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Locally advanced and locally recurrent rectal cancer

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LOCALLY ADVANCED AND LOCALLY RECURRENT RECTAL CANCER

IMPROVING MULTIMODALITY TREATMENT

EVA L. K. VOOGT

LOCALLY ADVANCED AND LOCALLY RECURRENT RECTAL CANCER

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LOCALLY ADVANCED AND LOCALLY RECURRENT RECTAL CANCER

IMPROVING MULTIMODALITY TREATMENT

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CHAPTER 1

GENERAL INTRODUCTION AND OUTLINE OF THE THESIS

INTRODUCTION

Rectal cancer, a malignant tumour arising from the inner wall of the last part of the large intestine, is the 7th most common cancer in the world with about 732.000 new cases in 2020. With approximately 339.000 deaths yearly it is the 10th most deadly cancer in the world, and constituting 3.4% of all cancer related deaths. Rectal cancer is 3 to 4 times more common in developed countries than in developing countries and is predominantly diagnosed in men older than 65 years.[1] Surgery is the cornerstone of the management of rectal cancer. The extent of the surgery or the need for neoadjuvant treatment depends on the local extent of the tumour and the presence or absence of lymph node and/or distant metastases. When the tumour is confined to the rectal wall, local excision or surgery according to the TME principles can be performed.[2] TME surgery involves removal of the rectum and the entire circumferential perirectal tissue along the avascular plane (i.e. the Holy Plane).[3] The goal of surgery is attaining a resection with clear resection margins (R0 resection), as this is the single most important prognostic factor for survival after surgery in patients with rectal cancer.[4] However, when rectal cancer invades the perirectal tissue and extends into or beyond the mesorectal fascia (MRF), TME surgery is not sufficient to attain an R0 resection.[5,6] In this thesis, these rectal tumours invading or extending into or beyond the MRF are defined as locally advanced rectal cancer (LARC). This differs from the international literature and Dutch guideline, where a broader definition is used. Internationally, LARC is usually defined as stage II (clinical T3 or T4 tumour, without pathological lymph nodes) or stage III disease (presence of pathological lymph nodes, regardless of extend of the tumour, i.e. T-stage). In the Dutch guideline, LARC is defined as any clinical T4 tumour and/or MRF involvement and/or pathological lymph nodes and/or extramesorectal pathological lymph nodes.[7] However, stage III disease can be resected with standard TME surgery and has excellent long-term outcomes.[8] Patients with 'true-LARC' represent a different group. In these patients, neoadjuvant treatment with chemoradiotherapy is required to attain an R0 resection, as it has the ability to downstage the local tumour, thereby facilitating the resection.[8–12] Despite neoadjuvant chemoradiotherapy, in 25% of patients with LARC a TME resection is not sufficient to achieve an R0 resection and a resection beyond TMEI, i.e. an extended resection, is required.[13] Extended resections, either multivisceral resections or total exenterations, are major surgeries often requiring reconstructive surgery, and are accompanied with a high postoperative morbidity rate and a profound impact on the quality of life.[14–19] Such resections are performed in tertiary referral centres only.

Owing to the introduction of neoadjuvant treatment and TME surgery, local recurrence rates after curative treatment for primary rectal cancer are low, ranging between

6-10%.[10,20,21] Nevertheless, if a rectal tumour recurs locally, i.e. locally recurrent rectal cancer (LRRC), it has a clear negative impact on the quality of life as it is associated with a high morbidity including pain, bleeding, and fistulation.[22] Moreover, mortality in patient with LRRC is high with 5-year overall survival rates of approximately 30%.[23–26] As in LARC, an R0 resection is imperative for cure: after attaining an R0 resection 5-year overall survival rates vary between 48%-58%, whereas a resection without clear margins (R1/2 resection) results in a 5-year overall survival of 10%-18%.[23,26–29] According to the European Society for Medical Oncology (ESMO) guidelines, neoadjuvant chemoradiotherapy is therefore the standard of care in patients with LRRC.[2] However, a large proportion of patients has already been treated with chemoradiotherapy for the primary tumour. In these patients, reirradiation with a dose of 30 Gy has been proven safe and effective.[30,31] Nevertheless, radical surgery after neoadjuvant therapy in LRRC is challenging. Due to previous removal of the mesorectum the anatomical boundaries have disappeared, causing ingrowth in other organs and structures. Combined with the narrow shape of the pelvis and the need to preserve vital structures, such as nerves and vasculature, this makes these resections difficult. As a result, extended procedures involving resection of the bladder, internal genital organs, sacrum, and/or pelvic side wall are the rule rather than the exception, and often require reconstructive surgery.[15–18,32,33] As in LARC, these surgeries are concentrated in tertiary referral centres.

Despite current neoadjuvant treatment strategies and extended surgeries, an R1 resection occurs in approximately 10-20% of LARC and 40% of LRRC patients.[25,34,35] In these cases, intraoperative radiotherapy (IORT) may be delivered. IORT has the ability to deliver a boost of radiotherapy to the area that is at risk for tumour involvement while shielding dose-limiting structures, thereby overcoming the problem of exceeding the tolerance level of normal tissue. IORT may be delivered using different methods: intraoperative electron beam radiotherapy (IOERT) and high-dose-rate brachytherapy (HDR-IORT) are some of the commonly used methods in current clinical practice. Previous studies suggested that, in patients with an R1 resection, IORT may beneficial with regard to preventing local recurrence.[36–38]

Although recurrence rates for patients with primary rectal cancer are low, disease recurrence in patients with LARC is still a major concern with distant metastases rates ranging between 25%-40% and it being the most important cause of death in these patients.[10,20,21] In this context, the addition of systemic intravenous chemotherapy to the current neoadjuvant treatment with chemoradiotherapy has become of growing interest in the past years, as it may improve outcomes in patients with LARC. At first, and in line with the treatment for colon cancer, chemotherapy was administered in the adjuvant setting. However, several randomised trials failed to demonstrate a benefit

in survival with this treatment.[39,40] This has been ascribed to the poor compliance rates due to high rates of postoperative morbidity. Consequently, administration of chemotherapy in the neoadjuvant setting has been gaining attention as it potentially improves the tolerability and compliance of chemotherapy, and therefore may enable a higher efficacy. Neoadjuvant chemotherapy may be prescribed prior to the neoadjuvant (chemo)radiotherapy, referred to as induction chemotherapy, or between (chemo) radiotherapy and surgery, referred to as consolidation chemotherapy.

Theoretically, neoadjuvant chemotherapy may reduce the rate of distant metastases by eliminating micrometastases that may be present. Moreover, the addition of neoadjuvant chemotherapy may improve local downstaging more than can be achieved by chemoradiotherapy alone, and thereby improve the chance of attaining an R0 resection or even a pathological complete response. A pathological complete response is associated with improved long-term outcomes compared with patients with residual disease.[41] Moreover, improved local downstaging may enable a more conservative surgical approach, and, in case of a clinical complete response, even a non-surgical approach in a wait-and-see setting. The latter seems to be a safe option, although questions remain regarding patient selection, the criteria for a clinical complete response, and the follow-up protocol.[42,43]

Given these theoretical advantages, induction chemotherapy also gained interest in the treatment of patients with LRRC. Distant failures are an even greater concern compared with LARC and there is much to be gained in terms of the number of R0 resections and local recurrence rates.

OUTLINE OF THIS THESIS

The aim of this thesis is to gain insight in the results of the multimodality treatment of patients with LARC and LRRC, with the purpose to improve this treatment and thereby improve the quality of life and long-term oncological outcomes. The first part of this thesis focuses on patient selection, preoperative imaging, and peroperative approach. The second part focuses on neoadjuvant treatment, specifically induction chemotherapy. The third part provides a general discussion, future perspectives, and a summary of this thesis.

Part I: Patient selection, imaging and peroperative approach

Approximately 50% of patients with LRRC present with synchronous distant metastases.[44] Historically, patients with synchronous metastases were considered incurable and were offered treatment with palliative intent. However, in patients with primary rectal cancer, metastatic disease does not preclude patients from starting a curative treatment, provided that an R0 resection of the primary tumour and an R0 resection or ablation of the solitary or oligometastatic disease can be attained.[45] To assess if a curative treatment is feasible in LRRC patients with synchronous metastases, **Chapter 2** presents a single-centre, retrospective cohort study evaluating the oncological outcomes of patients with LRRC without metastases, those with a history of metastases, and those with synchronous metastases.

Older patients undergoing cancer treatment are more prone to postoperative morbidity and mortality, mostly due to underlying comorbidities. Nevertheless, improvements in the pre-, peri- , and postoperative care in patients with non-advanced colorectal cancer have resulted in comparable morbidity and mortality rates to that in younger patients. Whether this also applies to elderly patients with clinical T4 primary rectal cancer or LRRC is evaluated in **Chapter 3** in a single centre, retrospective, cohort study.

In rectal cancer, high-resolution magnetic resonance imaging (MRI) has emerged as the primary method of pelvic imaging, as it can assist in selecting patients who are suitable for neoadjuvant treatment, it can guide surgeons in the surgical planning, and it can identify poor prognostic features.[46,47] The latter is especially important, since the presence of poor prognostic features may have consequences for the treatment strategy. In this respect, MRI detected extramural vascular invasion (mrEMVI) and tumour deposits (TDs) gained much attention over the past years. Both mrEMVI and TDs have shown to be unfavourable prognosticators with regard to the metastasis and disease-free survival.[48,49] **Chapter 4** presents a single centre, retrospective, cohort study in which we evaluated the incidence and features of mrEMVI and TDs before and

after neoadjuvant treatment in patients with LARC and their relation to the long-term oncological outcomes.

Alongside the initial assessment of the tumour, MRI in the restaging setting, i.e. after neoadjuvant treatment, can also assist in evaluating the degree of tumour regression. To systematically evaluate tumour regression, an MRI-based tumour regression (mrTRG) score, which grades the degree of fibrotic response, has been proposed by the MERCURY study group.[50] In LARC, this mrTRG score has proven to be highly reproducible amongst radiologists as well as a prognostic factor for survival.[51,52] In **Chapter 5** the reproducibility of mrTRG in LRRC is evaluated in a retrospective cohort study, as well as the predictive value with regard to the pathological response.

For advanced rectal tumours sometimes a total pelvic exenteration is required in order to completely remove the tumour. This results in the need for a urinary diversion. The formation of a conduit not only comes with specific per- and postoperative complications, but also leads to psychological and social challenges. Creating a conduit that is associated with as little complications possible is therefore important for these patients. **Chapter 6** presents a multicentre retrospective cohort study describing the outcomes after two different types of conduits: an ileal and a colon conduit.

Chapter 7 focuses on intraoperative radiotherapy (IORT). IORT can be delivered as IOERT or HDR-IOR and both modalities have their own advantages and disadvantages with regard to the application.[38,53] However, it is unknown whether the effectivity and thereby outcomes differ between both methods. In the retrospective study presented in this chapter, the long-term oncological outcomes of patients who received IOERT and HDR-IORT after an R1 resection for LARC or LRRC treated in two large tertiary referral centres are compared.

Part II: Neoadjuvant treatment

Part II of this thesis focuses on neoadjuvant treatment in LARC and LRRC, and specifically on the addition of induction chemotherapy to neoadjuvant chemoradiotherapy.

In **Chapter 8** the value of the addition of induction chemotherapy to neoadjuvant chemoradiotherapy with regard to the pathological and clinical complete response rate is investigated in a retrospective, matched case-control study, including patients with LARC with prognostically poor characteristics.

Chapters 9 presents a retrospective, single centre, cohort study performed in patients with LRRC, evaluating the pathological response after treatment with induction

chemotherapy followed by chemo(re)irradiation and its predictive value with regard to the long-term oncological outcomes.

In **Chapter 10** a research letter is presented, showing new data from a large retrospective cohort. In this cohort the additional value of induction chemotherapy to neoadjuvant chemo(re)irradiation in patients with LRRC with regard to the pathological response, the R0 resection rate and disease-free survival was evaluated.

The outcomes of chapter 9 and 10, resulted in the initiation of an international, multicentre, randomised controlled, phase 3 study: the PelvEx II study. **Chapter 11** presents the study protocol of this study. In the PelvEx II study, patients with LRRC without distant metastasis will be randomised between treatment with induction chemotherapy followed by chemo(re)irradiation and surgery or chemo(re)irradiation and surgery alone.

Part III

Finally, in **Chapter 12** the findings of this thesis are discussed and a future perspective is drawn. In **Chapter 13** a summary of the main results of this thesis is given. In **Chapter 14** an impact paragraph is provided and **Chapter 15** contains the appendices.

REFERENCES

1. World Health Organization. Global Cancer Observatory. https://gco.iarc.fr/. Accessed January 13, 2021.
2. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Suppl 4):iv22-iv40. doi:10.1093/annonc/mdx224
3. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg*. 1982;69(10):613-616. doi:10.1002/bjs.1800691019
4. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, Van De Velde CJH, Van Krieken JHJM. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: Not one millimeter but two millimeters is the limit. *Am J Surg Pathol*. 2002;26(3):350-357. doi:10.1097/00000478-200203000-00009
5. De Wilt JHW, Vermaas M, Ferenschild FTJ, Verhoef C. Management of locally advanced primary and recurrent rectal cancer. *Clin Colon Rectal Surg*. 2007;20(3):255-264. doi:10.1055/s-2007-984870
6. Mariathasan AB, Boye K, Giercksky KE, et al. Beyond total mesorectal excision in locally advanced rectal cancer with organ or pelvic side-wall involvement. *Eur J Surg Oncol*. 2018;44(8):1266-1232vt. doi:10.1016/j.ejso.2018.03.029
7. Federatie Medisch Specialisten. Neoadjuvante (chemo)radiotherapie bij het lokaal gevorderd rectum carcinoom. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/primaire_behandeling_rectumcarcinoom_bij_crc/neoadjuvante_chemo_radiotherapie_bij_het_lokaal_gevorderd_rectumcarcinoom_rc.html. Published 2020. Accessed February 23, 2022.
8. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi:10.1056/NEJMoa010580
9. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. *N Engl J Med*. 2004;351(71):1731-1740. doi:10.1056/nejmoa040694
10. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836
11. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol*. 2006;24(28):4620-4625. doi:10.1200/JCO.2006.06.7629
12. Bosset JF, Calais G, Mineur L, et al. Fluorouracil-based adjuvant chemotherapy after preoperative chemoradiotherapy in rectal cancer: Long-term results of the EORTC 22921 randomised study. *Lancet Oncol*. 2014;15(2):184-190. doi:10.1016/S1470-2045(13)70599-0
13. Helewa RM, Park J. Surgery for Locally Advanced T4 Rectal Cancer: Strategies and Techniques. *Clin Colon Rectal Surg*. 2016;29(2):106-113. doi:10.1055/s-0036-1580722

14. Gezen C, Kement M, Altuntas YE, et al. Results after multivisceral resections of locally advanced colorectal cancers: An analysis on clinical and pathological t4 tumors. *World J Surg Oncol*. 2012;10:39. doi:10.1186/1477-7819-10-39

15. van den Heijkant F, Vermeer TA, Vrijhof EJEJ, Nieuwenhuijzen GAP, Koldewijn EL, Rutten HJT. Psoas hitch ureteral reimplantation after surgery for locally advanced and locally recurrent colorectal cancer: Complications and oncological outcome. *Eur J Surg Oncol*. 2017;43(10):1869-1875. doi:10.1016/j.ejso.2017.05.018

16. Bosman SJ, Vermeer TA, Dudink RL, De Hingh IHJT, Nieuwenhuijzen GAP, Rutten HJT. Abdominosacral resection: Long-term outcome in 86 patients with locally advanced or locally recurrent rectal cancer. *Eur J Surg Oncol*. 2014;40(6):699-705. doi:10.1016/j.ejso.2014.02.233

17. Holman FA, Martijnse IS, Traa MJ, et al. Dynamic article: Vaginal and perineal reconstruction using rectus abdominis myocutaneous flap in surgery for locally advanced rectum carcinoma and locally recurrent rectum carcinoma. *Dis Colon Rectum*. 2013;56(2):175-185. doi:10.1097/DCR.0b013e31827a267c

18. Hagemans JAW, Rothbarth J, Kirkels WJ, et al. Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly. *Eur J Surg Oncol*. 2018;44(10):1548-1554. doi:10.1016/j.ejso.2018.06.033

19. Vermaas M, Ferenschild FTJ, Verhoef C, et al. Total pelvic exenteration for primary locally advanced and locally recurrent rectal cancer. *Eur J Surg Oncol*. 2007;33(4):452-458. doi:10.1016/j.ejso.2006.09.021

20. den Dulk M, Krijnen P, Marijnen CAM, et al. Improved overall survival for patients with rectal cancer since 1990: The effects of TME surgery and pre-operative radiotherapy. *Eur J Cancer*. 2008. doi:10.1016/j.ejca.2008.05.004

21. van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582. doi:10.1016/S1470-2045(11)70097-3

22. Camilleri-Brennan J, Steel R. The impact of recurrent rectal cancer on quality of life. *EurJ-SurgOncol*. 2001;27(4):349-353.

23. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Color Dis*. 2011;13(7):732-742. doi:10.1111/j.1463-1318.2009.02167.x

24. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *Eur J Surg Oncol*. 2018;44(1):100-107. doi:10.1016/j.ejso.2017.11.013

25. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y

26. Holman FA, Bosman SJ, Haddock MG, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. *Eur J Surg Oncol*. 2017;43(1):107-117. doi:10.1016/j.ejso.2016.08.015

27. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388

28. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866-1873. doi:10.1002/bjs.10645

29. Hagemans JAW, van Rees JM, Alberda WJ, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *Eur J Surg Oncol*. 2020;46(3):448-454. doi:10.1016/j.ejso.2019.10.037

30. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569

31. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: A systematic review. *Radiother Oncol*. 2014;113(2):151-157. doi:10.1016/j.radonc.2014.11.021

32. Kusters M, Dresen RC, Martijn H, et al. Radicality of Resection and Survival After Multimodality Treatment is Influenced by Subsite of Locally Recurrent Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1444-1449. doi:10.1016/j.ijrobp.2009.01.015

33. Ferenschild FTJ, Vermaas M, Verhoef C, et al. Total pelvic exenteration for primary and recurrent malignancies. *World J Surg*. 2009;33(7):1502-1508. doi:10.1007/s00268-009-0066-7

34. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer. *Ann Surg*. 2019;269(2):315-321. doi:10.1097/SLA.0000000000002528

35. Platt E, Dovell G, Smolarek S. Systematic review of outcomes following pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer. *Tech Coloproctol*. 2018;22(11):835-845. doi:10.1007/s10151-018-1883-1

36. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1032-1040. doi:10.1016/j.ijrobp.2014.01.014

37. Ferenschild FTJ, Vermaas M, Nuyttens JJME, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum*. 2006;49(9):1257-1265. doi:10.1007/s10350-006-0651-x

38. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol*. 2013;22(1):22-35. doi:10.1016/j.suronc.2012.11.001

39. Collette L, Bosset JF, Den Dulk M, et al. Patients with curative resection of cT3-4 rectal cancer after preoperative radiotherapy or radiochemotherapy: Does anybody benefit from adjuvant fluorouracil-based chemotherapy? A trial of the European Organisation for Research and Treatment of Cancer Rad. *J Clin Oncol*. 2007;25(28):4379-4386. doi:10.1200/JCO.2007.11.9685

40. Breugom AJ, Van Gijn W, Muller EW, et al. Adjuvant chemotherapy for rectal cancer patients treated with preoperative (chemo)radiotherapy and total mesorectal excision: A Dutch Colorectal Cancer Group (DCCG) randomized phase III trial. *Ann Oncol*. 2015;26(4):696-701. doi:10.1093/annonc/mdu560

41. Maas M, Nelemans J, Marañón G, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835-844. doi:10.1016/S1470-2045(10)70172-8

42. Habr-Gama A, Perez RO, Nadalin W, et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: Long-term results. *Ann Surg*. 2004;240(4):711-717. doi:10.1097/01.sla.0000141194.27992.32

43. López-Campos F, Martín-Martín M, Fornell-Pérez R, et al. Watch and wait approach in rectal cancer: Current controversies and future directions. *World J Gastroenterol*. 2020;26(29):4218-4239. doi:10.3748/WJG.V26.I29.4218

44. van den Brink M, Stiggelbout AM, van den Hout WB, et al. Clinical Nature and Prognosis of Locally Recurrent Rectal Cancer After Total Mesorectal Excision With or Without Preoperative Radiotherapy. *J Clin Oncol*. 2004;22(19):3958-3964. doi:10.1200/jco.2004.01.023

45. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422. doi:10.1093/annonc/mdw235

46. Brown G, Davies S, Williams GT, et al. Effectiveness of preoperative staging in rectal cancer: Digital rectal examination, endoluminal ultrasound or magnetic resonance imaging? *Br J Cancer*. 2004;91(1):23-29. doi:10.1038/sj.bjc.6601871

47. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg*. 2003;90(3). doi:10.1002/bjs.4034

48. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer*. 2017;116(12):1513-1519. doi:10.1038/bjc.2017.99

49. Lord AC, D'Souza N, Shaw A, et al. MRI-Diagnosed Tumour Deposits and EMVI Status Have Superior Prognostic Accuracy to Current Clinical TNM Staging in Rectal Cancer. *Ann Surg*. 2020:Publish Ahead of Print. doi:10.1097/SLA.0000000000004499

50. Siddiqui MRS, Gormly KL, Bhoday J, et al. Interobserver agreement of radiologists assessing the response of rectal cancers to preoperative chemoradiation using the MRI tumour regression grading (mrTRG). *Clin Radiol*. 2016;71(9):854-862. doi:10.1016/j.crad.2016.05.005

51. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29(28):3753-3760. doi:10.1200/JCO.2011.34.9068

52. Sclafani F, Brown G, Cunningham D, et al. Comparison between MRI and pathology in the assessment of tumour regression grade in rectal cancer. *Br J Cancer*. 2017;117(10):1478-1485. doi:10.1038/bjc.2017.320

53. Nag S, Willet CG, Gunderson LL, Harrison LB, Calvo FA, Biggs P. IORT with Electron-Beam, High-Dose-Rate Brachytherapy or Low-KV/Electronic BRachytherapy: Methodological Comparisons. In: *Intraoperative Irradiation: Techniques and Results*. 2nd ed. Totowa, NJ: Humana Press; 2011:99-115.

PART I

PATIENT SELECTION, IMAGING AND PEROPERATIVE APPROACH

CHAPTER 2

IMPACT OF A HISTORY OF METASTASES OR SYNCHRONOUS METASTASES ON SURVIVAL IN PATIENTS WITH LOCALLY RECURRENT RECTAL CANCER

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ABSTRACT

Aim

Patients with locally recurrent rectal cancer (LRRC) frequently present with either synchronous metastases or a history of metastases. This study was conducted to evaluate whether LRRC patients without metastases have a different oncological outcome compared to patients with a history of metastases treated with curative intent or patients with potentially curable synchronous metastases.

Method

All consecutive LRRC patients who underwent intentionally curative surgery between 2005 and 2017 in a large tertiary hospital were retrospectively reviewed and categorised as having no metastases, a history of (curatively treated) metastases or synchronous metastases. Patients with unresectable distant metastases were excluded from the analysis.

Results

Of the 349 patients who were analysed, 261 (75%) had no metastases, 42 (12%) had a history of metastases, and 46 (13%) had synchronous metastases. The 3-year metastasis-free survival was 52%, 33%, and 13% in patients without metastases, with a history of metastases, and with synchronous metastases, respectively ($p < 0.001$) A history of metastases did not influence overall survival (OS), but there was a trend towards a worse OS in patients with synchronous metastases compared with patients without synchronous metastases (hazard ratio 1.43; 95% CI 0.98-2.11).

Conclusion

LRRC patients with a history of curatively treated metastases have an OS comparable to that in patients without metastases and should therefore be treated with curative intent. However, LRRC patients with synchronous metastases have a poor metastasis-free survival and worse OS; in these patients, an individualised treatment approach to observe the behaviour of the disease is recommended.

INTRODUCTION

The European Society for Medical Oncology guidelines for the management of patients with metastatic (colo-)rectal cancer specify treatment strategies based on the possibility of achieving a resection with clear resection margins (R0 resection) of the primary tumour and an R0 resection or ablation of the solitary or oligometastatic disease.[1] In marginally resectable metastatic lesions, induction chemotherapy may enable conversion of these lesions to a resectable or ablatable state.[1] This concept has led to the development of treatment strategies comprising a combination of neoadjuvant (chemo)radiotherapy and systemic treatment in patients with metastatic primary rectal cancer, resulting in long-term survival rates exceeding 50%.[2,3]

Similarly, the treatment of locally recurrent rectal cancer (LRRC) is intended to achieve an R0 resection – the most important prognostic factor for survival. Depending on local protocol, treatment may comprise neoadjuvant chemo(re)irradiation and extensive surgery with/without intraoperative radiotherapy.[4–7] Induction chemotherapy is currently being evaluated as a promising addition to this treatment to improve resectability and oncological outcomes.[8,9]

Synchronous systemic disease is a major problem in LRRC, as approximately 50% of patients present with distant metastases.[10] In particular, patients who develop LRRC within one year after the primary resection or those treated with neoadjuvant radiotherapy for the primary tumour are prone to early development of metastatic disease.[10]

As metastatic disease is considered an indicator of aggressive tumour biology, treatment options for LRRC patients with synchronous metastases or a history of metastases (m-LRRC) are usually limited to palliative intent, thereby resulting in poor survival rates.[11–14] However, it is unclear whether these metastases progress rapidly or whether treatment with curative intent might be feasible in some patients.

In our centre, the treatment principles for metastatic primary rectal cancer are applied in patients with m-LRRC. Metastatic disease is considered to be cured if patients with a history of metastases have no signs of recurrent metastatic disease. Synchronous metastases are considered curable if an R0 resection of the LRRC and radical treatment of the metastases can be achieved.

This study aimed to comparatively evaluate oncological outcomes in LRRC patients without metastases, those with a history of metastases and those with synchronous metastases.

METHODS

Patients

The data of consecutive LRRC patients treated at the Catharina Hospital (CZE), a national tertiary referral centre for LRRC, were prospectively collected in a database and retrospectively reviewed. This study selected all LRRC patients who underwent a curative resection between January 2005 and December 2017. Patients with local unresectable disease or untreatable distant metastases and patients with progressive disease during neoadjuvant treatment who did not undergo a resection were excluded.

Selected patients were categorised as follows: without metastases (no metastases); with curatively treated synchronous or metachronous metastases with the primary tumour (history of metastases); and with resectable metastases diagnosed simultaneously with the LRRC, during neoadjuvant treatment, or perioperatively (synchronous metastases). Patients with both a history of metastases and synchronous metastases, were categorised as having 'synchronous metastases'.

This study was approved by the local medical ethics board (Medical Research Ethics Committees United - Nieuwegein, registration number W19.031).

Treatment local recurrence

The optimal treatment strategy and timing for all patients were determined at a multidisciplinary team (MDT) meeting attended by a specialised surgical oncologist, medical oncologist, radiation oncologist, radiologist, nuclear medicine specialist and pathologist. Patients were eligible for curative treatment if an R0 resection of the LRRC and curative treatment of metastatic disease were achievable.

Curative treatment generally comprised neoadjuvant chemoradiotherapy with concomitant capecitabine administered twice daily. Radiotherapy dose was 50-50.4 Gy, delivered in 25-28 fractions of 1.8-2.0 Gy. In the case of previous radiotherapy, the dose was 30-30.6 Gy, delivered in 15-17 fractions of 1.8-2.0 Gy. The gross tumour volume was expanded with a margin of at least 1 cm for the clinical target volume. The planning target volume consisted of the clinical target volume plus a 2 cm margin.

Since 2010, induction chemotherapy before chemo(re)irradiation has been introduced as a treatment option to improve local downstaging and, thereby, resectability.

The surgical approach depended on the location and extent of the LRRC and was performed by experienced surgical oncologists. For the purpose of this study, we categorised the type of resection as low anterior resection, abdominoperineal resection, multivisceral resection or nonvisceral resection. A multivisceral resection was defined as a resection including a resection of the rectum and at least one pelvic organ/structure (i.e., bladder, prostate, vesicles, uterus, vagina, ovaries, sacrum). A nonvisceral resection was defined as a resection of the recurrence without a resection of the rectum.

In the case of involved or narrow resection margins and when deemed feasible, intraoperative radiotherapy (IORT; dose 10-12.5 Gy) was administered. IORT was delivered by electron beam radiotherapy. In earlier years this was delivered using an Elekta SL-25 linear accelerator (Elekta Oncology Systems, Stockholm, Sweden). From 2016 onwards, IORT was delivered using a Mobetron 2000 linear accelerator (IntraOp Inc., Sunnyvale CA, USA).

Treatment distant metastases

The treatment strategy for synchronous metastases was determined in an MDT meeting. Liver metastases were treated with surgery, radiofrequency ablation or stereotactic radiotherapy, all performed in the referring or a partnering hospital. Lung metastases were treated with metastasectomy or stereotactic radiotherapy. Lung and liver metastases were treated either during the interval between neoadjuvant (chemo)radiotherapy and surgery or postoperatively. In case of peritoneal metastases, cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) was performed simultaneously with the LRRC resection. Inguinal or para-aortic lymph node metastases were treated with a lymphadenectomy simultaneous with the LRRC resection if residual disease was suspected after neoadjuvant treatment.

Follow-up

Patients were followed up in the CZE or in the referring hospital, according to the patient's preference. Follow-up was performed according to the Dutch guidelines for colorectal cancer and consisted of carcinoembryonic antigen measurements four times a year during the first 2 years and twice a year during years 3-5. Ultrasonography of the liver and chest radiography or a thoracoabdominal computed tomography scan was performed twice a year during the first 2 years and once a year thereafter.

Endpoints and statistical analysis

Continuous data were reported as median (interquartile range), and categorical data as count (percentage). To compare individual variables, the Mann-Whitney *U* and Chi-square tests were performed as appropriate.

The endpoints were overall survival (OS: time between the date of LRRC surgery and the date of death or last follow-up), local recurrence-free survival (LRFS: time between the date of LRRC surgery and the date of histologically or radiologically proven local re-recurrence or last follow-up), and metastasis-free survival (MFS: time between the date of LRRC surgery and the date of histologically or radiologically proven distant metastases or last follow-up).

The OS, LFRS and MFS were estimated using the Kaplan-Meier method, and differences were assessed using the log-rank test. For multivariable analyses, the Cox regression method was applied using all variables with a $p < 0.100$ in the univariable analyses. Two-sided p values <0.05 were considered statistically significant. Statistical analysis was performed using IBM SPSS® version 23 for Windows® (IBM, Armonk, NY, USA).

RESULTS

Patients

Of the 349 patients who met the selection criteria, 261 (75%) never had distant metastases, 42 (12%) had a history of metastases and 46 (13%) had synchronous metastases; 14/46 patients also had a history of metastases. All included patients underwent pelvic surgery as well as treatment for their metastatic disease. Patient characteristics and details of the primary and recurrent tumour are shown in *Tables 1* and *2*, respectively. Patients with synchronous metastases had a shorter interval between resection of the primary tumour and the LRRC (26 months) than patients without metastases and patients with a history of metastases (31 and 42 months respectively, $p = 0.014$). Patients with synchronous metastases more often received induction chemotherapy for their LRRC than patients without or those with a history of metastases ($p = 0.033$), and the latter more often underwent (chemo)reirradiation for the LRRC than patients with synchronous metastases, who underwent full-course (chemo)radiotherapy more often ($p = 0.012$). Intraoperative radiotherapy was delivered in 82.8% of the patients. A multivisceral resection was performed in 238 patients; details about the organs resected with this multivisceral resection are shown in *Table S1*.

Table 1 Baseline and primary tumour characteristics

		Total[a]	No metastases	History of metastases	Synchronous metastases	*p* value
		N=349 (%)	N=261 (%)	N=42 (%)	N=46 (%)	
Gender	Female	121 (34.7)	93 (35.6)	12 (28.6)	16 (34.8)	0.694
	Male	228 (65.3)	168 (64.4)	30 (71.4)	30 (65.2)	
Age at resection (years)	Median [IQR]	64 [58-71]	65 [59-72]	62 [58-69]	63 [52-69]	0.074
ASA	I-II	279 (85.3)	220 (87.3)	26 (78.8)	33 (78.6)	0.186
	III	48 (14.7)	32 (12.7)	7 (21.2)	9 (21.4)	
Tumour stage	pT1/T2	71 (20.7)	60 (23.5)	6 (14.3)	5 (10.9)	0.082
	pT3/T4	272 (79.3)	195 (76.5)	36 (85.7)	41 (89.1)	
Nodal stage	pN0	151 (44.4)	121 (47.8)	12 (29.3)	18 (39.1)	0.063
	pN1/2	189 (55.6)	132 (52.2)	29 (70.7)	28 (60.9)	
Neoadjuvant radiotherapy	None	146 (41.8)	108 (41.4)	11 (26.2)	27 (58.7)	0.036
	Short-course radiotherapy	104 (29.8)	80 (30.7)	14 (33.3)	10 (21.7)	
	Full-course (chemo)radiotherapy	99 (28.4)	73 (28.0)	17 (40.5)	9 (19.6)	
Type of surgery	TEM	13 (3.7)	13 (5.0)	0 (0)	0 (0)	0.011
	Rectosigmoid resection/LAR	236 (67.6)	178 (68.2)	22 (52.4)	36 (78.3)	
	Abdominoperineal resection	100 (28.7)	70 (26.8)	20 (47.6)	10 (21.7)	
Adjuvant therapy	None	285 (81.7)	222 (85.1)	27 (64.3)	36 (78.3)	0.004
	Adjuvant chemotherapy	64 (18.3)	39 (14.9)	15 (35.7)	10 (21.7)	

Abbreviations: ASA = American Society of Anaesthesiologists Physical Status, IQR = interquartile range, LAR = low anterior resection, TEM = transanal endoscopic microsurgery.

[a] Numbers do not always add up to 349 due to missing values (ASA n = 22; tumour stage n = 6; nodal stage n = 9).

Table 2 Recurrent tumour characteristics, treatment and outcomes

		Total	No metastases	History of metastases	Synchronous metastases	*p* value
		N=349 (%)	N=261 (%)	N=42 (%)	N=46 (%)	
Time to recurrence (months)a	Median [IQR]	31 [19-50]	31 [19-49]	42 [34-63]	26 [17-47]	0.013
Number of recurrence	1	296 (84.8)	229 (87.7)	30 (71.4)	37 (80.4)	0.016
	2-3	53 (15.2)	32 (12.3)	12 (28.6)	9 (19.6)	
Multifocality	No	310 (88.8)	235 (90.0)	36 (85.7)	39 (84.8)	0.460
	Yes	39 (11.2)	26 (10.0)	6 (14.3)	7 (15.2)	
Induction chemotherapy	No	237 (67.9)	186 (71.3)	27 (64.3)	24 (52.2)	0.033
	Yes	112 (32.1)	75 (28.7)	15 (35.7)	22 (47.8)	
Neoadjuvant radiotherapy	None	27 (7.7)	14 (5.4)	8 (19.0)	5 (11.1)	0.012
	Short-course radiotherapy	3 (0.9)	2 (0.8)	0 (0)	1 (2.2)	
	Full-course (chemo)radiotherapy	117 (33.5)	88 (33.7)	9 (21.4)	20 (43.5)	
	(Chemo)reirradiation	202 (57.9)	157 (60.2)	25 (59.5)	20 (43.5)	
Type of surgery	Low anterior resection	54 (15.5)	39 (14.9)	5 (11.9)	10 (21.7)	0.744
	Abdominoperineal resection	25 (7.2)	17 (6.5)	4 (9.5)	4 (8.7)	
	Nonvisceral resection	32 (9.2)	24 (9.2)	5 (11.9)	3 (6.5)	
	Multivisceral resection	238 (68.2)	181 (69.3)	28 (66.7)	29 (63.0)	
Intraoperative radiotherapy	No	60 (17.2)	43 (16.5)	8 (19.0)	9 (19.6)	0.828
	Yes	289 (82.8)	218 (83.5)	34 (81.0)	37 (80.4)	
Resection margin	R0	219 (62.8)	166 (63.6)	29 (69.0)	24 (52.2)	0.224
	R1/R2	130 (37.2)	95 (36.4)	13 (31.0)	22 (47.8)	
Histology[b]	Adenocarcinoma	287 (92)	216 (92)	32 (91)	39 (89)	0.657
	Mucinous carcinoma	26 (8)	18 (8)	3 (9)	5 (11)	
Postoperative complications	Clavien-Dindo 1-2	254 (72.8)	191 (73.2)	31 (73.8)	32 (69.6)	0.868
	Clavien-Dindo 3-5	95 (27.2)	70 (26.8)	11 (26.2)	14 (30.4)	

Abbreviations: IQR = interquartile range.

[a] Duration between primary surgery and current recurrence; missing values in n = 8.

[b] Missing values n = 36, as these patients had a complete pathologic response.

Location and treatment of metastases

Details about the types of metastases are shown in *Table 3*. The majority of the patients with a history of metastases had liver metastases (n = 23, 54%), which were mainly treated with metastasectomy (n = 22). Thirteen patients had lung metastases (31%), mainly treated with metastasectomy (n = 11). Seven patients (17%) had peritoneal metastases that were treated with CRS ± HIPEC.

Patients with synchronous metastases mostly presented with liver or peritoneal metastases (n = 15 and n = 18, 32% and 39%, respectively), which were mainly treated with metastasectomy (n = 11) or CRS ± HIPEC, respectively. Lymph node metastases (n = 6, 13%) either disappeared after neoadjuvant treatment (n = 3) or required additional lymphadenectomy (n = 3).

Table 3 Location, extent and treatment of metastases

	History of metastases (N=42)	**Synchronous metastases (N=46)**	
		History of metastases	**Synchronous metastases**
Liver[a]	23	9	15
Single	10	3	9
Multiple	13	6	6
Treatment[b,c]			
Resection (e.g. metastasectomy, hemihepatectomy)	22	8	11
RFA	4	3	1
Stereotactic radiotherapy	0	0	2
Systemic chemotherapy	0	0	2
Lung[a]	13	2	6
Single	11	1	3
Multiple	2	1	3
Treatment			
Resection	11	2	1
Stereotactic radiotherapy	2	0	4
Unknown	0	0	1
Peritoneal[a,d]	7	5	18
Single (PCI≤2)	3	1	6
Multiple(PCI >2)	4	4	12
Treatment			
Cytoreductive surgery + HIPEC	3	2	10
Cytoreductive surgery - HIPEC	4	3	8

Table 3 (Continued)

	History of metastases (N=42)	Synchronous metastases (N=46)	
		History of metastases	Synchronous metastases
Lymph nodes (inguinal/para-aortic)[a]	3	1	6
Single	2	0	2
Multiple	1	1	4
Treatment			
Metastasectomy	3	0	3
Systemic chemotherapy	0	1	3
Other[a]	0	0	2
Single	NA	NA	2
Multiple	NA	NA	0
Treatment			
Metastasectomy	NA	1	2
Systemic chemotherapy	NA	0	1

Abbreviations: HIPEC = hyperthermic intraperitoneal chemotherapy, NA = not applicable, PCI = peritoneal cancer index, RFA = radiofrequency ablation.

[a] The numbers are not in agreement with the number of patients with metastases as some patients were diagnosed with metastases in more than one organ.

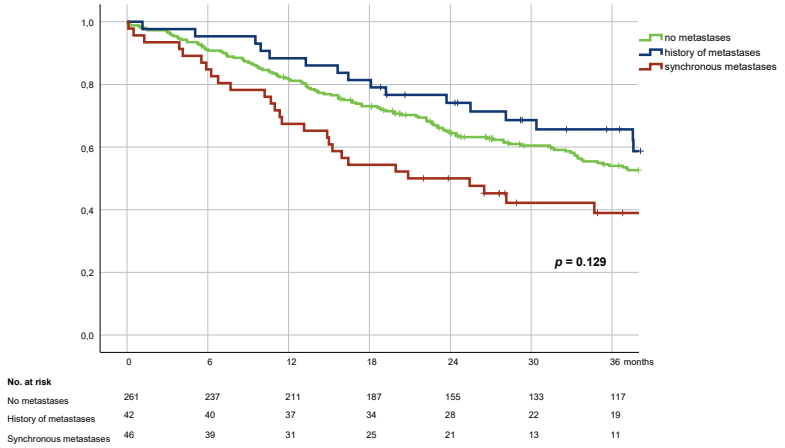
[b] One patient could have undergone multiple treatments in cases of multiple metastases (e.g., metastasectomy and RFA).

[c] Only the definitive treatment for a specific metastasis is listed. If neoadjuvant chemotherapy was administered before metastasectomy, the chemotherapy was not scored as a treatment.

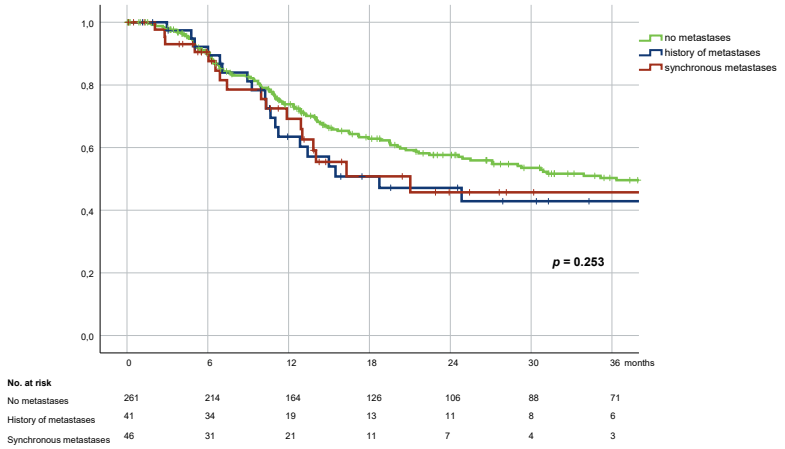
[d] Including metastases in the ovary and abdominal wall.

Overall survival

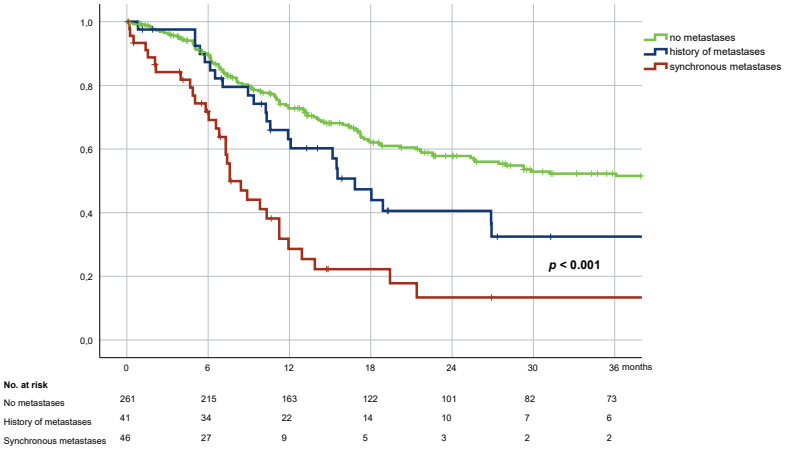
The 3-year OS rate in all patients was 53% (median 39.7 months), and 54%, 65%, and 39% (median 43.0, 40.7, and 20.8 months) in patients without metastases, with a history of metastases, and with synchronous metastases, respectively (p = 0.129; *Figure 1a*). When comparing groups separately, no significant difference in OS was observed in patients without metastases versus those with a history of metastases (p = 0.592), without metastases versus synchronous metastases (p = 0.071), and a history of metastases versus synchronous metastases (p = 0.091). A comparison between patients with synchronous metastases and those without synchronous metastases showed a trend towards a significant difference in the 3-year OS (39% vs. 56% respectively, p = 0.051).



No. at risk							
No metastases	261	237	211	187	155	133	117
History of metastases	42	40	37	34	28	22	19
Synchronous metastases	46	39	31	25	21	13	11



No. at risk							
No metastases	261	214	164	126	106	88	71
History of metastases	41	34	19	13	11	8	6
Synchronous metastases	46	31	21	11	7	4	3



No. at risk							
No metastases	261	215	163	122	101	82	73
History of metastases	41	34	22	14	10	7	6
Synchronous metastases	46	27	9	5	3	2	2

Figure 1 Overall survival (a), local recurrence-free survival (b) and metastasis-free survival (c) in LRRC patients without metastases, with a history of metastases and with synchronous metastases

Local recurrence

The 3-year LRFS rate in all patients was 49% (median LRFS 31.2 months), and 51%, 40%, and 46% in patients without metastases, with a history of metastases, and with synchronous metastases, respectively ($p = 0.253$; *Figure 1b*). There was no significant difference in the LRFS between patients without metastases and those with a history of metastases ($p = 0.116$), without metastases versus synchronous metastases ($p = 0.437$), or a history of metastases versus synchronous metastases ($p = 0.550$).

Distant recurrence

The 3-year MFS rate in all patients was 45% (median 25.6 months), and 52%, 33%, and 13% in patients without metastases, with a history of metastases, and with synchronous metastases, respectively ($p < 0.001$; *Figure 1c*). Subgroup comparisons showed no significant difference between patients without metastases and those with a history of metastases ($p = 0.087$). Significant differences existed between patients without metastases and those with synchronous metastases ($p < 0.001$) and those with a history of metastases versus those with synchronous metastases ($p = 0.003$).

Univariable and multivariable analyses

The results of univariable and multivariable analyses are shown in *Table 4*. After multivariable analysis, older age (hazard ratio [HR] 1.62; 95% CI 1.23-2.14; $p = 0.001$), positive lymph nodes with the primary resection (HR 1.38; 95% CI 1.02-1.89; $p = 0.040$) and a resection with involved margins (R1/2 resection) (HR 2.06; 95% CI 1.55-2.74; $p < 0.001$) were associated with a worse OS, whereas neoadjuvant treatment with full-course (chemo)radiotherapy (HR 0.42; 95% CI 0.21-0.81; $p = 0.010$) and (chemo) reirradiation (HR 0.50; 95% CI 0.30-0.84; $p = 0.009$) were associated with an improved OS.

In LRFS, positive lymph nodes with the primary resection (HR 1.43; 95% CI 1.01-2.01; $p = 0.044$) and an R1/2 resection (HR 3.98; 95% CI 2.83-5.59; $p < 0.001$) were associated with a worse LRFS, whereas neoadjuvant treatment with full-course (chemo)radiotherapy (HR 0.34; 95% CI 0.16-0.88; $p = 0.014$) and (chemo)reirradiation (HR 0.52; 95% CI 0.29-0.91; $p = 0.024$) were associated with an improved LRFS.

The MFS was negatively associated with a positive lymph node stage of the primary tumour (HR 1.76; 95% CI 1.27-2.45; $p = 0.001$) and an R1/2 resection (HR 2.25; 95% CI 1.64-3.09; $p < 0.001$), whereas neoadjuvant treatment with (chemo)reirradiation positively influenced the MFS (HR 0.50; 95% CI 0.29-0.86; $p = 0.013$). Moreover, patients with synchronous metastases had a worse MFS (HR 3.25; 95% CI 2.11-5.02; $p < 0.001$).

Table 4 Results of uni- and multivariable analyses

	Overall survival						Local recurrence-free survival						Metastasis-free survival					
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Age																		
≤65	1.00	-		1.00	-		1.00	-					1.00	-				
>65	1.43	1.10-1.86	**0.008**	1.62	1.23-2.14	**0.001**	0.81	0.59-1.12	0.202				0.84	0.62-1.14	0.260			
Gender																		
Female	1.00	-					1.00	-					1.00	-				
Male	1.06	0.81-1.39	0.681				1.24	0.88-1.73	0.214				1.07	0.78-1.46	0.684			
ASA																		
1-2	1.00	-					1.00	-					1.00	-				
3-4	1.08	0.74-1.60	0.685				0.67	0.39-1.16	0.155				1.12	0.72-1.74	0.615			
T-stage primary																		
T0/T1/T2	1.00	-		1.00	-		1.00	-					1.00	-				
T3/T4	1.43	1.01-2.02	**0.042**	1.36	0.92-2.01	0.119	1.18	0.79-1.76	0.413				1.32	0.90-1.94	0.150			
N-stage primary																		
N0	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-		1.00	-	
N1/N2	1.58	1.20-2.08	**0.001**	1.38	1.02-1.89	**0.040**	1.70	1.22-2.36	**0.002**	1.43	1.01-2.01	**0.044**	1.75	1.28-2.40	**0.001**	1.76	1.27-2.45	**0.001**
Neoadjuvant radiotherapy primary	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-				
No	1.29	0.94-1.76	0.113	0.96	0.53-1.72	0.879	1.90	1.28-2.83	**0.001**	1.01	0.51-2.00	0.973	1.04	0.72-1.49	0.838			
Short-course radiotherapy	1.42	1.03-1.96	**0.033**	1.03	0.57-1.86	0.933	2.44	1.65-3.61	**<0.001**	1.12	0.57-2.19	0.750	1.15	0.80-1.66	0.443			
Full-course (chemo) radiotherapy																		
Type of surgery primary	1.00	-					1.00	-					1.00	-				
TEM	0.95	0.48-1.86	0.875				0.90	0.39-2.04	0.791				2.11	0.78-5.73	0.142			
Rectosigmoid/LAR Abdominoperineal resection	1.17	0.58-2.35	0.660				1.15	0.49-2.68	0.751				2.34	0.85-6.47	0.102			

Table 4 (Continued)

	Overall survival						Local recurrence-free survival						Metastasis-free survival					
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Adjuvant therapy primary																		
None	1.00	-					1.00	-					1.00	-				
Chemotherapy	1.03	0.73-1.45	0.870				1.19	0.80-1.76	0.396				1.31	0.90-1.90	0.153			
Number of recurrence																		
1	1.00	-					1.00	-					1.00	-				
2-3	0.99	0.68-1.44	0.954				1.22	0.80-1.88	0.356				1.14	0.76-1.73	0.524			
Induction chemotherapy																		
No	1.00	-					1.00	-		1.00	-		1.00	-		1.00	-	
Yes	0.99	0.73-1.35	0.960				1.59	1.15-2.19	**0.005**	1.41	0.99-2.02	0.055	1.43	1.04-1.95	**0.026**	1.20	0.85-1.69	0.301
Neoadjuvant radiotherapy LRRC	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-		1.00	-	
None	0.93	0.22-3.99	0.920	0.79	0.17-3.74	0.764	0.87	0.20-3.82	0.856	1.09	0.22-5.49	0.915	0.35	0.05-2.61	0.304	0.29	0.04-2.21	0.231
Short-course radiotherapy	0.46	0.27-0.76	**0.003**	0.42	0.21-0.81	**0.010**	0.25	0.13-0.46	**<0.001**	0.34	0.16-0.88	**0.014**	0.50	0.29-0.86	**0.012**	0.64	0.35-1.19	0.157
Full-course (chemo) radiotherapy	0.63	0.39-1.02	**0.058**	0.50	0.30-0.84	**0.009**	0.59	0.34-1.02	0.058	0.52	0.29-0.91	**0.024**	0.48	0.29-0.81	**0.006**	0.50	0.29-0.86	**0.013**
(Chemo) reirradiation																		
Type of surgery LRRC																		
LAR	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-				
APR	1.40	0.75-2.66	0.293	1.32	0.67-2.58	0.425	2.09	0.97-4.53	**0.061**	1.56	0.69-3.51	0.287	1.17	0.60-2.29	0.645			
Multivisceral resection	1.41	0.95-2.08	**0.085**	1.09	0.70-1.71	0.698	2.06	1.18-3.59	**0.011**	1.22	0.67-2.26	0.537	1.07	0.69-1.65	0.767			
Nonvisceral resection	1.34	0.77-2.35	0.300	0.99	0.53-1.83	0.970	1.76	0.85-3.64	0.129	0.77	0.35-1.69	0.507	1.17	0.64-2.15	0.603			
Intraoperative radiotherapy																		
None	1.00	-					1.00	-					1.00	-				
Yes	0.83	0.59-1.18	0.299				1.17	0.75-1.83	0.477				1.11	0.74-1.68	0.609			

Table 4 (Continued)

	Overall survival						Local recurrence-free survival						Metastasis-free survival					
	HR	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Metastases																		
No	1.00	-		1.00	-		1.00	-					1.00	-		1.00	-	
History	0.89	0.58-1.36	0.579	0.76	0.48-1.20	0.240	1.44	0.91-2.27	0.119				1.47	0.94-2.30	**0.092**	1.36	0.85-2.17	0.205
Synchronous	1.43	0.98-2.11	**0.066**	1.25	0.83-1.87	0.288	1.22	0.73-2.03	0.450				3.28	2.19-4.91	**<0.001**	3.25	2.11-5.02	**<0.001**
Number of metastases																		
Single	1.00	-					1.00	-					1.00	-				
Multiple	1.19	0.68-2.07	0.542				0.88	0.47-1.67	0.700				1.32	0.77-2.26	0.315			
Resection margin																		
R0	1.00	-		1.00	-		1.00	-		1.00	-		1.00	-		1.00	-	
R1/2	2.14	1.61-2.85	**<0.001**	2.06	1.55-2.74	**<0.001**	3.92	2.85-5.41	**<0.001**	3.98	2.83-5.59	**<0.001**	2.13	1.57-2.89	**<0.001**	2.25	1.64-3.09	**<0.001**

Abbreviations: ASA = American Society of Anaesthesiologists Physical Status, HR = hazard ratio, LAR = low anterior resection, LRRC = locally recurrent rectal cancer, TEM = transanal endoscopic microsurgery.
p-values in bold indicate statistically significant differences.

DISCUSSION

This study, performed in a large cohort of 349 surgically treated LRRC patients, evaluated whether the oncological outcomes in highly selected LRRC patients with a history of metastases or with synchronous metastases were comparable to the oncological outcomes in LRRC patients without metastases. We observed an inferior MFS in patients with a history of metastases or synchronous metastases compared with patients without metastases, with a trend towards a worse OS in patients with synchronous metastases.

The 3-year MFS was worse in patients with a history of metastases (33%) than in patients without metastases (52%), although this difference was not statistically significant. Nonetheless, the clinical impact of this inferior MFS is high, as newly developed metastases potentially require (invasive) treatment. Despite the poor MFS, patients with a history of metastases showed a 3-year OS comparable to that in patients without metastases. The lack of impact of the inferior MFS on OS possibly indicates a relatively favourable tumour biology in patients with a history of curatively treated metastases, as the previous distant metastases were curatively treatable and allowed a sufficiently long disease-free interval to develop a LRRC that was considered feasible for curative treatment. It is reasonable to assume that distant metastases developing during post-treatment follow-up of m-LRRC have a similar favourable tumour biology.

The 3-year MFS in patients with synchronous metastases (13%) was significantly worse compared to patients without synchronous metastases. In contrast to patients with a history of metastases, this poor MFS tended to result in a poor OS compared to patients without metastases, suggesting aggressive tumour behaviour. As patients with LRRC and synchronous metastases were historically considered incurable and usually offered palliative treatment, there is limited scope for comparisons with the literature. Some institutions have reported findings from (sub)groups of LRRC patients with synchronous metastases who underwent intentionally curative treatment. Hagemans et al. recently reported on 193 surgically treated LRRC patients of whom 12% had treatable synchronous metastases, and observed a 3-year OS of 65%, which is slightly superior to that in our study.[12] Kishan et al. observed a more similar 3-year OS rate to our study (51.6%) in their retrospective review of 25 patients, wherein 40% of patients had synchronous metastases.[15] Kishan et al. also found that the presence of synchronous distant metastases was not associated with OS, which was also reported by Schurr et al. in a study on 38 patients with synchronous metastases, and is in line with the present study.[15,16] However, the relatively small patient population in these studies could have resulted in less statistical power. A few small studies reported on the survival in

patients with synchronous metastases specifically, presenting similar median OS rates compared with our study.[17,18] Previous work by our group showed a median OS of 27 months in LRRC patients with synchronous metastases.[9] In this previous study, all patients were treated with induction chemotherapy, which may explain the favourable OS. However, all of the above mentioned studies, including the current study, reported on a selected group of patients, hindering direct interstudy comparison. In particular, most studies did not report on patients who began curative neoadjuvant treatment but did not undergo surgery due to progressive disease, resulting in a highly selected group of patients with a relatively favourable prognosis.

In LRRC, local control is imperative in securing quality of life as it relieves patients from tumour-related debilitating symptoms.[19] If an R0 resection is achievable, extensive surgical intervention should therefore be considered. However, in the presence of synchronous metastases caution is warranted, as synchronous metastases are associated with a short MFS. This should be counterbalanced against the morbidity of neoadjuvant treatment and surgery. Thus, patient selection is of paramount importance in the presence of synchronous metastases. A possible strategy to ensure a better patient selection might include a prolonged observation of tumour behaviour, in an extended neoadjuvant treatment course comprising induction chemotherapy and chemoradiotherapy. Patients who respond well to the treatment are more likely to benefit from locoregional treatments, whereas extensive surgery may be omitted in patients with rapid progression. This staged approach is comparable to the 'liver-first' approach in patients with primary rectal cancer and synchronous liver metastases, wherein resection of liver metastases precedes resection of the primary tumour, thus precluding interruption by possible complications of the latter. A concurrent advantage of this approach is that neoadjuvant chemotherapy is used to treat and observe the response of liver metastases and primary tumour. Since tumour progression of liver metastases under neoadjuvant chemotherapy is associated with poor outcomes, in these patients extensive surgery for the rectal tumour could be avoided.[20–22]

The retrospective study design confers apparent limitations, although the prospectively maintained database ensured only few missing values (≤6.3% in *Table 1* and ≤0.9% in *Table 2*). Another limitation of the study is that it selected only patients who underwent surgery for the LRRC, excluding patients in whom surgery was omitted due to local or systemic progression during neoadjuvant therapy. Consequently, this study presents a highly selected group. Furthermore, in the group of patients with synchronous metastases a minority also had a history of metastases, who had a worse MFS than patients with synchronous metastases. However, due to low patient numbers, these groups were not analysed separately. During this study period, the treatment

regimen was changed in 2010 with the addition of induction chemotherapy, which was administered significantly more frequently in patients with synchronous metastases. Again, no subgroup analysis was performed due to the low number of patients with a history of metastases or synchronous metastases before 2010.

The strength of this study is that the study population comprises a true sample of surgically treated patients at a large tertiary referral centre, which provides insight into the outcomes of a curative treatment approach that might greatly benefit a highly selected group of patients.

In conclusion, curative treatment of LRRC in patients with a history of metastases is possible in selected patients. Whether curative treatment should be offered to LRRC patients with synchronous metastases is questionable. Using a tailored approach, wherein the response to treatment and the natural behaviour of the disease can be observed for a prolonged duration, may enable selection of those patients who are likely to benefit from locoregional treatment of metastases and LRRC, while sparing others extensive surgery and the associated morbidity.

REFERENCES

1. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422. doi:10.1093/annonc/mdw235
2. Van Dijk TH, Tamas K, Beukema JC, et al. Evaluation of short-course radiotherapy followed by neoadjuvant bevacizumab, capecitabine, and oxaliplatin and subsequent radical surgical treatment in primary stage IV rectal cancer. *Ann Oncol*. 2013;24(7):1762-1769. doi:10.1093/annonc/mdt124
3. Kok END, Havenga K, Tanis PJ, et al. Multicentre study of short-course radiotherapy, systemic therapy and resection/ablation for stage IV rectal cancer. *Br J Surg*. 2020;107(5):537-545. doi:doi: 10.1002/bjs.11418
4. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol*. 2008;15(7):1937-1947. doi:10.1245/s10434-008-9896-z
5. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388
6. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569
7. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Color Dis*. 2011;13(7):732-742. doi:10.1111/j.1463-1318.2009.02167.x
8. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg*. 2018;105(4):447-452. doi:10.1002/bjs.10694
9. Voogt ELK, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4
10. van den Brink M, Stiggelbout AM, van den Hout WB, et al. Clinical Nature and Prognosis of Locally Recurrent Rectal Cancer After Total Mesorectal Excision With or Without Preoperative Radiotherapy. *J Clin Oncol*. 2004;22(19):3958-3964. doi:10.1200/jco.2004.01.023
11. Detering R, Karthaus EG, Borstlap WAA, et al. Treatment and survival of locally recurrent rectal cancer: A cross-sectional population study 15 years after the Dutch TME trial. *Eur J Surg Oncol*. 2019;45(11):2059-2069. doi:10.1016/j.ejso.2019.06.016
12. Hagemans JAW, van Rees JM, Alberda WJ, et al. Locally recurrent rectal cancer; long-term outcome of curative surgical and non-surgical treatment of 447 consecutive patients in a tertiary referral centre. *Eur J Surg Oncol*. 2020;46(3):448-454. doi:10.1016/j.ejso.2019.10.037

13. Martin TA, Ye L, Sanders AJ, Lane J, Jiang WG. Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In: *Madame Curie Bioscience Database*. Austin (TX): Landes Bioscience; 2013. https://www.ncbi.nlm.nih.gov/books/NBK164700/.

14. Leong L. Clinical Relevance of Targeting Cancer Metastases. In: *Madame Curie Bioscience Database*. Austin (TX): Landes Bioscience; 2013. https://www.ncbi.nlm.nih.gov/books/NBK154382/.

15. Kishan AU, Voog JC, Wiseman J, et al. Standard fractionation external beam radiotherapy with and without intraoperative radiotherapy for locally recurrent rectal cancer: The role of local therapy in patients with a high competing risk of death from distant disease. *Br J Radiol*. 2017;90(1076):20170134. doi:10.1259/bjr.20170134

16. Schurr P, Lentz E, Block S, et al. Radical redo surgery for local rectal cancer recurrence improves overall survival: A single center experience. *J Gastrointest Surg*. 2008;12(7):1232-1238. doi:10.1007/s11605-008-0517-8

17. Cyr DP, Zih FS, Wells BJ, et al. Long-term outcomes following salvage surgery for locally recurrent rectal cancer: A 15-year follow-up study. *Eur J Surg Oncol*. 2020;46(6):1131-1137. doi:10.1016/j.ejso.2020.02.032

18. Hartley JE, Lopez RA, Paty PB, Wong WD, Cohen AM, Guillem JG. Resection of Locally Recurrent Colorectal Cancer in the Presence of Distant Metastases: Can It Be Justified? *Ann Surg Oncol*. 2003;10(3):227-233. doi:https://doi.org/10.1245/ASO.2003.05.039

19. You YN, Habiba H, Chang GJ, Rodriguez-Bigas MA, Skibber JM. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2011;18(4):989-996. doi:10.1245/s10434-010-1218-6

20. Verhoef C, Van Der Pool AEM, Nuyttens JJ, Planting AST, Eggermont AMM, De Wilt JHW. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2009;52(1):23-30. doi:10.1007/DCR.0b013e318197939a

21. Ayez N, Burger JWA, Van Der Pool AE, et al. Long-term results of the "liver first" approach in patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2013;56(3):281-287. doi:10.1097/DCR.0b013e318279b743

22. Adam R, Pascal G, Castaing D, et al. Tumor Progression While on Chemotherapy. *Ann Surg*. 2004;240(6):1052-1064. doi:10.1097/01.sla.0000145964.08365.01

13. Martin TA, Ye L, Sanders AJ, Lane J, Jiang WG. Cancer Invasion and Metastasis: Molecular and Cellular Perspective. In: *Madame Curie Bioscience Database*. Austin (TX): Landes Bioscience; 2013. https://www.ncbi.nlm.nih.gov/books/NBK164700/.

14. Leong L. Clinical Relevance of Targeting Cancer Metastases. In: *Madame Curie Bioscience Database*. Austin (TX): Landes Bioscience; 2013. https://www.ncbi.nlm.nih.gov/books/NBK154382/.

15. Kishan AU, Voog JC, Wiseman J, et al. Standard fractionation external beam radiotherapy with and without intraoperative radiotherapy for locally recurrent rectal cancer: The role of local therapy in patients with a high competing risk of death from distant disease. *Br J Radiol*. 2017;90(1076):20170134. doi:10.1259/bjr.20170134

16. Schurr P, Lentz E, Block S, et al. Radical redo surgery for local rectal cancer recurrence improves overall survival: A single center experience. *J Gastrointest Surg*. 2008;12(7):1232-1238. doi:10.1007/s11605-008-0517-8

17. Cyr DP, Zih FS, Wells BJ, et al. Long-term outcomes following salvage surgery for locally recurrent rectal cancer: A 15-year follow-up study. *Eur J Surg Oncol*. 2020;46(6):1131-1137. doi:10.1016/j.ejso.2020.02.032

18. Hartley JE, Lopez RA, Paty PB, Wong WD, Cohen AM, Guillem JG. Resection of Locally Recurrent Colorectal Cancer in the Presence of Distant Metastases: Can It Be Justified? *Ann Surg Oncol*. 2003;10(3):227-233. doi:https://doi.org/10.1245/ASO.2003.05.039

19. You YN, Habiba H, Chang GJ, Rodriguez-Bigas MA, Skibber JM. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2011;18(4):989-996. doi:10.1245/s10434-010-1218-6

20. Verhoef C, Van Der Pool AEM, Nuyttens JJ, Planting AST, Eggermont AMM, De Wilt JHW. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2009;52(1):23-30. doi:10.1007/DCR.0b013e318197939a

21. Ayez N, Burger JWA, Van Der Pool AE, et al. Long-term results of the "liver first" approach in patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2013;56(3):281-287. doi:10.1097/DCR.0b013e318279b743

22. Adam R, Pascal G, Castaing D, et al. Tumor Progression While on Chemotherapy. *Ann Surg*. 2004;240(6):1052-1064. doi:10.1097/01.sla.0000145964.08365.01

CHAPTER 3

AGE-RELATED DIFFERENCES IN MORBIDITY AND MORTALITY AFTER SURGERY FOR PRIMARY CLINICAL T4 AND LOCALLY RECURRENT RECTAL CANCER

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ABSTRACT

Aim

Outcomes in elderly patients (≥75 years) with non-advanced colorectal cancer have improved. It is unclear whether this is also true for elderly patients with clinical T4 rectal cancer (cT4RC) or locally recurrent rectal cancer (LRRC). We aimed to compare age-related differences in morbidity and mortality after curative treatment for cT4RC and LRRC.

Methods

All cT4RC and LRRC patients without distant metastasis who underwent curative surgery between 2005 and 2017 in the Catharina Hospital (Eindhoven, the Netherlands) were included. Morbidity and mortality were evaluated based on age (<75 and ≥75 years) and date of surgery (2005-2011 and 2012-2017).

Results

Overall, 72 of 474 (15.2%) cT4RC and 53 of 293 (18.1%) LRRC patients were ≥75 years. No significant differences in the incidence of Clavien-Dindo I-IV complications were observed between age groups. However, in elderly cT4RC patients, cerebrovascular accidents occurred more frequently (4.2% vs. 0.5%, $p = 0.03$). Between 2005-2011 and 2012-2017, 30-day mortality improved from 7.5% to 3.1% and from 10.0% to 0.0% in elderly cT4RC and LRRC patients, respectively. The 1-year mortality during 2012-2017 was worse in elderly than in younger patients (28.1% vs. 6.2%, $p = 0.001$ for cT4RC and 27.3% vs. 13.8%, $p = 0.06$ for LRRC). In elderly cT4RC and LRRC patients, 44.4% and 46.2% died due to non-cancer-related causes, while only 27.8% and 23.1% died due to disease recurrence, respectively.

Conclusion

Although the 30-day mortality in elderly cT4RC and LRRC patients improved after curative treatment, the 1-year mortality in elderly patients continued to be high, which requires more awareness for the elderly after hospitalisation.

INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide with 43% of patients being older than 75 years.[1] Approximately 10% of all CRC patients are diagnosed with locally advanced rectal cancer (LARC) and 6-10% will eventually develop locally recurrent rectal cancer (LRRC).[2] The optimal treatment for patients with LARC and LRRC is neoadjuvant therapy followed by surgery.[3] In LRRC, in particular, involvement of the lateral and posterior pelvic wall is more common since visceral fasciae, which act as natural barriers for tumour infiltration, have already been removed during primary tumour surgery. Therefore, even more extended extra-anatomical resections are often needed in LRRC. These extended resections are associated with postoperative complication rates ranging from 41.5% to 57%.[4,5]

Almost 30–50% of surgical procedures are performed in patients >65 years, and with the increase in the elderly population worldwide the incidence may increase further.[1,6,7] In general, elderly patients have multiple comorbidities with varying physical conditions. According to recent literature, most patients <75 years are physically healthy, whereas over 50% of patients ≥75 years have more than two chronic disorders.[8,9] The elderly often experience difficulty coping with complications and longer recovery periods along with increased mortality in the first postoperative year.[10–12] However, improvements in CRC care have led to better outcomes in elderly patients.[13–15] The difference in the postoperative and 1-year mortality rates between younger and elderly CRC patients has decreased with comparable outcomes.[11,14,15] However, it is unclear if this is also true for clinical T4 rectal cancer (cT4RC) or LRRC patients treated with curative intent.

The primary aim of this study was to evaluate the morbidity and mortality of elderly (≥75 years) and younger (<75 years) patients with cT4RC and LRRC treated with curative intent. Changes in morbidity and mortality were also analysed over time in order to evaluate whether improvements in care could have contributed to better outcomes in elderly patients.

METHODS

Patients and treatment

Patients who underwent curative surgery for primary cT4RC or LRRC at the Catharina Hospital (Eindhoven, the Netherlands), a tertiary referral centre for such patients, between 2005 and 2017, were included. Patients with peritoneal or incurable distant metastases were excluded. All patients with cT4RC had a histological diagnosis and

radiological confirmation of visceral peritoneum or surrounding organ involvement. Diagnosis of LRRC was based on histology or imaging. Positron emission tomography CT was performed to exclude distant metastases and distinguish between fibrosis or LRRC when a biopsy could not be obtained and CT of chest and abdomen was performed to detect distant metastases. All patients underwent pelvic MRI for accurate staging before and after neoadjuvant treatment. Most patients with cT4RC underwent neoadjuvant treatment according to the Dutch National Guidelines for rectal cancer.[16] The majority underwent long-course chemoradiation with up to 50.4 Gy in 28 fractions with concomitant oral capecitabine. LRRC patients who were previously irradiated underwent reirradiation with 30 Gy with concomitant oral capecitabine.[17] LRRC patients without a history of pelvic irradiation received a full course of irradiation (50.4 Gy) with concomitant oral capecitabine.[17] Some patients with extensive disease also received neoadjuvant induction chemotherapy followed by (re)irradiation with or without concomitant chemotherapy to achieve downstaging. Details of this treatment regimen and the influence on outcomes have been reported previously.[18] After 8-12 weeks, surgery was performed combined with intraoperative radiotherapy at a dose of 10-12.5 Gy at the margins considered at risk (perioperatively or positive margins confirmed by intraoperative frozen section analysis).

Clinical data and Follow-up

Patients' characteristics, data on treatment, pathology and additional clinical (e.g., complications, hospital readmission) and demographic data were retrospectively extracted from the medical records. Complications were scored using the Clavien-Dindo classification.[19] Follow-up data were obtained from the medical records, the referral hospital, or the patient's general practitioner. Follow-up was calculated as the interval between surgery and last contact or death. The minimum follow-up of all patients was 1 year (if alive). During follow-up, local recurrence and distant metastases were recorded. The Municipal Administrative Databases were consulted to obtain information on survival data. If a patient died during follow-up, the specific cause of death was investigated. Treatment-induced deterioration, as a cause of mortality, was defined as deterioration of the physiological status after hospital discharge leading to death, regardless of postoperative complications and without signs of relapsing disease, cardiopulmonary disease or cerebrovascular accidents.

Statistical analyses

Statistical analyses were performed using SPSS Statistics 25.0 software (IBM, Endicott, NY, USA), separately for cT4RC and LRRC. The study period was divided into two time periods of 7 and 6 years, respectively (2005-2011 and 2012-2017). The primary endpoint was postoperative mortality (30-day, 90-day, and 1-year). Secondary

endpoints were postoperative complications (Clavien-Dindo classification) and causes of 1-year mortality. Comparisons were stratified by age (<75 and ≥75 years) and date of surgery (2005-2011 and 2012-2017). Intergroup comparisons were analysed using the Chi-square test or Fisher's exact test, when appropriate, for non-continuous data. Independent *t* tests or Mann-Whitney *U* tests were used for normally and non-normally distributed continuous data, respectively. A *p* value of <0.05 was considered statistically significant. All tests were two-sided. Survival rates for both patient groups were estimated separately and stratified by age group using the Kaplan-Meier method and compared using the log-rank test. Relative survival rates were calculated as the absolute survival amongst cT4RC and LRRC patients divided by the expected survival for the general population with the same sex and age. In-depth analyses were performed to identify the specific cause of death.

RESULTS

A total of 767 patients were included. Of the 474 cT4RC and 293 LRRC patients, 72 (15.2%) and 53 (18.1%) were ≥75 years, respectively. The median follow-ups were 3.8 and 2.8 years for cT4RC and LRRC patients, respectively. In the LRRC group, one patient was lost to follow-up in the first postoperative year. Clinical and demographic characteristics for cT4RC and LRRC patients are presented in *Tables 1* and *2*, respectively. In both groups, elderly patients had significantly higher comorbidities.

Postoperative morbidity

No significant differences were observed in the incidence of Clavien-Dindo grade I-IV complications based on age in either the cT4RC or LRRC groups, but patients <75 years were more likely to have an uncomplicated postoperative course than patients ≥75 years ($p = 0.02$ for cT4RC, and $p = 0.001$ for LRRC). More pulmonary complications were observed among cT4RC and LRRC patients ≥75 years than among patients <75 years (22.2% vs. 8.7%, $p = 0.001$ for cT4RC, and 26.4% vs. 14.2%, $p = 0.03$ for LRRC). Older cT4RC patients experienced more postoperative delirium and cerebrovascular accidents than younger patients (11.1% vs. 1.0%, $p < 0.001$ for delirium, and 4.2% vs. 0.5%, $p = 0.03$ for cerebrovascular accidents). More delirium was also observed in LRRC patients ≥75 years than in patients <75 years (17.0% vs. 2.5%, $p < 0.001$). Other than fascial dehiscence in LRRC patients (9.4% vs. 1.7%, $p = 0.01$), surgical complications and reintervention rates (endoscopic, radiological, and surgical) were not significantly different between elderly and younger cT4RC and LRRC patients (16.7% vs. 18.4%, $p = 0.72$, and 41.5% vs. 28.7%, $p = 0.07$, respectively). A more detailed description of complications in both groups is presented in *Table 3*.

Table 1 Demographic, clinical and tumour characteristics of cT4RC patients (n=474), stratified by age (<75 and ≥75 years)

	<75 years n=402 n (%)	**≥75 years n= 72 n (%)**	***p* value**
Mean age in years at time of surgery (±SD)	61.4 (8.6)	79.2 (3.6)	<0.001
Median follow-up in years (IQR)	4.0 (2.7-5.5)	2.5 (1.1-4.9)	<0.001
Male	235 (58.5)	39 (54.2)	0.50
Comorbidity			<0.001
None	148 (36.8)	9 (12.5)	
1 comorbidity	121 (30.1)	18 (25.0)	
2 comorbidities	64 (15.9)	18 (25.0)	
≥3 comorbidities	53 (13.2)	23 (31.9)	
Missing	16 (4.0)	4 (5.6)	
ASA classification			0.02
I-II	328 (81.6)	50 (69.4)	
III	60 (14.9)	21 (29.2)	
Missing	14 (3.5)	1 (1.4)	
Neoadjuvant treatment			<0.001
None	-	2 (2.8)	
Short-course radiotherapy (5x5Gy)	17 (4.2)	9 (12.5)	
Long-course radiotherapy	10 (2.5)	9 (12.5)	
Chemoradiation	358 (89.1)	46 (63.9)	
Other	17 (4.2)	6 (8.3)	
Type of surgery			<0.001
Low anterior resection	184 (45.8)	25 (34.7)	
Abdominoperineal/abdominosacral resection	176 (43.8)	34 (47.2)	
Hartmann resection	8 (2.0)	8 (11.1)	
Pelvic exenteration[a]	32 (8.0)	3 (4.2)	
Other	2 (0.5)	2 (2.8)	
Extended (multivisceral) resection[b]	200 (49.8)	50 (69.4)	0.01
Intraoperative radiotherapy	278 (69.2)	47 (65.3)	0.51
Radical resection (R0)	356 (88.6)	56 (77.8)	0.01

Abbreviations: ASA = American Society of Anesthesiologists, cT4RC = clinical T4 rectal cancer, Gy= Gray, IQR = interquartile range, SD = standard deviation.

[a] Pelvic exenteration was defined as an en bloc resection of the rectum including complete removal of the bladder and reproductive organs (prostate/seminal vesicles, or uterus, ovaries and/or vagina).[2]

[b] Extended (multivisceral) resection is used for other combinations of resections than exenteration.

Table 2 Demographic, clinical and tumour characteristics of LRRC patients (n=293), stratified by age (<75 and ≥75 years)

	<75 years n= 240 n (%)	**≥75 years n= 53 n (%)**	***p* value**
Mean age in years at time of surgery (±SD)	62.7 (8.2)	78.6 (3.2)	<0.001
Median follow-up in years (IQR)	2.8 (1.4-4.1)	2.3 (0.9-3.9)	0.09
Male	161 (67.1)	36 (67.9)	0.91
Comorbidity			0.008
None	90 (37.5)	9 (17.0)	
1 comorbidity	70 (29.2)	14 (26.4)	
2 comorbidities	44 (18.3)	16 (30.2)	
≥ 3 comorbidities	36 (15.0)	14 (26.4)	
ASA classification			0.36
I-II	204 (85.0)	41 (77.4)	
III	28 (11.7)	10 (18.9)	
Missing	8 (3.3)	2 (3.8)	
Neo-adjuvant treatment			0.09
None	16 (6.7)	5 (9.4)	
Reirradiation only	7 (2.9)	1 (1.9)	
Reirradiation with concomitant chemotherapy	143 (59.6)	23 (43.4)	
Full-course irradiation with concomitant chemotherapy	69 (28.8)	20 (37.7)	
Full-course irradiation only	5 (2.1)	4 (7.5)	
Type of surgery			0.01
Low anterior resection	37 (15.4)	6 (11.3)	
Abdominoperineal/abdominosacral resection	91 (37.9)	22 (41.5)	
Hartmann resection	10 (4.2)	4 (7.5)	
Pelvic exenteration[a]	38 (15.8)	7 (13.2)	
Debulking	60 (25.0)	8 (15.1)	
Other	4 (1.7)	6 (11.3)	
Extended (multivisceral) resection[b]	131 (54.6)	28 (52.8)	0.82
Intraoperative radiotherapy	208 (86.7)	38 (71.7)	0.008
Radical resection (R0)	139 (57.9)	38 (71.7)	0.06

Abbreviations: ASA = American Society of Anesthesiologists, IQR = interquartile range, LRRC = locally recurrent rectal cancer, SD = standard deviation.

[a] Pelvic exenteration was defined as an en bloc resection of the rectum including complete removal of the bladder and reproductive organs (prostate/seminal vesicles, or uterus, ovaries and/or vagina).[2]

[b] Extended (multivisceral) resection is used for other combinations of resections than exenteration

Table 3 Details on postoperative outcomes of cT4RC and LRRC patients, stratified by age (<75 and ≥75 years)

	cT4RC		LRRC	
	<75 years n= 402 n (%)	**≥75 years n= 72 n (%)**	**<75 years n= 240 n (%)**	**≥75 years n= 53 n (%)**
Median admission time in days (IQR)	9.0 (7.0-14.0)	9.0 (7.0-16.0)	12.0 (7.0-17.0)	12.0 (8.0-20.5)
Median admission on ICU in days (IQR)	1.0 (0.0-1.0)a	1.0 (1.0-2.0)a	1.0 (1.0-2.0)	1.0 (1.0-2.5)
Surgical complications[b]	136 (33.8)	26 (36.1)	130 (54.2)	35 (66.0)
Anastomotic leakage	19 (4.7)	4 (5.6)	10 (4.2)	3 (5.7)
Clavien-Dindo ≥ 3	3 (0.7)	2 (2.8)	7 (2.9)	2 (3.8)
Presacral abscess	46 (11.4)	5 (6.9)	48 (20.0)	12 (22.6)
Clavien-Dindo ≥ 3	28 (7.0)	2 (2.8)	36 (15.0)	9 (17.0)
Intra-abdominal abscess	15 (3.7)	1 (1.4)	23 (9.6)	6 (11.3)
Clavien-Dindo ≥ 3	9 (2.2)	-	14 (5.8)	6 (11.3)
Ileus	49 (12.2)	14 (19.4)	62 (25.8)	13 (24.5)
Clavien-Dindo ≥ 3	1 (0.2)	2 (2.8)	2 (0.8)	-
Fascial Dehiscence	8 (2.0)	2 (2.8)	4 (1.7)[a]	5 (9.4)[a]
Wound infection	44 (10.9)	9 (12.5)	57 (23.8)	15 (28.3)
Abdominal	24 (6.0)	4 (5.6)	27 (11.3)	4 (7.5)
Perineal	20 (5.0)	5 (6.9)	30 (12.5)	11 (20.8)
Non-surgical complications[b]	136 (33.8)[a]	39 (54.2)[a]	111 (46.3)[a]	34 (64.2)[a]
Urologic	95 (23.6)	20 (27.8)	79 (32.9)	24 (45.3)
Pulmonary	35 (8.7)[a]	16 (22.2)[a]	34 (14.2)[a]	14 (26.4)[a]
Cardiac	25 (6.2)	9 (12.5)	15 (6.3)	5 (9.4)
Venous thromboembolism	11 (2.7)	-	5 (2.1)	1 (1.9)
Neurological				
Cerebrovascular accident	2 (0.5)[a]	3 (4.2)[a]	1 (0.4)	1 (1.9)
Delirium	4 (1.0)[a]	8 (11.1)[a]	6 (2.5)[a]	9 (17.0)[a]
Complication Grade according to Clavien-Dindo				
None	154 (38.3)a	17 (23.6)[a]	55 (22.9)[a]	2 (3.8)[a]
Grade I-II	167 (41.5)	38 (52.8)	108 (45.0)	25 (47.2)
Grade IIIa + IIIb	57 (14.2)	8 (11.1)	60 (25.0)	16 (30.2)
Grade IV	14 (3.5)	4 (5.6)	10 (4.2)	4 (7.5)
Grade V	6 (1.5)[a]	5 (6.9)[a]	4 (1.7)[a]	4 (7.5)[a]
Missing	4 (1.0)	-	3 (1.3)	2 (3.8)

Abbreviations: cT4RC = clinical T4 rectal cancer, ICU = intensive care unit, IQR = interquartile range, LRRC = locally recurrent rectal cancer, SD = standard deviation.

[a] $p < 0.05$

[b] Number of patients that had at least one surgical or one non-surgical complication, respectively.

Mortality

The 30-day mortality decreased over time for both cT4RC and LRRC patients ≥75 years, from 7.5% and 10.0%, respectively, for the period 2005-2011, to 3.1% and 0.0%, respectively, for the period 2012-2017. Comparable 30-day mortality rates were observed for cT4RC and LRRC patients <75 years in both time periods (0.5% vs. 1.5% for cT4RC, respectively, and 2.9% vs. 1.4% for LRRC, respectively). The 30-day mortality rates were significantly different between cT4RC patients <75 and ≥75 years in the period 2005-2011, but were comparable for the latter period (p = 0.01 and p = 0.46, respectively). Among LRRC patients, no significant differences in 30-day mortality were observed based on age in either time period. The 90-day mortality rates did not improve over time. For cT4RC patients, the 90-day mortality rates in the period 2012-2017 were 9.4% and 2.1% for patients ≥75 years and those <75 years, respectively. The corresponding rates for patients with LRRC were 9.1% and 2.2%, respectively.

The 1-year mortality rate for cT4RC patients ≥75 years was significantly worse than for patients <75 years and did not improve over time (22.5% vs. 5.8%, p = 0.002 for 2005-2011, and 28.1% vs. 6.2%, p = 0.001 for 2012-2017). Among LRRC patients <75 years, the 1-year mortality improved non-significantly over time (20.6% vs. 13.8%, p = 0.16) and no improvements over time were observed among elderly patients. The differences in 1-year mortality between the two age groups for LRRC were not significant (p > 0.99 for 2005-2011, and p = 0.06 for 2012-2017). For both cT4RC and LRRC patients, assessing relative survival did not change these results. A more detailed description of mortality rates during the first year and overall and cancer-specific survival for the entire study period are presented in *Tables 4* and *5*, respectively. In *Figure 1-4* Kaplan-Meier curves on absolute 1-year survival for the different time periods are presented. The causes of death in the first postoperative year have been summarised in *Table 6*.

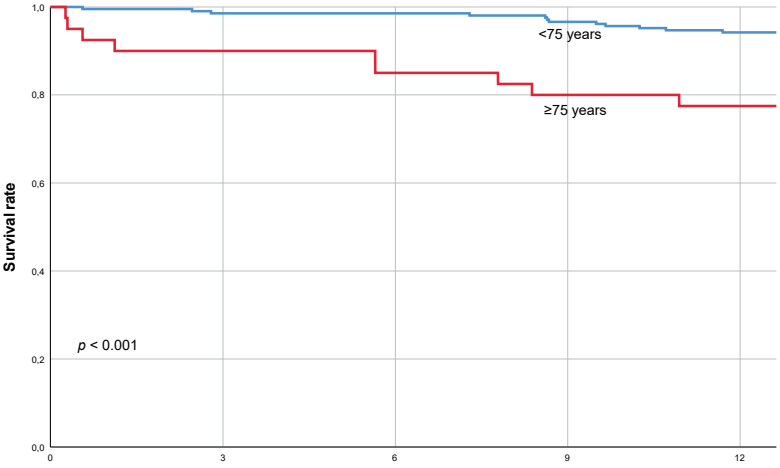
Table 4 Absolute mortality rates of both cT4RC and LRRC patients after surgery, stratified by age (<75 and ≥75 years) and period of surgery (2005-2011 and 2012-2017)

2005-2011						
	cT4RC			**LRRC**		
	<75 years n=207	**≥75 years n=40**	***p* value**	**<75 years n=102**	**≥75 years n=20**	***p* value**
30-day	0.5%	7.5%	0.01	2.9%	10.0%	0.19
90-day	1.4%	10.0%	0.01	2.9%	10.0%	0.19
1-year	5.8%	22.5%	0.002	20.6%	20.0%	>0.99
2012-2017						
	cT4RC			**LRRC**		
	<75 years n=195	**≥75 years n=32**	***p* value**	**<75 years n=138**	**≥75 years n=33**	***p* value**
30-day	1.5%	3.1%	0.46	1.4%	0.0%	>0.99
90-day	2.1%	9.4%	0.06	2.2%	9.1%	0.09
1-year	6.2%	28.1%	0.001	13.8%	27.3%	0.06

Abbreviations: cT4RC = clinical T4 rectal cancer, LRRC = locally recurrent rectal cancer

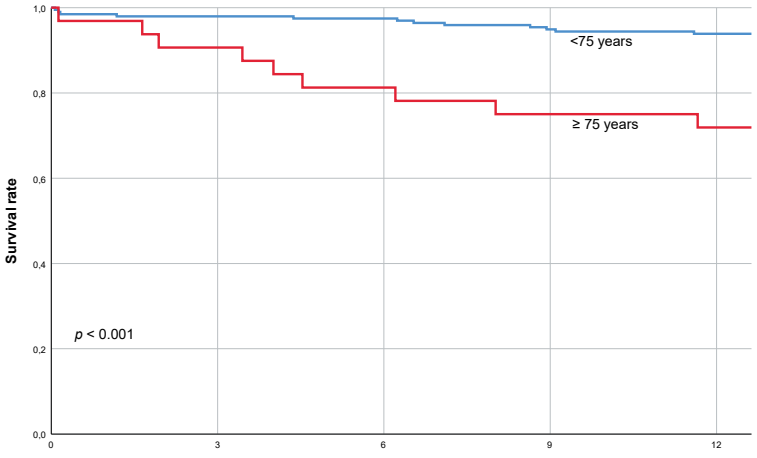
Table 5 Overall, cancer-specific and disease-free survival rates for cT4RC and LRRC patients stratified by age (<75 and ≥75 years) for the period 2005-2017

Overall survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.94	0.75	0.83	0.76
3-years	0.79	0.54	0.56	0.45
5-years	0.65	0.37	0.31	0.17
	$p < 0.001$		$p = 0.06$	
Cancer-specific survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.95	0.83	0.87	0.82
3-years	0.82	0.66	0.61	0.56
5-years	0.73	0.56	0.35	0.32
	$p = 0.001$		$p = 0.56$	
Disease-free survival				
	cT4RC <75 years	**cT4RC ≥ 75 years**	**LRRC <75 years**	**LRRC ≥ 75 years**
1-year	0.83	0.82	0.60	0.66
3-years	0.69	0.55	0.33	0.44
5-years	0.62	0.48	0.25	0.41
	$p = 0.10$		$p = 0.08$	



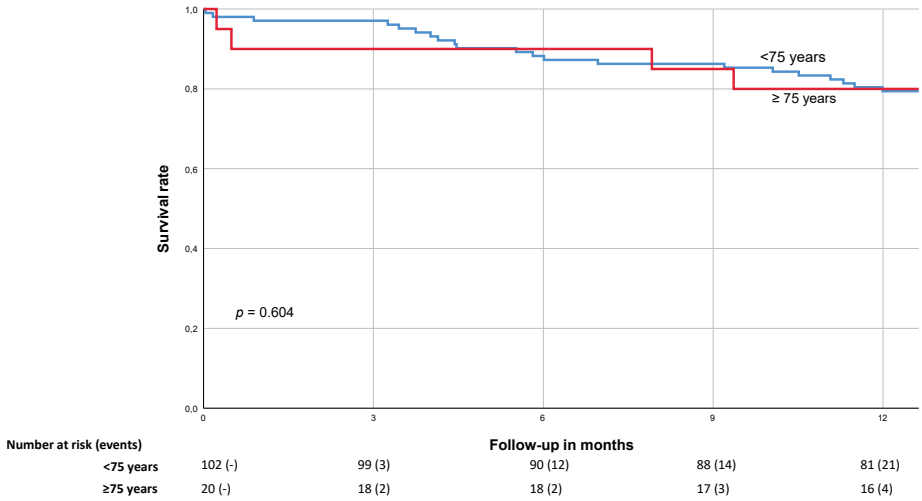
Number at risk (events)					
<75 years	207 (-)	204 (3)	204 (3)	200 (7)	195 (12)
≥75 years	40 (-)	36 (4)	34 (6)	32 (8)	31 (9)

Figure 1 Kaplan-Meier curve for absolute 1-year survival for cT4RC patients for the period 2005-2011 (n=247), stratified by age (<75 and ≥75 years)



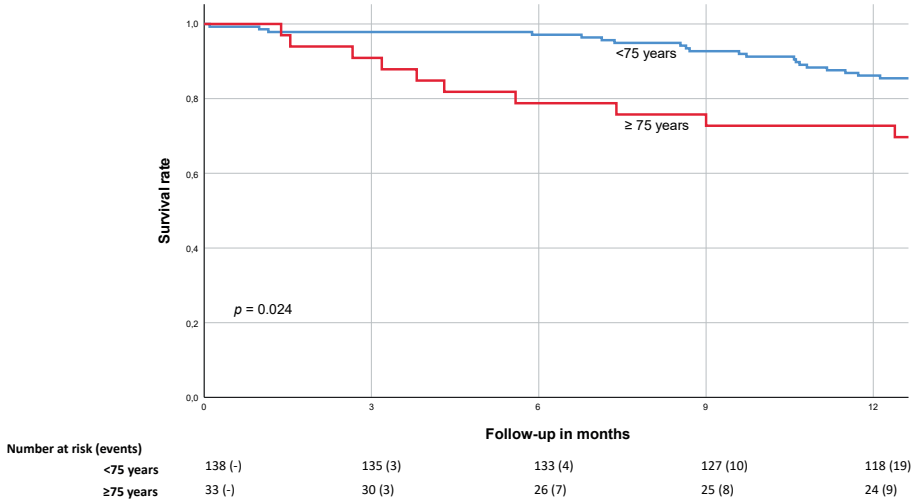
Number at risk (events)					
<75 years	195 (-)	191 (4)	190 (5)	185 (10)	183 (12)
≥75 years	32 (-)	29 (3)	26 (6)	24 (8)	23 (9)

Figure 2 Kaplan-Meier curve for absolute 1-year survival for cT4RC patients for the period 2012-2017 (n=227), stratified by age (<75 and ≥75 years)



Number at risk (events)					
<75 years	102 (-)	99 (3)	90 (12)	88 (14)	81 (21)
≥75 years	20 (-)	18 (2)	18 (2)	17 (3)	16 (4)

Figure 3 Kaplan-Meier curve for absolute 1-year survival for LRRC patients for the period 2005-2011 (n=122), stratified by age (<75 and ≥75 years)



Number at risk (events)					
<75 years	138 (-)	135 (3)	133 (4)	127 (10)	118 (19)
≥75 years	33 (-)	30 (3)	26 (7)	25 (8)	24 (9)

Figure 4 Kaplan-Meier curve for absolute 1-year survival for LRRC patients for the period 2012-2017 (n=171), stratified by age (<75 and ≥75 years)

Table 6 Causes of death of all cT4RC and LRRC patients who died in the first year post-operatively, stratified by age (<75 and ≥75 years)

	cT4RC		LRRC	
	<75 years n= 24 n (%)	**≥75 years n= 18 n (%)**	**<75 years n= 40 n (%)**	**≥75 years n= 13 n (%)**
In-hospital mortality[a]	6 (25.0)	5 (27.8)	4 (10.0)	4 (30.8)
Out-of-hospital mortality				
Treatment-induced deterioration[b]	1 (4.2)	2 (11.1)	6 (15.0)	4 (30.8)
Relapsing disease	11 (45.8)	5 (27.8)	25 (62.5)	3 (23.1)
Cardiopulmonary disease	-	2 (11.1)	2 (5.0)	2 (15.4)
Other	-	1 (5.6)	-	-
Unknown	6 (25.0)	3 (16.7)	3 (7.5)	-

Abbreviations: cT4RC = clinical T4 rectal cancer, LRRC = locally recurrent rectal cancer.
[a] Any combination of complications leading directly or indirectly to death during hospital admission (e.g., renal insufficiency, cardiac failure, respiratory failure etc.). In-depth analyses did not show specific major groups of complications.
[b] Deterioration of the physiological status of the patient after discharge from the hospital, leading to death without signs of relapsing disease, cardiopulmonary disease or cerebrovascular accidents.

DISCUSSION

In this study, we compared the morbidity and mortality of elderly and younger cT4RC and LRRC patients and analysed differences over time. In elderly cT4RC and LRRC patients, the 30-day mortality rates improved over the years to 3.1% and 0.0%, respectively, which were comparable with younger patients. Unfortunately, the 90-day and 1-year mortality rates were still significantly worse for elderly patients. Approximately 25% of elderly cT4RC or LRRC patients died in the first postoperative year, compared to 6.0% and 16.7% of younger patients, respectively, over the entire study period. Of the elderly patients who died in the first postoperative year, most died due to treatment-induced or non-cancer-related causes. Disease recurrence was, however, the main cause of death in patients <75 years.

More non-surgical complications were observed in elderly patients; however, no significant differences in the incidence of surgical complications and reinterventions were observed between the two age groups. Clavien-Dindo grade ≥ 3 complications occurred in 19% and 31% of young cT4RC and LRRC patients, and 24% and 45% of elderly cT4RC and LRRC patients, respectively, which is comparable to other studies in

which 25% of cT4RC and 36% of LRRC patients experienced grade ≥ 3 complications.[20,21] Although the morbidity of elderly patients remains high, the 30-day mortality has improved over time, which is observed for all stages of colon and rectal cancer and probably reflects improved perioperative and postoperative care.[14,15,22–25] The literature also showed improvements in 1-year mortality and comparable survival for elderly and younger patients with stage I-III CRC, but in this study of cT4RC and LRRC patients no improvements in 90-day and 1-year overall mortalities were observed.[14,15] We found no significant influence of postoperative complications on mortality among elderly patients and, as many patients died after hospitalisation due to deterioration, a delayed effect of treatment on the physical condition of these patients could be hypothesised. Among patients with LRRC, higher mortality rates were also observed among elderly, but the differences were smaller when compared with patients <75 years than those observed among cT4RC patients. It is likely that poor oncological behaviour of these recurrent tumours has a relatively large influence on survival for both age groups.

The mortality rates presented in this study are based on relatively small patient groups, but are supported by population-based studies on outcomes in LARC in Northern European countries and the US, where reported 30- and 90-day mortality rates range from 4.0% to 14.5%, depending on stage.[13,26] Another Dutch study with LARC and LRRC patients treated with total pelvic exenteration found 90-day mortality rates similar to ours.[2] Our 1-year mortality rates are also in accordance with other studies which range from 21% to 26.5% for locally advanced cases.[2,13]

In our institution, surgery for cT4RC and LRRC is performed open with extended or multivisceral resections, whereas minimally invasive surgery is standard of care for non-advanced cases. Extended tumour involvement in the pelvic wall was more often observed in LRRC than cT4RC, requiring more extensive extra-anatomical exenterations such as unilateral or bilateral pelvic side wall or sacral resections (*Supplementary Table 1*). It has been hypothesised that when stressors reach a certain threshold and homeostatic mechanisms are no longer able to compensate, functional decline with impaired health status and further diminishment of physiological reserve capacity may occur, leading to decreased resilience to future stressors.[27] The impact of major rectal surgery and hospitalisation could therefore induce increased vulnerability with a higher risk of death in the first postoperative year when other stressors appear. Although this effect is more often seen in frail people, this phenomenon could explain the higher mortality rates seen in this study in contrast to other studies of stage I-III CRC patients.[14,15]

Patients' physiological status was evaluated preoperatively by a surgeon and an anaesthesiologist, and multidisciplinary team meeting decisions were based on tumour and patient characteristics and preferences. If the surgeon or anaesthesiologist suspected a poor physiological status, the patient was referred to a geriatrician for a more comprehensive geriatric screening and to improve performance status. Identifying frailty in elderly patients is important as it is a predictor of postoperative complications and shorter life expectancy.[28,29] Although all elderly patients in this study were preoperatively considered fit for multimodality treatment and surgery, the 1-year mortality rates remained high, which shows how extremely difficult it is to distinguish elderly patients at risk for increased mortality in the first postoperative year from those who are not. As not all of our patients underwent a geriatric assessment, estimating frailty and 1-year mortality risk should be considered for every elderly patient with cT4RC or LRRC.

Another possible intervention to improve outcomes could be prehabilitation. Supervised prehabilitation programmes have shown promise in improving physical condition and outcomes in patients unfit for surgery, but the role of these programmes in this specific patient group remains unclear.[30,31] In our study, all patients were instructed to increase their protein intake and physical activity in the preoperative period, but a supervised prehabilitation programme was not standard of care during the study period.

The most benefit towards improving mortality rates in elderly patients may be gained in the period after hospitalisation. Our results show that a major part of the 1-year mortality in elderly patients occurs in this period, regardless of postoperative complications or disease progression. Elderly patients who are hospitalised after surgery spend a considerable time in bed, leading to rapid muscle loss.[32,33] Sarcopenia has been associated with decreased physical reserve capacity and increased 1-year mortality.[34] Preserving muscle mass in both the early and late postoperative phases may increase physical functioning and prevent 1-year mortality in this specific age group. Therefore, rehabilitation programmes should be part of a total prehabilitation, Enhanced Recovery After Surgery and rehabilitation pathway, and must be initiated immediately after surgery and continue after discharge.[33] A pilot study showed that elderly patients who received rehabilitation after abdominal emergency surgery had better 'Timed Up and Go' outcomes at 6 weeks after discharge in comparison with those receiving standard care.[32] As high 'Timed Up and Go' scores are a risk factor for both long-term institutionalisation and mortality in senior patients, improving this with a rehabilitation programme may result in reduced vulnerability and mortality.[35,36] Additionally, in patients undergoing other types of major gastrointestinal surgery,

improvements have been seen in relevant parameters for cardiorespiratory fitness (e.g., VO_2 max and the 6-min walking test) after a multidisciplinary rehabilitation programme, although the influence of these programmes on postoperative outcomes and survival remains unclear.[37] In elderly patients with cT4RC or LRRC, survival outcomes may be improved by combining prehabilitation, enhanced recovery, and rehabilitation programmes. Studies focusing on this topic in cT4RC or LRRC patients are lacking, and future studies would be of interest.

Other than oncological and survival outcomes, functional outcomes including quality of life can also play a major role in the decision-making process, especially in the elderly population. It is known that the quality of life in elderly CRC patients improves after surgery and is comparable to that in younger patients.[38] Unfortunately, in our study we did not have information about the quality of life. However, earlier studies performed by our research group showed that patients with LRRC had lower health-related quality of life outcomes after surgery when compared with patients with non-advanced disease or LARC, regardless of age.[39] More outcomes with respect to the quality of life and functional outcomes of this patient group should be addressed in future prospective studies.

This paper will help educate clinicians and elderly cT4RC and LRRC patients about the possible outcomes and expectations after surgery. In our study, a median length of 9 days of hospital admission for elderly cT4RC patients was observed, with only 24% having major complications (Clavien-Dindo ^{3} 3) and 18% undergoing reinterventions (endoscopic, radiological, and surgical). For elderly LRRC patients, median length of hospital admission was 12 days, 45% of them had major complications (Clavien-Dindo > 3) and 42% had to undergo reinterventions (endoscopic, radiological, and surgical). Although postoperative mortality is low, clinicians should be aware of the increased vulnerability and mortality in these elderly in the first postoperative year.

The strength of this study lies in the availability of many clinically relevant variables in a unique population of cT4RC and LRRC patients with a low prevalence of missing values. Although this is one of the largest single-centre studies with detailed data in this specific population without interhospital variations, the relatively small patient population could have resulted in less statistical power and it could be argued that it lacks generalisability to other centres. An important limitation of this study is that we were only able to study those patients who underwent surgery, with no information on patients who died preoperatively, or were not eligible for or declined surgery. Furthermore, as we are a referral centre for these advanced and recurrent cases, the referral of patients could have resulted in some selection bias. The retrospective nature of this study is another

limitation, with underestimation of minor complications due to lack of documentation. However, by accurately and thoroughly studying the medical records and contact with referral hospitals and general practitioners, an underestimation of complications was kept to a minimum.

CONCLUSION

Advances in rectal cancer care have led to equal short-term postoperative outcomes in elderly and younger patients, but 90-day and 1-year mortality rates did not improve over time. Approximately one out of four elderly cT4RC and LRRC patients died in the first postoperative year and, as the majority died after hospitalisation without disease recurrence, more awareness is needed towards patient care in the period after hospitalisation.

REFERENCES

1. Millan M, Merino S, Caro A, Feliu F, Escuder J, Francesch T. Treatment of Colorectal Cancer in the Elderly. *World J Gastrointest Oncol*. 2015;7(10):204-220. doi:10.4251/wjgo.v7.i10.204
2. Hagemans JAW, Rothbarth J, Kirkels WJ, et al. Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly. *Eur J Surg Oncol*. 2018;44(10):1548-1554. doi:10.1016/j.ejso.2018.06.033
3. Courtney D, McDermott F, Heeney A, Winter DC. Clinical review: Surgical management of locally advanced and recurrent colorectal cancer. *Langenbeck's Arch Surg*. 2014;399(1):33-40. doi:10.1007/s00423-013-1134-x
4. Mohan HM, Evans MD, Larkin JO, Beynon J, Winter DC. Multivisceral resection in colorectal cancer: A systematic review. *Ann Surg Oncol*. 2013;20(9):2929-2936. doi:10.1245/s10434-013-2967-9
5. Yang TX, Morris DL, Chua TC. Pelvic exenteration for rectal cancer: A systematic review. *Dis Colon Rectum*. 2013;56(4):519-531. doi:10.1097/DCR.0b013e31827a7868
6. Yang R, Wolfson M, Lewis MC. Unique Aspects of the Elderly Surgical Population: An Anesthesiologist's Perspective. *Geriatr Orthop Surg Rehabil*. 2011;2(2):56-64. doi:10.1177/2151458510394606
7. Deiner S, Westlake B, Dutton RP. Patterns of surgical care and complications in elderly adults. *J Am Geriatr Soc*. 2014;62(5):829-835. doi:10.1111/jgs.12794
8. Ouchi Y, Rakugi H, Arai H, et al. Redefining the elderly as aged 75 years and older: Proposal from the Joint Committee of Japan Gerontological Society and the Japan Geriatrics Society. *Geriatr Gerontol Int*. 2017;17(7):1045-1047. doi:10.1111/ggi.13118
9. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B. Epidemiology of multimorbidity and implications for health care, research, and medical education: A cross-sectional study. *Lancet*. 2012;380(9836):37-43. doi:10.1016/S0140-6736(12)60240-2
10. Dekker JWT, Van Den Broek CBM, Bastiaannet E, Van De Geest LGM, Tollenaar RAEM, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol*. 2011;18(6):1533-1539. doi:10.1245/s10434-011-1671-x
11. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol*. 2008;9(5):494-501. doi:10.1016/S1470-2045(08)70129-3
12. Schiphorst AHW, Verweij NM, Pronk A, Hamaker ME. Age-related guideline adherence and outcome in low rectal cancer. *Dis Colon Rectum*. 2014;57(8):967-975. doi:10.1097/DCR.0000000000000145
13. Claassen YHM, Bastiaannet E, van Eycken E, et al. Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe. *Eur J Surg Oncol*. 2019;45(8):1396-1402. doi:10.1016/j.ejso.2019.03.041
14. Brouwer NPM, Heil TC, Olde Rikkert MGM, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. *Eur J Cancer*. 2019;116:1-9. doi:10.1016/j.ejca.2019.04.036

15. Ketelaers SHJ, Orsini RG, Burger JWA, Nieuwenhuijzen GAP, Rutten HJT. Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. *Eur J Surg Oncol*. 2019;45(11):2052-2058. doi:10.1016/j.ejso.2019.06.017

16. Federation of Medical Specialists. Dutch National Guidelines Colorectal Cancer. 2014. https://richtlijnendatabase.nl/richtlijn/colorectaal_carcinoom_crc/startpagina_-_crc.html.

17. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569

18. Voogt ELK, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4

19. Clavien PA, Barkun J, De Oliveira ML, et al. The Clavien-Dindo Classification of Surgical Complications Five-Year Experience. *Ann Surgeryg*. 2009;250(2):187-196. doi:10.1097/SLA.0b013e3181b13ca2

20. Berkel AEM, Woutersen DP, van der Palen J, Klaase JM. Prognostic Factors for Postoperative Morbidity and Tumour Response After Neoadjuvant Chemoradiation Followed by Resection for Rectal Cancer. *J Gastrointest Surg*. 2014;18(9):1648-1657. doi:10.1007/s11605-014-2559-4

21. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Outcome in patients with resectable locally recurrent rectal cancer after total mesorectal excision with and without previous neoadjuvant radiotherapy for the primary rectal tumor. *Ann Surg Oncol*. 2014;21(2):520-526. doi:10.1245/s10434-013-3306-x

22. van Rooijen SJ, Huisman D, Stuijvenberg M, et al. Intraoperative modifiable risk factors of colorectal anastomotic leakage: Why surgeons and anesthesiologists should act together. *Int J Surg*. 2016;36(Pt A):183-200. doi:10.1016/j.ijsu.2016.09.098

23. Miller TE, Roche AM, Mythen M. Fluid management and goal-directed therapy as an adjunct to Enhanced Recovery After Surgery (ERAS). *Can J Anesth*. 2015;62(2):158-168. doi:10.1007/s12630-014-0266-y

24. Bainbridge D, Martin J, Arango M, Cheng D. Perioperative and anaesthetic-related mortality in developed and developing countries: A systematic review and meta-analysis. *Lancet*. 2012;380(9847):1075-1081. doi:10.1016/S0140-6736(12)60990-8

25. Tejedor P, Pastor C, Gonzalez-Ayora S, Ortega-Lopez M, Guadalajara H, Garcia-Olmo D. Short-term outcomes and benefits of ERAS program in elderly patients undergoing colorectal surgery: a case-matched study compared to conventional care. *Int J Colorectal Dis*. 2018;33(9):1251-1258. doi:10.1007/s00384-018-3057-z

26. Sineshaw HM, Yabroff KR, Tsikitis VL, Jemal A, Mitin T. Early mortality after resection of locally advanced rectal cancer in elderly United States patients. *J Clin Oncol*. 2019;37(15_suppl):11529. doi:10.1200/jco.2019.37.15_suppl.11529

27. Lang PO, Michel JP, Zekry D. Frailty syndrome: A transitional state in a dynamic process. *Gerontology*. 2009;55(5):539-549. doi:10.1159/000211949

28. Fagard K, Leonard S, Deschodt M, et al. The impact of frailty on postoperative outcomes in individuals aged 65 and over undergoing elective surgery for colorectal cancer: A systematic review. *J Geriatr Oncol*. 2016;7(6):479-491. doi:10.1016/j.jgo.2016.06.001

29. Lin HS, Watts JN, Peel NM, Hubbard RE. Frailty and post-operative outcomes in older surgical patients: A systematic review. *BMC Geriatr*. 2016;16(1):157. doi:10.1186/s12877-016-0329-8

30. Barberan-Garcia A, Ubré M, Roca J, et al. Personalised Prehabilitation in High-risk Patients Undergoing Elective Major Abdominal Surgery : A Randomized Blinded Controlled Trial. *Ann Surg*. 2018;267(1):50-56. doi:10.1097/SLA.0000000000002293

31. Hughes MJ, Hackney RJ, Lamb PJ, Wigmore SJ, Christopher Deans DA, Skipworth RJE. Prehabilitation Before Major Abdominal Surgery: A Systematic Review and Meta-analysis. *World J Surg*. 2019;43(7):1661-1668. doi:10.1007/s00268-019-04950-y

32. McComb A, Warkentin LM, McNeely ML, Khadaroo RG. Development of a reconditioning program for elderly abdominal surgery patients: The Elder-friendly Approaches to the Surgical Environment-BEdside reconditioning for Functional ImprovemenTs (EASE-BE FIT) pilot study. *World J Emerg Surg*. 2018;13(1):21. doi:10.1186/s13017-018-0180-7

33. Hoogeboom TJ, Dronkers JJ, Hulzebos EHJ, Van Meeteren NLU. Merits of exercise therapy before and after major surgery. *Curr Opin Anaesthesiol*. 2014;27(2):161-166. doi:10.1097/ACO.0000000000000062

34. Otten L, Stobäus N, Franz K, et al. Impact of sarcopenia on 1-year mortality in older patients with cancer. *Age Ageing*. 2019;48(3):413-418. doi:10.1093/ageing/afy212

35. Bergland A, Jørgensen L, Emaus N, Strand BH. Mobility as a predictor of all-cause mortality in older men and women: 11.8 year follow-up in the Tromsø study. *BMC Health Serv Res*. 2017;17(1):22. doi:10.1186/s12913-016-1950-0

36. Huisman M, Ghignone F, Ugolini G, et al. Long-Term Survival and Risk of Institutionalization in Onco-Geriatric Surgical Patients: Long-Term Results of the PREOP Study. *J Am Geriatr Soc*. March 2020. doi:10.1111/jgs.16384

37. Bolger JC, Loughney L, Tully R, et al. Perioperative prehabilitation and rehabilitation in esophagogastric malignancies: A systematic review. *Dis Esophagus*. 2019;32(9):doz058. doi:10.1093/dote/doz058

38. Rønning B, Wyller TB, Nesbakken A, et al. Quality of life in older and frail patients after surgery for colorectal cancer-A follow-up study. *J Geriatr Oncol*. 2016;7(3):195-200. doi:10.1016/j.jgo.2016.03.002

39. Traa MJ, Orsini RG, Den Oudsten BL, et al. Measuring the health-related quality of life and sexual functioning of patients with rectal cancer: Does type of treatment matter? *Int J Cancer*. 2014;134(4):979-987. doi:10.1002/ijc.28430

CHAPTER 4

PROGNOSTIC IMPLICATIONS OF MRI-DETECTED EMVI AND TUMOUR DEPOSITS AND THEIR RESPONSE TO NEOADJUVANT THERAPY IN CT3 AND CT4 RECTAL CANCER

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ABSTRACT

Purpose

Magnetic resonance imaging-detected extramural venous invasion (mrEMVI) and tumour deposits (TDs) are risk factors for the development of local recurrence and distant metastases (DMs) in rectal cancer. However, little is known about their response to neoadjuvant treatment and its relation to oncological outcomes. This study evaluated the incidence and features of mrEMVI and TDs before and after neoadjuvant treatment in relation to the development of local recurrence and DMs.

Methods and materials

Patients with cT3/4 rectal cancer without synchronous metastases who underwent surgery in a tertiary referral hospital were retrospectively analysed. MRI scans were re-evaluated for the presence of mrEMVI, the occurrence of TDs, and response to neoadjuvant therapy (mr-vTRG).

Results

In total, 277 patients were included, of whom 163 (58.8%) presented with mrEMVI. TDs were present in 56.4% of mrEMVI-positive and 9.6% of mrEMVI-negative patients ($p <$ 0.001). The 5-year DM rate was significantly higher in mrEMVI-positive patients with and without TDs (45.2% and 35.9%, respectively) compared with mrEMVI-negative patients (25.7%, $p = 0.012$). After neoadjuvant treatment, the 5-year DM rate of patients with mr-vTRG 3-5 was 46.1%, while good responders (mr-vTRG 1-2) had a DM rate similar to mrEMVI-negative patients (25.7% and 25.7%, respectively; $p = 0.002$). The occurrence of TDs and larger mrEMVI size resulted in a lower likelihood of regression of mrEMVI.

Conclusion

The prevalence of mrEMVI and TDs in cT3-4 rectal cancer is high and is associated with worsened oncological outcomes. MrEMVI regression (mr-vTRG 1-2), which occurs in 25% of the cases, leads to oncological outcomes similar to those in patients without mrEMVI on baseline MRI.

INTRODUCTION

Despite the introduction of standardised surgical techniques and neoadjuvant (chemo) radiotherapy ([C]RT) in rectal cancer, local recurrence rates remain around 5 to 10%, and distant recurrent rates are between 25 and 40%.[1–6] Magnetic resonance imaging (MRI) has been recognised as an essential tool to identify tumour characteristics with high accuracy and reproducibility and guide the multidisciplinary teams in personalised neoadjuvant treatment decision-making.

In recent years, extramural vascular invasion (EMVI) has gained special interest in this respect. Brown et al. have defined MRI-detected EMVI (mrEMVI) as a 'serpiginous extension of tumour signal within a vascular structure' and described a potential role for mrEMVI in the risk stratification of patients with rectal cancer.[7] Six studies were reviewed in a meta-analysis, consisting of 1262 patients, which showed that mrEMVI-positive patients developed metachronous metastasis 3.91 times more frequently compared with mrEMVI-negative patients.[8]

In 2014, Chand et al. described a newly developed MRI-based tumour regression grade (TRG) scale specifically for mrEMVI (mr-vTRG) in a study including 62 patients.[9] Regression of the tumour volume of mrEMVI was divided in a 5-point scale describing no regression (mr-vTRG 5) to complete regression (mr-vTRG 1). Their study showed diminished disease-free survival (DFS) in patients with an mrEMVI response of 50% or less (mr-vTRG 4-5) after (C)RT.

A large meta-analysis by Lord et al., including 19980 patients, showed that tumour deposits (TDs) are highly associated with EMVI. When TDs were present, there was a pooled hazard ratio (HR) of 1.77 (95% confidence interval [CI], 1.37-2.11) for adverse DFS.[10] A recent study showed that distinguishing TDs from lymph node metastases with MRI was possible and that the presence of TDs was a predictor for diminished overall survival and DFS.[11]

The detection of mrEMVI and TDs as a prognostic biomarker in patients who generally receive (C)RT could result in the identification of high-risk patients and more personalised treatment strategies. Therefore, this study aimed to identify mrEMVI and TDs as prognostic biomarkers in a large cohort of patients with cT3/T4 rectal cancer in a single national tertiary referral centre. In addition, we investigated whether treatment with neoadjuvant (C)RT is sufficient in these patients.

METHODS AND MATERIALS

Patients

All consecutive patients who underwent surgery for cT3 and cT4 rectal cancer between January 2009 and December 2015 at a tertiary referral hospital for locally advanced and recurrent rectal cancer in the Netherlands were identified from a prospectively collected database. All baseline and, if present, restaging MRI scans were re-evaluated. Furthermore, data regarding patient and tumour characteristics, treatment, and follow-up were obtained. The presence of synchronous metastatic disease, a non-curative resection (R2-resection), or poor-quality MRI were reasons for exclusion.

Radiological assessment

The MRI scans of all patients were re-evaluated by two experienced radiologists with specific expertise in abdominal radiology and trained in the assessment of mrEMVI. Both radiologists were blinded to the patient characteristics and follow-up data. When there were any inconsistencies in the reported results between the radiologists, the MRI scans were reviewed by both radiologists and consensus was reached. At least T2-weighted images in the sagittal and transversal planes of sufficient quality and with a slice thickness between 3 and 5 mm were present. All MRI scans were evaluated for height and length of the tumour as well as cTNM stage and mesorectal fascia (MRF) involvement. In addition, special attention was given to the occurrence of mrEMVI. On pretreatment MRI, mrEMVI was evaluated for the length of vascular invasion, the location of the involved vein (superior rectal, medial and/or inferior rectal vein), and the occurrence of vascular TDs near the affected vein. TDs were defined as irregular, nodule-like structures in line with a vessel without the typical characteristics of a lymph node, as described by Lord et al.[11] On restaging MRI, the ycTNM stage, TRG, mr-vTRG, and presence of TDs were evaluated.

Tumour and mrEMVI regression grading

Response of the tumour and, if present, mrEMVI was evaluated by MRI tumour regression grading, mrTRG and mr-vTRG, respectively. Tumour and mrEMVI regression grades were both scored on T2-weighted images using a 5-point scale. For the evaluation of tumour response, the mrTRG system as previously described by Patel et al. was used: mrTRG 5, no response (tumour has the same appearance as at baseline); mrTRG 4, slight response (minimal fibrosis/mucinous degeneration, mostly tumour); mrTRG 3, moderate response (~50% fibrosis/mucin and intermediate signal representing residual tumour); mrTRG 2, good response (dense hypointense fibrosis and minimal residual tumour); and mrTRG 1, complete radiological tumour response (no evidence of treated tumour).[12]

The assessment of mrEMVI on restaging MRI (mr-vTRG) was based on the 5-point scoring system introduced by Chand et al.: mr-vTRG 5, minimal fibrosis of tumour signal within lumen; mr-vTRG 4, less than 25% fibrosis of tumour signal; mr-vTRG 3, 25-49% fibrosis of tumour signal; mr-vTRG 2: 50-75% fibrosis of tumour signal; mr-vTRG 1, tumour signal replaced by vessel fibrosis.[9] *Figure 1* shows examples of patients with mrEMVI on primary MRI with complete (mr-vTRG 1), moderate response (mr-vTRG 3), and no response (mr-vTRG 5) on restaging MRI.

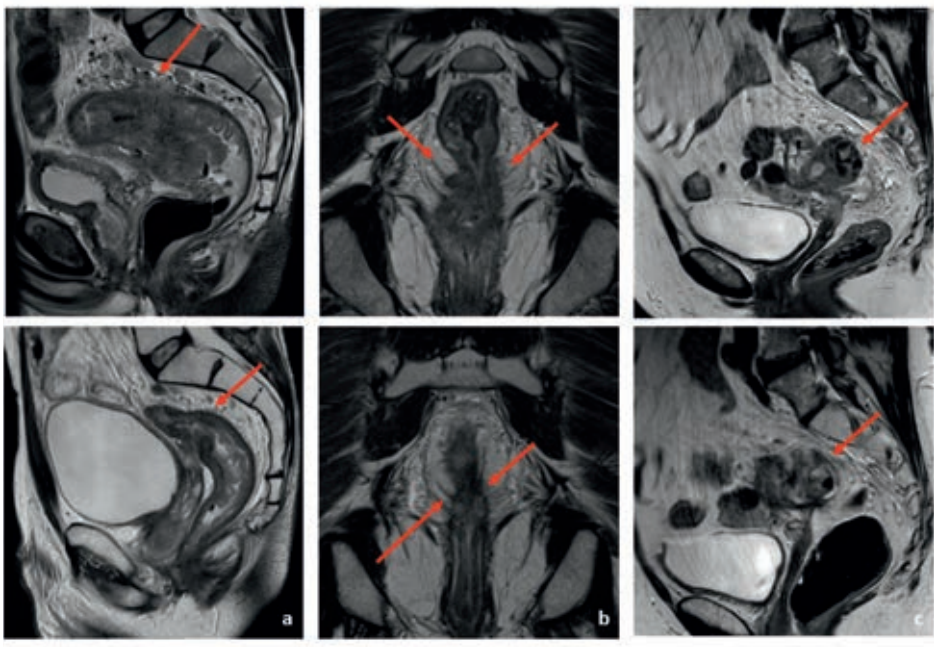


Figure 1 Magnetic resonance imaging (MRI) scans of patients with mrEMVI on primary imaging with complete response (mr-vTRG 1, *fig. 1a*), moderate response (mr-vTRG 3, *fig 1b*), and no response (mr-vTRG 5, *fig 1c)* on restaging MRI

Treatment strategies

Individual treatment strategies of all patients were discussed in multidisciplinary team meetings. According to the Dutch guidelines, no neoadjuvant therapy was administered to patients with cT3N0 rectal cancer with extramural invasion ≤ 5 mm and no involvement of the MRF. In patients with cT3N0 rectal cancer with extramural invasion > 5 mm without an involved MRF or N1 status, 5 x 5 Gy short-course RT was administered. Long-course (C)RT, which consisted of 45-50 Gy in fractions of 1.8–2 Gy with concomitant oral chemotherapy, was given in patients with a threatened MRF or N2 status. Restaging MRI was performed 6 weeks after completion of (C)RT. In general, patients underwent surgery within 8-12 weeks after the end of neoadjuvant (C)RT,

according to national guidelines. Intraoperative radiotherapy was delivered in cases of involved or threatened margins as determined during surgery.

Pathology and follow-up

All specimen were evaluated by an experienced pathologist according to the national guidelines. A resection with clear resection margins (R0) was considered as such if both the circumferential and distal resection margins were free of viable tumour tissue. All patients were monitored according to a standardised follow-up scheme for at least 5 years. This consisted of routine carcinoembryonic antigen level measurements and computed tomography scans and, if indicated, a positron emission tomography or MRI scan. If follow-up was performed in a referring hospital, follow-up data were obtained.

Statistical analysis

Statistical analyses were performed using the IBM SPSS® statistical package version 24 (IBM, Armonk, New York, USA). A p value < 0.050 was considered significant. Individual variables were compared with t tests and the Chi-square tests. Local recurrence-free, distant metastasis-free, disease-free, and overall survival curves were constructed using the Kaplan-Meier method. To determine the risk factors, the effects of co-variables were analysed using a univariable Cox regression model. Subsequently, multivariable analysis was performed for covariables that showed a significant effect in the univariable analysis (p < 0.100). This study was approved by the local medical ethical committee (W19.031).

RESULTS

Patients

A total of 277 consecutive patients who underwent surgery for *c*T3/4 rectal cancer between 2009 and 2015 were included. *Figure 2* shows a diagram illustrating patient flow. The median follow-up after surgery was 47.6 months (interquartile range [IQR], 34.2 – 62.8 months). On primary MRI, 163 patients (58.8%) presented with mrEMVI, of whom 92 (56.4%) also had TDs, while only 11 patients (9.6%) had TDs in the mrEMVI-negative group (p < 0.001). There was no difference in the size of EMVI in patients with TDs (median 18mm; IQR, 13.0-33.5) or without TDs (median 18mm, IQR: 10.0-31.5, p = 0.363). In 88 (54%) of the 163 patients, the mrEMVI was located in the medial rectal vein; in 61 patients (37.4%) it was located in the superior rectal vein; and in 6 patients (3.7%) it was located in the inferior rectal vein. Both the medial and superior rectal vein were involved in 7 patients (4.3%), and both the medial and inferior rectal vein in 1 patient (0.6%). Baseline characteristics of all included patients, separated for patients with and

without mrEMVI at primary MRI, are shown in *Table 1*. MrEMVI generally occurred in higher T- and N-stage tumours.

Table 1 Baseline characteristics versus mrEMVI presence at primary MRI

	No. of patients (n=277)	**mrEMVI – (n=114)**	**mrEMVI + (n=163)**	***p* value ***
Age (years, mean ± SD)	65 ± 10.3	65 ± 10.5	64 ± 10.3	0.369
Sex				0.504
Male	166 (59.9)	71 (62.3)	95 (58.3)	
Female	111 (40.1)	43 (37.7)	68 (41.7)	
Length of the tumour in mm (mean ± SD)	50.4 ± 18.6	48.4 ± 16.5	52.5 ± 20.5	0.091
cT stage				0.002
cT3	132 (47.7)	67 (58.8)	65 (39.9)	
cT4	145 (52.3)	47 (41.2)	98 (60.1)	
Clinical mesorectal fascia involvement				0.001
No	61 (22.0)	37 (32.5%)	24 (14.7)	
Yes	216 (78.0)	77 (67.5)	139 (85.3)	
cN stage				0.003
cN0	68 (24.5)	38 (33.3)	30 (18.4)	
cN1	75 (27.1)	34 (29.8)	41 (25.2)	
cN2	134 (48.4)	42 (36.8)	92 (56.4)	
Deposits				<0.001
No	174 (62.8)	103 (90.4)	71 (43.6)	
Yes	103 (37.2)	11 (9.6)	92 (56.4)	
Neoadjuvant therapy				< 0.001
5 x 5 Gy	33 (11.9)	23 (20.2)	10 (6.1)	
(Chemo)radiotherapy	244 (88.1)	91 (79.8)	153 (93.9)	
Time between RT and surgery (median, IQR)	12.9 (10.3-17.1)	10.6 (8.1-13.7)	13.9 (10.9-17.7)	<0.001
Type of surgery				0.030
LAR/Hartmann resection	144 (52.0)	49 (43.0)	95 (58.3)	
APR	79 (28.5)	41 (36.0)	38 (23.3)	
Extended resection	54 (19.5)	24 (21.1)	30 (18.4)	

Table 1 (Continued)

	No. of patients (n=277)	**mrEMVI – (n=114)**	**mrEMVI + (n=163)**	***p* value ***
Application of IORT				<0.001
No	189 (68.2)	106 (93.0)	83 (50.9)	
Yes	88 (31.8)	8 (7.0)	80 (49.1)	
Pathological margin involvement				0.703
R0	253 (91.3)	105 (92.1)	148 (90.8)	
R1	24 (8.7)	9 (7.9)	15 (9.2)	
pT stage				<0.001
pT0	32 (11.6)	19 (16.7)	13 (8.0)	
pT1	15 (5.4)	10 (8.8)	5 (3.1)	
pT2	64 (23.1)	36 (31.6)	28 (17.2)	
pT3	133 (48.0)	35 (30.7)	98 (60.1)	
pT4	33 (11.9)	14 (12.3)	19 (11.7)	
pN stage				0.010
pN0	191 (69)	90 (78.9)	101 (62)	
pN1	56 (20.2)	15 (13.2)	41 (25.2)	
pN2	30 (10.8)	9 (7.9)	21 (12.9)	
Harvested lymph nodes (median, IQR)	16 (12-22)	16 (13–22)	16 (12-22)	0.990
Tumour histology (n = 268)				0.505
Adenocarcinoma	224 (80.9)	88 (77.2)	136 (83.4)	
Mucinous carcinoma	17 (6.1)	7 (6.1)	10 (6.1)	
Signet cell carcinoma	34 (12.3)	18 (15.8)	16 (9.8)	

Abbreviations: APR = abdominoperineal resection, AV = anal verge, IORT = intraoperative radiotherapy, LAR = low anterior resection, RT = radiotherapy.
Values in parentheses are percentages.
* Chi-square test or Fisher's exact test was used for categorical variables and the *t*-test or Mann-Whitney *U* test for continuous variables.

A restaging MRI scan was present for 246 (88.8%) of the 277 patients that received (C)RT and was performed a median of 6.1 weeks (IQR, 4.9-10 weeks) after the end of neoadjuvant treatment. Patients underwent surgery after a median of 12.3 weeks (IQR, 9.7-17.1 weeks) after the last radiotherapy date. As can be deduced from *Table 1*, there was no difference in the number of resections with clear margins between the mrEMVI-positive and mrEMVI-negative patients.

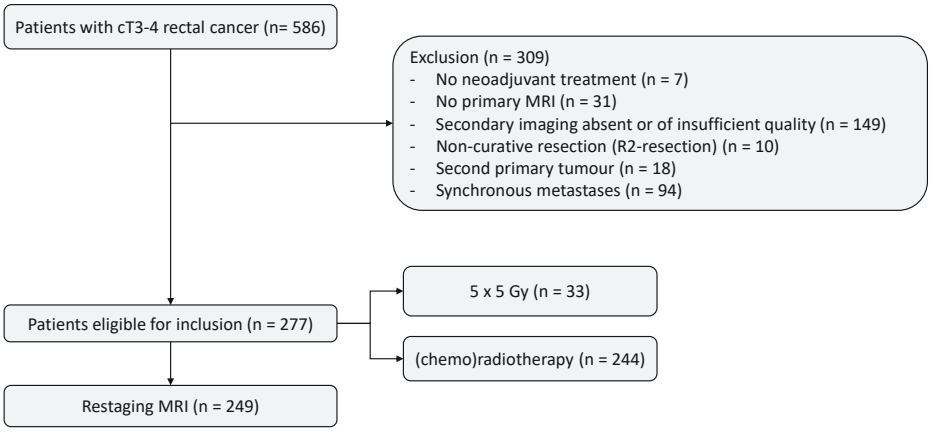
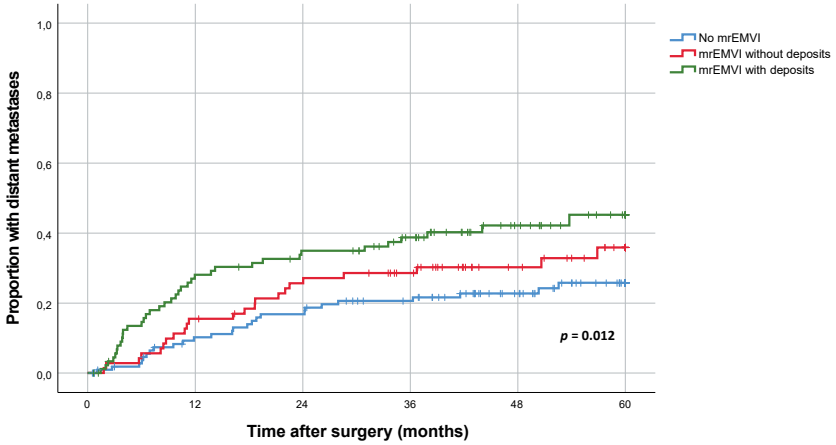


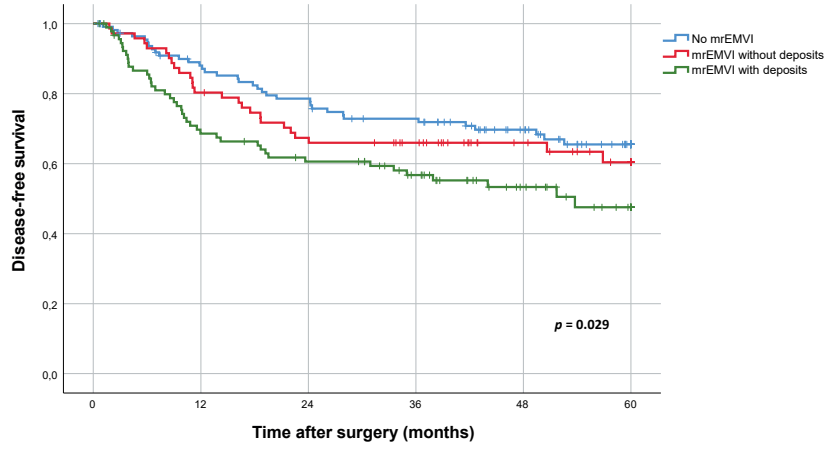
Figure 2 Flow diagram summarising patient flow

Of all patients, 86 patients developed distant metastases (DM), resulting in a 5-year DM rate of 34.7%. DM rates according to the occurrence of mrEMVI with or without additional TDs at baseline are shown in *Figure 3*. The presence of mrEMVI with additional TDs at baseline was associated with an increased 5-year DM rate of 45.2% (HR 2.2; 95% CI 1.3-3.5), compared with a rate of 35.9% (HR 1.4; 95% CI 0.8-2.5) when TDs were not present and a rate of 25.7% in patients without mrEMVI or TDs (p = 0.012). There was no difference in DM rate when looking at the location of the affected vein (p = 0.867). Furthermore, a diminished 5-year DFS rate was observed in patients with mrEMVI and the presence of additional TDs (47.5%; HR 2.0; 95% CI 0.2-3.1), compared with 60.4% in patients with mrEMVI without TDs (HR 1.3; 95% CI 0.8-2.2), and 65.5% in patients without mrEMVI or TDs (p = 0.029) (*Figure 3*). At 5 years, the overall local recurrence rate was 12.6%, which did not differ when looking at the occurrence of mrEMVI with or without additional TDs at baseline (p = 0.277). Uni- and multivariable analyses are shown in e*Tables 1 and 2*. Resection margin involvement was the main predictor of local recurrence, DM, and a decreased DFS. In addition, patients with mrEMVI with TDs (HR 1.4; 95% CI 0.8-2.5) and without additional TDs (HR 2.1; 95% CI 1.3-3.4; p = 0.017) had a significantly higher risk for the development of DM.



No. at risk

No mrEMVI	114	95	88	78	58	36
mrEMVI without deposits	71	60	51	44	28	18
mrEMVI with deposits	92	64	56	45	26	14



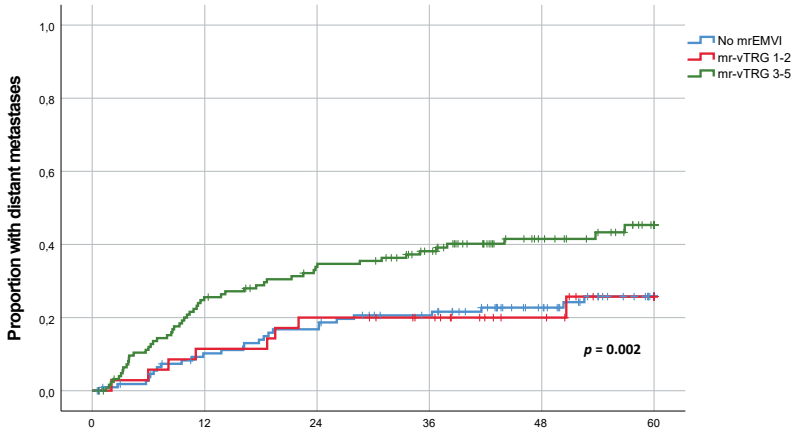
No. at risk

No mrEMVI	114	93	83	74	55	33
mrEMVI without deposits	71	57	47	41	27	18
mrEMVI with deposits	92	61	52	41	24	12

Figure 3 Kaplan-Meier analysis of distant metastases according to the presence of extramural vascular invasion (EMVI) detected by magnetic resonance imaging (MRI) with or without tumour deposits. (log-rank test p = 0.012) and Kaplan-Meier analysis of disease-free survival according to the presence of MRI-detected extramural vascular invasion (mrEMVI) with or without additional deposits. (log-rank test p = 0.029)

mrEMVI response

In all, 161 of 163 patients with mrEMVI at baseline underwent a restaging MRI, of whom 95% received long-course (C)RT and 5% received short-course 5 x 5 Gy radiotherapy. Response of mrEMVI after neoadjuvant therapy (mr-vTRG) was observed in 140 (87.0%) of the 161 patients (mr-vTRG 1, 5.6%; mr-vTRG 2, 16.1%; mr-vTRG 3, 33.5%; and mr-vTRG 4, 31.7%). Thus, of all 161 patients with mrEMVI at baseline and a restaging MRI, 35 patients (21.7%) had a response of 75% or more (mr-vTRG 1-2), whereas 126 patients (78.3%) had an mr-vTRG 3-5. e*Figure 1* shows DM rates per mr-vTRG grade compared with patients without mrEMVI at baseline. Mr-vTRG 3-5 was associated with a high 5-year DM rate of 46.1% (HR 2.1; 95% CI 1.3-3.4), compared with a rate of 25.7% for mr-vTRG 1-2 (HR 0.97; 95% CI 0.4-2.1) and 25.7% for patients without mrEMVI at baseline (p = 0.002) (*Figure 4)*. In addition, mr-vTRG 3-5 was associated with a decreased 5-year DFS rate of 48.6% (HR 1.8; 95% CI 1.2-2.7) compared with 68.6% in patients with mr-vTRG 1-2 (HR 0.92; 95% CI 0.5-1.9) and 65.5% in patients without mrEMVI (p = 0.011). Local recurrence was not influenced by mr-vTRG (p = 0.141). Pretreatment factors related to mrEMVI regression grade are shown in *Table 2*. The occurrence of TDs and larger mrEMVI size resulted in a lower likelihood of regression of mrEMVI.



No. at risk						
No mrEMVI	114	95	88	78	58	36
mr-vTRG 1-2	35	31	28	24	16	10
mr-vTRG 3-5	126	91	77	63	37	21

Figure 4 Kaplan-Meier analysis of distant metastases according to the absence of MRI-detected extramural vascular invasion (mrEMVI) and MRI-based regression grade of EMVI (mr-vTRG). (log-rank test p = 0.002)

Table 2 MRI and response variables versus mr-vTRG

	mr-vTRG 1-2 (n = 35)	**mr-vTRG 3-5 (n = 126)**	***p* value ***
Neoadjuvant therapy			0.516
5 x 5 Gy	1 (2.9)	7 (5.6)	
(Chemo)radiotherapy	34 (97.1)	119 (94.4)	
cT stage			0.228
cT3	17 (48.6)	47 (37.3)	
cT4	18 (51.4)	79 (62.7)	
cN stage			0.226
cN0	9 (25.7)	19 (15.1)	
cN1	10 (28.6)	31 (24.6)	
cN2	16 (45.7)	76 (60.3)	
Length of the tumour in mm (mean ± SD)	59.7 ± 21.4	51.3 ± 19.6	0.340
Length of mrEMVI in mm (median, IQR)	13 (7-18)	21 (13-34)	<0.001
Involved vein			0.183
Superior rectal vein	9 (25.7)	52 (41.3)	
Superior and medial rectal vein	1 (2.9)	6 (4.8)	
Medial rectal vein	22 (62.9)	64 (50.8)	
Inferior rectal vein	3 (60)	3 (2.3)	
Inferior and medial rectal vein	0	1 (0.8)	
Deposits			0.001
No	24 (68.6)	46 (36.5)	
Yes	11 (31.4)	80 (63.5)	
Time between RT and MRI (median, IQR)	5.9 (4.9-11)	7.6 (5.1-10.8)	0.586

Abbreviations: AV = anal verge, Mr-vTRG = MRI detected EMVI tumour regression grade, RT = radiotherapy. Values in parentheses are percentages.
* Chi-square test or Fisher's exact test was used for categorical variables and *t*-test or Mann-Whitney *U* test for continuous variables.

Association between mrEMVI, deposits, and tumour response

The association between mrTRG, mr-vTRG, and the response of TDs are shown in *eTable 3*. Tumour response was less likely when there were more unfavourable characteristics (mrEMVI or TDs), and mrTRG was related to mr-vTRG; 72% of the patients with mrTRG 1-2 had a good to complete response of mrEMVI (mr-vTRG 1-2), whereas 87.5% of the patients with mrTRG 3-5 had a moderate to no response of mrEMVI (mr-vTRG 3-5). TDs

remained present in 77% of the patients in whom the tumour and the mrEMVI did not respond well, but in the other groups, the patient numbers were too low to assess adequate response. DM rates became gradually higher when there was less response.

Uni- and multivariable analyses of restaging characteristics

Since the response of mrEMVI, TDs and tumour were strongly related, only one factor could be included in the multivariable analyses on restaging MRI. e*Table 4* shows the multivariable analyses of the restaging mrEMVI characteristics. When looking at characteristics after (C)RT, patients with mr-vTRG 1-2 had a risk comparable with that of patients without mrEMVI at baseline (HR 1.0; 95% CI 0.5-2.3), whereas patients with mr-vTRG 3-5 had an almost two-fold higher risk for the development of metastatic disease (HR 2.0; 95% CI 1.3-3.3; $p = 0.006$). Additionally, DFS was similar in patients with mr-vTRG 1-2 and patients without mrEMVI (HR 1.0; 95% CI 0.5-2.0), but mr-vTRG 3-5 had a higher risk for diminished DFS (HR 1.7; 95% CI 1.1-2.6; $p = 0.024$).

DISCUSSION

This study describes the outcomes of 277 consecutive patients who underwent surgery for cT3/T4 rectal cancer in a national tertiary referral hospital for locally advanced and recurrent rectal cancer. Their MRI scans were re-evaluated to identify the prognostic value of mrEMVI characteristics, showing a high prevalence of mrEMVI of 58.8%. TDs were observed in more than half of the mrEMVI-positive patients. The presence of mrEMVI was associated with an increase in the 5-year DM rate and was even higher when additional TDs were present. This same trend was seen in the 5-year DFS rate. After (C)RT, in 21.7% of the patients with mrEMVI on primary MRI, a reduction of 75% or more (mr-vTRG 1-2) was seen. This improved the 5-year DM and DFS rate, comparable with that in patients without mrEMVI at initial diagnosis and significantly lower than that in patients with mr-vTRG 3-5. The occurrence of TDs and larger mrEMVI size resulted in a lower likelihood of regression of mrEMVI.

Chand et al. introduced mr-vTRG as a prognostic factor for the development of recurrent disease and lowered DFS in 62 patients. Similarly, the present study showed that a 'bad' response of mrEMVI is associated with diminished DFS rates and higher probability of disease recurrence. The present study, however, provides several new findings regarding mrEMVI. First, it shows that 'good' responders have similar oncological outcomes compared with mrEMVI-negative patients. Second, to our knowledge, this study is the first to show that TDs on MRI are a sign of 'progressive mrEMVI' with a lower likelihood of response. In the study by Chand et al., the division into 'good' and 'bad'

responders was different compared with the division used in our study. Chand et al. divided mrEMVI response into mr-vTRG 1-3 versus mr-vTRG 4-5, whereas in this study mrEMVI response was divided into mr-vTRG 1-2 and mr-vTRG 3-5, because mr-vTRG 1 and 2 showed very similar 5-year DM and DFS rates, as did mr-vTRG 3-5; this, these seemed to be a better division of response in this larger study.

The association between pathological-detected EMVI and extranodal tumour deposits (ENTDs) was shown in a meta-analysis by Lord et al., in which eight studies showed that ENTDs occurred twice as frequently in pEMVI-positive patients.[13] In addition, a negative effect of ENTDs on overall and disease-free survival was shown. Nagtegaal and Quirke speculated that TDs might originate from vascular structures (i.e., lymphatic or venous), nerves or occur in multiple patterns; however, in a number of cases the origin is hard to determine.[14] Lord et al. determined that MRI was an adequate tool to identify TDs that resulted in poor oncological outcomes.[11] The current study confirmed the finding that TDs can also be identified radiologically and thus can be used in treatment decision-making, rather than just being a finding in pathology afterward. In this study, the prevalence of mrEMVI was 58.8%, which is significantly higher than the combined prevalence of 34.6% (range: 19.8% - 57.4%) reported in the meta-analysis by Siddiqui et al.[8] However, when looking at studies with similar inclusion criteria, the reported prevalence is in line with other literature.[13] Furthermore, TDs were identified in 103 of 277 patients (37.2%); this is consistent with the systematic review by Lord et al. (median: 21.3%), although there was a wide dispersion (10.2% - 44.2%) among the included studies.[13] The differences in the reported incidence of MRI-detected and pathologically identified venous invasion and TDs may be caused by different definitions of venous invasion and TDs used by radiologists and pathologists. Furthermore, different staining techniques and the fact that histopathological slices are usually 1 cm, might be associated with a lower probability of detection and thus 'missed' pEMVI and ENTDs. In this study, we observed that in only 11 patients (9.1%) without mrEMVI TDs were present on primary MRI. Owing to these low patient numbers, we were unable to investigate the individual predictive value of TDs.

Large mrEMVI size and the presence of TDs near the mrEMVI on primary MRI seem to be useful as prognostic imaging markers to distinguish the 'good' and 'bad' mrEMVI responders after (C)RT. This could aid in identifying which patients might benefit from a more tailor-made neoadjuvant treatment regimen without causing overtreatment. A more intensified approach towards these patients (e.g., by neoadjuvant induction chemotherapy followed by chemoradiotherapy instead of chemoradiotherapy alone) might induce more mrEMVI downstaging and thereby potentially improve oncological outcomes. The role of induction chemotherapy before (C)RT has been investigated in

previous studies. In a retrospective cohort analysis of 811 patients, Cercek et al. showed a higher 1-year complete clinical response rate in patients who received (C)RT after induction chemotherapy compared with patients who received (C)RT and adjuvant chemotherapy (22% vs. 6%).[15] Furthermore, a higher pathological complete response rate was observed in patients who received six cycles of FOLFOX after (C)RT compared with patients who received (C)RT only (38% vs. 18%). Because the findings of the present study suggest that mrTRG and mr-vTRG are related, it might be hypothesised that induction chemotherapy has the potential to induce mrEMVI response. The question remains whether the presence of mrEMVI and TDs is just a sign of 'bad' biology, for which a more systemic approach might be needed.

Although this is, to our knowledge, the largest study to date investigating the role of mrEMVI features and TDs before and after (C)RT, the retrospective nature of this study has apparent shortcomings, so the statistical analyses should be interpreted with care. In this study, a total of 586 patients with cT3/4 rectal cancer were identified, of whom only 284 patients were eligible for inclusion. A total of 122 patients were excluded because of medical reasons such as synchronous metastases or a secondary tumour, and for 179 patients, MRI scans were not present or were of insufficient quality for good evaluation. In addition, patients with synchronous metastases were excluded, so the incidence of mrEMVI in patients with cT3/4 rectal cancer is probably even higher. Despite these limitations, we still can conclude that mrEMVI is a major issue in patients with locally advanced rectal cancer owing to its high incidence and its prognostic significance for increased metastatic disease and diminished survival. Unfortunately, the occurrence of mrEMVI is often not adequately reported by every radiologist. To ensure the quality of data in this study, all MRI scans were independently reviewed by two radiologists who were trained in the assessment of mrEMVI and TDs. Discrepancies were observed in 7% of the cases, after which consensus was obtained. Although evaluating diagnostic accuracy was not the purpose of this study, this indicates a low interobserver variability. In addition, multiple studies have shown that the regression grading technique is reliable and related to oncological outcome.[16–19] Previous studies by Taylor and Brown et al. showed that the assessment of MRI in patients with rectal cancer can be standardised and reproduced, in particular when adopting a specific pro forma-based system.[20,21] Hence, knowledge and awareness regarding the identification of mrEMVI and its prognostic value should be brought to the attention of radiologist and routinely evaluated in patients with rectal cancer.

CONCLUSIONS

The findings of this study showed a high prevalence of mrEMVI in patients with cT3/4 rectal cancer, resulting in high rates of DM and lower DFS rates in selected patients with these challenging tumours. However, these rates improved greatly after a good response to neoadjuvant (C)RT. Gaining knowledge about important clinical parameters regarding response could strengthen the importance of a restaging MRI, which is not only important for preoperative planning but could aid in clinical decision making in the MDT. Assessing risk factors for the development of DM could identify which patients might benefit from a more intensified approach, such as induction chemotherapy followed by chemoradiotherapy. This change in neoadjuvant treatment might result in more 'good' or 'complete' responders, even among patients with these challenging tumours. This study's findings may lead to a more tailor-made approach to avoid undertreatment or overtreatment.

REFERENCES

1. van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582. doi:10.1016/S1470-2045(11)70097-3
2. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836
3. Fokas E, Liersch T, Fietkau R, et al. Tumor regression grading after preoperative chemoradiotherapy for locally advanced rectal carcinoma revisited: Updated results of the CAO/ARO/AIO-94 trial. *J Clin Oncol*. 2014;32(15):1554-1562. doi:10.1200/JCO.2013.54.3769
4. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. *N Engl J Med*. 2004;351(71):1731-1740. doi:10.1056/nejmoa040694
5. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi:10.1056/NEJMoa010580
6. Swedisch Rectal Cancer Trial, Cedermark B, Dahlberg M, Glimelius B, Pahlman L, Rutqvist LE, Wilking N. Improved Survival with Preoperative Radiotherapy in Resectable Rectal Cancer. *N Engl J Med*. 1997;336(14):980-987. doi:10.1056/nejm199704033361402
7. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg*. 2003;90(3). doi:10.1002/bjs.4034
8. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer*. 2017;116(12):1513-1519. doi:10.1038/bjc.2017.99
9. Chand M, Swift RI, Tekkis PP, Chau I, Brown G. Extramural venous invasion is a potential imaging predictive biomarker of neoadjuvant treatment in rectal cancer. *Br J Cancer*. 2014;110(1):19-25. doi:10.1038/bjc.2013.603
10. Lord AC, Graham Martínez C, D'Souza N, Pucher PH, Brown G, Nagtegaal ID. The significance of tumour deposits in rectal cancer after neoadjuvant therapy: a systematic review and meta-analysis. *Eur J Cancer*. 2019;122:1-8. doi:10.1016/j.ejca.2019.08.020
11. Lord AC, D'Souza N, Shaw A, et al. MRI-Diagnosed Tumour Deposits and EMVI Status Have Superior Prognostic Accuracy to Current Clinical TNM Staging in Rectal Cancer. *Ann Surg*. 2020:Publish Ahead of Print. doi:10.1097/SLA.0000000000004499
12. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29(28):3753-3760. doi:10.1200/JCO.2011.34.9068
13. Lord AC, D'Souza N, Pucher PH, et al. Significance of extranodal tumour deposits in colorectal cancer: A systematic review and meta-analysis. *Eur J Cancer*. 2017;82:92-102. doi:10.1016/j.ejca.2017.05.027

14. Nagtegaal ID, Quirke P. Colorectal tumour deposits in the mesorectum and pericolon; a critical review. *Histopathology*. 2007;51(2):141-149. doi:10.1111/j.1365-2559.2007.02720.x

15. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071

16. Hunter CJ, Garant A, Vuong T, et al. Adverse features on rectal MRI identify a high-risk group that may benefit from more intensive preoperative staging and treatment. *Ann Surg Oncol*. 2012;19(4):1199-1205. doi:10.1245/s10434-011-2036-1

17. Bugg WG, Andreou AK, Biswas D, Toms AP, Williams SM. The prognostic significance of MRI-detected extramural venous invasion in rectal carcinoma. *Clin Radiol*. 2014;69(6):619-623. doi:10.1016/j.crad.2014.01.010

18. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229-236. doi:10.1002/bjs.5917

19. Schaap DP, Ogura A, Nederend J, et al. Prognostic implications of MRI-detected lateral nodal disease and extramural vascular invasion in rectal cancer. *Br J Surg*. 2018;105(13). doi:10.1002/bjs.10949

20. Taylor FGM, Swift RI, Blomqvist L, Brown G. A systematic approach to the interpretation of preoperative staging MRI for rectal cancer. *Am J Roentgenol*. 2008;191(6):1827-1835. doi:10.2214/AJR.08.1004

21. Brown PJ, Rossington H, Taylor J, et al. Standardised reports with a template format are superior to free text reports: the case for rectal cancer reporting in clinical practice. *Eur Radiol*. 2019;29(9):5152-5128. doi:10.1007/s00330-019-06028-8

CHAPTER 5

MRI TUMOUR REGRESSION GRADE IN LOCALLY RECURRENT RECTAL CANCER

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ABSTRACT

Background

This study aimed to investigate the agreement between magnetic resonance tumour regression grade (mrTRG) and pathological regression grade (pTRG) in patients with locally recurrent rectal cancer (LRRC). Also, the reproducibility of mrTRG was investigated.

Methods

All patients with LRRC who underwent a resection between 2010 and 2018 after treatment with induction chemotherapy and neoadjuvant chemo(re)irradiation in whom a restaging MRI was available were retrospectively selected. All MRI scans were reassessed by two independent radiologists using the mrTRG, and the pTRG was reassessed by an independent pathologist. The interobserver agreement between the radiologists as well as between the radiologists and the pathologist was assessed using the weighted kappa test. A subanalysis was performed to evaluate the influence of the interval between imaging and surgery.

Results

Out of 313 patients with LRRC treated during the study interval, 124 patients were selected. Interobserver agreement between the radiologists was fair (k = 0.28) using the two-tier grading system (mrTRG 1-2 versus mrTRG 3-5). For the lead radiologist, agreement with pTRG was moderate (k = 0.52; 95% CI 0.36-0.68) when comparing good (mrTRG 1-2, Mandard 1-2) and intermediate/poor responders (mrTRG 3-5, Mandard 3-5), and the agreement was fair between the other abdominal radiologist and pTRG (k = 0.39; 95% CI 0.22-0.56). A shorter interval (< 7 weeks) between MRI and surgery resulted in an improved agreement (k = 0.69), compared with an interval more than 7 weeks (k = 0.340). For the lead radiologist, the positive predictive value for predicting good responders was 95% (95% CI 71%-99%), whereas this was 56% (95% CI 44%-66%) for the other radiologist.

Conclusion

This study showed that, in LRRC, the reproducibility of mrTRG among radiologists is limited and the agreement of mrTRG with pTRG is low. However, a shorter interval between MRI and surgery seems to improve this agreement and, if assessed by a dedicated radiologist, mrTRG could predict good responders.

INTRODUCTION

In patients with locally advanced rectal cancer (LARC), the MRI-based tumour regression grade (mrTRG), a five-tier imaging-based scoring system based on the ability to distinguish between tumour and fibrosis, has proven to be reproducible among radiologists with a good interobserver agreement.[1,2] Moreover, mrTRG has proven to be a prognostic factor for disease-free (hazard ratio (HR) 3.28; 95% CI 1.22-8.80) and overall survival (HR 4.40; 95% CI 1.65-11.7) in these patients, although the agreement between mrTRG and pathological tumour regression grade (pTRG) seemed suboptimal.[2,3]

It is unknown whether mrTRG can be used in the treatment decision-making for patients presenting with locally recurrent rectal cancer (LRRC). LRRC requires intensive neoadjuvant treatment comprising chemo(re)irradiation followed by extensive surgery.[4–8] The goal of surgery is to achieve a resection with clear resection margins, as this is the most important prognostic factor for local recurrence-free and overall survival.[9–11] Previous studies from our group showed that the addition of induction chemotherapy to the neoadjuvant treatment in patients with LRRC enhances tumour response.[12,13] In addition, it was demonstrated that pTRG is an independent predictive variable for long-term oncological outcomes in patients with LRRC.[13] Obviously, pTRG can only be obtained postoperatively, and thus does not offer the opportunity to adapt treatment strategies. In that perspective, mrTRG may be more suitable in the decision-making process, as it provides an opportunity to consider non-operative therapy in case of clinical complete response. Therefore, this study aimed to investigate the agreement between mrTRG and pTRG in a retrospective cohort of patients with LRRC treated with induction chemotherapy and chemo(re)irradiation. Also, interobserver agreement between radiologists for mrTRG assessment was evaluated.

METHODS

Patients

All patients with LRRC who underwent a resection in the Catharina Hospital, Eindhoven – the Netherlands, a national tertiary referral centre for LRRC, are prospectively collected in a database. All consecutive patients with LRRC who underwent a resection with curative intent between 2010 and 2018 after treatment with induction chemotherapy followed by neoadjuvant chemo(re)irradiation were retrospectively selected. Patients in whom the baseline or restaging MRI was not available for reassessment were excluded. The study was waived by the local medical ethics committee (Medical Research Ethics Committees United Nieuwegein, registration number: W19.031).

Neoadjuvant and surgical treatment

At the Catharina Hospital, Eindhoven – the Netherlands, all patients with LRRC receive neoadjuvant chemo(re)irradiation. In this selected cohort, all patients received induction chemotherapy before this. Induction chemotherapy generally consisted of four cycles of CAPOX (capecitabine and oxaliplatin) or six cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). Initially, induction chemotherapy was reserved for patients with irresectable or marginally resectable disease. Gradually, the administration of induction chemotherapy became more common practice and finally became the local standard of care in 2016.[13] In radiotherapy-naïve patients, full-course radiotherapy was delivered with a cumulative dose of 50-50.4 Gy. In patients who previously received pelvic radiotherapy, radiotherapy was delivered with a cumulative dose of 30-30.6 Gy. The concomitant chemotherapy agent was capecitabine (825 mg/m2 twice a day on radiotherapy days).

The type and extent of the surgery was left to the discretion of the treating surgical oncologist. Intraoperative electron beam radiotherapy was delivered in a dose of 10-12.5 Gy when there were no clear resection margins or when there was tumour adherence to unresectable structures.

Radiological and pathological assessment

An MRI was performed at baseline, after finishing induction chemotherapy, and 4-6 weeks after completion of neoadjuvant (chemo)radiotherapy and consisted of at least T2-weighted axial, coronal, and sagittal planes performed on a 1.5T or 3T MRI system. MRIs were performed either in the tertiary referral hospital or in the referring hospital and were reassessed by an experienced abdomen radiologist with specific expertise in LARC and LRRC. Response was scored according to the mrTRG; mrTRG 1, low signal fibrosis only, no tumour signal; mrTRG 2, more than 75% fibrosis and minimal tumour signal intensity; mrTRG 3, 50% tumour/fibrosis; mrTRG 4, less than 25% fibrosis, predominant tumour signal; mrTRG 5, no fibrosis.[2] The radiologist was trained using mrTRG in primary tumours in a training program including post-neoadjuvant treatment reporting, conducted by leader experts in this field.[2] To evaluate the reproducibility of the mrTRG in LRRC a second experienced abdomen radiologist, who was also trained, independently assessed all imaging using the mrTRG. The radiologists were blinded for the pathological assessment and the clinical outcomes.

All specimens were revised by a specialised pathologist who was blinded to the radiological assessment as well as the clinical outcomes. On the primary assessment, in general, at least one section per centimetre maximum tumour bed diameter was sampled. The pathological response grade (pTRG) was scored according to the Mandard

classification; pTRG 1, complete response; pTRG 2, isolated cell nests; pTRG 3, more residual cancer cells but fibrosis still predominates; pTRG 4, residual cancer outgrowing fibrosis; pTRG 5, absence of regressive changes.[14]

Outcomes of interest

Outcomes of interest were the agreement between mrTRG and pTRG, and the interobserver radiological agreement. In addition, a subanalysis was performed to assess the agreement between mrTRG and pTRG in patients with a long interval versus a short interval between MRI and surgery, based on median interval values.

Statistical analysis

Continuous data were reported as median (interquartile range) and categorical data as count (percentage). The strength of agreement between mrTRG after completion of neoadjuvant treatment and the pathological response rate was assessed using the weighted *kappa* test (*k* value <0.20, poor agreement; *k* value = 0.21–0.40, fair agreement; *k* value = 0.41–0.60, moderate agreement; *k* value = 0.61–0.80, good agreement; and *k* value=0.81–1.00, very good agreement). This analysis was performed using the five categories of tumour regression, as well as using a two-tier regression scale, adapted from these standardised five-tier regression scales, i.e. Mandard 1-2 (good responders) versus Mandard 3-5 (intermediate/poor responders) and mrTRG 1-2 versus mrTRG 3-5.

The interobserver variability between the two radiologists regarding the assessment of mrTRG was analysed using the weighted *kappa* test, considering the five-tier regression scale as well as the two-tier regression scale, i.e. mrTRG 1-2 versus mrTRG 3-5.

Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of mrTRG with regard to the pTRG were calculated from two-by-two contingency tables using predefined categories (mrTRG 1-2 versus mrTRG 3-5 and pTRG 1-2 versus pTRG 3-5).

All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, NY, USA).

RESULTS

Patients

A total of 313 patients had a resection with curative intent for LRRC between 2010 and 2018, of whom 132 received induction chemotherapy followed by chemo(re)irradiation.

Eight patients were excluded because no baseline or restaging MRI was available, resulting in 124 selected patients (*Figure 1)*. Demographics, tumour characteristics, and details about the treatment are shown in *Table 1*. The median interval between the end of chemoradiotherapy and surgery was 13 weeks [IQR: 11-15 weeks]. Median interval between post-chemoradiotherapy MRI and surgery was 7 weeks [IQR: 5-8 weeks].

With respect of the pathology assessment in patients with a good response (Mandard 1-2), in 32 of 39 cases (82%) at least one section per centimetre maximum tumour bed diameter was sampled, whereas in 5 patients (10%) this could not be reassessed due to incompleteness of the report, and in 2 patients less than one section per centimetre tumour diameters was sampled.

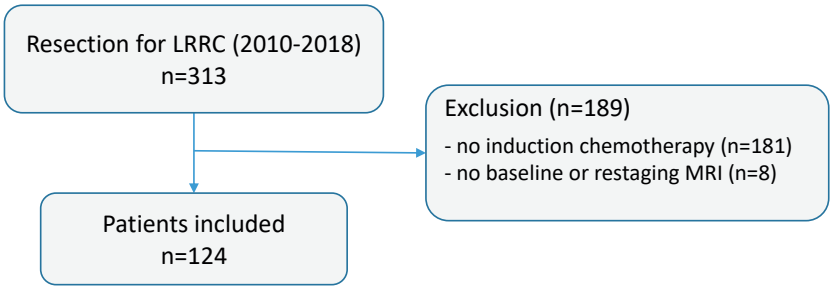

Figure 1 Flowchart showing patient selection

Table 1 Demographics and tumour characteristics

		Total (N=124) N (%)
Gender	Female	36(29)
	Male	88(71)
Age at resection (years)	Median [IQR]	65 [58-71]
Neoadjuvant radiotherapy primary tumour	None	31(25)
	Radiotherapy	33(27)
	Chemoradiotherapy	60(48)
Surgical procedure primary tumour	Rectosigmoid resection	16(13)
	LAR	63(51)
	APR	45(36)
Adjuvant therapy primary tumour	None	107(86)
	Chemotherapy	15(12)
	Radiotherapy	2(2)
Number local recurrence	First	108(87)
	Second/third	16(13)
Multifocality	Yes	27(22)
	No	97(78)
Number of involved compartments	1	25(20)
	2	57(46)
	3	25(20)
	4	17(14)
Neoadjuvant radiotherapy recurrence	(chemo)radiotherapy	20(16)
	(chemo)reirradiation	104(84)
Surgical procedure recurrence	LAR	13(11)
	APR	15(12)
	Multivisceral resection	72(58)
	Non-visceral resection	24(19)
Intraoperative electron beam radiotherapy	Yes	103(83)
	No	21(17)
Interval between end chemoradiotherapy and surgery (weeks)	Median [IQR]	13 [11-15]
Interval between last MRI and surgery (weeks)	Median [IQR]	7 [5-8]
Resection margin	R0	80(65)
	R1	41(33)
	R2	3(2)
Histology*	Adenocarcinoma	101(98)
	Mucinous carcinoma	2(2)

* Not applicable for patients with a complete pathological response
APR = abdominal perineal resection, IQR = interquartile range, LAR = low anterior resection

Agreement mrTRG – pTRG

There was a fair level of agreement (*k* = 0.30; 95% confidence interval [CI] 0.20-0.40) between the lead radiologist and the pathologist when using the five-tier grading system, and a moderate level of agreement (*k* = 0.52; 95% CI 0.36-0.68) when comparing good (mrTRG 1-2, Mandard 1-2) and intermediate/poor responders (mrTRG 3-5, Mandard 3-5). *Table 2* shows the agreement between the radiologists and the pTRG using the two-tier grading system, and the five-tier grading system. *Figure 2-6* show MRI imaging of cases in which the mrTRG assessment corresponded with the pTRG. *Figures 2* and *6* also show the corresponding histology images.

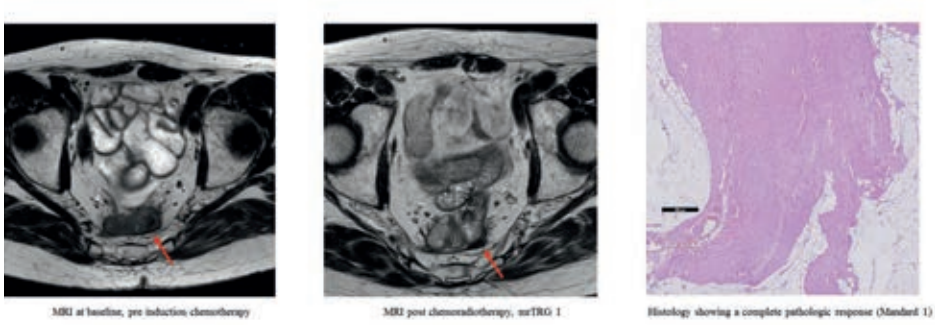

Figure 2 MRI at baseline and post chemoradiotherapy showing a complete radiological response (i.e. mrTRG 1) and the corresponding histology imaging showing a complete response (i.e. pTRG 1). In this case, restaging was performed <7 weeks

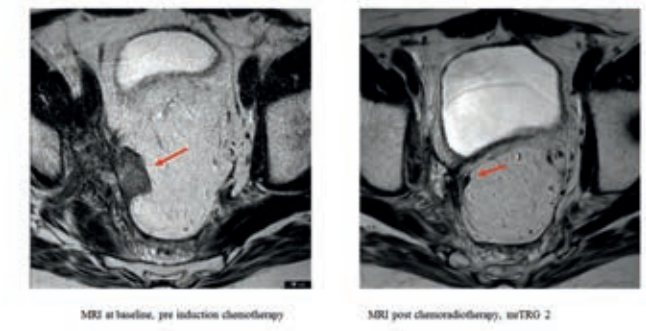

Figure 3 MRI at baseline and post chemoradiotherapy showing a near complete radiological response (i.e. mrTRG 2). In this case, restaging was performed < 7 weeks

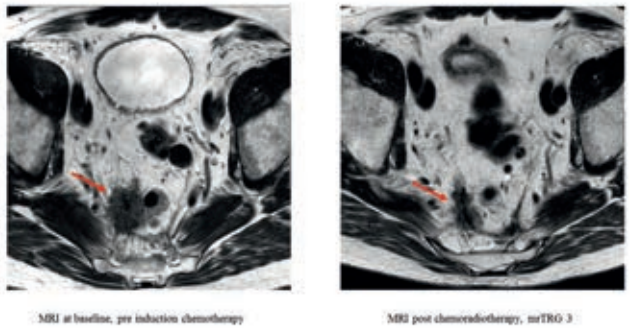

Figure 4 MRI at baseline and post chemoradiotherapy showing a moderate radiological response (i.e. mrTRG 3). In this case, restaging was performed > 7 weeks

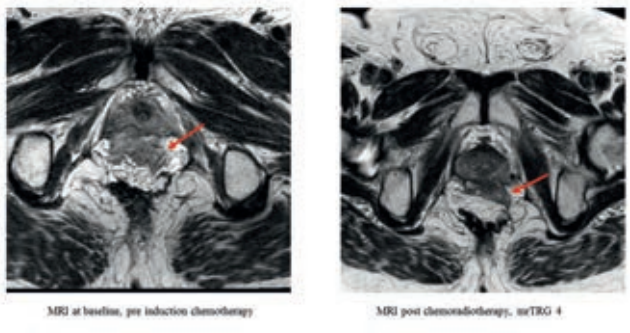

Figure 5 MRI at baseline and post chemoradiotherapy showing a slight radiological response (i.e. mrTRG 4). In this case, restaging was performed > 7 weeks

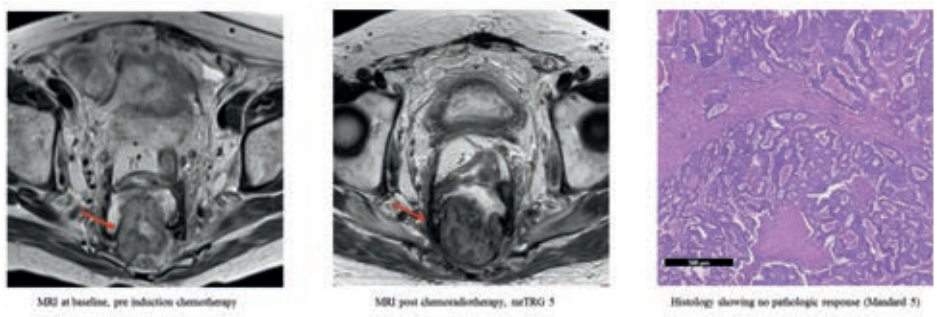

Figure 6 MRI at baseline and post chemoradiotherapy showing no radiological response (i.e. mrTRG 5) and the corresponding histology imaging showing no regressive changes (i.e. pTRG 5). In this case, restaging was performed < 7 weeks

Using the two-tier grading system, assessment of the agreement between pTRG and mrTRG in patients with a long interval between MRI and surgery (more than 7 weeks, n = 61) resulted in a fair agreement (*k* = 0.34, 95% CI 0.12-0.56), whereas the agreement was good in patients with a short interval (7 weeks or less; n = 63; *k* = 0.69, 95% CI 0.49-0.90). The five-tier system resulted in *k* values of 0.26 and 0.32 for long and short intervals respectively, and therefore seems less suitable for clinical use.

When using the two-tier grading system, the lead radiologist underestimated the presence of residual tumour in 1% of cases, correctly assessed the residual tumour in 82%, and overestimated the presence of residual tumour in 17% of cases.

The agreement between the other abdomen radiologist and the pTRG was fair (*k* = 0.25; 95% CI 0.14-0.35) using the five-tier grading, as well as when using the two-tier grading system (*k* = 0.39; 95% CI 0.22-0.56) (*Table 2)*.

Interobserver agreement

The mrTRG scores for both radiologists are shown in *Table 3*. The interobserver agreement between the two radiologists was moderate when using the five-tier regression scale (*k* = 0.44; 95% CI 0.34-0.54) and fair when using the adjusted regression scale comparing good responders (mrTRG 1-2) with intermediate/poor responders (mrTRG 3-5, *k* = 0.28; 95% CI 0.12-0.44).

Overall, sensitivity was 46% (95% CI 30%-63%), specificity was 99% (95% CI 94%-100%), PPV was 95% (95% CI 71%-99%), and NPV was 80% (95% CI 75%-84%) for the lead radiologist for predicting a good response (i.e. Mandard 1-2).

For the other abdomen radiologist, sensitivity was 64% (95% CI 47%-79%), specificity was 76% (95% CI 66%-85%), PPV was 56% (95% CI 44%-66%), and NPV was 82% (95% CI 75%-88%) for predicting a good response (i.e. Mandard 1-2).

Table 2 Comparison between mrTRG and pTRG

	2-tier grading system	pTRG[a]						
		Good responders (1-2)		**Intermediate/poor responders (3-5)**			**Total**	***k* value**
mrTRG[1]	Good responders (1-2)	18*		1			19	
	Intermediate/poor responders (3-5)	21		84			105	0.52
	Total	39		85[$]			124	
mrTRG[2]	Good responders (1-2)	25*		20			45	
	Intermediate/poor responders (3-5)	14		65[$]			79	0.39
	Total	39		85			124	
	5-tier grading system	**pTRG[a]**						
		1	2	3	4	5	**Total**	
mrTRG[1]	**1**	4	0	0	0	0	4	
	2	8	6	1	0	0	15	
	3	6	7	21	7	1	42	
	4	3	1	14	15	3	36	
	5	0	4	15	7	1	27	
	Total	21	18	51	29	5	124	0.30
mrTRG[2]	**1**	3	4	1	0	0	8	
	2	11	7	12	6	1	37	
	3	7	4	12	8	0	31	
	4	0	0	10	6	0	16	
	5	0	3	16	9	4	32	
	Total	21	18	51	29	5	124	0.25

mrTRG = magnetic resonance tumour regression grade, pTRG = pathologic regression grade

[1] Lead radiologist; [2] Second radiologist; [a] pTRG graded according to Mandard; * true positive; [$]true negative

Table 3 Agreement between radiologists

		mTRG[2]					
		1	**2**	**3**	**4**	**5**	**Total**
mrTRG[1]	1	2	2	0	0	0	4
	2	3	7	5	0	0	15
	3	3	19	11	5	4	42
	4	0	6	14	9	7	36
	5	0	3	1	2	21	27
	Total	8	37	31	16	32	124

mrTRG: magnetic resonance tumour regression grade
[1] Lead radiologist; [2] Second radiologist

DISCUSSION

This retrospective study aimed to investigate the correlation between the mrTRG and pTRG in patients with LRRC after treatment with induction chemotherapy and chemo(re)irradiation. A fair to moderate agreement between mrTRG and pTRG was observed, suggesting that the predictive value for pTRG is limited. Moreover, the interobserver agreement between the two radiologists was fair to moderate, indicating low reproducibility. However, there was a good agreement between the radiological assessment and pathology when the interval between MRI and surgery is short (≤7 weeks), and when assessed by the lead radiologist, mrTRG can safely predict good responders (PPV 95%).

Radiological evaluation of LRRC is often difficult due to postoperative changes in anatomy, previous radiotherapy, and the presence of fistula and/or abscesses. This hampers not only the initial assessment, but also makes evaluation of the mrTRG score more difficult. Despite those difficulties, the agreement between mrTRG and pTRG in this study (k = 0.30 and k = 0.25 for the lead radiologist and the other abdomen radiologist, respectively) was comparable with the literature on LARC (k = 0.24).[3]

Surgery for LRRC generally involves resection of multiple organs as well as soft tissue, bony, and vascular resections, resulting in complex procedures and the necessity of reconstructive surgery. This is associated with a high postoperative morbidity rate and an impaired quality of life.[10,15,16] Recently, it was reported that patients with LRRC with a pathological complete response have an excellent long-term survival.[13] Preoperative prediction of the pathological response potentially provides an opportunity to adopt

a non-operative treatment strategy in patients with a clinical complete response, which may be very valuable in the light of the complexity and impact on quality of life of LRRC surgery. To select patients with a clinical complete response, a high PPV is especially important, as a false-positive prediction can lead to undertreatment with possible disastrous consequences. In the present study, the mrTRG had a PPV for a good response of 95% when assessed by the lead radiologist; underestimation of the presence of residual tumour occurred in only one patient. This suggest that the mrTRG score has the potential to predict good responders.

However, in the present study overstaging was, as in LARC, much more frequent; in 17% of patients the presence of residual tumour was overestimated when using mrTRG.[17] In LARC, endoscopy and a digital exam may aid in assessing the response.[18] However, in LRRC, these diagnostic modalities are usually not sufficient due to the location and/or extent of the tumour and decisions therefore have to be made solely based on the assessment of the MRI. An MR grading system incorporating T2-weigthed as well as diffusion-weighted imaging (DWI) might be able to reduce overstaging and consequently improve the selection of complete responders. Although DWI has a greater vulnerability to susceptibility artifacts and careful interpretation of T2 shine-through effect is required, it has proven to improve the sensitivity of the mrTRG score without decreasing the specificity in restaging LARC.[19–21] Such a combined grading system has recently been proposed in patients with LARC and could be the focus of future research in LRRC.[22]

The interval between MRI and surgery may also play an important role in over- and understaging. As shown in this study, the agreement between mrTRG and pTRG was superior in cases with an interval of 7 weeks or less compared to the agreement in cases with an interval more than 7 weeks. This is consistent with previous studies that showed, in LARC, that a shorter interval between MRI and surgery resulted in a stronger association between the mrTRG and pTRG.[23] The length of interval may particularly play a role in mrTRG 3 cases. In these cases, a long interval may provide an opportunity for a continuation of response, or, although rare, progression of disease. Ideally, mrTRG should therefore be assessed shortly before surgery.

The interobserver variability between the radiologists was moderate when using the five-tier grading, which is comparable with what was found in a study performed by 35 radiologists assessing the mrTRG in patients with LARC.[1] However, when using the two-tier regression scale, the agreement was only fair. This indicates a suboptimal reproducibility of the mrTRG.

The level of agreement between the lead radiologist and the pTRG, and the other abdomen radiologist and the pTRG differed; the agreement was moderate for the lead radiologist, whereas this was fair for the other abdominal radiologist. Although both are experienced abdomen radiologists, the lead radiologist has specific expertise in LARC and LRRC and is the main radiologist responsible for the weekly LARC/LRRC multidisciplinary team (MDT) meeting. The presence of an MDT is crucial in the treatment of patients with colorectal cancer, as it improves their outcomes.[24] Moreover, MDT discussion improves the accuracy of MRI in staging rectal cancer.[25–27] It is reasonable to assume that more intensive involvement of the radiologist in the LARC/LRRC MDT improved the accuracy of the restaging assessments. For example, through participation in the MDT, the radiologist receives feedback from the discussion of the pathology of postoperative patients, strengthening the learning curve. This may explain the difference in agreement, in favour of the lead radiologist. Additionally, refining the definitions of the categories of tumour regression, especially in mucinous and fibrotic tumours, may contribute to improving the radiologist's performance.

This study has several limitations. mrTRG was only assessed by two radiologists. Ideally, this assessment would have been performed by a larger group. However, LRRC is rare and surgical treatment is centralised in only a small number of tertiary referral centres, and even in these centres the radiological expertise is usually limited to one or two radiologists. In addition, the interval between the MRI and surgery was long, which may have negatively influenced the agreement. Moreover, although pathological assessment is the gold standard for determining response, and Mandard provides a high accuracy in predicting prognosis, variable reproducibility has been reported.[28,29] The strength of this study is that this is the first study assessing mrTRG in patients with LRRC. Moreover, the size of this homogenous cohort of patients with LRRC is unique with a large series of patients analysed.

According to the present result, mrTRG can predict a good response after neoadjuvant treatment with chemotherapy and chemoradiotherapy for LRRC when assessed by an experienced, dedicated, and trained radiologist. However, the reproducibility of mrTRG between radiologists is limited and the agreement between mrTRG and pTRG is low in cases with a long interval between MRI and surgery. Therefore, mrTRG cannot simply be used as a predictor for pTRG and treatment decision-making during the MDT cannot yet be based on the mrTRG. Further studies are needed to evaluate the optimal timing of the MRI, the prognostic value of mrTRG, and the value of mrTRG in combination with other imaging modalities such as PET/CT in LRRC.

REFERENCES

1. Siddiqui MRS, Gormly KL, Bhoday J, et al. Interobserver agreement of radiologists assessing the response of rectal cancers to preoperative chemoradiation using the MRI tumour regression grading (mrTRG). *Clin Radiol*. 2016;71(9):854-862. doi:10.1016/j.crad.2016.05.005
2. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29(28):3753-3760. doi:10.1200/JCO.2011.34.9068
3. Sclafani F, Brown G, Cunningham D, et al. Comparison between MRI and pathology in the assessment of tumour regression grade in rectal cancer. *Br J Cancer*. 2017;117(10):1478-1485. doi:10.1038/bjc.2017.320
4. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569
5. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review. *Dis Colon Rectum*. 2016;59(2):148-156. doi:10.1097/DCR.0000000000000547
6. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Color Dis*. 2011;13(7):732-742. doi:10.1111/j.1463-1318.2009.02167.x
7. Vermaas M, Ferenschild F, Verhoef C, et al. Pre-operative radiotherapy improves outcome of multimodality treatment in recurrent rectal cancer. *Ann Surg Oncol*. 2006;11(S2):S108-S108. doi:10.1007/bf02524150
8. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Suppl 4):iv22-iv40. doi:10.1093/annonc/mdx224
9. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388
10. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y
11. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *Eur J Surg Oncol*. 2018;44(1):100-107. doi:10.1016/j.ejso.2017.11.013
12. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg*. 2018;105(4):447-452. doi:10.1002/bjs.10694
13. Voogt ELK, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4

14. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer.* 1994;73(11):2680-2686. doi:10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c

15. Glyn T, Frizelle F. Quality of life outcomes in patients undergoing surgery for locally recurrent rectal cancer. *Semin Colon Rectal Surg*. 2020;31(3). doi:10.1016/j.scrs.2020.100767

16. Esnaola NF, Cantor SB, Johnson ML, et al. Pain and quality of life after treatment in patients with locally recurrent rectal cancer. *J Clin Oncol*. 2002;20(21):4361-4367. doi:10.1200/JCO.2002.02.121

17. Lambregts DMJ, Boellaard TN, Beets-Tan RGH. Response evaluation after neoadjuvant treatment for rectal cancer using modern MR imaging: a pictorial review. *Insights Imaging*. 2019;10(1):15. doi:10.1186/s13244-019-0706-x

18. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: Characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum*. 2010;53(12):1692-1698. doi:10.1007/DCR.0b013e3181f42b89

19. Lambregts DMJ, Vandecaveye V, Barbaro B, et al. Diffusion-weighted MRI for selection of complete responders after chemoradiation for locally advanced rectal cancer: A multicenter study. *Ann Surg Oncol*. 2011;18(8):2224-2231. doi:10.1245/s10434-011-1607-5

20. Kim SH, Lee JM, Hong SH, et al. Locally advanced rectal cancer: Added value of diffusion-weighted MR imaging in the evaluation of tumor response to neoadjuvant chemo- and radiation therapy. *Radiology*. 2009;253(1):116-125. doi:10.1148/radiol.2532090027

21. Chandramohan A, Siddiqi UM, Mittal R, et al. Diffusion weighted imaging improves diagnostic ability of MRI for determining complete response to neoadjuvant therapy in locally advanced rectal cancer. *Eur J Radiol Open*. 2020;7:100223. doi:10.1016/j.ejro.2020.100223

22. Lee MA, Cho SH, Seo AN, et al. Modified 3-point mri-based tumor regression grade incorporating DWI for locally advanced rectal cancer. *Am J Roentgenol*. 2017;209(6):1247-1255. doi:10.2214/AJR.16.17242

23. West MA, Dimitrov BD, Moyses HE, et al. Timing of surgery following neoadjuvant chemoradiotherapy in locally advanced rectal cancer – A comparison of magnetic resonance imaging at two time points and histopathological responses. *Eur J Surg Oncol*. 2016;42(9):1350-1358. doi:10.1016/j.ejso.2016.04.003

24. Munro A, Brown M, Niblock P, Steele R, Carey F. Do Multidisciplinary Team (MDT) processes influence survival in patients with colorectal cancer? A population-based experience. *BMC Cancer*. 2015;15:686. doi:10.1186/s12885-015-1683-1

25. Yu L, Wang L, Tan Y, et al. Accuracy of magnetic resonance imaging in staging rectal cancer with multidisciplinary team: A single-center experience. *J Cancer*. 2019;10(26). doi:10.7150/jca.32685

26. Ye YJ, Shen ZL, Sun XT, et al. Impact of multidisciplinary team working on the management of colorectal cancer. *Chin Med J (Engl)*. 2012;125(2):172-177. doi:10.3760/cma.j.issn.0366-6999.2012.02.002

27. Swellengrebel HAM, Peters EG, Cats A, et al. Multidisciplinary discussion and management of rectal cancer: A population-based study. *World J Surg*. 2011;35:2125-2133. doi:10.1007/s00268-011-1181-9

28. Lindebjerg J, Hansborg N, Ploen J, Rafaelsen S, Jorgensen JCR, Jakobsen A. Factors influencing reproducibility of tumour regression grading after high-dose chemoradiation of locally advanced rectal cancer. *Histopathology*. 2011;59(1):18-21. doi:10.1111/j.1365-2559.2011.03888.x

29. Chetty R, Gill P, Govender D, et al. International study group on rectal cancer regression grading: Interobserver variability with commonly used regression grading systems. *Hum Pathol*. 2012;43(11):1917-1923. doi:10.1016/j.humpath.2012.01.020

CHAPTER 6

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 multivariable 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.

Conclusion

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 postoperative 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.

METHODS

Patients

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 either conducted 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 (25 Gy) or long-course (50 Gy) radiotherapy for LARC and re-irradiation (30 Gy) or long-course (50 Gy) 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 a 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 intraoperative radiation therapy (IORT) that was delivered as intraoperative electron beam radiotherapy (IOERT) in the CZE and as intraoperative 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 mobilised 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.

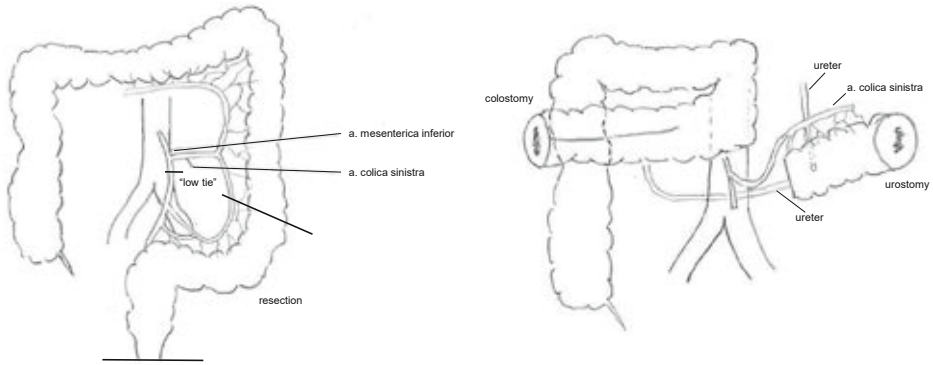

Figure 1 Schematic presentation of performing a colon conduit

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 hospitalisation, 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 radiological 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).

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 n = 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 ($p < 0.001$).

Table 1 Baseline characteristics colon conduit versus 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

Abbreviations: 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 versus ileal conduit

		Total (N=259) N (%)	Colon conduit (N=45) N (%)	Ileal conduit (N=214) N (%)	*p* value
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

Abbreviations: HIPEC = Hyperthermic intraperitoneal chemotherapy, IOBT = intraoperative brachytherapy, IOERT = intraoperative external beam radiotherapy, IORT= Intraoperative radiation therapy. NA = Not applicable

[a] Calculated as percentage of patient with synchronous metastasis.

Percentages may not add up to 100% due to rounding

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 ($p = 0.370$). 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 ($p = 0.256$).

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 3 Short-term general and surgical complications colon conduit versus ileal conduit

	Total (N=259) N (%)	Colon conduit (N=45) N (%)	Ileal conduit (N=214) N (%)	*p* value
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
Presacral 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

Table 4 Short-term urological complications colon conduit versus ileal conduit

	Total (N=259) N (%)	Colon conduit (N=45) N (%)	Ileal conduit (N=214) N (%)	*p* value
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)	

Abbreviations: NA = Not applicable.

[a] Percentage of anastomotic leakage is calculated of patients in which a specific anastomosis was performed.

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 versus ileal conduit

	Total (N=186) N (%)	**Colon conduit (N=44) N (%)**	**Ileal conduit (N=142) N (%)**	***p* value**
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 anastomoses[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)	

Abbreviations: NA = Not applicable.
[a] Percentage of anastomotic leakage is calculated of patients in which a specific anastomosis was performed.
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 hospitalisation.[8,18] In CZE, patients are frequently transferred to referring hospitals when they are clinically stable. This may have led to an underestimation of the hospital stay in patients treated in the CZE.

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 multivariable 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 metastases 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. Also, 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.

CONCLUSION

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.

REFERENCES

1. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol*. 2006;24(28):4620-4625. doi:10.1200/JCO.2006.06.7629
2. van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582. doi:10.1016/S1470-2045(11)70097-3
3. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. *Gut*. 2017;66(4):683-691. doi:10.1136/gutjnl-2015-310912
4. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer. *Ann Surg*. 2019;269(2):315-321. doi:10.1097/SLA.0000000000002528
5. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br J Surg*. 2018;105(6):650-657. doi:10.1002/bjs.10734
6. Russo P, Ravindran B, Katz J, Paty P, Guillem J, Cohen AM. Urinary diversion after total pelvic exenteration for rectal cancer. *Ann Surg Oncol*. 1999;6(8):732-738. doi:10.1007/s10434-999-0732-x
7. Fujisawa M, Nakamura T, Ohno M, et al. Surgical management of the urinary tract in patients with locally advanced colorectal cancer. *Urology*. 2002;60(6):650-657. doi:10.1016/S0090-4295(02)01987-8
8. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary Diversions after Cystectomy: The Association of Clinical Factors, Complications and Functional Results of Four Different Diversions. *Eur Urol*. 2008;53(4):834-842. doi:10.1016/j.eururo.2007.09.008
9. Bricker E. Bladder substitution after pelvic evisceration. *Surg Clin N Amer*. 1950;30(5):1511-1521. doi:10.1016/s0039-6109(16)33147-4.
10. Schmidt JD, Hawtrey CE, Buchsbaum HJ. Transverse colon conduit: a preferred method of urinary diversion for radiation treated pelvic malignancies. *J Urol*. 1975;113(3):308-313. doi:10.1016/S0022-5347(17)59469-0
11. Meijer RP, Mertens LS, Meinhardt W, Verwaal VJ, Dik P, Horenblas S. The colon shuffle: A modified urinary diversion. *Eur J Surg Oncol*. 2015;41(9):1264-1268. doi:10.1016/j.ejso.2015.02.007
12. Teixeira SC, Ferenschild FT, Solomon MJ, et al. Urological leaks after pelvic exenterations comparing formation of colonic and ileal conduits. *Eur J Surg Oncol*. 2012;38(4):361-366. doi:10.1016/j.ejso.2011.12.002
13. Bolmstrand B, Nilsson PJ, Holm T, Buchli C, Palmer G. Patterns of complications following urinary tract reconstruction after multivisceral surgery in colorectal and anal cancer. *Eur J Surg Oncol*. 2018;44(10):1513-1517. doi:10.1016/j.ejso.2018.06.017

14. Roth JD, Koch MO. Metabolic and Nutritional Consequences of Urinary Diversion Using Intestinal Segments to Reconstruct the Urinary Tract. *Urol Clin North Am*. 2018;45(1):19-24. doi:10.1016/j.ucl.2017.09.007

15. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae.

16. Brown KGM, Solomon MJ, Latif ER, et al. Urological complications after cystectomy as part of pelvic exenteration are higher than that after cystectomy for primary bladder malignancy. *J Surg Oncol*. 2017;115(3):307-311. doi:10.1002/jso.24511

17. Stotland PK, Moozar K, Cardella JA, et al. Urologic complications of composite resection following combined modality treatment of colorectal cancer. *Ann Surg Oncol*. 2009;16(10):2759-2764. doi:10.1245/s10434-009-0663-6

18. Lee DJ, Tyson MD, Chang SS. Conduit Urinary Diversion. *Urol Clin North Am*. 2018;45(1):25-36. doi:10.1016/j.ucl.2017.09.006

19. Yang Y, Wang G, He J, Zhang J, Xi J, Wang F. High tie versus low tie of the inferior mesenteric artery in colorectal cancer: A meta-analysis. *Int J Surg*. 2018;52:20-24. doi:10.1016/j.ijsu.2017.12.030

20. Fujii S, Ishibe A, Ota M, et al. Randomized clinical trial of high versus low inferior mesenteric artery ligation during anterior resection for rectal cancer. *BJS Open*. 2018;2(4):195-202. doi:10.1002/bjs5.71

21. Van der Aa F, Joniau S, Van Den Branden M, Van Poppel H. Metabolic Changes after Urinary Diversion. *Adv Urol*. 2011;2011:764325. doi:10.1155/2011/764325

CHAPTER 7

INTRAOPERATIVE ELECTRON BEAM RADIATION THERAPY (IOERT) VERSUS HIGH-DOSE-RATE INTRAOPERATIVE BRACHYTHERAPY (HDR-IORT) IN PATIENTS WITH AN R1 RESECTION FOR LOCALLY ADVANCED OR LOCALLY RECURRENT RECTAL CANCER

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ABSTRACT

Introduction

Intraoperative radiation therapy (IORT), delivered by intraoperative electron beam radiation therapy (IOERT) or high-dose-rate intraoperative brachytherapy (HDR-IORT), may reduce the local recurrence rate in patients with locally advanced and locally recurrent rectal cancer (LARC and LRRC, respectively). The aim of this study was to compare the oncological outcomes between both IORT modalities in patients with LARC or LRRC who underwent a microscopic irradical (R1) resection.

Methods

All consecutive patients who received IORT because of an R1 resection of LARC or LRRC between 2000 and 2016 in two tertiary referral centres were included. In LARC, a resection margin of ≤2 mm was considered R1. A resection margin of 0 mm was considered R1 in LRRC.

Results

In total, 215 patients with LARC were included, of whom 151 (70%) received IOERT and 64 (30%) received HDR-IORT; in addition, 158 patients with LRRC were included, of whom 112 (71%) received IOERT and 46 (29%) received HDR-IORT. After multivariable analyses, the overall survival was not significantly different between the two IORT modalities. The local recurrence-free survival was significantly longer in patients treated with HDR-IORT, both in LARC (hazard ratio [HR] 0.496; 95% CI 0.253-0.973; p = 0.041;) and LRRC (HR 0.567; 95% CI 0.349-0.920; p = 0.021). In patients with LARC, major postoperative complications were similar for both IORT modalities (IOERT, 30%; HDR-IORT, 27%), whereas in patients with LRRC, the incidence of major postoperative complications was higher after HDR-IORT (IOERT, 26%; HDR-IORT, 46%).

Conclusion

This study showed a significantly better local recurrence-free survival in favour of HDR-IORT in patients with an R1 resection for LARC or LRRC. Optimization of the IOERT technique seems warranted.

INTRODUCTION

Achievement of a resection with clear margins (R0 resection) is the most important goal in the treatment of locally advanced and locally recurrent rectal cancer (LARC and LRRC, respectively), as it offers the best prognosis in terms of recurrence-free and overall survival**.** Patients at risk for a resection without clear margins (R1 resection) are offered neoadjuvant treatment, consisting of external beam radiation therapy (EBRT) with a dose of 45 Gy to 50 Gy with concomitant chemotherapy, as this has been shown to be effective in local downstaging of the tumour and to increase the likelihood of achieving an R0 resection, thereby reducing the risk of local relapse.[1,2] In addition, in patients at risk for an R1 resection, multivisceral resections are usually necessary, requiring extensive expertise and thus centralization of care. Nevertheless, an R1 resection occurs in approximately 10 to 20% of patients with LARC and 40% of those with LRRC.[3–5] Preoperative radiation therapy with a dose of 45 Gy to 50 Gy cannot compensate for an R1 resection.[6] A dose in excess of 60 Gy may be able to eradicate microscopic residual disease; however, administration of radiation therapy at a dose higher than 50 Gy is associated with excessive toxicity, because this level of exposure exceeds the normal-tissue tolerance, which prohibits increasing the EBRT dosage.[7–9]

Intraoperative radiation therapy (IORT), the delivery of a single boost of radiation therapy during surgery, has the ability to deliver a higher dose to the areas at highest risk for tumour involvement while at the same time allowing dose-limiting structures and organs such as the ureters and small intestine to be positioned outside the radiation field, thus mitigating the problem of increased toxicity resulting from the application of a higher dosage of radiation therapy. The biological equivalent of one single fraction IORT equals 1.5 to 2.5 times the dose delivered by conventional fractionation.[8] Prior studies have suggested that use of IORT in patients with a positive microscopically circumferential resection margin reduces local recurrence rates.[10–12]

IORT can be delivered through different modalities, including intraoperative electron beam radiation therapy (IOERT) and high-dose-rate intraoperative brachytherapy (HDR-IORT), the former being the most frequently used based on the literature.[12,13] The advantages of IOERT in relation to HDR-IORT include shorter set-up and treatment times and a more homogeneous radiation dose to be delivered throughout the tissue depth. An important limitation of IOERT, however, is that the applicators are poorly suited to curved areas or narrow spaces. In contrast, HDR-IORT is a more time-consuming procedure, but the use of flexible applicators allows for application to any curved surface. In addition, with HDR-IORT, it is possible to irradiate a larger area, and

the steeper dose gradient between the target surface and the reference depth leads to a more concentrated dose to be delivered at the surface of the target area.[14]

This study aimed to compare the long-term oncological outcomes between patients who received either IOERT or HDR-IORT after an R1 resection for LARC or LRRC.

METHODS

Patients

All consecutive patients with LARC or LRRC who underwent a resection between 2000 and 2016 in the Catharina Hospital Eindhoven (CZE) or Erasmus MC Cancer Institute (EMC) were identified from a prospectively maintained database. We included all patients with an R1 resection after undergoing intentionally curative surgery in whom IORT was delivered by either IOERT or HDR-IORT. For the purpose of this study, in patients with LARC, an R1 resection was defined as a resection with involved or close margins (≤2 mm), as this margin was the cut-off value to deliver IORT based on a study by Nagtegaal et al.[15] In patients with LRRC, an R1 resection was defined as a resection with involved margins, in accordance with the literature.[16] Patients with peritoneal metastases, as well as patients who did not receive neoadjuvant radiation therapy, were excluded. The potential indication for IORT was determined during a multidisciplinary tumour board meeting, which included experienced surgeons, medical oncologists, radiation oncologists, and radiologists. The study was approved by both institutional local medical ethics committees (CZE registration number W19.031; EMC registration number MEC-2017-449). Follow-up was completed until January 1, 2020.

Neoadjuvant treatment and Surgical procedures

All patients received neoadjuvant radiation therapy, which was delivered in one of the two tertiary referral centres or in a referring hospital. In patients with LARC, neoadjuvant radiation therapy consisted of either short-course (25 Gy in five fractions of 5 Gy) or long-course (45-50.4 Gy in fractions of 1.8-2 Gy) EBRT. In patients with LRRC, neoadjuvant radiation therapy consisted of either long-course EBRT (45-50.4 Gy in fractions of 1.8-2 Gy) or reirradiation (30 Gy in fractions of 2 Gy). In case of long-course radiation therapy or reirradiation, concomitant capecitabine was administered (825 mg/m2 twice daily on radiation therapy days).

Induction chemotherapy, generally CAPOX (capecitabine, oxaliplatin) or FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin), was administered to a minority of patients before or after radiation therapy treatment. This was usually to treat and observe the

biological behaviour of synchronous metastases; induction chemotherapy was not considered the standard of care during the study period. After patients finished the neoadjuvant treatment course, pelvic magnetic resonance imaging was performed to assess the resectability.

The extent of pelvic surgery depended on the location of the tumour and the involvement of adjacent structures and was performed by experienced surgical oncologists. For specific reconstructive procedures, other specialists such as urologists or plastic surgeons were involved.

Intraoperative radiation therapy

In both referral centres, IORT was delivered in cases with clinically suspected narrow or involved margins or in cases with narrow or microscopically involved margins, based on assessment of frozen sections.

At the CZE, all patients who underwent surgery for LARC or LRRC were scheduled in an operating room with IORT facilities. The IORT was delivered by IOERT. In earlier years of the study, this was delivered using an Elekta SL-25 linear accelerator (Elekta Oncology Systems, Stockholm, Sweden).[17] From 2016 onward, IORT was delivered using a Mobetron 2000 linear accelerator (IntraOp Inc, Sunnyvale CA, USA). Generally, the IORT dose was 10 or 12.5 Gy. The dose was prescribed to the 90% isodose surface, generally ranging from 12 mm to 18 mm in depth, with energies ranging from 6 MeV to 8 MeV using a 30º to 45º beveled applicator of 5 cm to 7 cm in length. The rationale for the dosing strategy depended on the target area, the normal tissue at risk, and the anatomy of the patient.

At the EMC, all patients who underwent surgery for LARC or LRRC and in whom a resection margin of ≤ 2 mm was expected were planned in an operating room with IORT facilities. The IORT was delivered by high-dose-rate brachytherapy using a flexible intraoperative template (i.e. the FIT-procedure), which has been described previously.[18] In short, HDR-IORT was delivered using a flexible 5 mm-thick pad made of flexible silicon, with a dose of 10 Gy prescribed at a depth of 1 cm from the applicator surface. The size and shape were adjusted according to the surface of the area at risk.

Follow-up

Follow-up was performed according to the Dutch guidelines for colorectal cancer; carcinoembryonic antigen (CEA) measurements were performed four times a year during the first two years and twice a year during years 3 to 5. Ultrasonography of the liver was performed twice a year during the first two years and once a year

thereafter. In case of an elevated CEA concentration or new ultrasonography findings, a thoracoabdominal computed tomography (CT) scan or a fluorodeoxyglucose (FDG) positron emission tomography (PET)/CT scan was performed. At the EMC, ultrasonography was replaced by thoracoabdominal CT scan for the majority of patients with LRRC from 2011 onward.

Study endpoints and Statistics

Endpoints were overall survival (OS), local recurrence-free survival (LRFS), and the incidence of major postoperative complications. Overall survival was calculated from the date of surgery until the date of death from any cause, or was censored at the last follow-up. Local recurrence-free survival was calculated from the date of surgery until the date local recurrence was detected by imaging or histology, or was censored at the last follow-up or death. Postoperative complications were graded according to the Clavien-Dindo classification.[19] Major complications were defined as a complication of grade 3 or greater.

Continuous data were reported as medians and interquartile ranges (IQRs) and categorical data as counts and percentages. Group comparisons were performed using Mann-Whitney *U*, Chi-square, or Fisher exact tests, as appropriate. Survival analyses were performed using the Kaplan-Meier method, and data were compared using log-rank tests. Two-sided p values < 0.05 were considered statistically significant. Cox proportional hazards modeling was performed for multivariable analysis using the stepwise backward selection option. In addition to the type of IORT, variables identified with a p value < 0.50 in the univariable analysis were included in the multivariable analysis. Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM Corp, Armonk, New York, USA).

RESULTS

Locally advanced rectal cancer

In total, 1865 patients underwent a resection for LARC in one of the two tertiary referral centres between 2000 and 2016. An R1 resection was noted in 347 of 1865 patients, of whom 218 received IORT. Three patients were excluded from further analysis because of peritoneal metastases (two patients) or for having received no neoadjuvant radiation therapy (one patient). In 151 of the 215 included patients (70%), IORT was delivered by IOERT, whereas 64 patients (30%) received HDR-IORT. Patient, tumour, and treatment characteristics are summarized in *Table 1.* Most patients (73%) were diagnosed with a T4 tumour, and neoadjuvant treatment generally consisted of long-course radiation

therapy (91% of patients). Only a minority of patients (16%) were diagnosed with synchronous metastases. Most patients (61%) underwent a multivisceral resection. The procedure time was significantly longer in patients who received HDR-IORT compared with IOERT ($p < 0.001$).

The HDR-IORT was delivered with a prescribed dose of 10 Gy in all patients, effectively leading to an average dose of ±17 Gy at the target surface. The median treated area was not known. IOERT was delivered at a dose of 10 Gy at the 90% isodose surface in 130 patients (86%), a dose of 12.5 Gy in 20 patients (13%), and a dose of 15 Gy in one patient (1%). The median prescription depth (D90) was 14 mm (IQR 12-15 mm), with a median treated area of 28 cm^2 (IQR 27-32 cm^2).

Table 1 Patient, tumour and surgical characteristics in patients with locally advanced rectal cancer

		Total (N=215) N (%)	IOERT (N=151) N (%)	HDR-IORT (N=64) N (%)	*p* value
Gender	Female	64 (30)	46 (31)	18 (28)	0.732
	Male	151 (70)	105 (70)	46 (72)	
Age at resection	<70	156 (73)	105 (70)	51 (80)	0.127
	≥70	59 (27)	46 (31)	13 (20)	
Clinical tumour stage	cT3	57 (27)	35 (23)	22 (34)	0.094
	cT4	157 (73)	115 (77)	42 (66)	
Synchronous metastases	No	180 (84)	129 (85)	51 (80)	0.297
	Yes	35 (16)	22 (15)	13 (20)	
Neoadjuvant chemotherapy	No	196 (91)	139 (92)	57 (89)	0.480
	Yes	19 (9)	12 (8)	7 (11)	
Neoadjuvant radiation therapy	5x5 Radiation therapy	20 (9)	14 (9)	6 (9)	0.981
	(Chemo)radiation therapy	195 (91)	137 (91)	58 (91)	
Interval radiation therapy - surgery (weeks)	<8	31 (15)	21 (14)	10 (16)	0.137
	8-12	98 (46)	63 (42)	35 (55)	
	>12	85 (40)	66 (44)	19 (30)	

Table 1 (Continued)

		Total (N=215) N (%)	IOERT (N=151) N (%)	HDR-IORT (N=64) N (%)	*p* value
Surgical procedure	LAR	46 (21)	36 (24)	10 (16)	0.362
	APR	37 (17)	24 (16)	13 (20)	
	Multivisceral resection	132 (61)	91 (60)	41 (64)	
Procedure time (hour)	0-3	16 (8)	16 (11)	0 (0)	<0.001
	3-5	90 (43)	88 (61)	2 (3)	
	>5	102 (49)	40 (28)	62 (97)	
Adjuvant therapy	No	189 (88)	129 (86)	60 (94)	0.106
	Yes	25 (12)	21 (14)	4 (6)	
Pathological tumour stage	pT1/2	4 (2)	2 (1)	2 (3)	0.104
	pT3	128 (60)	96 (64)	32 (50)	
	pT4	82 (38)	52 (35)	30 (47)	
Pathological nodal stage	pN0	107 (50)	74 (49)	33 (52)	0.918
	pN1	70 (33)	50 (33)	20 (32)	
	pN2	36 (17)	26 (17)	10 (16)	
Resection margin, mm	0	93 (43)	64 (42)	29 (45)	0.844
	> 0 to ≤ 1	73 (34)	51 (34)	22 (34)	
	> 1 to ≤ 2	49 (23)	36 (24)	13 (20)	
Complications	Clavien-Dindo 0-II	140 (71)	93 (71)	47 (73)	0.665
	Clavien-Dindo III-V	56 (29)	39 (30)	17 (27)	

Abbreviations: APR = abdominoperineal resection, HDR-IORT = high-dose-rate intraoperative brachytherapy, IOERT = intraoperative electron beam radiation therapy, LAR = low anterior resection. Missing data were not included in group comparison. Percentages might not sum up to 100 owing to rounding.

Locally advanced rectal cancer – survival outcomes

The median OS was 48 months (IQR 19-111 months) for patients treated with HDR-IORT and 41 months (IQR 21-137 months) for patients treated with IOERT. For patients who received HDR-IORT, the 3-year and 5-year OS rates were 61% and 47%, respectively. This was not significantly different compared with patients who received IOERT (3-year and 5-year OS rates, 58% and 40%, respectively; $p = 0.980$). Median LRFS was not reached. The 3-year and 5-year LRFS rates for patients who received HDR-IORT were 82% and 79%, respectively. For patients who received IOERT, these rates were 71% and 65%, respectively ($p = 0.105$; *Figure 1)*.

Results of the univariable and multivariable analyses are shown in *Table* 2. After multivariable analysis, the IORT modality had no significant association with OS, whereas age, time between radiation therapy and surgery, pathological tumour and lymph node stage (pT and pN, respectively), and resection margin did. For LRFS, multivariable analysis showed a significantly favourable LRFS in patients treated with HDR-IORT compared with those treated with IOERT (HR 0.504; 95% CI 0.254-0.999; $p = 0.050$). In addition, the time between radiation therapy and surgery, pT stage, and resection margin were significantly related to the development of a local recurrence.

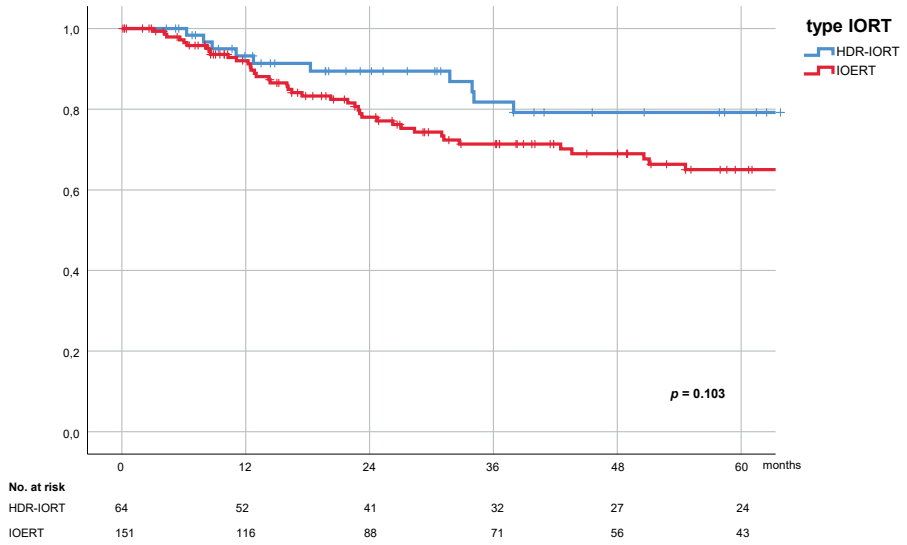

Figure 1 Kaplan-Meier curve for local recurrence-free survival in patients with locally advanced rectal cancer

Table 2 Univariable and multivariable analysis for overall and local recurrence-free survival in patients with locally advanced rectal cancer

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Type of IORT												
IOERT	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
HDR-IORT	1.002	0.712-1.411	0.989	1.096	0.757-1.586	0.627	0.579	0.297-1.126	0.108	0.504	0.254-0.999	**0.050**
Age												
<70	1.00	Ref		1.00	Ref		1.00	Ref				
≥70	1.443	1.026-2.031	0.035	2.131	1.478-3.073	**<0.001**	0.585	0.285-1.201	0.144			
Gender												
Male	1.00	Ref					1.00	Ref				
Female	1.251	0.894-1.752	0.192				1.486	0.838-2.636	0.175			
Clinical tumour stage												
T3	1.00	Ref					1.00	Ref				
T4	1.082	0.755-1.550	0.669				1.273	0.667-2.432	0.465			
Synchronous metastases												
No	1.00	Ref					1.00	Ref				
Yes	1.267	0.829-1.937	0.275				1.358	0.680-2.714	0.386			
Neoadjuvant chemotherapy												
No	1.00	Ref					1.00	Ref				
Yes	1.352	0.778-2.347	0.284				2.241	1.007-4.984	0.048			

Table 2 (Continued)

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Neoadjuvant radiation therapy												
5x5 Radiation therapy	1.00	Ref					1.00	Ref				
(Chemo)radiation therapy	0.666	0.390-1.135	0.135				0.538	0.229-1.265	0.155			
Time between RT and surgery, wk												
<8	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
8-12	1.056	0.662-1.685	0.818	0.952	0.592-1.530	0.838	1.985	0.688-5.721	0.204	2.187	0.749-6.383	0.152
>12	1.572	0.971-2.545	0.066	1.721	1.049-2.822	**0.032**	2.901	1.001-8.408	0.050	3.168	1.075-9.339	**0.037**
Type of surgery												
LAR	1.00	Ref					1.00	Ref				
APR	0.781	0.475-1.285	0.330				0.683	0.243-1.920	0.469			
Multivisceral resection	0.766	0.519-1.132	0.181				1.295	0.624-2.686	0.487			
Adjuvant therapy												
No	1.00	Ref					1.00	Ref				
Yes	1.012	0.619-1.655	0.962				1.518	0.713-3.232	0.279			
Pathological tumour stage												
T1-3	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
T4	2.082	1.513-2.865	<0.001	1.890	1.345-2.656	**<0.001**	2.768	1.591-4.816	<0.001	2.386	1.308-4.350	**0.005**

Table 2 (Continued)

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Pathologic lymph node stage												
N0	1.00	Ref		1.00	Ref		1.00	Ref				
N1	1.215	0.850-1.738	0.285	1.385	0.955-2.008	0.086	1.134	0.612-2.101	0.690			
N2	1.621	1.058-2.483	0.026	2.568	1.626-4.058	**<0.001**	1.414	0.659-3.033	0.374			
Resection margin, mm												
0	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
> 0 to ≤ 1 mm	0.624	0.438-0.889	0.009	0.546	0.372-0.803	**0.002**	0.541	0.294-0.993	0.047	0.552	0.286-1.065	0.076
> 1 to ≤ 2	0.488	0.315-0.756	0.001	0.402	0.248-0.652	**<0.001**	0.286	0.119-0.688	0.005	0.324	0.129-0.811	**0.016**
Complications												
Clavien-Dindo 0-II	1.00	Ref					1.00	Ref				
Clavien-Dindo III-V	0.996	0.689-1.439	0.982				0.984	0.511-1.929	0.984			

Abbreviations: APR = abdominoperineal resection, HDR-IORT = high-dose-rate intraoperative brachytherapy, HR = hazard ratio, IOERT = intraoperative electron beam radiation therapy, LAR = low anterior resection, RT = radiation therapy.

All variables in the univariable analysis with a p value < 0.50 were used in the multivariable analysis. For the multivariable analysis, only IORT and the variables with $p < 0.05$ are shown.

Locally recurrent rectal cancer

In total, 587 patients underwent a resection for LRRC in one of the two tertiary referral centres between 2000 and 2016. Of these 587 patients, 196 had an R1 resection, of whom 161 patients received IORT. Three patients were excluded from further analysis; one patient had peritoneal metastases, and two patients did not receive neoadjuvant radiation therapy. Of the 158 patients receiving IORT, 112 (71%) received IOERT and 46 patients (29%) received HDR-IORT. Patient, tumour, and treatment characteristics are shown in *Table 3*. Patients who received HDR-IORT received neoadjuvant (chemo)radiation therapy instead of (chemo)reirradiation more often than patient who received IOERT (p = 0.001). The interval between the end of neoadjuvant radiation therapy and surgery was significantly shorter in patients who received HDR-IORT than in patients who received IOERT (p = 0.001), but the procedure time was significantly longer (p < 0.001).

The HDR-IORT was delivered at a dose of 10 Gy in all patients, effectively leading to an average dose of ± 17 Gy at the target surface. The median treated area was not known. IOERT was delivered at a dose of 10 Gy at the 90% isodose surface in the majority of patients (n = 67, 60%), and in 45 patients (40%) 12.5 Gy was delivered. The prescription depth (D90) was 14 mm (IQR 12-20 mm), with a median treated area of 32 cm^2 (IQR 27-39 cm^2).

Locally recurrent rectal cancer – survival outcomes

The median OS was 28 months (IQR 17-43 months) for patients treated with HDR-IORT and 31 months (IQR 12-52 months) for patients treated with IOERT. The 3-year and 5-year OS rates were 39% and 12%, respectively, for patients who received HDR-IORT, which was not significantly different compared with patients who received IOERT (3-year and 5-year OS rates of 44% and 18%, respectively; p = 0.747). The median LRFS was 19 months (IQR 12-27 months) for patients treated with HDR-IORT and 14 months (IQR 12-16 months) for patients treated with IOERT. The 3-year and 5-year LRFS rates for patients who received HDR-IORT were 38% and 34%, respectively. For patients who received IOERT, these were 29% and 19%, respectively (p = 0.139; *Figure 2)*.

Table 4 shows the results of the univariable and multivariable analyses. As neoadjuvant radiation therapy for the primary tumour and the recurrent tumour were strongly correlated, only neoadjuvant radiation therapy for the primary tumour was included in the multivariable analysis. After multivariable analysis, the IORT modality had no significant association with OS, whereas age, and N-stage of the primary tumour did. For LRFS, multivariable analysis revealed a significantly favourable LRFS in patients treated with HDR-IORT compared with patients treated with IOERT (HR 0.567; 95% CI 0.349-0.920; p = 0.021). In addition, the pT stage and pN stage of the primary tumour were significantly related to the development of a local recurrence.

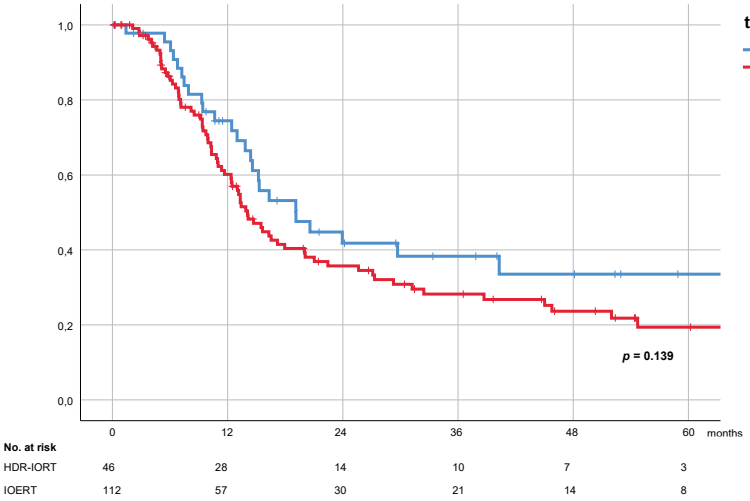

Figure 2 Kaplan-Meier curve for local recurrence-free survival in patients with locally recurrent rectal cancer

Table 3 Patient, tumour, and surgical characteristics in patients with locally recurrent rectal cancer

		Total (N=158) N (%)	IOERT (N=112) N (%)	HDR-IORT (N=46) N (%)	*p* value
Gender	Female	54 (34)	38 (34)	16 (35)	0.918
	Male	104 (66)	74 (66)	30 (65)	
Age at resection	<70	122 (77)	88 (79)	34 (74)	0.526
	≥70	36 (23)	24 (21)	12 (26)	
Clinical tumour stage, primary tumour	cT1-2	28 (18)	17 (16)	11 (24)	0.209
	cT3-4	128 (82)	93 (85)	35 (76)	
Clinical nodal stage, primary tumour	cN0	76 (49)	52 (47)	24 (52)	0.849
	cN1	50 (32)	36 (33)	14 (30)	
	cN2	30 (19)	22 (20)	8 (17)	
History metastases	Yes	21 (14)	13 (12)	8 (17)	0.400
	No	131 (86)	93 (88)	38 (83)	
Neoadjuvant treatment, primary tumour	None	67 (42)	39 (35)	28 (61)	0.008
	5x5 Radiation therapy	48 (30)	40 (35)	8 (17)	
	(Chemo) radiation therapy	43 (27)	33 (30)	10 (22)	

Table 3 (Continued)

		Total (N=158) N (%)	IOERT (N=112) N (%)	HDR-IORT (N=46) N (%)	*p* value
Surgical procedure, primary tumour	Local excision	5 (3)	3 (3)	2 (4)	0.670
	(Recto) sigmoid resection	15 (10)	9 (8)	6 (13)	
	LAR	82 (52)	60 (54)	22 (48)	
	APR	56 (35)	40 (36)	16 (35)	
Synchronous metastases	Yes	21 (13)	14 (13)	7 (15)	0.648
	No	137 (87)	98 (88)	39 (85)	
Neoadjuvant chemotherapy recurrence	Yes	28 (18)	22 (20)	6 (13)	0.324
	No	130 (82)	90 (80)	40 (87)	
Neoadjuvant radiation therapy recurrence	5x5 Radiation therapy	4 (3)	1 (1)	3 (7)	0.001
	(Chemo) radiation therapy	56 (35)	32 (29)	24 (52)	
	(Chemo) reirradiation	98 (62)	79 (71)	19 (41)	
Interval radiation therapy – surgery, wk	<8	30 (20)	13 (13)	17 (39)	0.001
	8-12	65 (44)	52 (50)	13 (30)	
	>12	53 (36)	39 (38)	14 (32)	
Surgical procedure	LAR	18 (11)	11 (10)	7 (15)	0.112
	APR	15 (10)	7 (6)	8 (17)	
	Multivisceral resection	108 (68)	81 (72)	27 (58)	
	Nonvisceral resection	17 (11)	13 (12)	4 (9)	
Procedure time, h	0-3	2 (1)	2 (2)	0 (0)	<0.001
	3-5	28 (19)	27 (26)	1 (2)	
	>5	120 (80)	76 (72)	44 (98)	
Adjuvant therapy	None	153 (100)	107 (100)	46 (100)	-
Complications	Clavien-Dindo 0-II	107 (68)	82 (74)	25 (54)	0.017
	Clavien-Dindo III-V	50 (32)	29 (26)	21 (46)	

Abbreviations: APR = abdominoperineal resection, HDR-IORT = high-dose-rate intraoperative brachytherapy, IOERT = intraoperative electron beam radiotherapy, LAR = low anterior resection. Missings not included in group comparison. Percentages may not sum up to 100 owing to rounding.

Table 4 Uni- and multivariable analysis for overall and local recurrence free survival in patients with locally recurrent rectal cancer

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Type of IORT												
IOERT	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
HDR-IOBT	1.062	0.737-1.531	0.747	1.168	0.792-1.722	0.433	0.711	0.451-1.120	0.141	0.567	0.349-0.920	**0.021**
Age												
<70	1.00	Ref		1.00	Ref		1.00	Ref				
≥70	1.753	1.191-2.581	0.004	1.942	1.301-2.900	**0.001**	1.476	0.916-2.379	0.110			
Gender												
Male	1.00	Ref					1.00	Ref				
Female	1.013	0.715-1.435	0.942				0.787	0.513-1.207	0.272			
Pathologic tumour stage, primary tumour												
T3	1.00	Ref					1.00	Ref		1.00	Ref	
T4	0.952	0.615-1.472	0.824				0.586	0.366-0.937	0.026	0.564	0.339-0.936	**0.027**
Pathologic lymph node stage, primary tumour												
N0	1.00	Ref		1.00	Ref		1.00	Ref		1.00	Ref	
N1	1.335	0.906-1.967	0.144	1.236	0.820-1.864	0.311	0.908	0.567-1.456	0.690	0.986	0.602-1.616	0.955
N2	1.820	1.165-2.842	0.008	1.879	1.199-3.001	**0.006**	1.914	1.135-3.229	0.015	2.099	1.228-3.588	**0.007**
History metastases												
No	1.00	Ref					1.00	Ref				

Table 4 (Continued)

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
Yes	1.542	0.954-2.492	0.077				1.070	0.569-2.012	0.834			
Neoadjuvant therapy, primary tumour												
None	1.00	Ref					1.00	Ref				
5x5 Radiation therapy	1.346	0.904-2.003	0.143				1.666	1.035-2.682	0.036			
Chemo)radiation therapy	1.594	1.046-2.428	0.030				1.932	1.183-3.153	0.008			
Surgery, primary tumour												
APR	1.00	Ref					1.00	Ref				
Local excision	1.219	0.446-3.332	0.699				0.886	0.272-2.890	0.841			
Rectosigmoid/LAR	1.279	0.460-3.559	0.637				0.886	0.584-1.346	0.572			
Synchronous metastases												
No	1.00	Ref					1.00	Ref				
Yes	1.220	0.751-1.981	0.423				0.971	0.530-1.778	0.924			
Neoadjuvant chemotherapy												
No	1.00	Ref					1.00	Ref				
Yes	1.191	0.765-1.854	0.438				1.447	0.891-2.350	0.135			
Neoadjuvant radiation therapy												
5x5 Radiation therapy	1.00	Ref					1.00	Ref				
(Chemo)radiation therapy	1.139	0.354-3.666	0.828				0.539	0.164-1.769	0.308			

Table 4 (Continued)

	Overall Survival						Local recurrence-free survival					
Variable	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**	**HR**	**95% CI**	***p* value**
(Chemo)reirradiadtion	1.512	0.475-4.815	0.484				0.922	0.288-2.950	0.891			
Time between RT and surgery, wk												
<8	1.00	Ref					1.00	Ref				
8-12	1.120	0.705-1.780	0.631				1.556	0.865-2.798	0.140			
>12	1.399	0.860-2.276	0.176				1.890	1.029-3.478	0.040			
Type of surgery												
LAR	1.00	Ref					1.00	Ref				
APR	0.807	0.380-1.711	0.575				1.143	0.476-2.748	0.765			
Multivisceral resection	0.923	0.556-1.532	0.755				1.226	0.631-2.381	0.548			
Non visceral resection	1.000	0.509-1.963	1.000				0.875	0.355-2.155	0.771			
Complications												
Clavien-Dindo 0-II	1.00	Ref					1.00	Ref				
Clavien-Dindo III-V	1.399	0.978-2.001	0.066				0.738	0.466-1.170	0.197			

Abbreviations: APR = abdominoperineal resection, HDR-IORT = high-dose-rate intraoperative brachytherapy, HR = hazard ratio, IOERT = intraoperative electron beam radiation therapy, LAR = low anterior resection, RT = radiotherapy.

All variables in the univariable analysis with a p value < 0.50 were used in the multivariable analysis. For the multivariable analysis, only IORT and the variables with $p < 0.05$ are shown.

Complications

Of the 215 patients with LARC, data on postoperative complications were available in 196 cases (91%). Major complications were comparable between the two groups, as 30% of patients treated with IOERT and 27% of patients treated with HDR-IORT had at least one complication with a Clavien-Dindo grade ≥ 3 ($p = 0.665$). In patients who experienced a major complication, the most common were presacral abscess (27%), bleeding (11%), abdominal wound dehiscence with evisceration (11%), intraabdominal abscess (9%), perineal wound necrosis (5%), leakage of the ureter or bladder reconstruction (5%), anastomotic leakage (5%), and ureter stenosis (5%) (*Supplementary Table 1*)**.** In-hospital mortality was observed in 2 of 151 patients (1%) in the IOERT group, whereas no in-hospital mortality was observed in the HDR-IORT group ($p = 0.546$).

Of the 158 patients with LRRC, data on postoperative complications were available in 157 cases (99%). In patients treated with HDR-IORT, a significantly greater number of major complications was observed compared with patients treated with IOERT (46% and 26%, respectively; $p = 0.017$). In patients who experienced a major complication, the most common were presacral abscess (26%), leakage of the ureter or bladder reconstruction (12%), abdominal wound dehiscence with evisceration (8%), and intraabdominal abscess (6%) (*Supplementary Table 2*). In-hospital mortality was observed in 4 of 112 patients (4%) in the IOERT group and in 1 of 46 patients (2%) in the HDR-IORT group ($p > 0.999$).

DISCUSSION

This retrospective study of data from two large tertiary referral centres showed a favourable LRFS for patients treated with HDR-IORT compared with those treated with IOERT after an R1 resection for LARC or LRRC. This difference suggests a dose-dependent efficacy of IORT, as HDR-IORT delivers a higher surface dose compared with IOERT. Moreover, the fact that one modality was more effective than the other indicates that IORT has a measurable effect on LRFS in R1 patients; to our knowledge, this has not been shown previously in a large comparative study.

Several published studies have assessed the feasibility and efficacy of administering IORT in patients with LARC and/or LRRC. The majority of these studies have focused on the use of IOERT and, to a lesser extent, HDR-IORT.[12] Only a few have reported on the use of both techniques, but to our knowledge, this is the first to compare the IOERT and HDR-IORT treatment modalities.[20,21]

The difference in LRFS between HDR-IORT and IOERT observed in the current study may have been caused by differences in dose distributions between the two IORT modalities. HDR-IORT is delivered at a much more concentrated dose to the surface of the target area; the estimated dose at the target surface was 170% of the prescribed 10 Gy dose at a 10 mm depth. IOERT delivers the radiation dose more homogenously throughout the tissue depth, but as a consequence, it delivers a surface dose equal to the prescribed dose. Adjusting the IOERT procedure by increasing the surface dose with the use of a bolus and adapting the dose at a 10 mm depth to ensure it is equal to the HDR-IORT prescribed dose could result in a dose distribution that is more similar to that of HDR-IORT.

In addition, the size of the treated surface may also play a role in the observed difference in LRFS between both IORT modalities. Although we could not specify the irradiated area for HDR-IORT in this study, previous work has shown that the average treated area is 73 cm^2 (range 25-170 cm^2), which is 2 to 3 times larger than the area treated with IOERT.[22] Furthermore, IOERT applicators are poorly suited to curved areas such as the presacral and posterolateral area, in contrast to the flexible applicators in HDR-IORT. However, we do not believe this have played a role in the better dose delivery by HDR-IORT, as we corrected for the problems caused by the rigid applicators, such as minor airgaps and a limited diameter of the tube.

In the patients with LRRC, significant baseline differences between the two IORT modalities were observed regarding the neoadjuvant treatment and the time between EBRT and surgery. Previous work published by Holman et al. showed that a waiting time shorter than 8 weeks, as was observed in the HDR-IORT group, resulted in better LRFS in patients with an R1 resection.[23,24] This factor could also have played a role in the observed difference in LRFS between HDR-IORT and IOERT treatment groups in this study. However, in the multivariable analysis, we adjusted for these differences.

There was no observed difference in major postoperative complications between the two IORT modalities in patients with LARC. On the other hand, in patients with LRRC, HDR-IORT was associated with a significantly greater number of major postoperative complications compared with IOERT. Hypothetically, HDR-IORT induces more tissue damage and necrosis, owing to a higher surface dosage and a larger irradiated surface area compared with IOERT, which may increase the likelihood of postoperative complications. This hypothesis could not be explored further within this study, owing to the low frequency of each distinct complication event.

Another significant difference observed between the two groups was the duration of the procedure. As mentioned, HDR-IORT is a more time-consuming procedure to perform, because it requires individual treatment planning as well as a longer application time. Thus, the difference in the duration of the procedure is mainly the result of the IORT modality and not the extent of the surgery itself.

Despite the aforementioned difference in neoadjuvant treatment (which is a result of referral patterns rather than treatment strategies) and the time between EBRT and IORT in patients with LRRC, there were no baseline differences between the IOERT and HDR-IORT groups. Furthermore, both hospitals followed the same national guidelines regarding diagnostics and neoadjuvant treatment planning, and the preoperative, perioperative, and postoperative protocols, as well as the follow-up schedule, were similar between both hospitals. Moreover, most surgeons responsible for performing the procedures involved in this study worked at both hospitals and agree that that the case mix in both hospitals was similar. Hence, we feel that this study provides a valid comparison of the two IORT modalities.

IORT was not delivered in all patients with an R1 resection in our institutions. In patients with LARC, treatment with IORT was not delivered in cases of palliative resections or as a consequence of an incorrect clinical judgement of the resection margin status, false-negatives based on analysis of frozen sections, or technical problems encountered during surgery (e.g., hemodynamic instability in the patient). In patients with LRRC, IORT was mainly omitted because of a high cumulative dose due to prior (intraoperative) irradiation that did not allow an additional IORT boost. In addition, palliative resections and surgical technical problems (e.g., hemodynamic instability in the patient) were reasons to omit IORT.

With the evolving neoadjuvant treatment strategies, it remains important to bear in mind the possibility of delivering IORT. A neoadjuvant treatment strategy in which neoadjuvant radiation therapy is followed by consolidation chemotherapy as proposed in the Rectal Cancer And Pre-operative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial results in a longer interval between the radiation therapy and IORT compared with the so-called "total neoadjuvant treatment" strategies, in which neoadjuvant radiation therapy is preceded by induction chemotherapy; thus, a shorter interval between radiation therapy and IORT exists.[25,26] Although a longer waiting time increases the chance of an R0 resection, a shorter interval seems to benefit the effect of IORT in case of an R1 resection (*Table 2*).[23,24]

Owing to the retrospective nature of this study, there were some apparent shortcomings. However, as a result of the prospective maintenance of the database, very few data were missing: specifically, 2% and 1.6% of the values reported in *Tables 2* and *4*, respectively. Nonetheless, we could not specifically report on long-term complications associated with IORT. In particular, it would be of interest to compare complications such as plexopathy and peripheral neuropathy, which are known to be dose-dependent late toxicities associated with pelvic IORT, between the two modalities.[27] Furthermore, the patterns of (re)recurrence (infield or outfield) were missing in 37% of patients with LARC and 24% of patients with LRRC, so no related conclusions could be drawn.

In conclusion, in this retrospective cohort study from two large tertiary referral centres, a significant difference in the efficacy of IORT modalities was observed in patients with an R1 resection for LARC or LRRC, in favour of HDR-IORT. Therefore, the CZE is currently in the process of adapting the IOERT procedure to improve outcomes, while limiting the toxicity, in patients with an R1 resection for LARC or LRRC.

REFERENCES

1. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836
2. Gérard JP, Conroy T, Bonnetain F, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: Results of FFCD 9203. *J Clin Oncol*. 2006;24(28):4620-4625. doi:10.1200/JCO.2006.06.7629
3. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer. *Ann Surg*. 2019;269(2):315-321. doi:10.1097/SLA.0000000000002528
4. Platt E, Dovell G, Smolarek S. Systematic review of outcomes following pelvic exenteration for the treatment of primary and recurrent locally advanced rectal cancer. *Tech Coloproctol*. 2018;22(11):835-845. doi:10.1007/s10151-018-1883-1
5. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y
6. Marijnen CAM, Nagtegaal ID, Kapiteijn E, et al. Radiotherapy does not compensate for positive resection margins in rectal cancer patients: Report of a multicenter randomized trial. *Int J Radiat Oncol Biol Phys*. 2003;55(5):1311-1320. doi:10.1016/S0360-3016(02)04291-8
7. Gunderson LL, Calvo FA, Willett CG, Harrison LB. Rationale and Historical Perspective of Intraoperative Irradiation. In: *Intraoperative Irradiation: Techniques and Results*. 2nd ed. Totowa, NJ: Humana Press; 2011:3-26.
8. Okunieff P, Sundararaman S, Metcalfe S, Chen Y. Biology of Large Dose per Fraction Irradiation. In: *Intraoperative Irradiation: Techniques and Results*. 2nd ed. Totowa, NJ: Humana Press; 2011:27-47.
9. Allee P, Tepper J, Gunderson L, Munzenrider J. Postoperative radiation therapy for incompletely resected colorectal carcinoma. *Int J Radiat Oncol Biol Phys*. 1989;17(6):1171-1176. doi:10.1016/0360-3016(89)90522-1
10. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1032-1040. doi:10.1016/j.ijrobp.2014.01.014
11. Ferenschild FTJ, Vermaas M, Nuyttens JJME, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum*. 2006;49(9):1257-1265. doi:10.1007/s10350-006-0651-x
12. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol*. 2013;22(1):22-35. doi:10.1016/j.suronc.2012.11.001

13. Calvo FA, Sole CV, Rutten HJT, et al. ESTRO/ACROP IORT recommendations for intraoperative radiation therapy in locally recurrent rectal cancer. *Clin Transl Radiat Oncol*. 2020;24:41-48. doi:10.1016/j.ctro.2020.06.007.

14. Nag S, Willet CG, Gunderson LL, Harrison LB, Calvo FA, Biggs P. IORT with Electron-Beam, High-Dose-Rate Brachytherapy or Low-KV/Electronic BRachytherapy: Methodological Comparisons. In: *Intraoperative Irradiation: Techniques and Results*. 2nd ed. Totowa, NJ: Humana Press; 2011:99-115.

15. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, Van De Velde CJH, Van Krieken JHJM. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: Not one millimeter but two millimeters is the limit. *Am J Surg Pathol*. 2002;26(3):350-357. doi:10.1097/00000478-200203000-00009

16. Bhangu A, Ali SM, Darzi A, Brown G, Tekkis PP. Meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer. *Color Dis*. 2012;14(12):1457-1466. doi:10.1111/j.1463-1318.2012.03005.x

17. Mannaerts GHH, Martijn H, Crommelin MA, Dries W, Repelaer Van Driel OJ, Rutten HJT. Feasibility and first results of multimodality treatment, combining EBRT, extensive surgery, and IOERT in locally advanced primary rectal cancer. *Int J Radiat Oncol Biol Phys*. 2000;47(2):425-433. doi:10.1016/S0360-3016(99)00492-7

18. Nuyttens JJ, Kolkman-Deurloo IKK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys*. 2004;58(1):106-112. doi:10.1016/S0360-3016(03)01494-9

19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae.

20. Vermaas M, Nuyttens JJME, Ferenschild FTJ, Verhoef C, Eggermont AMM, de Wilt JHW. Re-irradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. *Radiother Oncol*. 2008;87(3):357-360. doi:10.1016/j.radonc.2008.02.021

21. Martínez-Monge R, Nag S, Martin EW. Three different intraoperative radiation modalities (electron beam, high-dose-rate brachytherapy, and iodine-125 brachytherapy) in the adjuvant treatment of patients with recurrent colorectal adenocarcinoma. *Cancer*. 1999;86(2):236-247. doi:10.1002/(SICI)1097-0142(19990715)86:2<236::AID-CNCR7>3.0.CO;2-9

22. Kolkman-Deurloo IKK, Nuyttens JJ, Hanssens PEJ, Levendag PC. Intraoperative HDR brachytherapy for rectal cancer using a flexible intraoperative template: Standard plans versus individual planning. *Radiother Oncol*. 2004;70(1):75-79. doi:10.1016/j.radonc.2003.10.010

23. Holman FA, Bosman SJ, Haddock MG, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. *Eur J Surg Oncol*. 2017;43(1):107-117. doi:10.1016/j.ejso.2016.08.015

24. Holman FA, Haddock MG, Gunderson LL, et al. Results of intraoperative electron beam radiotherapy containing multimodality treatment for locally unresectable T4 rectal cancer: A pooled analysis of the Mayo Clinic Rochester and Catharina Hospital Eindhoven. *J Gastrointest Oncol*. 2016;7(6):903-916. doi:10.21037/jgo.2016.07.01

25. Nilsson PJ, van Etten B, Hospers GAP, et al. Short-course radiotherapy followed by neo-adjuvant chemotherapy in locally advanced rectal cancer - the RAPIDO trial. *BMC Cancer*. 2013;279. doi:10.1186/1471-2407-13-279

26. Ludmir EB, Palta M, Willett CG, Czito BG. Total neoadjuvant therapy for rectal cancer: An emerging option. *Cancer*. 2017;123(9):1497-1506. doi:10.1002/cncr.30600

27. Pilar A, Gupta M, Laskar SG, Laskar S. Intraoperative radiotherapy: Review of techniques and results. *Ecancermedicalscience*. 2017;11(750). doi:10.3332/ecancer.2017.750

PART II

NEOADJUVANT TREATMENT

CHAPTER 8

IMPROVED RESPONSE RATE IN PATIENTS WITH PROGNOSTICALLY POOR LOCALLY ADVANCED RECTAL CANCER AFTER TREATMENT WITH INDUCTION CHEMOTHERAPY AND CHEMORADIOTHERAPY WHEN COMPARED WITH CHEMORADIOTHERAPY ALONE: A MATCHED CASE-CONTROL STUDY

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ABSTRACT

Introduction

The addition of induction chemotherapy (ICT) to neoadjuvant chemoradiotherapy (CRT) has the potential to improve outcomes in patients with locally advanced rectal cancer (LARC). However, patient selection is essential to prevent overtreatment. This study compared the complete response (CR) rate after treatment with and without ICT of LARC patients with prognostically poor characteristics.

Methods

All LARC patients who were treated with neoadjuvant CRT, whether or not preceded by ICT, and who underwent surgery or were considered for a wait-and-see strategy between January 2016 and March 2020 in the Catharina Hospital Eindhoven, were retrospectively selected. LARC was defined as any T4 tumour, or a T2/T3 tumour with extramural venous invasion and/or tumour deposits and/or N2 lymph node status, and/or mesorectal fascia involvement (T3 tumours only). Case-control matching was performed based on the aforementioned characteristics.

Results

Of 242 patients, 178 (74%) received CRT (CRT-group) and 64 patients (26%) received ICT followed by CRT (ICT-group). In the ICT-group, 3 patients (5%) did not receive the minimum of three cycles. In addition, in this selected cohort, compliance with radiotherapy was 100% in the ICT-group and 97% in the CRT-group. The CR rate was 30% in the ICT-group and 15% in the CRT-group ($p = 0.011$). After case-control matching, the CR rate was 28% and 9%, respectively ($p = 0.013$).

Conclusion

Treatment including ICT seemed well tolerated and resulted in a high CR rate. Hence, this treatment strategy may facilitate organ preservation and improve survival in LARC patients with prognostically poor characteristics.

INTRODUCTION

Patients with locally advanced rectal cancer (LARC), typically defined as a tumour involving or extending beyond the mesorectal fascia (MRF), have a particularly high risk of an incomplete resection resulting in higher rates of local recurrence and distant metastases and a decreased survival.[1–3] In addition to an involved or threatened MRF, the occurrence of mesorectal lymph node metastases is another important predictive and prognostic factor for overall survival (OS) and disease-free survival (DFS). Furthermore, the number of lymph node metastases has been shown to be positively correlated with a worse OS and DFS.[4,5] Moreover, over the past few years, several other poor prognostic factors have been identified. The role of histological and magnetic resonance imaging (MRI) based extramural venous invasion (mrEMVI) as a prognostic factor has become a growing area of interest.[6,7] A meta-analysis including 1262 rectal cancer patients demonstrated that the occurrence of mrEMVI resulted in an increased risk for the development of synchronous and metachronous distant metastases and decreased survival rates.[8,9] Along with EMVI, tumour deposits (TD) have been demonstrated to be associated with EMVI and have also shown to be a predictor for poor oncological outcome.[10] A recent study by Lord et al. showed that the presence of mrEMVI and/or TD independently resulted in a higher risk for distant metastases (hazard ratio [HR] 6.53; 95% confidence interval [CI] 2.52–16.91; $p < 0.001$) and decreased DFS (HR 2.20; 95% CI 1.39–3.59; $p = 0.002$).[11] In patients with these unfavourable tumour characteristics, neoadjuvant chemoradiotherapy (CRT) is the standard of care.[12–14] Nevertheless, in these patients, local and distant recurrence rates remain high ranging between 5-10% and 25-40% respectively.[15] In recent years, several studies have investigated the role of adding induction chemotherapy (ICT) to the treatment regimen to improve these results.[16–23] It was demonstrated that ICT was feasible, safe, and well tolerated. However, considerable variations have been reported regarding the effect of ICT on the R0 resection rate and long-term outcomes. Various studies also reported on the clinical and pathological complete response (cCR and pCR, respectively) rate, because both can serve as surrogate endpoints for DFS and OS.[12,24] Nevertheless, these rates also varied. We hypothesised that, to improve outcomes while preventing overtreatment, an intensified neoadjuvant treatment might be especially beneficial for patients with the abovementioned prognostically poor tumour characteristics. Therefore, the aim of this study was to explore whether the addition of induction chemotherapy to chemoradiotherapy in patients with prognostically poor LARC improved the complete response (CR) rate when compared with treatment with chemoradiotherapy alone.

METHODS

Patients

The Catharina Hospital Eindhoven (CZE), a tertiary referral centre for LARC, organises a weekly regional, multidisciplinary, multicentre team (MDT) meeting in which all patients with advanced rectal cancer are discussed to determine the optimal treatment strategy. All consecutive LARC patients discussed at the MDT, who completed neoadjuvant CRT treatment, whether or not preceded by ICT, and who underwent surgery at the CZE or were considered for a wait-and-see (W&S) strategy between January 2016 and March 2020 were retrospectively selected for the present study. LARC was defined as any T4 tumour, a T3 tumour with EMVI and/or TD and/or MRF involvement and/or N2 lymph node status, or a T2 tumour with EMVI and/or TD and/or N2 lymph node status. This study was approved by the local medical ethics board (registration number W19.031).

Radiological assessment

At baseline, i.e. pre-treatment, a pelvic MRI was performed, consisting of T2-weighted axial, coronal, and sagittal planes and axial diffusion-weighted imaging (DWI). All radiological reports were retrospectively reviewed. If the presence or absence of EMVI, TD, MRF involvement, or lymph node involvement was not specifically noted in the radiological report, the scan was re-evaluated with regard to these tumour characteristics by an experienced radiologist with specific expertise in advanced rectal cancer (J.N.).

Neoadjuvant treatment

From 2016 onwards, ICT was gradually introduced as a part of our treatment strategy for patients presenting with poor prognostic tumour characteristics. However, most patients were discussed in our MDT meeting by the time CRT was already completed. Hence, these patients could serve as a control group for those who were treated with ICT followed by CRT. ICT generally consisted of 3 cycles of CAPOX (capecitabine, oxaliplatin) or 4 cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). In case of stable or responsive disease, assessed according to RECIST 1.1, and acceptable toxicity, one additional cycle of CAPOX or two additional cycles of FOLFOX were administered before or after the neoadjuvant CRT.[25] Neoadjuvant CRT was delivered with a cumulative dose of 50-50.4 Gy in fractions of 1.8-2 Gy with concomitant capecitabine twice daily orally on radiotherapy days with a dose of 825 mg/m2.

Final treatment

Four to eight weeks after finishing chemoradiotherapy, an MRI was performed to evaluate local tumour response. Response was assessed according to the 5-point MRI

based tumour regression (mrTRG) scale.[26]. In case of a radiological complete response, a W&S strategy was proposed in the MDT meeting and discussed with the patient. In case patients were interested in an organ preserving approach, they were scheduled for a sigmoidoscopy. If there were no signs of vital tumour tissue, patients entered the W&S strategy. All other patients were scheduled for surgery. The technique and extent of the surgical procedure was at the discretion of the surgeon. Intraoperative radiotherapy was delivered via electron beam radiotherapy with a linear accelerator in case of an involved or threatened surgical resection margin.

Follow-up

All patients who underwent surgery were monitored using routine CEA measurements (4 times a year during years 1-3, twice a year during years 4-5) and thoracoabdominal CT-scans or ultrasonography of the liver and chest radiography (twice a year during year 1, yearly during years 2-5) for a period of 5 years. The follow-up protocol for patients in the W&S strategy was intensified by the addition of endoscopy (4 times a year during year 1, twice a year during years 2-5) and MRI (4 times a year during year 1, twice a year during years 2-5).

Complete response

The endpoint of this study was the complete response rate. In patients undergoing surgery, the pathological response was assessed using the Mandard classification.[27] A pCR was defined as Mandard 1: absence of viable tumour cells in the resection specimen. A cCR was defined as sustained absence of disease for a minimum of 12 months under active surveillance, calculated from the date of MRI after finishing chemoradiotherapy. The term CR was used to define patients who had either a pCR or a sustained cCR.

Statistical analysis

Statistical analyses were performed using IBM SPSS Statistics version 25.0 (IBM, Armonk, New York, USA). Continuous data are reported as median (interquartile range) and categorical as count (percentage). Group comparisons were made using the Chi-square test or Fisher's exact test, as appropriate. For continuous variables, the Mann-Whitney *U* test was used. All tests were performed two-sided and a p value < 0.05 was considered significant. Follow-up in the W&S strategy was calculated from the date of MRI after completing CRT until the date of last follow-up.

Case-control matching without replacement using SPSS was performed to correct for confounding variables. An exact control was randomly selected for each patient who

received ICT. Control cases were matched on cT stage (2/3/4), cN stage (N0/N+), MRF involvement, and the presence of EMVI and TD.

RESULTS

Patients

A total of 242 patients were included, of whom 178 (74%) were treated with neoadjuvant chemoradiotherapy (CRT-group) and 64 (26%) with induction chemotherapy followed by chemoradiotherapy (ICT-group). All patients treated with ICT were discussed during our MDT before the start of the neoadjuvant treatment, whereas 67% of the patients in the CRT-group were referred to our MDT only after completing neoadjuvant therapy. Patient and tumour characteristics are shown in *Table 1*. At baseline, i.e. before start of the neoadjuvant treatment, EMVI and TDs were significantly more observed in the ICT-group than in the CRT-group (84% vs. 56% and 56% vs. 24%, respectively, $p < 0.001$).

Table 1 Patient and tumour characteristics$

		CRT (N=178)	ICT+CRT (N=64)	*p* value
Gender	Female	70 (39.3)	23 (35.9)	0.633
	Male	108 (60.7)	41 (64.1)	
Age	<70	128 (71.9)	49 (76.6)	0.471
	≥70	50 (28.1)	15 (23.4)	
ASA*	I-II	142 (82.6)	43 (79.6)	0.277
	III	30 (17.4)	10 (18.5)	
	IV	0 (0)	1 (1.9)	
WHO perfomance status**	0-1	147 (91.3)	61 (96.8)	0.411
	2	10 (6.2)	2 (3.2)	
	3	4 (2.5)	0 (0)	
Previous chemotherapy treatment	No	178 (100)	64 (100)	NA
MRI baseline	Yes	176 (98.9)	63 (98.4)	1.000
	Only CT	2 (1.1)	1 (1.6)	
Tumour stage	T2	5 (2.8)	0 (0)	0.457
	T3	88 (49.4)	35 (54.7)	
	T4	85 (47.8)	29 (45.3)	

Table 1 (Continued)

		CRT (N=178)	ICT+CRT (N=64)	*p* value
Nodal stage	N0	28 (15.7)	5 (7.8)	0.211
	N1	62 (34.8)	21 (32.8)	
	N2	88 (49.4)	38 (59.4)	
MRF involvement	Yes	152 (85.4)	46 (71.9)	0.016
	No	26 (14.6)	18 (28.1)	
EMVI	Yes	99 (55.6)	54 (84.4)	<0.001
	No	79 (44.4)	10 (15.6)	
Tumour deposits	Yes	42 (23.6)	36 (56.3)	<0.001
	No	136 (76.4)	28 (43.8)	
Synchronous metastases	Yes	14 (7.9)	5 (7.8)	0.989
	No	164 (92.1)	59 (92.2)	

[$]: Tumour characteristics were assessed on baseline MRI, i.e., pre neoadjuvant treatment.
*: Not applicable for patients not scheduled for surgery (n=16).
**: Missing values n=17 in CRT group and n=1 in ICT+CRT group
p values pertain to all outcomes of the variable
Abbreviations: ASA= American Society of Anaesthesiologist classification, CRT = chemoradiotherapy, EMVI = extramural venous invasion, ICT = induction chemotherapy, MRF = mesorectal fascia, MRI = magnetic resonance imaging, NA = not applicable, WHO = world health organisation performance status

Neoadjuvant treatment

Details on the neoadjuvant treatment are shown in *Table 2.* ICT consisted of CAPOX (88%), CAPOX-bevacizumab (5%), or FOLFOX (8%). Most patients were administered 3 or 4 cycles (42% and 27%, respectively). Three patients did not complete the minimum of 3 scheduled cycles because of toxicity. Overall, 30% of the patients (n = 19) had some dose reduction of the chemotherapy and 11% of the patients (n = 7) were admitted to the hospital due to any kind of adverse event.

Table 2 Neoadjuvant treatment – original cohort

		CRT (N=178)	ICT+CRT (N=64)	*p* value
Type induction chemotherapy	CAPOX	-	56 (87.5)	NA
	CAPOX-bevacizumab	-	3 (4.7)	
	FOLFOX	-	5 (7.8)	
Number of cycles administered	1	-	1 (1.6)	NA
	2	-	2 (3.1)	
	3	-	27 (42.2)	
	4	-	17 (26.6)	
	5	-	7 (10.9)	
	6	-	8 (12.5)	
	7	-	2 (3.1)	
Dose reduction induction chemotherapy	Yes	-	19 (29.7)	NA
	No	-	45 (70.3)	
Admission during induction chemotherapy	Yes	-	7 (10.9)	NA
	No	-	57 (89.1)	
Dose reduction radiotherapy during CRT	Yes	5 (2.8)	0 (0)	0.329
	No	173 (97.2)	64 (100)	
Type chemotherapy during CRT	Capecitabine	178 (100)	62 (96.9)	0.069
	Tegafur/ gimeracil/ oteracil	0 (0)	2 (3.1)	
Dose reduction chemotherapy during CRT	Yes; planned	2 (1.1)	2 (3.1)	0.408
	Yes; unplanned	6 (3.4)	1 (1.6)	
	No	170 (95.5)	61 (95.3)	
Admission during CRT	Yes	8 (4.5)	1 (1.6)	0.452
	No	170 (95.5)	63 (98.4)	

Abbreviations: CAPOX = capecitabine, oxaliplatin, CRT = chemoradiotherapy, FOLFOX = 5-fluorouracil, leucovorin, oxaliplatin, ICT = induction chemotherapy, NA = not applicable
p values pertain = to all outcomes of the variable

All patients were administered long-course CRT; in the CRT-group 5 patients (3%) had an early discontinuation of the radiotherapy, whereas none of the patients in the ICT-group had an early discontinuation (p = 0.329). Concomitant chemotherapy was capecitabine, except for 2 patients (3%) in the ICT-group in whom concomitant tegafur/gimeracil/oteracil was administered due to toxicity of capecitabine during the ICT (p = 0.069). Admission during CRT was required in 8 patients (4.5%) in the CRT-group and in 1 patient (1.6%) in the ICT-group (p = 0.452).

Final treatment

In the CRT-group, 9 patients (5%) entered a W&S strategy and 169 patients (95%) were directly scheduled for surgery. In the ICT-group, 14 patients (22%) entered a W&S strategy and 50 patients (78%) underwent surgery directly. The surgical characteristics are shown in *Supplementary table 1.* The median interval between CRT and MRI was significantly shorter in the ICT-group than in the CRT-group (4 vs. 6 weeks, respectively, p < 0.001). The interval between CRT and surgery was longer in the CRT-group than in the ICT-group (14 vs. 13 weeks, p = 0.038). In the ICT-group, more patients underwent an extended resection or low anterior resection, whereas in the CRT-group, more patients underwent an abdominoperineal resection. The rate of major postoperative complications (Clavien-Dindo 3-5) were comparable between the two groups (13% vs. 22%, p = 0.145). For patients entering the W&S strategy, the median follow-up time was 27 months (IQR 14-29 months) in the CRT-group and 16 months (IQR 12-21 months) in the ICT-group (p = 0.025).

Response

In the CRT-group, 8 patients (4%) had a sustained cCR; 1 had regrowth after 6 months of follow-up. In the ICT-group, 10 patients (16%) had a sustained cCR; 4 had regrowth within 5-12 months of follow-up. A pCR was observed in 20 patients (11%) in the CRT-group and in 9 (14%) in the ICT-group (p = 0.550), resulting in a CR of 16% versus 30%, respectively (p = 0.015, *Table 3*).

Table 3 Treatment and response

		Original cohort		
		CRT (N=178)	**ICT+CRT (N=64)**	***p* value**
Final treatment	Wait-and-see strategy (Success)	8 (3.9)	10 (15.6)	0.001
	Wait-and-see strategy (Failed)	1 (1.1)	4 (6.3)	
	Surgery	169 (94.9)	50 (78.1)	
	*R0 resection^*	*147 (87.5)*	*45 (90.0)*	*0.632*
	R1/2 resection	*21(12.5)*	*5 (10.0)*	
Response	pCR	20 (11.2)	9 (14.1)	0.010
	sustained cCR	8 (4.5)	10 (15.6)	
	no pCR/sustained cCR	150 (84.3)	45 (70.3)	
Overall response	CR	28 (15.7)	19 (29.7)	0.015
	no CR	151 (84.8)	45 (70.3)	
		Matched cohort		
		CRT (N=53)	**ICT+CRT (N=53)**	***p* value**
Final treatment	Wait-and-see strategy (Success)	1 (1.9)	8 (15.1)	0.009
	Wait-and-see strategy (Failed)	0 (0)	2 (3.8)	
	Surgery	52 (98.1)	43 (81.1)	
	*R0 resection^*	*41 (80.4)*	*38 (88.4)*	*0.293*
	R1/2 resection	*10 (19.6)*	*5 (11.6)*	
Response	pCR	4 (7.5)	7 (13.2)	0.022
	sustained cCR	1 (1.9)	8 (15.1)	
	no pCR/sustained cCR	48 (90.6)	38 (71.7)	
Overall response	CR	5 (9.4)	15 (28.3)	0.013
	no CR	48 (90.6)	38 (71.7)	

Abbreviations: cCR = clinical complete response, CR = complete response (pCR plus cCR), CRT = chemoradiotherapy, ICT = induction chemotherapy, pCR = pathological complete response, R0 resection = resection with clear resection margins, R1/2 resection = resection without clear resection margins
^: resection margin was only calculated for patients undergoing surgery
p values pertain to all outcomes of the variable

Case control matching

In the selected group of 242 patients there were several tumour characteristics at baseline which differed between the two treatment groups. To diminish the influence of these confounders, exact case-control matching was performed, resulting in 53 patients in both treatment groups each. Baseline and tumour characteristics are shown

in *Table 4;* tumour stage, MRF involvement, EMVI and TD were equally present in both groups. Surgical characteristics in the matched cohort are shown in *Supplementary Table 2.* The interval between CRT and MRI was significantly shorter in the ICT-group than in the CRT-group (4 vs. 6.5 weeks, respectively, $p < 0.001$). The interval between CRT and surgery did not differ significantly between the CRT-group and the ICT-group (14 vs. 13 weeks, respectively, $p = 0.068$).

In the matched cohort, one patient (2%) in the CRT-group entered a W&S strategy and 52 patients (98%) underwent surgery after neoadjuvant treatment, whereas in the ICT-group 10 patients (19%) entered a W&S strategy and 43 (81%) underwent surgery (*Table 3*).

The pCR rate was not significantly different between both groups ($p = 0.339$); however, the CR rate was significantly higher in the ICT-group (28%) than in the CRT-group (9%; $p = 0.013$).

Table 4 Patient and tumour characteristics – matched cohort

		CRT (N=53)	ICT+CRT (N=53)	*p* value
Gender	Female	25 (47.2)	19 (35.8)	0.237
	Male	28 (52.9)	34 (64.2)	
Age	<70	40 (75.5)	40 (75.5)	1.000
	≥70	13 (24.5)	13 (24.5)	
Tumour stage	T3	23 (43.3)	24 (45.3)	0.845
	T4	30 (56.6)	29 (54.7)	
Nodal stage	N0	4 (7.5)	4 (7.5)	1.000
	N1	19 (35.8)	20 (37.7)	
	N2	30 (56.6)	29 (54.7)	
MRF involvement	Yes	46 (86.8)	45 (84.9)	0.780
	No	7 (13.2)	8 (15.1)	
EMVI	Yes	45 (84.9)	45 (84.9)	1.000
	No	8 (15.1)	8 (15.1)	
Tumour deposits	Yes	26 (49.1)	26 (49.1)	1.000
	No	27 (50.9)	27 (50.9)	
Synchronous metastases	Yes	10 (18.9)	5 (9.4)	0.164
	No	43 (81.1)	48 (90.6)	

Abbreviations: CRT = chemoradiotherapy, EMVI = extramural venous invasion, ICT = induction chemotherapy, MRF = mesorectal fascia.
p values pertain to all outcomes of the variable

DISCUSSION

The results of this study suggest that the addition of induction chemotherapy to neoadjuvant chemoradiotherapy in patients with prognostically poor LARC results in a higher CR rate than neoadjuvant chemoradiotherapy alone.

The addition of ICT to the neoadjuvant treatment regimen in patients with LARC has previously been studied. However, comparison was hampered because of the different treatment regimens that have been used. Studies that were concerned with CAPOX or FOLFOX administered prior to CRT, reported pCR/CR rates that varied between 15-33%.[16–19] One of the explanations for this variation could be the different inclusion criteria, since tumour diameter and T stage are predictors for response to neoadjuvant treatment.[28–30] Patients included in these studies had more favourable tumour characteristics than those in the present study, since only 5-20% of the included patients in these studies were diagnosed with a cT4 tumour and the proportion of patients with a cT3 MRF positive tumour was small or even absent. Nevertheless, even when comparing our results to those in studies that included patients with comparable tumour characteristics, the results vary. In the study by Dewdney et al., MRF involvement was present in 56% of the patients and EMVI positivity was observed in 74% of patients.[21] The observed CR rate of 16% was inferior to that in the present study. In contrast, Schou et al., who also included a comparable population with 65% cT3 MRF+ tumours and 43% cT4 tumours, reported a pCR rate of 25%, which was comparable to the CR rate in the present study.[22] The largest study to date reporting on the outcomes of ICT in LARC is the study from Cercek et al.[20] They reported a superior CR rate of 36% in the ICT-group. However, only 12% of the patients in that study had a cT4 tumour and the proportion of cT3 tumour with MRF involvement was not reported. Overall, definitions of LARC were different between the abovementioned studies, making an accurate comparison difficult, and no meaningful conclusions can be drawn. The present study, however, represents a cohort of truly advanced rectal cancer tumours, especially in the matched cohort.

Induction chemotherapy was well tolerated in our study, which is in accordance with the literature.[16–19] Only 3 patients (5%) did not complete the minimum scheduled 3 cycles and although 30% of the patients had a dose reduction, only 11% of all patients required hospitalisation during the ICT. Moreover, compliance with radiotherapy was excellent in both treatment groups. Notably, only patients undergoing final treatment (surgery or W&S strategy) were selected in this study, which may have positively biased these compliance rates. Postoperative complications between the two treatment groups were comparable, indicating that intensified treatment with ICT did not negatively

influence subsequent treatment. Moreover, the rate of postoperative complications was comparable to that reported in the literature.[22,23,31]

The median interval between the end date of CRT and surgery was 13 and 14 weeks in the ICT-group and CRT-group, respectively. A long interval between CRT and surgery is supported by several retrospective studies which demonstrated that higher pCR rates were achieved with an interval exceeding 8 weeks.[32,33] This was confirmed in a meta-analysis and several randomised trials.[34–37] Nevertheless, Sloothaak et al. also showed that an interval longer than 11 weeks was not beneficial with regard to the pCR rate.[33] The interval between CRT and restaging MRI was significantly shorter in the ICT-group than in the CRT-group. The optimal timing of reassessment is still controversial, and there are no clear guidelines, resulting in considerable variability.[38] However, it is known that the tumoricidal effect of CRT increases over time and there is evidence supporting that a longer interval may increase response rates.[39] Recent reports that routinely included MRI to select patients for a W&S strategy used an interval of 8 weeks.[40] In comparison, the interval in the ICT-group in this study was relatively short with an interval of 4 weeks. However, in the present study, a W&S strategy was not the primary goal. Nevertheless, given the high rate of cCR, such a strategy seems feasible even in patients with prognostically poor LARC. Hence, a longer interval may be beneficial in identifying more cCR. Notably, despite the shorter interval in the ICT-group, a higher cCR rate was already observed in this group than in the CRT-group.

The retrospective study design has inherent limitations. However, there were only few missing data. More importantly, an attempt was made to limit the effect of possible confounders by conducting a case-control matching. Nevertheless, since CZE is a tertiary referral centre for LARC requiring multivisceral surgery and IORT, a substantial proportion of our LARC patients are referred once evaluation after neoadjuvant therapy shows insufficient response, thus preventing routine TME surgery. All these patients were treated with CRT alone. It is likely that patients with a good response to CRT, in whom routine TME surgery or a W&S strategy was possible, were not referred to our hospital. This may have introduced a selection bias adversely affecting the CR rate in the CRT-group and may have influenced compliance rates to CRT. Furthermore, data on patients with progressive disease under neoadjuvant treatment were incomplete and we could therefore not include these patients.

In order to adequately assess a sustained cCR, a minimum follow-up time of 12 months is common as most local regrowth after apparent cCR occurs within this period and cCR is thus most likely to persist beyond this period.[41–44] In this study the median follow-up was 27 months (min. 13 months, max. 40 months) in the CRT-group and 16 months

(min. 12 months, max. 23 months) in the ICT-group. The shorter median follow-up in the ICT-group may have resulted in a lower regrowth rate in these patients.

Both cCR and pCR are surrogate endpoints for overall survival, because they proved to be of prognostic value in previous studies.[12,24] Nevertheless, not all studies support this finding.[45] In the present study, follow-up was too short to report long-term survival outcomes.

In conclusion, the CR rate after treatment with induction chemotherapy followed by chemoradiotherapy in patients with prognostically poor LARC was high. Furthermore, induction chemotherapy was well tolerated in our cohort, and no additional peri-operative complications were observed. However, a prospective study is warranted to draw any definitive conclusions. In the Netherlands, we are currently setting up the MEND-IT trial: a single-arm prospective trial including only patients with prognostically poor LARC.

REFERENCES

1. Nagtegaal ID, Marijnen CAM, Kranenbarg EK, Van De Velde CJH, Van Krieken JHJM. Circumferential margin involvement is still an important predictor of local recurrence in rectal carcinoma: Not one millimeter but two millimeters is the limit. *Am J Surg Pathol*. 2002;26(3):350-357. doi:10.1097/00000478-200203000-00009
2. Taylor FGM, Quirke P, Heald RJ, et al. Preoperative magnetic resonance imaging assessment of circumferential resection margin predicts disease-free survival and local recurrence: 5-year follow-up results of the MERCURY study. *J Clin Oncol*. 2014;32(1):34-43. doi:10.1200/JCO.2012.45.3258
3. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi:10.1056/NEJMoa010580
4. Gunderson LL, Jessup JM, Sargent DJ, Greene FL, Stewart AK. Revised TN categorization for colon cancer based on national survival outcomes data. *J Clin Oncol*. 2010;28(2):264-271. doi:10.1200/JCO.2009.24.0952
5. Karjol U, Jonnada P, Chandranath A, Cherukuru S. Lymph Node Ratio as a Prognostic Marker in Rectal Cancer Survival: A Systematic Review and Meta-Analysis. *Cureus*. 2020;12(5):e8047. doi:10.7759/cureus.8047
6. Brown G, Radcliffe AG, Newcombe RG, Dallimore NS, Bourne MW, Williams GT. Preoperative assessment of prognostic factors in rectal cancer using high-resolution magnetic resonance imaging. *Br J Surg*. 2003;90(3). doi:10.1002/bjs.4034
7. Smith NJ, Barbachano Y, Norman AR, Swift RI, Abulafi AM, Brown G. Prognostic significance of magnetic resonance imaging-detected extramural vascular invasion in rectal cancer. *Br J Surg*. 2008;95(2):229-236. doi:10.1002/bjs.5917
8. Schaap DP, Ogura A, Nederend J, et al. Prognostic implications of MRI-detected lateral nodal disease and extramural vascular invasion in rectal cancer. *Br J Surg*. 2018;105(13). doi:10.1002/bjs.10949
9. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer*. 2017;116(12):1513-1519. doi:10.1038/bjc.2017.99
10. Lord AC, Graham Martínez C, D'Souza N, Pucher PH, Brown G, Nagtegaal ID. The significance of tumour deposits in rectal cancer after neoadjuvant therapy: a systematic review and meta-analysis. *Eur J Cancer*. 2019;122:1-8. doi:10.1016/j.ejca.2019.08.020
11. Lord AC, D'Souza N, Shaw A, et al. MRI-Diagnosed Tumour Deposits and EMVI Status Have Superior Prognostic Accuracy to Current Clinical TNM Staging in Rectal Cancer. *Ann Surg*. 2020:Publish Ahead of Print. doi:10.1097/SLA.0000000000004499
12. Maas M, Nelemans J, Marañón G, et al. Long-term outcome in patients with a pathological complete response after chemoradiation for rectal cancer: a pooled analysis of individual patient data. *Lancet Oncol*. 2010;11(9):835-844. doi:10.1016/S1470-2045(10)70172-8

13. Braendengen M, Tveit KM, Berglund A, et al. Randomized phase III study comparing preoperative radiotherapy with chemoradiotherapy in nonresectable rectal cancer. *J Clin Oncol*. 2008;26(22):3687-3694. doi:10.1200/JCO.2007.15.3858

14. De Caluwé L, Van Nieuwenhove Y, Ceelen WP. Preoperative chemoradiation versus radiation alone for stage II and III resectable rectal cancer. *Cochrane database Syst Rev*. 2013;(2):CD006041. doi:10.1002/14651858.CD006041.pub3

15. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836

16. Fernández-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: Long-term results of the Spanish GCR-3 phase II randomized trial. *Ann Oncol*. 2015;26(8):1722-1728. doi:10.1093/annonc/mdv223

17. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: The Brown University Oncology Group CONTRE study. *Am J Clin Oncol Cancer Clin Trials*. 2017;40(3):283-287. doi:10.1097/COC.0000000000000149

18. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. *Lancet Oncol*. 2010;11(3):241-248. doi:10.1016/S1470-2045(09)70381-X

19. Maréchal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: A randomized multicentric phase II study. *Ann Oncol*. 2012;23(6):1525-1530. doi:10.1093/annonc/mdr473

20. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071

21. Dewdney A, Cunningham D, Tabernero J, et al. Multicenter randomized phase II clinical trial comparing neoadjuvant oxaliplatin, capecitabine, and preoperative radiotherapy with or without cetuximab followed by total mesorectal excision in patients with high-risk rectal cancer (EXPERT-C). *J Clin Oncol*. 2012;30(14):1620-1627. doi:10.1200/JCO.2011.39.6036

22. Schou J V., Larsen FO, Rasch L, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. *Ann Oncol*. 2012;23(10):2627-2633. doi:10.1093/annonc/mds056

23. Calvo FA, Sole C V., Serrano J, et al. Preoperative chemoradiation with or without induction oxaliplatin plus 5-fluorouracil in locally advanced rectal cancer: Long-term outcome analysis. *Strahlentherapie und Onkol*. 2014;190(2):149-157. doi:10.1007/s00066-013-0469-0

24. Martens MH, Maas M, Heijnen LA, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. *J Natl Cancer Inst*. 2016;108(12):djw171. doi:10.1093/jnci/djw171

25. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1). *Eur J Cancer*. 2009;45(2):228-247. doi:10.1016/j.ejca.2008.10.026

26. Patel UB, Brown G, Rutten H, et al. Comparison of magnetic resonance imaging and histopathological response to chemoradiotherapy in locally advanced rectal cancer. *Ann Surg Oncol*. 2012;19(9):2842-2852. doi:10.1245/s10434-012-2309-3
27. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680-2686. doi:10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c
28. Fischer J, Eglinton TW, Richards SJG, Frizelle FA. Predicting pathological response to chemoradiotherapy for rectal cancer: a systematic review. *Expert Rev Anticancer Ther*. 2021. doi:10.1080/14737140.2021.1868992
29. Tan Y, Fu D, Li D, et al. Predictors and risk factors of pathologic complete response following neoadjuvant chemoradiotherapy for rectal cancer: A population-based analysis. *Front Oncol*. 2019;13(9):497. doi:10.3389/fonc.2019.00497
30. van der Sluis FJ, van Westreenen HL, van Etten B, van Leeuwen BL, de Bock GH. Pretreatment identification of patients likely to have pathologic complete response after neoadjuvant chemoradiotherapy for rectal cancer. *Int J Colorectal Dis*. 2018;33(2):149-157. doi:10.1007/s00384-017-2939-9
31. Berkel AEM, Woutersen DP, van der Palen J, Klaase JM. Prognostic Factors for Postoperative Morbidity and Tumour Response After Neoadjuvant Chemoradiation Followed by Resection for Rectal Cancer. *J Gastrointest Surg*. 2014;18(9):1648-1657. doi:10.1007/s11605-014-2559-4
32. Wolthuis AM, Penninckx F, Haustermans K, et al. Impact of interval between neoadjuvant chemoradiotherapy and TME for locally advanced rectal cancer on pathologic response and oncologic outcome. *Ann Surg Oncol*. 2012;19(9):2833-2841. doi:10.1245/s10434-012-2327-1
33. Sloothaak DA, Geijsen DE, van Leersum NJ, et al. Optimal time interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg*. 2013;100(7):933-939. doi:10.1002/bjs.9112
34. Akgun E, Caliskan C, Bozbiyik O, et al. Randomized clinical trial of short or long interval between neoadjuvant chemoradiotherapy and surgery for rectal cancer. *Br J Surg*. 2018;105(11):1417-1425. doi:10.1002/bjs.10984
35. Evans J, Bhoday J, Sizer B, et al. Results of a prospective randomised control 6 vs 12 trial: Is greater tumour downstaging observed on post treatment MRI if surgery is delayed to 12-weeks versus 6-weeks after completion of neoadjuvant chemoradiotherapy? *Ann Oncol*. 2016;27(Suppl 6):VI149. doi:10.1093/annonc/mdw370.01
36. Du D, Su Z, Wang D, Liu W, Wei Z. Optimal Interval to Surgery After Neoadjuvant Chemoradiotherapy in Rectal Cancer: A Systematic Review and Meta-analysis. *Clin Colorectal Cancer*. 2018;17(1):13-24. doi:10.1016/j.clcc.2017.10.012
37. Garcia-Aguilar J, Smith DD, Avila K, Bergsland EK, Chu P, Krieg RM. Optimal timing of surgery after chemoradiation for advanced rectal cancer: Preliminary results of a multicenter, nonrandomized phase II prospective trial. *Ann Surg*. 2011;254(11):97-102. doi:10.1097/SLA.0b013e3182196e1f
38. Detering R, Borstlap WAA, Broeders L, et al. Cross-Sectional Study on MRI Restaging After Chemoradiotherapy and Interval to Surgery in Rectal Cancer: Influence on Short- and Long-Term Outcomes. *Ann Surg Oncol*. 2019;26(2):437-448. doi:10.1245/s10434-018-07097-7

39. West MA, Dimitrov BD, Moyses HE, et al. Timing of surgery following neoadjuvant chemoradiotherapy in locally advanced rectal cancer – A comparison of magnetic resonance imaging at two time points and histopathological responses. *Eur J Surg Oncol*. 2016;42(9):1350-1358. doi:10.1016/j.ejso.2016.04.003

40. López-Campos F, Martín-Martín M, Fornell-Pérez R, et al. Watch and wait approach in rectal cancer: Current controversies and future directions. *World J Gastroenterol*. 2020;26(29):4218-4239. doi:10.3748/WJG.V26.I29.4218

41. van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. *Lancet*. 2018;391(10139):2537-2545. doi:10.1016/S0140-6736(18)31078-X

42. Habr-Gama A, Perez RO, Nadalin W, et al. Long-term results of preoperative chemoradiation for distal rectal cancer correlation between final stage and survival. *J Gastrointest Surg*. 2005;90(1):90-101. doi:10.1016/j.gassur.2004.10.010

43. Habr-Gama A. Assessment and management of the complete clinical response of rectal cancer to chemoradiotherapy. *Colorectal Dis*. 2006;8(s3):21-24. doi:10.1111/j.1463-1318.2006.01066.x

44. Habr-Gama A, Perez RO, Proscurshim I, et al. Patterns of Failure and Survival for Nonoperative Treatment of Stage c0 Distal Rectal Cancer Following Neoadjuvant Chemoradiation Therapy. *J Gastrointest Surg*. 2006;10(10):1319-1329. doi:10.1016/j.gassur.2006.09.005

45. Petrelli F, Borgonovo K, Cabiddu M, Ghilardi M, Lonati V, Barni S. Pathologic complete response and disease-free survival are not surrogate endpoints for 5-year survival in rectal cancer: An analysis of 22 randomized trials. *J Gastrointest Oncol*. 2017;8(1):39-48. doi:10.21037/jgo.2016.11.03

CHAPTER 9

IMPROVED OUTCOMES FOR RESPONDERS AFTER TREATMENT WITH INDUCTION CHEMOTHERAPY AND CHEMO(RE)IRRADIATION FOR LOCALLY RECURRENT RECTAL CANCER

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ABSTRACT

Background

Despite improvements in the multimodality treatment for patients with locally recurrent rectal cancer (LLRC), oncological outcomes remain poor. This study evaluated the effect of induction chemotherapy and subsequent chemo(re)irradiation on the pathological response and the rate of resections with clear margins (R0 resection) in relation to long-term oncological outcomes.

Methods

All consecutive patients with LRRC treated in the Catharina Hospital Eindhoven who underwent a resection after treatment with induction chemotherapy and subsequent chemo(re)irradiation between January 2010 and December 2018 were retrospectively reviewed. Induction chemotherapy consisted of CAPOX/FOLFOX. Endpoints were pathological response, resection margin and overall survival (OS), disease-free survival (DFS), local recurrence-free survival (LRFS) and metastasis-free survival (MFS).

Results

A pathological complete response was observed in 22 patients (17%), a "good" response (Mandard 2-3) in 74 patients (56%), and a "poor" response (Mandard 4-5) in 36 patients (27%). An R0 resection was obtained in 83 patients (63%). The degree of pathological response was linearly correlated with the R0 resection rate (p = 0.026). In patients without synchronous metastases, pathological response was an independent predictor for LRFS, MFS and DFS (p = 0.004, p = 0.003 and p = 0.024, respectively), whereas R0 resection was an independent predictor for LRFS and OS (p = 0.020 and p = 0.028, respectively).

Conclusions

Induction chemotherapy in addition to neoadjuvant chemo(re)irradiation is a promising treatment strategy for patients with LRRC with high pathological response rates that translate into improved oncological outcomes, especially when an R0 resection has been achieved.

INTRODUCTION

Over the past decades, there have been significant improvements in the treatment of patients with rectal cancer. Due to the introduction of total mesorectal excision (TME) and the development of neoadjuvant (chemo)radiotherapy, the rate of locally recurrent rectal cancer (LRRC) has decreased from 20-30% to 6-10%.[1–3] However, patients who develop LRRC remain to have a limited prognosis with 5-year overall survival rates of approximately 30%.[4–7]

The most important prognostic factor influencing survival after surgery is a clear resection margin (R0 resection).[1,2,8–11] Achieving an R0 resection is challenging because of distorted anatomy due to previous TME surgery, the difficult distinction between fibrosis and malignant tissue after radiotherapy, and the ingrowth of the recurrent neoplasm into other structures, such as the adjacent organs, pelvic side wall, and the sacrum. To achieve downsizing of the local recurrence and consequently more R0 resections, neoadjuvant treatment with chemoradiotherapy is recommended.[12] However, a proportion of patients with LRRC have already received (chemo)radiotherapy for their primary tumour. Previous studies have shown that in these patients reirradiation with a dose of 30 Gy combined with capecitabine is safe and effective.[2,8] Alongside an R0 resection, a pathological complete response (pCR) may be of prognostic value in predicting long-term outcomes for LRRC patients.[13,14] Despite neoadjuvant treatment with chemo(re)irradiation, R0 resections are achieved in only 60% of cases and pCR rates are low (± 8%).[7,15]

The addition of induction chemotherapy to neoadjuvant chemo(re)irradiation may improve local downsizing and thereby improve the R0 resection and pCR rates. Furthermore, induction chemotherapy may eradicate occult micrometastases. Ultimately, this may improve long-term oncological outcomes. Our preliminary results showed a promising pCR rate with this treatment regimen.[16]

The current study evaluated the effect of induction chemotherapy administered prior to neoadjuvant chemo(re)irradiation on the pathological response and the R0 resection rate in an extended cohort and the predictive value of the pathological response on oncological outcomes.

METHODS

Patients

All patients with LRRC treated at the Catharina Hospital Eindhoven, a national tertiary referral centre for patients with advanced rectal cancer, were prospectively collected in a database. All consecutive patients who underwent a resection between January 2010 and December 2018 after neoadjuvant treatment with induction chemotherapy followed by neoadjuvant radiotherapy or reirradiation with or without concomitant chemotherapy were retrospectively identified and reviewed. From 2010 until 2014, induction chemotherapy was mostly administered to patients with irresectable or marginally resectable disease. From 2015 onward, the administration of induction chemotherapy became more common practice and evolved to the local standard of care in 2016. The decision to administer induction chemotherapy was made during a multidisciplinary tumour (MDT) board meeting including experienced surgeons, medical oncologists, radiation oncologists, radiologists, and nuclear medicine specialists. The present study was approved by the local medical ethics committee (registration number: W19.031).

Neoadjuvant treatment regimen

The general treatment regimen consisted of three cycles of CAPOX (capecitabine and oxaliplatin) or four cycles of FOLFOX (leucovorin, 5-fluorouracil, oxaliplatin). Induction chemotherapy was followed by radiotherapy with concomitant chemotherapy.

Radiotherapy dose depended on whether the patient had received previous radiotherapy. In radiotherapy-naïve patients, full course radiotherapy was delivered with a cumulative dose of 45-50 Gy in 25 fractions of 1.8-2 Gy. In case of previous radiotherapy, reirradiation consisted of 30-30.6 Gy in 15-17 fractions of 1.8-2 Gy. Concomitant chemotherapy agent was capecitabine (825 mg/m2 bid on radiotherapy days).

All patients were assessed for radiological response 2-3 weeks after completing the induction chemotherapy and 4-6 weeks after finishing the subsequent (chemo) radiotherapy. Restaging consisted of a pelvic MRI and a thoracoabdominal CT-scan with or without the addition of FDG-PET. All restaging imaging was discussed during the MDT meeting in our tertiary referral centre. In case of a radiological good response to induction chemotherapy, consolidation chemotherapy during the waiting time between (chemo)radiotherapy and surgery was considered. Consolidation chemotherapy consisted of one or two cycles of CAPOX or FOLFOX.

Surgery and Pathology

The type of surgery depended on the location of the recurrence and involvement of adjacent structures and was performed by experienced surgical oncologists. In accordance with the type of reconstructions, other specialists, such as a urologist or a plastic surgeon, were consulted. When assessed as necessary and feasible, e.g., when there was tumour adherence or no adequate soft tissue margin for a clear resection margin, intraoperative electron beam radiotherapy (IOERT) was administered in a dose of 10-12.5 Gy.

Synchronous metastases were treated during the waiting time between (chemo) radiotherapy and surgery or after surgery. Treatment consisted of local resection or otherwise local therapy, including radiofrequency ablation, microwave ablation, or stereotactic radiotherapy. Hyperthermic intraperitoneal chemotherapy (HIPEC) with mitomycin C was administered peroperative in case of limited peritoneal metastases.

Pathological specimens were revised by a specialised pathologist. Pathological response was scored according to the Mandard classification.[17] For survival analyses, pathological response was categorized as "complete" (Mandard 1), "good" (Mandard 2-3) or "poor" response (Mandard 4-5). An R0 resection was defined as a resection without tumour cells in any of the resection margins. An R1 resection was considered a resection with microscopically involved margins, and an R2 resection was considered a gross incomplete resection.

Study endpoints

Endpoints were pathological response, resection margin and overall, local recurrence-free, metastasis-free, and disease-free survival, as well as toxicity and complications caused by the treatment regimen. Overall survival (OS) was calculated from the date of start treatment until the date of death from any cause or censored at last follow-up. Local recurrence-free survival (LRFS) was calculated from the date of surgery until the date of local recurrence detected by imaging or histology or censored at last follow-up or death. Metastasis-free survival (MFS) was calculated from the date of surgery until the date of histologically or radiologically proven distant metastases or censored at last follow-up or death. Disease-free survival (DFS) was calculated from the date of surgery until the date of local recurrence or distant metastases or censored at last follow-up or death. Toxicity was retrospectively scored according to the Common Toxicity Criteria of the National Cancer Institute, and complications were scored according to the Clavien-Dindo classification.[18,19]

Statistics

Continuous data were reported as median (interquartile range) and categorical as count (percentage). Group comparisons were made using Chi-square or Mann-Whitney *U* test as appropriate. Survival analyses were performed using the (reversed) Kaplan-Meier method and comparisons were made using log-rank test. Multivariable analysis using the Cox proportional hazards model was performed on variables with a $p < 0.1$ on univariable analysis. Two-sided p values < 0.05 were considered statistically significant. All statistical analyses were performed using IBM SPSS Statistics version 25.0 for Windows (IBM Corp, Armonk, NY).

RESULTS

Patients and Treatment characteristics

In total, 132 patients with LRRC were treated with induction chemotherapy and subsequent (chemo)(re)irradiation and surgery between January 2010 and December 2018. Patient characteristics and characteristics about the primary tumour are presented in *Table 1*, and *Table 2* shows the characteristics of the recurrent tumour. Most patients included had a first recurrence (n = 116, 88%). Twenty-nine patients (22%) had a history of metastases at time of diagnosis of the recurrence, and 35 patients were diagnosed with synchronous metastases (27%).

Induction chemotherapy consisted of CAPOX in 97 patients (73%). In 22 of 97 patients, bevacizumab was added to the induction chemotherapy. Ten patients (8%) received FOLFOX. Twenty-five (19%) patients received another chemotherapy regimen (mainly FOLFIRI). In the majority of patients, induction chemotherapy was followed by (chemo) reirradiation (82%). Consolidation chemotherapy was administered in 15% of patients.

Pathological response, Resection margin, and Oncological outcomes

A pathological complete response was observed in 22 of 132 patients (17%), Mandard 2 in 21 (16%), Mandard 3 in 53 (40%), Mandard 4 in 31 (24%), and Mandard 5 in 5 (4%) patients. A clear resection margin was achieved in 83 patients (63%), an R1 resection in 46 patients (35%), and 3 patients had an R2 resection (2%).

Median OS, DFS, LRFS, and MFS for all patients were 47, 12, 18, and 18 months, respectively. OS, DFS, LRFS, and MFS were 52, 13, 21, and 26 months for patients without synchronous metastases (n = 97) and 27, 7, 11, and 8 months for patients with synchronous metastases (n = 35) [95% confidence interval (CI) 0.792-2.968; $p = 0.205$, 95% CI 1.900-4.967; $p < 0.001$, 95% CI 0.833-2.777; $p = 0.173$, 95% CI 2.061-6.306; $p <$

0.001, respectively]. Due to the differences in oncological outcomes between these two groups, the results of patients with and without synchronous metastases will be discussed separately in the following sections.

Table 1 Baseline and primary tumour characteristics

		Total (N=132) N (%)
Gender	Female	37 (28)
	Male	95 (72)
Age (years)[a]	Median [IQR]	65 [58-71]
ASA[a]	I	3 (2)
	II	107 (81)
	III	22 (17)
Tumour stage[b]	T2	11 (8)
	T3	92 (70)
	T4	27 (21)
Nodal stage[c]	N0	41 (31)
	N1	46 (35)
	N2	41 (31)
Neoadjuvant radiotherapy	None	36 (27)
	Radiotherapy	34 (26)
	Chemoradiotherapy	62 (47)
Surgical procedure	Sigmoid resection	18 (14)
	LAR	67 (51)
	APR	47 (36)
Adjuvant therapy[d]	None	113 (86)
	Chemotherapy	17 (13)
	Radiotherapy	3 (2)

Abbreviations: APR = abdominoperineal resection, IQR = interquartile range, LAR = low anterior resection.

[a] At time of surgery for recurrent tumour. [b] Missing value in N = 2. [c] Missing value in N = 4.

[d] One patient received both adjuvant chemotherapy and radiotherapy.

Table 2 Characteristics recurrent tumour and treatment

		Total (N=132) N (%)
Number local recurrence	First	116 (88)
	Second/third	16 (12)
Multifocality	Yes	27 (20)
	No	105 (80)
Lateral involvement	Yes	69 (52)
	No	63 (48)
History of metastases	Yes	29 (22)
	No	103 (78)
Synchronous metastases	Yes	35 (27)
	No	97 (73)
Type metastasis[a]	Liver	13
	Lung	10
	Inguinal lymph nodes	2
	Peritoneal	10
	Other	3
Neoadjuvant radiotherapy	(chemo)radiotherapy	24 (18)
	(chemo)reirradiation	108 (82)
Surgical procedure	LAR	14 (11)
	APR	16 (12)
	Multivisceral resection	50 (38)
	Total pelvic exenteration	25 (19)
	Resection n.o.s.	27 (20)
HIPEC	Yes	8 (4)
	No	124 (96)
IOERT	Yes	111 (84)
	No	21 (16)
Time to recurrence (months)[b]	Median [IQR]	32 [21 - 51]
Time radiotherapy-surgery (weeks)	Median [IQR]	12 [10-14]
Blood loss (ml)	Median [IQR]	2350 [1225 - 3500]

Abbreviations: APR = abdominoperineal resection, HIPEC = hyperthermic intraperitoneal chemotherapy, IOERT = intraoperative electron beam radiotherapy, LAR = low anterior resection, Resection n.o.s: resection not otherwise specified, resection recurrence without bowel resection.

[a] Some patients had metastases in more than one organ.

[b] Time between primary surgery and current recurrence.

Patients without synchronous metastases

A complete pathological response was observed in 18 patients (19%), a "good" response in 56 patients (Mandard 2-3, 58%), and a "poor" response in 23 patients (Mandard 4-5, 24%).

Univariable analyses are shown in *Table 3*. For overall survival, only resection margin remained significant after multivariable analysis (95% CI 1.059-4.272; $p = 0.034$), with a hazard ratio (HR) of 2.1 for death after an irradical resection. Median survival for patients with an R0 resection was 54 months versus 29 months otherwise. When comparing complete responders with non-complete responders (Mandard 2-5), multivariable analyses demonstrated a significant improved effect of complete response for OS with a 3-year OS of 92% versus 57% respectively (HR 4.706; 95% CI 1.063-20.833; $p = 0.045$; *Figure 1a, b*).

For disease-free survival, only response remained significant after multivariable analysis (HR 2.070; 95% CI 0.904-4.736 for "good" responders and HR 3.525; 95% CI 1.388-8.951 for "poor" responders; $p = 0.024$). Median DFS for complete responders, good responders, and poor responders was 35, 14, and 11 months, respectively.

For local recurrence-free survival, response (HR 2.232; 95% CI 0.787-6.328 for "good" responders and HR 5.684; 95% CI 1.776-18.191 for "poor" responders; $p = 0.004$), resection margin (HR 2.104; 95% CI 1.125-3.933; $p = 0.020$), and lymph node status of the primary tumour (HR 0.816; 95% CI 0.388-1.719 for N1 and HR 2.156; 95% CI 1.001-4.640 for N2; $p = 0.036$) remained significant after multivariable analysis (*Figure 1a, b*).

For metastasis-free survival, only response was significant after univariable analyses ($p = 0.003$). Hazard ratios were 2.0 and 5.0 for good and poor responders compared with complete responders. Median MFS for complete responders was not reached (3-year MFS 75%), 45 months for good responders, and 11 months for poor responders (*Figure 1a, b*).

Table 3 Univariable analyses for risk factors for distant metastasis, local recurrence, disease-free and overall survival

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age			0.710			0.491			0.856			0.514
	1.007	0.971-1.044		0.989	0.957-1.021		0.997	0.970-1.026		1.013	0.974-1.053	
Gender			0.642			0.349			0.522			0.785
Female	1.00			1.00			1.00			1.00		
Male	1.192	0.567-2.507		1.378	0.705-2.693		1.208	0.677-2.157		0.904	0.437-1.870	
ASA			0.926			0.730			0.285			0.898
1-2	1.00			1.00			1.00			1.00		
3	1.050	0.373-2.957		0.835	0.299-2.329		0.575	0.209-1.585		1.081	0.328-3.558	
T stage primary			0.644			0.650			0.985			0.746
2	1.00			1.00			1.00			1.00		
3	0.718	0.297-1.735		1.459	0.520-4.098		1.072	0.484-2.375		1.193	0.419-3.398	
4	0.576	0.175-1.892		1.770	0.531-5.903		1.049	0.389-2.827		0.767	0.170-3.466	
N stage primary			0.792			**0.034**			0.150			0.366
0	1.00			1.00			1.00			1.00		
1	1.018	0.477-2.171		0.726	0.361-1.461		0.842	0.459-1.542		0.744	0.332-1.668	
2	1.304	0.603-2.818		1.827	0.928-3.607		1.536	0.839-2.810		1.311	0.613-3.022	
Neoadjuvant RTx primary			0.696			**0.043**			**0.055**			0.171
None	1.00			1.00			1.00			1.00		

Table 3 (Continued)

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
5x5Gy radiotherapy	1.191	0.492-2.888		1.539	0.637-3.718		1.765	0.834-3.738		1.216	0.466-3.177	
(Chemo)radiotherapy	1.401	0.635-3.095		2.558	1.162-5.629		2.319	1.165-4.613		2.061	0.890-4.771	
Type of surgery primary			0.156			0.837			0.309			0.093
Sigmoid resection	1.00			1.00			1.00			1.00		
LAR	1.678	0.489-5.749		1.334	0.511-3.484		1.857	0.721-4.779		0.694	0.248-1.938	
APR	2.695	0.798-9.101		1.311	0.488-3.521		2.113	0.811-5.501		1.519	0.555-4.1607	
Adjuvant chemotherapy			0.756			0.637			0.792			0.914
No	1.00			1.00			1.00			1.00		
Yes	1.148	0.481-2.739		0.840	0.408-1.731		0.916	0.478-1.757		1.049	0.438-2.516	
Number local recurrence			0.241			0.917			0.462			0.588
1st	1.00			1.00			1.00			1.00		
2nd/3rd	0.241	0.152-1.606		0.952	0.376-2.411		0.729	0.314-1.692		1.302	0.501-3.383	
History metastases			0.833			0.734			0.398			0.416
No	1.00			1.00			1.00			1.00		
Yes	0.833	0.382-2.170		1.141	0.534-2.441		1.325	0.690-2.543		0.610	0.185-2.010	
Neoadjuvant radiotherapy			0.535			0.182			0.312			0.376
(Chemo)radiotherapy	1.00			1.00			1.00			1.00		
(Chemo)reirradiation	0.782	0.360-1.700		1.877	0.744-4.733		1.466	0.698-3.076		1.533	0.595-3.946	

Table 3 (Continued)

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Type of surgery			0.797			0.890			0.763			0.833
LAR	1.00			1.00			1.00			1.00		
APR	0.571	0.104-3.134		1.702	0.421-6.889		1.679	0.482-5.846		0.533	0.058-4.900	
Multivisceral resection	1.145	0.393-3.331		1.451	0.508-4.143		1.662	0.651-4.244		1.228	0.417-3.617	
Resection nos	1.198	0.383-3.745		1.404	0.460-4.282		1.536	0.567-4.158		1.301	0.406-4.168	
IOERT			0.848			0.866			0.542			0.682
No	1.00			1.00			1.00			1.00		
Yes	0.918	0.384-2.193		1.077	0.456-2.544		1.277	0.581-2.808		0.682	0.283-1.645	
Resection margin			0.112			**<0.001**			**<0.001**			**<0.001**
R0	1.00			1.00			1.00			1.00		
R1/2	1.678	0.887-3.176		3.595	2.042-6.330		2.541	1.524-4.236		3.271	1.699-6.298	
Response			**0.003**			**<0.001**			**0.002**			**0.012**
pCR	1.00			1.00			1.00			1.00		
Good response	1.689	0.627-4.552		2.893	1.112-7.526		2.278	1.053-4.927		6.236	1.461-26.624	
Poor response	4.361	1.585-12.000		6.754	2.467-18.494		4.296	1.869-9.876		9.501	2.124-42.497	

Abbreviations: APR = abdominoperineal resection, IOERT = intraoperative electron beam radiotherapy, LAR = low anterior resection, pCR = pathological complete response, Resection n.o.s = resection not otherwise specified, resection recurrence without bowel resection, RTx = radiotherapy.

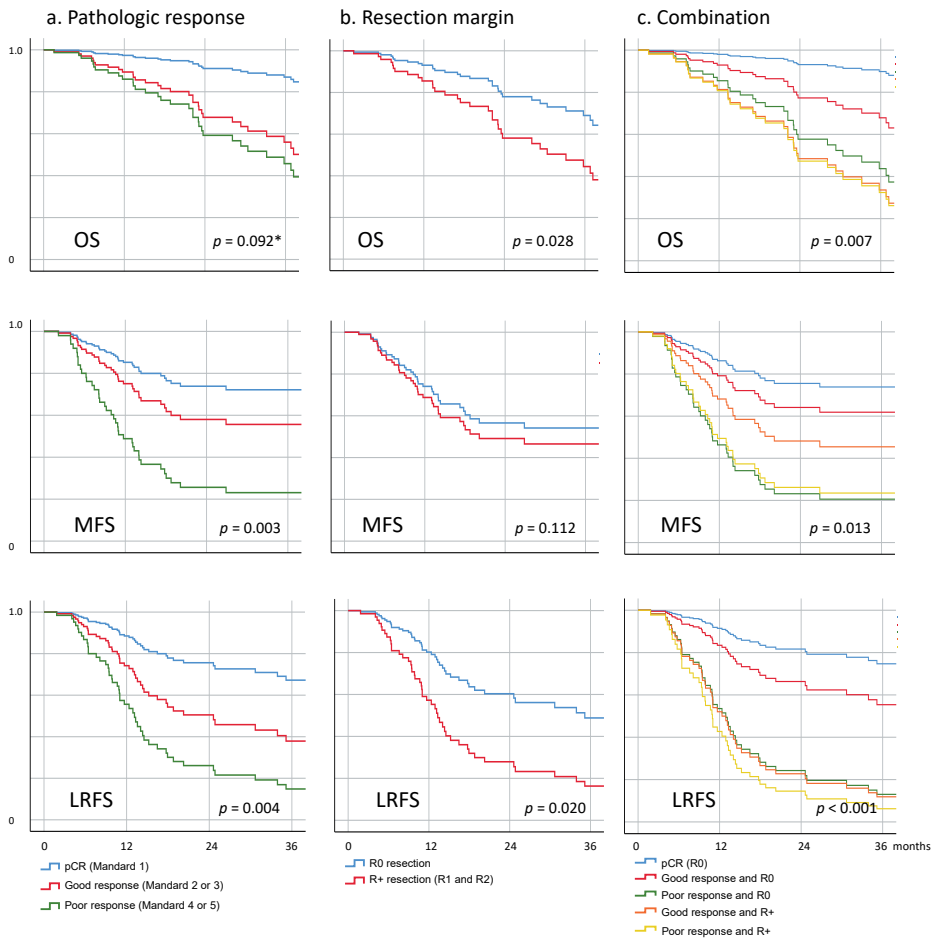

Figure 1 Pathological response to treatment (a) and achievement of R0 resection (b) are independent prognostic variables after multivariable analysis. Combination of these variables helps to fine-tune prognosis (c)

Abbreviations: OS = overall survival, MFS = metastasis-free survival, LRFS = local recurrence-free survival.
* Only for complete versus non-complete responders significant (p = 0.045).

For all oncological outcome parameters, both response and complete resection were the most independent predictive variables. By definition, all complete responders have an R0 resection. However, there is also a linear relation between increasing response and the rate of R0 resections (p = 0.026, *Figure 2*). Therefore, both variables were combined to see whether outcome prediction can be fine-tuned and may help to make treatment decisions. Five new categories were analysed: pCR (automatically R0), good response and R0 resection, poor response and R0 resection, good response and R1/R2 (R+) resection, and finally, poor response and R+ resection. In *Figure 1c*, the

outcome of combining these variables is shown. Complete responders consistently demonstrate an excellent outcome for OS, MFS, and LRFS. In addition, patients with a good response and R0 resection (n = 45) show an outcome almost as good as patients with a pCR for all outcome parameters. Poor responders with an R0 resection (n = 16) have a less favourable metastasis-free survival compared with good responders with an R+ resection (n = 29). Patients with a poor response and R0 resection have a similar LRFS compared with patients with a good response but R+ resection.

Patients with synchronous metastases

Patients presenting with LRRC and synchronous metastases had overall a poor oncological outcome. None of the patients had a DFS extending beyond two years. An R0 resection was a prognostic factor for overall survival and local recurrence (HR 0.237; 95% CI 0.063-0.894; $p = 0.033$ and HR 0.236; 95% CI 0.73-0.768; $p = 0.016$ respectively). Median OS was not reached for patients with an R0 resection (3-year OS 68%) and median OS was 23 months after an irradical resection. Median LRFS was not reached for patients with an R0 resection (3- year LRFS 72%) and median LRFS was 10 months after an R+ resection. Median MFS was 8 months irrespective of response to treatment or resection margin.

Toxicity and Complications

Data on toxicity caused by induction chemotherapy were available for 125 of 132 patients. Grade 3-4 toxicity was observed in 12 of 125 patients (10%). No grade 5 toxicity was seen. Details on chemoradiotherapy toxicity were available for 121 of 132 patients. Grade 3-4 toxicity was reported in only 2 of 121 patients (2%), and no grade 5 toxicity was seen.

Postoperatively, the most common complications were ileus/gastroparesis (n = 31), urological complications (n = 21), pneumonia (n = 19), presacral abscess (n = 17), urinary tract infection (n = 14), and wound infection (n = 13). Major postoperative complications (Clavien-Dindo ≥ 3) were observed in 41 of 132 patients (31%). There was no in-hospital mortality, but one patient died within 30 days of surgery as she refused further treatment. In the 41 patients with major postoperative complications there were 46 complications with a Clavien-Dindo ≥ 3 of which 34 complications required a surgical reintervention, 10 required an endoscopic/radiological intervention, and 3 required ICU admittance. The type of complications are shown in *Table 4*.

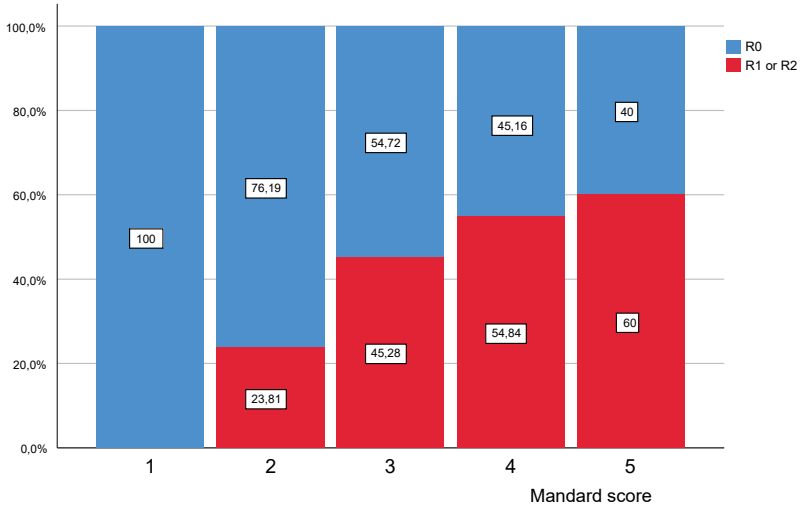

Figure 2 Significant linear relation between increasing Mandard score and probability of a positive resection margin

Abbreviations: R0 = resection with clear margins, R1/2 = resection with involved margins.

Table 4 Complications Clavien-Dindo ≥ 3

	Total N=46
Presacral abscess	13 (28)
Intraabdominal abscess	6 (13)
Urological	8 (17)
Ileus/gastroparesis	4 (9)
Wound infection	3 (7)
Wound dehiscence	3 (7)
Pneumonia	2 (4)
Anastomotic leakage	1 (2)
Colon perforation	1 (2)
Compartment syndrome lower leg	1 (2)
Metabolic acidosis	1 (2)
Other	3 (8)

DISCUSSION

In this study, we observed a 17% pathological complete response rate in patients with locally recurrent rectal cancer after treatment with induction chemotherapy and chemo(re)irradiation resulting in an excellent 3-year overall survival of 92% in these patients. In addition, this study shows pathological response to be a powerful prognostic variable of improved oncological outcomes in LRRC patients, especially when an R0 resection has been achieved.

Comparing the pathological complete response rate with the literature is challenging, because data are limited on neoadjuvant treatment strategies for locally recurrent rectal cancer. The administration of induction chemotherapy before chemoradiotherapy has been studied to a greater extent in patients with locally advanced rectal cancer (LARC), although evidence is mainly from retrospective nature or phase II trials. When focusing only on studies that administered either neoadjuvant CAPOX or FOLFOX followed by (chemo)radiotherapy, the results are inconsistent. Some studies showed a rather disappointing pCR rate when comparing their results with the pCR rate after chemoradiotherapy alone as reported in the literature, whereas others demonstrated promising pCR rates ranging between 33-40%.[20–27] The pCR rate in our study is rather low when compared with the latter findings in LARC; however, it has to be noted that LRRC has proven to be relatively chemoradio-resistant. Hence, it is to be expected that pCR rates are lower in patients with recurrent disease even if treatment regimens are comparable. The pCR rate of 17% is comparable with pCR rates after chemoradiotherapy for LARC.[15] When comparing our results with previously reported pCR rates in patient with LRRC, our treatment regimen with induction chemotherapy and chemoradiotherapy seems superior to treatment with neoadjuvant chemoradiotherapy alone as pCR rates are 17% versus 4-9% respectively.[14–16] The current findings are in line with the results published earlier by our group in which a 17% pCR rate was observed after treatment with induction chemotherapy followed by reirradiation.[16] Another study performed by our group demonstrated a 31% pCR rate, but it has to be noted that in this study only lateral recurrences were included, and these recurrences may represent a different etiology.[28]

The 92% 3-year OS for patients with a pCR in this study is superior to the survival rates reported for patients with LRRC after treatment with solely neoadjuvant (chemo) radiotherapy. For R0 resections, 3-year OS varies between 40 and 55%.[1,10,11,29,30] Data on survival for LRRC patients with a pCR are limited. Wiig et al. showed a 80% 3-year survival for LRRC after pCR.[14] Our preliminary results also showed a 3-year survival of

92% for patients with a pCR.[16] Notably, more than half of complete responders had recurrent disease at 3 years.

Although patients with a pCR have excellent oncological outcomes, patients with a good response (Mandard 2-3) also showed improved outcomes. There have been no previous reports about the prognostic value of response on neoadjuvant treatment in patients with locally recurrent rectal cancer. There have been several studies assessing the prognostic value of tumour regression in patients with LARC. Most studies showed that the extent of response was a significant independent prognostic factor for long-term oncological outcomes, which supports the findings in our study.[31–35] Together with the observation that there is a significant linear relation between the degree of response and the R0 resection rate, this underlines the necessity of adequate neoadjuvant treatment in patients with LRRC. Potential bias caused by whether or not patients received neoadjuvant treatment for the primary tumour was investigated by Chi-square test (data not shown) and showed no correlation, suggesting that induction chemotherapy is sufficient for tumour downstaging regardless of prior treatment. Future research to establish whether a correlation exists between radiological and pathological response could help to identify patients in whom a different treatment approached may be justified.

The R0 resection rate in this study was 63%, which is consistent compared to findings in the literature after treatment with neoadjuvant chemoradiotherapy alone. However, in this study 21% of the included patients were considered irresectable at primary staging.

For patients with synchronous metastases the story seems different. LRRC patients with synchronous metastases clearly have a more aggressive biological behaviour of their tumour, which is characterised by rapid progression and decreased disease-free survival. For these patients, a different approach and different counselling may be indicated.

This study is limited by its retrospective character. Many patients underwent their preoperative treatment in the referring hospitals and therefore data on toxicity of treatment are not complete. Besides, drop-out rates during neoadjuvant treatment were not available as progressive disease under induction chemotherapy may have occurred and these patients have never been referred back for surgery. Nevertheless, the available data on toxicity implicates that treatment was well tolerated. Furthermore, neoadjuvant treatment regimen combining induction chemotherapy with chemoradiotherapy resulted in major postoperative morbidity in 32% of the patients. This percentage is comparable to the literature, suggesting that the addition

of induction chemotherapy does not lead to more postoperative complications when comparing it with the current standard treatment of neoadjuvant chemoradiotherapy.[4,36]

The retrospective character of this study also leads to heterogeneity regarding oncological history and manifestation of the local recurrence of the patients included in this study. This study is however a good representation of the clinical practice and is, to our knowledge, the largest series to date of patients treated with induction chemotherapy and subsequent chemo(re)irradiation for locally recurrent rectal cancer.

CONCLUSIONS

This study shows a high pCR rate in patients with LRRC after treatment with induction chemotherapy and chemo(re)irradiation, translating into exceptional outcomes in these patients. In addition, response to neoadjuvant treatment is a powerful predictor of improved oncological outcome, underlining the importance of achieving a good response. To determine whether the addition of induction chemotherapy to chemo(re) irradiation in the treatment of LRRC improves outcomes for curative treatment of LRRC in general, a randomised controlled trial is warranted.

REFERENCES

1. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569
2. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review. *Dis Colon Rectum*. 2016;59(2):148-156. doi:10.1097/DCR.0000000000000547
3. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi:10.1056/NEJMoa010580
4. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. *Color Dis*. 2011;13(7):732-742. doi:10.1111/j.1463-1318.2009.02167.x
5. Kusters M, Dresen RC, Martijn H, et al. Radicality of Resection and Survival After Multimodality Treatment is Influenced by Subsite of Locally Recurrent Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1444-1449. doi:10.1016/j.ijrobp.2009.01.015
6. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *Eur J Surg Oncol*. 2018;44(1):100-107. doi:10.1016/j.ejso.2017.11.013
7. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y
8. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1129-1139. doi:10.1016/j.ijrobp.2005.09.017
9. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol*. 2008;15(7):1937-1947. doi:10.1245/s10434-008-9896-z
10. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388
11. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866-1873. doi:10.1002/bjs.10645
12. Tekkis P, Road F. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. *Br J Surg*. 2013;100(8):1009-1014. doi:10.1002/bjs.9192

13. Vermaas M, Ferenschild FTJ, Nuyttens JJME, et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer. *Dis Colon Rectum*. 2005;48(5):918-928. doi:10.1007/s10350-004-0891-6

14. Wiig JN, Larsen SG, Dueland S, Giercksky KE. Clinical outcome in patients with complete pathologic response (pT0) to preoperative irradiation/chemo-irradiation operated for locally advanced or locally recurrent rectal cancer. *J Surg Oncol*. 2005;92(1):70-75. doi:10.1002/jso.20340

15. Yu SKT, Bhangu A, Tait DM, Tekkis P, Wotherspoon A, Brown G. Chemoradiotherapy response in recurrent rectal cancer. *Cancer Med*. 2014;3(1):111-117. doi:10.1002/cam4.169

16. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg*. 2018;105(4):447-452. doi:10.1002/bjs.10694

17. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680-2686. doi:10.1002/1097-0142(19940601)73:11<2680::aid-cncr2820731105>3.0.co;2-c

18. Common Terminology Criteria for Adverse Events (CTCAE) v.5.0. National Cancer Institute. 2009. https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf.

19. Dindo D, Demartines N, Clavien P-A. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. *Ann Surg*. 2004;240(2):205-213. doi:10.1097/01.sla.0000133083.54934.ae.

20. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, l. *J Clin Oncol*. 2010;28(5):859-865. doi:10.1200/JCO.2009.25.8541

21. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol*. 2006;24(4):668-674. doi:10.1200/JCO.2005.04.4875

22. Chua YJ, Barbachano Y, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin before chemoradiotherapy and total mesorectal excision in MRI-defined poor-risk rectal cancer: a phase 2 trial. *Lancet Oncol*. 2010;11(3):241-248. doi:10.1016/S1470-2045(09)70381-X

23. Yu X, Wang QX, Xiao WW, et al. Neoadjuvant oxaliplatin and capecitabine combined with bevacizumab plus radiotherapy for locally advanced rectal cancer: results of a single-institute phase II study. *Cancer Commun (London, England)*. 2018;38(1):24. doi:10.1186/s40880-018-0294-z

24. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant Chemotherapy First, Followed by Chemoradiation and Then Surgery, in the Management of Locally Advanced Rectal Cancer. *J Natl Compr Canc Netw*. 2014;12(4):513-519. doi:10.6004/jnccn.2014.0056

25. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. *Lancet Oncol*. 2015;16(8):957-966. doi:10.1016/S1470-2045(15)00004-2

26. Perez K, Safran H, Sikov W, et al. Complete neoadjuvant treatment for rectal cancer: The Brown University Oncology Group CONTRE study. *Am J Clin Oncol Cancer Clin Trials*. 2017;40(3):283-287. doi:10.1097/COC.0000000000000149

27. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071

28. Kusters M, Bosman SJ, Van Zoggel DMGI, et al. Local Recurrence in the Lateral Lymph Node Compartment: Improved Outcomes with Induction Chemotherapy Combined with Multimodality Treatment. *Ann Surg Oncol*. 2016;23(6):1883-1889. doi:10.1245/s10434-016-5098-2

29. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br J Surg*. 2018;105(6):650-657. doi:10.1002/bjs.10734

30. Tanis PJ, Doeksen A, Van Lanschot JJB. Intentionally curative treatment of locally recurrent rectal cancer: A systematic review. *Can J Surg*. 2013;56(2):135-144. doi:10.1503/cjs.025911

31. Vecchio FM, Valentini V, Minsky BD, et al. The relationship of pathologic tumor regression grade (TRG) and outcomes after preoperative therapy in rectal cancer. *Int J Radiat Oncol Biol Phys*. 2005;62(3):752-760. doi:10.1016/j.ijrobp.2004.11.017

32. Peng YF, Yu WD, Pan H Da, et al. Tumor regression grades: Potential outcome predictor of locally advanced rectal adenocarcinoma after preoperative radiotherapy. *World J Gastroenterol*. 2015;21(6):1851-1856. doi:10.3748/wjg.v21.i6.1851

33. Mace AG, Pai RK, Stocchi L, Kalady MF. American joint committee on cancer and college of American pathologists regression grade: A new prognostic factor in rectal cancer. *Dis Colon Rectum*. 2015;58(1):32-44. doi:10.1097/DCR.0000000000000266

34. Mancini R, Pattaro G, Diodoro MG, et al. Tumor Regression Grade After Neoadjuvant Chemoradiation and Surgery for Low Rectal Cancer Evaluated by Multiple Correspondence Analysis: Ten Years as Minimum Follow-up. *Clin Colorectal Cancer*. 2018;17(1):e13-e19. doi:10.1016/j.clcc.2017.06.004

35. Rödel C, Martus P, Papadoupolos T, et al. Prognostic Significance of Tumor Regression After Preoperative Chemoradiotherapy for Rectal Cancer. *J Clin Oncol*. 2005;23(34):8688-8696. doi:10.1200/JCO.2005.02.1329

36. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer. *Ann Surg*. 2019;269(2):315-321. doi:10.1097/SLA.0000000000002528

CHAPTER 10

CURATIVE TREATMENT OF LOCALLY RECURRENT RECTAL CANCER: IS INDUCTION CHEMOTHERAPY WARRANTED?

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Locally recurrent rectal cancer (LRRC) is associated with severe morbidity and a poor prognosis, even after treatment with curative intent. This is caused by a high rate of locoregional recurrence and distant metastases. A resection with clear resection margins (R0 resection) is the most important prognostic factor for survival.[1] To increase the R0 resection rate, downstaging of LRRC with neoadjuvant treatment is the standard of care, with full-course chemoradiotherapy considered the treatment of choice.[2] Nevertheless, R0 resection rates remain low. Moreover, previous radiotherapy for the primary tumour hinders the administration of radiotherapy, although reirradiation is considered the standard of care in some countries.[3]

To improve outcomes for patients with LRRC, induction chemotherapy (ICT) is increasingly being applied; ICT may increase downstaging by itself and enhance tumour sensitivity to radiotherapy by improving tumour vascularity. Moreover, it has the potential to eradicate micrometastases.

Evidence for additional value of ICT in LRRC is lacking. In the Catharina Hospital Eindhoven, a tertiary referral centre, the current standard of care is ICT in addition to chemo(re)irradiation (CRT). Initially, ICT was offered only to patients with unresectable LRRC. Since 2014, it has been implemented gradually for all patients with LRRC, with 48% of surgically treated patients receiving ICT in 2015 up to 88% in 2019.

The authors recently reported the results for 132 patients with LRRC treated with ICT + CRT and surgery. The pathological complete response (pCR) rate was 17%. However, the R0 resection rate was not superior to rates reported in other studies describing different treatment strategies.[4]

To further explore these findings, results for patients who underwent surgery for LRRC between 2009 and 2013 (period 1; ICT not standard of care) were compared with those for patients who underwent surgery between 2014 and 2018 (period 2; ICT local standard of care). In period 1, 20 of 127 patients (15.7%) received ICT compared with 113 of 171 patients (66.1%) in period 2 ($p < 0.001$). The pCR rate was 7.9% and 15.8%, respectively ($p = 0.040$). However, the R0 resection rate did not differ significantly (59.1% vs. 68.4%, respectively, $p = 0.095$). The 3-year disease-free survival (DFS) was also comparable; 26.2% (median 12.8 months) versus 25.1% (median 12.3 months), respectively ($p = 0.893$, *Figure 1a*).

In addition, patients with LRRC who received ICT + CRT (n = 133, 48.7%) were compared with those who received CRT alone (n = 140, 51.3%) between 2010 and 2018. The pCR rate was 16.5% in the ICT + CRT group versus 8.6% in the CRT group ($p = 0.046$).

Again, the R0 resection rate did not differ significantly (63.2% vs. 64.3%, respectively; $p = 0.846$). The 3-year DFS was also similar: 21.3% (median 11.9 months) versus 26.7% (median 12.9 months), respectively ($p = 0.412$) (*Figure 1b*).

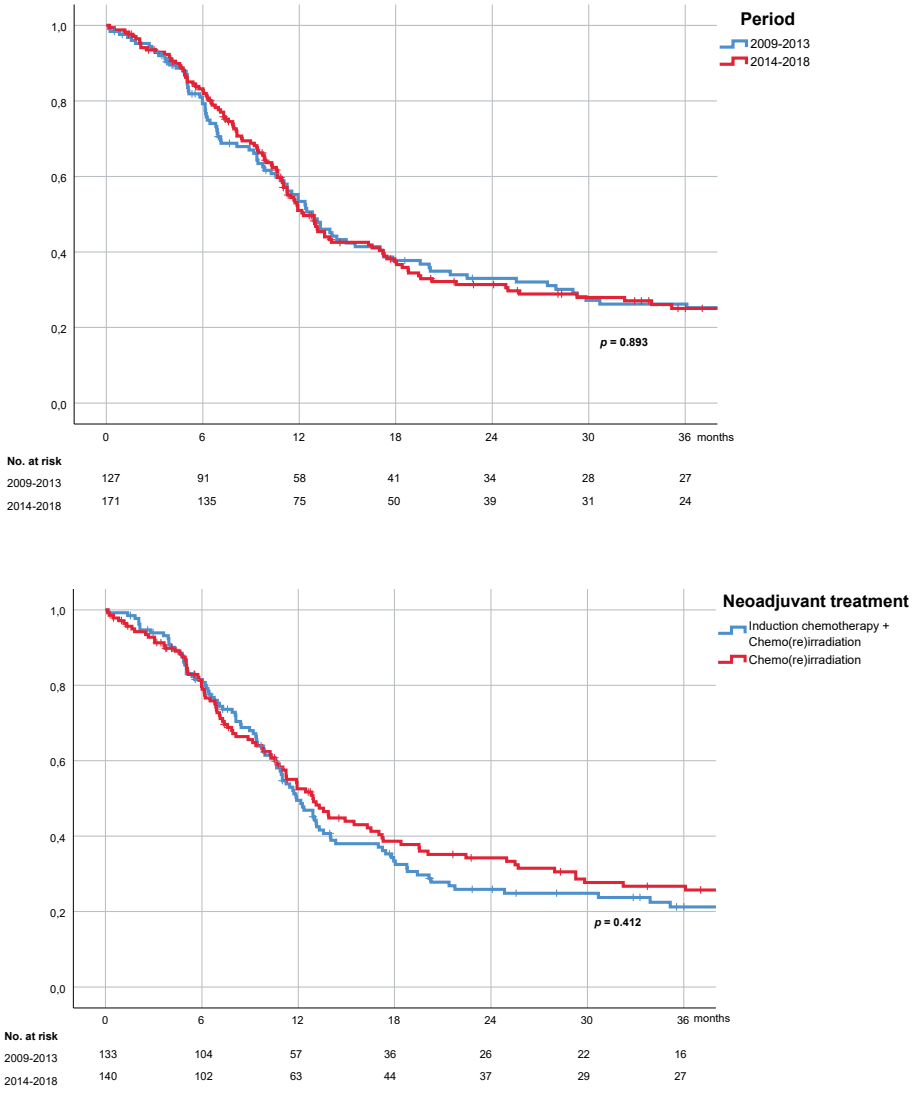

Figure 1 Disease-free survival according to treatment period and type of neoadjuvant treatment

Disease-free survival in **a** period 2009-2013 (induction chemotherapy not local standard of care) versus period 2014-2018 (induction chemotherapy local standard of care), and **b** after treatment with induction chemotherapy, chemo(re)irradiation and surgery versus chemo(re)irradiation and surgery alone. **a** $p = 0.893$, **b** $p = 0.412$

Many confounding factors may explain why the R0 resection rate and DFS did not seem to benefit from the addition of ICT: patients receiving ICT + CRT more often received radiotherapy for the primary tumour (72.9% vs. 48.6%, $p < 0.001$); in the ICT + CRT group, more patients received reirradiation than in the CRT group (81.2% vs. 53.6%, $p < 0.001$); in both analyses, patients treated with ICT more often had synchronous metastases; escalation of treatment by adding ICT was considered justified specifically in patients with the poorest prognosis; and no data were available for patients in whom surgery was omitted owing to toxicity or progressive disease.

Although the increased pCR rate implied increased downstaging, the lack of effect on the R0 resection rate and DFS do not substantiate the efficacy of ICT in the treatment of LRRC. Additionally, data on toxicity and compliance are lacking. An RCT is warranted; the PelvEx II trial will randomise patients with LRRC after previous partial or total mesorectal resection, without synchronous distant metastases, to receive either ICT followed by CRT and surgery or CRT alone and surgery.[5]

REFERENCES

1. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866-1873. doi:10.1002/bjs.10645
2. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2017;28(Suppl 4):iv22-iv40. doi:10.1093/annonc/mdx224
3. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569
4. Voogt ELK, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4
5. PelvEx Collaborative. Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomised controlled study (PelvEx II). *BJS Open - In Press*. 2021.

CHAPTER 11

INDUCTION CHEMOTHERAPY FOLLOWED BY CHEMORADIOTHERAPY VERSUS CHEMORADIOTHERAPY ALONE AS NEOADJUVANT TREATMENT FOR LOCALLY RECURRENT RECTAL CANCER: STUDY PROTOCOL OF A MULTICENTRE, OPEN-LABEL, PARALLEL-ARMS, RANDOMISED CONTROLLED STUDY (PELVEX II)

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ABSTRACT

Background

A resection with clear margins (R0 resection) is the most important prognostic factor in patients with locally recurrent rectal cancer (LRRC). However, this is achieved in only 60% of patients. The aim of this study is to investigate whether the addition of induction chemotherapy to neoadjuvant chemo(re)irradiation improves the R0 resection rate in LRRC.

Methods

This multicentre, international, open-label, phase III, parallel-arms study will enrol 364 patients with resectable LRRC after previous or total mesorectal resection without synchronous distant metastases or recent chemo- and/or radiotherapy treatment. Patients will be randomised to receive either induction chemotherapy (three 3-weekly cycles of CAPOX (capecitabine, oxaliplatin), four 2-weekly cycles of FOLFOX (5-fluorouracil, leucovorin, oxaliplatin) or FOLFIRI (5-fluorouracil, leucovorin, irinotecan)) followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm). Tumours will be restaged using MRI and, in the experimental arm, a further cycle of CAPOX or two cycles of FOLFOX/FOLFIRI will be administered before chemoradiotherapy in case of stable or responsive disease. The radiotherapy dose will be 25 x 2.0 Gy or 28 x 1.8 Gy in radiotherapy-naïve patients, and 15 x 2.0 Gy in previously irradiated patients. The concomitant chemotherapy agent will be capecitabine administered twice daily at a dose of 825 mg/m^2 on radiotherapy days. The primary endpoint of the study is the R0 resection rate. Secondary endpoints are long-term oncological outcomes, radiological and pathological response, toxicity, postoperative complications, costs, and quality of life.

Discussion

This trial protocol describes the PelvEx II study. PelvEx II , designed as a multicentre, open-label, phase III, parallel-arms study, is the first randomised study to compare induction chemotherapy followed by neoadjuvant chemo(re)irradiation and surgery with neoadjuvant chemo(re)irradiation and surgery alone in patients with locally recurrent rectal cancer, with the aim of improving the number of R0 resections.

BACKGROUND

Locally recurrent rectal cancer (LRRC) occurs in 6-10% of patients who undergo intentionally curative surgery for primary rectal cancer.[1,2] To cure patients with LRRC, achieving a resection with clear resection margins (R0 resection) is imperative.[2–8] When an R0 resection is achieved, 5-year overall survival rates vary between 48% and 58%, whereas a resection without clear resection margins (R1/2 resection) results in a 5-year survival of only 10-18%. Moreover, incomplete resections are associated with 5-year local re-recurrence rates of 70-80%, and often result in severe morbidity, poor quality of life, and/or death [5,6,9–13]

Unfortunately, the attempt to achieve an R0 resection often fails because of challenging anatomy due to previous surgery, the presence of fibrosis as a result of previous radiotherapy, and the involvement of other structures such as the adjacent organs, pelvic side wall, and sacrum. To increase the chance of achieving an R0 resection, neoadjuvant treatment with chemoradiotherapy is considered the standard of care in many institutions.[14] In patients who received pelvic radiotherapy previously, reirradiation with a dose of 30 Gy has been proven to be safe and effective.[3,15] Despite the use of neoadjuvant chemo(re)irradiation, R0 resections are achieved in only 60% of patients.[16,17] Therefore, there is ongoing research to optimise the treatment strategy for patients with LRRC.

Potential benefits and disadvantages of induction chemotherapy

Induction chemotherapy in addition to neoadjuvant chemo(re)irradiation has the potential to induce more local tumour downstaging than can be achieved with chemoradiotherapy alone owing to the supplementary effect of the induction chemotherapy, and possibly also the synergistic effect of induction chemotherapy and chemoradiotherapy.[18] Improved local downstaging may subsequently increase the R0 resection rate, which has been identified as the main prognostic factor for overall survival.[6–8] When local downstaging is excellent, a pathological complete response (pCR) can be achieved, which is a predictive variable for survival in patients with LRRC.[19] With improved local downstaging, the proportion of patients with a pCR may also increase. Alongside the local effect, induction chemotherapy may also have the potential to eradicate micrometastases.[20]

The addition of induction chemotherapy also has potential drawbacks. First, induction chemotherapy is associated with toxicity.[21] Second, chemotherapy-induced morbidity could delay, reduce, or prevent subsequent treatment with chemoradiotherapy and surgery. Third, when chemoradiotherapy is preceded by induction chemotherapy, the

toxicity of chemoradiotherapy may be increased. Finally, the prolonged and intensified neoadjuvant course may influence the patient's performance status and may have a negative effect on the surgical morbidity and mortality rates. Furthermore, prolonged neoadjuvant treatment may increase the risk of disease progression and secondary unresectability.

Current evidence

Induction chemotherapy, whether or not in combination with neoadjuvant chemoradiotherapy, is increasingly being used in the treatment of LRRC, although evidence for this approach is lacking.[22] Several retrospective studies and phase II clinical trials performed to investigate the role of induction chemotherapy in patients with primary locally advanced rectal cancer (LARC) have reported high R0 resection rates.[23–26] However, other studies, including comparative studies, did not demonstrate superior R0 resection rates after the addition of induction chemotherapy to neoadjuvant treatment.[27–29]

Several studies investigating this treatment regimen in LARC used pCR as the primary endpoint. As in the studies focusing on the R0 resection rate, the results were mixed. Some studies described promising pCR rates, whereas others found no effect of adding induction chemotherapy with regard to the pCR rate.[30–34] Regardless of the effect of this treatment on the R0 resection or pCR rate, induction chemotherapy seemed feasible: compliance rates with the chemotherapy as well as with the subsequent chemoradiotherapy were high, and toxicity and postoperative morbidity was acceptable.[28,33,35]

The available literature regarding induction chemotherapy in addition to chemoradiotherapy for patients with LRRC is limited; currently only three retrospective studies have been published.[19,36,37] The first study, which focused on patients with lateral local recurrence, reported a high R0 resection rate of 85% in a subgroup of 13 patients who were treated with induction chemotherapy followed by chemoradiotherapy.[36] In the second and third studies, 58 and 132 patients respectively underwent induction chemotherapy followed by chemo(re)irradiation. Both studies reported promising pCR rates of 17%, but the R0 resection rates did not appear to have improved.[19,37] However, in both studies induction chemotherapy was initially administered to patients with unresectable disease or prognostically unfavourable characteristics, which may have had a negative impact on the R0 resection rate.

Rationale for the study

Although the real benefit provided by the addition of induction chemotherapy to chemoradiotherapy and surgery for LRRC has not yet been established, its use is increasing.[22]

This study will randomise patients with LRRC to receive either induction chemotherapy followed by chemoradiotherapy and surgery (experimental arm) or chemoradiotherapy and surgery alone (control arm). As an R0 resection is the single most important prognostic factor for survival in patients with LRRC, the main hypothesis to be tested will be an increase in the R0 resection rate in the experimental arm compared with the control arm.

METHODS

Study design and setting

This is a multicentre, international, open-label, phase III, parallel-arms study that will randomise eligible patients in a 1:1 ratio to receive either induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm). The study is registered with ClinicalTrials.gov (NCT04389086), including the list of centres enrolling for the trial. Surgical treatments will be limited to centres that perform at least 10 resections of LRRC per year (expert centres). Induction chemotherapy and chemoradiotherapy will be administered in expert centres and selected non-expert centres. This is protocol version 4.0, dated 10 December 2020.

Participants

Patients 18 years or older, with resectable histopathologically or clinically proven LRRC after previous partial or total mesorectal resection, with a WHO performance status of ≤ 1 will be eligible for study participation. Patients with distant metastases at the time of randomisation or in the previous 6 months, those who have undergone chemotherapy and/or radiotherapy in the past 6 months, patients with any contraindication to chemotherapy and/or radiotherapy and/or surgery, and those with concurrent malignancies that interfere with the planned study treatment or the prognosis of resected LRRC, will be excluded.

Recruitment

Participants will be identified either by physicians in expert centres or by physicians in non-expert centres who will then refer the patients to an expert centre. All eligible

patients will be reviewed in a multidisciplinary team (MDT) meeting in an expert centre to assess whether the patient meets the inclusion and exclusion criteria. The multicentre, international involvement in this study will ensure adequate participant enrolment to reach the targeted sample size.

Interventions

Eligible patients who have signed informed consent will be randomised by the coordinating investigator in a 1:1 ratio using a software randomisation program (ALEA Clinical, FormsVision, Abcoude, Netherlands). Patients will be stratified for previous chemotherapy, previous radiotherapy, and expert centre. After randomisation, the treating surgical oncologist will refer the patient to the medical oncologist (experimental arm) or radiation oncologist (control arm). The study flowchart is shown in *Figure 1.* Study interventions and timelines for patients allocated to the experimental and control arms are presented in *Tables 1* and *2* respectively.

Table 1 Schedule interventions and assessments experimental arm

	Before allocation	After allocation			Follow-up	
	Outpatient clinic	**Induction chemotherapy**	**Chemoradiotherapy**	**Surgery**	**Years 1-3**	**Years 4-5**
Screening						
Eligibility screen	☒					
Informed consent	☒					
Randomisation	☒					
Interventions						
Induction chemotherapy		☒				
Chemoradiotherapy			☒			
Surgery				☒		
Thoracoabdominal CT	☒	☒[A]	☒[B]		☒[E]	☒[H]
Pelvic MRI	☒	☒[A]	☒[B]			
Questionnaires	☒				☒[F]	
CEA level					☒[G]	☒[E]
Translational research: blood	☒	☒[A]	☒[C]	☒[D]	☒[H]	
Translational research: tissue				☒		
Assessments						
Baseline characteristics	☒					
Toxicity of induction chemotherapy		☒				
Toxicity of chemoradiotherapy			☒			

Table 1 (Continued)

	Before allocation	After allocation			Follow-up	
	Outpatient clinic	**Induction chemotherapy**	**Chemoradiotherapy**	**Surgery**	**Years 1-3**	**Years 4-5**
Radiological response		☒	☒			
Pathological response				☒		
Surgical characteristics				☒		
Postoperative morbidity				☒		
Progression-free survival					☒ G	☒ E
Local recurrence-free survival					☒ G	☒ E
Disease-free survival					☒ G	☒ E
Overall survival					☒ G	☒ E
Quality of life	☒				☒ F	
Costs	☒				☒ F	

A after 3 (CAPOX) or 4 (FOLFOX/FOLFIRI) cycles; **B** 4-6 weeks after finishing chemoradiotherapy; **C** after finishing chemoradiotherapy and before surgery; **D** 3 months post-surgery; **E** 6-monthly; **F** 3 and 12 months postoperative; **G** 3-monthly; **H** yearly

Table 2 Schedule interventions and assessments control arm

	Before allocation	After allocation		Follow-up	
	Outpatient clinic	**Chemoradiotherapy**	**Surgery**	**Years 1-3**	**Years 4-5**
Screening					
Eligibility screen	☒				
Informed consent	☒				
Randomisation	☒				
Interventions					
Induction chemotherapy					
Chemoradiotherapy		☒			
Surgery			☒		
Thoracoabdominal CT	☒	☒ [A]		☒ [D]	☒ [G]
Pelvic MRI	☒	☒ [A]			
Questionnaires	☒			☒ [E]	
CEA level				☒ [F]	☒ [D]
Translational research: blood	☒	☒ [B]	☒ [C]	☒ [G]	
Translational research: tissue			☒		
Assessments					
Baseline characteristics	☒				
Toxicity of chemoradiotherapy		☒			
Radiological response		☒			

Table 2 (Continued)

	Before allocation	After allocation		Follow-up	
	Outpatient clinic	**Chemoradiotherapy**	**Surgery**	**Years 1-3**	**Years 4-5**
Pathological response			☒		
Surgical characteristics			☒		
Postoperative morbidity			☒		
Progression-free survival				☒ F	☒ D
Local recurrence-free survival				☒ F	☒ D
Disease-free survival				☒ F	☒ D
Overall survival				☒ F	☒ D
Quality of life	☒			☒ E	
Costs	☒			☒ E	

A 4-6 weeks after finishing chemoradiotherapy; **B** after finishing chemoradiotherapy and before surgery; **C** 3 months post-surgery; **D** 6-monthly; **E** 3 and 12 months postoperative; **F** 3-monthly; **G** yearly

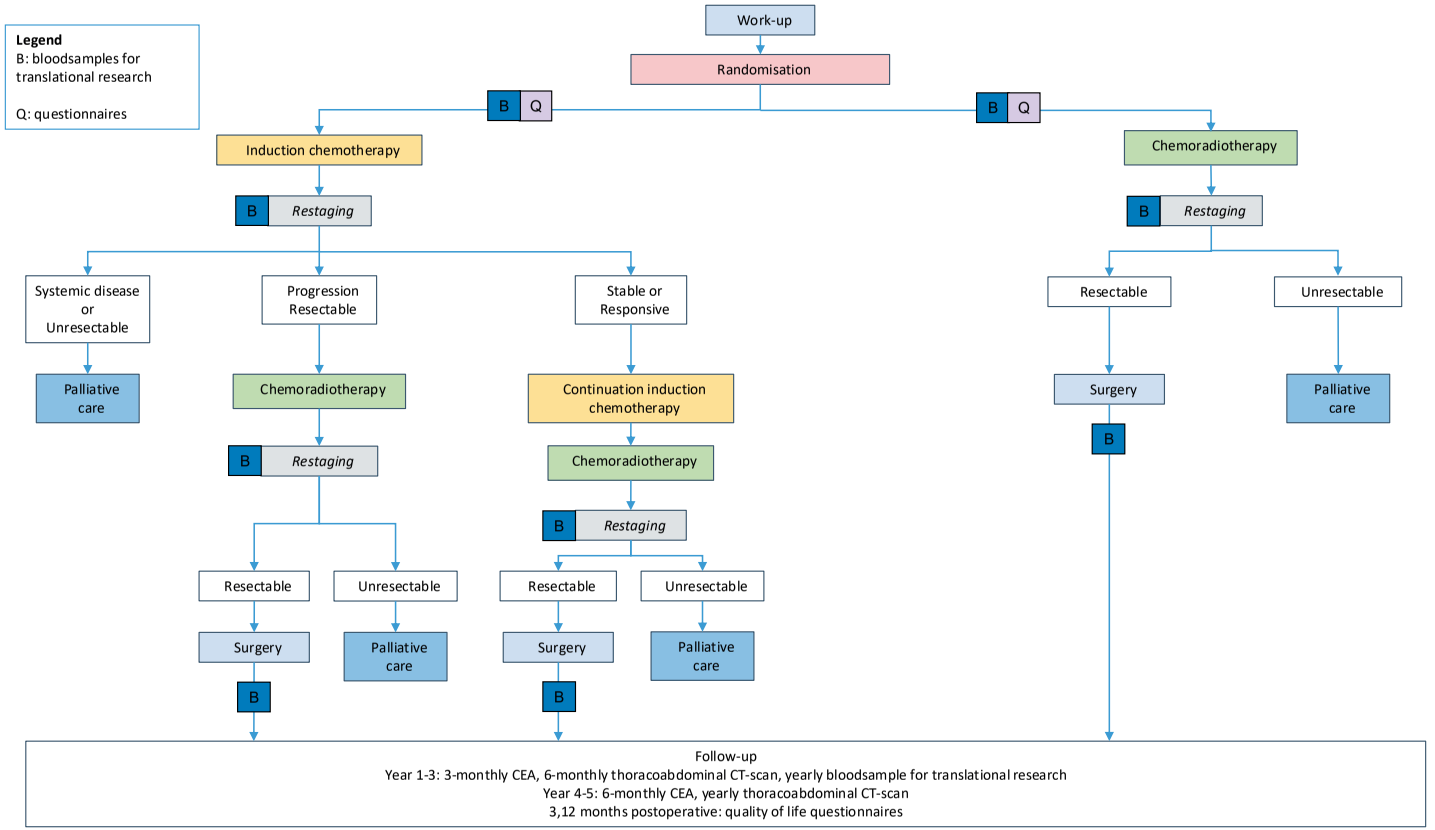


Figure 1 Study flowchart

Induction chemotherapy

Patients allocated to the experimental arm will start treatment with induction chemotherapy within 4 weeks after randomisation. Induction chemotherapy will consist of either three 3-weekly cycles of CAPOX (Oxaliplatin 130 mg/m^2 body-surface area (BSA), intravenously (i.v.) on day 1, capecitabine 1000 mg/m^2 BSA, orally, twice daily on day 1-14), four 2-weekly cycles of FOLFOX (85 mg/m^2 BSA of oxaliplatin i.v. on day 1, 400 mg/m^2 BSA of leucovorin i.v. on day 1, 400 mg/m^2 BSA of bolus 5-fluorouracil i.v. on day 1 followed by 2400 mg/m^2 BSA of continuous 5-fluorouracil i.v. on days 1-2), or four 2-weekly cycles of FOLFIRI (180 mg/m^2 BSA of irinotecan i.v. on day 1, 400 mg/m^2 BSA of leucovorin i.v. on day 1, 400 mg/m^2 BSA of bolus 5-fluorouracil i.v. on day 1 followed by 2400 mg/m^2 BSA of continuous 5-fluorouracil i.v. on days 1-2). The choice of chemotherapy agent will be left to the physician's discretion.

After three cycles of CAPOX or four cycles of FOLFOX or FOLFIRI, a pelvic MRI will be performed for local restaging and high-dose thoracoabdominal CT scan for restaging of possible distant metastases. Restaging imaging will be discussed during a dedicated MDT meeting in one of the expert centres. If a patient develops distant metastases or local disease becomes unresectable, best palliative treatment will be offered according to the standard of care. If a patient has progressive local disease, but surgery is still considered feasible, no further systemic therapy will be administered and patients will start treatment with chemoradiotherapy. If a patient has stable or responsive disease, induction chemotherapy will be continued with either one 3-weekly cycle of CAPOX or two 2-weekly cycles of FOLFOX or FOLFIRI.

Chemoradiotherapy

Patients in the experimental arm will start chemoradiotherapy within 3-5 weeks after the first day of the last cycle of chemotherapy. Patients in the control arm will start chemoradiotherapy within 4 weeks after randomisation. The radiotherapy dose will depend on whether the patient received radiotherapy previously. In radiotherapy-naïve patients, full-course radiotherapy will consist of 25 x 2.0 Gy or 28 x 1.8 Gy radiotherapy. In patients with a history of radiotherapy, the radiotherapy dose will consist of 15 x 2.0 Gy. The target volume will be defined by the gross, clinical, and planning target volume (GTV, CTV, and PTV, respectively), and will be similar for radiotherapy-naïve and previously irradiated patients. The GTV contains all macroscopic visible tumour, the CTV includes the GTV with a margin of 1 cm, without adjustment of the CTV towards other organs, and the PTV includes the CTV with a margin that can be determined according to local policy. Concomitant chemotherapy will comprise capecitabine, administered orally at a dose of 825 mg/m^2 twice daily on radiotherapy days. In the event of unacceptable toxicity caused by capecitabine during induction chemotherapy,

concomitant tegafur/gimeracil/oteracil administered orally at a dose of 25mg/m^2 twice daily on radiotherapy days may be prescribed at physician's discretion.

Restaging

Four to 6 weeks after the last day of radiotherapy, a pelvic MRI will be performed for local restaging and a high-dose thoracoabdominal CT scan for restaging of possible distant metastases. Restaging imaging will be discussed during a dedicated MDT meeting in one of the expert centres. In the event of distant metastases or unresectable local disease, best palliative treatment will be offered. Patients with resectable disease will undergo surgery.

Surgery

Surgery will be performed by experienced surgical oncologists within 10-14 weeks after completion of chemoradiotherapy. Type of surgery will depend on the location of the recurrent tumour and possible involvement of adjacent structures, and will be left to the discretion of the surgeon. When deemed necessary and feasible by the surgeon and radiation oncologist, intraoperative radiotherapy may be administered by either intraoperative electron beam radiotherapy or high-dose-rate intraoperative brachytherapy.[38,39]

Follow-up

Patients will be followed-up at 3, 6, 9, 12, 15, 18, 21, 24, 27, 30, 33, 36, 42, 48, 54, and 60 months after surgery. At each follow-up, a blood sample will be taken to determine the level of carcinoembryonic antigen (CEA). If the CEA level increases compared with the previous CEA level or the level rises above 5.0µg/L, high-dose thoracoabdominal CT scan will be performed. At 6, 12, 18, 24, 30, 36, 48, and 60 months after surgery, high-dose thoracoabdominal CT scan will be performed regardless of the CEA level.

Questionnaires

All participants will be asked to provide separate informed consent to receive validated quality of life questionnaires (European Organisation for Research and Treatment of Cancer QLQ-C30 and QLQ-CR29; EuroQol EQ-5D-5L™ (EuroQol Group, Rotterdam, the Netherlands)). Patients will receive questionnaires at inclusion, and 3 and 12 months after surgery either by mail or digitally, according to their own preference.

Translational research

All participants will be asked to provide separate informed consent for the collection of blood samples and/or tumour tissue for future translational research. If patients give such consent, an additional 20 ml blood will be drawn during regular blood

draws before start of the induction chemotherapy (experimental arm only), before chemoradiotherapy, before surgery, 3 months after surgery, and once a year during 3 years of follow-up, resulting in seven samples per patient in the experimental arm and six samples per patient in the control arm. Tumour tissue will be collected by the pathologist, fresh frozen, and stored until further use.

Central multidisciplinary team meetings

During the study's inclusion period, a monthly central MDT meeting will be organised for quality control. All newly included patients will be discussed during this meeting, which has been designed as a teleconference. In addition, eligible patients will be discussed in the event of uncertainty about whether they meet the inclusion and/or exclusion criteria. Patients who are under treatment at the time of the central MDT meeting, or who completed treatment, will only be discussed if there are remarkable findings, such as progression of disease resulting in unresectability.

Outcomes

The primary outcome of the study is the proportion of patients with a clear resection margin. A resection margin is considered clear (R0), if there are no tumour cells in any of the resection surfaces as determined by microscopy (resection margin > 0mm).

Secondary outcomes are:

- 3-year and 5-year local re-recurrence-free survival, defined as the interval between surgery and local re-recurrence;
- 3-year and 5-year progression-free survival, defined as the interval between randomisation and progression of local recurrence, local re-recurrence, distant metastases or death;
- 3-year and 5-year metastasis-free survival, defined as the interval between randomisation and development of distant metastases;
- 3-year and 5-year disease-free survival, defined as the interval between surgery and local re-recurrence, distant metastases or death;
- 3-year and 5-year overall survival, defined as the interval between randomisation and death;
- Pathological response, graded according to the Mandard grading system[40];
- Radiological response, scored according to the magnetic resonance tumour regression grade (mrTRG);
- Compliance rate with induction chemotherapy (i.e., the number of patients receiving CAPOX, FOLFOX or FOLFIRI as initial regimen will be tabulated, and dose modification and reason will be summarised for each regimen);

- Toxicity of induction chemotherapy, scored from day 1 of the first cycle of induction chemotherapy until 1 month after the last administration, and graded according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0;
- Compliance rate with chemoradiotherapy, calculated as the total radiotherapy dose received divided by the total planned dose;
- Toxicity of chemoradiotherapy, scored from the start of radiotherapy until 3 months after the final dose of radiotherapy, and graded according to the CTCAE version 5.0;
- Number of patients undergoing surgery;
- Surgical characteristics (e.g., type of resection, ostomy, use of intraoperative radiotherapy, blood loss, duration of operation, intraoperative complications);
- Major surgical morbidity rate scored from the date of surgery to 3 months after surgery, and graded according to the Clavien-Dindo classification[41];
- Quality of life, assessed with EQ-5D-5L™, QLQ-C30 and QLQ-CR29 questionnaires at inclusion, and at 3 and 12 months after surgery;
- Cost-effectiveness and cost-utility, based on the Dutch costing guidelines for healthcare, the case report forms, and the EQ-5D-5L™ questionnaire.

Sample size

Currently, an R0 resection is achieved in approximately 60% of patients undergoing surgery after treatment with neoadjuvant chemoradiotherapy.[16,17] However, 25% of patients who start neoadjuvant chemotherapy are not eligible for surgery owing to progressive disease, i.e. local progression, distant progression, or death from progression.[12] This means that an R0 resection is obtained in only 45% of patients (75% of 60%) who start with intentionally curative treatment. The study hypothesis is that there will be a 15% increase in the R0 resection rate (45% to 60%) for patients in the experimental arm. A Chi-square test with a 5% two-sided significance level indicated that the study would have 80% power to detect a significant difference of 15% between the two groups (given that the percentage in the control group is 45%) when the sample size in each group is 173 patients. With an expected dropout of 5%, the total requirement was calculated as 364 patients.

Statistical methods

Demographics, patient, and tumour characteristics will be presented for each treatment arm. Continuous data will be reported as mean (standard deviation) or median (interquartile range or 95% confidence interval), depending on the distribution. Categorical data will be reported as count with percentage. All statistical tests will be two-sided and a p value < 0.05 will be classified as statistically significant. Patients

initially randomised but considered ineligible afterwards, based on information that should have been available before randomisation, will be excluded from all analyses.

Analysis of the primary endpoint of this study, the proportion of patients with an R0 resection, will be based on the intention-to-treat principal using the Fisher's exact test. In addition, a per-protocol analysis will be performed as a sensitivity analysis.

All survival curves will be constructed according to the Kaplan-Meier method, and the log-rank test will be used to compare treatment arms, adjusting for the stratification factors at randomisation (previous radiotherapy, previous systemic therapy, and expert centre). In addition, hazard ratios will be calculated using a Cox proportional hazard regression model, adjusting for stratification factors. Metastasis-free survival, progression-free survival, and overall survival will be based on the intention-to-treat group. Local re-recurrence-free survival and disease-free survival analyses will include only patients who underwent surgery.

Data on surgical characteristics, histopathological characteristics, and major surgical morbidity will be presented by treatment arm, and will be derived only for patients who underwent surgery. The number of patients undergoing surgery will be analysed in the intention-to-treat population. Comparison between treatment arms will be done by means of Fisher's exact test.

The absolute and relative incidence of toxicities related to the administration of induction chemotherapy or chemoradiotherapy will be presented per treatment arm, and analysed in all patients who received at least one dose of neoadjuvant chemotherapy (experimental arm) or chemoradiotherapy (control arm). Comparison between treatment arms will be done by means of Fisher's exact test.

Comparison of health-related quality of life between the two treatment arms at baseline and over time will be performed by a random-effects regression model and will be based on the intention-to-treat group.

Incremental cost-effectiveness and cost-utility ratios will be calculated for the extra costs per additional surviving patient and the extra costs per additional quality-adjusted life year respectively. Non-parametric bootstrapping, drawing samples of the same size as the original samples and with replacement, will be applied to generate 95% confidence intervals for (differences in) costs and health outcomes. Cost-effectiveness planes will be displayed and cost-effectiveness acceptability curves are drawn for willingness-to-pay values up to €100.000.

Data collection and management

A central study database (Netherlands Comprehensive Cancer Institute [IKNL], Utrecht, Netherlands) with an electronic case report form will be used to record all data required to address the primary and secondary objectives. Local data management will be undertaken by the IKNL or an in-hospital qualified local data management team. Questionnaires will be collected centrally by the coordinating investigators and recorded using an ISO 27001-certified information security system (Research Manager, Deventer, Netherlands).

Data safety monitoring board

A central data safety monitoring board (DSMB), consisting of a medical oncologist, a surgical oncologist, and a statistician, has been assigned to monitor the safety of the study participants, and to protect the validity and credibility of the study. Members of the DMSB are independent and have no competing interest. After 100 patients have undergone surgery, the DSMB will review the safety data. Inclusion will be continued during interim analysis. At the interim analysis, the number of patients who cannot complete the full course of chemoradiotherapy and the number of patients with major postoperative morbidity (Clavien-Dindo ≥ 3) will be tabulated and discussed. Examining these safety and logistic aspects will not affect the total sample size or the actual alpha level at final analysis. After the interim analysis, the DSMB will recommend the trial steering committee (TSC) whether the study should be continued or terminated. Should the TSC decide not to fully implement the advice of the DSMB, it must explain to the medical ethical committee why (part of) the advice of the DSMB will not be followed.

Harms

All serious adverse events (SAEs) or suspected unexpected serious adverse events (SUSARs) will be reported by the physician to the study coordinator within 24 hours and without undue delay after obtaining knowledge of the event. The coordinating investigator will report the SAEs/SUSARs through the web portal *ToetsingOnline* (https://www.toetsingonline.nl) to the medical ethical committee that approved the protocol. The time window for recording SAEs and SUSARs is from randomisation until 3 months after surgery, or 1 month after the last day of neoadjuvant treatment for patients with progressive disease and who did not undergo surgery. SAEs and SUSARs will be followed up until resolved or until a stable situation has been reached.

Auditing

The study will be monitored by independent qualified monitors. The monitor plan is based on the assessment that the study carries a moderate risk for the participants.

Research ethics approval

This study was approved by the Medical Research Ethics Committees United, Nieuwegein, the Netherlands (R20.035), the Dutch Competent Authority (Centrale Commissie Mensgebonden Onderzoek, The Hague, the Netherlands; NL73593.100.20), and all institutional review boards of the participating study centres. The study will be submitted to the competent authorities, central ethical committees, and institutional review boards of the participating international centres.

Protocol amendments

All substantial amendments will be notified to the (principal) investigators, institutional review boards of all study centres, the medical ethical committee, the competent authority, and trial registries.

Consent and assent

Informed consent will be obtained by the treating physician in one of the expert centres. Patients will be allowed to provide separate permission for the collection of blood and/or tissue samples for translational research, and for receiving quality of life questionnaires.

Confidentiality

Individual patient information obtained as a result of this study is considered confidential and its handling will conform with the Dutch Personal Data Protection Act (AVG). Patients' confidentiality will be ensured by use of study numbers.

Declaration of interests

The investigators declare no financial or other competing interests.

Access to data

Access to the final dataset is reserved for the central data manager, study statistician, coordinating investigator, and trial steering committee. There are no contractual agreements that limit this access.

Ancillary and post-study care

The study has no provision for ancillary or post-study care.

Dissemination policy

The results of this study will be dispersed by publishing the results in international peer-reviewed journals and by offering an abstract to international (surgical) oncological congresses. Any publication, abstract, or presentation based on patients included

in this study must be approved by the trial steering committee and coordinating investigator. The principal manuscript resulting from this study will be published by group authorship (PelvEx Collaborative).

DISCUSSION

This randomised controlled trial will investigate the role of induction chemotherapy in patients with LRRC. The results of this study will demonstrate whether or not induction chemotherapy has additional value in the treatment of patients with non-metastasized resectable LRRC with regard to the R0 resection rate; this group of patients has had a poor prognosis so far.

The rationale for R0 resection as the primary outcome in this study was based on the fact that R0 resection is the most important prognostic factor for survival in patients undergoing surgery for LRRC. Ultimately, an increase in the R0 resection rate should lead to an improvement in the local re-recurrence-free and overall survival. Because of the relatively rarity of LRRC as a result of improvements in the treatment of primary rectal cancer, and the fact that approximately 50% of patients with LRRC will not be eligible for inclusion in this study owing to distant metastases or unresectable local disease, survival parameters could not be used as the primary outcome, as power calculations showed that the sample size would be unfeasible.[42,43]

The rationale for the induction chemotherapy regimen chosen in this study is based on studies in (metastatic) colorectal cancer. In those first-line studies, doublet therapy resulted in better response rates and an improved survival compared with monotherapy.[44–47] Results of triplet therapy among patients with metastatic colorectal cancer have been conflicting.[48,49] In addition, although higher response rates have been observed for triplet therapy compared with doublet therapy in patients with right-sided metastatic colorectal cancer, this has not been observed in patients with left-sided disease.[50,51] Moreover, triplet therapy is associated with more toxicity, and in patients with LLRC, in particular, toxicity of treatment is considered a major limitation often precluding curative treatment.[52] Therefore, doublet therapy is the treatment regimen of choice. Since doublet therapy with capecitabine and oxaliplatin (CAPOX), 5-fluorouracil, leucovorin, and oxaliplatin (FOLFOX), and 5-fluorouracil, leucovorin, and irinotecan (FOLFIRI) have a similar efficacy, all are incorporated in the present study protocol.[46,53,54]

There are three other ongoing trials investigating the optimal treatment for patients with LRRC. The French GRECCAR15 study (Chemotherapy Followed by Pelvic Reirradiation

Versus Chemotherapy Alone as Pre-operative Treatment for Locally Recurrent Rectal Cancer; NCT03879109) is randomising between induction chemotherapy, chemoreirradiation, and surgery versus induction chemotherapy and surgery in previously irradiated patients. The primary outcome measure is the R0 resection rate. The Japanese JCOG1801 study (Surgery Plus Chemo Versus Chemoradiotherapy Followed by Surgery Plus Chemo for Locally Recurrent Rectal Cancer; NCT04288999) is randomising between surgery followed by adjuvant chemotherapy versus neoadjuvant chemoradiotherapy, surgery, and adjuvant chemotherapy (CAPOX/FOLFOX) in radiotherapy-naïve patients, with local recurrence-free survival as the primary outcome measure. The Chinese NARC study (Efficacy and Safety Study of Neoadjuvant in Treating Patients with Resectable Local Recurrent Rectal Cancer; NCT01271192) is randomising between surgery followed by adjuvant chemotherapy versus neoadjuvant chemoradiotherapy, surgery, and adjuvant chemotherapy, with overall survival as the primary outcome measure. The results of these studies will be actively monitored to assess whether their results have any implications for the present study protocol.

REFERENCES

1. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. www.nejm.org.
2. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of Locally Recurrent Rectal Carcinoma in Previously (Chemo)Irradiated Patients: A Review. *Dis Colon Rectum*. 2016;59(2):148-156. doi:10.1097/DCR.0000000000000547
3. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. *Br J Surg*. 2014;101(10):1280-1289. doi:10.1002/bjs.9569
4. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: A multicentric phase II study. *Int J Radiat Oncol Biol Phys*. 2006;64(4):1129-1139. doi:10.1016/j.ijrobp.2005.09.017
5. Dresen RC, Gosens MJ, Martijn H, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. *Ann Surg Oncol*. 2008;15(7):1937-1947. doi:10.1245/s10434-008-9896-z
6. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388
7. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866-1873. doi:10.1002/bjs.10645
8. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *Eur J Surg Oncol*. 2018;44(1):100-107. doi:10.1016/j.ejso.2017.11.013
9. Kusters M, Dresen RC, Martijn H, et al. Radicality of Resection and Survival After Multimodality Treatment is Influenced by Subsite of Locally Recurrent Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2009;75(5):1444-1449. doi:10.1016/j.ijrobp.2009.01.015
10. Holman FA, Bosman SJ, Haddock MG, et al. Results of a pooled analysis of IOERT containing multimodality treatment for locally recurrent rectal cancer: Results of 565 patients of two major treatment centres. *Eur J Surg Oncol*. 2017;43(1):107-117. doi:10.1016/j.ejso.2016.08.015
11. Mannaerts G, Martijn H, Rutten H, Hanssens P, Wiggers T. Local tumor control and (disease-free) survival after surgery with pre- and intraoperative radiotherapy for primary non-resectable rectal carcinoma and local recurrence. *Ned Tijdschr Geneeskd*. 2001;145(30):1460-1466.
12. Hagemans JAW, van Rees JM, Alberda W, Rothbarth J, Nuyttens JJME, van Meerten E, Verhoef C BJ. Locally recurrent rectal cancer; long-term outcome of curative surgical and palliative treatment of 447 consecutive patients in a tertiairy referral centre. *Eur J Surg Oncol*. 2020;46(3):448-454. 10.1016/j.ejso.2019.10.037.

13. Camilleri-Brennan J, Steel R. The impact of recurrent rectal cancer on quality of life. *EurJ-SurgOncol*. 2001;27(4):349-353.

14. Glynne-Jones R, Wyrwicz L, Tiret E, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann Oncol*. 2018;29(Suppl 4):iv263. doi:10.1093/annonc/mdx224

15. Guren MG, Undseth C, Rekstad BL, et al. Reirradiation of locally recurrent rectal cancer: A systematic review. *Radiother Oncol*. 2014;113(2):151-157. doi:10.1016/j.radonc.2014.11.021

16. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y

17. Yu SKT, Bhangu A, Tait DM, Tekkis P, Wotherspoon A, Brown G. Chemoradiotherapy response in recurrent rectal cancer. *Cancer Med*. 2014;3(1):111-117. doi:10.1002/cam4.169

18. Milas L, Hunter NR, Mason KA, Milross CG, Saito Y, Peters LJ. Role of Reoxygenation in Induction of Enhancement of Tumor Radioresponse by Paclitaxel. *Cancer Res*. 1995;55(16):3564-3568.

19. Voogt ELK, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4

20. Hospers G, Bahadoer RR, Dijkstra EA, et al. Short-course radiotherapy followed by chemotherapy before TME in locally advanced rectal cancer: The randomized RAPIDO trial. [abstract]. *J Clin Oncol*. 2020;38(15_suppl). doi:10.1200/jco.2020.38.15_suppl.4006

21. Braun MS, Seymour MT. Balancing the efficacy and toxicity of chemotherapy in colorectal cancer. *Ther Adv Med Oncol*. 2011;3(1):43-52. doi:10.1177/1758834010388342

22. Hardiman KM, Antunez AG, Kanters A, Schuman AD, Regenbogen SE. Clinical and pathological outcomes of induction chemotherapy before neoadjuvant radiotherapy in locally-advanced rectal cancer. *J Surg Oncol*. 2019;120(2):308-315. doi:10.1002/jso.25474

23. Chau I, Brown G, Cunningham D, et al. Neoadjuvant capecitabine and oxaliplatin followed by synchronous chemoradiation and total mesorectal excision in magnetic resonance imaging-defined poor-risk rectal cancer. *J Clin Oncol*. 2006;24(4):668-674. doi:10.1200/JCO.2005.04.4875

24. Cercek A, Goodman KA, Hajj C, et al. Neoadjuvant Chemotherapy First, Followed by Chemoradiation and Then Surgery, in the Management of Locally Advanced Rectal Cancer. *J Natl Compr Canc Netw*. 2014;12(4):513-519.

25. Masi G, Vivaldi C, Fornaro L, et al. Total neoadjuvant approach with FOLFOXIRI plus bevacizumab followed by chemoradiotherapy plus bevacizumab in locally advanced rectal cancer: the TRUST trial. *Eur J Cancer*. 2019;110:32-41. doi:10.1016/j.ejca.2019.01.006

26. Schou J V., Larsen FO, Rasch L, et al. Induction chemotherapy with capecitabine and oxaliplatin followed by chemoradiotherapy before total mesorectal excision in patients with locally advanced rectal cancer. *Ann Oncol*. 2012;23(10):2627-2633. doi:10.1093/annonc/mds056

27. Fernández-Martos C, Pericay C, Aparicio J, et al. Phase II, randomized study of concomitant chemoradiotherapy followed by surgery and adjuvant capecitabine plus oxaliplatin (CAPOX) compared with induction CAPOX followed by concomitant chemoradiotherapy and surgery in magnetic resonance imaging-defined, l. *J Clin Oncol*. 2010;28(5):859-865. doi:10.1200/JCO.2009.25.8541

28. Fernández-Martos C, Garcia-Albeniz X, Pericay C, et al. Chemoradiation, surgery and adjuvant chemotherapy versus induction chemotherapy followed by chemoradiation and surgery: Long-term results of the Spanish GCR-3 phase II randomized trial. *Ann Oncol*. 2015;26(8):1722-1728. doi:10.1093/annonc/mdv223

29. Garcia-Aguilar J, Chow OS, Smith DD, et al. Effect of adding mFOLFOX6 after neoadjuvant chemoradiation in locally advanced rectal cancer: A multicentre, phase 2 trial. *Lancet Oncol*. 2015;16(8):957-966. doi:10.1016/S1470-2045(15)00004-2

30. Tang J, Wu X, Bai Y, et al. Long-Term Outcome of Oxaliplatin and Capecitabine (XELOX) Concomitant with Neoadjuvant Radiotherapy and Extended to the Resting Period in High Risk Locally Advanced Rectal Cancer. *J Cancer*. 2018;9(8):1365-1370. doi:10.7150/jca.23874

31. Yu X, Wang QX, Xiao WW, et al. Neoadjuvant oxaliplatin and capecitabine combined with bevacizumab plus radiotherapy for locally advanced rectal cancer: results of a single-institute phase II study. *Cancer Commun (London, England)*. 2018;38(1):24. doi:10.1186/s40880-018-0294-z

32. Golo D, But-Hadzic J, Anderluh F, et al. Induction chemotherapy, chemoradiotherapy and consolidation chemotherapy in preoperative treatment of rectal cancer - long-term results of phase II OIGIT-01 Trial. *Radiol Oncol*. 2018;52(3):267-274. doi:10.2478/raon-2018-0028

33. Maréchal R, Vos B, Polus M, et al. Short course chemotherapy followed by concomitant chemoradiotherapy and surgery in locally advanced rectal cancer: A randomized multicentric phase II study. *Ann Oncol*. 2012;23(6):1525-1530. doi:10.1093/annonc/mdr473

34. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071

35. Calvo FA, Sole C V., Serrano J, et al. Preoperative chemoradiation with or without induction oxaliplatin plus 5-fluorouracil in locally advanced rectal cancer: Long-term outcome analysis. *Strahlentherapie und Onkol*. 2014;190(2):149-157. doi:10.1007/s00066-013-0469-0

36. Kusters M, Bosman SJ, Van Zoggel DMGI, et al. Local Recurrence in the Lateral Lymph Node Compartment: Improved Outcomes with Induction Chemotherapy Combined with Multimodality Treatment. *Ann Surg Oncol*. 2016;23(6):1883-1889. doi:10.1245/s10434-016-5098-2

37. van Zoggel DMGI, Bosman SJ, Kusters M, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. *Br J Surg*. 2018;105(4):447-452. doi:10.1002/bjs.10694

38. Biggs P, Willet CG, Rutten HJT, Ciocca M, Gunderson LL, Calvo FA. Intraoperative Electron Beam Irradiation: Physics and Techniques. In: *Intraoperative Irradiation: Techniques and Results*. Second Edi. Totowa, NJ: Humana Press; 2011:51-72.

39. Furhang EE, Silanpaa JK, Hu KS, Harrison LB. HDR-IORT: Physics and Techniques. In: *Intraoperative Irradiation: Techniques and Results*. Second Edi. Totowa, NJ: Humana Press; 2011:73-84.

40. Mandard AM, Dalibard F, Mandard JC, et al. Pathologic assessment of tumor regression after preoperative chemoradiotherapy of esophageal carcinoma. Clinicopathologic correlations. *Cancer*. 1994;73(11):2680-2686. http://www.ncbi.nlm.nih.gov/pubmed/8194005. Accessed January 18, 2019.

41. Clavien PA, Barkun J, De Oliveira ML, et al. The Clavien-Dindo Classification of Surgical Complications Five-Year Experience. *Ann Surgeryg*. 2009;250(2):187-196. doi:10.1097/SLA.0b013e3181b13ca2

42. Heriot AG, Tekkis PP, Darzi A, Mackay J. Surgery for local recurrence of rectal cancer. *Color Dis*. 2006;8(9):733-747. doi:10.1111/j.1463-1318.2006.01018.x

43. van den Brink M, Stiggelbout AM, van den Hout WB, et al. Clinical Nature and Prognosis of Locally Recurrent Rectal Cancer After Total Mesorectal Excision With or Without Preoperative Radiotherapy. *J Clin Oncol*. 2004;22(19):3958-3964. doi:10.1200/jco.2004.01.023

44. Douillard JY, Cunningham D, Roth AD, et al. Irinotecan combined with fluorouracil compared with fluorouracil alone. as first-line treatment for metastatic colorectal cancer: a multicentre randomised trial. *Lancet*. 2000;355(9209):1041-1047. doi:10.1016/S0140-6736(00)02034-1

45. de Gramont A, Figer A, Seymour M, et al. Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. *J Clin Oncol*. 2000;18(16):2938-2947. doi:10.1200/JCO.2000.18.16.2938

46. Tournigand C, André T, Achille E, et al. FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: A randomized GERCOR study. *J Clin Oncol*. 2004;22(2):229-237. doi:10.1200/JCO.2004.05.113

47. Grothey A, Sargent D, Goldberg RM, Schmoll HJ. Survival of patients with advanced colorectal cancer improves with the availability of fluorouracil-leucovorin, irinotecan, and oxaliplatin in the course of treatment. *J Clin Oncol*. 2004;22(7):1209-1214. doi:10.1200/JCO.2004.11.037

48. Falcone A, Ricci S, Brunetti I, et al. Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin, and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: The gruppo oncologico nor. *J Clin Oncol*. 2007;25(13):1670-1676. doi:10.1200/JCO.2006.09.0928

49. Souglakos J, Androulakis N, Syrigos K, et al. FOLFOXIRI (folinic acid, 5-fluorouracil, oxaliplatin and irinotecan) vs FOLFIRI (folinic acid, 5-fluorouracil and irinotecan) as first-line treatment in metastatic colorectal cancer (MCC): A multicentre randomised phase III trial from the Hellenic Oncolog. *Br J Cancer*. 2006;94(6):798-805. doi:10.1038/sj.bjc.6603011

50. Cremolini C, Loupakis F, Antoniotti C, et al. FOLFOXIRI plus bevacizumab versus FOLFIRI plus bevacizumab as first-line treatment of patients with metastatic colorectal cancer: Updated overall survival and molecular subgroup analyses of the open-label, phase 3 TRIBE study. *Lancet Oncol*. 2015;16(13):1306-1315. doi:10.1016/S1470-2045(15)00122-9

51. Cremolini C, Antoniotti C, Lonardi S, et al. Primary tumor sidedness and benefit from FOLFOXIRI plus bevacizumab as initial therapy for metastatic colorectal cancer. Retrospective analysis of the TRIBE trial by GONO. *Ann Oncol*. 2018;29(7):1528-1534. doi:10.1093/annonc/mdy140

52. Falcone A, Cremolini C, Masi G, et al. FOLFOXIRI/bevacizumab versus FOLFIRI/bevacizumab as first-line treatment in unresectable metastatic colorectal cancer (mCRC) patients: Reults of the phase III TRIBE trial by GONO group. *J Clin Oncol*. 2013;31(15_suppl):3505-3505.

53. Arkenau HT, Arnold D, Cassidy J, et al. Efficacy of oxaliplatin plus capecitabine or infusional fluorouracil/leucovorin in patients with metastatic colorectal cancer: A pooled analysis of randomized trials. *J Clin Oncol*. 2008;26(36):5910-5917. doi:10.1200/JCO.2008.16.7759

54. Sobrero A, Bennicelli E. Chemotherapy: Which drug and when? *Ann Oncol*. 2010;21(Suppl 7):vii130-3. doi:10.1093/annonc/mdq293

PART III

GENERAL DISCUSSION, FUTURE PERSPECTIVE, SUMMARY, IMPACT AND APPENDICES

CHAPTER 12

GENERAL DISCUSSION AND FUTURE PERSPECTIVES

DISCCUSION AND FUTURE PERSPECTIVES

Over the past decades, the treatment of patients with primary rectal cancer has substantially improved. The most significant impact was made by the introduction of Total Mesorectal Excision (TME) surgery, resulting in a major reduction of the local recurrence rate and an improved survival.[1–3] In addition, neoadjuvant treatment regimens were developed. In the pre-TME era, radiotherapy was administered in the adjuvant setting.[4,5] After the introduction of TME surgery there was a paradigm shift to the neoadjuvant setting as several trials showed an improved local recurrence-free survival and less toxicity with this treatment regimen.[6–8] As a consequence of these two developments, local recurrence rates decreased from 20-30% to 6-10%.[6,8,9] Nevertheless, surgery for locally advanced rectal cancer (LARC), i.e. rectal tumours invading or extending into or beyond the mesorectal fascia (MRF), still often involves major resections and distant metastases rates are a major concern with a high incidence ranging between 25% and 40%.[7,9] Moreover, locally recurrent rectal cancer (LRRC) is associated with a high morbidity, extensive surgery, and a limited prognosis with a 5-year overall survival (OS) of only 30%.[10–16]

Considering these facts, the aim of this thesis was to gain insights that could improve the multimodality treatment of patients with LARC and LRRC, in order to ultimately improve the quality of life and long-term surgical and oncological outcomes. The first part focused on patient selection, preoperative imaging using magnetic resonance imaging (MRI), and peroperative approach. The second part focused on the neoadjuvant treatment, in particular the addition of induction chemotherapy to chemoradiotherapy,

PART I

Patient selection is a key element in the treatment of patients with LARC and LRRC. Neoadjuvant treatment is intensive and surgery is associated with a high rate of postoperative morbidity and mortality. Moreover, it has a profound impact on the quality of life.[10–12,17,18] It is therefore important to adequately select those patients who are most likely to benefit from such an extensive treatment, in order to prevent unnecessary interventions.

In LRRC, the presence of metastatic disease has long been considered a reason to preclude curative treatment.[19] However, in the Catharina Hospital Eindhoven, these patients were offered treatment with curative intent in line with the guidelines for metastatic primary rectal cancer.[20] A retrospective comparison of 349 patients, of whom 261 (75%) had no distant metastases, 42 (12%) had a history of metastases, and 46 (13%) had synchronous metastases, showed that the metastasis-free survival

(MFS) was significantly worse in those with synchronous metastases compared to those without metastases. However, the 3-year OS was comparable between these two groups. Despite the low number of patients with a history of metastases, these findings suggest that in patients with a history of metastases treatment with curative intent, including neoadjuvant treatment and extensive surgery, is justified. Nevertheless, when counselling patients with a history of metastases, it is reasonable to inform patients about the probability of developing distant metastases as this will most likely result in the need for additional (invasive) treatment in the course of the disease.

In patients with synchronous metastases, the MFS and OS were worse compared to patients without (a history of) metastases. For patients with synchronous metastases it is therefore questionable whether we should suggest to these patients that their treatment has a "curative intent", as long-term survival seems limited in these patients. Nevertheless, gaining local control in cases of LRRC may be extremely valuable for securing quality of life.[21] Therefore, the presence of synchronous metastases demands a tailored approach, considering the extent of the distant metastases (e.g., number, location, and size), the extent of the surgery required to remove the recurrent disease, patients' physiological status, and patients' preferences. If local treatment is pursued in these patients, we propose a neoadjuvant treatment regimen including induction chemotherapy and chemoradiotherapy, as this provides an opportunity to observe the response to treatment. A lack of response after induction chemotherapy, i.e. no regression or even progression of the distant metastases, can be considered as a poor prognosticator.[22–24] In these patients a surgical approach is unlikely to provide any benefit for the patient.

Worth noting is that this study does not report on patients in whom surgery was omitted due to non-responsive or progressive synchronous metastases. Insight in the proportion of patients that do not proceed to surgery could support the counselling and aid in the treatment decision making. Therefore, we are currently registering these patients too in our database.

With an increase in life expectancy, the incidence of older patients with colorectal cancer will increase. In the past, there was reluctance to offer intensive, curative treatment to elderly patients, as previous studies reported high rates of postoperative morbidity and mortality in these patients.[25–27] However, improvements in the care of elderly patients with non-advanced colorectal cancer have resulted in better outcomes in these patients.[28,29] In a retrospective study of patients with the most advanced stage of rectal cancer, i.e. 474 patients with clinical T4 rectal cancer (cT4RC) and 293 with LRRC, we showed that the 30-day mortality rate in patients with cT4RC and LRRC improved

over time and that they are now comparable to those in younger patients. However, the 90-day and 1-year mortality rate in elderly patients with cT4RC and LRRC remained higher compared to that in younger patients. Remarkably, elderly patients mostly died due to treatment-induced or non-cancer-relates causes, whereas in younger patients distant or local recurrence of the rectal cancer was the main cause of death. Improvements focusing on prehabilitation, enhanced recovery, and rehabilitation directly postoperative as well as in the post-hospitalisation phase may be key to improve outcomes in the elderly. In patients with non-advanced colorectal cancer, the Enhanced Recovery After Surgery (ERAS) protocol is the standard of care for guidance in the pre-, peri- and postoperative phase. Implementation of the ERAS protocol has shown to have a positive effect on the length of hospital stay, hospital readmission rate, morbidity, and mortality rate.[30] For patients with cT4RC and LRRC there is no such protocol. Owing to the extensiveness of the surgery in cT4RC and LRRC and the associated higher complication rate compared with surgery for non-advanced colorectal cancer, the ERAS protocol cannot be directly adopted in these patients. Therefore, the ERAS protocol is currently being adjusted to suit the specific difficulties, challenges, and needs of patients with LARC and LRRC. Once adjusted, this protocol will be implemented in all cT4RC and LRRC patients in the Catharina Hospital Eindhoven. After a sufficient period of time, short- and long-term outcomes will be evaluated and compared to the outcomes prior to the implementation of the protocol. Since elderly patients are generally more frail than younger patients, they have an increased vulnerability after major surgery. We believe that a good adherence to an ERAS protocol specifically compiled for cT4RC and LRRC will greatly benefit these patients. When the modified ERAS protocol proves to be effective, it may be disseminated and implemented across the Netherlands.

Pelvic MRI is an essential tool in the staging of LARC, because it is currently the most accurate technique to identify specific tumour characteristics. MRI-detected extramural vascular invasion (EMVI) and tumour deposits (TDs) are two such characteristics which are associated with an unfavourable prognosis.[31–33] In a retrospective cohort study on 277 patients with clinical T3 or T4 rectal cancer without synchronous metastases, we observed an EMVI prevalence of 58.8%, and TDs were highly associated with the presence of EMVI (56.4% TD-positive patients in the presence of EMVI, 9.6% TD-positive patients in the absence of EMVI). The presence of EMVI and TDs resulted in a significantly higher distant metastases rate and a decreased disease-free survival (DFS) compared to patients without these features on baseline MRI. However, a good response to neoadjuvant chemoradiotherapy, scored according to the mr-vTRG score, resulted in long-term outcomes comparable to patients who were EMVI-negative at baseline. On the contrary, patients with a poor response had an almost two-fold higher risk for the development of distant metastases and a diminished DFS. This suggest

that response on EMVI is an important prognosticator. The addition of induction chemotherapy to chemoradiotherapy has been previously studied in patients with rectal cancer and showed to induce an improved tumour response compared to treatment with chemoradiotherapy alone.[34] Perhaps such treatment regimen may also result in an improved response of EMVI and TDs, possibly resulting in a better distant metastasis-free and disease-free survival.

However, in order to be able to decide which patients should be treated with an intensified neoadjuvant treatment regimen, it is crucial that these patients are accurately identified: the radiologist has an essential role in identifying and reporting these characteristics when assessing an MRI. In the literature, the prevalence of EMVI and TDs are highly variable, ranging between 9%-61% and 10-44% respectively. This may indicate inconsistent detection and reporting of these characteristics.[32,35] Knowledge and expertise must therefore be created regarding the detection of EMVI and TDs among radiologists. Once the interobserver variability is improved, EMVI status could perhaps be incorporated in the TNM staging, as TNM is an important determinant in guiding treatment.

MRI not only plays a pivotal role in the primary staging of rectal cancer, but also in restaging. To quantify the degree of regression after neoadjuvant treatment in primary rectal cancer, the magnetic resonance tumour regression grade (mrTRG) has been developed. This score is based on the ability to distinguish between tumour and fibrosis and may assist in selecting patients with a clinical complete response (cCR) for a wait-and-see strategy in which surgery is omitted to avoid the morbidity associated with rectal surgery.[36,37]

In LRRC, implementation of a non-operative approach may be valuable given the complexity and impact on quality of life of LRRC surgery and the high probability of the occurrence of distant metastases. In a retrospective cohort including 124 patients, a first attempt was made to evaluate the mrTRG in patients with LRRC. The interobserver agreement between two experienced radiologists with regard to the mrTRG was only fair (k = 0.28) using a two-tier grading system (i.e. mrTRG 1-2 versus mrTRG 3-5), suggesting a low reproducibility. For the lead radiologist, there was a moderate agreement with the pTRG (k = 0.52) and a positive predictive value for predicting good responders (i.e. Mandard 1-2) of 95%. This suggests that mrTRG can predict a good response after neoadjuvant treatment for LRRC when assessed by an experienced, dedicated and trained radiologist. However, the moderate agreement with the pTRG and the occurrence of overestimation of residual tumour showed that mrTRG alone is not sufficient to identify patients eligible for a non-operative approach. In LARC,

endoscopy and digital rectal examination are important additional tools to assess the response. In LRRC, these tools are usually not applicable owing to previous surgery (e.g., abdominoperineal resection), and the location and/or extent of the tumour (e.g., extraluminal).[38] Possibly, incorporation of diffusion weight imaging (DWI) and positron emission tomography (PET)/computed tomography (CT) may be helpful additional tools to identify patients with a clinical complete response. In addition, the timing of restaging MRI should be optimised as this seems pivotal for an accurate assessment. The agreement between mrTRG and pTRG improved with an interval less than 7 weeks between MRI and surgery (k = 0.69), which is in line with previous studies.[39] We therefore recommend repeating the MRI when this interval exceeded 7 weeks and especially when refraining from surgery may be preferable.

When performing surgery on a patient with LARC or LRRC there is a lot to take into consideration. Especially when there is tumour invasion in surrounding structures and resection of these adjacent structures is necessary to attain an R0 resection. In the case of tumour invasion of the bladder, prostate, or urethra, a complete cystectomy, i.e. pelvic exenteration, is required. Consequently, reconstruction with an urinary diversion is essential. When choosing the type of diversion, the associated postoperative complications and the impact on the quality of life should be taken into consideration. An ileal conduit, commonly known as a Bricker reconstruction, and a colon conduit are the most used diversions in current practice.[40–43] When performing an ileal conduit, an ileal segment is isolated from the bowel, requiring an ileo-ileal anastomosis, whereas in the case of a colon conduit the distal segment of the already transected descending colon is used as a conduit for the ureters, not requiring an additional anastomosis. In a retrospective comparison between two hospitals, including 259 patients with LARC and LRRC, the complications after an ileal (n = 214) and colon conduit (n = 45) were evaluated. Surgical and urological complications were fairly comparable. However, the formation of a colon conduit avoided the risk of an ileo-ileal anastomotic leakage, which was observed in 4% of patients receiving an ileal conduit. Moreover, an ileal conduit was associated with a higher rate of postoperative ileus (21% versus 7%, p = 0.024). Therefore, we prefer and recommend a colon conduit in those patients receiving an end colostomy.

Inherent to the retrospective nature of this study, short-term complication may have been underreported. Moreover, long-term follow-up was available in only 72% of the patients. Currently, the PelvEx 3 study, initiated by the international PelvEx Collaborative and designed as a prospective multicentre study, is recruiting patients to assess the complications of an urinary diversion following pelvic exenteration. In this study, the 30-day, 6-months and 1-year complications will be prospectively assessed. In addition,

it will assess the impact of an urinary diversion on the quality of life. This prospective study is of great value to accurately assess complications and quality of life after the formation of an urinary diversion and may provide additional information to what has been reported previously.

A resection without clear resection margins (R1 resection) is associated with a high local recurrence rate and decreased survival. [14,16,44,45] The risk of an R1 resection is especially increased if resection margins appear narrow on staging MRI or if a difficult resection is expected due tumour location, ingrowth of the tumour in surrounding structures, or the presence of fibrosis. Intraoperative radiotherapy (IORT) may be able to decrease the local recurrence rate in case of an R1 resection.[46–48] IORT can be delivered through intraoperative electron beam radiotherapy (IOERT) or high-dose-rate brachytherapy (HDR-IORT), both with modality specific advantages and disadvantages.[48] In a retrospective comparison between two hospitals, one hospital delivering IOERT and the other hospital delivering HDR-IORT, the long-term oncological outcomes of 215 patients with LARC and 161 with LRRC were compared. Both in LARC and LRRC, a favourable local recurrence-free survival (LRFS) was observed for patients treated with HDR-IORT compared to patients treated with IOERT. Noteworthy, this difference in LRFS implies that IORT has a measurable effect, which was never shown in a large comparative study before and strengthens the recommendation to refer patients with LARC or LRRC, who generally have a high risk for an R1 resection, to a centre with IORT facilities.

In the current study, both IOERT and HDR-IORT were delivered in the same dose, i.e. 10 Gray. However, owing to the steeper dose gradient between the target surface and the reference depth, in HDR-IORT a higher dose is delivered at the surface of the target area compared with IOERT. This disparity in dose distribution appears to offer a sound explanation for the difference in LRFS. Therefore, the IOERT dose distribution has been optimised in such way that the dose at the tissue surface is now to a level comparable to HDR-IORT, while keeping the dose at 9 mm depth at the same value (10 Gy) to prevent an increase in dose-related postoperative morbidity.

PART II

In Part I of this thesis, we showed that a good response to neoadjuvant treatment in the presence of EMVI and TDs is beneficial with regard to the long-term outcomes. In addition to EMVI and TDs, several other tumour characteristics are associated with a worse survival; among them mesorectal fascia (MRF) involvement and locoregional lymph node metastases. The addition of induction chemotherapy to chemoradiotherapy in patients with these prognostically poor characteristics may enhance response rates.

In a retrospective matched-cohort study we compared the complete response (CR) rate in patients with LARC with prognostically poor tumour characteristics (i.e. T4, T3 with EMVI and/or TDs and/or MRF involvement and/or N2 lymph node status, T2 with EMVI and/or TDs and/or N2 lymph node status) who were treated with induction chemotherapy and chemoradiotherapy (ICT-group) to the CR rate in patients treated with chemoradiotherapy alone (CRT-group). The CR rate defined patients who had either a pathological complete response (pCR) after surgical resection or patients in a wait-and-see (W&S) strategy with a sustained clinical complete response (cCR) for a minimum of 12 months under active surveillance. After matching, both the cCR and pCR rate were higher in the ICT-group (cCR: 15.1% versus 1.9%, pCR: 13.2% versus 7.5%), resulting in a significantly higher CR rate in the ICT-group (28.3% versus 9.4%, $p = 0.022$).

In this study, we selected all patients who underwent surgery at the Catharina Hospital Eindhoven or in whom a W&S strategy was initiated. Since the administration of induction chemotherapy is not the standard of care, this treatment regimen was only administered after consensus in our weekly multidisciplinary team (MDT) meeting. Noteworthy, two-thirds of patients in the CRT-group were referred to our MDT meeting after completing neoadjuvant therapy. It is likely that patients with a complete or good response after chemoradiotherapy, in whom routine TME surgery or a W&S strategy was possible, were not referred to our hospital. This may have negatively influenced the CR rate in the CRT-group. Therefore, no definitive conclusions can be drawn based on the results of this study and future research is warranted.

Recently, two large randomised controlled trials have been performed investigating the addition of neoadjuvant chemotherapy in LARC; the RAPIDO trial (doublet consolidation chemotherapy after short-course radiotherapy versus chemoradiotherapy) and the PRODIGE 23 trial (triplet induction chemotherapy followed by chemoradiotherapy, surgery and adjuvant chemotherapy versus chemoradiotherapy, surgery and adjuvant chemotherapy).[49,50] Both studies observed an improved outcome (i.e. DFS or disease-related treatment failure) with the use of neoadjuvant chemotherapy. However, the treatment schedule used in the RAPIDO trial prolongs the interval between radiotherapy and surgery, which is suboptimal in high-risk rectal cancer if IORT is required. Moreover, at the 40th Congress of the European Society of Surgical Oncology in November 2021, results were shown suggesting that the RAPIDO treatment schedule resulted in increased local recurrence rates compared to treatment with chemoradiotherapy alone, which may be especially relevant in those patients that may benefit from IORT.[51]

In the PRODIGE 23 trial, the majority of patients was diagnosed with LARC without high-risk features, which might results in unnecessary exposure to toxic treatment. Therefore, the optimal treatment for patients with high-risk LARC remains a question.

In 2020 our research group in the Catharina Hospital Eindhoven received a grant from ZonMw (Topspecialistische Zorg en Onderzoek – de Multidisciplinaire behandeling van het complexe rectumcarcinoom) to set-up four research projects regarding the treatment of LARC and LRRC. One of these studies, the MEND-IT study, will prospectively evaluate the CR rate in patients with high-risk LARC. This single-arm, multicentre, prospective trial will include 128 patients with rectal cancer with at least one prognostically poor feature on baseline MRI, i.e. MRF involvement, grade 4 EMVI, TDs, or extramesorectal lymph nodes. Treatment will consist of 6 cycles of FOLFOXIRI (oxaliplatin, irinotecan, leucovorin, 5-fluorouracil) followed by full-course chemoradiotherapy. Intensified neoadjuvant chemotherapy with FOLFOXIRI is considered justified in these patients given their poor prognosis. The use of triplet chemotherapy is supported by the recently published PRODIGE 23 trial, showing a high compliance to treatment with triplet induction chemotherapy followed by chemoradiotherapy and surgery in combination with an acceptable toxicity.[50] The MEND-IT study has started accrual in November 2021.

There is still much to be gained in the treatment of patients with LRRC. Despite the use of neoadjuvant chemoradiotherapy, or chemoreirradiation in previously irradiated patients, and extended surgery the R0 resection rate is only 60% and long-term survival is limited.[14,16,52] With the aim to improve these outcomes, the Catharina Hospital Eindhoven started administering induction chemotherapy (i.e. CAPOX (capecitabine, oxaliplatin), FOLFOX (5-fluorouracil, leucovorin, oxaliplatin), or FOLFIRI (5-fluorouracil, leucovorin, irinotecan)) in addition to chemo(re)irradiation from 2010 onward. In a retrospective cohort study, including 132 patients, we evaluated the outcomes of this treatment regimen with regard to the pCR and R0 resection rate. A high pCR rate of 17% was observed, which resulted in an exceptional 3-year OS of 92% in these patients. Besides, pathological response proved to be of prognostic value in LRRC for oncological outcomes. Moreover, there was a linear correlation between the degree of pathological response and the R0 resection rate. Although this was not a comparative study, the results were promising. However, the R0 resection rate in this cohort was only 63%, which is consistent with the rate after treatment with neoadjuvant chemoradiotherapy alone. We hypothesised that the R0 resection rate in this cohort study was negatively affected by the fact that 21% of the patients were considered irresectable at primary staging.

To further explore these finding, we retrospectively compared the outcomes of patients treated with induction chemotherapy followed by chemo(re)irradiation (ICT-group) with those treated with chemo(re)irradiation alone (CRT-group). We also compared the results of two time periods: in the period 2009-2013 induction chemotherapy in addition to chemo(re)irradiation was not the local standard of care in contrast to the latter period, from 2014 to 2018. In both comparisons, the pCR rate was higher in the ICT-group. However, the R0 resection rate and the DFS were comparable. In both comparisons, the ICT-groups reflected a group of patients who were considered to have the poorest prognosis. Additionally, in both comparisons, patients in the ICT-group more often had synchronous metastases and were more often treated with chemoradiotherapy for the primary tumour: both indicators that these tumours may have been prognostically worse than those in the CRT-group. This may explain the non-superior R0 resection rate and DFS in the ICT-group compared to the CRT-group.

Besides, although treatment with induction chemotherapy seemed feasible in the abovementioned retrospective studies given the low rate of grade 3-4 toxicity, no data were available on the number of patients in whom surgery was omitted, either owing to toxicity or progressive disease. This may have resulted in an underestimation of the feasibility of this treatment regimen. Given the outcomes and the remaining questions and uncertainties following these retrospective studies, no definitive recommendations can be made with regard to the efficacy of induction chemotherapy in the treatment of patient with LRRC.

The awarding of the ZonMw grant enabled us to set-up an international, multicentre, randomised controlled trial: the PelvEx II study. This study, which started accrual in November 2020, will randomise 364 patients to receive either induction chemotherapy (CAPOX, FOLFOX, or FOLFIRI) followed by neoadjuvant chemo(re)irradiation and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm). The primary endpoint of the study is the R0 resection rate, as this is the single most important prognostic factor for survival in patients with LRRC.

The PelvEx II study will not only give an answer to the question whether the addition of induction chemotherapy can improve outcomes for patients with LRRC, but also offers an opportunity to improve the quality of care for these patients in general by providing uniform guidelines. The involvement of more than 20 national centres will enhance centralisation of care to dedicated centres in the Netherlands. Another quality improvement will be made through the monthly national MDT that is organised during the accrual period of the PelvEx II study. This MDT, which is attended by surgical oncologists of the centres performing LRRC surgery and a radiologist, was primarily

established as a quality control to ensure appropriate inclusion according to the in- and exclusion criteria. However, and maybe even more importantly, it offers an excellent opportunity to exchange practices and knowledge contributing to the quality of surgery.

Furthermore, there is currently no (inter)national guideline for the delivery of radiotherapy in LRRC. While setting-up the PelvEx II study it became clear that this resulted in inconsistencies in the delineation plans for the delivery of (re)irradiation in LRRC, even when comparing national centres with expertise in this field. The PelvEx II study offers the opportunity to develop a formal guideline to standardise the delivery of (re)irradiation in LRRC.

For the imaging of LRRC there is also no (inter)nationally recognised guideline available. The PelvEx II will also be used to develop a standardised scanning and reporting protocol for initial and restaging imaging using MRI, to improve the care of LRRC in general.

These quality assurance projects that will greatly improve the quality of care for patients with LRRC received an additional grant from the Dutch Cancer Society (KWF).

In conclusion, this thesis resulted in several new insights: in elderly patients with cT4RC and LRRC there is still a need for improvement in order to achieve similar long-term outcomes to that in younger patients, synchronous metastases with LRRC require a personalised approach but do not preclude local treatment, increasing response in patients with LARC with a poor prognosis (presence of EVMI and TDs) may improve long-term outcomes, mrTRG alone is not sufficient in identifying clinical complete responders in LRRC, a colon conduit is a good alternative for an ileal conduit after pelvic exenteration in LARC and LRRC, and the former IOERT technique appears to have been inferior compared to HDR-IORT when it comes to the local recurrence-free survival. These insights resulted in several new research ideas, such as the development of an ERAS protocol specifically for LARC and LRRC, and the adaptation of the dose distribution of IOERT.

Moreover, this thesis showed that treatment with induction chemotherapy in LARC and LRRC is promising but has not been established yet: with two prospective studies now recruiting this will be further researched. While awaiting these results, the PelvEx II study facilitates the centralisation of care, the development of guidelines for the multimodality treatment of LRRC, and nationwide and international cooperation. This will result in an improved quality of care for all LRRC patients.

REFERENCES

1. Heald RJ, Husband EM, Ryall RDH. The mesorectum in rectal cancer surgery—the clue to pelvic recurrence? *Br J Surg*. 1982;69(10):613-616. doi:10.1002/bjs.1800691019
2. Wibe A, Møller B, Norstein J, et al. A national strategic change in treatment policy for rectal cancer--implementation of total mesorectal excision as routine treatment in Norway. A national audit. *Dis Colon Rectum*. 2002;45(7):857-866. http://www.ncbi.nlm.nih.gov/pubmed/12130870. Accessed January 18, 2019.
3. Kapiteijn E, Putter H, Van De Velde CJH. Impact of the introduction and training of total mesorectal excision on recurrence and survival in rectal cancer in The Netherlands. *Br J Surg*. 2002;89(9):1142-1149. doi:10.1046/j.1365-2168.2002.02196.x
4. Krook JE, Collins RT, Kubista TP, et al. Effective surgical adjuvant therapy for high-risk rectal carcinoma. *N Engl J Med*. 1991;324(11):709-715. doi:10.1056/NEJM199103143241101
5. Douglass H, Moertel C, Mayer R, et al. Survival after postoperative combination treatment of rectal cancer. *N Engl J Med*. 1986;315(20):1294-1295.
6. Kapiteijn E, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. *N Engl J Med*. 2001;345(9):638-646. doi:10.1056/NEJMoa010580
7. Sauer R, Becker H, Hohenberger W, et al. Preoperative versus Postoperative Chemoradiotherapy for Rectal Cancer. *N Engl J Med*. 2004;351(71):1731-1740. doi:10.1056/nejmoa040694
8. Sauer R, Liersch T, Merkel S, et al. Preoperative versus postoperative chemoradiotherapy for locally advanced rectal cancer: Results of the German CAO/ARO/AIO-94 randomized phase III trial after a median follow-up of 11 years. *J Clin Oncol*. 2012;30(16):1926-1933. doi:10.1200/JCO.2011.40.1836
9. van Gijn W, Marijnen CAM, Nagtegaal ID, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer: 12-year follow-up of the multicentre, randomised controlled TME trial. *Lancet Oncol*. 2011;12(6):575-582. doi:10.1016/S1470-2045(11)70097-3
10. van den Heijkant F, Vermeer TA, Vrijhof EJEJ, Nieuwenhuijzen GAP, Koldewijn EL, Rutten HJT. Psoas hitch ureteral reimplantation after surgery for locally advanced and locally recurrent colorectal cancer: Complications and oncological outcome. *Eur J Surg Oncol*. 2017;43(10):1869-1875. doi:10.1016/j.ejso.2017.05.018
11. Holman FA, Martijnse IS, Traa MJ, et al. Dynamic article: Vaginal and perineal reconstruction using rectus abdominis myocutaneous flap in surgery for locally advanced rectum carcinoma and locally recurrent rectum carcinoma. *Dis Colon Rectum*. 2013;56(2):175-185. doi:10.1097/DCR.0b013e31827a267c
12. Hagemans JAW, Rothbarth J, Kirkels WJ, et al. Total pelvic exenteration for locally advanced and locally recurrent rectal cancer in the elderly. *Eur J Surg Oncol*. 2018;44(10):1548-1554. doi:10.1016/j.ejso.2018.06.033
13. Westberg K, Palmer G, Hjern F, et al. Population-based study of factors predicting treatment intention in patients with locally recurrent rectal cancer. *Br J Surg*. 2017;104(13):1866-1873. doi:10.1002/bjs.10645

14. Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer – A national population-based study. *Eur J Surg Oncol*. 2018;44(1):100-107. doi:10.1016/j.ejso.2017.11.013

15. Hagemans JAW, van Rees JM, Alberda W, Rothbarth J, Nuyttens JJME, van Meerten E, Verhoef C BJ. Locally recurrent rectal cancer; long-term outcome of curative surgical and palliative treatment of 447 consecutive patients in a tertiairy referral centre. *Eur J Surg Oncol*. 2020;46(3):448-454. 10.1016/j.ejso.2019.10.037.

16. PelvEx Collaborative. Factors affecting outcomes following pelvic exenteration for locally recurrent rectal cancer. *Br J Surg*. 2018;105(6):650-657. doi:10.1002/bjs.10734

17. Bosman SJ, Vermeer TA, Dudink RL, De Hingh IHJT, Nieuwenhuijzen GAP, Rutten HJT. Abdominosacral resection: Long-term outcome in 86 patients with locally advanced or locally recurrent rectal cancer. *Eur J Surg Oncol*. 2014;40(6):699-705. doi:10.1016/j.ejso.2014.02.233

18. Glyn T, Frizelle F. Quality of life outcomes in patients undergoing surgery for locally recurrent rectal cancer. *Semin Colon Rectal Surg*. 2020;31(3). doi:10.1016/j.scrs.2020.100767

19. Detering R, Karthaus EG, Borstlap WAA, et al. Treatment and survival of locally recurrent rectal cancer: A cross-sectional population study 15 years after the Dutch TME trial. *Eur J Surg Oncol*. 2019;45(11):2059-2069. doi:10.1016/j.ejso.2019.06.016

20. Van Cutsem E, Cervantes A, Adam R, et al. ESMO consensus guidelines for the management of patients with metastatic colorectal cancer. *Ann Oncol*. 2016;27(8):1386-1422. doi:10.1093/annonc/mdw235

21. You YN, Habiba H, Chang GJ, Rodriguez-Bigas MA, Skibber JM. Prognostic value of quality of life and pain in patients with locally recurrent rectal cancer. *Ann Surg Oncol*. 2011;18(4):989-996. doi:10.1245/s10434-010-1218-6

22. Verhoef C, Van Der Pool AEM, Nuyttens JJ, Planting AST, Eggermont AMM, De Wilt JHW. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2009;52(1):23-30. doi:10.1007/DCR.0b013e318197939a

23. Ayez N, Burger JWA, Van Der Pool AE, et al. Long-term results of the "liver first" approach in patients with locally advanced rectal cancer and synchronous liver metastases. *Dis Colon Rectum*. 2013;56(3):281-287. doi:10.1097/DCR.0b013e318279b743

24. Adam R, Pascal G, Castaing D, et al. Tumor Progression While on Chemotherapy. *Ann Surg*. 2004;240(6):1052-1064. doi:10.1097/01.sla.0000145964.08365.01

25. Claassen YHM, Bastiaannet E, van Eycken E, et al. Time trends of short-term mortality for octogenarians undergoing a colorectal resection in North Europe. *Eur J Surg Oncol*. 2019;45(8):1396-1402. doi:10.1016/j.ejso.2019.03.041

26. Dekker JWT, Van Den Broek CBM, Bastiaannet E, Van De Geest LGM, Tollenaar RAEM, Liefers GJ. Importance of the first postoperative year in the prognosis of elderly colorectal cancer patients. *Ann Surg Oncol*. 2011;18(6):1533-1539. doi:10.1245/s10434-011-1671-x

27. Rutten HJ, den Dulk M, Lemmens VE, van de Velde CJ, Marijnen CA. Controversies of total mesorectal excision for rectal cancer in elderly patients. *Lancet Oncol*. 2008;9(5):494-501. doi:10.1016/S1470-2045(08)70129-3

28. Brouwer NPM, Heil TC, Olde Rikkert MGM, et al. The gap in postoperative outcome between older and younger patients with stage I-III colorectal cancer has been bridged; results from the Netherlands cancer registry. *Eur J Cancer*. 2019;116:1-9. doi:10.1016/j.ejca.2019.04.036

29. Ketelaers SHJ, Orsini RG, Burger JWA, Nieuwenhuijzen GAP, Rutten HJT. Significant improvement in postoperative and 1-year mortality after colorectal cancer surgery in recent years. *Eur J Surg Oncol*. 2019;45(11):2052-2058. doi:10.1016/j.ejso.2019.06.017

30. Varadhan KK, Neal KR, Dejong CHC, Fearon KCH, Ljungqvist O, Lobo DN. The enhanced recovery after surgery (ERAS) pathway for patients undergoing major elective open colorectal surgery: A meta-analysis of randomized controlled trials. *Clin Nutr*. 2010;29(4):434-440. doi:10.1016/j.clnu.2010.01.004

31. Smith NJ, Shihab O, Arnaout A, Swift RI, Brown G. MRI for detection of extramural vascular invasion in rectal cancer. *Am J Roentgenol*. 2008;191(5):1517-1522. doi:10.2214/AJR.08.1298

32. Lord AC, D'Souza N, Pucher PH, et al. Significance of extranodal tumour deposits in colorectal cancer: A systematic review and meta-analysis. *Eur J Cancer*. 2017;82:92-102. doi:10.1016/j.ejca.2017.05.027

33. Siddiqui MRS, Simillis C, Hunter C, et al. A meta-analysis comparing the risk of metastases in patients with rectal cancer and MRI-detected extramural vascular invasion (mrEMVI) vs mrEMVI-negative cases. *Br J Cancer*. 2017;116(12):1513-1519. doi:10.1038/bjc.2017.99

34. Cercek A, Roxburgh CSD, Strombom P, et al. Adoption of total neoadjuvant therapy for locally advanced rectal cancer. *JAMA Oncol*. 2018;4(6):e180071. doi:10.1001/jamaoncol.2018.0071

35. Chand M, Siddiqui MRS, Swift I, Brown G. Systematic review of prognostic importance of extramural venous invasion in rectal cancer. *World J Gastroenterol*. 2016;22(4):1721-1726. doi:10.3748/wjg.v22.i4.1721

36. Siddiqui MRS, Gormly KL, Bhoday J, et al. Interobserver agreement of radiologists assessing the response of rectal cancers to preoperative chemoradiation using the MRI tumour regression grading (mrTRG). *Clin Radiol*. 2016;71(9):854-862. doi:10.1016/j.crad.2016.05.005

37. Patel UB, Taylor F, Blomqvist L, et al. Magnetic resonance imaging-detected tumor response for locally advanced rectal cancer predicts survival outcomes: MERCURY experience. *J Clin Oncol*. 2011;29(28):3753-3760. doi:10.1200/JCO.2011.34.9068

38. Habr-Gama A, Perez RO, Wynn G, Marks J, Kessler H, Gama-Rodrigues J. Complete clinical response after neoadjuvant chemoradiation therapy for distal rectal cancer: Characterization of clinical and endoscopic findings for standardization. *Dis Colon Rectum*. 2010;53(12):1692-1698. doi:10.1007/DCR.0b013e3181f42b89

39. West MA, Dimitrov BD, Moyses HE, et al. Timing of surgery following neoadjuvant chemoradiotherapy in locally advanced rectal cancer – A comparison of magnetic resonance imaging at two time points and histopathological responses. *Eur J Surg Oncol*. 2016;42(9):1350-1358. doi:10.1016/j.ejso.2016.04.003

40. Nieuwenhuijzen JA, de Vries RR, Bex A, et al. Urinary Diversions after Cystectomy: The Association of Clinical Factors, Complications and Functional Results of Four Different Diversions. *Eur Urol*. 2008;53(4):834-842. doi:10.1016/j.eururo.2007.09.008

41. Bricker E. Bladder substitution after pelvic evisceration. *Surg Clin N Amer*. 1950;30(5):1511-1521. doi:10.1016/s0039-6109(16)33147-4.

42. Schmidt JD, Hawtrey CE, Buchsbaum HJ. Transverse colon conduit: a preferred method of urinary diversion for radiation treated pelvic malignancies. *J Urol*. 1975;113(3):308-313. doi:10.1016/S0022-5347(17)59469-0

43. Meijer RP, Mertens LS, Meinhardt W, Verwaal VJ, Dik P, Horenblas S. The colon shuffle: A modified urinary diversion. *Eur J Surg Oncol*. 2015;41(9):1264-1268. doi:10.1016/j.ejso.2015.02.007

44. Alberda WJ, Verhoef C, Schipper MEI, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. *Dis Colon Rectum*. 2015;58(7):677-685. doi:10.1097/DCR.0000000000000388

45. PelvEx Collaborative. Surgical and Survival Outcomes Following Pelvic Exenteration for Locally Advanced Primary Rectal Cancer. *Ann Surg*. 2019;269(2):315-321. doi:10.1097/SLA.0000000000002528

46. Alberda WJ, Verhoef C, Nuyttens JJ, et al. Intraoperative radiation therapy reduces local recurrence rates in patients with microscopically involved circumferential resection margins after resection of locally advanced rectal cancer. *Int J Radiat Oncol Biol Phys*. 2014;88(5):1032-1040. doi:10.1016/j.ijrobp.2014.01.014

47. Ferenschild FTJ, Vermaas M, Nuyttens JJME, et al. Value of intraoperative radiotherapy in locally advanced rectal cancer. *Dis Colon Rectum*. 2006;49(9):1257-1265. doi:10.1007/s10350-006-0651-x

48. Mirnezami R, Chang GJ, Das P, et al. Intraoperative radiotherapy in colorectal cancer: Systematic review and meta-analysis of techniques, long-term outcomes, and complications. *Surg Oncol*. 2013;22(1):22-35. doi:10.1016/j.suronc.2012.11.001

49. Bahadoer RR, Dijkstra EA, van Etten B, et al. Short-course radiotherapy followed by chemotherapy before total mesorectal excision (TME) versus preoperative chemoradiotherapy, TME, and optional adjuvant chemotherapy in locally advanced rectal cancer (RAPIDO): a randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;22(1):29-42. doi:10.1016/S1470-2045(20)30555-6

50. Conroy T, Bosset JF, Etienne P, et al. Neoadjuvant chemotherapy with FOLFIRINOX and preoperative chemoradiotherapy for patients with locally advanced rectal cancer (UNICANCER-PRODIGE 23): a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol*. 2021;Apr 13: S1. doi:10.1016/S1470-2045(21)00079-6

51. Bahadoer R, Dijkstra E. Patterns of locoregional failure and distant metastases in patients treated for locally advanced rectal cancer in the RAPIDO trial. *Eur J Surg Oncol*. 2022;48(2):e34.

52. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and Late Outcomes of Surgery for Locally Recurrent Rectal Cancer: A Prospective 10-Year Study in the Total Mesorectal Excision Era. *Ann Surg Oncol*. 2015;22(8):2677-2684. doi:10.1245/s10434-014-4317-y

CHAPTER 13

SUMMARY

SAMENVATTING

SUMMARY

Locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC) are both challenging conditions. This thesis aims to further improve the multimodality treatment of patients with LARC and LRRC, in order to ultimately improve quality of life and long-term oncological outcomes in these patients. To achieve this, several studies were conducted. The studies presented in part one focus on patient selection, imaging, and peroperative approach in LARC and LRRC. In part two, the studies focus on the neoadjuvant treatment in LARC and LRRC, in particular the addition of induction chemotherapy to chemoradiotherapy.

This chapter provides a summary of the main findings of these studies.

Part I: Patient selection, imaging and peroperative approach
Patients with locally recurrent rectal cancer (LRRC) frequently present with either synchronous metastases or a history of metastases. In **Chapter 2**, the oncological outcomes of patients with LRRC without metastases are compared to that in patients with a history of metastases treated with curative intent or patients with potentially curable synchronous metastases. The 3-year overall survival in patients with a history of metastases was comparable to that in patients without metastases (65% and 54%, respectively). However, in patients with synchronous metastases a worse 3-year overall survival was observed (39%).

In **Chapter 3**, the morbidity and long-term outcomes of elderly patients (≥ 75 years) with clinical T4 (cT4) or LRRC is evaluated over time and compared to that in younger patients. Postoperative morbidity was higher in elderly patients than in younger patients (73.4% vs. 61.7% for cT4, $p = 0.02$ and 96.2% vs. 77.1%, $p = 0.001$ for LRRC). The 30-day mortality has decreased over time, and is now similar in both age groups (< 75 years 1.5% vs. ≥ 75 years 3.1%, $p = 0.46$ for cT4 and < 75 years 1.4% vs. ≥ 75 years 0%, $p > 0.99$ for LRRC). However, the 1-year mortality rates did not improve over time and were significantly worse in elderly patients than in younger patients (28.1% vs. 6.2%, $p = 0.001$ for cT4 and 27.3% vs. 13.8%, $p = 0.06$ for LRRC). Elderly mainly died because of treatment-induced or non-cancer-related causes rather than disease recurrence, which was the main cause of death in patients < 75 years.

In **Chapter 4**, the incidence and features of magnetic resonance imaging-detected extramural venous invasion (mrEMVI) and tumour deposits (TDs) in cT3-4 rectal cancer before and after neoadjuvant treatment in relation to long-term oncological outcomes are described. The prevalence of mrEMVI and TDs was high and was associated with an

increased 5-year distant metastases rate (45.2% for EMVI+ TDs+ vs. 35.9% for EMVI+ TDs- vs. 25.7% for EMVI-, $p = 0.012$) and a worse 5-year disease-free survival (47.5% for EMVI+ TDs+ vs. 60.4% for EMVI+ TDs- vs. 65.5% for EMVI-, $p = 0.029$). Response of EMVI to neoadjuvant chemoradiotherapy was negatively influenced by the occurrence of TDs and larger mrEMVI size. However, a good response to neoadjuvant chemoradiotherapy resulted in long-term outcomes comparable to that in patients without mrEMVI.

In **Chapter 5**, the magnetic resonance imaging (MRI) based tumour regression grade (mrTRG), which has been developed to assess the tumour response to neoadjuvant treatment in patients with primary rectal cancer, is evaluated in a cohort of patients with LRRC. All MRI scans were reassessed by two independent radiologists: the agreement between them was fair ($k = 0.28$) using a two-tier grading system (i.e. mrTRG 1-2 vs. mrTRG 3-5). For the lead radiologist, the agreement with the pathological TRG (pTRG) was moderate ($k = 0.52$; 95% CI 0.36-0.68) when comparing good (mrTRG 1-2, Mandard 1-2) and intermediate/poor responders (mrTRG 3-5, Mandard 3-5). However, an interval between MRI and surgery shorter than 7 weeks seems to improve this agreement ($k = 0.69$). Moreover, if assessed by a dedicated radiologist, the positive predictive value for predicting good responders was 95% (95% CI: 71%-99%).

In **Chapter 6**, the short- and long-term complications of an ileal and colon conduit after surgery for LARC and LRRC are presented in a large cohort of two tertiary referral hospitals. Urological complications and major morbidity rates (Clavien-Dindo ≥ 3) were comparable between colon and ileal conduits (16% vs. 24%, $p = 0.226$ for urological complications and 31% vs. 41%, $p = 0.233$ for major morbidity). However, formation of an ileal conduit resulted in anastomotic leakage of the ileo-ileal anastomosis in 4% of the patients, which was avoided in patients receiving a colon conduit. In addition, an ileal conduit was associated with a higher rate of postoperative ileus (21% vs. 7%, $p = 0.024$).

In **Chapter 7**, the long-term oncological outcomes of two intraoperative radiotherapy modalities, intraoperative electron beam radiotherapy (IOERT) and high-dose-rate intraoperative brachytherapy (HDR-IORT), are compared in patients with LARC or LRRC who underwent a microscopic irradical (R1) resection in two tertiary referral centres. Although the 3-year overall survival was not significantly different between the groups, the local recurrence-free survival was significantly longer in patients treated with HDR-IORT than in IOERT, both in LARC ($p = 0.041$; HR 0.496; 95% CI 0.253-0.973) and LRRC ($p = 0.021$; HR 0.567; 95% CI 0.349-0.920).

Part II: Neoadjuvant treatment

In **Chapter 8**, a matched case-control study is presented in which the complete response (CR) rate, i.e. pathological and clinical complete response rate combined, after treatment with induction chemotherapy and chemoradiotherapy was compared with that after treatment with chemoradiotherapy in a cohort of patients with LARC with prognostically poor tumour characteristics. Prognostically poor characteristics were defined as any T4, or a T2/3 tumour with extramural invasion, and/or tumour deposits, and/or N2 lymph node status, and/or mesorectal fascia involvement (T3 tumour only). Treatment including induction chemotherapy resulted in significantly higher CR rate compared to treatment with chemoradiotherapy alone (28% vs. 9%, $p = 0.013$).

In **Chapter 9**, the pathological response in patients with LRRC after treatment with induction chemotherapy followed by chemoradiotherapy was assessed. A high pathological complete response rate (17%) was observed that resulted in a promising 3-year overall survival of 92% in these patients. Moreover, pathological response showed to be a powerful prognostic variable for improved oncological outcomes, especially when a resection with clear resection margins (R0 resection) can be achieved.

In **Chapter 10**, a research letter further exploring the results in chapter 9 is presented. In this study, the pathological complete response (pCR) rate, R0 resection rate and disease-free survival (DFS) were compared in a cohort in which induction chemotherapy was not standard of care (2009 - 2013) with a cohort in which induction chemotherapy was standard of care (2014 -2018). In addition, all patients between 2010-2018 receiving induction chemotherapy followed by chemoradiotherapy were compared with patients receiving chemoradiotherapy. In both comparisons, the pCR rate was significantly better after treatment including induction chemotherapy compared with chemoradiotherapy alone (15.8% vs. 7.9%, $p = 0.040$ and 16.5% vs. 8.6%, $p = 0.046$). However, the R0 resection rate and DFS were comparable between both treatment groups (68.4% vs. 59.1% and 64.3% vs. 63.2% for the R0 resection rate; 26.2% vs. 25.1% and 21.3% vs. 26.7% for the DFS).

In **Chapter 11**, the study protocol of the PelvEx II trial is described. The PelvEx II study is an international, multicentre, open-label, parallel-arms, randomised controlled trial in patients with LRRC. In this study, 364 patients will be randomised in a 1:1 ratio to receive either induction chemotherapy followed by neoadjuvant chemoradiotherapy and surgery (experimental arm) or neoadjuvant chemoradiotherapy and surgery alone (control arm). The primary endpoint of the study is the R0 resection rate. Secondary endpoints are long-term survival, radiological and pathological response, toxicity, postoperative morbidity, health-related costs and quality of life.

SAMENVATTING

Het lokaal gevorderde rectumcarcinoom (LARC) en het lokaal recidiverend rectumcarcinoom (LRRC) zijn complexe aandoeningen. Dit proefschrift heeft als doel de multimodale behandeling van patiënten met LARC en LRRC te verbeteren, om zo uiteindelijk de kwaliteit van leven en de lange termijn uitkomsten van deze patiënten te verbeteren. Om dit te bereiken zijn er verschillende studies uitgevoerd. De studies gepresenteerd in deel één van dit proefschrift richten zich op patiëntselectie, beeldvorming en de peroperatieve behandeling in zowel LARC als LRRC. In deel twee van dit proefschrift richten de onderzoeken zich op de neoadjuvante behandeling bij LARC en LRRC, in het bijzonder de toevoeging van inductie chemotherapie. Dit hoofdstuk geeft een samenvatting van de belangrijkste bevindingen van deze studies.

Deel I: Patiëntselectie, beeldvorming en peroperatieve behandeling
Patiënten met lokaal recidiverend rectumcarcinoom (LRRC) presenteren zich vaak met synchrone metastasen ofwel een voorgeschiedenis van metastasen. In **Hoofdstuk 2** worden de oncologische uitkomsten van patiënten met LRRC zonder metastasen vergeleken met die van patiënten met een voorgeschiedenis van metastasen die in opzet curatief behandeld zijn en met patiënten met behandelbare synchrone metastasen. De 3-jaars overleving van patiënten met een voorgeschiedenis van metastasen was vergelijkbaar met die van patiënten zonder metastasen (respectievelijk 65% en 54%). Echter, bij patiënten met synchrone metastase werd een slechtere 3-jaars overleving waargenomen (39%).

In **Hoofdstuk 3** worden de morbiditeit en lange termijn uitkomsten van oudere patiënten (≥ 75 jaar) met een klinisch T4 (cT4) rectumcarcinoom of een LRRC geëvalueerd over de tijd en vergeleken met die van jongere patiënten. De postoperatieve morbiditeit was hoger in oudere patiënten dan in jongere patiënten (73.4% vs. 61.7% in cT4, p = 0.02 en 96.2% vs. 77.1%, p = 0.001 in LRRC). De 30-dagen mortaliteit is in de loop van de jaren afgenomen en is nu vergelijkbaar tussen beide leeftijdsgroepen (< 75 jaar 1.5% vs. ≥ 75 jaar 3.1%, p = 0.46 in cT4 en < 75 jaar 1.4% vs. ≥ 75 jaar 0%, p > 0.99 in LRRC). Echter, de 1-jaars mortaliteit verbeterde niet over de tijd en bleef significant slechter in oudere patiënten in vergelijking tot jongere patiënten (28.1% vs. 6.2%, p = 0.001 in cT4 en 27.3% vs. 13.8%, p = 0.06 in LRRC). Ouderen stierven voornamelijk door behandeling geïnduceerde oorzaken dan wel aan niet-kanker gerelateerde doodsoorzaken, terwijl recidiverende ziekte de belangrijkste doodsoorzaak was in patiënten jonger dan 75 jaar.

In **Hoofdstuk 4** worden de incidentie en kenmerken van op magnetische resonantie beeldvorming (MRI) gedetecteerde extramurale veneuze invasie (mrEMVI) en tumor

deposities (TDs) in cT3-4 rectumcarcinoom voor en na neoadjuvante behandeling beschreven in relatie tot de oncologische uitkomsten op lange termijn. De prevalentie van mrEMVI en TDs was hoog en ging gepaard met een verhoogde 5-jaars kans op afstandsmetastasen (45.2% in EMVI+ TDs+ vs. 35.9% in EMVI+ TDs- vs. 25.7% in EMVI-, $p = 0.012$) en een slechtere ziektevrije 5-jaars overleving (47.5% in EMVI+ TDs+ vs. 60.4% in EMVI+ TDs- vs. 65.5% in EMVI-, $p = 0.029$). De respons van EMVI op neoadjuvante chemoradiotherapie werd negatief beïnvloed door de aanwezigheid van TDs en grotere mrEMVI-grootte. Een goede respons op neoadjuvante chemoradiotherapie resulteerde echter in lange termijn resultaten vergelijkbaar met die in patiënten zonder mrEMVI.

In **Hoofdstuk 5** wordt de op MRI gebaseerde tumorregressiegraad (mrTRG), die ontwikkeld is om de tumorrespons op neoadjuvante behandeling in patiënten met een primair rectumcarcinoom te beoordelen, geëvalueerd in een cohort van patiënten met LRRC. Alle MRI scans werd opnieuw beoordeeld door twee onafhankelijke radiologen: de overeenstemming tussen hen was matig ($k = 0.28$) met behulp van een tweeledig systeem (d.w.z. mrTRG 1-2 vs. mrTRG 3-5). Voor de leidende radioloog was de overeenstemming met de pathologische TRG (pTRG) redelijk ($k = 0.52$; 95% 0.36-0.68) bij het vergelijken van goede (mrTRG 1-2, Mandard 1-2) met matige/slechte responders (mrTRG 3-4, Mandard 3-5). Een interval tussen MRI en operatie korte dan 7 weken lijkt deze overeenstemming te verbeteren ($k = 0.69$). Bovendien, indien beoordeeld door een radioloog met expertise, was de positief voorspellende waarde voor het voorspellen van goede respons 95% (95% CI 71%-99%).

In **Hoofdstuk 6** worden de korte en lange termijn complicaties van een ileum en colon conduit na chirurgie voor LARC en LRRC gepresenteerd in een groot cohort uit twee tertiaire verwijscentra. Het percentage urologische complicaties en ernstige morbiditeit (Clavien-Dindo ≥ 3) was vergelijkbaar tussen beide urostoma's (16% vs. 24%, $p = 0.226$ voor urologische complicaties en 31% vs. 41%, $p = 0.233$ voor ernstige morbiditeit). Echter, het creëren van een ileum conduit leidde bij 4% van de patiënten tot een lekkage van de ileo-ileale anastomose, wat werd vermeden bij patiënten met een colon conduit. Bovendien was een ileum conduit geassocieerd met een hoger percentage postoperatieve ileus (21% vs. 7%, $p = 0.024$).

In **Hoofdstuk 7** worden de lange termijn oncologische uitkomsten van twee intraoperatieve radiotherapie modaliteiten, intraoperatieve elektronen radiotherapie (IOERT) en high-dose rate intraoperatieve brachytherapie (HDR-IORT), vergeleken bij patiënten met LARC of LRRC die een microscopisch irradicale (R1) resectie hebben ondergaan in twee tertiaire verwijscentra. Hoewel de 3-jaars overleving niet significant verschillend was tussen de groepen, was de lokaal recidief-vrije overleving significant

langer in patiënten behandeld met HDR-IORT dan met IOERT, zowel in LARC (p = 0.041; HR 0.496; 95% CI 0.253-0.973) als LRRC (p = 0.021; HR 0.567; 95% CI 0.349-0.920).

Deel II: Neoadjuvante behandeling

In **Hoofdstuk 8** wordt een gematchte case-control studie gepresenteerd waarin de complete respons (CR), d.w.z. pathologisch en klinisch complete respons gecombineerd, na behandeling met inductie chemotherapie en chemoradiotherapie werd vergeleken met die na behandeling met chemoradiotherapie in een cohort van patiënten met LARC met prognostisch slechte tumorkarakteristieken. Prognostisch slechte tumorkarakteristieken werden gedefinieerd als elke T4 tumor, of een T2/3 tumor met extramurale veneuze invasie en/of tumor deposities en/of N2 lymfeklierstatus en/of betrokkenheid van de mesorectale fascie (alleen T3-tumor). Behandeling met inductie chemotherapie en chemoradiotherapie resulteerde in een significant hoger percentage CR vergeleken met behandeling met alleen chemoradiotherapie (28% vs. 9%, p = 0.013).

In **Hoofdstuk 9** werd de pathologische respons onderzocht in patiënten met LRRC na behandeling met inductie chemotherapie gevolgd door chemoradiotherapie. Er werd een hoog percentage pathologisch complete respons gevonden (17%), wat resulteerde in een veelbelovende 3-jaars overleving van 92% in deze groep patiënten. Bovendien bleek de pathologische respons een sterke prognostische variabele voor oncologische uitkomsten, met name wanneer er tevens een resectie met vrije resectievlakken (R0 resectie) bereikt kan worden.

In **Hoofdstuk 10** wordt een onderzoek gepresenteerd waarin de resultaten uit hoofdstuk 9 nader worden onderzocht. In deze studie werd het percentage pathologisch complete respons (pCR), het percentage R0-resecties en de ziekte-vrije overleving (ZVO) vergleken in een cohort waarin inductie chemotherapie geen standaardbehandeling was (2009 – 2013) met een cohort waarin inductie chemotherapie wel standaard werd toegepast (2014 – 2018). Tevens werden alle patiënten die tussen 2010 en 2018 inductie chemotherapie kregen gevolgd door chemoradiotherapie vergeleken met patiënten die alleen chemoradiotherapie kregen. In beide vergelijkingen was het percentage pCR significant beter na behandeling bestaande uit inductie chemotherapie in vergelijking met chemoradiotherapie alleen (15.8% vs. 7.9%, p = 0.040 en 16.5% vs. 8.6%, p = 0.046). Het R0-resectie percentage en de ZVO was echter vergelijkbaar tussen beide behandelgroepen (68.4% vs. 59.1% en 64.3% vs. 63.2% voor R0-resectie; 26.2% vs. 25.1% en 21.3% vs. 26.7% voor ZVO).

In **Hoofdstuk 11** wordt het studieprotocol van de PelvEx II studie beschreven. De PelvEx II studie is een internationale, multicenter, open-label, parallelle armen,

gerandomiseerde, gecontroleerde studie in patiënten met LRRC. In deze studie zullen 364 patiënten worden gerandomiseerd in een 1:1 ratio voor het krijgen van ofwel inductie chemotherapie gevolgd door neoadjuvante chemoradiotherapie en chirurgie (experimentele arm) ofwel neoadjuvante chemoradiotherapie en chirurgie alleen (controle arm). Het primaire eindpunt van de studie is het percentage R0-resecties. Secundaire eindpunten zijn lange termijn overleving, radiologische en pathologische respons, toxiciteit, postoperatieve morbiditeit, gezondheid-gerelateerde kosten en kwaliteit van leven.

CHAPTER 14

IMPACT PARAGRAPH

IMPACT PARAGRAPH

This thesis focused on patients with locally advanced rectal cancer (LARC) and locally recurrent rectal cancer (LRRC). LARC is an advanced stage of rectal cancer, in which the tumour grows beyond the wall of the rectum or shows other characteristics of locally advanced disease, such as involvement of the locoregional lymph nodes. In patients with LRRC, the tumour has recurred in the pelvis after previous successful treatment of rectal cancer.

Both LARC and LRRC require neoadjuvant treatment (i.e. treatment prior to surgery) followed by surgery. The current standard of neoadjuvant treatment consist of chemoradiotherapy, i.e. irradiation of the pelvis combined with oral chemotherapy. Surgical resection for LARC and, especially LRRC, is often an extended procedure involving the resection of multiple pelvic structures and/or organs. A total pelvic exenteration (i.e., resection of the rectum, bladder and reproductive organs) requiring reconstructive surgery is not uncommon. Not surprisingly, these surgeries are accompanied with a high postoperative morbidity rate and a profound impact on the quality of life.

In patients with LARC, distant metastases are a major concern with it being the most important cause of death in these patients. Although the rate of LRRC has decreased over the past decades owing to improvements in the treatment of primary rectal cancer, the prognosis for patients with LRRC is still poor, as only 30% of these patients are alive at 5 years after diagnosis.

This illustrates there is still much to gain in this specific population. In this thesis we therefore aimed to improve the treatment of patients with LARC and LRRC, with the purpose to ultimately improve their quality of life and long-term surgical as well as oncological outcomes.

The treatment of LARC and LRRC requires a multimodality approach. A surgical oncologist, medical oncologist, radiation oncologist, and radiologist are therefore all essential in the treatment of these patients. Depending on the need and type of reconstructive surgery other specialist are also involved. The results of the studies included in this thesis provide relevant knowledge applicable in the clinical decision-making of all of these physicians.

Among other things, we concluded that in elderly patients with LARC and LRRC there is still a need for improvement in order to achieve similar long-term outcomes to that

in younger patients and there is a need for better patients selection or better pre-, peri-, and postoperative care in these patients. With regard to patient selection we also observed that the presence of distant metastases in patients with LRRC requires a personalised approach giving the worse prognosis in this specific group. Furthermore, we observed that, to improve long-term outcomes in LARC and LRRC, achieving tumour response by means of neoadjuvant treatment is essential, and that in the assessment of this response after neoadjuvant treatment an MRI alone is not sufficient in LRRC. Besides, we found that a urostomy formed with a part of the colon is a good alternative for a urostomy formed with a part of the small intestine given the lower postoperative morbidity, and that intraoperative radiotherapy using a brachytherapy (HDR-IORT) appears more effective when compared with intraoperative radiotherapy using electron beam radiotherapy (IOERT) in patients with LARC and LRRC with microscopically residual tumour.

The above mentioned findings also resulted in new research questions and ideas. For example, a peri-and postoperative protocol adjusted to the specific challenges and needs of patients with LARC and LRRC was developed; whether this will improve morbidity and mortality will be evaluated. Moreover, the IOERT procedure was optimised in order to improve outcomes.

As such, these results are not just of interest for the treating physicians, but also for the patients themselves as these results support improvement of treatment and outcomes.

In the second part of this thesis, we investigated whether the addition of induction chemotherapy (i.e. intravenous chemotherapy administered prior to the chemoradiotherapy) could aid in improving the outcomes of patients with LARC and LRRC. Retrospective data showed promising results, but were inconsistent and therefore no definitive recommendations could be made regarding the use of induction chemotherapy. However, it did result in the awarding of two grants, enabling us to further research this. The MEND-it study will prospectively evaluate the additional value of induction chemotherapy in patients with LARC; the PelvEx II study is designed for patients with LRRC.

The PelvEx II study randomises patients with LRRC into two treatment groups: a) induction chemotherapy followed by chemoradiotherapy and surgery and b) chemoradiotherapy and surgery. This study not only aims to find an answer to the question whether induction chemotherapy is a valuable addition to the treatment of patients with LRRC, but also aims to improve the quality of care of these patients in general.

Firstly, we aim to do so by centralisation of care in so called expert centres. This will guarantee expertise of the treating physicians, which will hopefully result in the delivery of care that better meets the needs of the patient and its disease.

Moreover, with this study we also aim to develop uniform guidelines for the delivery of radiotherapy and the assessment of imaging in LRRC. Through the international involvement within this study, these guidelines will have a worldwide platform for implementation.

In spite of the absence of conclusive evidence of its value, treatment incorporating induction chemotherapy is increasingly being used worldwide. However, this is a long and intensive treatment regimen that is associated with treatment-related morbidity and inevitable costs. Therefore, a well-designed study to evaluate this treatment regimen is required.

From a patient perspective the effectiveness of a treatment is obviously of utmost importance. In addition, improvement in the quality of life and manageable side effects of treatment are also highly important. Within the PelvEx II study all of these aspects of treatment will be studied. In such way, the results of this study will show whether treatment with induction chemotherapy is a beneficial treatment from a patients perspective.

On the other hand, from a societal perspective, it is also desirable to offer the appropriate care to the right patients in order to ensure targeted use of resources. Therefore, the PelvEx study will also study the cost-effectiveness and cost-utility of both treatment regimens provided within the study.

APPENDICES

SUPPLEMENTARY DATA

LIST OF PUBLICATIONS

DANKWOORD

CURRICULUM VITAE

SUPPLEMENTARY DATA

CHAPTER 2

Supplementary Table 1 Multivisceral resections

	Total*	No metastases	History of metastases	Synchronous metastases	
Multivisceral resection	**N=238 (%)**	**N=181 (%)**	**N=28 (%)**	**N=29 (%)**	***p* value**
Resection bladder (partial/complete)	73(31)	52(29)	9(32)	12(41)	0.384
Resection prostate (partial/complete)	51(21)	38(21)	7(25)	6(21)	0.886
Resection vesicle(s) (uni-/bilateral)	83(35)	65(36)	8(29)	10(35)	0.749
Resection uterus	36(15)	28(16)	2(7)	6(21)	0.372
Resection vagina (posterior wall/complete)	60(25)	48(27)	6(21)	6(21)	0.708
Resection ovaria (uni-/bilateral)	34(17)	30(17)	1(4)	3(10)	0.160
Resection sacrum					
S2-3	42(18)	34(19)	3(11)	5(17)	0.611
S4	29(12)	23(13)	5(18)	1(3)	
S5-os coccyx	40(17)	29(16)	6(21)	5(17)	
No sacral resection	127(53)	95(53)	14(50)	18(62)	

*Numbers do not add up to 238 as in one patient multiple organs could have been resected.

CHAPTER 3

Supplementary Table 1 Details on the extent of exenteration, stratified by age group for both cT4RC and LRRC patients

	cT4RC		LRRC	
	<75 years n = 32 n (%)	**≥75 years n = 3 n (%)**	**<75 years n = 38 n (%)**	**≥75 years n = 7 n (%)**
Sacral resections	3 (9.4)	-	20 (52.6)	5 (71.4)
Pelvic side wall resections				
Unilateral	12 (37.5)	-	18 (47.4)	1 (14.3)
Bilateral	1 (3.1)	-	10 (26.3)	3 (42.9)

CHAPTER 4

eTable 1 Univariable analyses for risk factors for distant metastasis, local recurrence, disease-free survival and overall survival

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age			0.608			0.265			0.845			0.020
Up to 67 years old	1.00			1.00			1.00			1.00		
68 years or older	1.118	0.730-1.714		0.666	0.326-1.361		0.961	0.648-1.426		1.671	1.086-2.572	
Sex			0.466			0.909			0.380			0.637
Female	1.00			1.00			1.00			1.00		
Male	1.117	0.760-1.822		1.040	0.529-2.047		1.196	0.802-1.785		1.113	0.713-1.737	
cTstage			0.909			0.176			0.939			0.170
3	1.00			1.00			1.00			1.00		
4	1.025	0.671-1.566		1.606	0.808-3.191		0.985	0.669-1.450		1.357	0.877-2.101	
cNstage			0.103			0.277			0.056			0.947
0	1.00			1.00			1.00			1.00		
1	1.762	0.915-3.391		2.157	0.819-5.681		1.937	1.074-3.491		0.906	0.501-1.639	
2	1.904	1.047-3.464		1.484	0.580-3.799		1.865	1.080-3.222		0.967	0.577-1.621	
Mesorectal fascia involvement			0.191			0.364			0.343			0.053
No	1.00			1.00			1.00			1.00		
Yes	1.438	0.835-2.477		1.504	0.624-3.626		1.261	0.781-2.038		1.797	0.993-3.252	
mrEMVI and deposits			0.014			0.377			0.032			0.280
No mrEMVI	1.00			1.00			1.00			1.00		
mrEMVI without deposits	1.440	0.822-2.525		1.772	0.782-4.020		1.220	0.734-2.027		0.797	0.446-1.424	
mrEMVI with deposits	2.111	1.277-3.490		1.489	0.656-3.382		1.805	1.151-2.830		1.267	0.786-2.073	

eTable 1 (Continued)

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Neoadjuvant treatment			0.458			0.916			0.714			0.217
5 x 5 Gy radiotherapy	1.00			1.00			1.00			1.00		
(chemo)radiotherapy	0.794	0.431-1.461		1.058	0.373-2.998		0.897	0.501-1.605		0.696	0.392-1.237	
Type of surgery			0.177			0.328			0.137			0.012
LAR	1.00			1.00			1.00			1.00		
APR	1.362	0.831-2.232		1.754	0.834-3.686		1.362	0.867-2.140		1.632	0.981-2.715	
Extended resection	1.614	0.943-2.761		1.401	0.571-3.437		1.593	0.976-2.601		2.194	1.288-3.738	
Margin involvement			<0.001			0.002			<0.001			<0.001
R0	1.00			1.00			1.00			1.00		
R1	2.897	1.597-5.257		3.723	1.614-8.589		3.054	1.782-5.233		4.522	2.625-7.792	

Abbreviations: APR = abdominoperineal resection, LAR = low anterior resection, MrEMVI = MRI detected extramural venous invasion.

eTable 2 Multivariable analyses for risk factors for distant metastasis, local recurrence, disease-free survival and overall survival

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age												0.029
Up to 67 years old										1.00		
68 years or older										1.623	1.052-2.504	
cNstage									0.074			
0							1.00					
1							1.973	1.095-3.554				
2							1.665	0.995-2.902				
Type of surgery												0.182
LAR										1.00		
APR										1.430	0.850-2.404	
Extended resection										1.646	0.939-2.888	
Mesorectal fascia involvement										1.00		0.349
										1.350	0.721-2.530	
mrEMVI and deposits			0.017						0.046			
No mrEMVI	1.00						1.00					
mrEMVI without deposits	1.434	0.818-2.514					0.957	0.472-1.942				
mrEMVI with deposits	2.071	1.252-3.425					1.609	1.049-2.467				
Margin involvement			0.001			0.002			<0.001			<0.001
R0	1.00			1.00			1.00			1.00		
R1	2.816	1.552-5.111		3.723	1.614-8.589		2.923	1.697-5.034		3.864	2.224-6.711	

Abbreviations: MrEMVI = MRI detected extramural venous invasion.

eTable 3 Schematic overview of the relationship between relation between mrTRG, mr-vTRG and the response of deposits

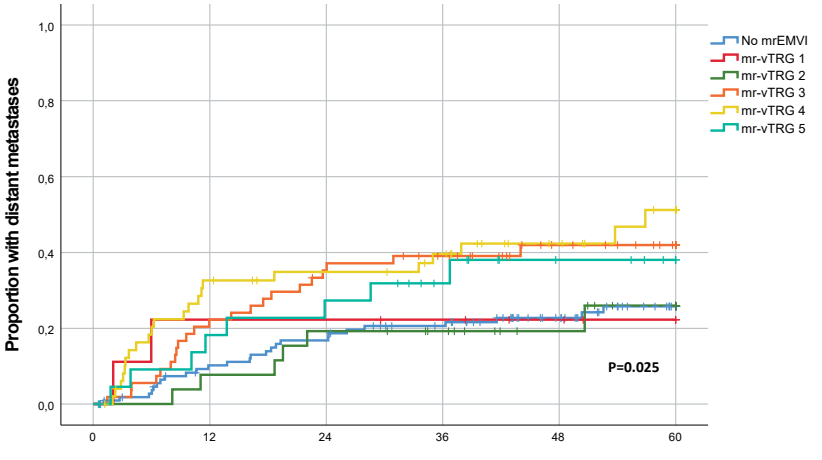
Characteristics on MRI	No. with restaging MRI	Tumor response	mrEMVI response	Deposit response	5-year DM rate
mrEMVI- deposits- n = 103 (37)	n = 75	mrTRG I-II, n = 22 (29)	n.a.	n.a.	20%
		mrTRG III-V, n = 53 (71)	n.a.	n.a.	25.4%
mrEMVI- deposits+ n = 11 (4)	n = 11	mrTRG I-II, n = 2 (18)	n.a.	deposits-, n = 2 (100)	
				deposits+, n = 0 (0)	
		mrTRG III-V, n = 9 (82)	n.a.	deposits-, n = 2 (22)	
				deposits+, n = 7 (78)	
mrEMVI+ deposits- n = 71 (26)	n = 70	mrTRG I-II, n = 16 (23)	mr-vTRG I-II, n = 11 (68)	n.a.	27.3%
			mr-vTRG III-V, n = 5 (31)	n.a.	20%
		mrTRG III-V, n = 54 (77)	mr-vTRG I-II, n = 13 (24)	n.a.	35.9%
			mr-vTRG III-V, n = 41 (76)	n.a.	40.2%
mrEMVI+ deposits+ n = 92 (33)	n = 91	mrTRG I-II, n = 9 (10)	mr-vTRG I-II, n = 7 (78)	deposits-, n = 5 (71)	
				deposits+, n = 2 (29)	
			mr-vTRG III-V, n = 2 (22)	deposits-, n = 2 (100)	
				deposits+, n = 0 (0)	
		mrTRG III-V, n = 82 (90)	mr-vTRG I-II, n = 4 (5)	deposits-, n = 4 (100)	
				deposits+, n = 0 (0)	
			mr-vTRG III-V, n = 78 (95)	deposits-, n = 18 (23)	45.4%
				deposits+, n = 60 (77)	52.2%

DM rates not mentioned in groups with less than 10 patients.
Abbreviations: MrEMVI = MRI detected extramural venous invasion, mrTRG = MRI detected tumor regression grade, mr-vTRG = MRI detected EMVI tumor regression grade.

eTable 4 Multivariate analyses for risk factors at restaging for distant metastasis, local recurrence, disease-free survival and overall survival

	Distant metastasis			Local recurrence			Disease-free survival			Overall survival		
Variable	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***	**HR**	**95% CI**	***p***
Age												0.032
Up to 67 years old										1.00		
68 years or older										1.610	1.043-2.484	
Mr-vTRG EMVI			0.006			0.225			0.024			
No	1.00			1.00			1.00					
Mr-vTRG 1-2	1.019	0.461-2.254		0.924	0.257-3.322		0.966	0.478-1.953				
Mr-vTRG 3-5	2.040	1.272-3.273		1.791	0.860-3.731		1.711	1.123-2.608				
Type of surgery												0.071
LAR										1.00		
APR										1.528	0.917-2.547	
Extended resections										1.823	1.060-3.133	
Margin involvement			0.002			0.004			<0.001			<0.001
R0	1.00			1.00			1.00			1.00		
R1	2.629	1.444-4.785		3.392	1.462-7.874		2.845	1.655-4.889		3.946	2.278-6.836	

Abbreviations: APR = abdominoperineal resection, LAR = low anterior resection, Mr-vTRG = MRI detected EMVI tumor regression grade.



No. at risk						
No mrEMVI	114	95	88	78	58	36
mr-vTRG 1	9	7	7	6	4	2
mr-vTRG 2	26	24	21	18	12	8
mr-vTRG 3	54	42	34	29	17	10
mr-vTRG 4	51	33	29	25	16	10
mr-vTRG 5	21	16	14	9	4	1

Supplementary Figure 1 Kaplan-Meier analysis of distant metastases according to the absence of MRI-detected extramural vascular invasion (mrEMVI) and MRI-based regression grade of EMVI (mr-vTRG). (log-rank test $p = 0.025$)

CHAPTER 5

no supplementary data

CHAPTER 6

no supplementary data

CHAPTER 7

Supplementary table 1 Type major postoperative complications LARC

	N (%)
Presacral abscess	15 (27)
Abdominal wound dehiscence with evisceration	8 (14)
Bleeding	6 (11)
Intraabdominal abscess	5 (9)
Leakage ureter/bladder/psoas hitch	3 (5)
Perineal wound necrosis	3 (5)
Anastomotic leakage	3 (5)
Ureter stenosis	3 (5)
Respiratory insufficiency	2 (4)
Ileus	2 (4)
Septic bleeding	2 (4)
Peroperative hemorrhage	2 (4)
Stoma necrosis	1 (2)
Occlusion a. femoralis stent	1 (2)
Reanimation (PEA)	1 (2)
Relaparotomy to remove suture from uterus	1 (2)
Wound abscess	1 (2)
Blowout caecum due to oedema ostomy	1 (2)

Abbreviations: LARC = locally advanced rectal cancer, PEA = pulseless electrical activity.
Some patients had ≥1 major complication.

CHAPTER 8

Supplementary Table 1 Surgery and postoperative complications – original cohort

		CRT (N=169)	ICT+CRT (N=50)	*p* value
Interval between CRT and MRI (weeks)	Median [IQR]	6 [5-8]	4 [4-5]	<0.001
Interval between CRT and surgery (weeks)	Median [IQR]	14 [11-16]	13 [10-14]	0.038
Type of surgery[$]	open	144 (85.7)	39 (78.0)	0.192
	laparoscopic	24 (14.3)	11 (22.0)	
Type of surgery	TEM	1 (0.6)	0 (0)	0.006
	taTME	2 (1.2)	3 (6.0)	
	LAR	59 (34.9)	20 (40.0)	
	APR	61 (36.1)	7 (14.0)	
	Extended resection*	46 (27.2)	20 (40.0)	
Anastomosis	Yes	64 (37.9)	30 (60.0)	0.005
	No	105 (62.1)	20 (40.0)	
IOERT	Yes	77 (45.6)	20 (40.0)	0.487
	No	92 (54.4)	30 (60.0)	
HIPEC	Yes	6 (3.6)	0 (0)	0.341
	No	163 (96.4)	50 (100)	
Procedure time (minutes)	Median [IQR]	201 [147-257]	215 [134-264]	0.772
Admission (days)	Median [IQR]	8 [6-11]	7 [5-12]	0.123
Postoperative complications	Clavien-Dindo 0-2	147 (87.0)	39 (78.0)	0.145
	Clavien-Dindo 3-5	22 (13.0)	11 (22.0)	
Inhospital mortality	Yes	4 (2.4)	0 (0)	0.576
	No	165 (97.6)	50 (100)	

[$] Missing n=1 (TEM)

* Extended surgery: APR or LAR with resection of at least one other organ (i.e. bladder, prostate, vesicle(s), uterus, posterior wall vagina, ovaria)

Abbreviations: APR = abdominoperineal resection, CRT = chemoradiotherapy, HIPEC = hyperthermic intraperitoneal chemotherapy, ICT = induction chemotherapy, IOERT = intraoperative external beam radiotherapy, IQR = interquartile range, LAR = low anterior resection, taTME = transanal total mesorectal excision.

p values pertain to all outcomes of the variable

Supplementary Table 2 Surgery and postoperative complications - matched cohort

		CRT (N=52)	ICT+CRT (N=43)	*p* value
Interval between RT and MRI	Median [IQR]	6.5 [4-8]	4 [4-5.5]	<0.001
Interval between RT and surgery (weeks)	Median [IQR]	14 [12-16]	13 [10-14]	0.068
Type of surgery	open	48 (92.3)	36 (83.7)	0.216
	laparoscopic	4 (7.7)	7 (16.3)	
Type of surgery	taTME	0 (0)	1 (2.3)	0.052
	LAR	24 (46.2)	16 (37.2)	
	APR	16 (30.8)	7 (16.3)	
	Extended resection*	12 (23.1)	19 (44.2)	
Anastomosis	Yes	23 (44.2)	24 (55.8)	0.261
	No	29 (55.8)	19 (44.2)	
IOERT	Yes	27 (51.9)	20 (46.5)	0.600
	No	25 (48.1)	23 (53.5)	
HIPEC	Yes	3 (5.8)	0 (0)	0.249
	No	49 (94.2)	43 (100)	
Procedure time (minutes)	Median [IQR]	196 [151-254]	216 [132-271]	0.782
Admission (days)	Median [IQR]	9 [7-12]	7 [5-12]	0.024
Postoperative complications	Clavien-Dindo 0-2	46 (88.5)	36 (83.7)	0.503
	Clavien-Dindo 3-5	6 (11.5)	7 (16.3)	
Inhospital mortality	Yes	1 (1.9)	0 (0)	1.000
	No	51 (98.1)	43 (100)	

* Extended surgery: APR or LAR with resection of at least one other organ (i.e. bladder, prostate, vesicle(s), uterus, posterior wall vagina, ovaria)
Abbreviations: APR = abdominoperineal resection, CRT: chemoradiotherapy, HIPEC = hyperthermic intraperitoneal chemotherapy, ICT = induction chemotherapy, IOERT = intraoperative external beam radiotherapy, IQR = interquartile range, LAR = low anterior resection, taTME = transanal total mesorectal excision. *p* values pertain to all outcomes of the variable

CHAPTER 9

no supplementary data

CHAPTER 10

no supplementary data

CHAPTER 11

no supplementary data

LIST OF PUBLICATIONS

THIS THESIS

1. **Voogt ELK***, van Zoggel DMGI*, Kusters M, et al. Impact of a history of metastases or synchronous metastases on survival in patients with locally recurrent rectal cancer. *Color Dis*. 2021;23(5):1120-1131. doi:10.1111/codi.15537

2. Ketelaers SHJ, **Voogt ELK**, Simkens GA, et al. Age-related differences in morbidity and mortality after surgery for primary clinical T4 and locally recurrent rectal cancer. *Color Dis*. 2021;23(5):1141-1152. doi:10.1111/codi.15542

3. Schaap DP, **Voogt ELK**, Burger JWA, et al. Prognostic Implications of MRI-Detected EMVI and Tumor Deposits and Their Response to Neoadjuvant Therapy in cT3 and cT4 Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2021;111(3):816-825. doi:10.1016/j.ijrobp.2021.06.013

4. **Voogt ELK**, Nordkamp S, van Zoggel DMGI, et al. MRI tumour regression grade in locally recurrent rectal cancer. *BJS Open.* 2022 May 2;6(3):zrac033. doi:10.1093/bjsopen/zrac033

5. **Voogt ELK***, Hagemans JAW*, Rothbarth J, et al. Outcomes of urinary diversion after surgery for locally advanced or locally recurrent rectal cancer with complete cystectomy; ileal and colon conduit. *Eur J Surg Oncol*. 2020;46(6):1160-1166. doi:10.1016/j.ejso.2020.02.021

6. **Voogt ELK**, Nieuwenhuijzen GAP, van Rees JM, et al. Intraoperative Electron Beam Radiation Therapy (IOERT) Versus High-Dose-Rate Intraoperative Brachytherapy (HDR-IORT) in Patients With an R1 Resection for Locally Advanced or Locally Recurrent Rectal Cancer. *Int J Radiat Oncol Biol Phys*. 2021;110(4):1032-1043. doi:http://dx.doi.org/10.1016/j.ijrobp.2021.02.006

7. **Voogt ELK***, Schaap DP*, van den Berg K, et al. Improved response rate in patients with prognostically poor locally advanced rectal cancer after treatment with induction chemotherapy and chemoradiotherapy when compared with chemoradiotherapy alone: A matched case-control study. *Eur J Surg Oncol*. 2021;47(9):2429-2435. doi:10.1016/j.ejso.2021.05.017

8. **Voogt ELK**, van Zoggel DMGI, Kusters M, et al. Improved outcomes for responders after treatment with induction chemotherapy and chemo(re)irradiation for locally recurrent rectal cancer. *Ann Surg Oncol*. 2020;27(9):3503-3513. doi:https://doi.org/10.1245/s10434-020-08362-4

9. **Voogt ELK**, Nordkamp S, Nieuwenhuijzen GAP, et al. Curative treatment of locally recurrent rectal cancer: is induction chemotherapy warranted? *Br J Surg*. 2021;108(6):e213-e214. doi:http://dx.doi.org/10.1093/bjs/znab065

10. PelvEx Collaborative (**Voogt ELK** first author). Induction chemotherapy followed by chemoradiotherapy versus chemoradiotherapy alone as neoadjuvant treatment for locally recurrent rectal cancer: study protocol of a multicentre, open-label, parallel-arms, randomized controlled study (PelvEx II). *BJS open*. 2021;5(3):zrab029. doi:http://dx.doi.org/10.1093/bjsopen/zrab029

OTHER

11. **Voogt ELK**, Burger PWA, Rutten HJT. ASO Author Reflections: Addition of Induction Chemotherapy Prior to Neoadjuvant Chemo(Re)Irradiation in Patients with Locally Recurrent Rectal Cancer to Improve Long-Term Outcomes. *Ann Surg Oncol*. 2020;27(9):3514-3515. doi:10.1245/s10434-020-08446-1

12. **Voogt ELK**, Schaap DP, van den Berg K, et al. Reply to: Use of induction chemotherapy in locally advanced rectal cancers to increase the response rates: Is it actually helping? *Eur J Surg Oncol*. 2021;47(9):2473-2474. doi:10.1016/j.ejso.2021.06.021

13. Nordkamp S, **Voogt ELK,** van Zoggel DMGI, Martling A, Holm T, Jansson Palmer G, Suzuki C, Nederend J, Kusters M, Burger JWA, Rutten HJT, Iversen H. Locally recurrent rectal cancer: oncological outcomes with different treatment strategies in two tertiary referral units. *Br J Surg*. 2022 Jun 14;109(7):623-631. doi: 10.1093/bjs/znac083. PMID: 35416250.

14. van Zoggel DMGI, **Voogt ELK**, van Lijnschoten IG, et al. Metabolic positron emission tomography/CT response after induction chemotherapy and chemo(re)irradiation is associated with higher negative resection margin rate in patients with locally recurrent rectal cancer. *Color Dis*. 2021 Jan;24(1):59-67. doi:10.1111/codi.15934

15. van der Klauw AL, **Voogt ELK**, Frouws MA, Baeten CIM, Snijders HS. Is sterile exposure in perianal procedures necessary? A single-institution experience and results from a national survey. *Tech Coloproctol*. 2021;25(5):539-548. doi:10.1007/s10151-021-02422-x

16. Schaap DP, de Valk KS, Deken MM, et al. Carcinoembryonic antigen-specific, fluorescent image-guided cytoreductive surgery with hyperthermic intraperitoneal chemotherapy for metastatic colorectal cancer. *Br J Surg*. 2020;107(4):334-337. doi:10.1002/bjs.11523

17. PelvEx Collaborative. Perioperative management and anaesthetic considerations in pelvic exenterations using Delphi methodology: results from the PelvEx Collaborative. *BJS open*. 2021;5(1):zraa055. doi:10.1093/bjsopen/zraa055

18. PelvEx Collaborative. Simultaneous pelvic exenteration and liver resection for primary rectal cancer with synchronous liver metastases: results from the PelvEx Collaborative. *Color Dis*. 2020;22(10):1258-1262. doi:10.1111/codi.15064

19. PelvEx Collaborative. The impact of the COVID-19 pandemic on the Management of Locally Advanced Primary/Recurrent Rectal Cancer. *Br J Surg*. 2020;107(11):e547-e548. doi:10.1002/bjs.11893

20. PelvEx Collaborative. The global cost of pelvic exenteration: in-hospital perioperative costs. *Br J Surg*. 2020;107(11):e470-e471. doi:10.1002/bjs.11924

21. PelvEx Collaborative. Predicting outcomes of pelvic exenteration using machine learning. *Color Dis*. 2020;22(12):1933-1940. doi:10.1111/codi.15235

22. PelvEx Collaborative. Management strategies for patients with advanced rectal cancer and liver metastases using modified Delphi methodology: results from the PelvEx Collaborative. *Color Dis*. 2020;22(9):1184-1188. doi:10.1111/codi.15007

23. PelvEx Collaborative. Contemporary Management of Locally Advanced and Recurrent Rectal Cancer: Views from the PelvEx Collaborative. *Cancers*. 2022 Feb 24;14(5):1161. doi: 10.3390/cancers14051161

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Lieve **Liz**, who is this - ik kan hier nog altijd zo hard om lachen. Wat mooi dat een ontmoeting in een hotel in Tanzania – in handdoek - tot zo'n vriendschap kan leiden.

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CURRICULUM VITAE

Eva Louise Krijntje Voogt werd op 21 oktober 1990 geboren in het Reinier de Graaf Ziekenhuis te Delft. In 2008 behaalde zij haar Gymnasium diploma aan het Christelijk Lyceum Delft, waarna zij Geneeskunde ging studeren aan de Universiteit Leiden. Tijdens haar studie voltooide zij de opleiding tot snowboardleraar, waarna zij veel tijd in Oostenrijk doorbracht. Tevens volgde zij tijdens haar studie een extra curriculaire stage in het Korle-Bu Teaching Hospital in Accra, Ghana. Haar keuze-coschappen liep zij op de Spoedeisende Hulp van het Vlietland Ziekenhuis in Schiedam en in het Sengerema Designated District Hospital in Sengerema, Tanzania. Haar oudste coschap liep zij bij de chirurgie in het Groene Hart Ziekenhuis te Gouda. Hier startte zij na haar afstuderen in 2015 ook met haar eerste baan als arts niet in opleiding tot specialist. Bijna twee jaar later maakte zij de overstap naar het Erasmus Medisch Centrum te Rotterdam. In september 2018 verhuisde zij naar Eindhoven om daar als arts-onderzoeker onder leiding van prof dr. Harm Rutten, prof. dr. Kees Verhoef en dr. Pim Burger te starten met haar promotieonderzoek. Tijdens haar promotieonderzoek heeft zij onder andere een tweetal subsidies binnen gehaald, waardoor de PelvEx II en MEND-IT studie gerealiseerd konden worden. Op 1 juli 2021 begon Eva aan haar opleiding tot chirurg in het Franciscus Gasthuis & Vlietland.