints. Four patients with lymphedema had received radiotherapy for the rectal tumour, with inguinal nodes partly in the radiation field. Two of these patients also had received a high-dose palliative radiotherapy specifically on the inguinal nodes, but already had experienced lymphedema before palliative radiotherapy.

Table 2. Inguinal lymph node metastases and histopathological characteristics and follow up

		Total	Curative intent	Palliative intent
		N=27 N (%)	N=19 N (%)	N=8 N (%)
Time from Dx rectal cancer until ILNM	Months median (IQR)	6 (1-30)	4 (0-4)	24 (4-56)
Onset ILNM	Synchronous	15 (56%)	13 (68%)	2 (25%)
	Metachronous	12 (44%)	6 (32%)	6 (75%)
Location ILNM	Unilateral	19 (70%)	14 (74%)	5 (63%)
	Bilateral	8 (30%)	5 (26%)	3 (38%)
Solitary ILNM	No	8 (30%)	3 (16%)	5 (63%)
	Yes	19 (70%)	16 (84%)	3 (38%)
Distant metastases elsewhere	Liver	1 (4%)	1 (5%)	0 (%)
	Lung	1 (4%)	0 (%)	1 (13%)
	Peritoneal	2 (7%)	1 (5%)	1 (13%)
	Iliac lymph nodes and para aortic	1 (4%)	0 (%)	1 (13%)
	Lung and spinal bone	1 (4%)	0 (%)	0 (%)
	Liver and iliac lymph nodes	2 (7%)	1 (5%)	1 (13%)
	Lung and iliac lymph nodes	2 (7%)	0 (%)	1 (13%)
Neoadjuvant CTx ILNM	No	17 (63%)	9 (47%)	N/A
	Yes	10 (27%)	10 (53%)	N/A
ILND	No dissection	10 (37%)	2 (11%)	8 (100%)
	Upfront	7 (26%)	7 (37%)	0 (0%)
	Simultaneous with rectal tumour	4 (15%)	4 (21%)	0 (0%)
	Metachronous during FU rectal cancer	6 (22%)	6 (37%)	0 (0%)
Histopathology Inguinal lymph nodes specimen [¥]				
Positive lymph nodes	No	N/A	4 (24%)	N/A
	Yes	N/A	13 (76%)	N/A
Total number of harvested nodes	Median (range)	N/A	12 (3 -16)	N/A
Total number of positive nodes	Median (range)	N/A	1 (0 – 11)	N/A
Follow up after surgical treatment				
Disease status at last follow up	No evidence of disease	N/A	5 (29%)	N/A
	Distant metastases	N/A	7 (41%)	N/A
	Local recurrence rectal cancer and distant metastases	N/A	7 (41%)	N/A
	Inguinal lymph node recurrence[±]	N/A	2 (12%)	N/A

Dx = diagnosis; ILNM = Inguinal lymph node metastases; ILND = Inguinal lymph node dissection; CTx = Chemotherapy; FU = follow up; [†] No resection due to progressive disease; [¥] 17 patients and 22 dissection specimens, due to five bilateral ILN; [±] Nodal recurrence in dissected site. Numbers do not add up due to rounding.

HISTOPATHOLOGICAL RESULTS AFTER ILND

Histopathologic evaluation was performed for 22 dissection specimens from 17 patients. The median number of lymph nodes found was 12 (range 3 – 26) and the median number of positive lymph nodes was 1 (range 0 – 11). In four patients treated with curative intent, no positive lymph nodes were found. Three of these four patients had received neoadjuvant chemotherapy and were considered complete responders. In one patient without neoadjuvant therapy, three negative nodes were recovered, but four tumour deposits in the specimen were found, and this patient experienced local and distant recurrence during the follow-up period. In the remaining 13 patients, positive lymph nodes were found. Of these 13 patients, 5 had received neoadjuvant chemotherapy for ILNM.

FOLLOW UP, RECURRENCE AND SURVIVAL

The median follow up period for survivors in the total cohort of 27 patients was 79 months (95% CI 46.9 - 111.1) during which 20 patients died. The median overall survival for the total cohort was 19 months (95% CI 5.8 - 32.2). There was no significant difference in survival between synchronous or metachronous ILNM ($p = 0.86$) and bilateral or unilateral ILNM ($p = 0.05$).

Curative intent

Of 19 patients treated with curative intent, 2 had progressive disease under neoadjuvant therapy and experienced distant metastases, whereas the primary rectal tumour and the ILNM remained in situ. At last follow-up visit, 5 of the 17 patients who underwent ILND had no evidence of disease. Of these 17 patients, 2 experienced a local ILNM recurrence, accompanied by local recurrence of the rectal tumour and systemic metastases. Another five patients experienced local recurrence of the rectal tumour with distant metastases, and five patients experienced distant metastases only.

At last follow-up visit, seven patients were alive, and all these patients had undergone ILND. Three patients were alive with local rectal tumour recurrence and distant metastases, including one patient with ILNM recurrence. Four patients were alive with no evidence of disease, and one patient had died with no evidence of disease.

Survival curves are shown in Figure 2. The median overall survival for all 19 patients treated with curative intent after diagnosis was 27 months (95% CI 11.6 - 42.4). The 1- and 5-year estimated overall survival rates were 79% and 34% respectively.

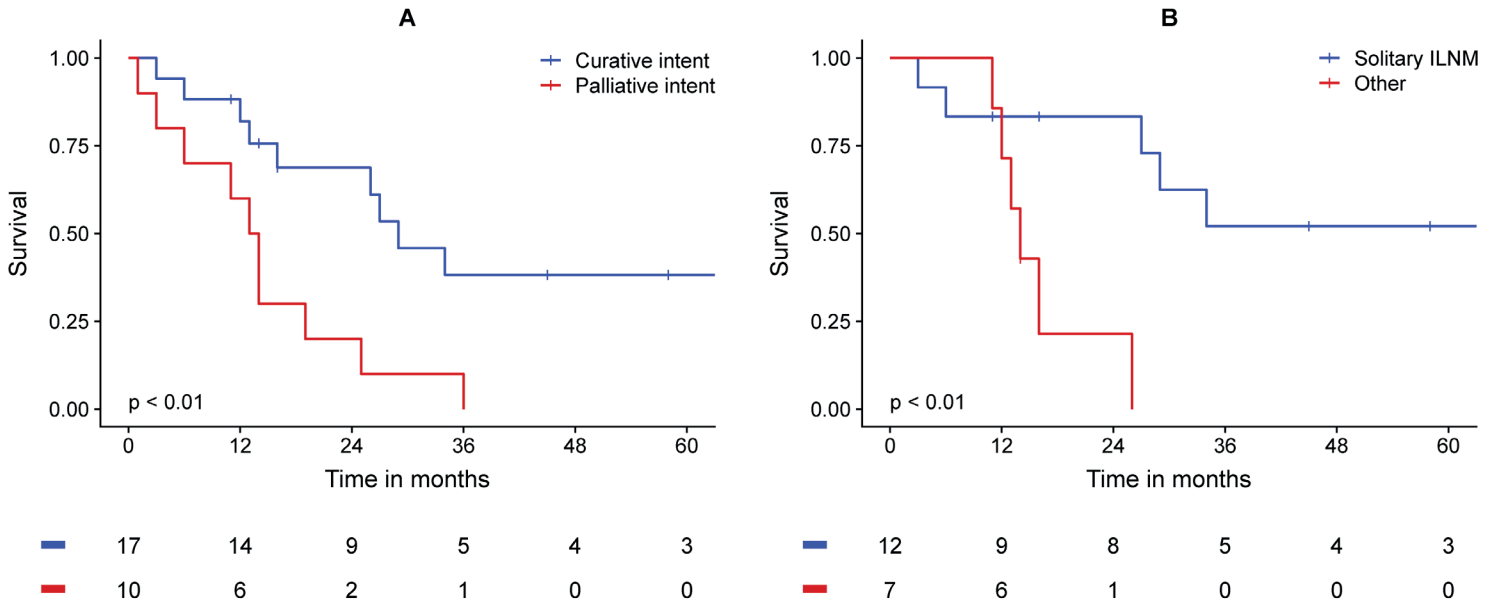

Figure 2. Overall survival

A. Curative intent versus palliative intent

B. Patients with curative intent: Solitary ILNM with primary LARC vs Other (ILNM with other metastases N = 3 or LRRC N = 2 or progressive disease under chemotherapy N = 2) For 12 patients with solitary ILNM from primary rectal cancer without systemic metastases who underwent curative ILND, the median overall survival period was 74 months (95% CI 18.0;130.0) with 1- and 5-year estimated overall survival rates of 83% and 52%, respectively.

Three patients underwent ILND with resection of the primary rectal tumour and resection of metastases elsewhere (liver, n = 2 and peritoneal, n = 1). Two of these patients died of systemic disease at 13 and 26 months of follow-up evaluation and one patient, who underwent ILND and surgery for primary rectal cancer with liver metastases only, at this writing is still alive after 14 months of follow-up evaluation with locally recurrent rectal cancer and recurrent liver metastases. The two patients that underwent ILND with simultaneous resection of locally recurrent rectal cancer died of systemic disease with respectively 12 and 13 months of follow-up evaluation.

Palliative treatment intent

At last follow-up visit, all eight patients treated with palliative intent had died of the disease. The median overall survival was 13 months (95% CI 1.9 - 24.1), with 1- and 3-year estimated overall survival rates of 63% and 0% respectively.

DISCUSSION

In this study, a 5-year survival rate of 52% was achieved 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. Patients treated with curative surgery mostly experienced lymphedema and palliatively treated patients mostly had severe pain.

In 1990 Graham et al.(7) was one of the first to describe management of ILNM. Their study identified 40 patients with ILNM from rectal cancer divided into three groups: (1) unresectable primary tumours, (2) recurrent disease after abdominoperineal resection with palliative treatment, and (3) solitary ILNM treated with ILND. None of the patients survived 5 years, but the median survival was highest in the solitary ILNM group (inguinal metastases only), with two patients having no evidence of disease at the last follow-up visit (one patient died of myocardial infarction, and one patient was alive with 15 months of follow-up evaluation). These authors concluded that only in case of solitary ILNM, the situation for eight patients in their study, a resection may be warranted. Tocchi et al. (4) reported a mean, not median, survival of 14.8 months in 21 patients with ILNM from rectal cancer, and none of the patients reached 5-year survival. Their study included five patients with ILNM only and supported the suggestion that ILND can be beneficial, although not curative, because a prolonged survival was achieved for these patients. They concluded that ILNM is frequently associated with distant metastases (in 16 of 21 patients of their series), and in these cases, systemic therapy is the treatment of choice. Luna-Pérez et al.(6) described a 5-year survival of 0% for 32 patients with ILNM from rectal adenocarcinoma,

27 of whom also had systemic metastases. They concluded that surgery for isolated ILNM may prolong survival, but that ILNM should be considered as systemic disease and treated palliatively as indicated.

More recent studies by Bardia et al.(2) and Adachi et al.(5) retrospectively reviewed small groups of patients with ILNM and concluded that patients with isolated ILNM are a different subset of patients. Bardia et al.(2) studied six patients with solitary ILNM and the mean survival for these patients was 40 months. Adachi et al.(5) studied 10 patients with ILNM, 8 of whom had solitary ILNM and underwent ILND. They reported a 5-year overall survival rate of 75% in these patients. Adachi et al.(5) also reported a better prognosis for patients with metachronous metastases, but our study did not find any difference in survival for metachronous compared to synchronous metastases. This may be explained by the definitions Adachi et al.(5) used for synchronous (up to 1 year after diagnosis of the primary rectal cancer) and metachronous metastases (> 1 year after diagnosis of the primary rectal cancer) or by the small number of patients in both studies.

The current study presents the largest group of patients with ILNM caused by rectal cancer who were treated with curative intent since the study by Luna-Pérez et al.(6) in 1999. However, the majority of the patients in the latter study had distant metastases as well and may not be considered candidates for curative treatment. The results of previous studies presenting smaller groups of patients are confirmed: ILNM caused by rectal cancer should not necessarily be considered an incurable disease, especially in case of primary rectal cancer and the absence of other systemic metastases. In this study a median OS of 74 months with 1- and 5-year estimated overall survival rates of 83% and 52%, respectively, was reached for this group.

In line with all other previously published studies, our study showed a poor prognosis for the patients with ILNM and distant metastases to other sites.(2,4-7) These results suggest that these patients should be treated with palliative intent. The current study included three patients who underwent resection of ILNM combined with resection of additional metastases. Only one patient, who underwent ILND and liver metastases resection, at this writing is still alive at 14 months follow-up evaluation, with systemic recurrence. In addition, both patients with locally recurrent rectal cancer who underwent resection of the rectal tumour with ILND died within 13 months. Due to small numbers, no conclusions can be drawn, and it is unclear whether surgery was at all beneficial for these patients. Currently, in the Netherlands, the ORCHESTRA trial is being performed to assess the beneficial effects of added local treatment with systemic treatment in case of systemic disease and possibly will provide evidence in the future.(13)

The mortality and morbidity associated with ILND have been described for ILNM caused by melanoma and anal cancer, but few described morbidity after ILND for rectal cancer. (14-16) The mortality is low, but the morbidity associated with this procedure is high. Short-term wound complications such as dehiscence, infection, and seroma are reported to reach 60%, and lymphedema can occur. (14-16) In our study, 6 (35%) of 17 patients experienced postoperative complications. All the patients with inguinal complications had received (partial) prior irradiation on inguinal nodes. The numbers were small in the current study, but the negative impact of radiation therapy is well known. Radiation therapy impairs wound healing and can increase the incidence of lymphedema.(17) Recent series indicate that routine inguinal lymph node radiation is not necessary.(17,18) The optimal balance between inguinal radiotherapy and the extent of surgery is unclear, but the morbidity of the combined procedure should not be underestimated.

In the current study only ILND (i.e., superficial groin dissections) were performed and no deep groin dissection. In 12 of the 17 patients who underwent ILND, distant metastases occurred outside the pelvic region, including four patient with simultaneous iliac node recurrence. This could imply that a formal deep groin dissection in all these patients for a superficial ILNM would have been overtreatment with considerable morbidity.

Our study was limited by its small numbers, referral bias from other centres and its retrospective nature. Inguinal lymph node metastases from rectal adenocarcinoma are relatively rare, and most previous studies contain small and heterogeneous groups of patients, collected before the era of total mesorectal excision (TME) surgery and before neoadjuvant therapy was widely accepted. Although the current study presents a small cohort, it provides proof that solitary ILNM from rectal adenocarcinoma does not equal incurable disease. This is supported by previous reports.

Conclusions

Surgical treatment of ILNM from rectal adenocarcinoma may result in prolonged survival and possibly in cure. Inguinal lymph node metastases should not be considered as an incurable disease, especially in patients with primary rectal cancer and solitary ILNM. The prognosis for patients with ILNM and distant metastases elsewhere or recurrent rectal cancer is worse, and the value of surgery is unclear.

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Chapter 6

Feasibility of a subcutaneous gluteal turnover flap without donor site scar for perineal closure after abdominoperineal resection for rectal cancer

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ABSTRACT

Purpose

Abdominoperineal resection (APR) carries a high risk of perineal wound morbidity. Perineal wound closure using autologous tissue flaps has been shown to be advantageous, but there is no consensus as to the optimal method. The aim of this study was to evaluate the feasibility of a novel gluteal turnover flap (GT-flap) without donor site scar for perineal closure after APR.

Methods

Ten patients who underwent APR for primary or recurrent rectal cancer were included in a prospective non-randomised pilot study in two academic centres. Perineal reconstruction consisted of a unilateral subcutaneous GT-flap, followed by midline closure. Feasibility was defined as uncomplicated perineal wound healing at 30 days in at least five patients, and a maximum of two flap failures.

Results

Out of 17 potentially eligible patients, 10 patients underwent APR with GT-flap assisted perineal wound closure. Seven patients had pre-operative radiotherapy. Median added theatre time was 38 minutes (range 35-44). Two patients developed perineal dehiscence, likely because of too large width of the skin island. Two other patients developed purulent discharge and excessive haemoserous discharge, respectively, resulting in four complicated wounds at 30 days. No flap failure occurred, and no radiological or surgical re-interventions were performed. Median length of hospital stay was 10 days.

Conclusions

The GT-flap for routine perineal wound closure after APR seems feasible with limited additional theatre time, but success seems to depend on correct planning of the width of the flap. The potential for reducing perineal morbidity should be evaluated in a randomised controlled trial.

INTRODUCTION

To date, abdominoperineal resection (APR) for low rectal cancer still carries a significant risk of perineal wound problems (1). 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 postoperatively (2), but incidence of perineal complications have even been reported to occur in up to 66% after APR and primary closure (3). In addition, patients may experience persisting perineal pain, or develop a chronic perineal sinus or perineal hernia (4-6).

The high risk of perineal morbidity after APR is related to the creation of a large pelvic dead space with bacterial contamination, making the surgical-site susceptible for infection. Furthermore, use of pre-operative radiotherapy significantly impairs the healing capacity of this dead space – secondary to the decreased angiogenesis. To prevent these wound problems, immediate soft tissue reconstruction has been advocated (7). The rationale is that by obliterating the surgical dead space with well-vascularised tissues, the risk of wound breakdown and infection is reduced. Another reason is related to the concept that autologous tissue may add strength to the (partially) excised pelvic floor muscles, which may potentially reduce the risk of perineal hernia formation. There is however 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 (8-11). However, there are potential disadvantages to these techniques. These include the need for a plastic surgeon, a substantially increased theatre time and the potential for donor site and recipient site complications, while often sacrificing the benefits of laparoscopy (12-17). Moreover, as a large percentage of patients will not develop healing difficulties, immediate reconstruction with large muscle flaps might be an unnecessary risk and expense. An optimal harm-benefit ratio of reconstructive techniques is especially important in relatively low-risk patients undergoing non-extensive resections without pre-operative radiotherapy. There is an urgent need for a simple and minimally-invasive technique for routine perineal wound closure after APR. We propose a novel unilateral subcutaneous gluteal turnover flap (GT-flap) without additional scarring or donor site morbidity.

The aim of this pilot study was to determine the feasibility of this procedure in patients who underwent APR for primary or recurrent rectal cancer.

METHODS

Design and patients

A prospective longitudinal multicentre interventional cohort study was performed in 10 consecutive patients at two academic medical centres. All patients scheduled for extralevatory APR were pre-operatively informed on the study at the outpatient clinics. Written informed consent was obtained for all participants. Inclusion criteria were adult patients (age ≥ 18 years) and planned for APR for primary or recurrent rectal cancer. Exclusion criteria were need for total pelvic exenteration, sacral resection above S4/S5, severe concomitant diseases affecting wound healing (i.e. renal failure requiring dialysis, liver cirrhosis, peripheral vascular disease with Fontaine grade 3 or higher), or enrolment in other trials expected to influence perineal wound healing.

On day seven and day 30 after surgery, the perineal wound was evaluated by residents or surgeons using the Southampton wound score (supplementary table 1). Postoperative pain was assessed using the visual analogue scale (VAS) which ranged from 0 (no pain) to 10 (worst pain). In addition, photographs were taken, and all appointed wound scores were centrally reviewed by the trial coordinators (RDB and PJT). Patient demographics, neo-adjuvant treatment, tumour characteristics and surgical details were intra-operatively collected. Postoperatively, type and extent of any wound event or any other adverse event, and all medical, radiological and surgical interventions were recorded to the last day of follow-up. The study protocol has been approved by the Institutional Review Board of the Amsterdam UMC, University of Amsterdam, and the Erasmus MC (NL58380.018.16).

Surgical procedure

APR started with skin incision close to the anus with subsequent dissection along the external sphincter, in order to preserve as much perineal skin and subcutaneous fat as possible without compromising oncologically safety.

Perineal reconstruction is then performed using a unilateral, semilunar, de-epithelialized, subcutaneous GT-flap (figure 1). Creation of the GT-flap starts with drawing of a semi-circular incision adjacent to the surgical defect of approximately two-and-a-half centimetre in width. Success of the flap is contingent upon obtaining tension-free closure at the midline. For this reason, the flap can only be a few centimetres in width. Pre-operative mapping of the perforators is not deemed necessary due to the broad base of the turnover flap and its robust blood supply. Furthermore, due to the design of the flap, there is no need to elevate the flap on a single perforator. The flap is de-epithelialized followed by incision through the skin and slightly lateral dissection towards the gluteus muscle. It is important to perform the de-epithelialisation before dissecting the flap, as this makes it

easier. The flap is then hinged into the defect, and the dermis is anchored to the contra-lateral remnants of the levator muscles. Next, a vacuum drain is positioned on top of the flap and the subcutaneous fat and perineal skin are closed in a layered fashion in the midline over the flap.

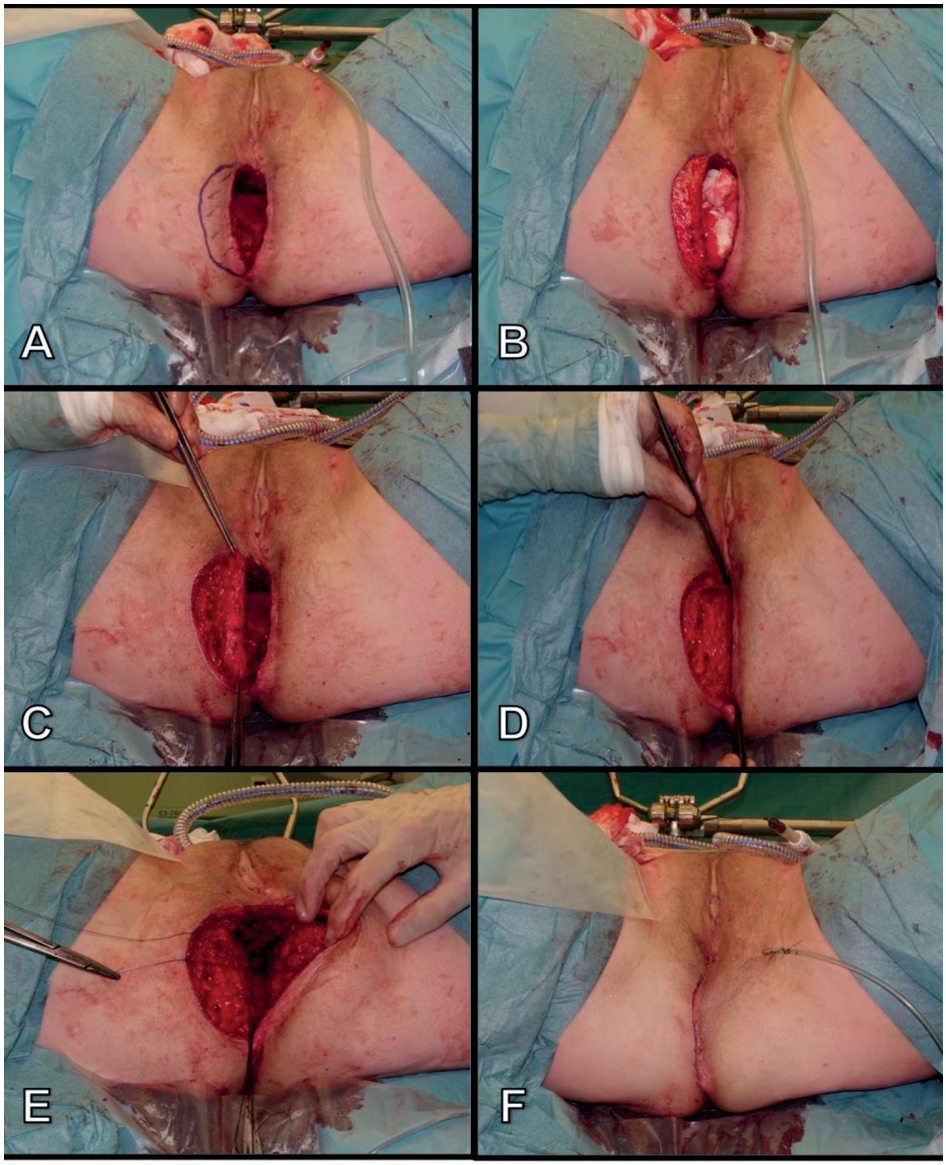

Fig. 1 Reconstruction of an abdominoperineal defect using a gluteal turnover flap. a) marking of the flap, b) de-epithelialisation of the dermis, c) flap after having transected onto the gluteal fascia, d) rotation of the flap e) fixation of flap to the contra-lateral remnants of pelvic floor muscles, f) midline scar following layered closure of the ischio-rectal and perineal tissues over the flap.

Patients were allowed to mobilise on the first postoperative day, but were instructed not to sit directly on the perineal wound the first few days. The drain was removed after at least 3 days according to the surgeons' judgement.

Feasibility criteria and secondary outcome measures

The procedure was deemed feasible if 1) no more than five patients had a complicated wound healing at 30 days postoperatively, 2) including no more than two flap failures. Complicated wound healing was defined as a Southampton wound score equal or greater than II (supplementary table 1). We hypothesised that, since the flap is covered and not visually accessible for evaluation of flap perfusion, flap failure would eventually result in wound breakdown. Therefore, flap failure was defined as a Southampton wound score of V.

Secondary endpoints were median length of the procedure, hospital stay duration, number of specific complications, and number of re-interventions and re-admissions.

Statistical analysis

Categorical data were expressed as absolute numbers with corresponding proportions, and continuous data according to distribution as means with standard deviation (SD) or medians with interquartile range (IQR). The treatment effect was determined based on a per-protocol analysis. All analyses were performed with IBM SPSS statistics, version 24.0.0 (IBM Corp., Armonk, NY, United States).

RESULTS

Among 17 eligible patients, 11 were willing to participate and signed informed consent. Patient characteristics are demonstrated in table 1. Mean age was 64 years, and seven were male. Indications for APR were primary rectal cancer (n=8), recurrent rectal cancer (n=2), and one patient that had a clinical diagnosis of rectal cancer, but appeared to have recurrent prostate cancer on postoperative pathological examination. Pre-operative radiotherapy was given in eight patients.

Surgical details are shown in table 2. In one patient, it was considered unfeasible to obtain tension-free midline closure using a GT-flap due to the large size of the perineal skin defect after resection. A GT-flap with midline perineal closure could be performed in the remaining 10 patients. Median total theatre time was 305 minutes (IQR 249-370 minutes), and median time taken for flap harvesting and insertion into the neo-pelvic floor was 38 minutes (IQR 35-44 minutes).

Table 1. Patient characteristics

Patient	*Age (yr)*	*Sex*	*BMI[b] (Kg/m²)*	*ASA[c]*	*Smoking*	*Diabetes*	*Prior pelvic surgery*	*Indication*	*Distance ARJ[e] (Cm)*	*Threatened MRF[g]*	*Neo-adjuvant therapy*
1	59	F	28.4	II	Never	Yes	Hysterectomy	Primary rectal cancer	1	Yes	Radio-chemotherapy
2	67	F	23.1	II	Never	No	None	Primary rectal cancer	3	Yes	Radio-chemotherapy
3	79	M	28.7	II	Never	No	None	Recurrent prostate cancer	NA[f]	NA[f]	None
4	48	M	31.8	II	Never	No	Transanal TME[d]	Recurrent rectal cancer	0	NA[f]	None
5	68	M	27.8	III	Never	No	None	Primary rectal cancer	4	Yes	Radio-chemotherapy
6[a]	71	M	27.93	III	Stopped > 10 yr	No	Prostatectomy	Primary rectal cancer	0	Yes	Radio-chemotherapy
7	68	F	33.9	II	Never	No	None	Primary rectal cancer	0	Yes	Radio-chemotherapy
8	66	M	26.5	I	Stopped < 10 yr	No	None	Primary rectal cancer	1	No	None
9	44	M	32.7	II	Stopped < 10 yr	No	None	Primary rectal cancer	Missing	Yes	Radio-chemotherapy
10	73	F	30.0	III	Stopped > 10 yr	Yes	Hysterectomy	Primary rectal cancer	Missing	Yes	Radio-chemotherapy
11	68	M	27.2	I	Stopped < 10 yr	No	Laparoscopic TME[d]	Recurrent rectal cancer	9	NA[f]	Radio-chemotherapy

[a] *Patient was excluded intra-operatively*
[b] *Body mass index*
[c] *American Society of Anaesthesiologists classification*
[d] *Total mesorectal excision*
[e] *Anorectal junction*
[f] *Not applicable*
[g] *Mesorectal fascia*

Table 2. Surgical details and intra-operative outcome

Patient	*Type of APR*[a]	*Position*	*Abdominal approach*	*Perineal approach*	*Adjacent organ resection*	*Intraop RTX*[d]
1	Extralevator	Lithotomy	Open	Open	None	No
2	Extralevator	Lithotomy	Open	Open	None	No
3	Extralevator	Lithotomy	Open	Open	None	No
4	Extralevator	Lithotomy	Laparoscopic	Open	None	No
5	Extralevator	Lithotomy	Open	Open	None	No
6	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
7	Extralevator	Lithotomy	Open	Open	None	No
8	Extralevator	Prone	Laparoscopic	Open	None	No
9	Extralevator	Lithotomy	Laparoscopic	TAMIS[c]	None	No
10	Extralevator	Lithotomy	Laparoscopic	TAMIS[c]	Posterior vaginectomy	No
11	Extralevator	Lithotomy	Open	Open	Left pelvic sidewall	Yes

[a]*Abdominoperineal resection*
[b]*Not applicable*
[c]*Transperineal minimally invasive surgery using GelPOINT path and Airsea*
[d]*Intra-operative radiotherapy*
[e]*Time in minutes*

Surgical outcome

Median follow-up duration was 33 days (IQR 27-35 days). Postoperative outcome is displayed in table 3. Median length of hospital stay was 10 days (IQR 8-12 days). In total, four patients had a complicated perineal wound healing at 30 days (Southampton wound score ≥ II). Two patients developed a superficial dehiscence of a few centimetres in depth, of whom one had concomitant pus discharge. The underlying GT-flaps were unaffected (figure 2). Retrospective evaluation of these two patients revealed that the design of the flap was too wide, resulting in tension on the perineal wound after midline closure. Both patients needed no further treatment besides irrigation with saline. One patient developed perineal infection with a small pus pocket necessitating manual drainage and antibiotic therapy for seven days. The last patient with a complicated wound healing at 30 days developed perineal pain secondary to a non-infected perineal seroma, which required manual drainage at the outpatient clinic. There were no cases of flap necrosis. With a total of four complicated perineal wounds at 30 days and no flap failures, predefined feasibility criteria were met.

Two more patients had perineal seroma, but both resolved within 30 days and without further treatment. In the remaining four patients, the perineal wound healed uneventful. Perineal pain at seven days was reported for seven patients with a median VAS score of 0. Perineal pain at thirty days was reported for six patients with a median VAS score of 1. During follow-up, there were no re-admissions, and no radiological or surgical re-interventions.

Omentoplasty	*Abdominal drain*	*Type of surgeon*	*Buttock*	*Perineal drain*	*Skin closure*	*Reconstruction time*[e]	*Total theatre time*[e]
Yes	Yes	Plastic	Left	Yes	Transcutaneous	42	207
Yes	Yes	Plastic	Left	Yes	Transcutaneous	55	510
Yes	Yes	General	Left	Yes	Transcutaneous	45	302
No	Yes	Plastic	Left	Yes	Intracutaneous	35	151
Yes	Yes	Plastic	Right	Yes	Transcutaneous	38	305
NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
Yes	Yes	General	Left	Yes	Transcutaneous	36	327
No	Yes	Plastic	Right	Yes	Intracutaneous	Missing	Missing
No	Yes	Plastic	Left	Yes	Intracutaneous	35	310
No	No	General	Left	Yes	Intracutaneous	31	291
Yes	Yes	Plastic	Right	No	Transcutaneous	40	412

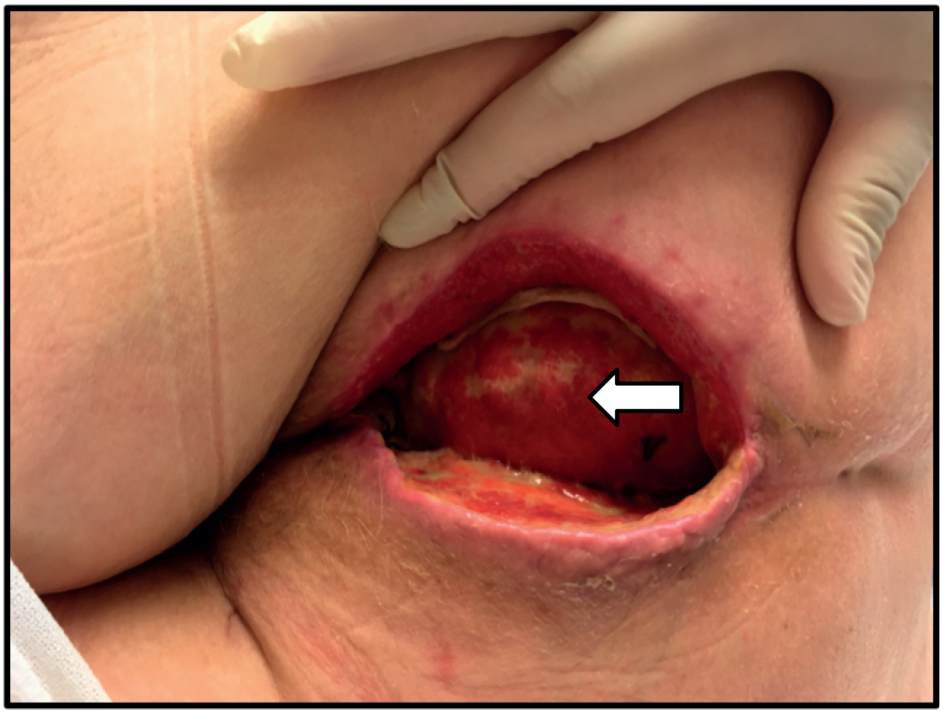

Fig. 2 Perineal wound dehiscence of 2,5 centimetre in depth with mild inflammation following abdominoperineal resection with insertion of gluteal turnover flap. The underlying sub cutis of the flap is still viable (white arrow), and ensures that there is no atmospheric connection to the intra-abdominal cavity.

Table 3. Short-term outcome after abdominoperineal resection and gluteal turnover flap

Patient	*Histopathology*	*Hospital stay (days)*	*7-day wound score*[c]	*30-day wound score*[c]	*VAS*[d] *7 days*	*VAS*[d] *30 days*	*Perineal complications*	*Perineal re-interventions*	*Other complications*	*Other interventions*	*Follow-up (days)*
1	pT0N0Mx	8	0	0	0	0	None	None	UTI[f], urinary retention	AB[e] for UTI[f]	35
2	pT0N0Mx	10	I	IV	2	1	Infection	Manual drainage and AB[e]	None	None	29
3	pT4N2Mx[a]	11	0	III	0	4	Dehiscence, Seroma	Manual drainage	None	None	36
4	pT3N0Mx	9	I	I	0	0	Seroma	Perineal irrigation	Ileus	TPN[g]	41
5	pT3N0Mx	10	0	0	0	1	None	None	Ileus, urinary retention, abscess right buttock	I&D[h] abscess	32
6	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]	NA[b]
7	pT3N0M1	13	IV	II	Missing	Missing	Dehiscence, Infection	None	UTI[e]	AB[d] for UTI[f]	34
8	pT2N2M1	6	0	0	2	Missing	None	None	Urinary retention	Tamsulosine	20
9	pT0N0Mx	6	II	III	3	Missing	Seroma	Manual drainage	None	None	19
10	pT3N1Mx	20	III	0	Missing	Missing	Seroma	None	Ileus, pneumonia, delirium	TPN[g], AB[e] for pneumonia, haldol	33
11	pT0N0Mx	8	0	0	Missing	3	None	None	Urinary retention	None	31

[a] *Recurrent prostate cancer*
[b] *Not applicable*
[c] *According to the Southampton Wound Scoring System*
[d] *Visual analogue pain rating scale measured in rest*
[e] *Antibiotic therapy*
[f] *Urinary tract infection*
[g] *Total parenteral nutrition*
[h] *Incision and drainage*

Additional postoperative complications included ileus (n=3), unrelated abscess on buttock (n=1), urinary retention (n=4), urinary tract infection (n=2), pneumonia (n=1), and delirium (n=1).

DISCUSSION

This pilot study aimed to determine the feasibility of the GT-flap in routine perineal reconstruction after APR. 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, thereby fulfilling our predefined feasibility criteria. Retrospective analysis of two cases of wound dehiscence revealed the critical part of the procedure, namely planning the appropriate width of the skin island that still allows for tension-free closure in the midline.

The GT-flap displays a favourable profile, compared to existing literature on flap-repair (7, 9). The flap seems to exhibit no partial necrosis or total flap loss as can be observed after muscle flaps, although the sample size is still small (18). The procedure can be combined with laparoscopy, contrary to conventional VRAM flaps for example. In addition, median additive theatre time was only 38 minutes, which included a learning curve and time needed for photographing the procedure. This is likely to decline in the future with increasing experience. Another benefit is the ease of flap harvesting, not necessarily requiring a plastic surgeon. Nonetheless, the procedure should preferably be performed by a surgeon already familiar with harvesting perforator flaps, or after initially being proctored by a plastic surgeon. Injury to the perforators can have serious consequences. If the flap is raised too large, this will lead to undue tension of the perineal skin, which can result in a major dehiscence. However, these basic principles of the technique are quite simple and easy to learn.

Another advantage of the GT-flap over other options is the symmetrical midline scarring, thereby preserving the gluteal cleft and restoring normal perineal aesthetics (figure 3). This is a major advantage compared to the VRAM or conventional gluteal flaps (e.g. V-Y transposition, SGAP, IGAP), which leave both large and visible scarring. Furthermore, no dissection of muscle is performed. Patients are allowed to mobilise directly. The GT-flap seems to avoid problems with balance, sitting or walking secondary to muscle weakness or pain that is often seen after gluteal muscle transpositions. Considering these benefits, the GT-flap may be very attractive for routine perineal wound closure after APR.

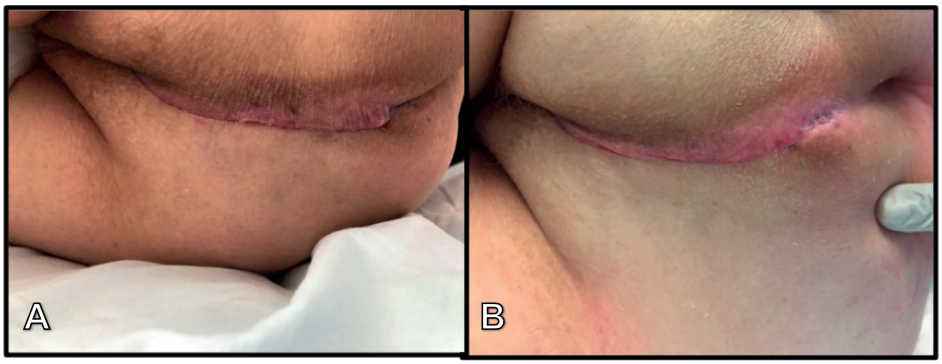

Fig. 3 Healed perineal wound with symmetrical midline scarring a) on day 7, and b) day 30 after abdomino-perineal resection and gluteal turnover flap for rectal cancer.

The GT-flap is only a valuable option if the perineal skin and subcutaneous fat can be maximally preserved from an oncological point of view. Therefore, distal rectal cancer without involvement of the perineal skin and subcutaneous fat requiring APR with a certain extent of resection of the levator muscles seems to be the optimal indication. If additional perineal skin has to be excised, for example in case of advanced anal cancer or radiation-induced skin fibrosis, there is a need for flap assisted closure that adds a skin island, such as the VRAM flap.

Due to the design of this pilot study of small sample size and with relatively short follow-up, it was not possible to assess the impact of the GT-flap on the risk of long-term perineal complications. A recent publication by Chasapi et al. reported on a similar reconstructive procedure in 14 patients undergoing APR for anorectal cancer (19). The type of flap used differed from the presently described technique by the fact that the flap was detached from the gluteal fascia with one remaining perforator for blood supply. They showed favourable outcome with only one patient suffering from superficial skin dehiscence, and one developing a perineal hernia 7 months after surgery. These findings support our feeling 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 next step is conducting a randomised controlled trial to determine the effectiveness of this intervention in reducing perineal morbidity after APR, both short-term and long-term.

Conclusions

The GT-flap is a technically feasible and safe method for perineal wound closure after APR in patients with primary or recurrent rectal cancer 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. Further research is warranted to assess

the potential for reducing perineal wound morbidity and to evaluate long-term quality of life.

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Chapter 7

A systematic review and meta-analysis on omentoplasty for the management of abdominoperineal defects in patients treated for cancer

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ABSTRACT

Objective

The objective of this systematic review and meta-analysis was to examine the effects of omentoplasty on pelviperineal morbidity following abdominoperineal resection (APR) in patients with cancer.

Background

Recent studies have questioned the use of omentoplasty for the prevention of perineal wound complications.

Methods

A systematic review of published literature since 2000 on the use of omentoplasty during APR for cancer was undertaken. Authors were requested to share their source patient data. Meta-analyses were conducted using a random-effects model.

Results

Fourteen studies comprising 1894 patients (n=839 omentoplasty) were included. The majority had APR for rectal cancer (87%). Omentoplasty was not significantly associated with the risk of pre-sacral abscess formation in the overall population (RR 1.11; 95% CI 0.79-1.56), nor in planned subgroup analysis (n=758) of APR with primary perineal closure for non-locally advanced rectal cancer (RR 1.06; 95% CI 0.68-1.64). No overall differences were found for complicated perineal wound healing within 30 days (RR 1.30; 95% CI 0.92-1.82), chronic perineal sinus (RR 1.08; 95% CI 0.53-2.20) and pelviperineal complication necessitating reoperation (RR 1.06; 95% CI 0.80-1.42) as well. An increased risk of developing a perineal hernia was found for patients submitted to omentoplasty (RR 1.85; 95% CI 1.26-2.72). Complications related to the omentoplasty were reported in 4.6% (95% CI 2.5-8.6%).

Conclusions

This meta-analysis revealed no beneficial effect of omentoplasty on pre-sacral abscess formation and perineal wound healing after APR, while it increases the likelihood of developing a perineal hernia. These findings do not support the routine use of omentoplasty in APR for cancer.

INTRODUCTION

The pelvic wound bed after abdominoperineal resection (APR) carries a high risk of morbidity.(1-3) 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%.(4) 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 a chronic perineal sinus.(5) Furthermore, patients may develop perineal pain and sitting problems, as well as a perineal hernia.(6, 7)

To improve perineal wound healing after APR, various reconstructive methods have been proposed. These include the use of a biological mesh and several tissue flaps, such as a pedicled omentoplasty (OP) or a vertical rectus abdominis muscle flap (VRAM).(8-10) The flaps serve to obliterate the often non-collapsible defect with healthy and well perfused tissue, which has been associated with reduced abscess formation and improved wound healing.(11, 12)

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.(13-16) 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 particularly seemed to increase the risk of perineal herniation.(6) These results challenge the value of OP for closure of the pelvic defect after APR. Therefore, the aim of this systematic review and meta-analysis was to assess the effects of OP following APR on pelviperineal morbidity and related problems in patients treated for cancer in the published literature since 2000.

METHODS

The study protocol was prospectively registered at PROSPERO (registration number: CRD42017073573) and followed Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidance.(17)

Search

The literature was systematically reviewed by searching in the PubMed-library for studies published between January 2000 and March 2017. The search was limited to publication

since 2000 to limit the influence of historical changes in surgical and peri-operative care, which better ties in to current practices. The search was rerun in June 2018 (Supplementary Digital Content 1). The search strategy only included terms relating to or describing neoplasms, surgical outcome and APR. Since most studies do not explicitly mention the use of OP in the title or abstract, this was not included as a search term. Additional articles were manually selected from the reference lists of the retrieved papers.

Eligibility

Original studies including patients undergoing APR for cancer and reporting on use of OP and perineal wound outcome were potentially eligible. Articles were restricted to the English language. Exclusion criteria were studies with no original data, individual case reports (<10 patients with OP), studies that did not report on at least one predefined outcome of interest, and studies that exclusively pertained to pelvic exenteration or benign disease.

Outcome parameters

The primary endpoint was incidence of pre-sacral abscess formation, as this was expected to be most consistently reported. Secondary endpoints were the rate of overall pelviperineal wound complications within 30 days, one year, and the total study period, wound healing time, specific pelviperineal morbidity (i.e. wound dehiscence, superficial wound infection, haemorrhage, perineal sinus), ileus (overall, and proportion requiring reoperation), perineal hernia (not specified), OP-related morbidity, operative time, and surgical perineal re-intervention. Pelviperineal complication included any pelvic or perineal wound event (including perineal hernia), and surgical perineal re-intervention any pelvic or perineal wound-related reoperation (including hernia repair). Perineal infection was categorized into superficial wound infection (including perineal abscess), and deep wound infection (i.e. pre-sacral abscess). Perineal haemorrhage included active perineal bleeding or hematoma (regardless of need for re-intervention). There was no definition given for pre-sacral abscess, perineal sinus and perineal hernia. Perineal hernia was based on the reporting of the source studies, and could vary from asymptomatic incidental CT finding to symptomatic perineal bulge requiring surgical repair.

Data collection and extraction

Two independent reviewers (RDB & CELK) scanned all abstracts identified by the search and cross-referencing. Full texts were retrieved for all studies that potentially met the inclusion criteria. Two reviewers (RDB & JAWH) further independently reviewed the eligibility of these studies in full text. Any disagreement on the eligibility of particular studies was resolved through consensus discussion with a third reviewer (PJT). Papers not meeting the inclusion criteria were excluded and listed with reason for omission (Figure 1). All authors

were contacted on three separate occasions to share either the source individual patient data or aggregate data, reported separately for OP and non-OP.

Data extraction included general study information, participant demographics, operative details, perineal wound outcome, length of follow-up, and information for assessment of the risk of bias. Any disagreement was solved by consensus discussion, if necessary with a third reviewer (PJT). In case of missing data, the study authors were contacted to request additional information.

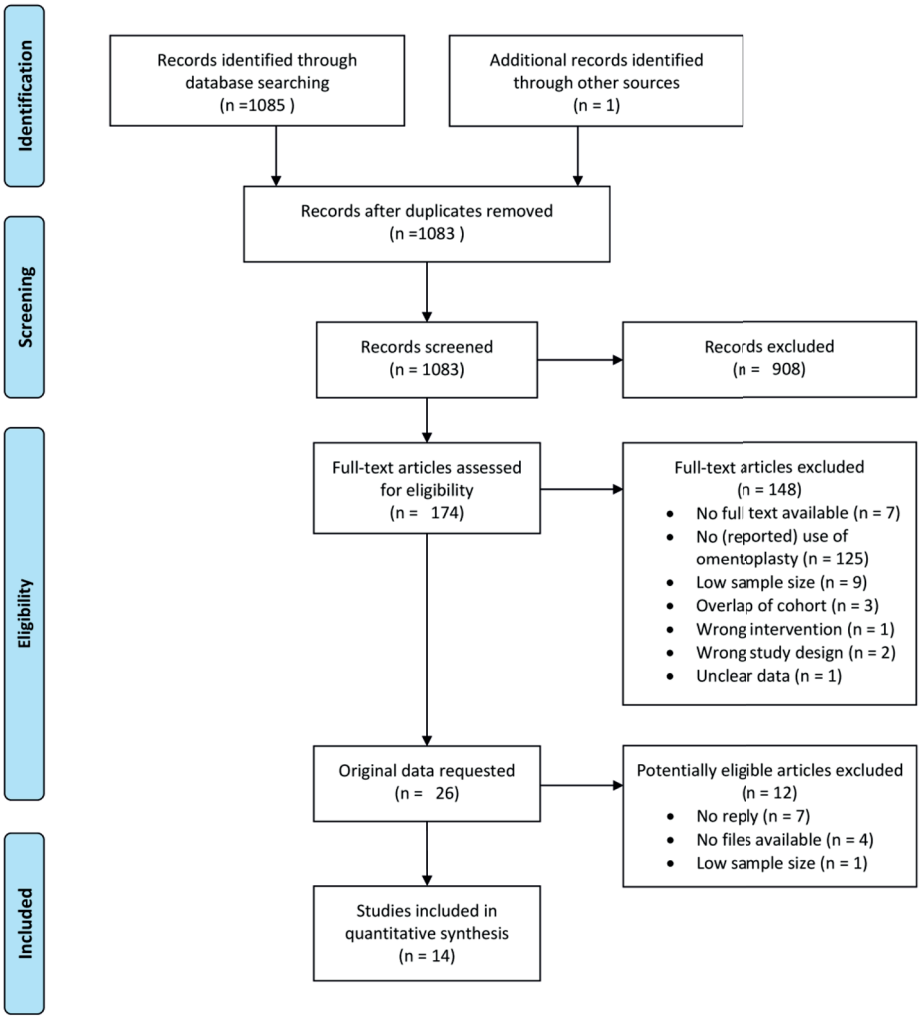

Figure 1. PRISMA flow diagram depicting the search strategy and study selection process.

The received source patient data was preferably used, and may slightly differ from the original publication. If this was not available, data from the original publication was used. The cohort of Musters et al. was updated using original patient files.(5) From the initial 104 patients of the BIOPEX study, 99 were entered in the analyses because of missing outcome data due to study exclusions.(4)

Assessment of risk of bias in included studies

Two reviewers (RDB & JAWH) independently assessed the risk of bias in the included studies using the Newcastle-Ottawa Scale (NOS) for non-randomized studies.(18, 19)

Data synthesis

All outcome measures were quantitatively summarized. If at least three comparative studies (≥10 cases in both groups) provided data on a study parameter, data were pooled in meta-analysis using Review Manager (RevMan 5; Cochrane Collaboration). Studies without a control (<10 cases of non-OP) were pooled in proportional meta-analysis using RStudio (version 3.5.1). Pooled estimates of effect were calculated along with corresponding 95% confidence interval (CI), using a random-effects model. The method as proposed by Wan et al. was used to approximate the estimation of the sample mean and standard deviation in case the median and interquartile range was given.(20) Dichotomous data were summarized by risk ratios (RR), and continuous data were presented as mean differences (MD). Heterogeneity between studies was perceived considerable when $I^2 \geq 75\%$.(21) Two-sided p-values <0.05 were considered statistically significant. Funnel plots were generated to assess for publication bias. The evidence along with the quality of the data were summarized in a GRADE summary of findings table.

Analysis of subgroups

In order to decrease potential bias introduced by diverse indication and surgical methods, a planned subgroup analysis was performed for patients that underwent APR with primary perineal closure for non-locally advanced rectal cancer. The additional exclusion criteria for the purpose of this subgroup analysis were reconstructions using a mesh and/or flap, other pelvic malignancies, pT4 stage, and adjacent organ resection. We also performed a planned subgroup analysis only in patients who received pre-operative radiotherapy.

RESULTS

Literature search and selection

The results of the literature search are displayed in Figure 1. After deduplication, the combined search yielded 1081 articles, of which 26 were identified as potentially eligible.

After contacting the authors, individual patient data were provided in six(4-6, 22-24) and aggregate data in four.(25-28) An additional of four studies with full text of the original paper only were included.(9, 10, 29, 30) Eleven studies without separate data for OP(31-41), and one study that eventually appeared to have included only one patient with OP(42) were excluded.

Study characteristics

General study descriptions are demonstrated in Table 1. Eleven studies had a control group (i.e. ≥10 cases of non-OP).(2, 4, 6, 9, 10, 22-24, 26, 28, 30) The quality of the included studies was moderate to good (range 5-9; Supplementary Table 2; Supplemental Digital Content 2). The 14 included studies covered a total of 1894 patients, of whom 839 underwent OP.

Table 1. Study descriptions of the included studies.

Study (Author)	Year	Country	Design	Quality*	Disease	Patients (N=1894)	OP (N=839)	Non-OP (N=1055)
De Broux *et al.*	2005	France	Retrospective cohort study	5	Rectal cancer	92	92	0
Lefevre *et al.*	2009	France	Retrospective cohort study	7	Anal cancer	95	52	43
Hultman *et al.*	2010	USA	Retrospective cohort study	5	Rectal cancer and anal cancer	70	29	41
Kirzin *et al.*	2010	France	Retrospective cohort study	6	Rectal cancer	109	19	90
Oida *et al.*	2012	Japan	Retrospective cohort study	8	Rectal cancer	45	20	25
Dumont *et al.*	2012	France	Retrospective cohort study	6	Rectal cancer, anal cancer and other	132	101	31
Hawkins *et al.*	2014	USA	Retrospective cohort study	8	Rectal cancer	251	109	142
Musters *et al.*	2014	Netherlands	Retrospective cohort study	9	Rectal cancer	128	50	78
Hardt *et al.*	2016	Germany	Retrospective cohort study	6	Anal cancer	17	16	1
Hellinga *et al.*	2016	Netherlands	Retrospective cohort study	5	Rectal cancer, anal cancer and other	24	20	4
Jones *et al.*	2017	United Kingdom	Prospective cohort study	6	Rectal cancer and anal cancer	266	42	224

Table 1. Study descriptions of the included studies. (continued)

Study (Author)	Year	Country	Design	Quality*	Disease	Patients	OP	Non-OP
						(N=1894)	(N=839)	(N=1055)
Musters *et al.*	2017	Netherlands	Prospective cohort study[a]	9	Rectal cancer	99	61	38
Blok *et al.*	2018	Netherlands	Retrospective cross-sectional cohort study	9	Rectal cancer	477	172	305
Baloch *et al.*	2018	Sweden	Retrospective cohort study	8	Rectal cancer, anal cancer and other	89	56	33

** Newcastle-Ottawa Quality Assesment Scale; OP: Omentoplasty a: randomized controlled trial of biomesh versus primary perineal closure, in which omentoplasty was at the discretion of the operating surgeon*

Pooled baseline characteristics of the two groups are demonstrated in Table 2. The indication for APR was predominantly rectal cancer (87.2%). The number of patients receiving neo-adjuvant radiotherapy was 82.5% in the OP group and 74.4% in the non-OP group. Similar proportions of adjacent organ resection were performed (21.4 % versus 18.2%) with slightly less additional reconstructive procedures in the OP group (17.8 % versus 27.5%). Median operative time was median 19 minutes longer for APR with OP, but not significantly different from the non-OP group. Median follow-up duration of the included studies ranged from 12-62 months (overall weighted mean 36.6 months). Supplementary Table 3 (Supplemental Digital Content 3) shows the baseline characteristics and operative details for each of the included studies.

Study endpoints

Supplementary Table 4 (Supplemental Digital Content 4) shows the outcomes for each of the included studies. The main findings of the study are summarized in Table 3. Visual inspection of the funnel plots for the main outcomes of interest did not suggest presence of significant publication bias (Supplementary Figure 1; Supplemental Digital Content 5).

Pre-sacral abscess

Twelve studies recorded the incidence of pre-sacral abscess formation.(4-6, 10, 22-29) The overall weighted mean proportion of pre-sacral abscess formation following OP was 8.7% (95% CI 6.1-12.3%). Considering nine comparative studies(4-6, 10, 22-24, 26, 28), pre-sacral abscesses similarly occurred after OP and non-OP (RR 1.11; 95% CI 0.79-1.56; $I^2 = 0\%$) (Figure 2.A). The risk of pre-sacral abscess was also similar in the predefined subgroup of APR with primary perineal closure for non-locally advanced rectal cancer (RR 1.06; 95% CI 0.68-1.64; $I^2 = 0\%$)(Figure 2.B).(4-6, 23, 24) Similarly, there was no reduced risk of developing

Table 2. Pooled baseline characteristics of study population with (OP) and without omentoplasty (Non-OP)

		All patients (N= 1894)		Non-locally advanced rectal cancer and primary perineal closure (N= 758)*	
		OP (N=839)	Non-OP (N=1055)	OP (N= 281)	Non-OP (N= 477)
Age	Years (Median [IQR])	64.3 [61.9 - 66.6]	64.0 [61.7 - 66.2]	64.9 [62.5 - 67.3]	66.2 [64.2 - 68.1]
Gender	Male	438 (52%)	659 (62%)	204 (73%)	321 (67%)
	Female	280 (33%)	355 (34%)	77 (27%)	156 (33%)
	NR	121 (14%)	178 (17%)	0 (0%)	0 (0%)
Disease	Rectal cancer	693 (83%)	959 (91%)	281 (100%)	477 (100%)
	Anal cancer	99 (12%)	52 (5%)	0 (0%)	0 (0%)
	Other malignant disease	18 (2%)	3 (0%)	0 (0%)	0 (0%)
	NR	29 (3%)	66 (6%)	0 (0%)	0 (0%)
Neoadjuvant therapy	None	104 (12%)	174 (16%)	18 (6%)	50 (10%)
	Short course RTx (25Gy)	93 (11%)	114 (11%)	86 (31%)	168 (35%)
	Long course RTx (40-60Gy)	78 (9%)	34 (3%)	15 (5%)	22 (5%)
	CRTx	319 (38%)	360 (34%)	147 (52%)	220 (46%)
	NR	245 (29%)	373 (35%)	0 (0%)	0 (0%)
Type of resection	APR	594 (71%)	793 (75%)	281 (100%)	477 (100%)
	APR with MVR	154 (18%)	175 (17%)	0 (0%)	0 (0%)
	Total pelvic exenteration	8 (1%)	1 (0%)	0 (0%)	0 (0%)
	NR	83 (10%)	86 (8%)	0 (0%)	0 (0%)
Perineal closure	Primary suturing	690 (82%)	765 (73%)	281 (100%)	477 (100%)
	Muscle flap reconstruction	42 (5%)	127 (12%)	0 (0%)	0 (0%)
	Mesh closure	107 (13%)	163 (15%)	0 (0%)	0 (0%)
	NR	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Follow up time	Months (Median [IQR])	36.6 [24.6 - 48.6]	36.6 [22.7 - 50.5]	37.9 [19.3 - 56.5]	36.8 [19.6 - 53.8]

OP: Omentoplasty; IQR: Interquartile range; NR: Not reported; RTx: Radiotherapy; CRTx: Chemoradiotherapy APR: Abdominoperineal resection; MVR: Multivisceral resection; Percentages might not add up due to rounding

pre-sacral abscesses after OP when only analysing the patients who have been treated with pre-operative radiotherapy (RR 0.94; 95% CI 0.61-1.45; I^2 = 0%).(2, 4, 6, 23, 24)

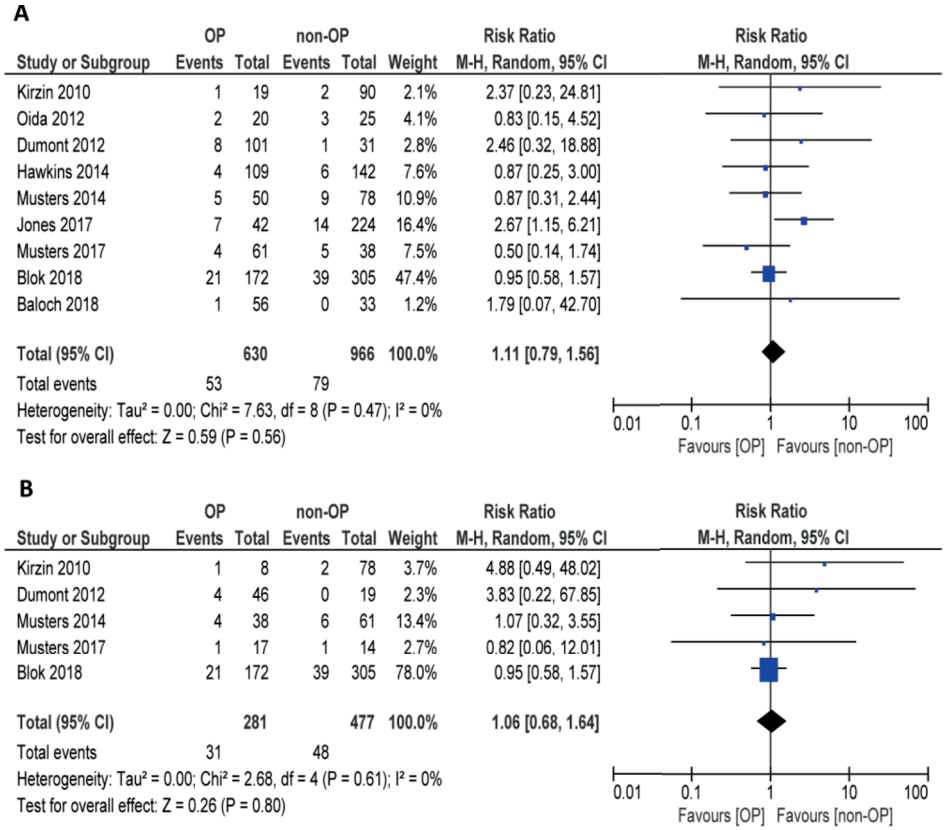

Figure 2. Meta-analyses comparing pre-sacral abscess formation between patients with and without omentoplasty in **A)** all patients who underwent APR for malignancy, and **B)** patients who underwent APR with primary perineal closure for non-locally advanced rectal cancer.

Perineal wound healing

Eight studies recorded the primary perineal wound healing.(2, 4, 24-29) The overall weighted mean cumulative proportion of complicated wound healing at 30 days following OP was 50.6% (95% CI 35.5-65.6%). In five comparative studies(2, 4, 24, 26, 28), the rate of complicated wound healing within 30 days was not significantly different after OP and non-OP (RR 1.30; 95% CI 0.92-1.82; I^2 = 74%). In subgroup analysis of APR with primary perineal closure for non-locally advanced disease, the association of OP with 30-day wound complications remained non-significant (RR 1.28; 95% CI 0.64-2.56; I^2 = 73%).(2, 4, 24) There was no reduced risk of pelviperineal morbidity within one year (RR 1.18; 95% CI 0.80-1.74; I^2 = 80%)(2, 4, 22, 24, 28) or within the total study period (RR 1.09; 95% CI 0.83-1.44; I^2 = 69%)(2, 4, 9, 10, 22-24, 28, 30) for patients submitted to OP.

Time to complete healing was not uniformly reported with regard to patient population (e.g. all patients or only those with dehiscence) and measuring unit (e.g. days or weeks) (Supplementary Table 4; Supplemental Digital Content 4). The included studies demonstrated no significant difference in time to achieve perineal wound healing in terms of mean number of days (MD 24 days in favour of non-OP; 95% CI minus 11 to 59; I^2 = 80%) (23, 24, 26, 30), or the proportion of patients in whom the perineal wound was healed within 3 months (RR 1.01; 95% CI 0.92-1.10; I^2 = 0%).(4, 6, 22, 23)

Table 3. GRADE Summary of findings table of the effects of omentoplasty for filling of the pelvic cavity following abdominoperineal resection

Patient population: Patients who underwent abdominoperineal resection for malignant disease

Intervention: Omentoplasty

Comparison: No omentoplasty

Outcomes	Relative effect	95% CI	I^2	No. of participants (studies)	Quality of the evidence (GRADE)
Complicated wound healing < 30 days	RR 1.30	0.92-1.82	74%	853 (5)	⊕⊕⊕⊕ High
Any complicated wound healing < follow-up	RR 1.09	0.83-1.44	69%	1033 (9)	⊕⊕⊕⊕ High
Superficial perineal infection	RR 0.85	0.45-1.62	78%	1100 (8)	⊕⊕⊕⊖ Moderate
Pre-sacral abscess	RR 1.11	0.79-1.56	0%	1596 (9)	⊕⊕⊕⊕ High
Perineal dehiscence	RR 1.21	0.96-1.53	54%	1621 (9)	⊕⊕⊕⊖ Moderate
Perineal haemorrhage	RR 1.39	0.29-6.58	25%	307 (3)	⊕⊕⊖⊖ Low
Persistent perineal sinus	RR 1.08	0.53-2.20	56%	1370 (8)	⊕⊕⊕⊖ Moderate
Perineal hernia	RR 1.85	1.26-2.72	0%	1584 (9)	⊕⊕⊕⊖ Moderate
Ileus	RR 0.90	0.62-1.31	0%	789 (6)	⊕⊕⊕⊖ Moderate
Reoperation for pelviperineal complication	RR 1.06	0.80-1.42	0%	1401 (9)	⊕⊕⊕⊕ High

GRADE Working Group grades of evidence

High quality: further research is very unlikely to change our confidence in the estimate effect

Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate

Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate

Very low quality: we are very uncertain about the estimate

RR: risk ratio; CI: confidence interval; I2: test for heterogeneity

Specific pelviperineal complications

The pooled proportions of specific pelviperineal complications following OP are demonstrated in Supplementary Figure 2 (Supplemental Digital Content 6). After OP, the overall weighted mean incidence of wound dehiscence was 32.2% (95% CI 22.6-43.5%)(2, 4, 6,

9, 22-24, 26-29), which was 20.0% (95% CI 11.4-32.9%) for superficial perineal infection (2, 4, 9, 10, 23-29), 4.1% (95% CI 1.6-10.5%) for haemorrhage(2, 9, 24), and 8.0% (95% CI 5.1-12.4%) for perineal sinus.(2, 4, 6, 9, 22-24, 28, 29) There were no statistically significant differences among patients with and without OP in terms of perineal wound dehiscence (RR 1.21; 95% CI 0.96-1.53; I^2 = 54%)(2, 4, 6, 9, 22-24, 26, 28), superficial perineal infection (RR 0.85; 95% CI 0.45-1.62; I^2 = 78%)(2, 4, 9, 10, 23, 24, 26, 28), pelviperineal haemorrhage (RR 1.39; 95% CI 0.29-6.58; I^2 = 25%)(2, 9, 24), or chronic perineal sinus (RR 1.08; 95% CI 0.53-2.20; I^2 = 56%)(2, 4, 6, 9, 22-24, 28) (Supplementary Figure 3, Supplemental Digital Content 7).

Ileus

Twelve studies recorded the incidence of ileus.(2, 4, 6, 9, 10, 23-29) In the OP-group, the overall weighted mean proportion of ileus was 7.8% (95% CI 4.2-14.2%)(2, 4, 9, 10, 23-26, 29), and 3.8% (95% CI 2.3-6.2%) required reoperation for ileus.(2, 4, 6, 25, 27-29) Considering eight comparative studies, overall incidence of ileus was not significantly different with or without OP (RR 0.90; 95% CI 0.62-1.31; I^2 = 0%)(2, 4, 9, 23, 24, 26), nor the proportion of ileus requiring reoperation (RR 1.19; 95% CI 0.58-2.44; I^2 = 0%). (2, 4, 6, 28)

Perineal hernia

Twelve studies evaluated the incidence of perineal hernia.(2, 4, 6, 9, 22, 24-30) The overall weighted mean proportion of perineal hernia was 8.9% (95% CI 5.7-13.7%) in those undergoing OP. Nine comparative studies recorded the incidence of perineal hernia.(2, 4, 6, 9, 22, 24, 26, 28, 30) The risk of perineal hernia was significantly increased in those submitted to OP compared to non-OP (RR 1.85; 95% CI 1.26-2.72; I^2 = 0%)(Figure 3.A). This association remained similar in those who underwent APR with primary perineal closure for non-locally advanced disease (RR 1.83; 95% CI 1.17-2.87; I^2 = 0%)(Figure 3.B).(2, 4, 6, 24)

Omental flap complications

Among eight studies, the weighted mean proportion of OP-related complications was 4.6% (95% CI 2.5-8.6%).(2, 4, 9, 10, 25, 27-29) Specific complications of the OP included signs of inflammation of the omentum (n=1), partial omental necrosis (n=1), total omental infarction (n=1), perineal dehiscence with omental protrusion due to necrosis of the OP (n=4), haemorrhagic shock due to bleeding of the gastro-epiploic artery (n=1) and internal herniation of small bowel underneath the OP (n=1).

Surgical re-intervention

In twelve studies on OP, the overall weighted mean proportion of pelviperineal complications necessitating surgery (including hernia repair) was 12.6% (95% CI 9.0-17.4%)(2, 4,

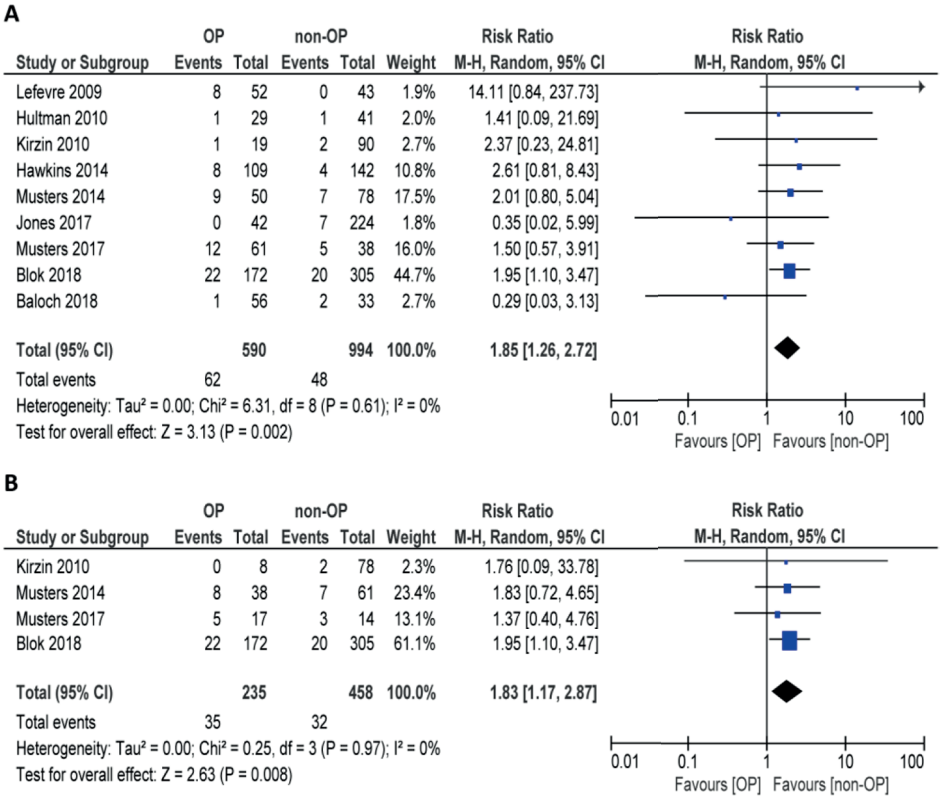

Figure 3. Meta-analyses comparing perineal hernia development between patients with and without omentoplasty in **A)** all patients who underwent APR for malignancy, and **B)** patients who underwent APR with primary perineal closure for non-locally advanced rectal cancer.

6, 9, 10, 22, 23, 25, 27-30), without significant difference between OP and non-OP (RR 1.06; 95% CI 0.80-1.42; I^2 = 0%).(2, 4, 6, 9, 10, 22, 23, 28, 30) Hernia repair tended to be more frequent in the OP group (RR 1.71; 95% CI 0.87-3.35; I^2 = 0%).(2, 4, 6, 28) Problems related to the OP itself were reason for reoperation in 3.8% (95% CI 1.9-7.6%). (2, 4, 9, 25, 27, 28)

DISCUSSION

In the current literature review with mainly source patient data, we found no evidence to suggest that OP reduces pelviperineal abscess formation, nor that OP enhances perineal wound healing considering any other endpoint, or that OP reduces the risk of small bowel obstruction. Similarly, no beneficial effect of OP was found in planned subgroup analysis of patients that underwent APR with primary perineal closure for non-locally advanced can-

cer, thereby likely reducing the risk of allocation bias. Furthermore, OP itself is associated with a small risk of complications and appears to be associated with perineal herniation.

The absence of any beneficial effects of OP as found in the present meta-analysis is in contrast to literature on autologous tissue flaps for perineal wound closure following APR.(11, 43) In particular, the use of a VRAM flap is well established.(8, 30, 44) However, studies directly comparing muscle flaps and OP are scarce. A retrospective single institutional study by Lefevre et al.(30) which was included in the present review – found that VRAM flap closure was associated with less perineal morbidity, reduced healing time and no perineal herniation (0% vs 15.4%; P=0.0072) if compared to primary layered closure with OP. There are several potential explanations as to why OP is not associated with such favourable outcomes. Probably, the omentum is more likely to leave residual dead space, especially with thin patients. Furthermore, OP might have less robust blood supply after full mobilization, and compromised perfusion of an OP is sometimes difficult to recognize intra-operatively. An OP with partial necrosis of the most distal parts, which are subsequently placed in the perineal wound, will likely counterbalance any beneficial effect in other patients. But in our opinion, the most crucial difference between OP and VRAM flap reconstruction is the filling of anal dead space. The muscle, fascia, subcutaneous fat and skin of a VRAM flap are perfectly suited for reconstruction of the pelvic floor and perineal defect, while an OP only consists of loose fatty tissue that does not provide any strength. OP mainly fills the pre-sacral space, but the excised anal canal and sphincter complex seems to be the critical wound bed. The small bowel can fill the pre-sacral space in the absence of an OP, as will occur after VRAM flap reconstruction.

Incidence of perineal hernia was around 10%, and is likely to even be an underestimation of the true incidence because of the retrospective design of most included studies. In meta-analysis, perineal hernia correlated significantly with the use of OP. This finding has recently been demonstrated in a nationwide study(6), but was felt to be counterintuitive by some surgeons, and probably best explained by wider resections in the OP-group. But this phenomenon may also be explained by the properties of an OP. As previously mentioned, the fatty and non-fibrous omentum is not providing any strength to the neo-pelvic floor, and even puts continuous pressure on the perineal skin in a standing position. It is understandable that, in case of a bulky OP with a long vascular pedicle, such redundant bulk of fat is more likely to descend below the level of the pelvic floor than a few loops of small bowel that are often restricted by a certain mesenteric length. The omental fat is certainly more likely to result in perineal bulging than VRAM flap closure where muscle and fascia is added to the neo-pelvic floor.(30)

Two systematic reviews on the value of OP after APR have been published previously, both in contradiction with the current meta-analysis.(45, 46) Compared to the review of Nilsson et al.(46), only one study(29) is overlapping, and only three(9, 10, 29) out of 14 studies are overlapping with the review by Killeen et al.(45) Most of the older studies that were included in both previous reviews, concern a small sample size and diversity regarding patient population and surgical methods, with only few comparative series. In addition, the rather historical studies have restricted generalizability, especially considering the less frequent use of pre-operative radiotherapy. Strengths of the current review are restricted inclusion of publication since 2000, more comparative studies, and the use of primary source patient data, even if the original publication was not intended to study the effect of OP. Furthermore, benign pathology such as IBD was excluded, in contrast to the previous reviews. This resulted in more homogeneous patient populations with higher internal and external validity than previous systematic reviews published on the subject.(45, 46) These methodological issues may explain the contradictory findings.

The main limitation of our study is the potential for a certain degree of allocation bias. In the absence of randomized controlled trials, it could be that surgeons selectively applied OP in those with a larger empty space after resection, and therefore an a priori greater risk of wound complications and hernia. To reduce potential confounding, a subgroup analysis was performed by excluding extended resections and additional reconstructive procedures. Even then, however, the potential for allocation bias cannot be excluded. A second limitation is that the definition of outcome variables in the source studies may be variable. In particular, the lack of a clear definition for pre-sacral abscess and perineal hernia (i.e. symptomatic perineal bulge or asymptomatic radiological finding) could potentially have influenced our results. However, reporting of perineal hernia was predominantly based on retrospective analysis of patient records, most likely not including small and asymptomatic radiological hernias . Also, total number of events were used for meta-analysis of perineal hernia, not properly taking into account the development of perineal hernia over time and differences among studies regarding duration of follow-up.

Based on the available literature, OP does not seem indicated for decreasing perineal wound complications after APR for cancer, nor does biological mesh closure.(4) 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(8), there remains the issue of donor and recipient site morbidity.(43, 47) A smaller flap without donor site problems such as the perineal turnover flap(48) seems attractive. We are currently evaluating the effectiveness of a modified gluteal turnover flap(49) for routine use after APR, and we

consider larger fascio-cutaneous gluteal or VRAM flaps only for the wider perineal defects with a high risk of sinus formation.

Conclusions

In this systematic review and meta-analysis, that is reflecting current surgical practice of patients who are submitted to APR for malignant disease, we found no evidence to support the use of an OP for reducing pelviperineal morbidity. Additionally, use of OP has an added risk of OP associated complications, and seems to be associated with the long-term likelihood of developing perineal hernia.

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LIST OF SUPPLEMENTAL DIGITAL CONTENT

Supplemental Digital Content 1.docx; Supplementary Table 1. Electronic search strategy in the PUBMED-library.
Supplemental Digital Content 2.docx; Supplementary Table 2. Quality assessment of the included studies by the Newcastle Ottawa Scale.
Supplemental Digital Content 3.docx; Supplementary Table 3. Baseline characteristics and operative details for each of the included studies.
Supplemental Digital Content 4.docx; Supplementary Table 4. Outcomes for each of the included studies.
Supplemental Digital Content 5.docx; Supplementary Figure 1. Funnel plot analyses for the detection of publication bias.
Supplemental Digital Content 6.docx; Supplementary Figure 2. Pooled proportions of the outcome measures in the presence of an omentoplasty.
Supplemental Digital Content 7.docx; Supplementary Figure 3. Meta-analyses of pelviperineal morbidity and ileus comparing patients with and without omentoplasty in all patients and in a subgroup of patients who underwent APR with primary perineal closure for non-locally advanced rectal cancer.

PART II

MANAGEMENT OF LOCALLY ADVANCED AND LOCALLY RECURRENT RECTAL CANCER

Chapter 8

Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre

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ABSTRACT

Introduction

The majority of patients with locally recurrent rectal cancer (LRRC) present with extensive metastatic disease or an unresectable recurrence, and will be treated palliatively. Only a minority of patients will be eligible for potential cure by surgical treatment. The aim of this study is to evaluate the long-term outcome of surgical treatment and non-surgical treatment of patients with LRRC.

Methods

All patients with LRRC referred to our tertiary institute between 2000 and 2015 were retrospectively analysed. Patients were discussed in a multidisciplinary tumour board (MDT) and eventually received curative surgical or non-surgical treatment. Overall survival (OS) was compared by resection margin status and non-surgical treatment.

Results

A total of 447 patients were discussed in our MDT of which 193 patients underwent surgical treatment and 254 patients received non-surgical treatment. Surgically treated patients were significantly younger, received less neoadjuvant therapy for the primary tumour, had less metastasis at diagnosis and more central recurrences. The 5-year OS was 51% for R0-resections and 34% for R1-resections. Although numbers with R2-resections were too small to implicate prognostic significance, there was no difference in 5-year OS between R2-resections and non-surgical treatment (10% vs. 4%, p=0.282). In a subgroup analysis the OS of R2-patients was even poorer compared to optimal palliative treated patients with combined chemotherapy and radiotherapy(22 vs 29 months, p=0.413).

Conclusions

R2-resections do not result in a survival benefit compared to non-surgical treatment in this non-randomized series. Patients with a high chance on a R2-resection could be offered non-surgical treatment, without local resection.

INTRODUCTION

The introduction of total mesorectal excision (TME) and neoadjuvant (chemo-) radiotherapy have drastically decreased local recurrence rates after surgery for rectal cancer over the last decades. Locally recurrent rectal cancer (LRRC) still occurs in 6-10% of the surgically treated patients.(1-5) The development of LRRC has a major impact on quality of life, mostly by the occurrence of severe pain, bleeding and fistulation.(6)

Most patients with LRRC present with extensive metastatic disease or an unresectable local recurrence.(7-10) These patients can be offered non-surgical treatment, consisting of external beam radiotherapy, chemotherapy, a combination of both or comfort care.(11) Palliative external beam radiotherapy may relief pelvic pain complaints and chemotherapy may delay disease progression and prolong survival.(7, 8, 11-13) A minority of patients presenting with LRRC can potentially be cured by surgical resection. The long-term outcome of surgical treatment mainly depends on the ability to achieve a clear resection margin.(10, 14, 15) Management of LRRC remains a challenge both for curative surgical treatment and non-surgical treatment.

The aim of the current study is to evaluate the long-term outcome of a large cohort of patients with LRRC and determining the outcome of curative surgical treatment and non-surgical treatment in these patients.

Patients and Methods

All consecutive patients with confirmed LRRC discussed in the multidisciplinary tumour board (MDT) of the Erasmus MC Cancer Institute, a tertiary referral hospital, from 2000-2015 were retrospectively analysed. LRRC was defined as local recurrence of rectal cancer in the pelvic area. This MDT included experienced surgeons, radiologists, radiation oncologists and medical oncologists. If needed, gynaecologists, urologists, pathologists and plastic surgeons were invited to join the meeting.

Data was collected from all referring hospitals, general practitioners and obtained from hospital notes, operation notes, histopathological and imaging reports. The local medical ethics committee of our institution approved this study (MEC-2017-448).

Surgical treatment

Surgical treatment was considered feasible in patients with resectable metastatic disease and/or non-metastasized LRRC with a realistic chance of a R0/R1-resection, as discussed by the MDT. R0-resections were defined as any radical resection (no tumour invasion in the resection plane, tumour-free margin of >1 mm); R1-resections as microscopically involved

margins (tumour invasion in resection plane on microscopic assessment, tumour-free margin of ≤1 mm); R2-resections as macroscopically involved margins or massive invasion into the resection surface on pathology report.

Patients were usually scheduled for neoadjuvant (chemo) radiotherapy. Radiotherapy-naïve patients were planned for long course radiotherapy (44.6-52Gy) and previously irradiated patients received a short course re-irradiation (27-30Gy). From 2006 onwards, all patients received concurrent Capecitabine during radiotherapy as reported previously.(16) Induction chemotherapy was occasionally administered. After neoadjuvant therapy, patients were restaged (CT Thorax/Abdomen and Pelvic MRI) and discussed in the MDT to evaluate development of distant metastases, tumour response of the local recurrence and clinical condition, which may alter the decision for surgical treatment to palliative treatment.(17) Surgical planning was made by the MDT based on imaging after restaging after neoadjuvant therapy.

Surgical procedures included low anterior resection (LAR), abdominoperineal resection (APR) with and without multivisceral resection (MVR), and both posterior exenteration and total pelvic exenteration. Surgery was usually performed at our institute and in some cases in the referring hospital. In our institute, the multimodality approach for LRRC included intra-operative brachytherapy (IOBT) with a single dose of 10Gy. Patients received IOBT in case of a positive circumferential resection margin (CRM) or a narrow margin (CRM ≤ 2mm) on frozen sections taken preoperatively. In addition, patients received IOBT in case of peroperatively expected or uncertain achievement of radical margins, i.e. due to fibrosis and patient with an expected peroperative R2-resection.(18, 19) Surgical complications were scored according to the Clavien-Dindo classification.(20)

Non-surgical treatment

Patients receiving non-surgical treatment usually had extensive metastatic disease, unresectable local recurrence or a poor clinical condition. There was no standard policy regarding the choice of non-surgical treatment. Non-surgical treatment consisted of radiotherapy or chemotherapy, either with or without hyperthermia or a combination of both and comfort care. Generally, patients with symptomatic LRRC were treated with radiotherapy and those with asymptomatic metastasized or unresectable LRRC were treated with chemotherapy. Hyperthermia was usually administered to previously irradiated patients due to the limited radiation dose available for their local recurrence. The choice of dose and fractioning of radiotherapy was largely based on the clinical judgment of the radiation oncologists and this resulted in heterogeneity in the radiotherapy management. Comfort care was provided for patients who were unable to receive or did not desire any treatment with radiotherapy or chemotherapy.

Statistical analysis

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). Group comparisons were made using Chi-square or Mann-Whitney-U-test as appropriate. Survival and follow-up were calculated from the date of LRRC diagnosis until death or last follow-up. Survival rates and follow-up were calculated by the (reversed) method of Kaplan-Meier and comparisons by log-rank test. For all analyses, patients were divided into two groups: 1) patients who underwent surgery and 2) patients who received non-surgical treatment including those patients who were previously considered eligible for surgical treatment. Statistical analyses were performed using IBM SPSS Statistics v24.0.0 for Windows (IBM Corp, Armonk, New York, USA).

RESULTS

A total of 447 consecutive patients with LRRC were discussed in our MDT. A flowchart of included patients is displayed in figure 1. After discussion in the MDT, 244 patients (55%) were considered candidates for surgery. This decision was reversed in 51 patients after restaging after neoadjuvant therapy, as described in figure 1. In total, 193 patients underwent surgical treatment and 254 patients received non-surgical treatment. Patient, primary and recurrent tumour characteristics are outlined in table 1. Treatment and follow-up are depicted in table 2.

Time to recurrence after primary rectal cancer resection

The median time from primary tumour resection to the diagnosis of LRRC was 23 months (IQR 11 – 39 months). In more than half of the patients (55%) LRRC developed within 2 years and in almost all patients within 5 years (88%). A total of 162 patients (36%) presented with synchronous metastases at diagnosis of LRRC: the predominant location was lung only (34%), followed by liver only (28%), other (24%) or liver and lung (14%).

The median time to diagnosis of LRRC was significantly shorter in patients with incomplete primary tumour resections compared to patients with complete resections (10 vs. 24 months, $p<0.001$) and in patients who had received neoadjuvant radiotherapy for the primary tumour compared to no radiotherapy (21 vs. 24 months, $p=0.039$). More advanced primary pathological T-stage (T3-4 vs. T1-2) did not influence the median time to LRRC (21 vs. 24 months, $p=0.172$), nor lymph node positivity (21 vs. 23 months, $p=0.776$).

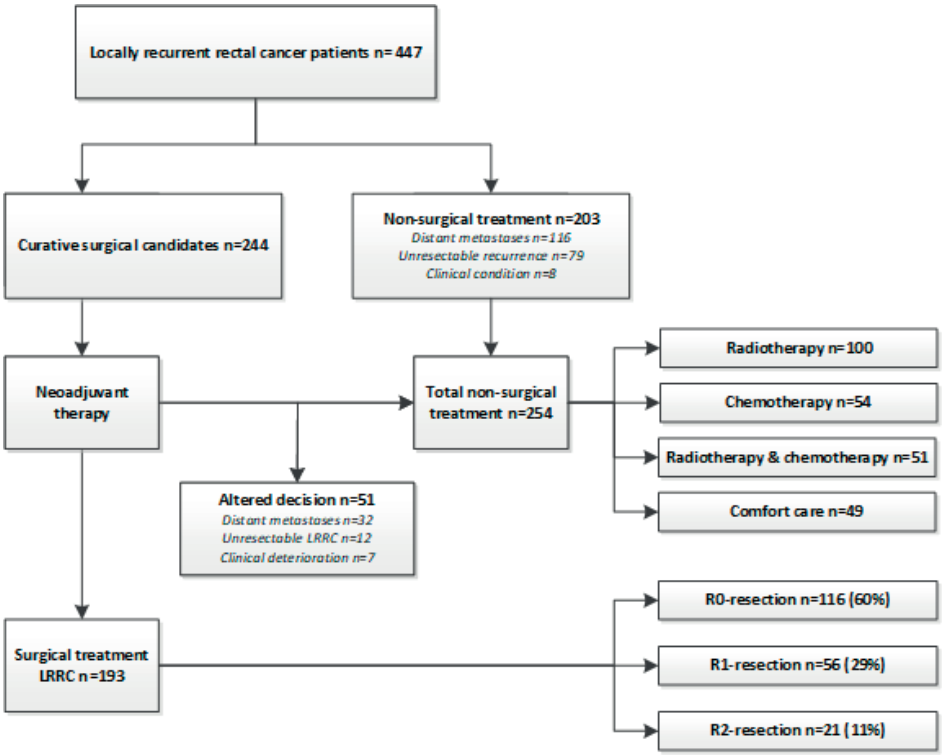

Figure 1. Flowchart of all referred LRRC patients

Surgical and non-surgical patients

There were significant baseline differences for patients who eventually underwent surgery (n=193) compared to all non-surgically treated patients (n=254) (Table 1). Surgically treated patients were significantly younger, less symptomatic at presentation of LRRC, received less radiotherapy for the primary tumour, had fewer incomplete primary tumour resections, had less frequent synchronous distant metastasis, more differences in terms of localization of the local recurrence and underwent different procedures for the primary rectal tumour. Patients with a central localization of the local recurrence were more likely to be scheduled for surgical treatment, whereas patients with a pre-sacral recurrence were more likely to receive non-surgical treatment.

Table 1. Patients, primary and recurrent tumour characteristics of surgical and palliative treatment

		Total (N=447)	Surgical (N=193)	Palliative (N=254)	P-value
Gender	Male	289 (65%)	125 (65%)	164 (65%)	0.965
	Female	158 (35%)	68 (35%)	90 (35%)	
Age at primary tumour resection	Median (IQR)	63 (56-70)	62 (54-67.5)	64 (56-72)	0.016*
Age at diagnosis LRRC	Median (IQR)	66 (58-73)	65 (57-71)	67 (58-75)	<0.001*
Neoadjuvant treatment primary tumour	None	256 (57%)	126 (65%)	130 (51%)	0.002**
	Short course RTx	49 (11%)	18 (9%)	31 (12%)	
	Long course RTx	62 (14%)	14 (7%)	48 (19%)	
	Chemoradiotherapy	80 (18%)	35 (18%)	45 (18%)	
Primary tumour resection	LAR	244 (55%)	112 (58%)	132 (52%)	<0.001**
	APR	106 (24%)	30 (16%)	76 (30%)	
	Rectosigmoid	55 (12%)	32 (17%)	23 (9%)	
	Exenterative surgery	21 (5%)	4 (2%)	17 (7%)	
	TEM	21 (5%)	15 (8%)	6 (2%)	
Primary tumour stage	Stage I	52 (13%)	30 (16%)	22 (10%)	0.076
	Stage II	139 (34%)	58 (31%)	81 (35%)	
	Stage III	186 (45%)	86 (46%)	100 (44%)	
	Stage IV	38 (9%)	12 (7%)	26 (11%)	
	Missing***	32	7	25	
Resection margin primary tumour	R0	381 (88%)	174 (96%)	207 (83%)	<0.001**
	R1	50 (12%)	8 (4%)	42 (17%)	
	Missing***	16	11	5	
Interval primary - LRRC	Median (IQR)	23 (11-39)	24 (12-40)	21 (10-37)	0.154
Recurrence within	24 months	246 (55%)	99 (52%)	147 (58%)	
	5 years	393 (88%)	174 (90%)	219 (86%)	
	10 years	433 (97%)	191 (99%)	242 (95%)	
Symptoms at diagnosis LRRC	Yes	262 (55%)	86 (45%)	176 (69%)	<0.001**
	No	185 (45%)	107 (55%)	78 (31%)	
Metastases at diagnosis LRRC	None	285 (64%)	172 (89%)	113 (45%)	<0.001**
	Lung	55 (12%)	11 (6%)	44 (17%)	
	Liver	45 (10%)	7 (4%)	38 (15%)	
	Lung & Liver	23 (5%)	0 (0%)	23 (9%)	
	Other	39 (9%)	3 (2%)	36 (13%)	
Location LRRC	Central	74 (18%)	54 (29%)	20 (9%)	<0.001**
	Anterior	62 (15%)	31 (17%)	31 (14%)	
	Posterolateral	53 (13%)	24 (13%)	29 (13%)	
	Anterolateral	34 (8%)	14 (8%)	20 (9%)	
	Lateral	59 (14%)	29 (16%)	30 (13%)	
	Pre-sacral	133 (31%)	33 (18%)	100 (44%)	
	Missing***	32	8	24	

*Mann Whitney U test ** Chi squared test *** *missing's not included in group comparison, percentages-might not add up due to rounding*

LRRC: Locally recurrent rectal cancer; IQR: interquartile range; RTx: radiotherapy; LAR: low anterior resection;APR: abdominoperineal resection; TEM: transanal endoscopic microsurgery

Surgical treatment

The majority of surgically treated patients received neoadjuvant therapy (90%) and more than half of the patients received (re-)chemoradiotherapy (62%). Some patients received induction chemotherapy (n=13) or radiation (n=38) or re-irradiation (n=9) without concurrent Capecitabine and 7 patients received solely induction chemotherapy. In 175 patients (91%) the surgical procedure was performed at our institute, while 18 procedures (9%) were performed in the referring hospitals. Neoadjuvant therapy and surgical procedures are described in Table 2.

Table 2. Treatment and follow up of LRRC in surgical and palliative treatment

	Surgical (N=193)	Palliative (N=254)
Neoadjuvant therapy LRRC		
None	19 (10%)	205 (81%)
Irradiation (50Gy)	38 (20%)	13 (5%)
Re-irradiation (30Gy)	9 (5%)	3 (1%)
Induction chemotherapy*	20 (10%)	9 (2%)
Chemoradiotherapy (50Gy)	61 (32%)	14 (6%)
Re-Chemoradiotherapy (30Gy)	59 (31%)	15 (6%)
Surgical procedure		
Total pelvic exenteration	43 (22%)	N/A
Posterior pelvic exenteration	27 (14%)	N/A
APR with MVR	26 (14%)	N/A
LAR with MVR	18 (9%)	N/A
Local resection with MVR	11 (5%)	N/A
APR only	25 (13%)	N/A
LAR only	26 (13%)	N/A
Local resection only	17 (7%)	N/A
IORT	86 (45%)	N/A
Follow up		
Alive at last FU	65 (34%)	9 (4%)
No evidence of disease at last FU	47 (24%)	N/A
Local re-recurrence	62 (32%)	N/A
Metastases (any)	88 (46%)	186 (73%)
Metastases (synchronous)	14 (7%)	138 (54%)
Metastases (metachronous)	74 (38%)	48 (19%)
Lung**	47 (53%)	63 (34%)
Liver	15 (17%)	46 (25%)
Lung and liver	10 (11%)	26 (14%)
Peritoneal	6 (7%)	15 (8%)
Lymphogenic	7 (8%)	20 (11%)
Other	3 (3%)	16 (9%)

* Combined with (chemo-)radiotherapy in 13 patients for surgical patients and 5 non-surgical patients; ** Location of metastases are reported as percentage within metastases; N/A: not applicable; APR: abdominoperineal resection; MVR: multivis ceral resection; LAR: low anterior resection; IORT: intraoperative radiation therapy; FU: follow up

Surgical results

R0-resections were achieved in 116 patients (60%), R1-resections in 56 patients (29%) and R2-resections in 21 patients (11%). The 30-day mortality and the in-hospital mortality rate were both 3% (n=5). Four patients died within 22 days and one patient died during admission at 67 days after surgery. Postoperative complications were registered in 176 out of 193 patients. A total of 59 (34%) patients experienced major complications (Clavien-Dindo ≥ 3). Most common complications were wound complications (23%), pre-sacral abscesses (11%) and urinary tract infections (9%). Surgical re-intervention was required in 26 patients (13%) and abscess drainage (i.e. pre-sacral or abdominal abscess) in 25 patients (13%). Complications for surgically treated patients are displayed in Table 3.

Table 3. Surgical complications

	Total (N=193)
Clavien-Dindo	
No complication	59 (34%)
Clavien-Dindo I	31 (18%)
Clavien-Dindo II	27 (15%)
Clavien-Dindo IIIA	21 (12%)
Clavien-Dindo IIIB	25 (14%)
Clavien-Dindo IVA	3 (2%)
Clavien-Dindo IVB	4 (2%)
Clavien-Dindo V	5 (3%)
Most common complications	
Wound complication	45 (23%)
Pre-sacral abscess	22 (11%)
Urinary tract infection	18 (9%)
Relaparotomy	18 (9%)
Pneumonia	15 (8%)
Sepsis	13 (7%)
Cardiac complication	12 (6%)
Nephrostomy	12 (6%)
Reintervention stoma	3 (2%)
Anastomotic leakage	3 (2%)
Any surgical reintervention	26 (13%)
Any abscess drainage	25 (13%)

Non-surgical treatment

A total of 254 patients received non-surgical treatment, including 51 patients who were first considered candidates for surgical treatment. These patients had received neoadjuvant therapy, but the aim of the treatment was altered as described previously. Patients were

treated by radiotherapy (n=100), by chemotherapy only (n=54), by combined radiotherapy and chemotherapy (n=51) or comfort care (n=49).

In 63 previously irradiated patients, re-irradiation was administered in varying doses of 15 to 48 Gy delivered in 3-15 fractions. Radiotherapy-naïve patients (n=88) received radiotherapy doses varying from 6-66Gy in 4-28 fractions. Almost half of the patients experienced pain (48%) of whom the majority (56%) needed pain consultation.

Follow-up and survival surgical and non-surgical treatment

The median follow-up time for the whole cohort was 26 months (IQR 11 – 45) and median follow-up for survivors was 120 months (IQR 68 – 142).

Survival surgically treated patients

The median follow-up of the 193 surgically treated patients was 42 months (IQR 29 - 70) and the median follow-up for survivors was 117 months (IQR 67 - 140). The estimated 1-, 3- and 5-year overall survival rates were 93%, 65% and 41%, respectively. The median overall survival was 47 months (IQR 29 – 156). The estimated 1-, 3- and 5-year local re-recurrence free survival rates were 81%, 64% and 63%, respectively. The median local re-recurrence free survival was not reached. At last follow-up 65 (34%) patients were alive, of whom 50 patients with no evidence of disease. Sixty-two patients developed a local re-recurrence and 74 patients developed metastases after surgery. Thirty-one patients were diagnosed with both. Recurrence patterns and death by resection margin are demonstrated in Table 4.

Survival non-surgically treated patients

The median follow-up of the 254 non-surgically treated patients was 15 months (IQR 7 – 29) and the median follow-up for survivors was 145 months (IQR 142-162). The estimated 1-, 3-, 5-year overall survival rates were 60%, 19%, 4%, respectively. The median survival was the highest for patients treated with combined radiotherapy and chemotherapy, followed by chemotherapy only, radiotherapy only and comfort care (29, 18, 14 and 7 months, respectively). There was no significant difference in median survival of metastasized and non-metastasized patients at diagnosis (14 vs. 18 months, p=0.293). Nine patients were alive at last follow-up. One patient, with a proven LRRC on imaging, had a complete radiologic response of the recurrence after treatment with radiotherapy and was alive at 162 months follow-up. Two patients, with histologically confirmed LRRCs, were alive at 145 and 142 months with stable systemic and local disease after an experimental chemotherapeutic treatment. Two patients, with histologically proven LRRC and systemic disease, were alive at 44- and 32-months follow-up, both receiving experimental chemotherapeutic treatment. Two patients with proven LRRC on imaging with systemic disease with highly

elevated carcinoembryonic antigen were alive at 44 and 32 months with slowly progressive systemic and local disease without treatment. Another two patients with histologically proven LRRC and systemic disease were alive, but were lost to follow-up at 21 and 10 months. Distant metastases were diagnosed in 186 patients. In 141 patients, distant metastases were diagnosed at presentation and 45 patients developed distant metastases during follow-up of non-surgical treatment.

Survival by resection margin vs. non-surgical treatment

Compared to patients treated non-surgically, there was a significant difference in 5-year overall survival in favour of patients with R0-resections (51% vs. 4%, p<0.001) and R1-resections (34% vs. 4%, p<0.001). There was no difference in overall survival between R2-resections and non-surgical treatment (10% vs. 4%, p=0.282). This is shown in figure 2. In a subgroup analysis, patients with a R2-resection had a prolonged median survival of 29 months (IQR 16 – 41) compared to 22 months (IQR 14 – 37) of the patients who were treated with palliative radiotherapy and chemotherapy, although this difference was not significant (p=0.413).

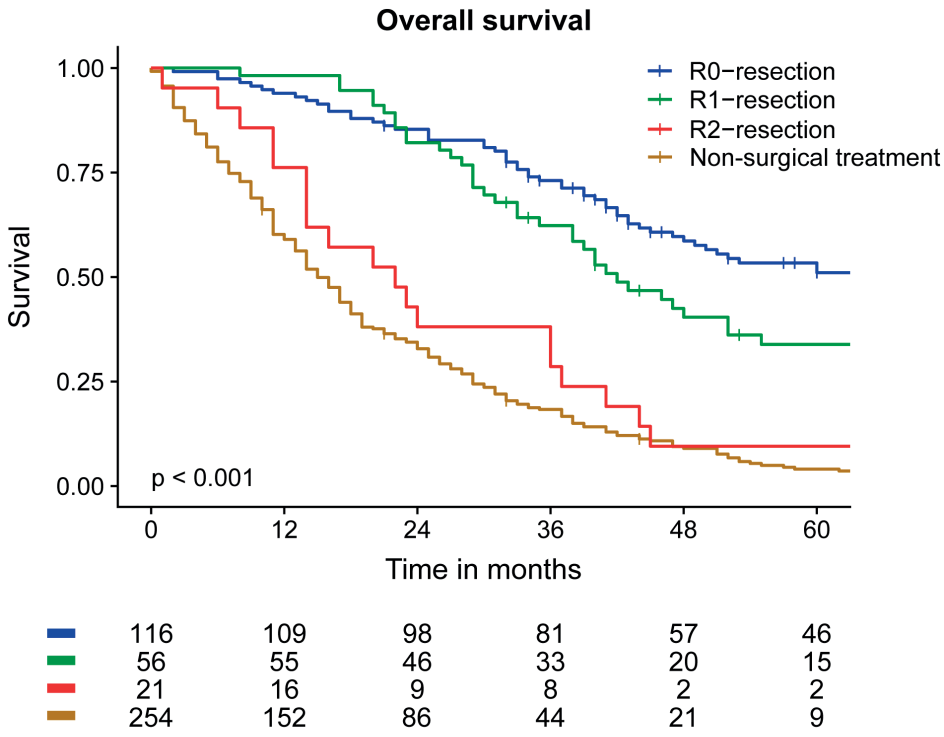

Figure 2. Overall survival according to surgical resection margin and non-surgical treatment

DISCUSSION

This large cohort of patients with LRRC, treated by surgical or non-surgical treatment, 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 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 overall survival of patients who underwent a R2-resection was poorer compared to patients who were treated non-surgically with combined radiotherapy and chemotherapy.

The 5-year overall survival rate for R0-resections in the present study is in line with previously reported outcomes of population-based studies and meta-analyses within a range of 43%-60%. Additionally, the poorer overall survival rate of R1-resections (range 14-36%) and the dismal overall survival rate of R2-resections (range 0-16%) are in line with the overall survival rates reported by others.(7-11, 14, 15) This confirms that resection margin status after surgical treatment for LRRC is the most important prognostic factor for overall survival. Unfortunately, not all LRRC patients are eligible for curative surgery.

The 5-year survival rate of 4% for all non-surgically treated patients in this study seems relative high compared to other series, which rarely exceeds 4%.(21, 22) However, a recently published study by Bhangu et al.(23) demonstrated a 3-year overall of approximately 35% for patients who did not undergo surgery, which is even higher compared to our 3-year overall survival of 19%. In line with our study, they reported an overall survival benefit in favour of R0- and R1-resections compared to non-operative management. In R2-resections, they were not able to find a survival benefit compared to non-operative management. Neither a large meta-analysis by their group was able to demonstrate a survival benefit for R2-resections compared to non-surgical treatment.(14, 23). These results are similar to our study, where we were not able to find a survival benefit of R2-resection compared to non-surgical treated patients. In a subgroup of patients who were treated by radiotherapy and systemic chemotherapy, a prolonged median survival was found compared to R2-resections (29 vs 22 months). Nevertheless, in our study the results of R-resections our limited by the small number of patients and cannot implicate statistical significance.

The survival benefit of R0- and R1-resections compared to non-surgical treatment seems clear in the current study. However, it is important to realize that these results may be influenced by a selection bias. This study includes patients who are referred and discussed in our MDT, the number of patients not suitable for surgery, and not referred to our MDT, may be even higher. The group of non-surgically treated patients contains a higher propor-

tion of patients with unfavourable characteristics compared to the surgically treated patients. Non-surgically treated patients had more synchronous distant metastases and more advanced local recurrences. These unfavourable characteristics may contribute to a poorer prognosis of the non-surgical group. In line with others, the overall survival of patients receiving only comfort care was poor with a median survival of 7 months. This median survival was poorer compared to R2-resections.(8, 10, 14, 23) However, it is important to realize these patients were generally in such poor clinical condition that they were not able to receive any form of treatment.

Untreated LRRC can cause severe impairment in quality of life mainly due to severe pain, but also fistula, obstruction or bleeding.(6, 24) 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.(11, 25, 26) 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.(27) This fact and the lack of a survival benefit of R2-resections suggest that LRRC surgery with a high chance on R2-resections should be abandoned and should only be performed when the potential benefit is clear.

Regarding the secondary findings, this study identified several factors associated with resectability of LRRC. Obviously, age is a factor to be considered candidate for LRRC surgery due to the high morbidity and mortality rates of LRRC surgery. Previous irradiation for the primary tumour was also associated with resectability. Presumably, neoadjuvant radiotherapy for the primary tumour is not able to prevent local recurrences in patients with unfavourable primary tumour characteristics, such as more residual disease or higher tumour load. These patients do also have a higher risk of developing distant metastases and were therefore disqualified for LRRC surgery.(28) Patients with a more extensive primary procedure had a lower chance to be considered candidates for LRRC surgery. Extensive primary surgery leads to local recurrences closely related to structures, which cannot be resected completely, while low anterior resections or local excisions (TEM, transanal endoscopic microsurgery) may lead to central recurrences. This makes localization of the local recurrence also associated with resectability, because central recurrences results more often into R0-resections.(29)

A promising strategy to improve resectability of LRRC is induction chemotherapy. However, improved resectability does not automatically guarantee a survival benefit. Other factors, such as tumour behaviour, have more impact on overall survival as well. In our study few patients received induction chemotherapy, but a retrospective cohort study by van Zoggel et

al.(30) compared outcomes of resection of LRRC in patients with induction chemotherapy followed by chemoradiotherapy to patients who received solely chemoradiotherapy. 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.(30) suggested that response rate to induction chemotherapy may be used as guidance to avoid overtreatment in patients with progressive disease under induction chemotherapy. Otherwise, in a previous 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.(31) Further research is warranted to evaluate the potential benefit of induction chemotherapy for treatment of LRRC.

Due to the retrospective nature of this analysis, this study has drawbacks. There was no standard protocol for non-surgical treatment. The choice of non-surgical treatment consisting of radiotherapy, chemotherapy, or only comfort care was judged on clinical factors. This resulted in a heterogenetic group of patients from critical ill patients not able to receive any form of treatment, to patients in good clinical condition, refusing surgery. Follow-up data of patients treated non-surgically was limited, because treatment was usually performed in the referring hospitals. Therefore, data of complication rates and quality of life in non-surgically treated patients was limited.

Furthermore, this study was only able to demonstrate survival differences. As mentioned above, quality of life may be even more important in the management of LRRC. Future research should focus on quality of life of surgical or palliative management of LRRC.

In conclusion, R0- and R1-resections of LRRC resulted in 5-year overall survival rates of 51% and 34%, respectively. Although numbers with R2-resections were too small to implicate prognostic significance, there was no significant difference between the 5-year overall survival for R2-resections and palliative treatment (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 on a R2-resection could be offered palliative treatment, without local resection.

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Chapter 9

Pelvic exenteration for invasive rectal cancer of the anterior compartment

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INTRODUCTION

The incidence of rectal cancer is increasing worldwide.(1) At the time of diagnosis of primary rectal cancer, approximately 10% of the patients have locally advanced rectal cancer (LARC) and approximately 6-10% of patients treated for primary rectal cancer will develop locally recurrent rectal cancer (LRRC).(2-6) Over the past decades the development of multimodality treatment for LARC and LRRC, including TME-surgery, neoadjuvant (chemo-) radiotherapy, surgical treatments and intraoperative radiation therapy (IORT), improved overall survival and local control after treatment.(3, 4, 7-10) The cornerstone of treatment for rectal cancer remains achievement of a clear resection margin.(11-13) 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.(5, 11, 13-19) Overall survival by resection margin status is significantly higher after R0 resection compared to R1 or R2 resections.(14, 18, 20) This emphasizes the importance of a radical resection margin with surgery. Standard abdominoperineal excision (APE) 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.

Surgical procedures during which more than one organ is resected are generally referred to as "multivisceral resections". Exenteration is derived from the Latin term ''exenterare" and is generally interpreted as "complete removal" of contents of a body cavity such as the pelvis. Complete en bloc removal of all organs of the pelvis is called "pelvic exenteration", or "total pelvic exenteration". In women, an anterior pelvic exenteration refers to removal of the bladder, uterus and ovaries, leaving the rectum in situ, posterior pelvic exenteration refers to removal of the rectum, uterus, ovaries and the posterior vaginal wall. Total pelvic exenteration refers to removal of the rectum, uterus, ovaries and bladder. In men, an anterior exenteration means removal of bladder, vesicles and prostate, but this procedure is more commonly referred to as a cystoprostatectomy. A total pelvic exenteration means removal of bladder, prostate, vesicles and rectum. For selective resections of organs or structures that do not result in a formal anterior, posterior or total pelvic exenteration, we use the term "modified exenteration".

Pelvic exenteration for advanced pelvic malignancies was first described by Brunschwig et al.(21) in 1948 as a palliative treatment of gynaecological cancer. The first series described had a high perioperative mortality and poor survival rates.(21, 22) Over time pelvic exenteration developed as a surgical technique for curative treatment for all pelvic malignancies with invasion of adjacent organs including urogenital cancers, rectal cancer and

recurrent malignancies, which were often previously treated with surgery and/or (chemo) radiotherapy.(23-25)

This chapter focuses on the treatment of locally advanced rectal cancer or recurrent rectal cancer with invasion of the male and female urogenitary tract with pelvic exenteration of the anterior compartment.

Diagnostics

Every patient should be discussed in a specialized multidisciplinary tumour board. The characteristics of different diagnostic modalities are discussed elsewhere. In case of locally advanced tumours and even more so in recurrent rectal cancer, accurate local staging is imperative. We use contrast enhanced MRI with diffusion weighted images. For this specific patient group, other modalities may have their use in detecting metastases, but they are not helpful in evaluating the local situation in the pelvis and preoperative decision-making.

One diagnostic modality may have its specific use in this population though: the MAGIII scan. Quite often, obstruction of one of the ureters has led to deterioration of the function of the affected kidney. The anastomosis between ureter and bowel for an urinary diversion may cause complications such as anastomotic leakage and pyelonephritis. Therefore, reanastomosing a kidney that has a little or no function should be considered a failure. A MAGIII scan can clarify the percentage of kidney function that is contributed by both kidneys. In case of a contribution of <15% we usually choose to either ligate the ureter or remove the kidney in case it is contaminated (usually by placement of a double J catheter following the discovery of a dilated pyelum).

Neoadjuvant induction therapy

Current guidelines advise neoadjuvant chemoradiotherapy for the treatment of advanced rectal cancer. Usually, a cumulative dose of 50 Gy in 25 fractions of 2 Gy combined with a chemotherapeutic regimen is administered.(26, 27) Neoadjuvant therapy could downsize the tumour and this may result in more radical resections and less local recurrence. For patients with locally recurrent rectal cancer the options for neoadjuvant therapy may be limited, because patients often received neoadjuvant therapy for the primary tumour. Currently, reirradiation with or without concomitant chemotherapy is standard, usually with a cumulative dose of 30 Gy delivered in 15 fractions of 2 Gy. There are promising strategies such as induction chemotherapy with 5-fluoracil and oxaliplatin with reirradiation in these patients, which may lead to a higher pathological complete response in these patients.(28) Neoadjuvant reirradiation may be combined with intraoperative radiation therapy or intraoperative brachytherapy to reduce local recurrence rates.(17, 29-32)

Surgical procedure

The nature of the surgical procedure depends on the extent of the tumour. In case of limited ingrowth in other organs, a selective resection can be sufficient. Resection of the ureter, uterus and part of the bladder are examples of selective procedures that are routinely performed in specialized centres. More extensive tumours and locally recurrent rectal cancer often require formal posterior and total pelvic exenterations.

Patients are under general anaesthesia and generally receive epidural anaesthesia and are placed in the lithotomy position. Patients with T4 rectal cancer or locally recurrent rectal cancer are generally not considered candidates for minimally invasive techniques, because tactile feedback is essential in achieving a radical resection. The procedure starts with a midline laparotomy. In our centre we routinely perform an omentoplasty and therefore, the midline incision may be advanced cranially further than strictly necessary for pelvic surgery. Since both locally advanced and locally recurrent rectal cancer are associated with a high incidence of systemic and peritoneal metastases, careful inspection of the whole abdomen is mandatory before continuing the procedure. After placement of an abdominal retractor, dissection is commenced depending on the nature of the tumour. In case of a primary tumour in situ, a normal TME approach is continued for as long as possible.

Ureter

In case of involvement of the ureter, the ureter is identified just above the level of the promontory and freed in a cranial and caudal direction, while preventing damage to the vasculature of the ureter itself. This is achieved by leaving the ureteral adventitia in place, rather than dissecting the ureter clean. We cut the ureter approximately one centimetre above the level of the tumour and insert a single J catheter. Fibrosis and tumour are often difficult to differentiate during surgery and any fibrous tissue is considered tumour for the sake of achieving radical resections. Transection of the ureter opens up the lateral compartment of the pelvis and facilitates radical resection of disease in this compartment. Further resection of all tissues involved is performed, as identified by palpation, macroscopy and guided by preoperative MRI. When the bladder is not involved, the distal ureter may be cut and ligated, although leaving the ureter open seldom causes leakage from the bladder, because of the ureterovesical valve. The ureter may be reinserted in the bladder using the so-called "psoas-hitch" technique. The bladder is mobilized on the contralateral and anterolateral side of the bladder. Ligation of the vesical artery and vein is usually not necessary. The bladder is incised transversely and fixed to the psoas muscle fascia just above the level of the anticipated anastomosis between ureter and bladder. The ureter is then inserted in the bladder through a small incision, spatulated and fixed with resorbable sutures. The transverse incision in the bladder is closed longitudinally, the single J catheter

is led out through the bladder wall, the abdominal wall and skin. We remove the single J splint 10 days after surgery when no signs of anastomotic leakage are present.

Lateral compartment

In case of involvement of the pelvic sidewall, which occurs frequently in locally advanced and recurrent rectal cancer, the internal iliac artery and vein, may also be transected to facilitate more extensive resections up to the acetabulum. Reconstruction of the internal iliac artery and vein is generally not needed because of sufficient collateral blood supply. In seldom cases, in which the external or common iliac vessels are involved, radical resection can sometimes be achieved by complete resection of the external or common iliac vessels.

In case of persistent lymph node metastases in the lateral compartment, a formal lymph node dissection of this area can be performed. The goal of lateral lymph node dissection is to resect all nodes in the pelvic side wall lateral from the internal iliac vessels after ligating these vessels while preserving the obturator nerve and sacral plexus. In some cases, en bloc resection with these structures is necessary for full clearance of all suspect lateral lymph nodes.(33-35) This procedure is associated with increased urinary and sexual dysfunction, prolonged operation time and possible increased blood loss.(36, 37) A recent meta-analysis showed no cancer specific advantages of extended lymphadenectomy for rectal cancer, but there is evidence suggesting that patients with persistent lateral lymph nodes after neoadjuvant (chemo) radiotherapy may benefit from mesorectal excision with lateral lymph node dissection. (36, 38-40)

Often, neoadjuvant therapy, recurrence and advanced disease result in a situation in which formal node dissections may be difficult to achieve technically. In such cases, achieving a radical resection is the goal, which will prove challenging enough as it is.

Partial cystectomy

Successful partial bladder resections are usually performed for radical resection of T4 sigmoidal cancer, because these tumours may involve the more cranial aspect of the bladder. It is important to identify the orifices of both ureters to prevent obstruction of the ureter while closing the defect. It is also important to consider whether the size of the remaining bladder, combined with the anticipated function after neoadjuvant therapy, may result in a functioning bladder. We strongly advise to have an urologist-oncologist present in the OR to assist in decision-making. When a small bladder remnant is unlikely to ever function properly a bladder resection and urinary diversion may be preferable. When partial resection is possible, we open the bladder cranially and choose the dissection planes on palpation and sight. We close the bladder with two layers of 3-0 slowly resorbable sutures. Lower tumours often involve the neck of the bladder and the orifices. Therefore, even small

bladder wall resections at this level often result in a bladder remnant that is impossible to reconstruct in such a manner that both ureters can be reinserted into a functional remnant. Again, we advise to involve the urologist-oncologist in decision-making. When partial resection is not feasible, a total pelvic exenteration is indicated (see below: total pelvic exenteration)

Partial prostatectomy

In case of limited involvement of the prostate, without involvement of the urethra, a partial resection of the prostate may be attempted. It should be noted that the urethra is close to the posterior capsula of the prostate. We insert a large diameter silicone urinary catheter to palpate the urethra. Softer catheters are palpated less easily. Dissection of the capsula of the prostate should be performed through a perineal approach, usually as part of an abdominoperineal excision (APE) of the rectum. After performing the usual steps of an APE as described elsewhere, we leave the anterior dissection as long as possible. We then identify the urethra by palpation of the silicone catheter and approach the capsula of the prostate caudally and laterally after lateral transection of the pelvic floor. The surgeon may now open the capsula of the prostate and include a layer of prostate in the resection specimen. Continuous palpation may clarify whether the tumour is resected completely and the surgeon can then return to the normal plane with or without including the seminal vesicles in the specimen. When complete removal of the seminal vesicles is performed, the surgeon should be aware that he is approaching the distal ureters from below. It is noteworthy that this type of resection often results in R2 resections, because the extra amount of tissue that can be resected is limited, palpation is difficult, especially in case of extensive fibrosis, and most surgeons are not accustomed to this dissection plane. We would advise to be cautious and refer these patients to a specialized centre, where conversion to a total pelvic exenteration can be performed as needed when perioperative frozen sections show involved resection margins. In case of damage to the urethra, repair will not result in healing of the urethra. A permanent suprapubic catheter may temporarily alleviate symptoms of urine leakage, but urinary deviation is usually indicated to restore quality of life.

In case the prostate cannot be saved, which is common in case of T4 tumours invading the prostate or locally recurrent disease in men, the prostate is resected completely and the urethra cannot be re-anastomosed, as high dose radiotherapy (which almost all patients have received) impairs proper healing of a vesico-urethral anastomosis. Therefore, we routinely perform a total pelvic exenteration in these cases, resecting both prostate and bladder and create an urinary diversion. For further details, see below (total pelvic exenteration).

Uterus and vaginal wall

Whereas in men, anterior T4 and recurrent rectal cancer may extend into bladder and prostate, in women, the uterus and posterior vaginal wall are the first to become involved in tumour extension. Tumour ingrowth into the body of the uterus is relatively rare, as the peritoneal reflection is located lower, at the level of the cervix. Tumour ingrowth at this level can easily be solved by resection of the uterus, as described for gynaecological cancer. The ovarian vessels and ligaments are ligated and the uterus mobilized. This can be done by opening the peritoneum and dissecting the bladder form the anterior aspect of the uterus. The vaginal wall is identified and cleared to the caudal aspect of the cervix. The ureters are identified up to their insertion in the bladder or at least up to the point that they are no longer at risk. We then identify the vasculature at the level of the cervix, isolate and either ligate it or use an energy device. When cutting of the many venous branches results in blood loss, it is imperative to be cautious with clamps, diathermy and energy devices, considering the proximity of the ureter. We then open the vagina anteriorly, below the palpated level of the cervix, using diathermy and cut the lateral and posterior aspect of the vaginal wall. The placement of clamps on the vaginal wall and lifting these facilitates separation of vagina and rectum. The rectum may be cut at the level desired. We close the vaginal wall with a slowly absorbable suture, taking care to not include the distal ureter in the sutures.

Involvement of the cervix and posterior vaginal wall is more common. We follow the same procedure as described above. When the anterior vaginal wall is opened, we perform an inspection and palpation of the vaginal wall and choose our level of dissection. Findings on the preoperative MRI also guide decision-making. The posterior wall is transected and the vaginal wall freed from the rectum. The lateral wall may be transected with diathermy, or an energy device. The defect in the vaginal wall may be large and when closed primarily, the remnant of the vagina may be small. This may be solved by performing some type of plasty. We routinely use a VRAM flap, in which case either skin, fascia or peritoneum may be used to replace the vaginal wall resected.(41) The alternative is to close the vagina primarily and refer the patient to the gynaecologist for dilatation at an early stage. There are no data proving one technique superior to the other. In case the urethra is involved, a total pelvic exenteration is indicated. In such cases, near complete removal of the vagina (colpectomy) is often unavoidable.

Total pelvic exenteration (TPE)

In case of extensive involvement of the bladder, the prostate in men or the urethra, a total pelvic exenteration is indicated for radical resection. In case of a primary rectal tumour, the rectosigmoid is mobilized and cut as usual. The ureters are identified and cut at the lowest level possible, while preserving the vasculature and keeping a safe margin from tumour

and fibrosis. The ureters are mobilized and single J catheters are inserted. Posteriorly, the rectum is mobilized according to TME principles when possible, or including fascia and periosteum when needed. Now, the easiest step is to free the bladder form the pelvic wall anterolaterally with diathermy or an energy device. This then leaves the lower vesical, prostatic or uterine arteries and veins, which may be ligated, but can be safely transected with an energy device. Rectum and bladder have now been freed posteriorly and laterally. The bladder should now be freed on the anterior side. Here, one can easily cause profuse bleeding from venous branches contributing to the internal iliac vein and the venous plexus located posteriorly of the symphysis. Careful dissection, combining diathermy and ligatures, should prevent extensive blood loss. An energy device is helpful, but should be used cautiously in this area. Large bites and rough tissue handling will result in unnecessary blood loss.

TPE in men:

Posterior to the symphysis, the dissection is continued over the neck of the bladder and the prostate in men. The fascia of the pelvic floor is incised just lateral and anterolateral of the neck of the bladder, which frees the bladder neck. Now, only the rectum, prostate and urethra remain fixed. Following the contours of the prostate, the urethra is cut distally. We leave a Foley catheter inserted, so we can easily palpate the urethra in an area that is difficult to visualize. The Foley catheter does not need to be removed but may be cut along with the urethra. Now we come back to the ventral side of the lower rectum. Depending on the extension of the tumour, the lower rectum may be spared, or an APE may be performed. In case of an APE, dissection anterior of the prostate can also be easily preformed from the perineum, in which case we choose a plain just posterior of the symphysis to include the prostate.

TPE in women:

Posterior to the symphysis, the dissection is continued over the neck of the bladder, after which the urethra may be cut and the anterior vaginal wall opened. The involved part of the vagina is included in the resection specimen, after which the rectum may be resected completely or transected at the desired level.

Urinary diversion

The standard option for urinary diversion is Bricker's diversion, as described elsewhere.(42) In case the descending colon or sigmoid is transected during the procedure, we prefer a colon conduit. The distal colon is cut leaving a segment of approximately 15-20 centimetre with an arterial pedicle. This may be the mesenteric inferior artery, the left colonic artery or in some cases, the left branch of the middle colic artery. After mobilization, both ureters may be anastomosed in exactly the same way as in Bricker's diversion. The urinary stoma

often needs to be placed on the left side of the abdomen and after mobilization of the transverse colon, the stoma for stool is then placed on the right side of the abdomen. The advantage of this approach is that Bricker's diversion results in an extra ileo-ileostomy with a risk of complications such as leakage, whereas diversion with a colon conduit does not require an extra anastomosis.

Intraoperative radiation therapy

When the lateral pelvic sidewall or dorsal structures are involved, achieving clear resection margins may be difficult despite extensive resections. In case of doubt, peroperative assessment of the resection margin can be performed by frozen sections. In patients with narrow or involved margins, intraoperative radiation therapy reduces the local recurrence rate.(17, 43) Therefore, we advocate intraoperative radiation therapy (IORT) in locally advanced rectal cancer in patients with involved or narrow (< 1 mm) circumferential resection margins and locally recurrent rectal cancer.

Mortality and morbidity

Improved surgical techniques, perioperative care and patient selection have reduced mortality and morbidity, but pelvic exenteration remains a procedure with a high risk of complications. (14, 15, 23, 44) The most common complications are listed in table 1. Perioperative 30-day mortality rates are reported in a range of 0% - 10%.(14, 18, 20, 44, 45) Especially in frail and elderly patients high perioperative mortality rates have been reported; up to 14%.(46) The overall morbidity rate has been described to be anywhere between 32-100%. (24, 44) Patients often have common complications such as (intraoperative) bleeding, wound infection, pneumonia and (pelvic) abscesses, but the removal of adjacent organs is associated with other complications than normally encountered in colorectal surgery. (25) Short term complications of urinary diversion are leakage or obstruction of the urinary enteric anastomosis. Long-term complications include urinary stenosis and fistulas.(47-49) These complications can sometimes be managed conservatively, but more often require reintervention by prolonged drainage, nephrostomy catheters or ureter reimplantation.(48) Perineal wound problems after exenterative surgery are also common: besides wound infection and abscesses on the short term, perineal hernia or fistulas can occur on the long term.(14, 24) Muscle flap reconstructions may improve perineal wound outcome and pelvic floor dysfunction, but failure of perineal reconstructions often results in catastrophic wound problems.(41, 50)

Table 1. Complications after pelvic exenteration

Gastrointestinal	*Anastomotic leakage*
	Intestinal obstruction
	Perineal hernia
	Parastomal hernia
	Fistula
Urinary diversion	*Urinoma*
	Anastomotic stricture
	Obstruction
	Fistula
	Bladder retention
	Urinary tract infection
General	*Haemorrhage*
	Wound infection
	Wound breakdown
	Presacral abscess
	Intra-abdominal abscess
	Muscle flap necrosis
	Pulmonary
	Venous thrombosis
	Central venous line infection

Oncological outcomes

Oncological outcomes after pelvic exenteration have improved over the last decades, since pelvic exenteration was first described by Brunschwig for advanced cervix cancer.(21, 23) A Summary of oncological results is displayed in table 2. Nowadays, 5-year survival rates after pelvic exenteration for locally advanced rectal cancer ranges between 22% to 66%. For pelvic exenteration for locally recurrent rectal cancer, 5-year survival rates are 0% to 37%.(19, 20, 44, 45) The 5-year local recurrence free survival rate for primary locally advanced rectal cancer is reported to be 65%- 88%. For locally recurrent rectal cancer, this is reported within a range of 38% to 60%. (16, 20, 44) Notably, these numbers are described by several single centre cohort studies and recent meta-analyses with a heterogeneous study population.

Table 2. Oncological outcomes

				Number of patients					5-year survival (%)		Clear margins (%)	
Author	**Year**	**Study type**	**Type of cancer**	**Total**	**LARC**	**LRRC**	**Morbidity (%)**	**Mortality (%)**	**LARC**	**LRRC**	**LARC**	**LRRC**
Vermaas(45)	2006	retrospective cohort study	LARC & LRRC	35	23	12	NR	3	52	32 (3-year)	83	58
Ferenschild(9)	2009	retrospective cohort study	LARC & LRRC	48	32	16	64	NR	66	8	82	58
Nielsen(61)	2011	prospective cohort study	LARC & LRRC	90	50	40	51	2	46	17	66	38
Yang(44)	2013	systematic review	LARC & LRRC	1049	629	420	57	2	52	18	73	NS
Kusters(62)	2014	retrospective cohort study	LARC	95	95	NA	NS	4	62	NA	87	NA
Bhangu(20)	2014	prospective cohort study	LARC & LRRC	100	55	45	53	0	78 (3-year)	65 (3-year)	91	62
Quyn(63)	2016	prospective cohort study	LARC	104	104	NA	31	1	62	NA	86	NA
Similis(16)	2017	systematic review	LARC & LRRC	1326	569	590	NR	NR	NS	NS	86	66
PelvEx Collaborative(14)	2017	meta-analysis	LARC	1291	1291	NA	38	1.5	56 (3-year R0)	NA	80	NA
PelvEx Collaborative(18)	2018	meta-analysis	LRRC	1184	NA	1184	32	2	NA	48 (3-year R0)	NA	55

LARC: Locally advanced rectal cancer LRRC: locally recurrent rectal cancer NR: not reported NS: not specified NA: not applicable

Although pelvic exenteration is a more radical approach compared to abdominoperineal resection or low anterior resection, oncological outcomes are not significantly worse, even when tumours requiring exenteration are likely to be more advanced.(51) 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 by more than twofold advantage as described by a recent systematic review.(16) Three-year survival rates are reported up to 82% for R0 resections, compared to 55% for R1 and 0% for R2 resections for primary locally advanced rectal cancer.(20) Similar differences in 3-year overall survival rates were found for locally advanced rectal cancer (R0 56.4%, R1 29.6% and R2 8.1%) and locally recurrent rectal cancer (R0 48.1%, R1 33.9% and R2 15%).

Quality of life

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. (52, 53) Although standard procedures in rectal cancer surgery have a significant impact on physical and mental health, body image and sexual functioning, the impact of pelvic exenteration is often thought to be much higher. On the other hand, the prognosis of patients with locally advanced or recurrent rectal cancer without treatment is poor, with a median survival of 1 year and a 5-year survival rate of 4.4%. Moreover, untreated locally advanced or locally recurrent rectal cancer is associated with severe symptoms such as pain, incontinence, fistula and unmanageable wounds, even with palliative radiotherapy or chemotherapy aimed solely at reducing symptoms. (54-57) A study that compared the quality of life of patients undergoing pelvic exenteration and patients who refrained from surgery, 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.(15, 58) At nine months after surgery, quality of life in the exenterative group was back at baseline.(15, 58) In addition, there appears to be no difference in quality of life when pelvic exenteration patients are compared to patients who underwent an abdominoperineal excision.(59)

Surgery for rectal cancer invading in the anterior compartment of the pelvis often results in sexual dysfunction. Men may experience erectile or ejaculatory disorders and in women, lubrication disorder and dyspareunia are common, especially when parts of the vaginal wall are resected. Both men and women report deterioration in body image.(53, 60)

Patients may experience major physical and mental changes before, during and after the surgical procedure. Therefore, it is advised to give extended counselling about the possible life changing events that patients will experience pre- and post-surgery.

Conclusions

In patients with locally advanced rectal cancer or recurrent rectal cancer with invasion of adjacent urogenitary organs pelvic exenteration is often the only potentially curative treatment option. Patient selection and preoperative assessment in a multidisciplinary tumour board is mandatory. The cornerstone of treatment is achievement of radical resection margins by surgery, which is the most important prognostic factor for overall survival. Induction therapy should be considered in case of expected narrow surgical margins. Perioperative mortality and morbidity is reduced over the last decades but remains high and needs to be taken in consideration before surgery. After surgery, quality of life is decreased but improves rapidly and in the longer term, patients report a good quality of life, comparable to patients who underwent less invasive procedures. Therefore, patients should not be denied exenterative surgery based on perceived poor quality of life.

Key points

- Achievement of a clear resection margin is the most important prognostic factor for overall survival.
- Perioperative mortality and morbidity is high after pelvic exenteration with a wide range of complications related to multivisceral resection, especially in frail and elderly patients.
- 5-year overall survival after pelvic exenteration for locally advanced rectal cancer ranges from 22% - 66% and for locally recurrent rectal cancer from 0% - 37%.
- Quality of life decreases shortly after surgery but increases rapidly after surgery and is higher within 3 months after surgery compared to patients who did not undergo exenteration and continues to improve to adequate or even baseline quality of life.

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Chapter 10

Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly

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ABSTRACT

Background

Total pelvic exenteration (TPE) is a radical approach for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) in case of tumour invasion into the urogenitary tract. The aim of this study is to assess surgical and oncological outcomes of TPE for LARC and LRRC in elderly patients compared to younger patients.

Methods

All patients who underwent TPE for LARC and LRRC between January 1990 and March 2017 were retrospectively analysed. Patients aged < 70 years were classified as younger and ≥ 70 years as elderly patients.

Results

In total 126 patients underwent TPE, of whom 88 younger and 38 elderly patients. Elderly patients had a significantly higher number of ASA > II patients (p = 0.01). Indication for surgery LARC (n = 73) and LRRC (n = 53) did not differ significantly. The 30-day mortality rate was significantly higher (p = 0.01) in elderly (13%) compared to younger patients (3%). Elderly patients experienced more anastomotic leakage (p = 0.02). Median overall survival (OS) was 75 months [95%CI 37.1;112.9] for elderly and 45 months [95%CI 22.4;67.8] for younger patients (p = 0.77), with 5-year OS rates of 51% for elderly and 44% for younger patients. Median disease specific survival (DSS) was 78 months [95%CI 69.1;86.9] for elderly and 60 months [95%CI 36.6;83.4] for younger patients (p = 0.34). The 5-year DSS rate was 67% and 49%, respectively.

Conclusions

TPE is an invasive treatment for rectal cancer with high 30-day mortality in elderly patients. Oncological outcomes are similar in elderly and younger patients. Therefore, TPE should not be withheld because of high age only, but careful patient selection is needed.

INTRODUCTION

The incidence of rectal cancer is increasing worldwide and increases with age.(1-3) At the time of diagnosis of primary rectal cancer approximately 10% of the patients have locally advanced rectal cancer (LARC) and approximately 6-10% of patients treated for primary rectal cancer will develop locally recurrent rectal cancer (LRRC).(4-8) Over the past decades the development of multimodality treatment for LARC and LRRC, including TME-surgery, neoadjuvant (chemo-)radiotherapy, surgical treatments and intra-operative radiotherapy (IORT), improved overall survival and local control after treatment.(5, 6, 9-12) Achievement of a radical resection margin in rectal surgery is a known important prognostic factor. 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. Total pelvic exenteration (TPE) is an invasive radical treatment modality and it comes with considerable morbidity and mortality.(11, 13, 14) Treatment of LARC and LRRC with TPE is a challenge, 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.(15-18) 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. The aim of this study is to compare mortality, morbidity, surgical and oncological outcomes between elderly and younger patients who underwent TPE for LARC or LRRC and to assess whether TPE is justified as a treatment for LARC and LRRC in the elderly patient.

Patients and Methods

All patients with LARC or LRRC who had undergone TPE with curative intent at the Erasmus MC Cancer Institute, a tertiary referral centre in the southwest region of the Netherlands, between February 1990 and March 2017 were identified from a prospectively maintained rectal cancer database. We retrospectively reviewed all data on patient demographics, (neo) adjuvant treatment, tumour characteristics, perioperative variables and short- and long-term surgical and oncological outcomes. Data was obtained from medical records, municipality registers and general practitioners. All patients were followed up by our institute and last update of follow up was performed on 28 February 2018. The present study was approved by the Erasmus MC local medical ethics committee (registration number MEC-2017-448).

Elderly patients were defined as patients aged ≥ 70 years at the time of operation and patients were defined as younger patients when aged < 70 years. All patients were dis-

cussed in a multidisciplinary tumour (MDT) board prior to neoadjuvant therapy and after neoadjuvant therapy for restaging prior to surgery. Initial tumour stage was assessed by physical examination, colonoscopy, histology and radiologic imaging. The American Joint Committee on Cancer (AJCC) TNM-classification was used according to the edition valid at the time of diagnosis (4th edition before 1998, 5th edition for 1998-2003, 6th edition for 2003-2010 and 7th edition from 2010 onwards).(19) Radiologic imaging usually consisted of CT-thorax and CT-abdomen and pelvic MRI. Additional diagnostics were performed when indicated, such as targeted echo, abdominal MRI, PET-CT, lymph node biopsy and tissue biopsy. Complications were scored according to the Clavien-Dindo classification.(20)

Neoadjuvant treatment

Neoadjuvant treatment consisted of chemoradiotherapy, chemotherapy only or radiotherapy only depending on tumour stage and patients comorbidities. Chemoradiotherapy usually consisted of a dose of 46 - 50 Gy delivered in fractions of 1.8 - 2 Gy with concomitant oral chemotherapy (Capecitabine 825 - 1000 mg/m2 for 5-7 days a week) during the whole course of neoadjuvant therapy. Patients treated with radiotherapy only usually received a short course with a total dose of 25 Gy delivered in 5 fractions of 5 Gy. Neoadjuvant treatment by chemotherapy alone was incidentally given. In case of LRRC, neoadjuvant treatment was determined by previous therapy for the primary tumour. In general, if patients were previously treated with (chemo) radiotherapy, patients received reirradiation with a dose of 30 Gy delivered in fractions of 2 Gy with concomitant Capecitabine. For patients who were not previously treated and with no contraindications for (chemo) radiotherapy, the same course for patients with LARC was administered.

Surgical procedures

Total pelvic exenteration was defined as en bloc resection of the rectum including complete removal of the bladder and additional resection of reproductive organs (prostate/seminal vesicles or uterus, ovaries and/or vagina) with or without sacrectomy. The anus and levatory muscles were usually resected, but were spared incidentally. Patients who had undergone anterior or posterior pelvic exenteration were excluded. Surgical approach for resection was either abdominal or abdominoperineal. In case of a possible microscopically involved positive resection margin, frozen sections were taken peroperatively and were instantly reviewed by a pathologist. In case of a narrow microscopically resection margin of < 2 mm or a clinical high risk of involved resection margins, intraoperative brachytherapy was administered with a dose of 10 Gy as previously described.(21) When possible, omentoplasty was performed to fill the pelvis. When feasible, primary perineal wound closure was performed. If this was not feasible, muscle flap reconstruction of the perineal defect was performed by the plastic surgeon with a vertical rectus abdominis myocutaneous (VRAM) or gracilis muscle flap. In collaboration with the urologist, an ileal conduit, unilateral

ureterocutaneostomy or colon conduit was performed as an urinary diversion. Ileo-ileal anastomosis was performed in patients with an ileal conduit and in patients with a colon conduit, an anastomosis is not necessary, with the exception of patients who underwent an additional bowel resection.

Statistical analysis

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). The method of Kaplan-Meier was used for survival analysis and comparisons were made using log rank test. Overall survival was calculated from the day of TPE until death or last follow up date and disease specific survival was calculated until cancer related death or last follow up date. Mann-Whitney U and Chi-squared test were performed as appropriate. Two-sided p-values < 0.05 were considered statistically significant. Statistical analysis were performed using IBM SPSS Statistics version 24.0.0 for Windows (IBM Corp, Armonk, New York, USA).

RESULTS

A total of 126 patients underwent TPE for rectal cancer between January 1990 and March 2017. Patient characteristics are depicted in Table 1. Eighty-eight patients (70%) were younger than 70 years and 38 patients (30%) were aged 70 years or older at the time of surgery. The median age in the elderly was 72.5 years [IQR 71–75.3] and 60.5 years [IQR 51–65.8] in the younger group. The elderly had a significantly higher number of patients with ASA score > II ($p = 0.01$) and cardiac comorbidities ($p < 0.01$). All but seven patients received neoadjuvant therapy and the majority (55%) received chemoradiotherapy.

Surgical results

Surgical results are shown in Table 1. Indications for surgery were LARC (n = 73) and LRRC (n = 53) and did not differ significantly ($p = 0.44$). There was no statistical difference between the surgical approach in both age groups ($p = 0.09$). The duration of surgery was significantly less ($p < 0.01$) in elderly patients with a median of 426 min (IQR 379 - 507) compared to younger patients with a median of 514 min (IQR 441 - 619). A muscle flap reconstruction was performed significantly more often ($p = 0.04$) in younger patients than in elderly patients: 17 patients (19%) versus two patients (5%), respectively. IORT was admitted in 37 younger patients (42%) and in seven elderly patients (18%) which was statistically significantly different ($p = 0.01$).

Histopathological results

Histopathological results are displayed in Table 1. In the younger patients, a clear resection margin (> 0 mm) was achieved in 74 patients (84%). Intra-operative radiotherapy (IORT) was administered to 27 patients with a resection margin of > 0 mm and < 2 mm. In the elderly patients, a clear resection margin was achieved in 36 patients (95%). IORT was administered to five patients with a resection margin of > 0 - 2 mm. The difference in the number of clear resection margins between younger and elderly patients was not statistically significant (p = 0.10).

Table 1. Patient characteristics, surgical and histopathological results

		Total (N = 126)	Age < 70 years (N = 88)	Age ≥ 70 years (N = 38)	P-value
Gender	Male	107 (85%)	73 (83%)	34 (89%)	0.35
	Female	19 (15%)	15 (17%)	4 (11%)	
Age	Median (IQR)	65 (56-70)	60.5 (51-65.8)	72.5 (71-75.3)	n/a
ASA	ASA I-II	108 (86%)	78 (94%)	30 (79%)	0.01[a]
	ASA > II	13 (10%)	5 (6%)	8 (21%)	
	Missing	5 (4%)			
Respiratory comorbidity	No	104 (83%)	71 (88%)	33 (87%)	0.90
	Yes	15 (12%)	10 (12%)	5 (13%)	
	Missing	7 (6%)			
Cardiac comorbidity	No	97 (77%)	74 (91%)	23 (61%)	<0.01[a]
	Yes	22 (18%)	7 (9%)	15 (39%)	
	Missing	7 (6%)			
Type of rectal cancer	LARC	73 (58%)	49 (56%)	24 (63%)	0.44
	LRRC	53 (42%)	39 (44%)	14 (37%)	
Neoadjuvant therapy	CTRTx[c]	70 (56%)	50 (57%)	20 (53%)	0.08
	RTx[d]	47 (37%)	34 (39%)	13 (34%)	
	CTx[e]	2 (2%)	2 (2%)	0 (0%)	
	None	7 (6%)	2 (2%)	5 (13%)	
Radiotherapy dose	Median (IQR)	50 (30-50)	50 (30-50)	50 (30-50)	0.15
Previous surgery	No	52 (41%)	30 (34%)	22 (58%)	0.03[a]
	Yes without anastomosis	44 (35%)	36 (41%)	8 (21%)	
	Yes with anastomosis	30 (24%)	22 (25%)	8 (21%)	
Surgical results					
Surgical approach	Abdominoperineal	74 (58%)	56 (64%)	18 (47%)	0.09
	Abdominal	52 (41%)	32 (36%)	20 (53%)	
Operation time	Median (IQR)	490 (415-580)	514 (441-619)	426 (379-507)	<0.01[b]
Blood loss (ml)	Median (IQR)	3000 (1362-5000)	3000 (1138-5500)	2500 (1625-3816)	0.52
Peroperative bleeding	No	99 (79%)	70 (80%)	29 (76%)	0.69
	Yes	27 (21%)	18 (20%)	9 (24%)	
MFR[f]	No	107 (85%)	71 (81%)	36 (95%)	0.04[a]

Table 1. Patient characteristics, surgical and histopathological results (continued)

		Total (N = 126)	Age < 70 years (N = 88)	Age ≥ 70 years (N = 38)	P-value
	Yes	19 (15%)	17 (19%)	2 (5%)	
Urinary diversion	Ileal conduit	90 (71%)	66 (75%)	24 (63%)	0.16
	Colon conduit	35 (28%)	22 (25%)	13 (34%)	
	Ureterocutaneostomy	1 (1%)	0 (0%)	1 (3%)	
Anastomosis	No	33 (26%)	20 (23%)	13 (34%)	0.18
	Yes	93 (74%)	68 (77%)	25 (66%)	
Omentoplasty	No	18 (14%)	12 (14%)	6 (16%)	0.75
	Yes	108 (86%)	76 (86%)	32 (84%)	
IORT[g]	No	82 (65%)	51 (58%)	31 (82%)	0.01[a]
	Yes	44 (35%)	37 (42%)	7 (18%)	
Hospital stay (days)	Median (IQR)	14 (11-21.5)	15 (11-23)	14 (11-17.3)	0.58
ICU stay (days)	Median (IQR)	2 (1-3)	1 (1-3)	2 (1-3.3)	0.81
Histopathological results					
Tumour size (cm)	Median (IQR)	4.0 (2.7-6.0)	4.0 (3.0-7.0)	4.0 (2.7-5.9)	0.39
Nodal status	N0	68 (73%)	46 (73%)	22 (73%)	0.97
	N+	25 (27%)	17 (27%)	8 (27%)	
	Missing	*33 patients*			
Clear resection margin	No	16 (13%)	14 (16%)	2 (5%)	0.10
	Yes	110 (87%)	74 (84%)	36 (95%)	
Resection margins					
Clear margin	> 2 mm	88 (70%)	57 (65%)	31 (82%)	0.22
Microscopically clear	> 0 mm & < 2 mm	22 (17%)	17 (19%)	5 (13%)	
Microscopically involved	< 0 mm	12 (10%)	10 (11%)	2 (5%)	
Macroscopically involved		4 (3%)	4 (5%)	0 (0%)	
Pathologic complete response	No	122 (97%)	85 (97%)	37 (97%)	0.82
	Yes	4 (3%)	3 (3%)	1 (3%)	
Follow up					
Local recurrence	No	94 (75%)	62 (70%)	32 (84%)	0.10
	Yes	32 (25%)	26 (30%)	6 (16%)	
Metastases	No	68 (54%)	48 (55%)	20 (53%)	0.84
	Yes	58 (46%)	40 (45%)	18 (47%)	

[a] Chi squared test [b] Mann-Whitney U test [c]: Chemoradiotherapy [d]: Radiotherapy [e]: Chemotherapy [f]: Muscle flap reconstruction [g]: Intra-operative radiotherapy
Percentages do not add up due to rounding

Postoperative mortality and morbidity

Mortality is shown in Table 2, complications in Table 3 and Clavien-Dindo scores are depicted in Table 4. In the elderly group five patients (13%) died within 30 days of surgery compared to two patients (2%) in the younger group, which was a statistically significant difference (p = 0.01). The 3, 6 and 12 months mortality rates were not significantly different. Three elderly

patients died of aspiration pneumonia, one patient died of sepsis after anastomotic leakage and one cause of death is unknown. In the younger group two patients ,died of intra-abdominal sepsis based on a necrotic urostoma in one patient and interloop abscesses in the other patient. There was a significant higher rate of anastomotic leakage in the elderly group (in case an anastomosis was performed); five patients (20%) compared to three patients (4%) in the younger group (p = 0.02). In all eight patients with anastomotic leakage, all leakages were related to the ileo-ileal anastomosis, which was performed in seven patients for an ileal conduit and in one patient for additional small bowel resection. Three elderly patients with anastomotic leakage had received previous surgery for primary rectal cancer, but an anastomosis was not performed at that time. All five other patients with anastomotic leakage did not undergo surgery before and had no anastomosis from previous surgery. There was no significant difference in median length of hospital stay, 15 days for elderly (IQR 11 - 23) and 14 days for younger patients (IQR 11 - 17), respectively, (p = 0.58).

Follow up and survival

The median follow up time was 48 months [95% CI 41.5;54.5] for elderly patients and 145 months [95% CI 69.0;221.0] for younger patients. At last follow up 17 patients (45%) were alive in the elderly group and 32 patients (36%) in the younger group. In the elderly group, local recurrence occurred in six patients (16%) and distant metastases in 18 patients (47%). In the younger group, 26 patients (30%) were diagnosed with a local recurrence and 40 patients (46%) with distant metastases.

Table 2. Mortality rates

		Total (N = 126)	Age < 70 years (N = 88)	Age ≥ 70 years (N = 38)	P-value
In hospital mortality	No	120 (95%)	86 (98%)	34 (89%)	0.05[a]†
	Yes	6 (5%)	2 (2%)	4 (11%)	
Died within 30 days	No	119 (94%)	86 (98%)	33 (87%)	0.01[a]
	Yes	7 (6%)	2 (2%)	5 (13%)	
Died within 60 days	No	116 (92%)	84 (95%)	33 (87%)	0.09
	Yes	10 (8%)	4 (5%)	5 (13%)	
Died within 90 days	No	115 (91%)	83 (94%)	33 (87%)	0.15
	Yes	11 (9%)	5 (6%)	5 (13%)	
Died within 6 months	No	112 (89%)	80 (91%)	32 (84%)	0.34
	Yes	13 (10%)	7 (8%)	6 (16%)	
Lost to follow-up[b]		1 (1%)	1 (1%)	0 (0%)	
Died within 1 year	No	101 (80%)	73 (83%)	28 (74%)	0.44
	Yes	21 (17%)	13 (15%)	8 (21%)	
Lost to follow-up[b]		4 (3%)	2 (2%)	2 (5%)	

† $p < 0.05$ [a] Chi squared test [b] Follow up less than one year

Table 3. Complications

		Total (N = 126)	Age < 70 years (N = 88)	Age ≥ 70 years (N = 38)	P-value
Anastomotic leakage[a]	No	85 (91%)	65 (96%)	20 (80%)	0.02[b]
	Yes	8 (9%)	3 (4%)	5 (20%)	
Urinary tract infection	No	111 (88%)	76 (86%)	35 (87%)	0.36
	Yes	15 (12%)	12 (14%)	3 (13%)	
Relaparotomy	No	99 (79%)	69 (78%)	30 (79%)	0.95
	Yes	27 (21%)	19 (22%)	8 (21%)	
Any surgical Reintervention	No	79 (63%)	53 (60%)	26 (68%)	0.38
	Yes	47 (37%)	35 (40%)	12 (32%)	
Any Abscess drainage	No	98 (78%)	67 (76%)	31 (82%)	0.50
	Yes	28 (22%)	21 (24%)	7 (18%)	
Pneumonia	No	109 (87%)	78 (89%)	31 (82%)	0.29
	Yes	17 (13%)	10 (11%)	7 (18%)	
Presacral abscess	No	101 (80%)	69 (78%)	32 (84%)	0.45
	Yes	25 (20%)	19 (22%)	6 (16%)	
Sepsis	No	101 (80%)	69 (78%)	32 (84%)	0.45
	Yes	25 (20%)	19 (22%)	6 (16%)	
Wound complication	No	73 (58%)	49 (56%)	24 (63%)	0.43
	Yes	53 (42%)	39 (44%)	14 (37%)	
Cardiac complication	No	110 (87%)	80 (91%)	30 (79%)	0.06
	Yes	16 (13%)	8 (9%)	8 (21%)	
Reintervention stoma	No	118 (94%)	82 (93%)	36 (95%)	0.74
	Yes	8 (6%)	6 (7%)	2 (5%)	
Urinoma	No	120 (95%)	85 (97%)	35 (92%)	0.28
	Yes	6 (5%)	3 (3%)	3 (8%)	
Nephrostomy	No	117 (93%)	82 (93%)	35 (92%)	0.83
	Yes	9 (7%)	6 (7%)	3 (8%)	
Clavien-Dindo ≥ 3	No	71 (56%)	49 (56%)	22 (58%)	0.82
	Yes	55 (44%)	39 (44%)	16 (42%)	

[a]In patients with anastomosis performed during this episode of surgery [b]Chi squared test

Table 4. Complications Clavien-Dindo

	Age < 70 years (N = 88)	Age ≥ 70 years (N = 38)
No complication	21 (24%)	5 (13%)
Clavien-Dindo I	13 (15%)	3 (8%)
Clavien-Dindo II	15 (17%)	14 (37%)
Clavien-Dindo IIIA	11 (13%)	3 (8%)
Clavien-Dindo IIIB	19 (22%)	4 (11%)
Clavien-Dindo IVA	3 (3%)	4 (11%)
Clavien-Dindo IVB	2 (2%)	0 (0%)
Clavien-Dindo V	4 (5%)	5 (13%)

Percentages do not add up due to rounding

Overall Survival

The estimated 3-year overall survival (OS) rate was 64% in elderly patients and 56% in younger patients. The estimated 5-year OS rate was 51% for elderly patients and 44% for younger patients. Median OS for elderly patients was 75 months [95% CI 37.1;112.9] and 45 months [95% CI 22.4;67.8] for younger patients (Figure 1a), this was not significantly different (p = 0.77).

Disease specific survival

The estimated 3-year disease specific survival (DSS) rate was 82% in elderly patients and 62% in younger patients. The estimated 5-year DSS rate was 67% in elderly patients and 49% in younger patients. Median DSS for elderly patients was 78 months [95% CI 69.1;86.9] and 60 months [95% CI 36.6;83.4] for younger patients (Figure 1b), this was not significantly different (p = 0.34).

Local recurrence free survival

There was no significant difference in local recurrence free survival (LRFS) between both groups (p = 0.15). Median LRFS was not reached in both groups. The estimate 3-year and 5-year LRFS rates were both 78% in elderly patients and 68% and 65% in younger patients, respectively (Figure 1c).

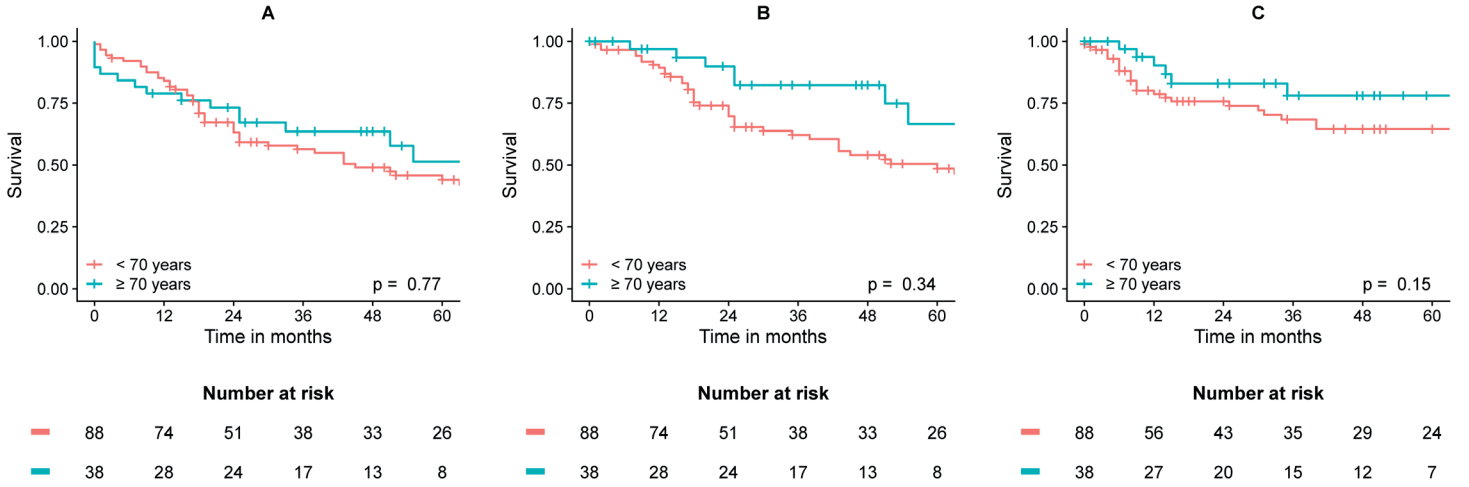

***Figure 1. A**. Overall survival by age <70 years vs ≥70 years. **B**. Disease specific survival by age <70 years vs ≥70 years. **C.** Local recurrence free survival by age <70 years vs ≥70 years.*

DISCUSSION

This study compares the results of total pelvic exenteration (TPE) for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) in younger and elderly patients. Oncological outcomes are similar, but perioperative mortality is higher among elderly patients during the first 30 days after surgery.

Previous studies showed that colorectal cancer surgery in the elderly patient comes with high mortality and morbidity and overall survival is not always improved.(15, 18, 22) Rutten et al. (18) 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. Six months after surgery the mortality rate was still higher in the elderly patients, 16% compared to 8% in the younger group, although not significant. Other series, by Quyn et al. (23) and the PelvEx Collaborative (14), who performed TPE for LARC reported a 30-day mortality of 1 - 1.5 % and 10% one-year mortality, but median age was 62 and 63 years in these cohorts and a comparison between age groups was not made. Reduction of the mortality rate within the first year postoperative remains a challenge in elderly patients.(24) In our institute, age is not a factor for preoperative counselling whether to perform an anastomosis, but in the present study, there was a significantly higher rate of anastomotic leakage in elderly patients, which is in concordance with other studies.(25, 26) Teixeira et al. described more complications after performance of an ileal conduit in comparison with a colon conduit.(27) In our study, seven out of eight patients with anastomotic leakage received an ileal conduit with an ileo-ileal anastomosis. A colon conduit may be preferable to an ileal conduit to prevent anastomotic leakage. In our series, one elderly patient died of sepsis based on anastomotic leakage. Aspiration pneumonia caused three deaths in elderly patients, which emphasizes the seriousness of this complication, especially in elderly patients. In general, elderly patients experienced a higher percentage of overall complications than younger patients which is in concordance with a previous systematic review of rectal cancer surgery between elderly and non-elderly patients by Manceau et al.(17)

Achievement of a clear resection margin is one of the most important prognostic factors for overall survival and can be achieved, if necessary, with pelvic exenteration.(14, 23) In the present study, the number of clear resection margins was similar to the range of 79% – 87% reported by others after TPE for rectal cancer.(13, 14, 23, 28) Notably, we found a difference in percentage of clear resection margins: 84% in younger patients and 95% in elderly patients. This difference was not statistically significant. In addition, our institute previously showed reduction of local recurrence rates with additional intra-

operative radiotherapy (IORT) for surgical treatment of LARC and others described acceptable survival of treatment with IORT for LARC.(29, 30) In our study IORT was administered significantly more often in younger patients compared to elderly patients (42% vs 18%, p = 0.01). In our institute, we generally perform intraoperative brachytherapy in case of resection margins < 2 mm. There was a higher percentage of resection margins < 2 mm in younger patients, which explains a higher rate of IORT in the younger group. Admission of intraoperative brachytherapy results in 2-3 hours extra operation time, it may be that surgeons are less willing to prolong the operation with such a long time in the elderly patient. In case of a doubtful resection margin, surgeons may be more willing to administer IORT in younger patients compared to elderly patients. The admission of intraoperative brachytherapy could also explain the significantly longer duration of surgery in younger patients compared to elderly patients.

In our study overall survival and disease specific survival did not differ significantly, but this cohort suggests that elderly patients have a better DSS (5-year disease specific survival rate of 67% in elderly compared to 49% in younger patients, p = 0.34). Before surgery, patients are assessed in a multidisciplinary tumour (MDT) board whether they are eligible for TPE. Conceivably, the MDT board is more reluctant to select elderly patients unless good clinical outcome is expected considering their comorbidities. Furthermore, referring physicians may have also selected fit patients for referral to our hospital. Younger patients are likely to be more easily considered for invasive surgery, even when tumour characteristics are unfavourable. Therefore, it could be that our results display a selection of better elderly patients and worse younger patients. Rutten et al.(18) described better oncological outcomes in elderly, but no improvement in overall survival. In their study, overall survival did not improve because of high perioperative mortality. To improve overall survival the challenge remains to reduce perioperative mortality and morbidity in the elderly by better patient selection and/or improving patients performance status prior to surgery.(31, 32) Perioperative chemotherapy may also help in selecting patients. Currently, in line with the national guideline, adjuvant chemotherapy in the treatment of rectal cancer is not standard of care in the Netherlands.(33-35) However, there may be a benefit of perioperative chemotherapy in selected colorectal cancer patients; this should not be denied on the basis of high age alone, as described by Papamichael et al.(36)

A recent study about pelvic exenteration by Radwan et al.(28) included patients, aged ≥ 70 years, who had undergone total pelvic exenteration for primary rectal cancer. The 5-year survival rate of 47% for rectal cancer patients was similar to our results, but the 3% 30-day mortality compares well to our 30-day mortality rate of 13%. However, only 31 out of 65 patients underwent total pelvic exenteration, while all other patients had undergone

posterior pelvic exenteration and no patients with locally recurrent rectal cancer were included.

Despite high morbidity and mortality after total pelvic exenteration in the elderly, which affects quality of life, the alternative outcome of no treatment is poor, with a reported 5-year survival rate of 4.4% for untreated rectal cancer.(37) Young et al.(38) described quality of life in patients following pelvic exenteration compared to patients who did not undergo exenteration for pelvic malignancies. Quality of life was decreased shortly after surgery, but improved rapidly within one month after surgery. At nine months after surgery, quality of life returned to baseline in the exenteration group and was similar to those patients who did not have surgery. After nine months, quality of life started to deteriorate in patients who did not have exenteration and was higher in patients who had undergone pelvic exenteration.(38) These results suggest that pelvic exenteration results in an acceptable quality of life and that quality of life actually starts decreasing within one year when TPE is not performed for this patient category.

Our data is collected over three decades and especially in the last two decades, our diagnostics (contrast enhanced MRI) and treatment (chemoradiotherapy, TME surgery, IORT) improved gradually. Exploratory assessment of our cohort divided over time showed no significant results. Although it seems that especially elderly patients benefit from improved treatment over time with increased survival and slightly decreased perioperative mortality, we have to conclude that these are very small subgroups of selected patients and that this should be assessed in larger cohorts.

Our study is limited by its retrospective nature and contains a selected group of patients. On the other hand, it contains a rather large homogenous group of patients who all underwent TPE for LARC or LRRC. Despite the fact of selection bias and possible differences in outcomes between LARC and LRRC, this study provides useful insights for outcomes of total pelvic exenteration in the elderly patient for locally advanced and locally recurrent rectal cancer. Finally, direct comparison between studies is difficult because of large difference in subsets of patients, age, type of malignancy, type of surgery and variance in definitions for total pelvic exenteration.

Conclusions

Total pelvic exenteration for locally advanced or locally recurrent rectal cancer is an invasive surgical approach, but should not be withheld from the elderly patient. Careful patient selection is needed to reduce perioperative mortality in elderly patients. If patients are selected carefully and perioperative mortality and morbidity can be reduced, this data sug-

gest that there is no significant difference in oncological outcome between younger and elderly patients after total pelvic exenteration.

Acknowledgements

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Chapter 11

Outcomes of urinary diversion after surgery for locally advanced or locally recurrent rectal cancer with complete cystectomy; ileal and colon conduit

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ABSTRACT

Introduction

Surgery for locally advanced rectal cancer (LARC) or locally recurrent rectal cancer (LRRC) may require total pelvic exenteration with the need for urinary diversion. The aim of this study was to describe outcomes for ileal and colon conduits after surgery for LARC and LRRC.

Methods

All consecutive patients from two tertiary referral centres who underwent total pelvic exenteration for LARC or LRRC between 2000 and 2018 with cystectomy and urinary reconstruction using an ileal or colon conduit were retrospectively analysed. Short- (≤30 days) and long-term (>30 days) complications were described for an ileal and colon conduit.

Results

259 patients with LARC (n =131) and LRRC (n =128) were included, of whom 214 patients received an ileal conduit and 45 patients a colon conduit. Anastomotic leakage of the ileo-ileal anastomosis occurred in 9 patients (4%) after performing an ileal conduit. Ileal conduit was associated with a higher rate of postoperative ileus (21% vs 7%, p = 0.024), but a lower proportion of wound infections than a colon conduit (14% vs 31%, p = 0.006). The latter did not remain significant in multivariate analysis. No difference was observed in the rate of uretero-enteric anastomotic leakage, urological complications, mortality rates, major complications (Clavien-Dindo ≥ 3), or hospital stay between both groups.

Conclusions

Performing a colon conduit in patients undergoing total pelvic exenteration for LARC or LRRC avoids the risks of ileo-ileal anastomotic leakage and may reduce the risk of a post-operative ileus. Besides, there are no other differences in outcome for ileal and colon conduits.

INTRODUCTION

In approximately 10% of all newly diagnosed patients with primary rectal cancer there is local invasion of the tumour in surrounding structures. In patients who develop a local recurrence, which occurs in approximately 6-10% of all patients treated for primary rectal cancer, invasion in adjacent organs, such as the bladder and/or the organs of the reproductive system, is even more common.(1–3) Radical surgery is essential for cure and the achievement of a clear resection margin is the most important prognostic factor for overall survival in these patients.(4,5) To achieve a clear resection margin in patients with tumour invasion in the bladder, prostate or urethra, a radical approach is indicated, which often requires partial or complete cystectomy (i.e. pelvic exenteration). When a complete cystectomy is performed patients require a urinary diversion.(6,7) Historically there are several urinary diversions, but in current practice the most common urinary diversions are an ileal conduit (i.e. Bricker) or a colon conduit.(8–11) In both cases, an isolated bowel segment (ileum or colon) is used as a conduit for the ureters, which is deviated through the abdominal wall as a urostomy. 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. Both procedures are associated with general surgical and urological complications. In addition, conduit specific complications may occur, such as metabolic changes or intra-abdominal complications of the urinary diversion, such as leakage of the uretero-entero anastomosis and ileus.(8,12–14)

The aim of this study was to describe the short- and long-term complications associated with an ileal and colon conduit after surgery for locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) in a pooled cohort of two large tertiary referral hospitals.

Patient and methods

All consecutive patients who underwent a total pelvic exenteration with complete cystectomy for LARC or LRRC with formation of an ileal or colon conduit in the Catharina Hospital Eindhoven (CZE) or the Erasmus MC Cancer Institute (EMC) between January 2000 and November 2018, were identified from a prospectively maintained database. CZE and EMC are both tertiary referral hospitals in the Netherlands. Both centres have an experienced multidisciplinary tumour board (MDT) in which all patients diagnosed with rectal cancer are discussed and evaluated for optimal multimodality treatment. This tumour board includes dedicated surgeons, radiologists, radiation oncologists, medical oncologists and urologists. If indicated, gynaecologists, pathologists and plastic surgeons participate in this meeting.

Data collection

All data on patient and tumour characteristics, (neo) adjuvant treatment, surgical procedures, perioperative variables, short- and long-term surgical and urological outcomes were retrospectively reviewed. All included patients were followed up for at least 30 days after surgery. Thereafter, follow-up was conducted either in the hospital in which the surgery was performed or in the patients' primary referring hospital. The present study was approved by both institutional local medical ethics committees (CZE; registration number: W19.031 and EMC registration number; MEC-2017-448).

Neoadjuvant treatment and surgical procedures

Patients were usually scheduled for neoadjuvant radiotherapy: short-course (25Gy) or long-course (50Gy) radiotherapy for LARC and re-irradiation (30Gy) or long course (50Gy) for LRRC, either with or without concurrent chemotherapy. Surgery was performed in collaboration with the surgical oncologist and urologist. Resection of the rectal tumour was performed by open abdominal or abdominoperineal approach. All patients underwent complete cystectomy and a urinary diversion was performed by ileal or colon conduit. The surgical procedures were similar in both CZE and EMC, except for the administration of intra-operative radiation therapy (IORT) that was delivered as intra-operative external beam radiotherapy (IOERT) in the CZE and as intra-operative brachytherapy (IOBT) in the EMC. In the EMC, the choice for either a colon conduit or an ileal conduit was made during surgery and was based on practical considerations; there were no reasons for choosing one technique or the other from an oncological perspective. A colon conduit was the preferred technique when this would avoid the need to make an extra anastomosis. In practice, this meant that patients who were to receive an end colostomy were selected for the colon conduit technique. In case a primary low anastomosis could be performed or a colon conduit could not prevent an extra anastomosis, an ileal conduit was routinely performed. In the CZE, the preferred method was to perform an ileal conduit.

An ileal conduit was performed as previously described by Bricker et al. In summary, an ileal segment of approximately 15 cm was isolated at 10 cm distance from the valve of Bauhin, and a hand sewed or stapled ileo-ileal anastomosis was performed.(9) Both ureters were spatulated and then separately hand sutured in one layer with PDS 4-0 side-to-end into the ileal segment. Subsequently, the distal end of the conduit was delivered through the abdominal wall and was matured.

To create a colon conduit a colon segment of approximately 15 cm was isolated.(10) This segment was the distal segment of the descending colon that was already transected during a procedure in which the rectum was removed. Oxygenation of this segment was supplied by the left colonic artery, which means that a low tie of the inferior mesenteric

artery was performed for the rectal resection. The colon conduit was often placed in the left hemiabdomen and the transverse colon was then mobilized to create a right-sided end colostomy, although colon conduits are usually mobile enough to facilitate placement on either side of the abdomen (Figure 1*)*. In some cases, the ureters were inserted in an already existing colostomy after which a new end colostomy was created for stool. Ureters were attached in the same way as described for Bricker's diversion. In both ileal and colon conduits single J stents (EMC 7 French and CZE 8 French) were placed in both ureters to ensure sufficient flow during the first 10 days. Stents were fixed to the bowel wall with 4-0 quickly absorbable braided sutures and led out through the ostomy. If no complications occurred stents were removed at day 9 and day 10 after surgery under antibiotic prophylaxis.

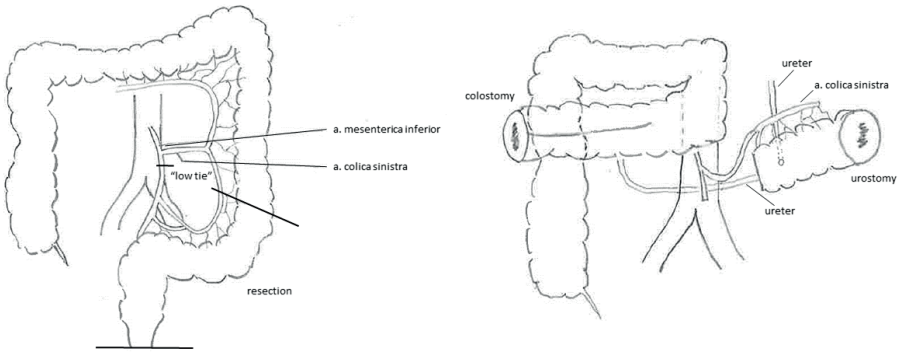

Figure 1. Schematic presentation of performing a colon conduit

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Complications

Short-term complications were defined as any complication within 30 days after surgery, during the primary hospital admission or during a readmission within 30 days. Long-term complications were defined as any complication that occurred more than 30 days after surgery, unless they occurred during the primary admission or a readmission within 30 days. Complications were graded according to the Clavien-Dindo classification.(15) Surgical and urological complications were identified from available data. Urological complications were defined as complications related to the urinary diversion or urogenitary tract or the ileo-ileal anastomosis performed for isolating the ileal conduit. Surgical complications were defined as any non-urological complication. A postoperative ileus was defined as two or more of the following: nausea/vomiting, inability to tolerate an oral diet, the absence of flatus, abdominal distention and/or radiological evidence of bowel distension without signs of a mechanical obstruction. During hospitalization, patients were daily observed for the occurrence of ileus. An anastomotic leakage was defined as a communication between the intra- and extraluminal compartments, determined by either clinical or radiologic evidence.

Statistical analysis

Continuous data were reported as median (interquartile range or 95% confidence interval) and categorical data were reported as count (percentage). Group comparisons were made using Chi-square or Mann-Whitney U test as appropriate. Long-term complication rates were calculated from the date of surgery until the last visit to the outpatient clinic. Two-sided p-values ≤ 0.05 were considered statistically significant. Multivariable logistic regression analysis was performed using all variables from table 1 and table 2 with a p-value <0.1. Nephrectomy was not used as a covariable in multivariable analysis due to low patient numbers. Statistical analyses were performed using SPSS version 24.0 (SPSS Inc., Chicago, IL) and R version 3.5.1 (http://www.r-project.org).

Table 1. Baseline characteristics colon conduit vs ileal conduit

		Total (N=259) N (%)	Colon conduit (N=45) N (%)	Ileal conduit (N=214) N (%)	P-value
Hospital	CZE	134 (52)	1 (2)	133 (62)	<0.001
	EMC	125 (48)	44 (98)	81 (38)	
Type of rectal cancer	LARC	131 (50)	28 (62)	103 (48)	0.086
	LRRC	128 (50)	17 (38)	111 (52)	
Gender	Female	45 (17)	7 (16)	38 (18)	0.723
	Male	214 (83)	38 (84)	176 (82)	
Age at resection	Median [IQR]	66.0 [58.0, 70.5]	66.0 [58.0, 70.0]	66.0 [58.0, 70.8]	0.937
ASA	I	42 (17)	7 (16)	35 (18)	0.944
	II	164 (67)	31 (69)	133 (67)	
	III	37 (15)	7 (16)	30 (15)	
Clinical tumour stage[a]	cT3	12 (9)	2 (7)	10 (10)	0.676
	cT4	119 (91)	26 (93)	93 (90)	
Clinical nodal stage	cN0	70 (46)	13 (37)	57 (48)	0.144
	cN1	34 (22)	12 (34)	22 (19)	
	cN2	49 (32)	10 (29)	39 (33)	
Clinical metastases	cM0	229 (88)	38 (84)	191 (89)	0.360
	cM1	30 (12)	7 (16)	23 (11)	
Neoadjuvant chemotherapy	No	213 (82)	40 (89)	173 (81)	0.199
	Yes[b]	46 (18)	5 (11)	41 (19)	
Neoadjuvant radiotherapy	None	25 (9)	4 (9)	21 (10)	0.113
	Radiotherapy	51 (20)	4 (9)	47 (22)	
	Chemoradiotherapy	182 (71)	37 (82)	145 (68)	
Interval radiotherapy – surgery (weeks)	Median [IQR]	11.0 [9.0, 15.0]	13.0 [10.0, 14.0]	11.0 [9.0, 15.0]	0.314

CZE: Catharina Hospital Eindhoven; EMC: Erasmus Medical Centre; LARC: Locally advanced rectal cancer; LRRC: Locally recurrent rectal cancer

[a] Only applicable for LARC; [b] 35 out of 46 patients had received induction chemotherapy in addition to other neoadjuvant therapy and 11 patients had received solely chemotherapy. Percentages may not add up to 100% due to rounding

Table 2. Surgical results colon conduit vs ileal conduit

		Total (N=259)	Colon conduit (N=45)	Ileal conduit (N=214)	P-value
		N (%)	N (%)	N (%)	
Approach	Abdominal	109 (42)	19 (42)	90 (42)	0.984
	Abdominoperineal	150 (58)	26 (58)	124 (58)	
HIPEC	Yes	5 (2)	0 (0)	5 (2)	0.300
Synchronous metastases resection[a]	Yes	8 (27)	3 (43)	5 (22)	0.269
IORT	IOBT	41 (16)	16 (36)	25 (12)	<0.001
	IOERT	105 (41)	1 (2)	104 (49)	
	No	113 (44)	28 (62)	85 (40)	
Ureter resection	Yes	2 (1)	0 (0)	2 (1)	NA
Nephrectomy	Yes	3 (2)	1 (1)	2 (1)	0.075
Length conduit (cm)	Median [IQR]	15.0 [15.0, 20.0]	15.0 [15.0, 20.0]	15.0 [15.0, 20.0]	0.372
Ileo-ileal anastomosis for ileal conduit	No	NA	NA	4 (2)	NA
	Yes	NA	NA	210 (98)	
Colo-anal anastomosis	No	228 (88)	44 (98)	184 (86)	0.027
	Yes	31 (12)	1 (2)	30 (14)	
Additional anastomosis	No	240 (93)	43 (96)	197 (92)	0.413
	Yes	19 (7)	2 (4)	17 (8)	
Ostomy	No ostomy	4 (2)	0 (0)	4 (2)	0.040
	Pre-existing ostomy	101 (39)	13 (29)	88 (41)	
	Loop ostomy	29 (11)	2 (4)	27 (13)	
	End ostomy	125 (48)	30 (67)	95 (44)	
Blood loss (ml)	Median [IQR]	3200.0 [2125.0, 5500.0]	3000.0 [2200.0, 3600.0]	3400.0 [2100.0, 6625.0]	0.088
Operation time (min)	Median [IQR]	437.0 [362.5, 517.2]	510.0 [439.0, 620.0]	420.0 [351.0, 495.0]	<0.001

NA: Not applicable; HIPEC: Hyperthermic intraperitoneal chemotherapy; IORT: Intra-operative radiation therapy; IOBT: intra-operative brachytherapy; IOERT: intra-operative external beam radiotherapy

[a]Calculated as percentage of patient with synchronous metastasis. Percentages may not add up to 100% due to rounding

RESULTS

Baseline characteristics are shown in Table 1. A total of 259 patients with locally advanced (n=131) or locally recurrent rectal cancer (n=128) were included for analyses. An ileal conduit was performed in 214 patients and more frequently in the CZE (CZE n=133, EMC=81) and a colon conduit in 45 patients and more frequently in the EMC (CZE n=1, EMC n=44) ($p < 0.001$). No other significant baseline differences were observed.

Surgical results

Surgical characteristics are shown in Table 2. All patients underwent pelvic exenteration with a cystectomy and resection of the (recurrent) rectal tumour. The length of the conduit was similar for both ileal and colon conduit (median 15 cm, IQR 15 – 20 cm). Patients with a colon conduit more often received an end colostomy, whereas patients with an ileal conduit more often had an ostomy from previous surgery (e.g. end colostomy after resection for the primary tumour)(p=0.040). Colo-anal anastomoses were more often performed in patients with an ileal conduit (p=0.027). The operation time was significantly shorter for patients receiving an ileal conduit than for those receiving a colon conduit with 420 minutes [IQR 351 – 495 min] versus 510 minutes [IQR 439-620], respectively ($p < 0.001$).

Anastomosis

In 210/214 patients with an ileal conduit an ileo-ileal anastomosis was performed, and in four patients no anastomosis was required because the pre-existing end ileostomy was used as a conduit (n=1) or a new end ileostomy was performed (n=3). In 30 patients with an ileal conduit, a colo-anal anastomosis was performed, and in 17 patients, an additional anastomosis was performed due to an additional bowel resection. In patients with a colon conduit, one colo-anal anastomosis was performed and two additional anastomoses due to additional bowel resection were performed.

Short-term surgical and urological complications

Short-term surgical and urological complications are displayed in Table 3 and 4. There was no statistical difference in major complications (Clavien-Dindo ≥ 3) and mortality rates (30-day mortality or in-hospital mortality) for patients with an ileal conduit compared to a colon conduit. There was no difference between hospital stay, reintervention rates and readmission rates between both groups. A postoperative ileus occurred more often in patients with an ileal conduit compared to patients with a colon conduit (21 vs. 7%, p=0.024, respectively), which remained significant after multivariable analysis (p=0.025). In patients with a colon conduit a wound infection (perineal and/or abdominal) was observed more often than in patients with an ileal conduit (31% vs. 16%, p=0.006), but this was not significant after multivariable analysis (p=0.37). No significant differences were

found when comparing the rate of urological complications or the reintervention rate for urologic complications between the two groups. Metabolic acidosis occurred in 6 patients (3%) with an ileal conduit, and did not occur in patients with a colon conduit (p=0.256).

Table 3. Short-term general and surgical complications colon conduit vs ileal conduit

	Total (N=259)	Colon conduit (N=45)	Ileal conduit (N=214)	P-value
	N (%)	N (%)	N (%)	
30-day mortality	14 (5)	1 (2)	13 (6)	0.299
In-hospital mortality	26 (10)	3 (7)	23 (11)	0.408
Major complications (Clavien-Dindo ≥ 3)	101 (39)	14 (31)	87 (41)	0.233
Any reintervention	90 (35)	11 (24)	79 (37)	0.110
Ileus	48 (19)	3 (7)	45 (21)	0.024
Wound infection (abdominal & perineal)	44 (17)	14 (31)	30 (14)	0.006
Pre-sacral abscess	47 (18)	7 (16)	40 (19)	0.620
Abdominal abscess	31 (12)	4 (9)	27 (13)	0.484
Ostomy complication	4 (2)	0 (0)	4 (2)	0.355
Fistula	6 (2)	1 (2)	5 (2)	0.963
Hospital stay in days (median [IQR])	14.0 [11.0, 18.5]	13.0 [11.0, 19.0]	14.0 [10.0, 18.0]	0.859
No readmission	217 (83)	36 (80)	179 (84)	0.230
Urological readmission	11 (4)	4 (9)	7 (3)	
Non-urological readmission	33 (13)	5 (11)	28 (13)	

Percentages may not add up to 100% due to rounding

Anastomotic leakage occurred in 6/210 patients (3%) with an ileo-ileal anastomosis. Anastomotic leakage of the ureter anastomosis occurred in 14/214 patients (7%) with an ileal conduit and in 3/45 patients (7%) with a colon conduit (p=0.976). Anastomotic leakage of the colo-anal anastomosis occurred in 7/30 patients (23%) with an ileal conduit. In the colon conduit group, only one colo-anal anastomosis was performed without leakage. In both groups, no leakage of additional anastomoses was observed.

When comparing only patients who underwent a resection through abdominoperineal approach, a postoperative ileus was still more often observed in patients who received an ileal conduit compared with a colon conduit (p=0.028). The wound infection rate did not differ. In a subanalysis comparing patients with LARC and LRRC, there were no significant differences in short-term surgical and urologic complications.

Table 4. Short-term urological complications colon conduit vs ileal conduit

	Total (N=259)	Colon conduit (N=45)	Ileal conduit (N=214)	P-value
	N (%)	N (%)	N (%)	
Urological complication	58 (22)	7 (16)	51 (24)	0.226
Urological reintervention	35 (14)	4 (9)	31 (14)	0.318
Urosepsis	9 (3)	1 (2)	8 (4)	0.614
Metabolic acidosis	6 (2)	0 (0)	6 (3)	0.256
Urinoma	12 (5)	2 (4)	10 (5)	0.947
Urinoma drainage	9 (3)	2 (4)	7 (3)	0.696
Urostomy complication	4 (2)	1 (2)	3 (1)	0.685
Hydronefrosis	22 (8)	1 (2)	21 (10)	0.097
Ureter stenosis	7 (3)	0 (0)	7 (3)	0.609
Urinary tract infection	16 (6)	3 (7)	13 (6)	0.881
Leakage ileo-ileal anastomosis [a]				
No	NA	NA	204 (97)	NA
Yes	NA	NA	6 (3)	
Leakage ureter - conduit anastomoses [a]				
No	242 (93)	42 (93)	200 (93)	0.976
Yes	17 (7)	3 (7)	14 (7)	
Leakage colo-anal anastomosis [a]				
No	24 (77)	1 (100)	23 (77)	0.538
Yes	7 (23)	0 (0)	7 (23)	
Leakage other anastomosis [a]				
No	19 (100)	2 (100)	17 (100)	NA
Yes	0 (0)	0 (0)	0 (0)	

[a] Percentage of anastomotic leakage is calculated of patients in which a specific anastomosis was performed
NA: Not applicable
Percentages may not add up to 100% due to rounding

Long-term complications

Long-term complications are presented in Table 5. In 72% of the patients (186 patients, colon conduit n=44, ileal conduit n=142) long-term complications after 30 days were registered. The median follow-up for survivors for long-term complications was 55 months (95% CI 55-65 months). No significant differences in long-term complications between both groups were observed. One patient (2%) with a colon conduit and five patients (4%) with an ileal conduit experienced metabolic acidosis (p=0.582). Three (2%) out of 139 patients with an ileal conduit presented with a late anastomotic leakage of the ileo-ileal anastomosis, 2/142 patients (1%) with uretero-ileal conduit leakage, and 2/21 patients (9%) with leakage of the colo-anal anastomosis. Patients with a colon conduit did not

experience anastomotic leakage 30 days after surgery. Twelve patients (9%) with an ileal conduit developed a fistula (n=8 entero-cutaneous, n=4 uretero-enteric) compared to four (9%) patients with a colon conduit (p=0.895) (all entero-cutaneous).

In a subanalysis, there were no significant differences in long-term surgical and urologic complications when comparing LARC with LRRC.

Table 5. Long-term complications colon conduit vs ileal conduit

	Total (N=186)	Colon conduit (N=44)	Ileal conduit (N=142)	P-value
	N (%)	N (%)	N (%)	
Urological complication	37 (20)	6 (14)	31 (22)	0.234
Urological reintervention	22 (12)	5 (11)	17 (12)	0.913
Urosepsis	4 (2)	1 (2)	3 (2)	0.949
Metabolic acidosis	6 (3)	1 (2)	5 (4)	0.682
Hydronefrosis	19 (10)	3 (7)	16 (11)	0.394
Percutaneous nephrostomy drainage	14 (7)	2 (5)	12 (9)	0.319
Urinary tract infection	19 (10)	4 (9)	15 (11)	0.778
Urinoma	0 (0)	0 (0)	0 (0)	NA
Ureter stenosis	16 (9)	4 (9)	12 (9)	0.895
Revision ureter stenosis	3 (2)	2 (5)	1 (1)	0.076
Revision urostomy	4 (2)	2 (5)	2 (1)	0.207
Fistula	16 (9)	4 (9)	12 (9)	0.895
Leakage ileo-ileal anastomosis[a]				
No	NA	NA	136 (98)	NA
Yes	NA	NA	3 (2)	
Leakage ureter - conduit anastomosis[a]				
No	184 (99)	44 (100)	140 (99)	0.429
Yes	2 (1)	0 (0)	2 (1)	
Leakage colo-anal anastomosis[a]				
No	20 (91)	1 (100)	19 (91)	0.746
Yes	2 (9)	0 (0)	2 (9)	

[a] Percentage of anastomotic leakage is calculated of patients in which a specific anastomosis was performed
NA: Not applicable. Percentages may not add up to 100% due to rounding

DISCUSSION

The present pooled retrospective cohort of 259 patients undergoing total pelvic exenteration with urinary diversion for LARC and LRRC describes few differences in surgical and urological complications between a colon conduit and an ileal conduit. 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.

Several studies reported on outcomes after multivisceral surgery with cystectomy and the formation of a urinary diversion. However, complications are usually described for all types of pelvic cancer, and as outcomes may differ for different types of cancer this complicates comparison between studies. In the case of LARC and LRRC, a complete ***en bloc*** bladder removal with the rectal tumour is often performed, which makes it prone to other complications than after primary cystectomy alone.(16,17) A recent study by Bolmstrand et al. described complications after urinary tract reconstruction in colorectal and anal cancer after partial or complete cystectomy.(13) They reported a rate of 35% major complications (Clavien-Dindo≥3), which is comparable with the 39% in our series. The rate of intestinal anastomotic leakage was 9% in their series compared to 7% in our study. In the present study, we did not find a significant difference when comparing the anastomotic leakages separately between the two types of conduit. However, 9 patients with an ileal conduit had an anastomotic leakage of the ileo-ileal anastomosis, which is obviously ruled out when a colon conduit is performed.

Teixeira et al. compared outcomes in 74 patients who received an ileal or a colon conduit for different types of pelvic malignancies.(12) Their study did not find significant differences for complications assessed separately, such as urinary leaks, small bowel fistula, sepsis or drained collections. However, when all complications were combined, a significantly higher incidence of complications in patients with an ileal conduit compared to a colon conduit was found (40% vs. 19%, respectively, $p<0.01$).(12)

In the present study, a postoperative ileus was observed significantly more often in patients with an ileal conduit compared to patients with a colon conduit (21% vs 7%, $p=0.024$). Prolonged duration of ileus is a known complication after formation of an ileal conduit and may lead to a prolonged hospitalization.(8,18) In CZE, patients are frequently transferred to referring hospitals when they are clinically stable. This may have led to an underestimation of hospital stay in CZE patients.

The proportion of patients with a wound infection (abdominal and/or perineal) was significantly higher in patients with a colon conduit. Several factors may influence wound healing such as surgical approach, extent of surgery, perineal or abdominal reconstruction (i.e. muscle flap reconstruction, omentoplasty), patient characteristics or even bacterial load from the conduit. This could not be explained clearly with the available data and multivariate analysis no longer showed a significant difference between groups.

Despite the possible favourable outcomes in terms of complications, and the fact that previous studies showed a low tie can be safely performed regarding oncological outcomes, a colon conduit is not always technically possible to perform.(19,20) For example, in case of macroscopic lymph node metastasis above the level of the left colic artery a high tie must be performed and a colon conduit can only be created when the blood supply via the middle colic artery and Riolan's arcade conduit is sufficient. Furthermore, in patients with LRRC a repeated resection of the descending colon can result in insufficient length and blood supply for the creation of a colon conduit.

In addition to an ileal or colon conduit, the formation of other types of urinary diversion such as an Indiana pouch, neobladder or double-barrelled wet colostomy are technically possible as well. However, in CZE and EMC reconstructions using an Indiana pouch or neobladder are not performed in patients with extensive colorectal malignancy as these reconstructions are associated with a higher complication rate in these patients.(17) The double-barrelled wet colostomy (DBWC) inherently has a benefit over the ileal or colon conduit, as it requires only one stoma. However, in our experience this type of diversion is unpleasant to take care of for patients and subsequently has a negative impact on the quality of life. Therefore, a DBWC is not performed in our institutions.

This study is limited by its retrospective nature. Improvement in multimodality treatment such as neoadjuvant therapies over the last decades may influence our results, but the majority of patients in our study were treated with neoadjuvant (chemo-)radiotherapy and there was no significant difference between both groups. Although treatment protocols are similar in both hospitals, there is an imbalance in the proportion of patients with an ileal or colon conduit, as CZE only performed one colon conduit. In addition, the admission of IORT is different in both hospitals; in CZE IOERT is administered whereas in EMC IOBT is administered. The significant difference in operation time between the ileal and colon conduit may be explained by the administration of mainly IOBT in the colon conduit group, as this is a more time-consuming procedure than IOERT. For the same reason, IOBT was only applied in case of positive fresh frozen sections, whereas IOERT was also administered in case of clinically threatened margins. Since a larger proportion of patients in this cohort was treated in the CZE where an ileal conduit was the preferred method, IORT was most frequently used in patients with an ileal conduit.

The use of an intestinal segment as urinary conduit may lead to metabolic changes, which may depend on the length and type of the conduit, ileal or colonic.(8,14,21) In the literature, a colon conduit is more often associated with metabolic acidosis than an ileal conduit. This study did not find a significant difference, although metabolic acidosis may be underreported.

Long-term follow-up was available in 70% of the patients with a wide range of follow-up time. Despite these limitations, this study still provides valuable information for the use of both an ileal and colon conduit.

Conclusions

The formation of an ileal or colon conduit in patients undergoing total pelvic exenteration for LARC or LRRC has similar urologic complications. However, the formation of a colon conduit rules out ileo-ileal anastomotic leakage. Besides, 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.

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Chapter 12

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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Chapter 13

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 structurers 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 preoperative (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.

Chapter 14

Summary in Dutch / Nederlandse samenvatting

Het colorectaal carcinoom is de derde meest voorkomende maligniteit in de westerse wereld en het rectumcarcinoom treft ongeveer één derde van alle patiënten met een colorectaal carcinoom. In Nederland zijn in 2018 ongeveer 4.000 patiënten gediagnostiseerd met een rectumcarcinoom. De behandeling van het rectumcarcinoom is de afgelopen decennia sterk verbeterd, maar de behandeling blijft uitdagend. Het doel van de behandeling is om de overleving te verbeteren en de kans op terugkeer te verminderen, en daarmee de kwaliteit van leven te verbeteren. Het primaire rectumcarcinoom kan vaak zonder voorbehandeling, in de vorm van chemotherapie of radiotherapie, worden behandeld door totaal mesorectale excisie. In gevallen dat het rectumcarcinoom is ingegroeid in omliggende structuren, zoals bij het lokaal voortgeschreden rectumcarcinoom of bij een lokaal recidief rectumcarcinoom, zal een uitgebreidere behandeling nodig zijn: een multimodaliteitsbehandeling met chemo- radiotherapie en een (uitgebreide) chirurgische resectie. Dit proefschrift heeft als doel om verschillende aspecten van het primaire, lokaal voortgeschreden en lokaal recidief rectumcarcinoom uiteen te zetten en aan te geven hoe de multimodaliteitsbehandeling is te verbeteren.

In **hoofdstuk 1** worden de verschillende onderzoeksvragen met onderbouwing beschreven die beantwoord zullen worden in dit proefschrift.

In **hoofdstuk 2** wordt de invloed van ziekenhuisvolumes op de korte en lange termijn onderzocht in een groot cohort uit de Dutch Snapshot Research Group. Volgens de Nederlandse richtlijnen moeten ziekenhuizen een minimumaantal resecties van het rectumcarcinoom per jaar verrichten om zo de kwaliteit te waarborgen. Er werd geen verschil gevonden in uitkomsten, zoals overleving en chirurgische uitkomsten, tussen ziekenhuizen met een laag volume (<20 resecties per jaar), gemiddeld volume (20-50 resecties per jaar) of een hoog volume (>50 resecties per jaar).

In **hoofdstuk 3** is ook onderzoek beschreven naar de invloed van ziekenhuisvolumes op overleving, echter nu in de grote nationale kankerregistratie-database met gegevens van 2005 – 2013. In dit onderzoek is gestratificeerd voor het klinisch stadium voor een primaire tumor (cT1-3) of het lokaal voortgeschreden rectumcarcinoom (cT4). Deze studie liet zien dat patiënten met een cT4-rectumcarcinoom een verbeterde overlevingskans hadden wanneer zij behandeld werden in een hoogvolumeziekenhuis. Dit verschil verdwijnt echter na correctie voor neoadjuvante therapie. Centralisatie van deze cT4-tumoren lijkt een positieve invloed te hebben op de uitkomsten voor patiënten met deze uitgebreide tumoren.

In **hoofdstuk 4** is wederom onderzoek geanalyseerd naar de invloed van volumenormen, ditmaal naar de perioperatieve uitkomsten. In uitgebreide tumoren (cT4) is de multimodaliteitsbehandeling en chirurgie vaak technisch veeleisend in vergelijking met minder

uitgebreide tumoren (cT1-3). Voor cT1-3 tumoren waren de perioperatieve uitkomsten voor hoogvolumeziekenhuizen niet superieur aan die in laag- of gemiddeldvolumeziekenhuizen. Echter, voor patiënten met cT4-tumoren zien we dat er uitgebreidere chirurgie wordt verricht in hoogvolumeziekenhuizen met dezelfde perioperatieve resultaten. Hoogvolumeziekenhuizen bieden mogelijk een betere multimodaliteitsbehandeling, wat uiteindelijk kan leiden tot betere uitkomsten. Het lijkt dat centralisatie voor deze cT4-tumoren een positieve invloed heeft.

In **hoofdstuk 5** onderzoeken we de behandeling van locoregionale metastasen naar de liesklieren van het rectumcarcinoom. Deze metastasen worden heden nog beschouwd als een systemische ziekte, maar er zijn aanwijzingen dat deze lokaal goed te behandelen zijn, door middel van chirurgie. In deze studie zien we dat patiënten met alleen metastasen naar de liesklieren en een primair rectumcarcinoom bij adequate behandeling een 5-jaarsoverleving van 52% hebben. Voor patiënten met metastasen elders of een lokaal recidief rectumcarcinoom zijn de uitkomsten slechter. Deze studie laat zien dat patiënten met metastasen alleen in de liesklieren en een primair rectumcarcinoom niet per se beschouwd moeten worden als patiënten met een systemische ziekte, en in opzet curatief behandeld kunnen worden.

In **hoofdstuk 6** beschrijven we een pilotstudie naar de bruikbaarheid van een nieuwe techniek voor het sluiten van de perineale wond na een abdominoperineale rectumresectie. Na een abdominoperineale resectie is er een grote kans op wondgenezingsstoornissen. Vele verschillende manieren van wondsluiting zijn reeds bekend, zoals het gebruik van myocutane flap. Deze hebben echter het nadeel dat elders een nieuwe wond gemaakt wordt. In de huidige studie onderzoeken we de bruikbaarheid van de gluteale turnover-flap, die direct na de operatie is te creëren zonder additionele schade aan te richten. In deze studie zien we dat de meerderheid van patiënten een ongecompliceerde wondgenezing had en de gluteale turnover-flap potentie heeft voor perineale wondsluiting. Dit zal echter moeten worden onderzocht in een grotere gerandomiseerde studie.

In **hoofdstuk 7** verrichten we ook onderzoek naar perineale wondgenezing. Op dit moment wordt in veel gevallen gebruik gemaakt van een omentumplastiek ter bevordering van de wondgenezing. Het idee van een omentumplastiek is om het kleine bekken op te vullen met het omentum en de genezende of beschermende werking van het omentum te benutten ter bevordering van de wondgenezing. In dit systematische review en meta-analyse zijn uit alle recente studies waar het gebruik van een omentumplastiek wordt toegepast gegevens opgevraagd. Een uitgebreide analyse van deze gegevens laat geen verbetering van de wondgenezing zien door het gebruik van een omentumplastiek. Het blijkt zelfs dat een omentumplastiek juist een verhoogde kans op een perineale hernia

geeft op de langere termijn. Het gebruik van een omentumplastiek lijkt niet het gewenste effect te hebben om perineale wondgenezing te verbeteren.

Hoofdstuk 8 beschrijft een groot cohort van patiënten met het lokaal recidief rectumcarcinoom. Deze patiëntengroep vereist een speciale behandeling. Het recidief carcinoom zit in het kleine bekken met soms doorgroei in aanliggende structuren zoals het urogenitale stelsel, daarnaast presenteert de meerderheid van deze patiënten zich met afstandsmetastasen. Het belangrijkste van de behandeling is het bereiken van een radicale resectiemarge. Als dit niet mogelijk is, dan is een behandeling met chemotherapie of radiotherapie een optie. Na een chirurgische behandeling, indien mogelijk, hebben patiënten met een R0- of R1-resectie een significant betere 5-jaarsoverleving van respectievelijk 51% en 34% dan patiënten met een R2-resectie (10%) of niet-chirurgische behandeling (4%). Patiënten met een R2-resectie hebben zelfs een slechtere overleving dan patiënten met optimale niet-chirurgische behandeling. Patiënten met een hoge kans op een R2-resectie kunnen in geselecteerde gevallen dus mogelijk niet chirurgisch behandeld worden, gezien de morbiditeit en mortaliteit van chirurgie. Niet chirurgisch behandelde patiënten kunnen echter veel lokale tumorklachten zoals pijn, fisteling en bloedingen ervaren. In beide gevallen dient rekening te worden gehouden met de kwaliteit van leven.

Hoofdstuk 9 toont een overzicht van de chirurgische behandeling van het lokaal voortgeschreden of recidief rectumcarcinoom indien er sprake is van ingroei in aanliggende organen zoals de blaas. In deze gevallen dient een totaal-exenteratie te worden verricht. Dit is een ingreep waarbij door middel van chirurgie de tumor vaak ***enbloc*** met het urogenitale stelsel bij de man of vrouw wordt verwijderd. Dit hoofdstuk beschrijft een overzicht van indicatie, procedure en uitkomsten op korte en lange termijn. De 5-jaarsoverleving varieert tussen 22% tot 66% voor het lokaal voortgeschreden rectumcarcinoom en 0% tot 37% voor het recidief rectumcarcinoom. De perioperatieve mortaliteit ligt tussen de 0% en 10%. Een radicale resectie-marge is de belangrijkste prognostische factor. Kwaliteit van leven is kort na de chirurgie verminderd maar verbetert al binnen drie maanden na de ingreep tot bijna op het oude niveau, terwijl bij onbehandelde patiënten de kwaliteit van leven achteruit gaat. Een totaal-exenteratie lijkt dus een gerechtvaardigde ingreep.

In **hoofdstuk 10** is onderzoek verricht naar de invloed van leeftijd en het uitvoeren van een totaal-exenteratie voor het lokaal voortgeschreden of recidief rectumcarcinoom. Het is algemeen bekend dat ouderen vaak een hogere mortaliteit en morbiditeit ervaren bij operaties. De oncologische uitkomsten kunnen echter gelijkwaardig zijn. In dit hoofdstuk zien we dat binnen 30 dagen na de operatie de perioperatieve mortaliteit bij ouderen (≥ 70 jaar) significant hoger is. Maar na 30 dagen verdwijnt dit verschil. De algehele overleving is niet significant verschillend. Als patiënten vooraf goed geselecteerd worden

in een multidisciplinair overleg, moet leeftijd niet de weerhoudende factor zijn voor een totaal-exenteratie.

In **hoofdstuk 11** vergelijken we de uitkomsten van het aanleggen van een colon-conduit en een ileum-conduit als urinedeviatie na een totaal-exenteratie. Beide procedures zijn geassocieerd met complicaties maar er zijn ook conduit-specifieke complicaties gerelateerd aan een conduit. In het geval van een ileum-conduit is er een kans op naadlekkage omdat er een extra ileo-ileale anastomose wordt gecreëerd, in ons cohort was dit 4%. Dit risico wordt vermeden bij het aanleggen van een colon-conduit. Daarnaast zagen wij een hoger percentage van postoperatieve ileus na het aanleggen van een ileum-conduit. De overige postoperatieve uitkomsten lieten geen significante verschillen zien. Het colon-conduit lijkt dus een bruikbaar alternatief voor een ileum-conduit voor patiënten die een eindstandig colostoma krijgen.

APPENDICES

1. LIST OF PUBLICATIONS

This thesis

The influence of hospital volume on long-term oncological outcome after rectal cancer surgery.

Jonker FHW, **Hagemans JAW**, Burger JWA, Verhoef C, Borstlap WAA, Tanis PJ; Dutch Snapshot Research Group.

Int J Colorectal Dis. 2017 Dec;32(12):1741-1747. doi: 10.1007/s00384-017-2889-2. Epub 2017 Sep 7.

PMID: 28884251

Hospital volume and outcome in rectal cancer patients; results of a population-based study in the Netherlands.

Hagemans JAW, Alberda WJ, Verstegen M, de Wilt JHW, Verhoef C, Elferink MA, Burger JWA.

Eur J Surg Oncol. 2019 Apr;45(4):613-619. doi: 10.1016/j.ejso.2018.12.018. Epub 2018 Dec 26.

PMID: 30600101

The impact of hospital volume on perioperative outcomes of rectal cancer.

Jonker FHW, **Hagemans JAW**, Verhoef C, Burger JWA.

Eur J Surg Oncol. 2017 Oct;43(10):1894-1900. doi: 10.1016/j.ejso.2017.07.009. Epub 2017 Jul 29.

PMID: 28822603

Treatment of Inguinal Lymph Node Metastases in Patients with Rectal Adenocarcinoma.

Hagemans JAW, Rothbarth J, van Bogerijen GHW, van Meerten E, Nuyttens JJME, Verhoef C, Burger JWA.

Ann Surg Oncol. 2019 Apr;26(4):1134-1141. doi: 10.1245/s10434-019-07191-4. Epub 2019 Feb 6.

PMID: 30725310

Feasibility of a subcutaneous gluteal turnover flap without donor site scar for perineal closure after abdominoperineal resection for rectal cancer.
Blok RD, **Hagemans JAW**, Burger JWA, Rothbarth J, van der Bilt JDW, Lapid O, Hompes R, Tanis PJ.
Tech Coloproctol. 2019 Aug;23(8):751-759. doi: 10.1007/s10151-019-02055-1. Epub 2019 Aug 20.
PMID: 31432332

A Systematic Review and Meta-analysis on Omentoplasty for the Management of Abdominoperineal Defects in Patients Treated for Cancer.
Blok RD*, **Hagemans JAW***, Klaver CEL, Hellinga J, van Etten B, Burger JWA, Verhoef C, Hompes R, Bemelman WA, Tanis PJ.
Ann Surg. 2020 Apr;271(4):654-662. doi: 10.1097/SLA.0000000000003266.
PMID: 30921047

Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre.
Hagemans JAW, van Rees JM, Alberda WJ, Rothbarth J, Nuyttens JJME, van Meerten E, Verhoef C, Burger JWA.
Eur J Surg Oncol. 2020 Mar;46(3):448-454. doi: 10.1016/j.ejso.2019.10.037. Epub 2019 Nov 3.
PMID: 31761506

Pelvic exenteration for invasive rectal cancer of the anterior compartment
Hagemans JAW, van Rees JM, Rothbarth J, Verhoef C, Burger JWA.
Wiley and Sons
Submitted

Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly.
Hagemans JAW, Rothbarth J, Kirkels WJ, Boormans JL, van Meerten E, Nuyttens JJME, Madsen EVE, Verhoef C, Burger JWA. Eur J Surg Oncol. 2018 Oct;44(10):1548-1554. doi: 10.1016/j.ejso.2018.06.033. Epub 2018 Jul 20. PMID: 30075979

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Eur J Surg Oncol. 2020 Feb 20. pii: S0748-7983(20)30123-2. doi: 10.1016/j.ejso.2020.02.021. [Epub ahead of print]
PMID: 32122756

Not in this thesis

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Hagemans JAW, Blinde SE, Nuyttens JJ, Morshuis WG, Mureau MAM, Rothbarth J, Verhoef C, Burger JWA.
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ASO Author Reflections: Salvage Surgery for Anal Cancer.
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de Boer NL, **Hagemans JAW**, Schultze BTA, Brandt-Kerkhof ARM, Madsen EVE, Verhoef C, Burger JWA.
Eur J Surg Oncol. 2019 Mar;45(3):389-393. doi: 10.1016/j.ejso.2018.12.015. Epub 2018 Dec 21. PMID: 30594405

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BJS Open. 2019 Mar 6;3(4):516-520. doi: 10.1002/bjs5.50153. eCollection 2019 Aug.
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PMID: 31255441

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Pelvex Collaborative
Ann Surg. 2019 Nov;270(5):899-905. doi: 10.1097/SLA.0000000000003533.
PMID: 31634184

Simultaneous pelvic exenteration and liver resection for primary rectal cancer with synchronous liver metastases: results from the PelvEx Collaborative
PelvEx Collaborative
Colorectal Dis. 2020;10.1111/codi.15064. doi:10.1111/codi.15064 [Epub ahead of print, 2020 Apr 15.]
PMID: 32294308

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Name PhD student: Jan Hagemans, MD	**PhD period**: March 2017 – March 2019
Erasmus MC department: Surgery, Division of Surgical Oncology	**Promotor**: prof. dr. C. Verhoef
Research school: Erasmus MC, MolMed	**Copromotor**: dr. J.W.A. Burger

PhD Training	Year	ECTS
Research courses		
- *OpenClinica training*	2017	1.0
- *Basic Introduction Course on SPSS*	2017	1.0
- *Microsoft Excel 2010 Basic*	2017	0.3
- *Research Integrity*	2017	0.3
- *Biostatistical Methods I: Basic Principles Part A (NIHES)*	2018	2.0
- *Microsoft Excel 2010 Advanced*	2018	0.3
- *Survival Analysis Course*	2018	1.0
Specific courses		
- *Advanced Life Support Course*	2016	1.0
- *Advanced Trauma Life Support*	2019	1.0
- *Fundamental Critical Care support*	2019	1.0
Presentations		
- **Annual Meeting Dutch Colorectal Cancer Group (DCCG)**	*2017 & 2018*	*1.0*
REACT-Trial: Adjuvant chemotherapy for prevention of recurrence in patients with detectable ctDNA after surgery for stage II-III rectal cancer		
- **European Society of Coloproctology (ESCP), Berlin, Germany**	2017	2.0
Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer		
- **Society of Surgical Oncology (SSO), Chicago, United States of America**	2018	2.0
Salvage abdominoperineal resection for squamous cell anal cancer: A 30-year single institution experience		
- **European Society of Surgical Oncology (ESSO), Budapest, Hungaria**	2018	6.0
- *Treatment of inguinal lymph node metastases in patients with rectal adenocarcinoma*		
- *Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly*		
- *Salvage abdominoperineal resection for squamous cell anal cancer: A 30-year single institution experience*		
(Inter)national Conferences		
- *Annual Science Day Surgery Erasmus MC 2017*	*2017*	1.0
- *NVVH Chirurgendagen 2017*	*2017*	1.0
- *Liver Metastasis Research Network 2017*	2017	1.0
- *18e Wondcongres 2017*	2017	1.0
- *Annual Science Day Surgery Erasmus MC 2018*	2018	1.0
- *NVVH Chirurgendagen 2018, NVVH*	2018	1.0
- *19e Wondcongres 2018*	2018	1.0
- *Annual Science Day Surgery Erasmus MC 2019*	2019	1.0
- *20e Wondcongres 2019*	2019	1.0

Teaching activities	Year	Workload (ECTS)
Supervising practicals and excursions		
- Basic Life Support examiner medical students 2018	2018	1.0
- Basic Life Support examiner medical students 2017	2017	1.0
Supervising Bachelor / Master students		
- B.T.A. Schultze	2017	2.0
- B. Galjart	2017	2.0
- J.M. van Rees	2018	2.0

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Robin, eerlijk gezegd nooit gedacht dat we na ruim anderhalf jaar ploeteren toch een mooi review eruit zouden persen en uiteraard ook de BIOPEX.

Eva, wat hebben we lief en leed gedeeld over jouw eerste en mijn laatste stuk, blij dat het in versie 30 een mooie publicatie is geworden!

Daniel-vriendjes, aan het mooie Lago di Daniel en op onze bekende gang op A1 hebben we een unieke leuke en hechte onderzoeksgroep gehad. Vrijdagochtend aan de pecannootbroodjes en vrijdagmiddag op het dak. Hoe hebben we het ooit allemaal afgekregen. De mannenkamer, de vrouwenkamer, het grachtenpand, de tafelvoetbaltafel, de pingpongtafel en natuurlijk de Na-21-flat, iedere kamer heeft te veel herinneringen om op te noemen. Bedankt allemaal voor de mooie tijd.

Diederik, Huppy, zonder jou geen proefschrift of in ieder geval een zonder figuren en tabellen. Jouw snelle oplossingen met computers hebben mij dagen aan overtikken bespaard. Als coin-investors hebben we het helaas niet gered, maar als onderzoekers gaat het ons vooralsnog aardig af! Bedankt voor alle hulp.

Pien, waar ik je heb leren kennen in de grotten van Maastricht is onze vriendschap pas echt tot leven gekomen tijdens het onderzoek. De Mathletes als een betweterig studiegroepje en uiteindelijk het Diamond Duo. We hebben zoveel ideeën dat er zelfs een bucketlist voor gemaakt moest worden. Concert at Sea is er al vanaf (helaas). De discipline en snelheid waarmee jij je proefschrift hebt afgerond heeft mij ook dat extra zetje in de rug gegeven en door jou kan ik tijdens mijn verdediging Engelse woorden moeiteloos uitspreken. Wat hebben we gelachen en wat gaan we nog lachen, bedankt!

Flex 21-OGC, wat was het wennen na de samensmelting tussen Noord en Zuid, de verwoede proeven om het bezit van de kamertjes en immuniteit. Expeditie Robinson was er niets bij. Het ultieme hoogtepunt na de samensmelting was natuurlijk de trip naar Boedapest en bar ''Click'' waar de bar altijd rijkelijk bezet was. Maar de ontelbare lunches in de pantry als hoogtepunt van de dag waren een genot en een garantie voor gezelligheid.

Wondcongresvrienden, het Wondcongres heeft altijd een belangrijke rol gespeeld tijdens mijn onderzoek. Een week voorafgaand aan de vergadering kon ik iedere dag al een half uur besteden aan het eventuele menu voor die avond. De gezelligheid stond altijd voorop met als hoogtepunt het Lustrum in Het Nieuwe Luxor Theater. Wound Wound Wound…..!

Chirurgen, assistenten en Forgerons van het Ikazia. Hier is het eigenlijk allemaal begonnen, in het kleine hokje van de SEH is mijn interesse voor de chirurgie meer en meer gegroeid. De tijd als Forgerons was fantastisch en nadat ik zelf was geopereerd in het Ikazia wist ik het zeker, ik wilde graag terugkeren naar het oude nest. Ik ben dan ook zeer gelukkig dat ik in deze mooie groep chirurgen en assistenten mijn opleiding kan vervolgen. Dr. den Hoed, dr. Vles, beste Ted en Wouter dank voor alle hulp en adviezen door de jaren heen!

Ketsheuvel, wat begonnen is als een GVB-cursus waar ik nooit aan deelgenomen heb, is uitgegroeid tot een gezellige club in Rotterdam. Eindeloze borrels en lunches bij WP en talloze LAN-avonden, die altijd garant staan voor onwijze gezelligheid. Uiteindelijk uitgegroeid tot ons eigen Team West waarmee we ook op sportief vlak elkaar tot het uiterste drijven. Louis en Hylke in het bijzonder, we hebben, denk ik, de meeste uren bij WP en online gezamenlijk doorgebracht en daar over uiterst belangrijke levensvragen en op medisch gebied enorm met elkaar kunnen relativeren. Dat we nog vele jaren door mogen gaan.

Matteo, Mick en Romke, de schaarse vrijdagavonden eens in de paar maanden voelen altijd alsof het een wekelijks samenzijn is. Een onwijs gelukkig toeval dat in Berlijn heeft plaatsgevonden is uitgegroeid tot een bijzonder waardevolle vriendschap tussen drie Bosschenaren en een eigenwijze Hagenees. Ik kijk uit naar de volgende vrijdag.

Tom, Geus, anderhalf jaar lang heb jij de Binnenweg en Breitnerstraat een stuk gezelliger gemaakt. Je hebt veel ups en downs van het promotietraject meegekregen, en daarnaast heb je het roer een paar keer om zien gaan, maar ik kan je nu vertellen: het roer is om.

Hockeymaatjes, hockey was altijd een rode draad en enorm genieten zowel bij Victoria als Rotterdam. Met name de TD's en iedere rit met Autootje Uno was onvergetelijk. De donderdagavonddinertjes met jullie, Linho, Kaas, Geus en Jaac waren een genot om te mee te maken.

JC Mañana, volgens mij heeft iedereen, behoudens Romke, nooit precies begrepen wat ik nou heb uitgevoerd. Een proefschrift over zonnebrand was wellicht een stuk interessanter geweest. Echter alle Saturdays, spelletjesavonden en vakanties gaven mij genoeg afleiding om de week iedere keer met een halve batterij te beginnen.

Eetclub, wat begonnen is als een avondje lasagne van Gis en knapperige asperges van Carl en Bert, is uitgegroeid tot een heerlijke avond waar jullie al mijn sappige ziekenhuisverhalen aanhoren. Maar ook het eindeloze geklaag over onderzoek en de uitleg dat ik geen coassistent meer ben. Het ventileren op avonden als deze maken mijn leven een stuk aangenamer. Dat er nog maar vele eetclubavonden en vakanties mogen volgen.

Lieve Carlijn en Frans, ik ben gelukkig dat ik jullie als leuke zus en broer mag hebben. Met jullie om mij heen is het leven altijd een feest. Wat bijzonder dat we allemaal arts zijn geworden, wellicht omdat de broertjes allebei hun oudere zus hebben gevolgd. Hoewel we allemaal arts zijn, kennen wij geen borrels en etentjes waar het altijd over het ziekenhuis gaat. Jullie humor en gezelligheid komen altijd weer terug in onze wekelijkse telefoontjes,

maar geven ook ruimte om lekker te ventileren over het leven. Ik kijk weer enorm uit naar onze eerstvolgende gezamenlijke vakantie, want voor mijn gevoel gaan we dan weer vijftien tot twintig jaar terug in de tijd toen we met ons drieën op de achterbank zaten met alle gevolgen van dien.

Lieve mama en papa, eindelijk is het zover. Zonder jullie steun was dit boekje er niet geweest. Jullie zijn altijd trouwe supporters, was het niet met applaus langs het veld dan was het wel met Bossche bollen aan de keukentafel. Ik word er onwijs gelukkig van als we 'even' kunnen bellen en dan weer helemaal up to date zijn over van alles en nog wat. Het is altijd een verademing om op de Willem van Oranjelaan te komen. De gezelligheid en gastvrijheid in combinatie met de beste chef-kok koester ik enorm. Ik hoop dat er nog vele mooie herinneringen zullen volgen. Bedankt voor alle steun alle jaren.

Lieve Chenette, jij kent mij eigenlijk al net zo lang of eigenlijk langer dan de weg naar dit proefschrift. De jaren voorafgaand waren vooral lang leve de lol samen. Daarna zijn we ''iets" serieuzer geworden en ben ik onwijs trots op je hoe hard je werkt, en toch altijd voor mij klaar staat. De laatste periode werd het gezeur over het proefschrift je wellicht eventjes te veel en ben je een jaartje naar Zwitserland verhuisd. Het was een jaar waarin we allesbehalve stil hebben gezeten, ontelbare tripjes voor dag en dauw hebben gemaakt die ons nog dichter bij elkaar hebben gebracht. Maar wat ben ik blij dat je weer bent teruggekomen om lekker te settelen in onze favoriete wijk en ons heerlijke leventje samen te vervolgen.

5. ABOUT THE AUTHOR

Jan Anton Willem Hagemans was born on October 7th, 1989 in 's-Hertogenbosch, the Netherlands, as youngest son of Wim Hagemans and Annette Hagemans-Hombergen and brother of Frans and Carlijn Hagemans. After finishing elementary school in Vught, he attended secondary school at the Sint-Janslyceum in 's-Hertogenbosch and graduated in the summer of 2008.

In September 2008, he started to study Medicine at the Erasmus University Medical School in Rotterdam. During his studies, he played and continued to play field hockey in the first team for HV Victoria (2008 – 2011 & 2014 – 2016) and HC Rotterdam (2011 – 2014). With HV Victoria, he became champion of the second Dutch national league in 2009. The greatest achievements with HC Rotterdam were winning the Championship of the first Dutch National Hockey League in 2013, the fourth place in the Euro Hockey League in 2013 and winner of the indoor Championship in 2014. During Medical School he joined 'Les Forgerons', a student team of the Emergency department of the Ikazia Hospital, in Rotterdam and he worked as operating room assistant at the Department of Surgery in Havenziekenhuis Rotterdam. Both of these jobs impressed him and his interests in the field of surgery developed more and more. Before starting his clinical internships, he finished his master research in peripheral nerve regeneration at the Department of Plastic and Reconstructive Surgery at the Erasmus Medical Centre (prof. dr. Hovius). In the beginning of 2016, he went to Sydney, Australia, for a clinical internship at the Surgical Oncology Unit of the Royal Prince Alfred Hospital (prof. dr. O. Nieweg) and the Melanoma Institute Australia (prof. dr. J. Thompson). After this internship, he did his final clinical internship at the Department of Surgery in the Ikazia Hospital Rotterdam (dr. P.T. den Hoed) and concurrently he started his research into rectal cancer.

He obtained his master degree of Medicine in June 2016. He started working as senior house officer and simultaneously started his research career at the Department of Surgical Oncology of the Erasmus MC Cancer Institute under supervision of prof. dr. C. Verhoef. In March 2017, he started as fulltime PhD-student for almost 2 years. In April 2019, he started working as senior house officer at the Department of Surgery in the Ikazia Hospital Rotterdam and In January 2020, he started with his surgical residency training under supervision of dr. P.T. den Hoed.