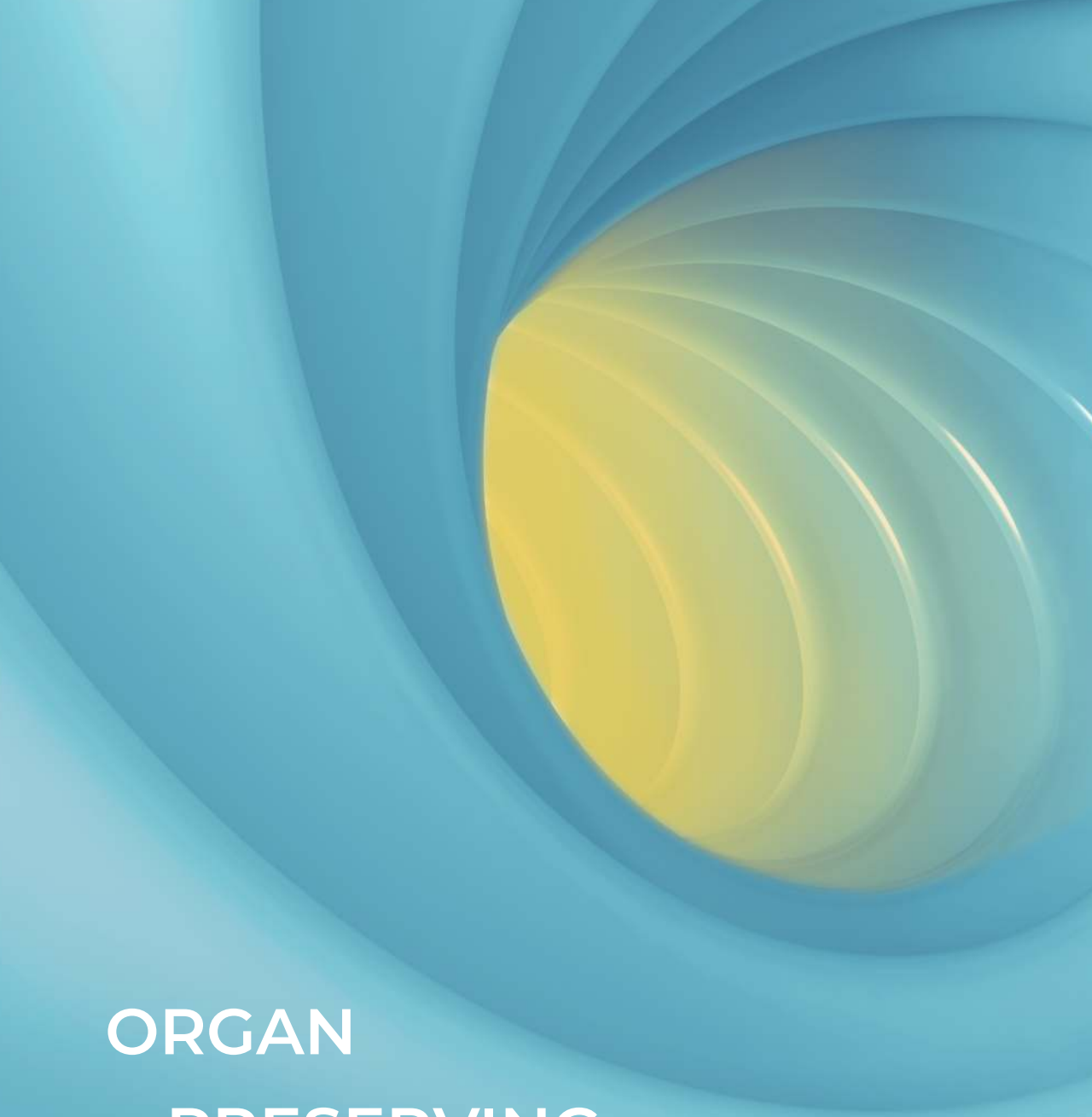

ORGAN PRESERVING STRATEGIES IN RECTAL CANCER

MAREILLE VERSEVELD

Organ Preserving Strategies in Rectal Cancer

Maria Verseveld

Orgaansparende strategieën bij endeldarmkanker

Organ Preserving Strategies in Rectal Cancer

Proefschrift

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Chapter 1

General introduction and thesis outline

GENERAL INTRODUCTION

Worldwide, approximately 1.8 million patients are diagnosed with colorectal cancer annually, of which approximately 700,000 patients are diagnosed with rectal cancer [1]. Colorectal cancer is the third most common type of cancer in both women and men. Risk factors for colorectal cancer include older age, male sex, or a positive family history of colorectal cancer. Furthermore, a Western lifestyle and dietary factors have been associated with an increased risk of rectal cancer. Colorectal cancer derives mainly from polyps; these polyps are thought to develop into cancer in approximately 10–15 years [2]. Rectal cancer cases constitutes approximately one-third of all colorectal cancer cases. Rectal cancer may be associated with complaints of obstruction, tenesmus, defaecation disorder, or rectal blood loss, but many patients with early-stage cancer are asymptomatic.

In the Netherlands, a national screening program for colorectal cancer was gradually implemented since 2014 for all adults aged 55–75 years. This screening and also aging of the population have caused a steep increase in the incidence of rectal cancer [3-6]. It is expected that the screening program will detect polyps before they become rectal cancer and tumours are detected in an early, asymptomatic stage.

A strict definition of the anatomical borders of the rectum was long lacking, but recently an expert-based Delphi consensus concluded that all tumours with a lower limit below the radiological landmark 'the sigmoid take-off', which can be identified as the junction of the sigmoid mesocolon with the mesorectum, are considered rectal cancer [7]. The rectum is enveloped by the mesorectal fascia including fat tissue, blood vessels, and the locoregional lymph nodes and is closely associated with the surrounding structures in the pelvis [8].

Advances in the treatment of rectal cancer

For decades, the outcomes of patients with rectal cancer were unsatisfactory, mainly owing to high local recurrence rates in patients with rectal cancer after surgery (approximately 30–40%) [9]. However, a great improvement in long-term outcomes has been achieved for patients with rectal cancer. Nowadays, the survival outcomes of patients with rectal cancer are at least equal to those of patients with colon cancer [10]. Several factors have contributed to the major improvements in local control and survival since the 1980s.

Probably the most substantial development was the standardization of a surgical technique based on embryonic planes by Professor Heald—total mesorectal excision (TME)—in 1986 [11]. It is a precise dissection of the mesorectal envelope comprising the rectum containing the tumour together with all the surrounding fatty tissue and the sheet of tissue that contains lymph nodes and blood vessels. Dissection is continued along the avascular plane between the presacral and mesorectal fascia, described as the holy plane (Heald's 'holy plane'). Shortly after the introduction of the TME technique, the Dutch TME

trial showed that preoperative radiotherapy has the potential to reduce local recurrence by 50% in patients with rectal cancer undergoing TME [12].

Another major improvement was the implementation of preoperative clinical staging and risk stratification with high-resolution magnetic resonance imaging (MRI), which enabled a more accurate preoperative assessment of the location of the tumour and extent of locoregional disease [13]. It is now known that the risk of local recurrence is mainly determined by the locoregional tumour stage, involvement of the circumferential margin, and involvement of the resection margins. Preoperative staging has consequences for preoperative (neoadjuvant) therapies. Through implementation of risk-adapted radiological classification as described below and administration of neoadjuvant therapies, current local recurrence rates are below 10% [5, 14, 15].

Staging rectal cancer and neoadjuvant therapies in the Netherlands

In the Dutch guidelines, preoperative treatment is recommended according to a risk stratification, predominantly based on MRI findings (table 1). In addition to MRI, full clinical staging of rectal cancer should include at least conventional imaging of the chest and a computed tomography (CT) scan of the abdomen (and thorax) for the detection of potential distant metastases. Finally, digital rectal examination is the best diagnostic tool in patients with distal rectal tumours to assess the fixation and distance of the lesion to the anorectal sphincter and to estimate the possibility of resection with primary anastomosis. Patients are generally classified into three groups based on the clinical staging.

1) In patients with selected very early rectal cancer (cT1), local excision (LE) is considered an adequate treatment option. In terms of preserving anorectal function, lowering morbidity, and improving the quality of life, local excision is superior than TME [16]. Several studies assessed the optimal treatment strategy for T1 rectal cancers and found that LE also proved to be oncologically safe in selected T1 rectal cancers. Consequently, LE is nowadays considered the treatment of choice in T1 rectal cancer [17-23].
   For patients with early rectal cancer with more invasion (cT2-3N0), radical resection is usually performed to remove the tumour, including all lymph nodes. TME surgery only without neoadjuvant treatment is the preferred treatment in these patients. Addition of preoperative radiotherapy has demonstrated inferior functional outcomes without improvement in local recurrence or survival.
2) Intermediate-risk rectal cancers, defined as cT1-3N1M0 rectal cancer, are primary resectable rectal cancers. Neoadjuvant short-course radiotherapy (SCRT; e.g. 5×5 Gy) is added to reduce the risk of local recurrence. The Dutch TME trial showed that preoperative SCRT has the potential to reduce local recurrence by 50% in patients with rectal cancer undergoing TME.
3) Patients with more advanced tumours, generally referred to as locally advanced or high-risk rectal cancer, are patients in whom the feasibility of radical surgery is uncertain

because of involvement of the mesorectal fascia or extended nodal involvement. In the literature, variable definitions for locally advanced rectal cancer are used, generally including cT3N2, cT3 tumours with close involvement of the mesorectal fascia or cT4N0-2 (Table 1). Patients with locally advanced disease at diagnosis have a higher likelihood of pelvic or distant recurrence than patients with early-stage tumours. The most important prognostic factor is the feasibility of a radical TME resection, which can be difficult because of the close involvement of adjacent organs in the small pelvis. In the Netherlands, nowadays, preoperative long-course radiotherapy with concurrent capecitabine (chemoradiotherapy, CRT) is adopted as the standard of care, especially with the aim of initiating tumour downstaging to increase the chances of R0 resection [24, 25]. The German Rectal Cancer Study group trial has showed that better compliance, local control, and survival can be achieved with preoperative CRT than with postoperative treatment [26]. However, long-course (chemo)radiotherapy can induce acute toxicity and has long-term effects on anorectal function compared with treatment with surgery alone [27, 28]. In addition, it is not yet clear whether long-term survival in patients treated with chemoradiotherapy is superior to patients treated with radiotherapy alone [28, 29]. In the international randomized RAPIDO trial, high-risk patients with rectal cancer were randomized to SCRT followed by six courses of chemotherapy (CAPOX) and subsequent surgery or long-course chemoradiotherapy followed by surgery and optional postoperative chemotherapy (CAPOX). Although the final results of this study have to be published, the authors found that a high compliance (84%) of preoperative systemic treatment could be achieved. Despite considerable toxicity, this systemic treatment did not lead to differences in surgical procedures or postoperative complications. Preliminary results, recently presented on ASCO, on whether the presumed oncological advantages (downstaging and better effects of systemic therapy) of the combination of preoperative SCRT and chemotherapy can be balanced against the disadvantages of toxicity seem promising; however, definitive results are awaited [30].

Table 1 TNM stage and Dutch guidelines for the treatment of rectal cancer
Based on the TNM classification 5th edition (17)

		Clinical TNM stage	Neoadjuvant treatment	Surgical treatment
Low risk	Stage I	cT1-3N0M0	None	TME
Intermediate risk	Stage II	cT1-3N1M0 ≤5 mm extramural invasion ≥1 mm margin to MRF	Short-course radiotherapy 5×5 Gy	TME
High risk	Stage III	cT1-3N2 or suspicious extramesorectal nodes cT3 with <1 mm distance to MRF cT4 tumour	Chemoradiotherapy 25–28 × 1.8–2.0 Gy with concomitant capecitabine	TME

As neoadjuvant therapies for advanced rectal tumours are increasingly successful and may lead to a significant reduction of the tumour or even to clinical complete response (cCR), rectal sparing strategies are appealing. However, a complete response of the tumour and pathological lymph nodes occurs only in a minority of patients with locally advanced rectal cancer. Most of them will have obvious residual tumours after neoadjuvant therapy, and for those, the only chance of curative treatment is radical surgery. In patients with intermediate rectal cancer, application of neoadjuvant (chemo)radiotherapy might even be more effective than in advanced tumours, leading to higher cCR rates, and thereby they may be increasingly eligible for rectal sparing strategies.

Multidisciplinary decision making and treatment is crucial in the modern treatment of patients with cancer. After full clinical staging, the best treatment approach is generally discussed in a meeting of a multidisciplinary team, at least including a surgeon, gastroenterologist, oncological radiotherapist, medical oncologist, radiologist, pathologist, and physician assistant [31, 32].

Restaging after neoadjuvant treatment

Restaging after long-course chemoradiotherapy in patients with locally advanced rectal cancer is generally performed to assess the treatment effect and determine the surgical approach. Simultaneously, restaging may detect metastases that develop or become evident during neoadjuvant therapy [33]. Another argument for performing restaging after neoadjuvant therapy with growing relevance is to identify patients with a cCR. In approximately 15–20% of all patients treated with long-course neoadjuvant CRT, the tumour and pathological lymph nodes will be completely resolved after neoadjuvant treatment and a 6–10-week waiting interval. A pooled analysis of Maas et al. has shown that patients with a pathological complete response (pCR) after neoadjuvant therapy have a favourable prognosis compared with patients with residual tumour [34].

Habr-Gama et al. were the first to suggest omitting surgery in patients with a cCR at the reassessment phase. In 2004, they reported the remarkable oncological results of the 'Watch-and-Wait' approach. This approach has gained considerable attention from patients and clinicians in recent years, as avoiding surgery sounds appealing to many. However, evidence on the risks of this approach as well as the functional outcomes of definitive chemoradiotherapy were largely unknown. In addition, the percentage of patients who achieve a cCR is largely variable, depending on the tumour stage at baseline and preoperative treatment strategy.

The International Watch & Wait Database (IWWD) recently reported results of a descriptive analysis after inclusion of more than 1000 patients from 47 centres in 15 countries. These patients received only neoadjuvant (chemo)radiotherapy and were kept under close surveillance: watchful waiting. They concluded that local regrowth occurred in 25.2% of the

patients, mostly in the first 2 years and >97.7% in the bowel wall. They also concluded that if regrowth was detected, local unsalvageable disease was rare [35].

THESIS OUTLINE

Screening for colorectal cancer leads not only to earlier detection of rectal cancer but also to an increase in detection of premalignant rectal polyps. These polyps slowly change in structure and invasion depth and become eventually malignant. The first stage of developing infiltrating cancer is an intramucosal carcinoma. These very-early-stage cancers are perfectly suitable for local treatment, and radical surgery such as total mesorectal excision seems to be overtreatment in such patients. The short-term outcome and recurrence rates of patients with intramucosal carcinoma treated with transanal surgery is investigated in **Chapter 2**.

Transanal endoscopic microsurgery (TEM) is reported to have minimal impact on anorectal function. Nevertheless, TEM is not broadly incorporated into the surgical armamentarium owing to its high costs and long learning curve. TEM has been largely replaced by transanal minimally invasive surgery (TAMIS). TAMIS was rapidly embraced by colorectal surgeons because it is easy to learn and fewer specialized instruments are required. However, the effect of TAMIS on quality of life (QOL) and functional outcome has not been established in large patient cohorts. The study described in **Chapter 3** investigates the impact on QOL and functional outcomes in patients treated with TAMIS in a tertiary referral centre.

Once the stage of benign or premalignant polyp is passed and early rectal cancer is suspected, a wide variety of treatment strategies can be applied. We reviewed the treatment strategies for patients with suspected T1 (cT1) rectal cancer in the Netherlands between 2005 and 2018 and examined whether the choice of treatment changed over time. Moreover, we investigated the accuracy of prediction of pathological T1 (pT1). These findings are described in **Chapter 4.**

Local excision techniques (LE) are more often used for very early rectal cancer, and it is a recommended treatment option for low risk T1 tumours in the Dutch colorectal guidelines [36]. To investigate whether or not this can be justified, a nationwide, population-based study was performed. Data of the national cancer registry (NCR) were used to study the number of patients who underwent LE only or primary TME. **Chapter 5** describes survival after LE not only for pT1 cancers but also for higher stages of rectal cancer in the past decade in the Netherlands in comparison with radical TME surgery.

The occurrence of complete response (CR) after (chemo)radiotherapy in rectal cancer has led to new treatment strategies. By successfully downsizing and downstaging rectal cancers, rectal sparing surgery or even omission of surgery seemed possible. **Chapter 6** describes the results of one of the first prospective multicentre trials investigating whether

rectum-preserving treatment after neoadjuvant chemoradiation therapy was feasible in early-stage rectal cancer.

It is remarkable that nearly all studies assessing rectal sparing therapy focus on patients with early-stage rectal cancer because these patients experience relatively good oncological outcomes and survival rates. Patients with locally advanced and metastasized rectal cancer are at high risk of disease progression and futile extensive pelvic surgery. The liver-first approach is treatment with preoperative systemic chemotherapy, followed by resection of colorectal liver metastases and resection of the primary tumour. However, extensive chemotherapy and radiotherapy treatment could lead to CR or near CR of the rectal tumour in such patients. Rectum preserving surgery or a watchful waiting protocol could be applied in these patients, and they can thus be spared from (futile) radical rectal surgery. Moreover, in patients unable to finish the liver-first protocol owing to therapy-related toxicity or progressive disease, extensive pelvic surgery may be futile and thus unnecessary. The retrospective study described in **Chapter 7** assesses prognostic factors in patients treated for rectal cancer with liver metastasis and investigates the number of patients in whom extensive lower pelvic surgery might have been omitted.

In **Chapter 8,** a summary and general discussion of the studies performed in this thesis are provided with future perspectives.

REFERENCES

1. Ferlay J, Colombet M, Soerjomataram I, Mathers C, Parkin DM, Pineros M, et al. Estimating the global cancer incidence and mortality in 2018: GLOBOCAN sources and methods. Int J Cancer. 2019 Apr 15;144(8):1941-53. PubMed PMID: 30350310. Epub 2018/10/24.
2. Day DW, Morson BC. The adenoma-carcinoma sequence. Major Probl Pathol. 1978;10:58-71. PubMed PMID: 359943. Epub 1978/01/01.
3. www.cijfersoverkanker.nl.
4. Benitez Majano S, Di Girolamo C, Rachet B, Maringe C, Guren MG, Glimelius B, et al. Surgical treatment and survival from colorectal cancer in Denmark, England, Norway, and Sweden: a population-based study. Lancet Oncol. 2019 Jan;20(1):74-87. PubMed PMID: 30545752. Pubmed Central PMCID: PMC6318222. Epub 2018/12/14.
5. Brenner H, Kloor M, Pox CP. Colorectal cancer. Lancet. 2014 Apr 26;383(9927):1490-502. PubMed PMID: 24225001. Epub 2013/11/15.
6. de Neree Tot Babberich MPM, Detering R, Dekker JWT, Elferink MA, Tollenaar R, Wouters M, et al. Achievements in colorectal cancer care during 8 years of auditing in The Netherlands. Eur J Surg Oncol. 2018 Sep;44(9):1361-70. PubMed PMID: 29937415. Epub 2018/06/26.
7. D'Souza N, de Neree Tot Babberich MPM, d'Hoore A, Tiret E, Xynos E, Beets-Tan RGH, et al. Definition of the Rectum: An International, Expert-based Delphi Consensus. Ann Surg. 2019 Dec;270(6):955-9. PubMed PMID: 30973385. Epub 2019/04/12.
8. Rodriguez-Luna MR, Guarneros-Zarate JE, Tueme-Izaguirre J. Total Mesorectal Excision, an erroneous anatomical term for the gold standard in rectal cancer treatment. Int J Surg. 2015 Nov;23(Pt A):97-100. PubMed PMID: 26409653. Epub 2015/09/28.
9. Nielsen MB, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. Colorectal Dis. 2011 Jul;13(7):732-42. PubMed PMID: 20041928. Epub 2010/01/01.
10. Holleczek B, Rossi S, Domenic A, Innos K, Minicozzi P, Francisci S, et al. On-going improvement and persistent differences in the survival for patients with colon and rectum cancer across Europe 1999-2007 - Results from the EUROCARE-5 study. Eur J Cancer. 2015 Oct;51(15):2158-68. PubMed PMID: 26421819. Epub 2015/10/01.
11. Heald RJ, Ryall RD. Recurrence and survival after total mesorectal excision for rectal cancer. Lancet. 1986 Jun 28;1(8496):1479-82. PubMed PMID: 2425199. Epub 1986/06/28.
12. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug 30;345(9):638-46. PubMed PMID: 11547717. Epub 2001/09/08.
13. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006 Oct 14;333(7572):779. PubMed PMID: 16984925. Pubmed Central PMCID: PMC1602032. Epub 2006/09/21.
14. Bouchard P, Efron J. Management of recurrent rectal cancer. Ann Surg Oncol. 2010 May;17(5):1343-56. PubMed PMID: 20041351. Epub 2009/12/31.
15. Glynne-Jones R, Wyrwicz L, Tiret E, Brown G, Rodel C, Cervantes A, et al. Rectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2017 Jul 1;28(suppl_4):iv22-iv40. PubMed PMID: 28881920. Epub 2017/09/09.
16. Plummer JM, Leake PA, Albert MR. Recent advances in the management of rectal cancer: No surgery, minimal surgery or minimally invasive surgery. World J Gastrointest Surg. 2017 Jun 27;9(6):139-48. PubMed PMID: 28690773. Pubmed Central PMCID: PMC5483413. Epub 2017/07/12.

17. Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005 Oct;242(4):472-7; discussion 7-9. PubMed PMID: 16192807. Pubmed Central PMCID: PMC1402341. Epub 2005/09/30.
18. Bhangu A, Brown G, Nicholls RJ, Wong J, Darzi A, Tekkis P. Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg. 2013 Oct;258(4):563-9; discussion 9-71. PubMed PMID: 23979270. Epub 2013/08/28.
19. Christoforidis D, Cho HM, Dixon MR, Mellgren AF, Madoff RD, Finne CO. Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer. Ann Surg. 2009 May;249(5):776-82. PubMed PMID: 19387326. Epub 2009/04/24.
20. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009 Dec;35(12):1280-5. PubMed PMID: 19487099. Epub 2009/06/03.
21. Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. Dis Colon Rectum. 2005 Feb;48(2):270-84. PubMed PMID: 15711865. Epub 2005/02/16.
22. Peng J, Chen W, Sheng W, Xu Y, Cai G, Huang D, et al. Oncological outcome of T1 rectal cancer undergoing standard resection and local excision. Colorectal Dis. 2011 Feb;13(2):e14-9. PubMed PMID: 20860716. Epub 2010/09/24.
23. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg. 2007 May;245(5):726-33. PubMed PMID: 17457165. Pubmed Central PMCID: PMC1877081. Epub 2007/04/26.
24. Bosset JF, Collette L, Calais G, Mineur L, Maingon P, Radosevic-Jelic L, et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med. 2006 Sep 14;355(11):1114-23. PubMed PMID: 16971718. Epub 2006/09/15.
25. Gerard JP, Conroy T, Bonnetain F, Bouche O, Chapet O, Closon-Dejardin MT, et al. Preoperative radiotherapy with or without concurrent fluorouracil and leucovorin in T3-4 rectal cancers: results of FFCD 9203. J Clin Oncol. 2006 Oct 1;24(28):4620-5. PubMed PMID: 17008704. Epub 2006/09/30.
26. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004 Oct 21;351(17):1731-40. PubMed PMID: 15496622. Epub 2004/10/22.
27. Bruheim K, Guren MG, Skovlund E, Hjermstad MJ, Dahl O, Frykholm G, et al. Late side effects and quality of life after radiotherapy for rectal cancer. Int J Radiat Oncol Biol Phys. 2010 Mar 15;76(4):1005-11. PubMed PMID: 19540058. Epub 2009/06/23.
28. McCarthy K, Pearson K, Fulton R, Hewitt J. Pre-operative chemoradiation for non-metastatic locally advanced rectal cancer. Cochrane Database Syst Rev. 2012 Dec 12;12:CD008368. PubMed PMID: 23235660. Epub 2012/12/14.
29. Braendengen M, Glimelius B. Preoperative radiotherapy or chemoradiotherapy in rectal cancer - Is survival improved? An update of the “Nordic” LARC study in non-resectable cancers. Radiother Oncol. 2018 Jun;127(3):392-5. PubMed PMID: 29778486. Epub 2018/05/21.
30. van der Valk MJM, Marijnen CAM, van Etten B, Dijkstra EA, Hilling DE, Kranenbarg EM, et al. Compliance and tolerability of short-course radiotherapy followed by preoperative chemotherapy and surgery for high-risk rectal cancer - Results of the international randomized RAPIDO-trial. Radiother Oncol. 2020 Jun;147:75-83. PubMed PMID: 32240909. Epub 2020/04/03.

31. Palmer G, Martling A, Cedermark B, Holm T. Preoperative tumour staging with multidisciplinary team assessment improves the outcome in locally advanced primary rectal cancer. Colorectal Dis. 2011 Dec;13(12):1361-9. PubMed PMID: 20958913. Epub 2010/10/21.
32. Heidelberg: VVSHMMoRCe, 2018. S-VB.
33. Ayez N, Alberda WJ, Burger JW, Eggermont AM, Nuyttens JJ, Dwarkasing RS, et al. Is restaging with chest and abdominal CT scan after neoadjuvant chemoradiotherapy for locally advanced rectal cancer necessary? Ann Surg Oncol. 2013 Jan;20(1):155-60. PubMed PMID: 22875644. Epub 2012/08/10.
34. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, 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 Sep;11(9):835-44. PubMed PMID: 20692872. Epub 2010/08/10.
35. van der Valk MJM, Hilling DE, Bastiaannet E, Meershoek-Klein Kranenbarg E, Beets GL, Figueiredo NL, 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 Jun 23;391(10139):2537-45. PubMed PMID: 29976470. Epub 2018/07/07.
36. Dutch Clinical Guideline Colorectal Cancer. Comprehensive Cancer Centre the Netherlands, Oncoline, 2014. http://oncoline.nl/colorectaalcarcinoom (accessed May 2018). 2018.

Chapter 2

Intramucosal carcinoma of the rectum can be safely treated with transanal endoscopic microsurgery; clinical support of the revised Vienna classification

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Surgical Endoscopy, 2014

ABSTRACT

Aim

The revised Vienna criteria were proposed for classifying rectal neoplasia and subsequent treatment strategies. Restaging intramucosal carcinoma to a non-invasive subgroup seems logical, but clinical support is lacking. In this study, we investigated whether distinction between intramucosal carcinomas (IMC) and rectal adenoma (RA) is of clinical relevance and whether these neoplasms can all be similarly and safely treated by transanal endoscopic microsurgery (TEM).

Methods

All consecutive patients with IMC and RA, treated with TEM between 1996 and 2010 in tertiary referral centre for TEM were included. Long-term outcome of 88 IMC was compared to 356 pure rectal adenomas (RA). Local recurrence (LR) rate was the primary endpoint. Risk factors for LR were analysed.

Results

LR was diagnosed in 7/88 patients (8.0 %) with IMC and in 33/356 patients with primary RA (9.3 %; p = 0.700) and LR-free survival did not differ (p = 0.438). Median time to recurrence was 10 months (IQR IMC 5–30; RA 6–16). Overall recurrence occurred mainly in the first 3 years (38/40; 95 %). None of the LR revealed malignancy on pathological evaluation. No differences could be found in complication rates (IMC 9 %; RA 13 %; p = 0.34). Metastases did not occur in either group. Independent risk factors for LR were irradical margins at final histopathology (HR 2.32; 95 % CI 1.17–4.59; p = 0.016) and more proximal tumours (HR 0.84; 95 % CI 0.77–0.92; P<0.001).

Conclusion

In this study, IMC of the rectum and RA have similar recurrence rates. This supports the revised Vienna classification. Both entities can be safely treated with TEM.

INTRODUCTION

In recent years, transanal endoscopic microsurgery (TEM) has emerged as the preferred surgical technique for benign rectal tumours. It has proven to be superior to other local excision techniques with regards to recurrence and complication rates.[1] It is also more cost-effective than total mesorectal excision (TME) in appropriately selected rectal lesions, with lower morbidity and mortality.[2]

Although TEM has achieved survival rates similar to TME in T1 carcinomas, the role of TEM in malignant rectal disease is still extensively being studied.[3-5] Given the important differences in treatment of benign and malignant tumours, timely differentiation between rectal adenomas and carcinomas is crucial. Pre-treatment histopathological diagnoses of colorectal lesions attributed by Western and Japanese pathologists have shown considerable discrepant.[6]

The Vienna classification, which was proposed in 2000, sought for consensus among Japanese and Western pathologists.[7] This classification is a biopsy-based diagnosis of gastrointestinal epithelial neoplasia. Lesions containing intramucosal carcinoma (defined as invasion into the lamina propria) were classified among those containing invasive neoplasia, thereby suggesting the necessity of major abdominal surgery. The Vienna classification was revised according to the clinical implications of the different lesion types. As such, intramucosal carcinoma was re-classified among those lesions containing high-grade dysplasia and confined to the mucosa.[8] (Table 1) Biopsy-based diagnoses can be limited by superficiality and sampling errors. Final diagnosis is based on examination of the resection specimen, which reveals the most severe grade of neoplasia. However, treatment strategies are merely grounded on preoperative biopsies, which may lead to overtreatment.

To our knowledge, there are no clinical studies specifically addressing the biological behaviour of rectal intramucosal carcinomas treated with TEM. In our large tertiary referral centre for TEM, the outcomes of rectal adenomas and rectal intramucosal carcinomas, both treated with TEM could be analysed. As resection specimens may be subject to inter- and intraobserver variability to a lesser extent, this study may lead to clinical evidence supporting the revised Vienna classification, and may have important consequences with regards to the choice of local or extensive surgical treatment in this specific subgroup of rectal tumours.

Table 1 The Vienna and revised Vienna classification of gastrointestinal epithelial neoplasia, with corresponding suggested management strategies

Vienna classification			
Original		Revised	Clinical management
1	Negative for neoplasia	Negative for neoplasia	Optional follow-up
2	Indefinite for neoplasia	Indefinite for neoplasia	Follow-up
3	Non-invasive low grade neoplasia (low grade adenoma/dysplasia)	Mucosal low grade neoplasia Low grade adenoma Low grade dysplasia	Endoscopic resection or follow-up
4	Non-invasive high-grade neoplasia	Mucosal highgrade neoplasia	Endoscopic or local surgical resection
High-grade adenoma/ dysplasia		4.1 High-grade adenoma/ dysplasia	
Non-invasive carcinoma (carcinoma in situ)		4.2 Non-invasive carcinoma (carcinoma in situ)	
Suspicion of invasive carcinoma		4.3 Suspicious for invasive carcinoma 4.4 Intramucosal carcinoma	
5	Invasive neoplasia Intramucosal carcinoma Submucosal carcinoma or beyond	Submucosal invasion by carcinoma	Extended surgical resection

METHODS

Patients and interventions

All consecutive patients undergoing TEM in the IJsselland Hospital, Capelle aan den IJssel, The Netherlands, from 1996 onwards are registered in a prospective database. For the current study, we selected all patients operated between 1996 and 2010, in whom histopathological evaluation of the resection specimen revealed RA (including low- and high-grade dysplasia) or IMC (including in situ carcinoma). Medical records of included patients were retrospectively reviewed. Patients with a synchronous colorectal malignancy and patients with more than one rectal polyp were excluded. All patients underwent standard diagnostic workup including history, physical examination with digital rectal examination, colonoscopy with biopsy, rigid rectoscopy and endorectal ultrasound. TEM was performed as described by Buess using a dedicated TEM rectoscope with stereoscopic eyepiece (Wolf GmbH, Knittlingen, Germany).[9] Procedures were mainly undertaken by two surgeons with extensive experience (EdG, PD). Resections could be performed full thickness or submucosally at the discretion of the surgeon. All defects were closed in the transverse direction using continuous sutures. In case of conversion to another surgical technique, patients were excluded.

Histopathological evaluation

TEM resection specimens were treated according to a standardised protocol as previously described.[10] Histopathological evaluation was performed by several different general pathologists. Pathologists did not distinctly differentiate between in situ carcinoma and IMC; both terms were interchangeably attributed to lesions confined to the mucosa and lamina propria. Resection margin status was scored as complete ([1 mm, R0), incomplete (B1 mm, R1) or uncertain (Rx).

Follow-up

Regular follow-up consists of rectoscopy at 6, 24, and 36 months after TEM and in case of suspected local recurrence. Surveillance colonoscopy was performed at 12 months after TEM and according to the national surveillance guideline thereafter. For each patient, follow-up data were recorded until their last endoscopy or death.

Data collection and outcome parameters

Demographic characteristics of patients were assessed. Collected tumour characteristics included maximum diameter, distance from the dentate line and histopathological margins of the resection specimen.

Outcome parameters of this study included local recurrence rates, recurrence-free survival and complication rates. Local recurrence was defined as the presence of histopathologically proven neoplastic tissue within 1 centimetre of the resection scar. Complications were defined as fever leading to prolonged hospital stay, wound dehiscence, urinary tract infection, urinary retention, need of abdominal surgery, fistula and cardiopulmonary complications.

Statistical analysis

Results for continuous variables were summarised using mean (standard deviation (SD)) or median (interquartile range (IQR)) for skewed data. Frequencies (%) were used to summarise categorical variables. Statistical differences were analysed by the Chi square test of independence for categorical data and the Student's t test or Mann–Whitney U test for continuous data between groups. Recurrence-free survival distribution was compared using Kaplan–Meier survival analysis and log-rank test. Patients were censored at time of local recurrence or last follow-up. Cox regression analysis was then used to adjust for differences in tumour characteristics and to identify predictors for local recurrence. The limit of significance was P = 0.05 (two-sided). Calculations were made in SPSS statistics package for Windows (International Business Machines Corp., Armonk. NY, USA), version 20.0.

RESULTS

Patients and lesions

In total, 465 patients underwent TEM of a RA or IMC. We excluded 21 patients because of synchronous colorectal malignancy or more than one rectal lesion. The remaining 444 patients were included in our analysis. Final histopathology revealed IMC in 88 (20 %) and RA in 356 (80 %) patients. Patient and tumour characteristics are summarised in Table 2. Patient demographics and tumour distance from the dentate line were comparable between groups. Rectal adenomas were significantly larger than intramucosal carcinomas (median diameter 4 versus 3 cm; (IQR IMC 1.5–5; RA 3–6; P = 0.001)). Resection margins were more often complete in patients with IMC than in those with RA (88 versus 77 %; P = 0.038).

Table 2 Patients and lesion characteristics

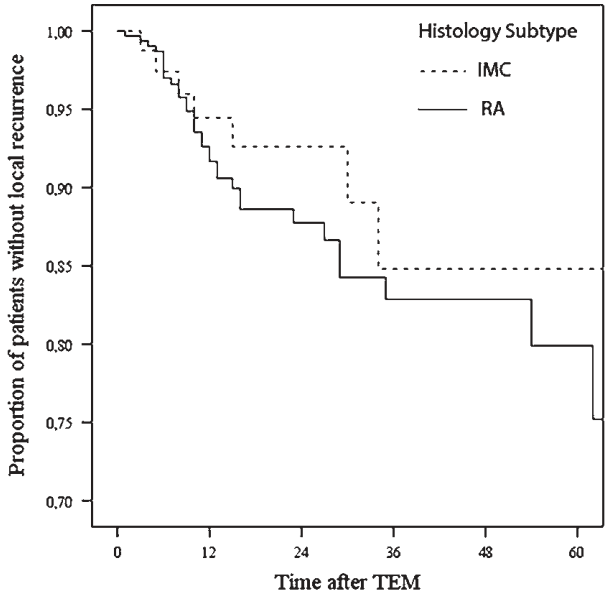
	Total (n = 444)	RA (n = 356)	IMC (n = 88)	P value
Patients				NS
Males, n (%)				NS
Age, mean (SD)	238 (54)	186 (52)	52 (58)	
Lesions	67 (12)	67 (11)	67 (13)	**0.001**
Median tumour size, (IQR) (cm)	4 (2.5–6)	4 (3–6)	3 (1,5–5)	**0.003**
Tumour size [3 cm, n (%)	257	219 (64)	38 (45)	NS
Distance to dentate line median (IQR) (per cm)	7 (5–10)	7 (5–10)	8 (5–10)	**0.038**
Histopathological radical margin after TEM, n (%)				
Yes, R0	352 (79)	275 (77)	77 (88)	
No, R1	75 (17)	68 (19)	7 (8)	
Unsure, Rx	17 (4)	13 (4)	4 (4)	

Bold values are statistically significant (P<0.05)
RA rectal adenoma; IMC intramucosal carcinoma

Follow-up

The median length of follow-up was 13 months (IQR 6–26) after resection of RA and 20 months (IQR 9–36) after resection of IMC (P = 0.24). Local recurrence was diagnosed in 7/88 patients after resection of IMC (8.0 %) and in 33/356 patients after resection of RA (9.3 %; P = 0.700). The median time to recurrence was 10 months (IQR IMC 5–30; RA 6–16). Most recurrences (n = 38/44; 95 %) developed during the first 3 years. Invasive carcinoma or progressive dysplasia was not diagnosed in any of the local recurrences. Metastatic disease did not occur in any of the patients. Survival analysis showed similar recurrence-free survival distributions for patients with IMC and RA, P = 0.438 (Fig. 1).

Fig. 1 Kaplan–Meier for recurrence-free survival distributions



Months	0	12	24	36	48	60
Patients at risk						
RA	356	194	97	56	33	19
IMC	88	55	34	19	11	3

After adjusting for factors that were significantly different between the groups (i.e. tumour size and radical margins), histologic subtype, e.g. IMC or RA, did not influence local recurrence (HR 1.22; 95 %CI 0.55–2.73; P = 0.625). To identify factors that did influence local recurrence, univariable and multivariable Cox regression analyses were performed (Table 3). Independent significant risk factors for local recurrence were incomplete margins (HR 2.32; CI 1.17–4.59; P = 0.016) and distance of the tumour from the dentate line; the more proximal the tumour was located, the lower the chance of LR (HR 0.84; CI 0.77–0.92; P<0.001). Incomplete margins did not occur more frequently in distal tumours.

Table 3 Risk factors for local recurrence

Risk factors	Univariable HR	95 % CI	Pvalue	Multivariable HR	95 % CI	P value
R1 vs. R0	3.26	1.69 – 6.28	<0.001	2.32	1.17–4.59	0.016
Male	1.74	0.91–3.34	0.095			
Age (per year)	1	0.97–1.03	0.977			
Histology; IMC vs. RA	1.22	0.55–2.73	0.625			
Distance to dentate line (per cm)	0.81	0.74–0.88	<0.001	0.84	0.77–0.92	<0.001
Tumour size[3 versus <3 cm	2.64	1.25–5.58	<0.001	1.77	0.81–3.86	0.153

HR hazard ratio; 95 % CI confidence Interval of 95 %

Morbidity

Complications did not differ between both groups (overall complication rate IMC n = 8; 9 %, RA n = 45; 13 %; P = 0.34). Also the types of complications did not differ (Table 4). TEM-related mortality was 0 % in both groups.

Table 4 Complications after TEM

Complications	IMC (n = 8)	RA (n = 45)
Fever[a]	1	6
Bleeding[b]	3	11
Abscess	0	8
Urinary retention	1	2
Urinary tract infection	1	3
Laparotomy ± stoma	1	3
Pain[a]	0	1
Fistula	0	1
Cardiopulmonary	1	10
Death	0	0

[a] Requiring prolonged admission;

[b] Requiring intervention (operation or transfusion)

IMC intramucosal carcinoma

RA rectal adenoma

DISCUSSION

In this study, the biological behaviour of rectal intramucosal carcinoma (including carcinoma in situ) and rectal adenoma (including low-grade and high-grade dysplasia) with regards to recurrence and metastatic potential is similar when treated by TEM. All consecutive patients could be successfully treated by TEM with comparable local recurrence rates below 10 % and similar complication rates. Moreover, recurrence-free survival remained comparable after adjusted analyses, taking into account the confounding of histopathologically complete margins and tumour size. Tumours situated closer to the anal verge appear to have an increased hazard of recurrence, despite comparable rates of complete margins.

The retrospective nature of our study allowed patient inclusion by resection specimen histopathology only, as opposed to preoperative biopsy specimens. When analysing resection specimens, differentiation between IMC and in situ carcinoma remains challenging for pathologists. The strict definition of in situ carcinoma is that it involves only the mucosa. It has not grown beyond the muscularis mucosa (inner muscle layer). IMC is defined as neoplastic cells with unquestionable invasion into the lamina propria mucosae.

In the current study, pathologists did not strictly distinguish between both entities. Therefore, both groups were analysed together, taking into account that this may harbour a possible bias. Considering the similar clinical management, as well as the similar recurrence and complication rates, this seems of no clinical importance. Although this study sample is quite large, there is a skewed distribution between both groups, which may have influenced some analyses. Nonetheless, considering the long time interval of patient inclusion, our sample likely represents the natural distribution of various dysplasia grades in rectal lesions.

The results of this study support the rationale of the revised Vienna criteria, which intended to improve reproducibility of biopsy-based diagnoses as well as clinical usefulness, considering the similar clinical implications of high-grade dysplasia, in situ carcinoma and IMC.[11] The biological background of similar behaviour among IMC, in situ carcinoma and high-grade dysplasia, is the absence of lymphatics in the lamina propria of the colon and rectum.[12-19] As a consequence, dysplastic cells have no potential for metastases even though they can migrate through the lamina propria. This implies that rectal lesions confined to the mucosa can be and should be treated with an organ sparing treatment. Naturally, with the conservation of the rectum, there is a risk of recurrent neoplasia in the rectum. However, in this study, all local recurrences were benign, and repeated treatment was feasible. Most importantly, no metastases were found in either of the groups.

Nevertheless, caution should be taken in biopsy-based treatment decisions, considering the risk of sampling error. The final establishment of the degree of dysplasia remains examination of the complete resection specimen. Therefore, the possibility of ''at least'' should be born in mind when interpreting a biopsy diagnosis [11]. On the other hand, this may cause overtreatment. For example, even in large rectal cancer trials, such as the Dutch

TME trial, 1.5 % of patients with presumed rectal cancer, based on biopsy, underwent TME for non-malignant disease.[20]

In anticipation of the widely implemented screening programmes for colorectal cancer, nomenclature and international guidelines must be clear, in order to improve multidisciplinary management of colorectal cancer. Whereas subdividing in situ carcinoma and IMC from low and high-grade dysplasia may remain important for research purposes, this subdivision does not have any clinical consequences. It was suggested earlier to use only low grade and high-grade dysplasia.[21] For clinical protocols, it may be sufficient to divide benign and malignant, as IMC, in situ carcinoma, high-grade neoplasia and low grade dysplasia, all have the same behaviour and can be treated and surveyed the same. In case of carcinoma invading the submucosa, TME remains the gold standard.

REFERENCES

1. Lin GL, Meng WC, Lau PY, Qiu HZ, Yip AW. Local resection for early rectal tumours: Comparative study of transanal endoscopic microsurgery (TEM) versus posterior trans-sphincteric approach (Mason's operation). Asian J Surg. 2006 Oct;29(4):227-32. PubMed PMID: 17098653. Epub 2006/11/14.
2. Maslekar S, Pillinger SH, Sharma A, Taylor A, Monson JR. Cost analysis of transanal endoscopic microsurgery for rectal tumours. Colorectal Dis. 2007 Mar;9(3):229-34. PubMed PMID: 17298620. Epub 2007/02/15.
3. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009 Dec;35(12):1280-5. PubMed PMID: 19487099. Epub 2009/06/03.
4. Langer C, Liersch T, Suss M, Siemer A, Markus P, Ghadimi BM, et al. Surgical cure for early rectal carcinoma and large adenoma: transanal endoscopic microsurgery (using ultrasound or electrosurgery) compared to conventional local and radical resection. Int J Colorectal Dis. 2003 May;18(3):222-9. PubMed PMID: 12673487. Epub 2003/04/04.
5. Winde G, Nottberg H, Keller R, Schmid KW, Bunte H. Surgical cure for early rectal carcinomas (T1). Transanal endoscopic microsurgery vs. anterior resection. Dis Colon Rectum. 1996 Sep;39(9):969-76. PubMed PMID: 8797643. Epub 1996/09/01.
6. Schlemper RJ, Itabashi M, Kato Y, Lewin KJ, Riddell RH, Shimoda T, et al. Differences in the diagnostic criteria used by Japanese and Western pathologists to diagnose colorectal carcinoma. Cancer. 1998 Jan 1;82(1):60-9. PubMed PMID: 9428480. Epub 1998/01/15.
7. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000 Aug;47(2):251-5. PubMed PMID: 10896917. Pubmed Central PMCID: PMC1728018. Epub 2000/07/18.
8. Schlemper RJ, Kato Y, Stolte M. Well-differentiated adenocarcinoma or dysplasia of the gastric epithelium: rationale for a new classification system. Verh Dtsch Ges Pathol. 1999;83:62-70. PubMed PMID: 10714196. Epub 2000/03/14.
9. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. [A system for a transanal endoscopic rectum operation]. Chirurg. 1984 Oct;55(10):677-80. PubMed PMID: 6510078. Epub 1984/10/01. Das System fur die transanale endoskopische Rectumoperation.
10. de Graaf EJ, Doornebosch PG, Stassen LP, Debets JM, Tetteroo GW, Hop WC. Transanal endoscopic microsurgery for rectal cancer. Eur J Cancer. 2002 May;38(7):904-10. PubMed PMID: 11978515. Epub 2002/04/30.
11. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut. 2002 Jul;51(1):130-1. PubMed PMID: 12077106. Pubmed Central PMCID: PMC1773259. Epub 2002/06/22.
12. Cooper HS, Patchefsky AS, Marks G. Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. Dis Colon Rectum. 1979 Apr;22(3):152-6. PubMed PMID: 446245. Epub 1979/04/01.
13. Frazin G, Zamboni G, Scarpa A, Dina R, Iannucci A, Novelli P. Hyperplastic (metaplastic) polyps of the colon. A histologic and histochemical study. Am J Surg Pathol. 1984 Sep;8(9):687-98. PubMed PMID: 6476197. Epub 1984/09/01.
14. Jass JR. Metaplastic polyps and polyposis of the colorectum. Histopathology. 1980 Sep;4(5):579. PubMed PMID: 7429436. Epub 1980/09/01.
15. Jass JR. Relation between metaplastic polyp and carcinoma of the colorectum. Lancet. 1983 Jan 1;1(8314-5):28-30. PubMed PMID: 6129371. Epub 1983/01/01.

16. Lane N. The precursor tissue of ordinary large bowel cancer. Cancer Res. 1976 Jul;36(7 PT 2):2669-72. PubMed PMID: 1277173. Epub 1976/07/01.
17. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012 Sep;107(9):1315-29; quiz 4, 30. PubMed PMID: 22710576. Pubmed Central PMCID: PMC3629844. Epub 2012/06/20.
18. Sumner HW, Wasserman NF, McClain CJ. Giant hyperplastic polyposis of the colon. Dig Dis Sci. 1981 Jan;26(1):85-9. PubMed PMID: 7460710. Epub 1981/01/01.
19. Urbanski SJ, Kossakowska AE, Marcon N, Bruce WR. Mixed hyperplastic adenomatous polyps--an underdiagnosed entity. Report of a case of adenocarcinoma arising within a mixed hyperplastic adenomatous polyp. Am J Surg Pathol. 1984 Jul;8(7):551-6. PubMed PMID: 6742315. Epub 1984/07/01.
20. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug 30;345(9):638-46. PubMed PMID: 11547717. Epub 2001/09/08.
21. Quirke P, Risio M, Lambert R, von Karsa L, Vieth M, International Agency for Research on C. European guidelines for quality assurance in colorectal cancer screening and diagnosis. First Edition--Quality assurance in pathology in colorectal cancer screening and diagnosis. Endoscopy. 2012 Sep;44 Suppl 3:SE116-30. PubMed PMID: 23012115. Epub 2012/10/04.

Chapter 3

Transanal minimally invasive surgery: impact on quality of life and functional outcome

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ABSTRACT

Background

Transanal minimally invasive surgery (TAMIS) is emerging as an alternative to transanal endoscopic microsurgery. Quality of life (QOL) and functional outcome are important aspects when valuing a new technique. The aim of this prospective study was to assess both functional outcome and QOL after TAMIS.

Methods

From 2011 to 2013, patients were prospectively studied prior to and at least 6 months after TAMIS for rectal adenomas and low-risk T1 carcinomas using a single- site laparoscopy port. Functional outcome was determined using the Faecal Incontinence Severity Index (FISI). Quality of life was measured using functional [Faecal Incontinence Quality of Life (FIQL)] and generic (EuroQol EQ-5D) questionnaires.

Results

The study population consisted of 24 patients 13 men, median age 59 (range 42–83) with 24 tumours [median distance from the dentate line 8 cm (range 2–17 cm); median tumour size 6 cm^2 (range 0.25–51 cm^2); 20 adenomas; 4 low-risk T1 carcinomas]. Postoperative complications occurred in one patient (4 %; grade IIIb according to Clavien Dindo classification). Compared to baseline, FISI remained unaffected (9.8 vs 7.3; P = 0.26), FIQL remained unaffected, and EuroQol EQ-5D improved (EQ-VAS: 77 vs 83; P = 0.04).

Conclusion

There was no detrimental effect of TAMIS on anorectal function. Overall QOL was improved after TAMIS, probably due to removal of the tumour, and at 6 months was equal to the general population.

INTRODUCTION

For the local resection of rectal adenomas and selected rectal carcinomas, transanal endoscopic microsurgery (TEM), as described by Buess, has emerged as the treatment of choice as it is superior to other local excision techniques.[1-3] Earlier studies have already shown that TEM has no impact on anorectal function and improves quality of life (QOL).[4-7] Nevertheless, TEM is not being broadly incorporated into the surgical armamentarium. This may be explained by its high costs and long

learning curve.[8, 9] Since 2010, single-site surgical ports are used as an alternative to the classical TEM rectoscope in transanal surgery. To date, many types of single ports have been explored transanally, such as the single-incision laparoscopic surgery port (SILS, Covidien, Mansfield, MA), the

Single Site Laparoscopic Access System (SSL, Ethicon Endo-Surgery, Cincinnati, OH) and the Gelpoint Path platform (Applied Medical, Rancho Santa Margarita, CA). Recently, the acronym TAMIS, meaning transanal minimally invasive surgery, is suggested to avoid commercial links. TAMIS seems to be embraced by colorectal surgeons more than TEM and has already proven to be a feasible and safe modification.[10] Furthermore, the technique of TAMIS is advocated to be easier to learn, and because no specialized insufflator or operating rectoscope is needed, it is more readily available.

As a next step, efficacy of TAMIS should be balanced against TEM, including its effect on anorectal function and QOL. To date, however, impact of TAMIS on the functional outcome and QOL is reported only scarcely and indirectly.[11] The aim of this prospective study was to analyse the functional outcome as well as QOL after TAMIS.

MATERIALS AND METHODS

Patients

The study population consisted of patients who were referred for local excision of a rectal tumour between May 2011 and April 2013. All patients were evaluated preoperatively according to a standard protocol including rigid rectoscopy, tumour biopsy and endorectal ultrasound. Only rectal adenomas and low-risk T1 carcinomas, i.e. well differentiated, no signs of lymphangio-invasion and 3 cm, were considered eligible for this study. Patients with a pre-existing stoma, patients who underwent conversion to another technique, patients in whom histology results post-operative revealed a [T1 carcinoma and patients who underwent a combined operation were excluded. Institutional review board approval was given prior to the commencement of the study, and in all patients, written informed consent was obtained.

Surgical procedure

Procedures were performed by two surgeons who are extensively ([500) experienced in TEM and moderately (50–100) experienced in TAMIS (P.D. and E.d.G.). TAMIS was performed using the Single Site Laparoscopic Access System (SSL, Ethicon Endo-Surgery, Cincinnati, OH), as previously described [10]. In brief, this procedure is performed by using a 360° rotatable port in combination with a 30°laparoscope, providing easy and quick reorientation of the instrumentation and easy specimen collection. A single enema was given 1 h before surgery. Preoperative antibiotics (cefazoline/metronidazole) were administered. All patients were operated under general anaesthesia in the lithotomy position. A pneumorectum of 12–15 mmHg was established using carbon dioxide insufflation. A full-thickness excision was performed. At the surgeon's discretion, the rectal wall defect was closed using a self-anchoring continuous suture. Operative time was defined as the time of inserting the SSL retractor until removal.

Data collection

An independent research coordinator not previously involved in the patients' care collected all data. Demographics, operative details, post-operative length of stay, post-operative complications and functional outcome were recorded for each patient. Before and 6 months after TAMIS, patients were asked to fill out a questionnaire to assess anorectal function and QOL. We evaluated functional outcome by means of a detailed questionnaire based on the Faecal Incontinence Severity Index (FISI) (range 0–61).[12] Quality of life was evaluated using the EuroQol EQ-5D/EQ-VAS scores (both, range 0–100) and the Faecal Incontinence Quality of Life (FIQL) score [overall score and four domains (lifestyle issues, coping–behaviour, depression and self-perception and embarrassment) (all, range 1–4)].[13] The EuroQol EQ-5D/VAS scores were compared with a sex- and agematched, community-based sample of healthy persons without co-morbidity.[14] Data are presented as medians and ranges. Changes within groups were evaluated using the nonparametric one-sample Wilcoxon's signed-rank test. Comparison of these changes between groups was conducted using the Mann–Whitney U test. A P value of <0.05 was considered statistically significant.

RESULTS

Between May 2011 and April 2013, 50 patients were found eligible for this study. Eighteen patients were excluded; in 14 patients, TAMIS was combined with another surgical technique and four patients required additional surgery because of high-risk T1 or more invasive carcinoma. Of the remaining 32 patients, 24 completed both preoperative and post-operative questionnaires (response rate 75 %) and were included for analysis. All patients had a minimal follow-up of 6 months (range 6–8). Eight patients did not provide us both the completed preoperative and post-operative questionnaires despite their informed consent and frequent encouragements. None of the eight nonresponding patients developed an early recurrence. Two patients experienced post-operative haemorrhage, both treated conservatively. Hence, the reason for non-responding is not quite clear.

The group consisted of 13 males and 11 females. Median age was 59 years (range 42–83). Median distance from the distal tumour margin to the dentate line was 8 cm (range 2–17 cm), and median tumour size was 6 cm^2 (range 0.25–51 cm^2). Twenty-four tumours were removed: 20 adenomas and 4 low-risk T1 carcinomas. The median proportion of the rectal circumference covered by the lesion was 25 % (range 5–50). Median operative time was 32 min (range 13–94). One patient (4 %) experienced a complication consisting of haemorrhage requiring re-operation (grade IIIb according to Clavien Dindo classification).

In hospital, mortality rate was zero. Median length of stay was 1 day (range 1–3 days; Table 1). The mean FISI score decreased from 9.8 ± 2.3 to 7.3 ± 2.2 (P = 0.26). Fifteen patients were completely continent after surgery (63 %). Five patients (21 %) had a minor deterioration in FISI score of 8 (range 5–12). The five patients who experienced an increase in FISI score had a significant shorter tumour distance to the dentate line (4.4 vs 7.4 cm; P = 0.04) and a significantly larger tumour size (21 vs 9 cm^2; P = 0.05). The EQ-VAS score in these patients was significantly lower (71 vs 86; P = 0.03). A schematic overview is provided in Fig. 1. The FIQL scores are shown in Table 2.

A significant improvement in the FIQL subscale ''coping behaviour'' was seen post-operatively (P = 0.02). In patients in whom the FISI score deteriorated, the FIQL scores were lower at 6 months after TAMIS in all four dimensions (All P<0.05). The size of the tumour and distance to the anal verge had no significant effect on these FIQL scores. The general QOL, as evaluated by EQ-VAS and EQ-5D, is presented in Table 3. From a patient perspective, the mean general QOL score (EQ-VAS) improved 6 months after TAMIS compared to baseline (P = 0.03). From a social perspective, the mean EQ-5D index score remained equal. EQ-VAS and EQ-5D scores were lower to those of the sex- and age-matched general population before surgery (both, P<0.01), yet were similar 6 months after TAMIS.

Table 1 Procedure-related characteristics

Median duration of operation in minutes (range)	32 (13–94)
Complications (N)	1/24 (4.2 %)
Re-operation for re-bleeding	1
Median length of hospital stay in days (range)	1 (1–3)

Fig. 1 FISI-scores before and after transanal minimally invasive surgery (TAMIS)

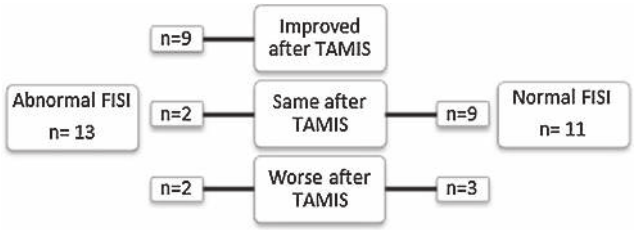

Table 2 Faecal Incontinence Quality of Life scores

	Preoperative	6 months after SPTS	P value
Lifestyle	3.8 (0.6)	3.9 (0.4)	0.15
Coping behaviour	3.0 (0.8)	3.6 (0.5)	0.02
Depression	3.6 (0.8)	3.7 (0.5)	0.27
Embarrassment	3.5 (0.5)	3.7 (0.4)	0.08
Total	3.5 (0.6)	3.7 (0.5)	0.12

Table 3 General quality of life scores

	Baseline (preoperative)	6 months after SPTS	Population
	N= 24	N= 24	N= 24
EQ-VAS	77 (12)	83* (14)	84 (7)
EQ-5D	82 (11)	88 (10)	89 (6)

Data are mean scores with standard deviation in parentheses. EQVAS score equates to QOL from a patient perspective, EQ-5D score equates to QOL from a social perspective. The population group was sex- and age- matched to the analysed patients and derived from a community-based sample of healthy individuals without co-morbidity

* P= 0.03 comparison with baseline

DISCUSSION

This is the first study focusing not only on anorectal functioning, but also on QOL following TAMIS, which makes this study unique. In this study, TAMIS proved to be a safe technique. Overall, anorectal functioning was not compromised, although in a small subset of patients FISI increased, depicting a deterioration in functioning.

To the best of our knowledge, there is only one other paper describing the impact of TAMIS on anorectal functioning. In the recent study by Schiphorst et al. [15], preoperative FISI scores were higher than in the current study (mean 21 vs 10). The only obvious differences between both studies seem to be median age (median 79 vs 59 years) and median tumour size (18 vs 6 cm^2), and this may attribute to the difference in preoperative FISI scores. Following TAMIS, in their study in 88 % of patients, continence improved, whereas in only two patients, functioning deteriorated at 6-month follow-up. In our study, in 79 % of patients, anorectal functioning improved, and in five patients, it decreased. As these numbers are limited, conclusions have to be mitigated, but in our series, deterioration occurred mainly in more distal located and larger tumours. To confirm whether these are the real contributing factors, further studies have to be awaited.

Regarding QOL, a significant improve in FIQL was observed in the subscale ''coping behaviour''. Tumour size and distance from the dentate line had no effect on these FIQL scores. We also observed a better general QOL score (EQ-VAS) after TAMIS (P = 0.03). We can only speculate on this improvement. However, besides removal of the tumour which may have led to incontinence-like symptoms, it seems reasonable a rejoice phenomenon plays a role. Finally, social QOL (EQ-5D) improved 6 months after TAMIS, and at that time point, was comparable to the general population.

Although our study population is small, it is a very homogenous group, including only patients with adenoma or a low-risk T1 carcinoma. Only patients who solely underwent TAMIS, using only one system, were included. Hereby, the possible influence of other systems or anal retractors on functional outcome is eliminated.

How are our results compared to studies following TEM? In earlier studies, we already showed TEM has no detrimental effect on anorectal functioning.[5] A recent study by Allaix showed TEM to be safe even after longterm follow-up. Our study shows TAMIS can compete with TEM as it comes to anorectal functioning and QOL.[16] However, long-term results have to be awaited. Also, as TEM has proven safe with respect to local recurrence rates in RA and T1 rectal carcinomas, TAMIS should produce equivalent results on these aspects, before it can be embraced safely.

In conclusion, TAMIS seems to be a safe procedure without compromising anorectal functioning and improves QOL in most patients. Nonetheless, more data, especially on long-term outcome and long-term functional results, will be required before concluding it is equal to TEM, the current gold standard procedure.

REFERENCES

1. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. [A system for a transanal endoscopic rectum operation]. Chirurg. 1984 Oct;55(10):677-80. PubMed PMID: 6510078. Epub 1984/10/01. Das System fur die transanale endoskopische Rectumoperation.
2. de Graaf EJ, Burger JW, van Ijsseldijk AL, Tetteroo GW, Dawson I, Hop WC. Transanal endoscopic microsurgery is superior to transanal excision of rectal adenomas. Colorectal Dis. 2011 Jul;13(7):762-7. PubMed PMID: 20345967. Epub 2010/03/30.
3. de Graaf EJ, Doornebosch PG, Stassen LP, Debets JM, Tetteroo GW, Hop WC. Transanal endoscopic microsurgery for rectal cancer. Eur J Cancer. 2002 May;38(7):904-10. PubMed PMID: 11978515. Epub 2002/04/30.
4. Cataldo PA, O'Brien S, Osler T. Transanal endoscopic microsurgery: a prospective evaluation of functional results. Dis Colon Rectum. 2005 Jul;48(7):1366-71. PubMed PMID: 15933798. Epub 2005/06/04.
5. Doornebosch PG, Gosselink MP, Neijenhuis PA, Schouten WR, Tollenaar RA, de Graaf EJ. Impact of transanal endoscopic microsurgery on functional outcome and quality of life. Int J Colorectal Dis. 2008 Jul;23(7):709-13. PubMed PMID: 18379797. Pubmed Central PMCID: PMC2386752. Epub 2008/04/02.
6. Doornebosch PG, Tollenaar RA, Gosselink MP, Stassen LP, Dijkhuis CM, Schouten WR, et al. Quality of life after transanal endoscopic microsurgery and total mesorectal excision in early rectal cancer. Colorectal Dis. 2007 Jul;9(6):553-8. PubMed PMID: 17573752. Epub 2007/06/19.
7. Planting A, Phang PT, Raval MJ, Brown CJ. Transanal endoscopic microsurgery: impact on fecal incontinence and quality of life. Can J Surg. 2013 Aug;56(4):243-8. PubMed PMID: 23883494. Pubmed Central PMCID: PMC3728243. Epub 2013/07/26.
8. Barendse RM, Dijkgraaf MG, Rolf UR, Bijnen AB, Consten EC, Hoff C, et al. Colorectal surgeons' learning curve of transanal endoscopic microsurgery. Surg Endosc. 2013 Oct;27(10):3591-602. PubMed PMID: 23572216. Epub 2013/04/11.
9. Maslekar S, Pillinger SH, Sharma A, Taylor A, Monson JR. Cost analysis of transanal endoscopic microsurgery for rectal tumours. Colorectal Dis. 2007 Mar;9(3):229-34. PubMed PMID: 17298620. Epub 2007/02/15.
10. Barendse RM, Doornebosch PG, Bemelman WA, Fockens P, Dekker E, de Graaf EJ. Transanal employment of single access ports is feasible for rectal surgery. Ann Surg. 2012 Dec;256(6):1030-3. PubMed PMID: 22504282. Epub 2012/04/17.
11. Albert MR, Atallah SB, deBeche-Adams TC, Izfar S, Larach SW. Transanal minimally invasive surgery (TAMIS) for local excision of benign neoplasms and early-stage rectal cancer: efficacy and outcomes in the first 50 patients. Dis Colon Rectum. 2013 Mar;56(3):301-7. PubMed PMID: 23392143. Epub 2013/02/09.
12. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Patient and surgeon ranking of the severity of symptoms associated with fecal incontinence: the fecal incontinence severity index. Dis Colon Rectum. 1999 Dec;42(12):1525-32. PubMed PMID: 10613469. Epub 1999/12/29.
13. Rockwood TH, Church JM, Fleshman JW, Kane RL, Mavrantonis C, Thorson AG, et al. Fecal Incontinence Quality of Life Scale: quality of life instrument for patients with fecal incontinence. Dis Colon Rectum. 2000 Jan;43(1):9-16; discussion-7. PubMed PMID: 10813117. Epub 2000/05/17.

14. Kind P, Dolan P, Gudex C, Williams A. Variations in population health status: results from a United Kingdom national questionnaire survey. BMJ. 1998 Mar 7;316(7133):736-41. PubMed PMID: 9529408. Pubmed Central PMCID: PMC28477. Epub 1998/04/08.
15. Schiphorst AH, Langenhoff BS, Maring J, Pronk A, Zimmerman DD. Transanal minimally invasive surgery: initial experience and short-term functional results. Dis Colon Rectum. 2014 Aug;57(8):927-32. PubMed PMID: 25003287. Epub 2014/07/09.
16. Allaix ME, Rebecchi F, Giaccone C, Mistrangelo M, Morino M. Long-term functional results and quality of life after transanal endoscopic microsurgery. Br J Surg. 2011 Nov;98(11):1635-43. PubMed PMID: 21713758. Epub 2011/06/30.

Chapter 4

Treatment of clinical T1 rectal cancer in the Netherlands; a population-based overview of clinical practice

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ABSTRACT

Introduction

Local excision is increasingly used as an alternative treatment for radical surgery in patients with early stage clinical T1 (cT1) rectal cancer. This study provides an overview of incidence, staging accuracy and treatment strategies in patients with cT1 rectal cancer in the Netherlands.

Materials and methods

Patients with cT1 rectal cancer diagnosed between 2005 and 2018 were included from the Netherlands Cancer Registry. An overview per time period (2005-2009, 2010-2014 and 2015-2018) of the incidence and various treatment strategies used, e.g. local excision (LE) or major resection, with/without neoadjuvant treatment (NAT), were given and trends over time were analysed using the Chi Square for Trend test. In addition, accuracy of tumour staging was described, compared and analysed over time.

Results

In total, 3033 patients with cT1 rectal cancer were diagnosed. The incidence of cT1 increased from 540 patients in 2005-2009 to 1643 patients in 2015-2018. There was a significant increased use of LE. In cT1N0/X patients, 9.2% received NAT, 25.5% were treated by total mesorectal excision (TME) and 11.4% received a completion TME (cTME) following prior LE. Overall accuracy in tumour staging (cT1=pT1) was 77.3%, yet significantly worse in cN1/2 patients, as compared to cN0 patients (44.8% vs 77.9%, respectively, $p<0.001$).

Conclusion

Over time, there was an increase in the incidence of cT1 tumours. Both the use of neoadjuvant therapy and TME surgery in clinically node negative patients decreased significantly. Clinical accuracy in T1 tumour staging improved over time, but remained significantly worse in clinical node positive patients.

INTRODUCTION

In the treatment of rectal cancer, surgery according to the principle of total mesorectal excision (TME) remains the cornerstone of curative treatment. However, TME has substantial morbidity and mortality.[1-3] In selected patients with low risk early-stage rectal cancer, local excision (LE) is an attractive and increasingly applied alternative to primary TME.[4-6] In terms of preserving anorectal function, lower morbidity and improved quality of life, LE is superior compared to TME.[7] LE seems oncologically safe in patients with clinical node negative pT1 rectal tumours in the absence of prognostic unfavourable histological factors, including poor differentiation grade, lymphatic or vascular invasion, tumour budding and positive resection margins. Consequently, LE is nowadays considered as the preferred treatment of choice for these patients.[4-6, 8-12]

If a cT1 rectal cancer proves to be high risk pT1 or more after LE, completion TME (cTME) is recommended in order to achieve optimal oncological outcome. Although cTME has similar oncological results as primary TME, the necessity of cTME after LE indicates that the patient has unnecessarily been exposed to LE and its risks.[13] When cTME is omitted and a local recurrence occurs during follow-up, salvage surgery is mandatory with often disappointing results.[14, 15] This emphasizes the need for accurate staging and diagnosis of pT1 cancers.[16]

In view of the increasing incidence and the changes in management of pT1 rectal cancer over the years, we evaluated the trends in incidence and treatment strategies for patients diagnosed with cT1 rectal cancer in the Netherlands between 2005 – 2018. In addition, we analysed the accuracy of clinical staging for pT1 tumours.

MATERIALS AND METHODS

Patient Selection

All data were extracted from the Netherlands Cancer Registry (NCR), a nationwide population-based registry including all newly diagnosed malignancies in the Netherlands. NCR data on patient characteristics, tumour characteristics and treatment are collected from hospital patient files and coded according to a national manual, e.g. to the International Classification of Diseases for Oncology (ICD-O) and stage according to the TNM classification.[11] Patients with a clinical T1 (any N) stage rectal and rectosigmoidal carcinoma (C19 and C20) aged ≥ 18 years old diagnosed between 2005 and 2018 were included in this retrospective study. All treatment methods were included, either with or without the application of (neo)adjuvant therapy. Patients with cT1M1 and those who did not receive (surgical) treatment were described but excluded from further analysis.

Staging modalities

The NCR database does not contain information on specific staging modalities used throughout the study period. Nonetheless, according to Dutch guidelines, the workup for patients diagnosed with rectal cancer consist of endoscopy with biopsy, chest X-ray, an abdominal CT-scan and an MRI of the rectum. Some specialized centres use endorectal ultrasound in addition to MRI, but it is not mandatory. Nodal metastasis was defined according to established radiological criteria: >3mm in the first version of the guideline, >5mm in the second version and the addition of morphological features in the revised version in 2014: 1) irregular boundary; 2) heterogeneous texture; 3) round shape. Short axis diameter < 5 mm, combined with all three malignant morphological features. Short axis diameter of ≥ 9 mm.).

Subgroups

The population was divided into cT1 patients without nodal involvement (cN0) or unknown nodal involvement (cNx) and those with nodal involvement (cN1/2). Further subdivision was based on the applied treatment strategy: neoadjuvant therapy (NAT) versus no neoadjuvant therapy (no NAT) and subsequently into LE only, primary TME and LE + cTME. Local excision was subdivided into endoscopic resection or transanal surgical excision. To analyse incidence and treatment trends over time, the cohort was subdivided into three time periods: 2005 – 2009, 2010 – 2014 and 2015 – 2018. These time periods are based on relevant events in time such as the introduction of MRI in rectal cancer patients (strongly advised since 2010 and guideline required in 2011)[17] and implementation of population screening in 2014.[17]

Endoscopic and Surgical Procedures

Local excision includes both endoscopic resection and transanal surgical excision techniques. Endoscopic techniques include endoscopic polypectomy, endoscopic submucosal dissection (ESD), endoscopic full-thickness resection (eFTR), or endoscopic mucosal resection (EMR). Transanal surgical excision techniques include transanal excision according to Parks, and any rigid or flexible transanal excision platform such as transanal endoscopic microsurgery (TEM), transanal endoscopic operation (TEO) and transanal minimally invasive surgery (TAMIS).

The TME group includes open, laparoscopic or robot-assisted surgery including low anterior resection (LAR), abdominoperineal excision (APE), Hartmann's procedure and rectosigmoidectomy. Noteworthy, for proximal rectal cancers it might be possible that a partial mesorectal excision has been performed. Unfortunately, these specific details are lacking. Completion TME (cTME) was defined as TME surgery within 6 months after primary LE, and includes patients with inadequate resection margins of local surgery, unfavourable histological features and incomplete margins. The 6-month time interval has been previ-

ously described and is likely to include all patients who underwent 'completion surgery'. [18, 19]

Statistical analysis

Descriptive statistics were used to describe all variables. Continuous variables are presented as median with interquartile range (IQR). Categorical variables are presented as frequency with percentages and statistically compared using the chi-square test or Fisher-exact test, as appropriate. Trend analyses were performed using the Chi Square for Trend test. When analysing trends between the three treatment groups (LE only, primary TME and LE + cTME), one treatment group (e.g., LE) was compared to the rest (e.g., primary TME and LE + cTME).

The accuracy of clinical tumour staging was determined by the number of patients with cT1 tumours who received endoscopic/surgical treatment, in whom a pT1 stage was confirmed after pathological examination of the resection specimen. Neoadjuvant therapy included radiation therapy (RTx), chemotherapy (CTx) or chemoradiation therapy (CRTx). Considering the potential pathological response that may be induced by neoadjuvant therapy, patients treated with neoadjuvant chemoradiation therapy were excluded from the analysis on accuracy of clinical staging. In addition, patients who were treated with neoadjuvant radiation therapy but underwent "delayed" endoscopic/surgical management (i.e. time from incidence to endoscopic/surgical treatment more than 8 weeks) were also excluded for this analysis because this could also induce downstaging.

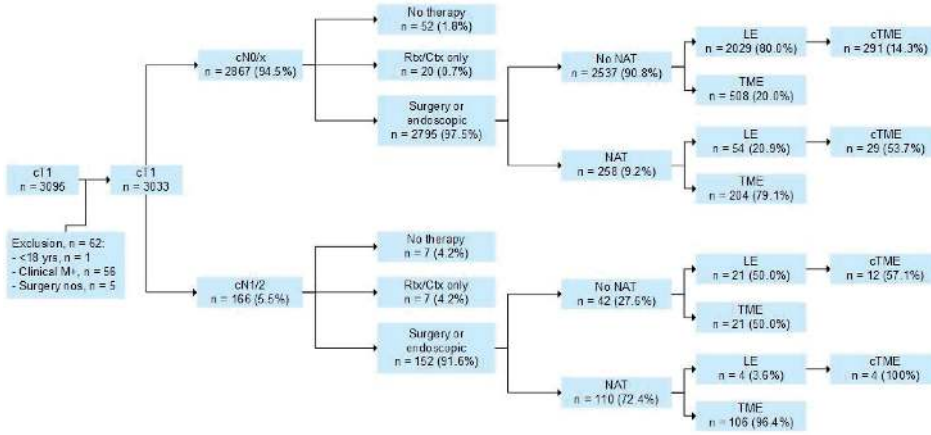
For all statistical tests, the threshold for significance was set at $P<0.05$. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 20.0) was used to prepare the database and for statistical analysis.

RESULTS

Patient selection and therapy

According to the NCR, a total of 45,874 Dutch patients were diagnosed with rectal and rectosigmoidal cancer between 2005 and 2018. Of those, 3095 patients (6.7%) were classified as cT1 rectal cancer. Fifty-six patients (1.8%) were diagnosed with distant metastases, one patient was aged <18 years and surgical management was not specified in five patients. After exclusion of these patients, a total of 3033 patients were included for further analysis. A flow diagram of patient selection, clinical nodal stage and given therapy is illustrated in **Figure 1**. Baseline patient and tumour characteristics and therapy strategies divided per clinical nodal stage are depicted in **Table 1**.

Figure 1. Flow diagram patient selection, nodal status and given therapy



Abbreviations: LE, local excision; TME, total mesorectal excision; cTME, completion TME; NAT, neoadjuvant therapy; CTx, chemotherapy; RTx, radiotherapy; nos= not otherwise specified

Table 1 Baseline characteristics Dutch patients with cT1 rectal cancer, subdivided by N stage, N (%) or median [IQR]

Characteristic	All (*n = 3033*)	N0/x (*n = 2867*)	N1/2 (*n = 166)*
Gender			
Female	1172 (38.6)	1108 (38.6)	64 (38.6)
Male	1861 (61.4)	1759 (61.4)	102 (61.4)
Age	68 [62- 74]	68 [62- 75]	67 [60- 74]
Treatment category			
No treatment	59 (1.9)	52 (1.8)	7 (4.2)
RTx/CTx only	27 (0.9)	20 (0.7)	7 (4.2)
Endoscopic/surgical	2947 (97.2)	2795 (97.5)	152 (91.6)
NAT [a]	*n = 2947*	*n = 2795*	*n = 152*
No	2579 (87.5)	2537 (90.8)	42 (27.6)
Yes	368 (12.5)	258 (9.2)	110 (72.4)
NAT category [b]	*n = 368*	*n = 258*	*n = 110*
CTx	1 (0.3)	1 (0.4)	0 (0)
RTx	325 (88.3)[c]	241 (93.4)[c]	84 (76.4)[c]
CRTx	42 (11.4)	16 (6.2)	26 (23.6)
Surgical treatment [a]	*n = 2947*	*n = 2795*	*n = 152*
LE only	1772 (60.1)	1763 (63.1)	9 (5.9)
Primary TME	839 (28.5)	712 (25.5)	127 (83.6)
LE + cTME	336 (11.4)	320 (11.4)	16 (10.5)
Type of LE [d]	*n = 2108*	*n = 2083*	*n = 25*
Endoscopic resection	1272 (60.3)	1257 (60.3)	15 (60.0)
Transanal surgical excision	836 (39.7)	826 (39.7)	10 (40.0)

Abbreviations: LE, local excision; TME, total mesorectal excision; cTME, completion TME; NAT, neoadjuvant therapy; CTx, chemotherapy; RTx, radiotherapy; CRTx, chemoradiotherapy

[a] in the subgroup of patients who were treated with an endoscopic/surgical procedure

[b] in the subgroup of patients who received NAT and were subsequently treated with an endoscopic/surgical procedure

[c] short-course radiation with early surgery was presumed in n=184 patients (56.6%), cN0/x n=134 (55.6%) and cN1/2 n=50 (59.5%)

[d] in the subgroup of patients who primarily underwent LE

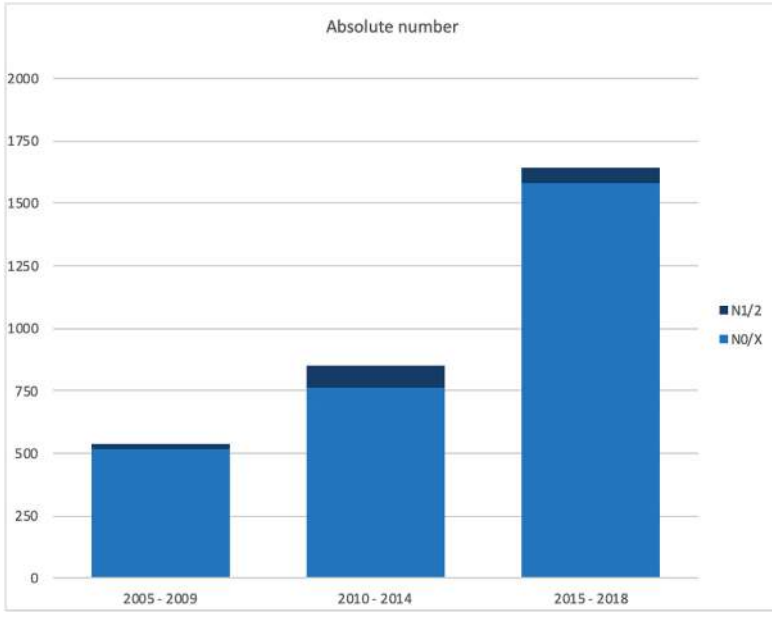
Of all included patients, most were men (61.4%). Median age was 68 years (IQR 62 – 74) and most patients were diagnosed with clinical N0/x tumours (2867 out of 3033, 94.5%). The majority of all patients (2947 out of 3033, 97.2%) underwent some kind of endoscopic or surgical treatment. A total of 59 patients (1.9%) were registered as not having received treatment at all. The majority of them were male (n=37, 62.7%) and their median age was 80 years (IQR 71 – 85). Twenty-seven patients (0.9%) were treated with chemotherapy, radiation therapy or chemoradiation therapy, without endoscopic or surgical therapy. In this group, most patients were male (n=22, 81.5%) and their median age was 81 years (IQR 66- 83).

Of the patients diagnosed with clinical N0/x stage, most did not receive NAT (90.8%) and were primarily treated by LE (80.0%). The patients diagnosed with clinical N1/2 stage usually received NAT (72.4%), frequently followed by a TME procedure (96.4%).

Trends in incidence and treatment over time

Throughout the incidence years, the absolute number of patients diagnosed with clinical T1 rectal cancer increased from 540 patients in 2005 – 2009, to 1643 patients in 2015 – 2018 (**Figure 2**). In all time periods, most patients were classified as clinical N0/x stage (94.5%, 2867 out of 3033 patients).

Figure 2. The absolute number of patients diagnosed with clinical T1 rectal cancer in The Netherlands



Neoadjuvant therapy

During the study period, there was a significant decrease in the use of NAT in patients with cT1N0/x rectal cancer, from 26.6% in 2005 – 2009 to 0.6% in 2015 – 2018 (P<0.001). For patients with cT1N1/2 rectal cancer NAT was administered in 75.0% of patients in 2005 – 2009 which was statistically not significantly different from 61.8% in 2015 – 2018 (P=0.085).

Surgical/endoscopic treatment

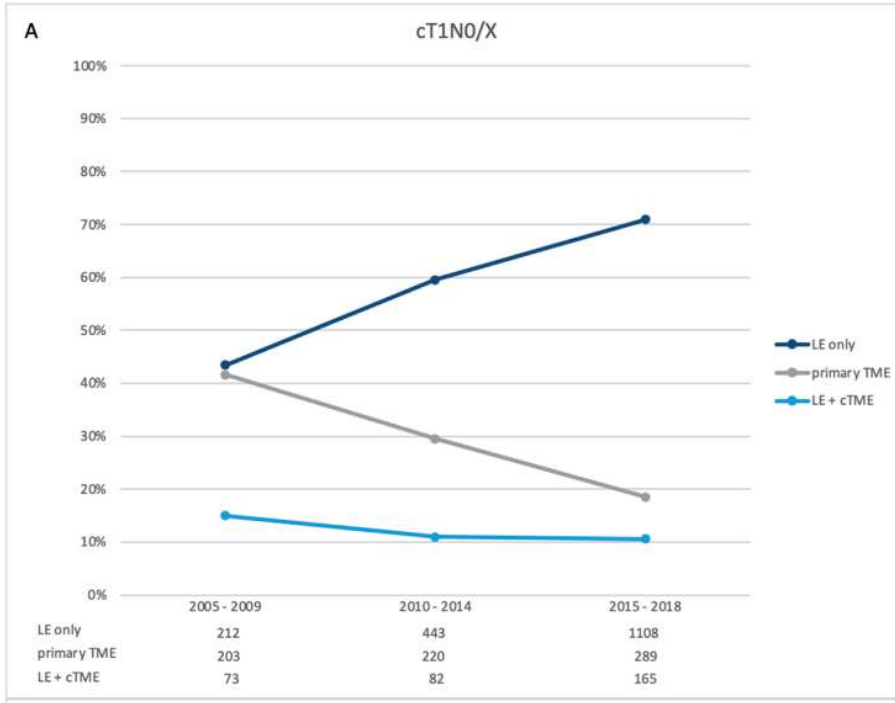
cT1N0/x

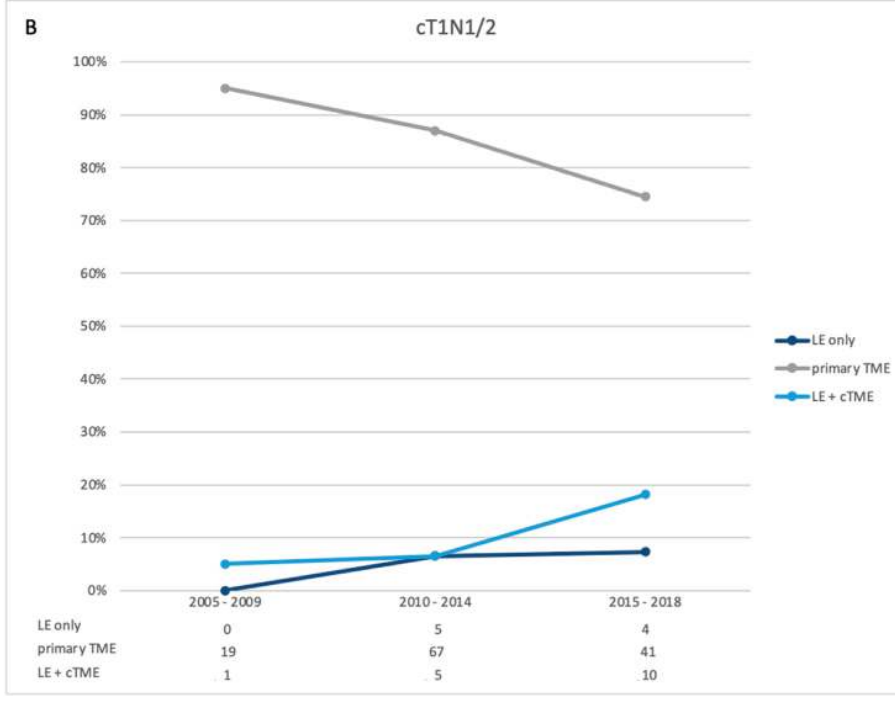
There was a significant increase over time towards LE as definitive endoscopic/surgical treatment compared to TME (primary and cTME) in patients with cT1N0/x rectal cancer, from 43.4% in 2005 - 2009 to 70.9% in 2015 – 2018 (P<0.001) (**Figure 3A**). The number of primary TME significantly decreased over time, from 41.6% in 2005 – 2009 to 18.5% in 2015 – 2018 (P<0.001), and simultaneously the number of cTME significantly decreased over time from 15.0% in 2005 – 2009 to 10.6% in 2015 – 2018 (P=0.016) (**Figure 3A**). In the group of patients primarily treated with LE (including those who eventually underwent cTME), the percentage of patients receiving endoscopic resection compared to transanal surgical excision significantly increased over time from 55.1% (157 out of 285 patients) in 2005 – 2009, to 52.6% (276 out of 525 patients) in 2010 – 2014, and finally to 64.7% (824 out of 1273 patients) in 2015 – 2018 (P<0.001).

cT1N1/2

There was no significant difference in time towards TME (primary and cTME) compared to LE as definitive treatment in patients with cT1N1/2 rectal cancer (P=0.320) (**Figure 3B**). The number of primary TME significantly decreased over time from 95.0% in 2005 – 2009 to 74.5% in 2015 – 2018 (P=0.017) and on the contrary the number of cTME significantly increased over time from 5.0% in 2005 – 2009 to 18.2% in 2015 – 2018 (P=0.016) (Figure 3B). There was no significant difference over time between endoscopic resections and transanal excisions in the small group of patients primarily treated with LE (including those who eventually underwent cTME), though a decreasing trend was observed for endoscopic resections namely 100% (1 out of 1 patients) in 2005 – 2009, 80.0% (8 out of 10 patients) in 2010 – 2014, and 42.9% (6 out of 14 patients) in 2015 – 2018 (P=0.051).

Figure 3. The proportion of patients with cT1N0/X (A) and cT1N1/2 (B) rectal cancer who were treated with LE only, primary TME or LE + cTME throughout the incidence years





Clinical tumour accuracy

Results for clinical tumour accuracy per time period and per clinical N stage are presented in **Table 2**. In the patients treated with endoscopic/surgical therapy (without neoadjuvant therapy except neoadjuvant short-course radiation therapy followed by early surgery), pathological confirmation of clinical T1 stage was observed in 2071 out of 2613 patients (79.3%).

During the study period, there was a significant increase in pathological confirmation of T1 stage, from 67.2% in 2005-2009 to 85.9% in 2015-2018 (P<0.001). Between patients staged with clinical N0/x stage and clinical N1/2 stage, there was a significant difference in this pathological confirmation (80.6% versus 52.7% respectively, P<0.001). There was considerable understaging in tumour stage in patients with clinical N1/2 disease, as 45.1% were diagnosed with pT2-4 stage.

The significant difference in pathological confirmation between patients staged with clinical N0/x stage and clinical N1/2 stage remained throughout all time periods (2005-2009: 68.5% versus 25.0%, P=0.009; 2010-2014: 74.2% versus 51.2%, P=0.004; 2015-2018: 86.5% versus 63.9%, P=0.001).

Table 2. Clinical tumour accuracy divided per time period and per clinical N stage, N=2613[a]

		pT0	pT1	pT2-4
All time periods	cT1N0/x (n=2522)	25 (1.0)	2032 (80.6)	465 (18.4)
	cT1N1/2 (n=91)	2 (2.2)	48 (52.7)	41 (45.1)
2005- 2009	cT1N0/x (n=387)	4 (1.0)	265 (68.5)	118 (30.5)
	cT1N1/2 (n=12)	0 (0)	3 (25.0)	9 (75.0)
2010- 2014	cT1N0/x (n=644)	12 (1.9)	478 (74.2)	154 (23.9
	cT1N1/2 (n=43)	1 (2.3)	22 (51.2)	20 (46.5)
2015- 2018	cT1N0/x (n=1491)	9 (0.6)	1289 (86.5)	193 (12.9)
	cT1N1/2 (n=36)	1 (2.8)	23 (63.9)	12 (33.3)

[a] Patients treated with neoadjuvant chemoradiation therapy, neoadjuvant radiation therapy with delayed endoscopic/surgical therapy or unknown time from incidence to endoscopic/surgical therapy or those classified as pTx were excluded

DISCUSSION

In this large nationwide study, we investigated the trends in incidence and treatment of clinically staged T1 rectal cancer in the Netherlands between 2005 and 2018. The absolute number of patients with cT1 rectal cancer more than tripled over this time period, from 540 patients in 2005-2009 to 1643 patients in 2015-2018. Furthermore, there was a significant increase in the use of LE and concurrently, a significant decrease in the use of neoadjuvant therapy and TME surgery for patients with clinical node negative T1 tumours.

In the Netherlands, an organized (not opportunistic) national screening program for colorectal cancer, coordinated by the National Institute of Public Health and Environment (RIVM) with biennial faecal immunochemical tests followed by a colonoscopy when positive, was gradually implemented in 2014 for all adults aged 55 to 75 years. In the years 2014-2018, approximately 76% of the invited people responded to the invitation. [20] Although the screening program caused a steep increase of cT1 rectal tumours, an increasing incidence was already observed before the actual start of the program. Pilot studies performed in densely populated areas in the Netherlands prior to this screening might be an explanation for this increasing incidence as well as an increasing awareness and improvements in diagnostic modalities.

Most patients were diagnosed without suspected nodal disease and thus potential candidates for LE (without NAT). Over time, in clinically node negative patients, the use of LE has gained ground. This is supported by recent literature increasingly recommending LE as an attractive alternative to TME surgery due to less procedure-related morbidity and mortality. [4-6, 8-10, 12] For patients with low risk pT1N0/x rectal cancer, organ preservation is the preferred approach in the Dutch colorectal cancer guidelines. However, the ideal endoscopic or transanal technique for such tumours is still debated as there is a clear lack of high-quality comparative studies.[21] The current study found that most patients with cT1N0/x rectal cancer who underwent LE received a form of endoscopic resection (~60%), and over a time a slight increase in endoscopic resections was observed.

Organ preservation strategies are also more commonly used in higher stages of rectal cancer in several ongoing clinical trials.[22] The current study observed that patients with cT1N1/2 rectal cancer were most frequently treated with TME, but a shift was observed in type of TME. Namely, a significant decrease of primary TME was observed and a significant increase in cTME. This finding may be partially explained by patients entering ongoing clinical trials on organ preservation strategies. Other reasons may be patient's choice or doctor's preference which are influenced by treatment related morbidity and oncologic control. Of note, the numbers in these analyses were very small.

Simultaneous to the increase in LE, the use of (unjustified) NAT in clinical node negative patients decreased. However, in 2005-2009 still 27% of the patients with cT1N0/x received NAT (predominantly radiation therapy). We presume this relatively high number of patients

can be partly explained by results from the Dutch prospective randomized TME trial published in 2001. In this trial a significant lower risk of recurrence was observed in patients treated with short-course radiation therapy followed by TME versus TME alone. This led to an increase of radiation therapy in all rectal cancer patients, including early-stage rectal cancer. Later, it became evident that patients with early rectal cancer without nodal involvement do not benefit from short-course radiation therapy and therefore surgery alone was proposed in the Dutch colorectal cancer guidelines as standard approach.[23] This led to a significant decrease in radiation therapy over time in these early rectal cancer patients.

If a suspected T1 rectal cancer proves to be a T2 or more invasive carcinoma after LE, cTME is recommended, leading to similar oncological results as primary TME surgery.[24]

In the present study, the proportion of cTME has significantly decreased over time for patients with clinical node negative disease. This might indicate that patient selection has improved, due to more accurate pre-operative staging. Another explanation might be the growing role for a rectal preserving strategy, in which high-risk pT1 and pT2 rectal carcinomas are subject of several studies. In those patients, adjuvant chemoradiotherapy is given as an alternative to cTME.[25] Although this strategy is not yet evidence based, this might contribute to the lower proportion of patients in whom cTME is performed. However, in earlier studies it was also found that fewer patients than expected were subject to cTME, possibly explained by patients and/or doctors' preference.[19] Whether these strategies achieve similar outcomes as compared to cTME, should be looked at with caution, and only be offered within clinical trials.[15, 26]

In the current study, clinical staging of pT1 tumours was accurate in 77%, which increased to 81% when only cN0/x patients were selected. Over the years, diagnostic accuracy for detection of pT1 tumours improved in patients clinically staged cT1N0/x, from 67% in 2005-2009 to 86% in the period from 2015 until 2018. This major improvement is likely caused by the implementation of high resolution MRI, enabling a more accurate preoperative assessment of the location of the tumour and locoregional disease extent.[27] Nonetheless, nodal staging in rectal cancer remains challenging as has been described in a previous study with data of the NCR.[26] This study reported that during the interval of our study period, clinical nodal staging was insufficient due to limitations in the capacity of MRI in detecting lymph node metastases and recommendations in the Dutch guidelines on criteria used for establishing suspected lymph nodes e.g., >3mm in the first version of the guideline, >5mm in the second version and the addition of morphological features in the revised version in 2014.

The use of preoperative MRI in rectal cancer is mandatory since 2011 in the Netherlands and is used in >95% of all rectal cancer patients.[17] More accurate tumour staging might (partially) explain the reduction in cTME procedures over time during the study period. Interestingly, correct diagnosis of pT1 was significantly worse in patients who had suspected positive lymph nodes as 45% of the patients had a higher pathological T stage (compared

with 18% in cN0/x patients). This may have a biological explanation, as higher tumour stages harbour a greater metastatic potential (i.e. 6-14% for T1 tumours, 17-23% for T2 tumours and 49-66% for T3 tumours).[28, 29] Although operator-dependent, endorectal ultrasound (ERUS) is an accurate method to preoperatively stage rectal cancers, especially early rectal cancers.[30] Three-dimensional ERUS may further improve staging accuracy.[31]

A small number of patients (27 out of 2613, 1%) revealed pT0 at histopathological examination after surgery. One of the possible explanations might be that the tumour was removed at biopsy and final results showed no tumour remnant. A pathological complete response after radiation therapy might be another explanation. As is reported previously, the rate of pathological complete response after short-course radiation therapy followed by early surgery is low (1.7% in the pre-planned interim analysis of the Stockholm III trial).[32] Unfortunately, our database does not contain exact dates of initiated neoadjuvant therapy, only date of primary diagnosis and date of surgery. Therefore, we choose a time period of 8 weeks from date of diagnosis to date of surgery, as this will have excluded most patients with reasonable potential for downstaging (e.g., those with short-course radiation therapy but delayed surgery after 4-8 weeks), but we cannot dispute that few patients with downstaging have been included.

Although this is an extensive and large nationwide study of 3033 patients with cT1 rectal cancer who have been treated over a time period of 14 years, this study has some limitations. First, diagnostic procedures, standards of care and follow-up strategies have changed over the course of time. Unfortunately, data on specific diagnostic modalities used throughout the study period is not available in the NCR. Therefore, possible relevant information on the various imaging modalities is lacking. Secondly, in the database of the NCR no specific tumour characteristics were registered for the total study population. Consequently, differentiation between low risk and high risk T1 rectal cancer could not be performed. This is valuable information, as the absence of lymphatic invasion, budding, submucosal invasion ≥ 1 mm, and poor histological differentiation are each associated with low risk of lymph node metastases.[28] Thirdly, no information regarding the performance status of patients was available for the total study population (e.g. preoperative Charlson Comorbidity Index or ASA classification). In addition, data on quality of life is also lacking. The current study did not focus on survival outcomes. This was previously addressed by our study group.[24] Finally, there is no consensus on the specified time interval for when to still define additional surgery as ‘completion surgery’ or when to define it as ‘salvage surgery’.[33] A 6-month cut-off has been described previously.[18, 19] This time period will most likely include all ‘completion surgeries’, but on the other hand may also include some patients with an early recurrence who by definition received ‘salvage surgery’.

CONCLUSION

The current study shows an increase in the incidence of cT1 rectal cancer throughout the years, and a concurrent increase in the use of LE was observed in clinical node negative patients. In addition, neoadjuvant therapy was prescribed less often for these patients, which is in line with national guidelines. Finally, pathological confirmation of pT1 rectal carcinomas increased throughout the years but was significantly higher in clinical node negative patients compared to clinical node positive patients, stressing the need for optimal preoperative staging.

REFERENCES

1. Brouwer NPM, Heil TC, Olde Rikkert MGM, Lemmens V, Rutten HJT, de Wilt JHW, 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 Jul;116:1-9. PubMed PMID: 31163335. Epub 2019/06/05.
2. Borowski DW, Bradburn DM, Mills SJ, Bharathan B, Wilson RG, Ratcliffe AA, et al. Volume-outcome analysis of colorectal cancer-related outcomes. Br J Surg. 2010 Sep;97(9):1416-30. PubMed PMID: 20632311. Epub 2010/07/16.
3. Paun BC, Cassie S, MacLean AR, Dixon E, Buie WD. Postoperative complications following surgery for rectal cancer. Ann Surg. 2010 May;251(5):807-18. PubMed PMID: 20395841. Epub 2010/04/17.
4. Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005 Oct;242(4):472-7; discussion 7-9. PubMed PMID: 16192807. Pubmed Central PMCID: PMC1402341. Epub 2005/09/30.
5. Bhangu A, Brown G, Nicholls RJ, Wong J, Darzi A, Tekkis P. Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg. 2013 Oct;258(4):563-9; discussion 9-71. PubMed PMID: 23979270. Epub 2013/08/28.
6. Peng J, Chen W, Sheng W, Xu Y, Cai G, Huang D, et al. Oncological outcome of T1 rectal cancer undergoing standard resection and local excision. Colorectal Dis. 2011 Feb;13(2):e14-9. PubMed PMID: 20860716. Epub 2010/09/24.
7. Plummer JM, Leake PA, Albert MR. Recent advances in the management of rectal cancer: No surgery, minimal surgery or minimally invasive surgery. World J Gastrointest Surg. 2017 Jun 27;9(6):139-48. PubMed PMID: 28690773. Pubmed Central PMCID: PMC5483413. Epub 2017/07/12.
8. Christoforidis D, Cho HM, Dixon MR, Mellgren AF, Madoff RD, Finne CO. Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer. Ann Surg. 2009 May;249(5):776-82. PubMed PMID: 19387326. Epub 2009/04/24.
9. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009 Dec;35(12):1280-5. PubMed PMID: 19487099. Epub 2009/06/03.
10. Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. Dis Colon Rectum. 2005 Feb;48(2):270-84. PubMed PMID: 15711865. Epub 2005/02/16.
11. Wittekind CGF, Hutter RVP, Klimpfinger M, Sobin LH. TNM Atlas; Illustrated Guide to the TNM Classification of Malignant Tumours. Chichester, United Kingdom: John Wiley And Sons Ltd; 2004.
12. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg. 2007 May;245(5):726-33. PubMed PMID: 17457165. Pubmed Central PMCID: PMC1877081. Epub 2007/04/26.
13. Verseveld M, de Graaf EJ, Verhoef C, van Meerten E, Punt CJ, de Hingh IH, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). Br J Surg. 2015 Jun;102(7):853-60. PubMed PMID: 25847025. Epub 2015/04/08.
14. Rahbari NN, Ulrich AB, Bruckner T, Munter M, Nickles A, Contin P, et al. Surgery for locally recurrent rectal cancer in the era of total mesorectal excision: is there still a chance for cure? Ann Surg. 2011 Mar;253(3):522-33. PubMed PMID: 21209587. Epub 2011/01/07.

15. Weiser MR, Landmann RG, Wong WD, Shia J, Guillem JG, Temple LK, et al. Surgical salvage of recurrent rectal cancer after transanal excision. Dis Colon Rectum. 2005 Jun;48(6):1169-75. PubMed PMID: 15793645. Epub 2005/03/29.
16. Brouwer NPM, Bos A, Lemmens V, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 2018 Dec 1;143(11):2758-66. PubMed PMID: 30095162. Pubmed Central PMCID: PMC6282554. Epub 2018/08/11.
17. Bokkerink GM, Buijs EF, de Ruijter W, Rosman C, Sietses C, Strobel R, et al. Improved quality of care for patients undergoing an abdominoperineal excision for rectal cancer. Eur J Surg Oncol. 2015 Feb;41(2):201-7. PubMed PMID: 25572974. Epub 2015/01/13.
18. Hershman MJ, Sun Myint A. Salvage surgery after inadequate combined local treatment for early rectal cancer. Clin Oncol (R Coll Radiol). 2007 Nov;19(9):720-3. PubMed PMID: 17826968. Epub 2007/09/11.
19. van Groningen JT, van Hagen P, Tollenaar R, Tuynman JB, de Mheen PJM, Doornebosch PG, et al. Evaluation of a Completion Total Mesorectal Excision in Patients After Local Excision of Rectal Cancer: A Word of Caution. J Natl Compr Canc Netw. 2018 Jul;16(7):822-8. PubMed PMID: 30006424. Epub 2018/07/15.
20. Cardoso R, Guo F, Heisser T, Hackl M, Ihle P, De Schutter H, et al. Colorectal cancer incidence, mortality, and stage distribution in European countries in the colorectal cancer screening era: an international population-based study. Lancet Oncol. 2021 Jul;22(7):1002-13. PubMed PMID: 34048685. Epub 2021/05/29.
21. Carrier G, Rouanet P. Transanal Surgery for benign tumor or early rectal cancer: state of the art and future prospects of the surgeon. Annals of Laparoscopic and Endoscopic Surgery. 2020;6.
22. Stijns RCH, Tromp MR, Hugen N, de Wilt JHW. Advances in organ preserving strategies in rectal cancer patients. Eur J Surg Oncol. 2018 Feb;44(2):209-19. PubMed PMID: 29275912. Epub 2017/12/26.
23. Ferenschild FT, Dawson I, de Graaf EJ, de Wilt JH, Tetteroo GW. Preoperative radiotherapy has no value for patients with T2-3, N0 adenocarcinomas of the rectum. Dig Surg. 2009;26(4):291-6. PubMed PMID: 19590212. Epub 2009/07/11.
24. Verseveld M, de Wilt JHW, Elferink MAG, de Graaf EJR, Verhoef C, Pouwels S, et al. Survival after local excision for rectal cancer: a population-based overview of clinical practice and outcome. Acta Oncol. 2019 Aug;58(8):1163-6. PubMed PMID: 31106636. Epub 2019/05/21.
25. Borstlap WA, Tanis PJ, Koedam TW, Marijnen CA, Cunningham C, Dekker E, et al. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer. BMC Cancer. 2016 Jul 21;16:513. PubMed PMID: 27439975. Pubmed Central PMCID: PMC4955121. Epub 2016/07/22.
26. Garcia-Aguilar J, Mellgren A, Sirivongs P, Buie D, Madoff RD, Rothenberger DA. Local excision of rectal cancer without adjuvant therapy: a word of caution. Ann Surg. 2000 Mar;231(3):345-51. PubMed PMID: 10714627. Pubmed Central PMCID: PMC1421005. Epub 2000/03/14.
27. Group MS. Diagnostic accuracy of preoperative magnetic resonance imaging in predicting curative resection of rectal cancer: prospective observational study. BMJ. 2006 Oct 14;333(7572):779. PubMed PMID: 16984925. Pubmed Central PMCID: PMC1602032. Epub 2006/09/21.
28. Bosch SL, Nagtegaal ID. Predicting lymph node metastases in pT1 rectal cancer. Recent Results Cancer Res. 2014;203:15-21. PubMed PMID: 25102995.
29. Ricciardi R, Madoff RD, Rothenberger DA, Baxter NN. Population-based analyses of lymph node metastases in colorectal cancer. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1522-7. PubMed PMID: 16979956. Epub 2006/09/19.

30. Boot J, Gomez-Munoz F, Beets-Tan RGH. Imaging of rectal cancer. Radiologe. 2019 Dec;59(Suppl 1):46-50. PubMed PMID: 31616956. Pubmed Central PMCID: PMC6914711. Epub 2019/10/17. Bildgebung des Rektumkarzinoms.
31. Schaffzin DM, Wong WD. Endorectal ultrasound in the preoperative evaluation of rectal cancer. Clin Colorectal Cancer. 2004 Jul;4(2):124-32. PubMed PMID: 15285819. Epub 2004/08/03.
32. Pettersson D, Lorinc E, Holm T, Iversen H, Cedermark B, Glimelius B, et al. Tumour regression in the randomized Stockholm III Trial of radiotherapy regimens for rectal cancer. Br J Surg. 2015 Jul;102(8):972-8; discussion 8. PubMed PMID: 26095256. Pubmed Central PMCID: PMC4744683. Epub 2015/06/23.
33. Jones HJS, Cunningham C, Nicholson GA, Hompes R. Outcomes following completion and salvage surgery for early rectal cancer: A systematic review. Eur J Surg Oncol. 2018 Jan;44(1):15-23. PubMed PMID: 29174708. Epub 2017/11/28.

Chapter 5

Survival after local excision for rectal cancer; a population-based overview of clinical practice and outcome

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INTRODUCTION

Rectal cancer (RC) is diagnosed in approximately 4200 patients annually in the Netherlands and its incidence is gradually increasing.[1] With the introduction of population-level colorectal cancer screening programs, the rate of patients in whom curative treatment is possible is expected to further increase.[1] The cornerstone of curative treatment for rectal cancer is total mesorectal excision (TME).[2] The high-quality oncological clearance of the tumour and regional lymph nodes must however be balanced against the risk of postoperative morbidity and mortality.[3] Because of the adverse effects of major abdominal surgery, local excision (LE) of rectal cancer may be an attractive alternative. Besides LE according to Parks, newer techniques such as Transanal Endoscopic Microsurgery (TEM), Transanal Minimally Invasive Surgery (TAMIS, using single port platforms) and Transanal Endoscopic Operations (TEO) have been introduced.

Initially used as a means to treat frail patients, LE proved to be oncologically safe in selected T1 rectal carcinomas and is now considered standard therapy.[4-7] However, LE for pT2 or more invasive carcinomas lead to unacceptable high local recurrence rates, with significant decrease in survival rates as compared to TME.[8, 9] Therefore, the possible risks involved with LE only in ≥ pT2 rectal cancer patients where curation is intended should be taken into account.[8]

Several studies have addressed the increase in LE for rectal cancers, yet, few studies report long-term follow-up data specified on this approach.[10-12] In this nationwide study we investigated the number of patients who underwent LE or primary TME only, and whether there was an increase in time. We studied the results of LE only for all T-stages and compared these results to the results of completion TME (cTME) following LE and primary TME surgery (without either neoadjuvant or adjuvant therapy) in terms of relative survival.

MATERIALS AND METHODS

Data were extracted from the Netherlands Cancer Registry (NCR), a nationwide population-based registry including all newly diagnosed malignancies. Main sources of notification are the automated pathology archive (PALGA) and the Hospital Discharge Register (HDR). NCR data on patient characteristics, tumour characteristics and treatment are collected from hospital patient files by specially trained registration clerks and coded according to a national manual. Topography and morphology are coded according to the International Classification of Diseases for Oncology (ICD-O) and stage according to the TNM classification.[13, 14] Data quality is high and completeness is estimated to be at least 95%.

Patient Selection

We selected patients with rectal and rectosigmoid cancer, diagnosed between 2005 and 2015. Three groups were selected; Group 1) patients who were treated with LE only; Group 2) patients in whom a completion TME (TME within 6 months of prior LE) was performed and Group 3) patients who were treated by primary TME.

The following inclusion criteria were applied to identify patients:

1) Adult patients (≥18 years) with adenocarcinoma; stage pT1 to pT4, clinical N0/x
2) Rectal or rectosigmoidal location (International Classification of Diseases for Oncology, third edition, codes: C199, C209)
3) No neo-adjuvant or adjuvant therapy
4) No metastatic disease

LE (TEM, TAE, TEO, TAMIS) and/or (c)TME including low anterior resection (LAR), Hartmann and abdominoperineal excision (APE)

The vital status of all patients was obtained by linking the NCR to the Municipal Personal Records Database. Follow-up was completed until January 31, 2017.

Statistical analysis

Continuous variables were presented as median ± range. Categorical variables were presented as frequency with percentages. Differences in patient and tumour characteristics between groups were tested using the $\chi 2$ test.

Relative survival (RS) was used as an estimation of disease-specific survival. It reflects survival of cancer patients, adjusted for survival of the general population with the same age and gender distributions. RS is calculated as the ratio of the observed rates for cancer patients to the expected rates for the general population using the Ederer method.[15]

Five year overall survival (5y OS) was calculated as the percentage of patients alive at 5 years after the date of (first) surgery.

Follow-up time was calculated from the date of diagnosis to death or alive up to the last date of follow up. Values of $p<0.05$ were considered statistically significant. Statistical Package for Social Sciences (SPSS, Chicago, IL, USA Version 25.0) was used to prepare the database and for statistical analysis. Relative survival was analysed in STATA (version 14.2).

RESULTS

According to the NCR, 46.877 patients were diagnosed with rectal and rectosigmoidal cancer between 2005 and 2015. In 1090 patients a LE was performed, of which 144 patients underwent a completion TME within 6 months after LE. Thus, in 946 patients LE was the only treatment for rectal cancer. In addition, a total of 5101 patients with cT1-4N0/x were identified in whom a primary TME only was performed.

Patient and tumour characteristics for all three groups (LE ***only***, LE followed by cTME and primary TME) are given in table 1. In the completion TME group the patients were significantly younger than in the LE only and primary TME group (***p<0.001***). There is a marked increase in the number of patients who underwent LE and primary TME over the years.

Table 1: Patient and tumour characteristics

	LE only	**LE followed by cTME**	**Primary TME**	**P-value**
N	946	144	5101	
Male: female	570(60.3%): 376(39.9%)	81(56.3%): 63 (43.8%)	3073(60.2%): 2029(39.8%)	*NS*
Age, median (range)	71 (35-95)	68 (30-89)	72 (20-99)	***P<0.001****
Year incidence, (n)				
2005	53	7	498	
2006	53	10	542	
2007	74	5	488	
2008	67	9	389	
2009	66	5	317	
2010	64	6	253	
2011	66	8	265	
2012	95	9	261	
2013	90	13	267	
2014	147	26	833	
2015	171	46	988	
Pathological T stage				
pT1	753 (79.6%)	37 (25.7%)	770 (15.1%)	
pT2	167 (17.7%)	78 (54.2%)	1832 (35.9%)	
pT3	26 (2.7%)	28 (19.4%)	2315 (45.4%)	
pT4	-	1 (0.7%)	184 (3.6%)	
Pathological N stage				
pN0	61 (6.4%)	117 (81.3%)	3945 (77.3%)	
pN1	4 (0.4%)	18 (12.5 %)	786 (15.5%)	
pN2	-	1 (0.7%)	283 (5.5%)	
pNx	881 (93.1%)	8 (5.6%)	87 (1.7%)	

Table 1: Patient and tumour characteristics (*continued*)

	LE only	LE followed by cTME	Primary TME	P-value
Residual tumour				
R0	771 (81.1%)	141 (97.9%)	4812 (94.3%)	
R1	57 (6.0%)	2 (1.4%)	123 (2.4%)	
R2	6 (0.6%)	-	48 (0.9%)	
Rx	112 (11.8%)	1 (0.7%)	119 (2.3%)	
Follow up in months, median (range)	43 (0 – 145)	33 (0 – 142)	35 (0 – 145)	

Abbreviations: LE = Local excision; cTME = completion Total Mesorectal Excision; TME = Total Mesorectal Excision; IQR = Inter Quartile Range; NS = not significant

*Patients in the LE group and primary TME group significantly older than in cTME group

In 790 patients following LE a pT1 rectal carcinoma was diagnosed. In 37 patients a cTME was performed. In those patients 5 had a poorly differentiated tumour, 1 patient had an unclear margin (Rx) but for the remaining 31 patients rationale for cTME could not be obtained from the database.

In 300 patients following LE a pT2 or more invasive cancer (pT3/4) was diagnosed. In 193 patients a cTME was omitted. In this group age was significantly higher compared to those patients in whom a cTME was performed (77 versus 68 years, ***p<0.001***).

Five years relative survival rates for pT1 rectal cancer were comparable for all procedures (Table 2). For pT2 tumours OS was significantly worse in those patient were LE was the only procedure (60% versus 80.1% (***p<0.001***) in cTME and 75.4% (***p<0.001***) in TME patients, however RS was comparable for all procedures. Only RS was worse for pT3-4 patients (Table 2).

Table 2: Differences in 5-year ***relative*** survival between patients, who underwent LE only versus patients who underwent completion surgery (cTME) or primary TME, split by pathological T-stage

	LE only		cTME		TME	
	N	**5y RS (95% CI)**	**N**	**5y RS (95% CI)**	**N**	**5y RS (95% CI)**
pT1	753	93.4 (88.7-97.5)	37	85.1 (60.5-98.8)	770	95.0 (90.4-98.9)
pT2	167	88.2 (73.9-100.43)	78	89.5 (70.8-100.33)	1832	92.9 (89.8-95.8)
pT3-4	26	20.4 (3.7-51.2)	29	73.4 (32.3-96.2)	2499	74.9 (72.0-77.7)

Abbreviations: LE = Local excision; cTME = completion Total Mesorectal Excision; TME = (primary) Total Mesorectal Excision; 5Y RS = 5 Year Relative Survival; CI = confidence interval

DISCUSSION

This retrospective nationwide data analysis shows that LE only for early staged (pT1-2) rectal cancer without neoadjuvant treatment is an acceptable and oncological safe treatment with 5-year relative survival rates comparable to TME surgery. Patients who underwent completion TME (cTME) had similar survival to both LE and TME only pT1-2 patients.[16] In contrast, relative survival after LE ***only*** in ≥pT3 invasive rectal cancer is worse compared to patients who underwent primary or completion TME.

Similar as in the present study, a previous study from the United States also showed an increase in LE as treatment for pT1 rectal cancer, but also for more invasive tumours. [10] Especially in the elderly population an increase in LE was observed, which is probably due to the fact that surgical morbidity after standard TME surgery is not insignificant and a reason for exploring less extensive treatment methods.[8, 17]

The present study demonstrates that overall survival is significantly worse in patients treated with LE ***only*** in case of pT2 rectal cancer compared to (c)TME. However, when relative survival was calculated, survival was similar to patients who underwent cTME or TME only. This is different from previous studies were only overall survival was usually presented. [18-20] Relative survival has the advantage of correcting for the expected survival of the population and since patients who underwent a LE population were elderly, this might have contributed to the good relative survival. [21] Patients in whom a (c)TME was omitted were significantly older in this study; it is very plausible that these patients are also more fragile. Presumably, with increasing age, increased burden of comorbidities and perioperative surgical morbidity might also contribute to the decision to withdraw from cTME. Unfortunately, this study is lacking exact data why patients did not undergo (c)TME.

In high-risk pT1 rectal cancer (tumour >3cm, poor differentiation, tumour budding, lymph and vascular invasion) local recurrences occur more often, which is a reason to perform cTME in pT1 tumours.[5, 22, 23] Unfortunately, information on these histopathological risk factors is insufficient or lacking in the NCR database. Differentiation between high or low risk T1 cancer could therefore, not be established. Especially in the decision making process with patients with early rectal cancer, these histopathological criteria are crucial in adequate patient selection for rectum preserving options. In the present study 37 patients with a pT1 tumour underwent cTME, possibly due to having a high-risk pT1 tumour. Importantly, relative survival in this presumed high-risk pT1 tumours treated with cTME was equal those with a primary TME or LE.

Moreover, histological prognostic features for lymph node metastases such as lymph-angio invasion, tumour budding, size of the tumour, submucosal invasion and other prognostic factors [23] were not reported in the NCR. It should therefore be emphasized that this study does not unambiguously demonstrate that pT2 rectal cancer can generally

be treated safely with LE. But apparently in the Netherlands the decision not to perform completion TME in pT1 and pT2 cancers did not lead to a decrease in relative survival.

In the present study there also was a marked increase in the number of patients who underwent primary TME without neo-adjuvant treatment. This is probably due to improvement of pre-operative imaging using MRI and to adjustment of the guidelines in the Netherlands in which short course radiotherapy was no longer advised in clinically node negative patients from 2012.[24, 25] The implementation of a nationwide screening program for colorectal cancer is another reason for the relatively steep increase in 2014 and 2015.[17, 26]

Several authors reported worsened outcome following cTME after prior LE.[27, 28] Concern is raised whether completion TME gives equal quality of the TME specimen, compared to primary TME.[27] In the present study cTME did not lead to different relative survival compared to primary TME for all pT stages. It should be taken into account that cTME was only performed in 144 patients, which is a relatively small group. Moreover, surgical difficulty and impairment of quality of life are known factors

With the increasing interest in organ preserving treatment for patients with rectal cancer, outcome of each local treatment option has to be investigated, and compared to standard TME surgery. Besides functional outcome and impact on quality of life, oncological outcome is of utmost importance in rectal cancer treatment. The present study shows that relative survival is worse in patients with pT3 or pT4 tumours. Thriving to refrain from radical surgery other treatment algorithms are current subject of studies. The TESAR trial is a study for patients who underwent a local excision, and final pathology reveals a high-risk pT1 or low-risk pT2 cancer. Eligible patient are subsequently randomized between adjuvant chemoradiotherapy or cTME.[29] Whether this adjuvant treatment strategy will lead to better outcome has to be awaited.

Although the present study is a large and nationwide representation of daily practice in the Netherlands, it has some limitations. First of all, the NCR has no data on local recurrence and only overall survival data are presented. Especially in patients who underwent local excision data on local intraluminal and nodal recurrences are important but could not be retrieved from the database. Also data on histopathological factors, co-morbidity or frailty is not available in the NCR, as mentioned previously. Lastly, data on reasons why patients did not undergo cTME is not available, making it possible that certain biases play a role in the results described in this study.

In conclusion, over the years an increase is seen in LE only and primary TME for rectal cancer in the Netherlands. LE only seems an oncological safe treatment option for patients with pT1 and pT2 tumours with similar long-term results to TME surgery. Since long-term relative survival is compromised after LE in case ≥ pT3 tumours, cTME should always be recommended in order to obtain overall survival results similar to primary TME surgery.

REFERENCES

1. Brouwer NPM, Bos A, Lemmens V, Tanis PJ, Hugen N, Nagtegaal ID, et al. An overview of 25 years of incidence, treatment and outcome of colorectal cancer patients. Int J Cancer. 2018 Dec 1;143(11):2758-66. PubMed PMID: 30095162. Pubmed Central PMCID: PMC6282554. Epub 2018/08/11.
2. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug 30;345(9):638-46. PubMed PMID: 11547717. Epub 2001/09/08.
3. Khoo CK, Vickery CJ, Forsyth N, Vinall NS, Eyre-Brook IA. A prospective randomized controlled trial of multimodal perioperative management protocol in patients undergoing elective colorectal resection for cancer. Ann Surg. 2007 Jun;245(6):867-72. PubMed PMID: 17522511. Pubmed Central PMCID: PMC1876970. Epub 2007/05/25.
4. Christoforidis D, Cho HM, Dixon MR, Mellgren AF, Madoff RD, Finne CO. Transanal endoscopic microsurgery versus conventional transanal excision for patients with early rectal cancer. Ann Surg. 2009 May;249(5):776-82. PubMed PMID: 19387326. Epub 2009/04/24.
5. Doornebosch PG, Zeestraten E, de Graaf EJ, Hermsen P, Dawson I, Tollenaar RA, et al. Transanal endoscopic microsurgery for T1 rectal cancer: size matters! Surg Endosc. 2012 Feb;26(2):551-7. PubMed PMID: 21993932.
6. Middleton PF, Sutherland LM, Maddern GJ. Transanal endoscopic microsurgery: a systematic review. Dis Colon Rectum. 2005 Feb;48(2):270-84. PubMed PMID: 15711865. Epub 2005/02/16.
7. Moore JS, Cataldo PA, Osler T, Hyman NH. Transanal endoscopic microsurgery is more effective than traditional transanal excision for resection of rectal masses. Dis Colon Rectum. 2008 Jul;51(7):1026-30; discussion 30-1. PubMed PMID: 18481147. Epub 2008/05/16. eng.
8. Leijtens JWA, Koedam TWA, Borstlap WAA, Maas M, Doornebosch PG, Karsten TM, et al. Transanal Endoscopic Microsurgery with or without Completion Total Mesorectal Excision for T2 and T3 Rectal Carcinoma. Dig Surg. 2019;36(1):76-82. PubMed PMID: 29791891. Pubmed Central PMCID: PMC6390444. Epub 2018/05/24.
9. Xu ZS, Cheng H, Xiao Y, Cao JQ, Cheng F, Xu WJ, et al. Comparison of transanal endoscopic microsurgery with or without neoadjuvant therapy and standard total mesorectal excision in the treatment of clinical T2 low rectal cancer: a meta-analysis. Oncotarget. 2017 Dec 29;8(70):115681-90. PubMed PMID: 29383191. Pubmed Central PMCID: PMC5777803.
10. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg. 2007 May;245(5):726-33. PubMed PMID: 17457165. Pubmed Central PMCID: PMC1877081. Epub 2007/04/26.
11. Bleday R, Breen E, Jessup JM, Burgess A, Sentovich SM, Steele G, Jr. Prospective evaluation of local excision for small rectal cancers. Diseases of the colon and rectum. 1997 Apr;40(4):388-92. PubMed PMID: 9106685. Epub 1997/04/01. eng.
12. Steele GD, Jr., Herndon JE, Bleday R, Russell A, Benson A, 3rd, Hussain M, et al. Sphincter-sparing treatment for distal rectal adenocarcinoma. Annals of surgical oncology. 1999 Jul-Aug;6(5):433-41. PubMed PMID: 10458680. Epub 1999/08/24. eng.
13. Fritz A PC, Jack A, et al. International classification of diseases for oncology. Third. Geneva: WHO; 2000. .
14. Wittekind C GF, Hutter RVP, Klimpfinger M, Sobin LH, editors. . TNM Atlas. Fifth. 2004.

15. Ederer F HF. Instructions to IBM 650 Programmers in Processing Survival Computations. Bethesda MD: National Cancer Institute. 1959.
16. Martijn H, Voogd AC, van de Poll-Franse LV, Repelaer van Driel OJ, Rutten HJ, Coebergh JW, et al. Improved survival of patients with rectal cancer since 1980: a population-based study. Eur J Cancer. 2003 Sep;39(14):2073-9. PubMed PMID: 12957462. Epub 2003/09/06. Eng.
17. Stijns RCH, Tromp MR, Hugen N, de Wilt JHW. Advances in organ preserving strategies in rectal cancer patients. Eur J Surg Oncol. 2018 Feb;44(2):209-19. PubMed PMID: 29275912. Epub 2017/12/26.
18. Bentrem DJ, Okabe S, Wong WD, Guillem JG, Weiser MR, Temple LK, et al. T1 adenocarcinoma of the rectum: transanal excision or radical surgery? Ann Surg. 2005 Oct;242(4):472-7; discussion 7-9. PubMed PMID: 16192807. Pubmed Central PMCID: PMC1402341. Epub 2005/09/30.
19. Bhangu A, Brown G, Nicholls RJ, Wong J, Darzi A, Tekkis P. Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg. 2013 Oct;258(4):563-9; discussion 9-71. PubMed PMID: 23979270. Epub 2013/08/28.
20. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009 Dec;35(12):1280-5. PubMed PMID: 19487099. Epub 2009/06/03.
21. Mariotto AB, Noone AM, Howlader N, Cho H, Keel GE, Garshell J, et al. Cancer survival: an overview of measures, uses, and interpretation. Journal of the National Cancer Institute Monographs. 2014 Nov;2014(49):145-86. PubMed PMID: 25417231. Pubmed Central PMCID: PMC4829054. Epub 2014/11/25. eng.
22. Bosch SL, Nagtegaal ID. What is "good quality" in rectal cancer surgery? The pathologist's perspective. Recent Results Cancer Res. 2014;203:41-6. PubMed PMID: 25102998.
23. Bosch SL, Teerenstra S, de Wilt JH, Cunningham C, Nagtegaal ID. Predicting lymph node metastasis in pT1 colorectal cancer: a systematic review of risk factors providing rationale for therapy decisions. Endoscopy. 2013 Oct;45(10):827-34. PubMed PMID: 23884793. Epub 2013/07/26.
24. Al-Sukhni E, Milot L, Fruitman M, Beyene J, Victor JC, Schmocker S, et al. Diagnostic accuracy of MRI for assessment of T category, lymph node metastases, and circumferential resection margin involvement in patients with rectal cancer: a systematic review and meta-analysis. Ann Surg Oncol. 2012 Jul;19(7):2212-23. PubMed PMID: 22271205.
25. Bokkerink GM, Buijs EF, de Ruijter W, Rosman C, Sietses C, Strobel R, et al. Improved quality of care for patients undergoing an abdominoperineal excision for rectal cancer. European journal of surgical oncology : the journal of the European Society of Surgical Oncology and the British Association of Surgical Oncology. 2015 Feb;41(2):201-7. PubMed PMID: 25572974. Epub 2015/01/13.
26. de Neree Tot Babberich MPM, Vermeer NCA, Wouters M, van Grevenstein WMU, Peeters K, Dekker E, et al. Postoperative Outcomes of Screen-Detected vs Non-Screen-Detected Colorectal Cancer in the Netherlands. JAMA Surg. 2018 Dec 1;153(12):e183567. PubMed PMID: 30285063. Epub 2018/10/05.
27. Hompes R, McDonald R, Buskens C, Lindsey I, Armitage N, Hill J, et al. Completion surgery following transanal endoscopic microsurgery: assessment of quality and short- and long-term outcome. Colorectal Dis. 2013;15(10):e576-81. PubMed PMID: 24635913. Epub 2014/03/19.
28. Morino M, Allaix ME, Arolfo S, Arezzo A. Previous transanal endoscopic microsurgery for rectal cancer represents a risk factor for an increased abdominoperineal resection rate. Surg Endosc. 2013 Sep;27(9):3315-21. PubMed PMID: 23479257. Epub 2013/03/13.

29. Borstlap WA, Tanis PJ, Koedam TW, Marijnen CA, Cunningham C, Dekker E, et al. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer. BMC Cancer. 2016 Jul 21;16:513. PubMed PMID: 27439975. Pubmed Central PMCID: PMC4955121. Epub 2016/07/22.

Chapter 6

Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study)

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ABSTRACT

Background

This prospective multicentre study was performed to quantify the number of patients with minimal residual disease (ypT0–1) after neoadjuvant chemoradiotherapy and transanal endoscopic microsurgery (TEM) for rectal cancer.

Methods

Patients with clinically staged T1–3N0 distal rectal cancer were treated with long-course chemoradiotherapy. Clinical response was evaluated 6–8 weeks later and TEM performed. Total mesorectal excision was advocated in patients with residual disease (ypT2 or more).

Results

The clinical stage was cT1N0 in ten patients, cT2N0 in 29 and cT3N0 in 16 patients. Chemoradiotherapy-related complications of at least grade 3 occurred in 23 of 55 patients, with two deaths from toxicity, and two patients did not have TEM or major surgery. Among 47 patients who had TEM, ypT0–1 disease was found in 30, ypT0N1 in one, ypT2 in 15 and ypT3 in one. Local recurrence developed in three of the nine patients with ypT2 tumours who declined further surgery. Postoperative complications grade I–IIIb occurred in 13 of 47 patients after TEM and in five of 12 after (completion) surgery. After a median follow-up of 17 months, four local recurrences had developed overall, three in patients with ypT2 and one with ypT1 disease.

Conclusion

TEM after chemoradiotherapy enabled organ preservation in one-half of the patients with rectal cancer.

INTRODUCTION

Major surgery for early rectal cancer patients leads to high cure rates, low local recurrence rates, but a high postoperative mortality risk with significant morbidity.[1-3] Therefore, other treatment regimens have been explored to avoid radical surgery.[4] After chemoradiotherapy a complete pathological response of the primary tumour is reported in 8–24 per cent of the patients. This concept has led to treatment of early rectal cancer with no surgery at all.[5, 6] However, a clinical complete response does not always correspond with a pathological complete response (pCR).[7-9] As a consequence, local excision after neoadjuvant therapy can be used to assess pathological response accurately.[10-14]

Transanal endoscopic microsurgery (TEM) is a local excision technique that is a valid alternative to radical surgery for early rectal cancer, such as well selected T1 rectal cancers.[15-18] It is also considered an option for patients who are unsuitable for major surgery because of co-morbidity or selected patients who require an abdominoperineal excision (APE) but refuse a colostomy.[19] Unfortunately, local excision alone leads to higher rates of local recurrence of up to 33 per cent and survival may be compromised compared with that after radical surgery.[19, 20] An important reason for local failures in rectal cancer is locoregional lymph node metastasis.[21, 22] This prospective multicentre feasibility study was performed in patients with early clinically node-negative rectal cancer (cT1–3 N0) to determine the number of patients with minimal residual disease (ypT0–1) after neoadjuvant 5-fluorouracil-based chemoradiotherapy.

METHODS

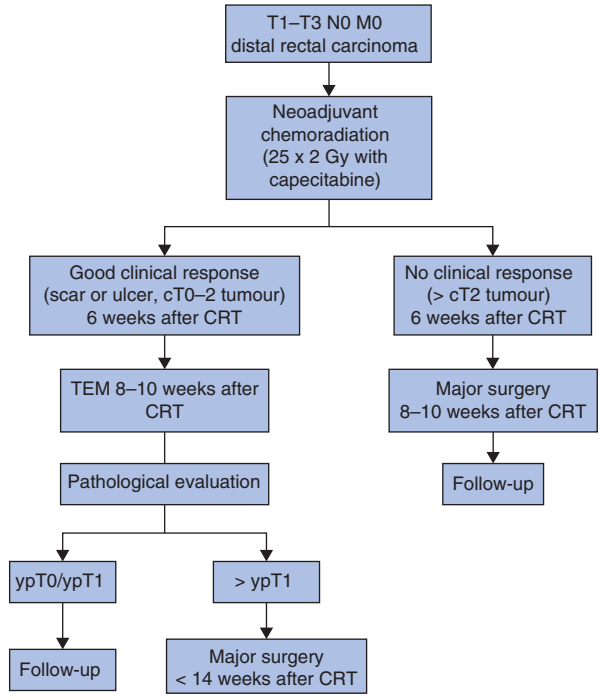
This non-randomized feasibility trial was designed to determine whether long-course chemoradiotherapy followed by TEM is an oncologically acceptable rectum-preserving treatment in early distal rectal cancer (***Fig. 1***). The CARTS study was initiated by the Dutch Colorectal Cancer Group and is registered at clinicaltrials. gov (NCT01273051). The medical ethics committee of Radboud University Nijmegen Medical Centre approved the study protocol.

Patients were included in 12 hospitals from December 2010 to August 2012, and considered eligible when they met the following inclusion criteria: distal adenocarcinoma of the rectum within 10 cm of the anal verge, staged as cT1–3N0M0, requiring treatment with APE or low anterior resection (LAR) with coloanal anastomosis, and age over 18 years. Rigid rectoscopy was used to determine the height of the tumour, and MRI for tumour and nodal status. Exclusion criteria were: low-risk T1 tumour (smaller than 3 cm, no signs of lymphangioinvasion); tumour ineligible for TEM (circular or intra-anal lesion); pre-existing faecal incontinence (unless soiling due to tumour); synchronous tumours; presence of

mesorectal lymph nodes larger than 5mm on short axis on MRI, CT and/or endorectal ultrasonography (ERUS); and contraindications to capecitabine use.[23] All patients were analysed prospectively with the usual investigations according to the Dutch guidelines for rectal cancer treatment, and tumours were staged according to the fifth edition of the American Joint Committee on Cancer criteria.[24, 25] In addition to MRI and CT, digital rectal examination (DRE), rectoscopy and ERUS were performed by the TEM surgeon to reassess the tumour and its eligibility, and to mark the exact location of the tumour.

Marking was done with multiple clips or tattoo ensuring correct excision of the original tumour area in the event of a (near) complete response after CRT. If considered eligible, patients were included after informed consent had been obtained. Six weeks after ending CRT, the effect of the therapy was evaluated by DRE, rectoscopy, ERUS and MRI.

Fig. 1 Flow chart for the CARTS study.



CRT, chemoradiotherapy; TEM, transanal endoscopic microsurgery

Neoadjuvant chemoradiation therapy

A total dose of 50Gy was given in 25 fractions of 2Gy, or 50·4Gy in 28 fractions of 1·8Gy, combined with capecitabine 825 mg/m^2 twice daily. The clinical target volume consisted of the tumour with mesorectal fat, internal iliac, obturator and presacral nodes. The upper field border was at the level of the promontory. Intensity-modulated radiotherapy or

three-dimensional conformal radiotherapy was mandatory. The National Cancer Institute Common Toxicity Criteria version 3.0 was used to score the toxicity of CRT.[26]

Surgery

Patients with a significant downsizing of the tumour (ycT0–2) underwent TEM 8–10 weeks after the last fraction of radiotherapy. After histological examination of the resected TEM specimen, all patients with a ypT2–3 tumour were to undergo completion total mesorectal excision within 4–6 weeks after TEM.

Patients who did not respond to CRT, or had an inadequate response, and had at least a cT3 tumour (more than ycT2) were to have major resection 8–10 weeks after the last fraction of radiotherapy. Postoperative complications were scored according to the Dindo–Demartines–Clavien classification.[27]

Transanal endoscopic microsurgery

TEM was done by colorectal surgeons with extensive experience in this procedure and who had been trained by one of the principal investigators of the study. TEM was performed by the conventional technique described by Buess and colleagues.[28] The aim was to achieve full-thickness bowel wall removal, including the original tumour bed, and closure of the bowel wall was preferred. The specimen was pinned on cork, fixed in formalin and sent to the pathologist according to a standard protocol.[16]

Total mesorectal excision

Mesorectal excision was carried out in either open or laparoscopically assisted procedures. Depending on tumour size and distance to the anal verge, LAR with colorectal or coloanal anastomosis or an APE could be performed.

Pathology

Microscopic evaluation of the specimen was undertaken using a standard protocol. After fixation for at least 48 h, the deep (lateral) resection margin was inked, and the specimen was sliced as thinly as possible (preferably 3–4 mm). Following inspection and photographic documentation, representative areas of the tumour were sampled, with a minimum of five samples, including the area of deepest tumour invasion. Microscopic evaluation of the specimen was performed, including invasion depth, differentiation grade and presence of lymphangioinvasion. Special attention was given to the resectionmargins;margins over 2mm were defined as oncologically safe in TEM. To assess the completeness of response (absence of vital tumour cells in the specimen), five tumour blocks were sampled initially. If no vital tumour was found, the whole area was blocked; if there was still none present, three levels were cut to exclude vital tumour.

Follow-up

For patients being observed after TEM surgery (ypT0–1), intensive follow-up was mandatory for early detection of possible local recurrence and distant metastases. In the first 2 years after surgery, carcinoembryonic antigen (CEA) levels were measured every 3 months, and rectal examination including DRE, rectoscopy and ERUS was performed. MRI of the pelvis, and CT of the thorax and abdomen were required every 6 months. After 2 years, CEA, DRE, rectoscopy and ERUS were undertaken every 6 months, and MRI of the pelvis and CT of the thorax and abdomen every 12 months.

Statistical analysis

The present study aimed to demonstrate the feasibility of this technique and was considered successful if 30 per cent or more of the included patients completed CRT and underwent TEM with complete resection of a ypT0–1 tumour. The study required a total of 55 patients. A three-step model for clinical trials was used for calculating patient numbers, with an α and β of 0·1.[29] Evaluation was carried out after the first 20 patients, of whom three had to complete the protocol successfully. After 33 patients, six had to be treated successfully to continue the study to completion. If this had not been achieved, the study would have been stopped.

RESULTS

Demographic and tumour characteristics for 55 patients included in the study are shown in ***Table 1***. The tumour could not be visualized on MRI in three patients, and the T category was determined by ERUS (2 cT1, 1 cT2). Five patients, initially staged as N0 at inclusion by the referring hospital, were scored as having node-positive status (all N1) after re-evaluation of the MRI, but these patients had already entered the study and were not excluded as they were initially thought eligible.

Table 1 Demographic and tumour characteristics

	No of patients* (*n*= 55)
Age (years)†	64 (39-82)
Sex ratio (M : F)	3·4 (3·0-5·0) 30 : 25
Tumour size (cm)‡	
Clinical tumour category cT1	10
cT2	29
cT3	16
Clinical node category cN0	50
cN1	5
Distance from anal verge (cm)‡	3·5 (2·0–6·0)

*Unless indicated otherwise; values are †median (range) and ‡median (i.q.r.).

Toxicity of chemoradiotherapy

Two patients died during neoadjuvant therapy, one from sepsis and one from possible arrhythmia. Post-mortem examination was declined. Two more patients were not able to complete the course of neoadjuvant therapy owing to toxicity. In total, 49 patients (89 per cent) received the complete dose of chemotherapy and radiotherapy in accordance with the protocol. Chemotherapy had to be reduced in two patients owing to gastrointestinal complications and hand–foot syndrome. Overall, 23 patients (42 per cent) developed at least grade 3 toxicity (***Table 2***).

Table 2 Adverse events during chemoradiotherapy

	Grade 3	Grade 4	Grade 5
Cardiac (arrhythmia)	2	0	0
Constitutional	6	0	0
Dermatological	1	0	0
Gastrointestinal	19	1	1
Genitourinary	2	0	0
Infectious	1	0	1
Pain	5	0	0
Total	36	1	2

A total of 39 grade 3–5 complications were experienced by 23 patients.

Surgical and pathological data

Four patients did not undergo surgical treatment. In three patients this was due to severe chemoradiotherapy-related toxicity (as described previously) and one was lost to follow-up.

Transanal endoscopic microsurgery

Of the remaining 51 patients, 47 had sufficient clinical downsizing (ycT0–2) and proceeded to TEM (***Fig. 2***). Pathological examination revealed ypT0–1 disease in 30 patients (21 ypT0, 9 ypT1). Resection margins were negative in all these patients, implying that the primary endpoint had been met in 30 (55 per cent) of 55 patients.

Primary major surgery

Four patients had a limited response to chemoradiotherapy, of whom three had LAR and one APE (***Fig. 2***, ***Table 3***). Pathology results showed ypT1N0 in two patients and ypT2N1 in the other two.

Fig. 2 Flow chart summarizing treatments received. CRT, chemoradiotherapy; TEM, transanal endoscopic microsurgery

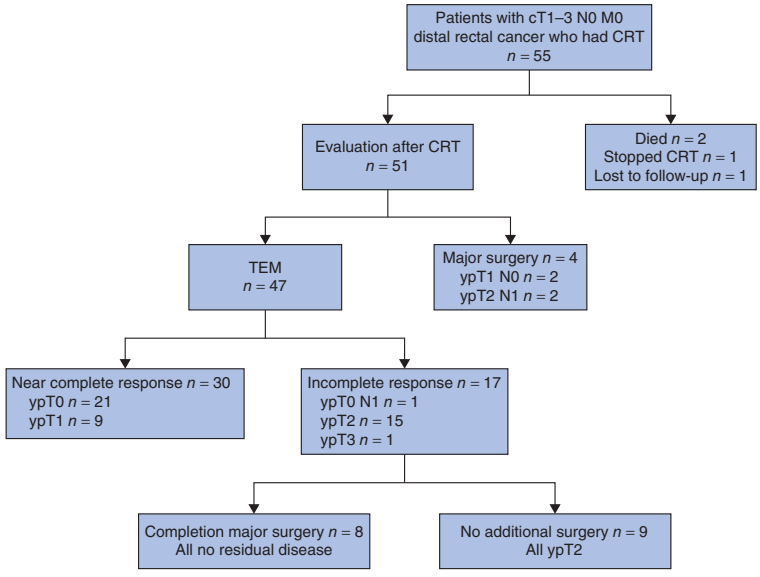


Table 3 Type of surgery performed in patients with an inadequate clinical response to chemoradiotherapy, an inadequate pathological response, or local recurrence

	No.of patients	Abdominoperineal excision	Low anterior resection
Primary surgery*	4	1	3
Completion surgery†	8	6	2
Surgery for local recurrence	3	3	0

*Patients with more than ycT2N0 disease after chemoradiotherapy; †patients with an inadequate pathological response (more than ypT0–1N0).

Completion major surgery

Seventeen patients were diagnosed with a ypT2–3 tumour or nodal involvement (1 ypT0N1, 15 ypT2, 1 ypT3) after TEM. Eight of these patients underwent additional major surgery (2 LAR, 6 APE). Perforation of the APE specimen occurred in one patient. Residual disease was not found in any of the specimens. The other nine patients did not undergo major surgery, even though they were advised that recurrence could develop and radical surgery was recommended by the protocol.

Perioperative complications

Fifty-one patients underwent surgery, of whom 13 of 47 in the TEM group and five of 12 in the major surgery group developed postoperative complications (***Table 4***).Two of the four patients treated primarily with major surgery developed a postoperative complication, and three of the eight patients in whom a completion resection was performed.

Table 4 Postoperative complications according to the Dindo–Demartines–Clavien classification

	TEM (*n*= 47)	Major surgery (*n*= 4)	Completion surgery (*n*= 8)
Grade I	4	0	2
Grade II	4	2	0
Grade IIIa	1	0	0
Grade IIIb	4*	0	1
Grade IV–V	0	0	0
Total	13	2	3

*One rectovaginal fistula requiring colostomy, one haemorrhage requiring reoperation, two presacral abcesses requiring stoma. TEM, transanal endoscopic microsurgery.

Early local and systemic recurrences

Median follow-up of whole cohort was 17 (i.q.r. 12–22) months. Three patients with a ypT2 tumour after TEM who refused further surgery developed a local recurrence within 1 year of follow-up. Two of these patients (including 1 with systemic metastases) underwent salvage APE. The patient without metastases was disease-free after a follow-up of

16 months. Of the nine patients with a ypT1 tumour after TEM, one developed a local recurrence after 9 months, had an APE, and remained disease-free at 22 months. None of the 21 patients with a ypT0 tumour after TEM developed a local recurrence.

The five patients with clinically node-positive disease were all treated by TEM after chemoradiotherapy. None has developed local or systemic recurrence so far (median follow-up 19 months).

DISCUSSION

This prospective multicentre study evaluated the response to chemoradiotherapy for distal rectal cancer using TEM for pathological evaluation and rectum-preserving surgery. Using a three-step model, the aim was to achieve a (near) complete response rate of more than 30 per cent, and this was exceeded. The introduction of standardized surgery in recent decades has significantly improved outcomes of patients with rectal cancer.[30] Not only did long-term survival improve, but the 5-year local recurrence rate decreased from 45 per cent to less than 10 per cent.[31, 32] Approximately 16 per cent of patients with locally advanced disease experience a pCR to long-course chemoradiotherapy.[6] Several studies have investigated organ-sparing techniques including TEM. Pioneering work was done in 1994, reporting a 38 per cent pCR rate in patients with T1–3 distal rectal cancers treated with radiation and local excision.[33] Subsequent studies10, reporting pCR rates ranging from 30 to 73 per cent forT2 and T3 tumours, were limited by their small size, varying chemoradiotherapy regimens and heterogeneous populations.[34-40] TEM after long-course neoadjuvant radiotherapy may be a worthy equivalent to (laparoscopic) mesorectal excision in selected patients with early distal rectal cancer.[41]

The first prospective multicentre trial (American College of Surgeons Oncology Group (ACOSOG) Z6041 study)11 included patients with cT1–2N0 disease for chemoradiotherapy, including oxaliplatin. Organ-sparing treatment was demonstrated to be feasible in 66 per cent of patients, similar to the proportion in the present study (55 per cent). Comparable results were achieved in a recent study, with rectum-preserving therapy in 68 per cent of patients with initial cT2–3N0–1 tumours.[42]

In the present study, TEM was used for accurate assessment of pathological response in case of a complete clinical response after chemoradiotherapy. Accurate prediction of response using imaging diagnostics and/or clinical evaluation remains challenging and biopsies of the original tumour bed are known to be unreliable.[14] It is not known whether TEM is sufficient for a pathological response to be established fully, as only the rectal wall is excised and mesorectal lymph nodes are left ***in situ***. A systematic review demonstrated that 2–27 per cent of ypT0 tumours harbour disease in the mesorectal lymph nodes (ypN+), suggesting that this might be a relevant issue.[43] Chemoradiotherapy-related toxicity is

a concern when treating patients with early rectal cancer. Two patients died in this study. Mortality data on chemoradiotherapy are scarce, but are reported to be below 1 per cent. [44] Four deaths (5·2 per cent) were reported in the EXPERT trial, owing to toxicity from neoadjuvant chemotherapy.[45] The EXPERT-C trial also reported two deaths (1·2 per cent) resulting from the toxicity of neoadjuvant treatment.[46] In the present study, the target volumes may have been relatively large for these small tumours. Nowadays, the authors would at least advise lowering the upper border.[47]

However, given that the target volumes were similar to those for locally advanced rectal cancer, similar morbidity was expected.

Another issue of concern is postoperative toxicity after TEM in patients receiving chemoradiation therapy. Here, the overall postoperative complication rate after primary TEM following chemoradiotherapy was 28 per cent (13 of 47). In similar studies11,42 complication rates varied between 27 and 54 per cent. If TEM is used for rectal cancer without neoadjuvant therapy, complication rates are much lower, between 5·3 and 23 per cent48,49. Although the present study included a relatively small number of patients, local recurrence after TEM was observed after a short median follow-up of 17 months. This is consistent with the results for ypT2 disease in other studies.[10, 42, 43, 47-49] Major excision is recommended for these patients, although several declined this extra operation in the present study. One of the drawbacks of a rectum-preserving approach using chemoradiotherapy is the overtreatment of patients needing completion surgery. These patients may be exposed to additional morbidity of chemoradiotherapy and TEM. A prospective randomized trial is planned to compare neoadjuvant therapy followed by a rectum-preserving policy (TEM or watchful waiting) with standard major surgery (total mesorectal excision) without neoadjuvant radiotherapy.

COLLABORATORS

Other members of the CARTS study group are: P. J. Tanis (Academic Medical Centre, Amsterdam), G.M. J. Bökkerink (Radboud University Medical Centre, Nijmegen), H. Rütten (Catherina Hospital, Eindhoven), P. G. Doornebosch (IJsselland Hospital, Capelle aan den Ijssel), E. J. Derksen (SlotervaartHospital, Amsterdam), R. S. Dwarkasing (Erasmus Medical Centre, Rotterdam), A. Cats (Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam), R. A. E.M. Tollenaar (Leiden University Medical Centre, Leiden), H. J. T. Rutten (Radboud University Medical Centre, Nijmegen), J. W. A. Leijtens (Laurentius Hospital, Roermond), G. P. van der Schelling (Amphia Hospital, Breda), A. J. ten Tije (AmphiaHospital, Breda),G. Lammering (Maastro Clinic, Maastricht), G. L. Beets (Maastricht University Medical Center, Maastricht), T. J. Aufenacker (Rijnstate Hospital, Arnhem), A. Pronk (Diakonessen Hospital, Utrecht), E. R. Manusama (Medical Centre Leeuwarden, Leeu-

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REFERENCES

1. Kim NK, Aahn TW, Park JK, Lee KY, Lee WH, Sohn SK, et al. Assessment of sexual and voiding function after total mesorectal excision with pelvic autonomic nerve preservation in males with rectal cancer. Dis Colon Rectum. 2002 Sep;45(9):1178-85. PubMed PMID: 12352233. Epub 2002/09/28.
2. 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 May;9(5):494-501. PubMed PMID: 18452860. Epub 2008/05/03.
3. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, 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 Jun;12(6):575-82. PubMed PMID: 21596621. Epub 2011/05/21.
4. Smith FM, Waldron D, Winter DC. Rectum-conserving surgery in the era of chemoradiotherapy. Br J Surg. 2010 Dec;97(12):1752-64. PubMed PMID: 20845400. Epub 2010/09/17.
5. Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Bailao Aguilar P, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013 Oct;56(10):1109-17. PubMed PMID: 24022527. Epub 2013/09/12.
6. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, 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 Sep;11(9):835-44. PubMed PMID: 20692872. Epub 2010/08/10.
7. Glynne-Jones R, Hughes R. Critical appraisal of the 'wait and see' approach in rectal cancer for clinical complete responders after chemoradiation. Br J Surg. 2012 Jul;99(7):897-909. PubMed PMID: 22539154. Epub 2012/04/28.
8. Hiotis SP, Weber SM, Cohen AM, Minsky BD, Paty PB, Guillem JG, et al. Assessing the predictive value of clinical complete response to neoadjuvant therapy for rectal cancer: an analysis of 488 patients. J Am Coll Surg. 2002 Feb;194(2):131-5; discussion 5-6. PubMed PMID: 11848629. Epub 2002/02/19.
9. Zmora O, Dasilva GM, Gurland B, Pfeffer R, Koller M, Nogueras JJ, et al. Does rectal wall tumor eradication with preoperative chemoradiation permit a change in the operative strategy? Dis Colon Rectum. 2004 Oct;47(10):1607-12. PubMed PMID: 15540288. Epub 2004/11/13.
10. Borschitz T, Wachtlin D, Mohler M, Schmidberger H, Junginger T. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol. 2008 Mar;15(3):712-20. PubMed PMID: 18163173. Epub 2007/12/29.
11. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., Chan E, Cataldo P, Marcet J, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol. 2012 Feb;19(2):384-91. PubMed PMID: 21755378. Pubmed Central PMCID: PMC5720824. Epub 2011/07/15.
12. Marks J, Nassif G, Schoonyoung H, DeNittis A, Zeger E, Mohiuddin M, et al. Sphincter-sparing surgery for adenocarcinoma of the distal 3 cm of the true rectum: results after neoadjuvant therapy and minimally invasive radical surgery or local excision. Surg Endosc. 2013 Dec;27(12):4469-77. PubMed PMID: 24057070. Epub 2013/09/24.
13. Perez RO, Habr-Gama A, Lynn PB, Sao Juliao GP, Bianchi R, Proscurshim I, et al. Transanal endoscopic microsurgery for residual rectal cancer (ypT0-2) following neoadjuvant chemoradiation therapy: another word of caution. Dis Colon Rectum. 2013 Jan;56(1):6-13. PubMed PMID: 23222274. Epub 2012/12/12.

14. Smith FM, Chang KH, Sheahan K, Hyland J, O'Connell PR, Winter DC. The surgical significance of residual mucosal abnormalities in rectal cancer following neoadjuvant chemoradiotherapy. Br J Surg. 2012 Jul;99(7):993-1001. PubMed PMID: 22351592. Epub 2012/02/22.
15. Bhangu A, Brown G, Nicholls RJ, Wong J, Darzi A, Tekkis P. Survival outcome of local excision versus radical resection of colon or rectal carcinoma: a Surveillance, Epidemiology, and End Results (SEER) population-based study. Ann Surg. 2013 Oct;258(4):563-9; discussion 9-71. PubMed PMID: 23979270. Epub 2013/08/28.
16. de Graaf EJ, Doornebosch PG, Stassen LP, Debets JM, Tetteroo GW, Hop WC. Transanal endoscopic microsurgery for rectal cancer. Eur J Cancer. 2002 May;38(7):904-10. PubMed PMID: 11978515. Epub 2002/04/30.
17. Doornebosch PG, Tollenaar RA, De Graaf EJ. Is the increasing role of Transanal Endoscopic Microsurgery in curation for T1 rectal cancer justified? A systematic review. Acta Oncol. 2009;48(3):343-53. PubMed PMID: 18855161. Epub 2008/10/16.
18. You YN, Baxter NN, Stewart A, Nelson H. Is the increasing rate of local excision for stage I rectal cancer in the United States justified?: a nationwide cohort study from the National Cancer Database. Ann Surg. 2007 May;245(5):726-33. PubMed PMID: 17457165. Pubmed Central PMCID: PMC1877081. Epub 2007/04/26.
19. De Graaf EJ, Doornebosch PG, Tollenaar RA, Meershoek-Klein Kranenbarg E, de Boer AC, Bekkering FC, et al. Transanal endoscopic microsurgery versus total mesorectal excision of T1 rectal adenocarcinomas with curative intention. Eur J Surg Oncol. 2009 Dec;35(12):1280-5. PubMed PMID: 19487099. Epub 2009/06/03.
20. Heintz A, Morschel M, Junginger T. Comparison of results after transanal endoscopic microsurgery and radical resection for T1 carcinoma of the rectum. Surg Endosc. 1998 Sep;12(9):1145-8. PubMed PMID: 9716769. Epub 1998/08/26.
21. Bosch SL, Nagtegaal ID. Predicting lymph node metastases in pT1 rectal cancer. Recent Results Cancer Res. 2014;203:15-21. PubMed PMID: 25102995.
22. Langer C, Liersch T, Suss M, Siemer A, Markus P, Ghadimi BM, et al. Surgical cure for early rectal carcinoma and large adenoma: transanal endoscopic microsurgery (using ultrasound or electrosurgery) compared to conventional local and radical resection. Int J Colorectal Dis. 2003 May;18(3):222-9. PubMed PMID: 12673487. Epub 2003/04/04.
23. Bokkerink GM, de Graaf EJ, Punt CJ, Nagtegaal ID, Rutten H, Nuyttens JJ, et al. The CARTS study: Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery. BMC Surg. 2011 Dec 15;11:34. PubMed PMID: 22171697. Pubmed Central PMCID: PMC3295682. Epub 2011/12/17.
24. Dutch Clinical Guideline Colorectal Cancer. Comprehensive Cancer Centre the Netherlands, Oncoline, 2014. http://oncoline.nl/colorectaalcarcinoom (accessed May 2018). 2018.
25. Fleming ID CJ, Henson DE, Hutter RVP, Kennedy BJ, Murphy GP et al. AJCC Cancer Staging Manual (5th edn). Lippincott-Raven: Philadelphia, 1997.
26. (CTCAE). NCICTCfAEv. 2015.
27. Dindo D, Demartines N, Clavien PA. Classification of surgical complications: a new proposal with evaluation in a cohort of 6336 patients and results of a survey. Ann Surg. 2004 Aug;240(2):205-13. PubMed PMID: 15273542. Pubmed Central PMCID: PMC1360123. Epub 2004/07/27.
28. Buess G, Hutterer F, Theiss J, Bobel M, Isselhard W, Pichlmaier H. [A system for a transanal endoscopic rectum operation]. Chirurg. 1984 Oct;55(10):677-80. PubMed PMID: 6510078. Epub 1984/10/01. Das System fur die transanale endoskopische Rectumoperation.

29. Chen TT. Optimal three-stage designs for phase II cancer clinical trials. Stat Med. 1997 Dec 15;16(23):2701-11. PubMed PMID: 9421870. Epub 1998/01/09.
30. den Dulk M, Krijnen P, Marijnen CA, Rutten HJ, van de Poll-Franse LV, Putter H, 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 Aug;44(12):1710-6. PubMed PMID: 18573654. Epub 2008/06/25.
31. Kapiteijn E, Marijnen CA, Colenbrander AC, Klein Kranenbarg E, Steup WH, van Krieken JH, et al. Local recurrence in patients with rectal cancer diagnosed between 1988 and 1992: a population-based study in the west Netherlands. Eur J Surg Oncol. 1998 Dec;24(6):528-35. PubMed PMID: 9870729. Epub 1998/12/31.
32. Kapiteijn E, Marijnen CA, Nagtegaal ID, Putter H, Steup WH, Wiggers T, et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med. 2001 Aug 30;345(9):638-46. PubMed PMID: 11547717. Epub 2001/09/08.
33. Mohiuddin M, Marks G, Bannon J. High-dose preoperative radiation and full thickness local excision: a new option for selected T3 distal rectal cancers. Int J Radiat Oncol Biol Phys. 1994 Nov 15;30(4):845-9. PubMed PMID: 7960986. Epub 1994/11/15.
34. Bonnen M, Crane C, Vauthey JN, Skibber J, Delclos ME, Rodriguez-Bigas M, et al. Long-term results using local excision after preoperative chemoradiation among selected T3 rectal cancer patients. Int J Radiat Oncol Biol Phys. 2004 Nov 15;60(4):1098-105. PubMed PMID: 15519780. Epub 2004/11/03.
35. Kennelly RP, Heeney A, White A, Fennelly D, Sheahan K, Hyland JM, et al. A prospective analysis of patient outcome following treatment of T3 rectal cancer with neo-adjuvant chemoradiotherapy and transanal excision. Int J Colorectal Dis. 2012 Jun;27(6):759-64. PubMed PMID: 22173716. Epub 2011/12/17.
36. Kim CJ, Yeatman TJ, Coppola D, Trotti A, Williams B, Barthel JS, et al. Local excision of T2 and T3 rectal cancers after downstaging chemoradiation. Ann Surg. 2001 Sep;234(3):352-8; discussion 8-9. PubMed PMID: 11524588. Pubmed Central PMCID: PMC1422026. Epub 2001/08/29.
37. Lezoche G, Baldarelli M, Guerrieri M, Paganini AM, De Sanctis A, Bartolacci S, et al. A prospective randomized study with a 5-year minimum follow-up evaluation of transanal endoscopic microsurgery versus laparoscopic total mesorectal excision after neoadjuvant therapy. Surg Endosc. 2008 Feb;22(2):352-8. PubMed PMID: 17943364. Epub 2007/10/19.
38. Marks G, Mohiuddin MM, Masoni L, Pecchioli L. High-dose preoperative radiation and full-thickness local excision. A new option for patients with select cancers of the rectum. Dis Colon Rectum. 1990 Sep;33(9):735-9. PubMed PMID: 2390908. Epub 1990/09/01.
39. Ruo L, Guillem JG, Minsky BD, Quan SH, Paty PB, Cohen AM. Preoperative radiation with or without chemotherapy and full-thickness transanal excision for selected T2 and T3 distal rectal cancers. Int J Colorectal Dis. 2002 Jan;17(1):54-8. PubMed PMID: 12018456. Epub 2002/05/23.
40. Schell SR, Zlotecki RA, Mendenhall WM, Marsh RW, Vauthey JN, Copeland EM, 3rd. Transanal excision of locally advanced rectal cancers downstaged using neoadjuvant chemoradiotherapy. J Am Coll Surg. 2002 May;194(5):584-90; discussion 90-1. PubMed PMID: 12025835. Epub 2002/05/25.
41. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012 Sep;99(9):1211-8. PubMed PMID: 22864880. Epub 2012/08/07.
42. Pucciarelli S, De Paoli A, Guerrieri M, La Torre G, Maretto I, De Marchi F, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum. 2013 Dec;56(12):1349-56. PubMed PMID: 24201388. Epub 2013/11/10.

43. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg. 2012 Jul;99(7):918-28. PubMed PMID: 22362002. Epub 2012/03/01.
44. Swellengrebel HA, Marijnen CA, Verwaal VJ, Vincent A, Heuff G, Gerhards MF, et al. Toxicity and complications of preoperative chemoradiotherapy for locally advanced rectal cancer. Br J Surg. 2011 Mar;98(3):418-26. PubMed PMID: 21254020. Epub 2011/01/22.
45. Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, 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 Feb 1;24(4):668-74. PubMed PMID: 16446339. Epub 2006/02/01.
46. Dewdney A, Cunningham D, Tabernero J, Capdevila J, Glimelius B, Cervantes A, 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 May 10;30(14):1620-7. PubMed PMID: 22473163. Epub 2012/04/05.
47. Nijkamp J, de Haas-Kock DF, Beukema JC, Neelis KJ, Woutersen D, Ceha H, et al. Target volume delineation variation in radiotherapy for early stage rectal cancer in the Netherlands. Radiother Oncol. 2012 Jan;102(1):14-21. PubMed PMID: 21903287. Epub 2011/09/10.
48. Bujko K, Sopylo R, Kepka L. Local excision after radio(chemo)therapy for rectal cancer: is it safe? Clin Oncol (R Coll Radiol). 2007 Nov;19(9):693-700. PubMed PMID: 17766096. Epub 2007/09/04.
49. Burger JW, de Graaf EJ, Doornebosch PG, Grunhagen DJ, Biermann K, de Wilt JH, et al. Local excision of rectal cancer after chemoradiation: feasibility depends on the primary stage. Int J Colorectal Dis. 2010 Sep;25(9):1141-2. PubMed PMID: 20217420. Pubmed Central PMCID: PMC2912719. Epub 2010/03/11.

Chapter 7

The liver-first approach for locally advanced rectal cancer and synchronous liver metastases

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ABSTRACT

Introduction

Patients with locally advanced rectal cancer (LARC) and synchronous liver metastases (sRLM) can be treated according to the liver-first approach. This study aimed to evaluate prognostic factors for completing treatment and in how many patients extensive lower pelvic surgery might have been omitted.

Methods

Retrospective analysis of all patients with LARC and sRLM treated at the Erasmus MC Cancer Institute according to the liver-first between 2003 and 2016.

Results

In total 129 consecutive patients were included. In 90 patients (70%) the liver-first was completed. Ten patients had a (near) complete response (ypT0-1N0) of their primary tumour. In 36 out of 39 patients not completing the liver-first protocol palliative rectum resection was withheld. Optimal cutoffs for CEA level (53.15 µg/L), size (3.85 cm) and number (4) of RLMs were identified.

A preoperative CEA level above 53.15 µg/L was an independent predictor for non-completion of the liver-first protocol ($p = 0.005$).

Conclusion

Ten patients had a (near) complete response of their primary tumour and, in retrospect, rectum sparing therapies could have been considered. Together with 36 patient in whom palliative rectum resection was not necessary this entails that nearly 40% patients with LARC and sRLM might be spared major pelvic surgery if the liver-first approach is applied. A predictor (CEA) was found for noncompletion of the liver-first protocol. The majority of patients underwent resection of both primary tumour and hepatic metastasis with curative intent. These findings together entail that the liver-first approach may be considered in patients with LARC and sRLM.

INTRODUCTION

The liver-first approach - preoperative systemic chemotherapy followed by hepatic resection for colorectal liver metastases (CRLM) and resection of the primary tumour as last procedure was first described in 2006.[1] This approach was initially considered for patients with advanced CRLM and a "normal" colorectal carcinoma (e.g. not locally advanced) because extensive metastases could not be treated in one session with the primary tumour. During the same period, our centre advocated the liver first approach for patients with locally advanced rectal cancer (LARC) and synchronous rectal liver metastases (sRLM).[2-4]

Low pelvic surgery after chemoradiotherapy (CRTx) is associated with considerable post-operative complications. This is a reason to treat the sRLM first, because postoperative morbidity of hepatic resections is generally low and patients who then have progressive disease may be spared the high morbidity of low pelvic surgery. Currently, only general prognostic factors and risk scores, such as the Fong criteria, are available to predict whether treatment will be completed.[5] These criteria might not be sufficient for patients with LARC and sRLM.

The liver-first approach also gives a good chance of an optimal pre-treatment (i.e. CRTx) of the LARC, hereby maximising the chance of a (near) complete response. These patients could be treated with watchful waiting or other rectum sparing therapies and might only need extensive lower pelvic surgery in case of recurrence of disease.

The aim of the current study was twofold: to evaluate currently available prognostic factors in patients treated for LARC and sRLM according to the liver-first protocol and to evaluate in how many patients extensive lower pelvic surgery might have been omitted when treated according to this approach for LARC and sRLM.

MATERIAL AND METHODS

This is a retrospective analysis of a prospectively maintained patient database, consisting of all patients who underwent resection for RLM in a tertiary referral centre in the Netherlands. The database comprises of multiple perioperative and clinicopathological characteristics of both primary rectal cancer and RLM. The current study was approved by the medical ethics committee of the Erasmus University Medical Centre Rotterdam (MEC-2018-1031).

Patients and treatment approach

Since 2003 all patients presented at our centre with LARC and sRLM are treated according to the liver-first approach. All consecutive patients between 2003 and 2016 were included in the current study. LARC was defined as tumour >5 cm, expected distance of

<2mm to mesorectal fascia or ingrowth of adjacent organ (T4) on MRI or lymph node positive tumour meaning 1 lymph node >8mm or 4 lymph nodes > 5mm on CT scan or MRI. Patients described in previous publications by this group were also included in the study [2,4]. Treatment for all patients was assessed in a multidisciplinary team (MDT). After systemic treatment with chemotherapy radiological tumour response was assessed. If no disease-progression was observed, laparotomy and liver resection were performed first. After liver surgery, neoadjuvant (C)RTxwas administered after consultation again by the MDT. After finishing (C)RTx, patients were re-staged by CT Thorax/Abdomen and low pelvic MRI. Surgery of the primary tumour was performed as last stage. Surgery was planned 6-10 weeks after neoadjuvant (C)RTx.[6] Complications were categorised according to the Clavien-Dindo classification.[7]

Pre-operative chemotherapy

CT-scan of thorax and abdomen and CEA levels assessed the response to pre-operative chemotherapy after two or three cycles. Response was defined as decrease in tumour size and CEA levels. In patients scheduled for resection, the interval between the last course of chemotherapy and liver surgery was at least four weeks. Bevacizumab was excluded from the last course of chemotherapy to ensure that the interval between the last course of bevacizumab and surgery was at least six weeks.

Liver resection

The pathological response was categorised as complete response (CR) when no vital tumour cells were found, as partial response (PR) when both vital tumour cells and treatment effects were found and as stable disease (SD) when merely vital tumour cell and no treatment effect was observed.

Statistical analysis

Categorical data are presented as absolute numbers and percentages. Continuous data are presented as medians (and interquartile ranges (IQR)) or means (with standard deviations (SD)). Different proportions between groups were tested using the Chi-squared test. Medians were compared using the Mann- Whitney U test. The Kaplan-Meier method was used to estimate survival. Follow-up was estimated using the reverse Kaplan-Meier method. Overall survival (OS) was considered the time between the date of resection of the sRLM and the date of death. Patients were censored when alive at last follow-up date. Uni- and multivariable binary logistic regression analysis was performed to evaluate prognostic factors for the completion of the liver-first protocol and Odds Ratios (OR) for these factors were calculated. All variables with p-values below 0.05 on univariable analysis were included in the multivariable analysis. Receiver operating characteristic (ROC) analysis was

used to identify the optimal cut-off points of the continuous variables (preoperative CEA, number and size of sRLM).

The area under the curve (AUC) was used to determine the discriminatory performance of the logistic regression model. P values below 0.05 were considered significant. All analyses were performed using SPSS (SPSS version 24.0, Inc., IBM Corporation, Chicago, Ill., USA) and R version 3.5.1 (http://www.r-project.org).

RESULTS

There were 152 patients with LARC and sRLM treated at our centre during the study period. In principle, all patients with LARC and sRLM, who are referred to our centre are treated according to the liver-first protocol since 2003. However, over the years there have been some exceptions. We identified 23 patients with LARC and sRLM who were not treated according to the liver-first protocol. The reasons for these exceptions are listed in Fig. 1.

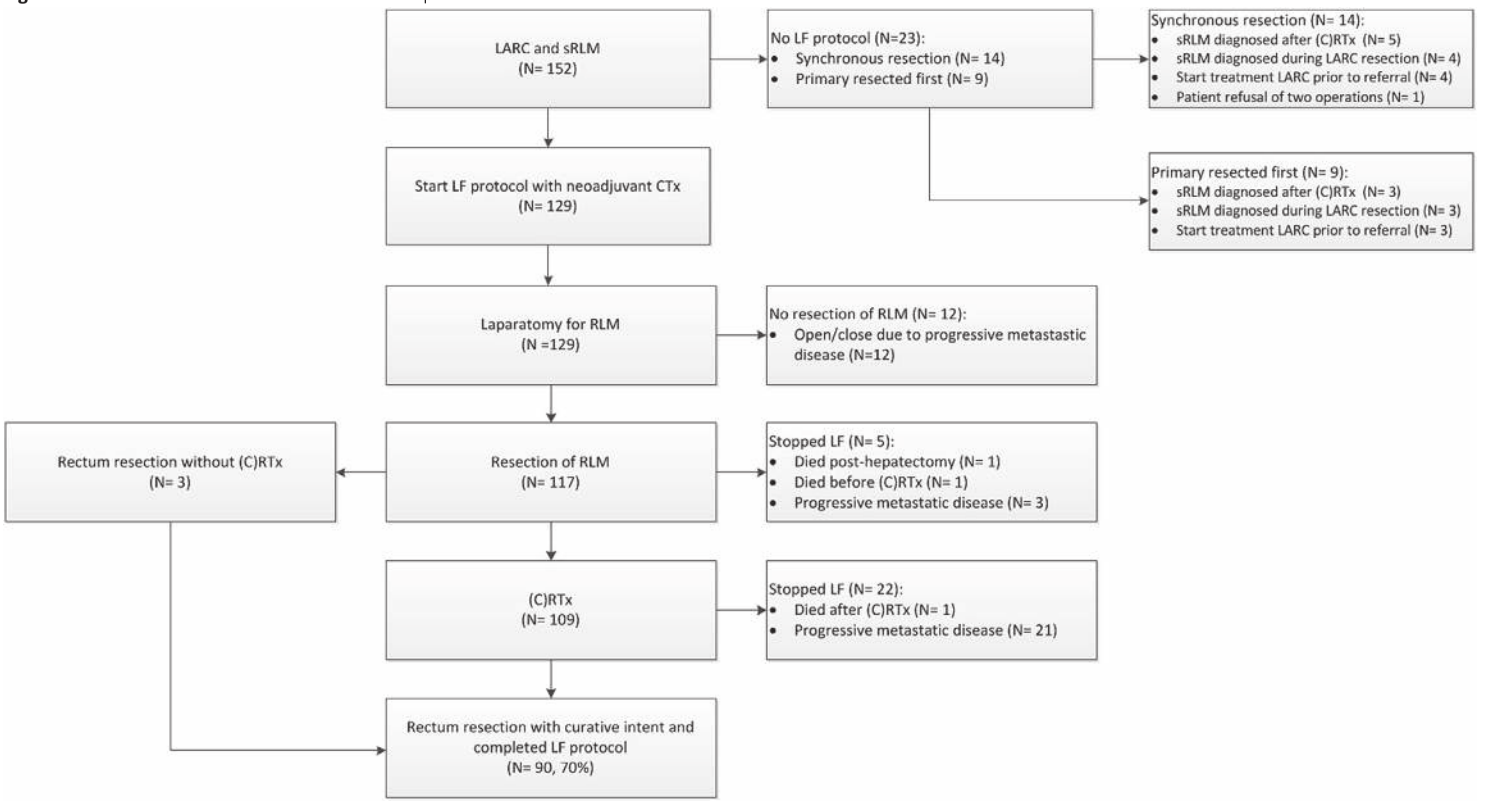
In total, 129 patients with LARC and sRLM were treated according to the liver-first protocol and included in the current study. Baseline characteristics are displayed in Table 1. A flowchart of the clinical course of these 129 patients is presented in Fig. 1.

Table 1
Preoperative baseline characteristics.

		Total (N = 129)	Completed LF (N = 90, 70%)	Not completed LF (N = 39, 30%)	P-value
Gender	Male	92 (71.3%)	69 (76.7%)	23 (59.0%)	0.041*
	Female	37 (28.7%)	21 (23.3%)	16 (41.0%)	
Age	Median (IQR)	62 (56–68)	63 (56–69)	62 (56–67)	0.565
ASA	ASA I-II	116 (89.9%)	78 (86.7%)	38 (97.4%)	0.062
	ASA > II	13 (10.1%)	12 (13.3%)	1 (2.6%)	
RLM characteristics					
Number of RLM	1 tumour	25 (19.4%)	17 (18.9%)	8 (20.5%)	0.830
	>1 tumour	104 (80.6%)	73 (81.1%)	31 (79.5%)	
Size of largest RLM	≤5 cm	106 (82.2%)	79 (87.8%)	27 (69.2%)	0.011*
	>5 cm	23 (17.8%)	11 (12.2%)	12 (30.8%)	
Preoperative CEA	≤200 μg/L	112 (91.1%)	81 (95.3%)	31 (81.6%)	0.014*
	>200 μg/L	11 (8.9%)	4 (4.7%)	7 (18.4%)	
	Missing	*6 patients*			
Bilobar metastasis	No	112 (91.1%)	81 (95.3%)	31 (81.6%)	0.018*
	Yes	11 (8.9%)	4 (4.7%)	7 (18.4%)	
EHD known preoperatively	No	110 (85.3%)	79 (87.8%)	31 (79.5%)	0.222
	Yes	19 (14.7%)	11 (12.2%)	8 (20.5%)	

LF = liver first protocol; IQR = interquartile range; ASA = American society of anaesthesiologists; Physical Status Classification System; RLM = rectal liver metastases; CEA = Carcinoembryonic antigen; EHD = extrahepatic disease; * = significant p-value.

Fig. 1. Flowchart of the clinical course of the 129 patients.



Pre-operative chemotherapy and response of the liver metastases

In accordance with the liver-first protocol, all 129 patients received pre-operative chemotherapy (median 4 cycles (IQR: 3-6)). Patients predominantly received capox (N=104, 81%). Other treatment regimens included folfox (N=13, 10%), folfiri (N=7, 8%), capecitabine (N=2, 2%), irinotecan (N=2, 2%) and folfirinox (N=1, 1%). Of one patient the type of chemotherapy was unknown. In 34 patients (26%) bevacizumab was added to the regimen. After chemotherapeutic treatment 5 patients (4%) had a complete radiological response, while 102 patients (79%) had responded partially and 20 patients (16%) had stable disease. Two patients (2%) had growth of their metastases despite systemic treatment, but were treated surgically nonetheless.

Surgical treatment and pathological response of the RLM

In total 117 of the 129 patients were treated surgically for RLM. In twelve patients (9%) RLMs were not resected due to intraoperatively discovered unexpected progression of metastatic disease. Of the 129 patients that underwent laparotomy for intended surgical treatment of sRLM 121 (94%) had no or only mild complications (Clavien-Dindo grade 0e2) and 8 patients (6%) had severe complications (Clavien-Dindo grade >2), of whom one patient (1%) died postoperatively. Histopathological evaluation of the liver tumours showed pathological PR in 84 patients (72%), CR in 12 patients (10%) and SD in 5 patients (5%). In 15 patients (13%) there was no pathological response evaluation available, due to treatment with ablative therapy only (N=5) or it was not reported in the pathology reports (N=10).

Rectal cancer

In 39 of the 129 patients (30%) the liver first protocol could not be completed. As stated, twelve patients did not undergo liver resection. In five patients sRLM were resected, but did not start with (C)RTx due to progressive metastatic disease or interim death. In the remaining 22 patients, 21 revealed progressive metastatic disease at restaging between liver and rectal surgery and one of them died before rectal surgery. In these 21 patients the median time between liver resection and restaging that revealed progressive metastatic disease was 3 months (IQR: 3.0-4.5). The treatment given regarding their primary tumour is displayed in Table 2. In 90 patients (70%) surgery of the rectum with curative intent was performed and the liver-first protocol was completed. Of these 90 patients, 78 (87%) did not experience any signs of obstruction that needed additional procedures. In eleven patients (12%) there was the need for a colostomy (5 prior to and 6 during the liver-first protocol) and in one patients (1%) a rectal stent was placed. Of the 90 patients that completed the treatment trajectory 77 (86%) had no or only mild complications (Clavien-Dindo grade 0-2) and 13 patients (14%) had severe complications (Clavien-Dindo grade >2), but no postoperative mortality was observed. Nine patients (10%) had a pathological complete response of the primary tumour and one patient had an ypT1N0 tumour.

Table 2
Treatment for primary tumour if not resected curatively.

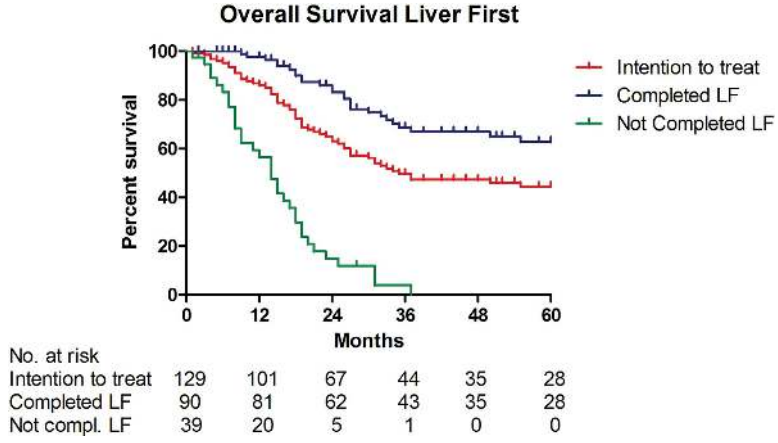
	N = 39 (%)
Palliative rectum resection	3 (7.7%)
Palliative (C)RTx and colostomy	9 (23.1%)
Colostomy	2 (5.1%)
Palliative (C)RTx	13 (33.3%)
Rectal stenting	1 (2.6%)
None or palliative CTx and/or pain medication only	10 (25.6%)
Died post hepatectomy	1 (2.6%)

(C)RTx = (chemo)radiotherapy; CTx = chemotherapy.

Follow-up and survival

Median follow-up of survivors was 58 months (IQR: (30-86 months)). Median OS of the complete intention to treat group was 35 months (IQR: 18-92 months). Median OS in the 90 patients that completed the liver-first protocol was not reached at five years. For the 39 patients that did not complete the liver-first protocol the median OS was 14 months (IQR: 8-19 months). The Kaplan-Meier curves are presented in Fig. 2.

Fig 2. Kaplan-Meier graphs for overall survival



Prognostic factors for non-completion of the liver-first protocol

No significant association between any of the tested variables and not completing the liver-first protocol was found. ROC analysis identified the optimal cut-offs for preoperative CEA (53.15 µg/L), size (3.85 cm) and number (4) of RLMs. The use of optimal cut-offs slightly improved performance of the logistic regression model, as the AUC increased from 0.699 to 0.713. The improved logistic regression model showed that patients with CEA levels above 53.15 µg/L have a higher odds for not-completion of the liver-first protocol (OR: 3.482; p = 0.005). Results of the logistic regression analyses are presented in Table 3. However, seventeen patients out of the 36 patients with a CEA level of >53.15 µg/L still completed the treatment sequence.

Table 3
Results of the logistic regression analyses.

Variables	Univariable		Multivariable	
	OR [95% CI]	P-value	OR [95% CI]	P-value
Uni- and multivariable binary logistic regression analysis for the non-completion of LF				
Male gender	0.438 [0.196–0.977]	0.044*	0.524 [0.216–1.271]	0.153
Age (cont.)	1.009 [0.971–1.048]	0.657		
ASA > II	0.171 [0.021–1.364]	0.096		
Number of RLM >1	0.902 [0.353–2.309]	0.830		
Size of metastasis >5 cm	3.192 [1.263–8.070]	0.014*	2.456 [0.917–6.578]	0.074
CEA > 200	4.573 [1.251–16.717]	0.022*	3.742 [0.968–14.464]	0.056
Bilobar RLM	1.883 [0.849–4.175]	0.120		
Pre-operative EHD	1.853 [0.681–5.043]	0.227		
Improved uni- and multivariable binary logistic regression analysis for the non-completion of LF				
Male gender	0.438 [0.196–0.977]	0.044*	0.481 [0.194–1.190]	0.113
Age (cont.)	1.009 [0.971–1.048]	0.657		
ASA > II	0.171 [0.021–1.364]	0.096		
Number of RLM >4	1.625 [0.751–3.518]	0.218		
Size of metastasis >3.85 cm	2.251 [1.021–4.962]	0.044*	1.470 [0.593–3.642]	0.405
CEA > 53.15	4.000 [1.746–9.162]	0.001*	3.482 [1.451–8.372]	0.005*
Bilobar RLM	1.883 [0.849–4.175]	0.120		
Pre-operative EHD	1.853 [0.681–5.043]	0.227		

LF = liver first protocol; OR = odds ratio; ASA = American society of anesthesiologists; CRLM = colorectal liver metastases; CEA = carcinoembryonic antigen; EHD = extra hepatic disease; * = significant p-value.

DISCUSSION

The current study presents the results of the largest series of patients treated for rectal cancer and sRLM according to the liverfirst protocol to date. New cut-off threshold for several wellknown risk factors that improve prognostication in patients with sRLM were identified. Most importantly, it demonstrated that in 92% (36 out of 39) of the patients not completing the liver-first protocol extensive pelvic surgery was eventually not necessary. Another ten patients had responded so well to the preoperative CTx and (C)RTx (ypT0N0 N=9 and ypT1N0 N=1) that rectum preservation could have been an option. This adds up to 36% (46 out of 129 patients) of the total group in whom omission of extensive rectal surgery could have been considered.

Patients with LARC and sRLM are at high risk of disease progression and futile extensive pelvic surgery. Therefore, the liver first approach could be the optimal approach in patients with sRLM, especially as it increases the possibilities for rectum sparing strategies. TAMIS or watchful waiting could be considered if a clinical (near) complete response is seen, as it is oncological safe to preserve the rectum in selected cases. However, should TAMIS be performed and if histopathology reveals a >ypT1N0 tumour, local and systemic recurrence is lurking and completing major excision is recommended.[8-14] Several studies have shown that pelvic surgery for rectal cancer is associated with high morbidity rates, resulting in long-term complications.[15, 16] However, in these studies stage IV patients are being disregarded. By applying the LF approach pre-eminently those patients are selected out who will not have any survival advantage from major surgery and can therefore be saved from this kind of surgery. Therefore, it is remarkable that nearly all attention for rectum sparing therapies goes out to patients with stage I and II (sometimes stage III) rectal cancer, since these patients experience relatively good oncological outcome and survival rates.[11, 13, 17, 18]

The majority (70%) of patients treated according to this protocol can be treated with curative intent. Similar results have been shown in multiple other studies.[1, 2, 4, 19] Recently, it was acknowledged by an intention-to-treat analysis, that no differences in completion rate between the classical approaches and the liver first approach are observed, showing that up to 35% of patients does not complete the full treatment trajectory irrespective of the chosen treatment approach.[20] In addition, no differences have been demonstrated in the literature between the three treatment sequences (liver-first, bowel-first or synchronous resection) in terms of OS, disease free survival or postoperative complication rates.[19, 21-25] However, no randomised controlled trial comparing the three sequences has been performed and therefore the currently available literature might subject to selection bias.

As stated, in this and other series describing the liver-first approach, approximately 30-40% of patients do not complete the full liver-first treatment protocol.[1, 2, 4, 19, 26] In order to define in which patients local treatment, rather than palliative chemotherapy is

desirable, this study evaluated prognostic factors for completion of the liver-first protocol. With regard to prognosis in patients with colorectal liver metastases several risk scores have been proposed, of which the Fong score is mostly utilized.[5, 27-29] The current study shows that the generally used risk factors have limited prognostic value for completion of the liver-first protocol, as the AUC only reached up to 0.699. When optimizing the cut-off values of continuous variables the AUC increases to 0.713, which still indicates only moderate discriminatory ability. In this study one significant prognostic variable with regard to completion of the protocol was found, namely CEA levels above 53.15 µg/L. This might be useful in counselling patients, yet cannot be used to withhold therapy according the liver first protocol as seventeen patients out of the 36 patients with a CEA level of >53.15 µg/L still completed the treatment sequence. No literature is available specifically describing prognostic factors for the noncompletion of the treatment sequence in patients treated for synchronous RLM, therefore external validation of the results of this study is warranted. Also further research is needed to identify new biomarkers that can improve patient stratification and selection before starting the liver-first protocol.

A proportion of incurable patients with the primary tumour in situ require additional surgical treatment nonetheless, due to obstruction, perforation or pain.[30, 31] In this study, three patients not completing the liver-first protocol ultimately underwent rectum excision. In addition, systemic chemotherapy induces rapid symptom relief in patients with high-risk rectal cancer.[32] This, combined with the fact that most patients in the current study did not need a surgical intervention, implies that it is relatively safe not to resect the primary rectal tumour. A recent systematic review and a meta-analysis comparing non-resection and resection in patients with unresectable stage IV CRC show similar complication and

symptom rates in both groups, which validates the currently obtained results.[30, 31] The systematic reviews failed to find a survival benefit.[30, 33] However, in contrast, a meta-analysis and a nationwide population-based study did.[31, 34] It seems as if there will only be certainty about whether or not the resection of the primary tumour is beneficial for overall survival in the case of unresectable metastases when the results of an ongoing randomised controlled trial (CAIRO 4) will be published.[35] Considering the fact that symptom rates are comparable between resected and non-resected patients and a survival benefit, if any, remains to be proven, the liver-first protocol is a reasonable approach in patients with synchronous RLM and rectal cancer.

This study has several limitations that should be acknowledged. This is a retrospective analysis of selected patients in a single institution. It should also be taken into account that some patients start the liver-first protocol, but have evident progression under chemotherapy and are therefore excluded from liver surgery, as limited yield should be expected from surgical treatment in case of disease progression during chemotherapeutic treatment.[36] Since the currently used database consists of patients who underwent laparotomy for intended surgical treatment of sRLM, patients that stopped the liver-first protocol before

resection of the RLMs were not included in this study. Therefore, it should be given consideration that a small proportion of patients that initially started the liver first protocol was not included in the analysis, which could have affected the results obtained.

CONCLUSION

The current study has shown that in this series over one-third of patients could be spared from extensive lower pelvic surgery. In patients not completing the liver-first protocol extensive pelvic surgery was ultimately was not necessary in 92% of the cases and a substantial proportion of patients could have been candidates for rectal preserving therapies. Although a predictor for the noncompletion of the liver-first protocol was found, this cannot be used to exclude patients from the liver first protocol as the majority of patients underwent resection of both the primary tumour and the hepatic metastasis with curative intent. These findings together entail that the liver-first approach may be considered in patients with LARC and sRLM.

REFERENCES

1. Mentha G, Majno PE, Andres A, Rubbia-Brandt L, Morel P, Roth AD. Neoadjuvant chemotherapy and resection of advanced synchronous liver metastases before treatment of the colorectal primary. Br J Surg. 2006 Jul;93(7):872-8. PubMed PMID: 16671066. Epub 2006/05/04.
2. Ayez N, Burger JW, van der Pool AE, Eggermont AM, Grunhagen DJ, de Wilt JH, 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 Mar;56(3):281-7. PubMed PMID: 23392140. Epub 2013/02/09.
3. van der Pool AE, de Wilt JH, Lalmahomed ZS, Eggermont AM, Ijzermans JN, Verhoef C. Optimizing the outcome of surgery in patients with rectal cancer and synchronous liver metastases. Br J Surg. 2010 Mar;97(3):383-90. PubMed PMID: 20101594. Epub 2010/01/27.
4. Verhoef C, van der Pool AE, Nuyttens JJ, Planting AS, Eggermont AM, de Wilt JH. The "liver-first approach" for patients with locally advanced rectal cancer and synchronous liver metastases. Dis Colon Rectum. 2009 Jan;52(1):23-30. PubMed PMID: 19273952. Epub 2009/03/11.
5. Fong Y, Fortner J, Sun RL, Brennan MF, Blumgart LH. Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg. 1999 Sep;230(3):309-18; discussion 18-21. PubMed PMID: 10493478. Pubmed Central PMCID: PMC1420876. Epub 1999/09/24.
6. de Bruin AF, Nuyttens JJ, Ferenschild FT, Planting AS, Verhoef C, de Wilt JH. Preoperative chemoradiation with capecitabine in locally advanced rectal cancer. Neth J Med. 2008 Feb;66(2):71-6. PubMed PMID: 18292610. Epub 2008/02/23.
7. Clavien PA, Barkun J, de Oliveira ML, Vauthey JN, Dindo D, Schulick RD, et al. The Clavien-Dindo classification of surgical complications: five-year experience. Ann Surg. 2009 Aug;250(2):187-96. PubMed PMID: 19638912. Epub 2009/07/30.
8. Borschitz T, Wachtlin D, Mohler M, Schmidberger H, Junginger T. Neoadjuvant chemoradiation and local excision for T2-3 rectal cancer. Ann Surg Oncol. 2008 Mar;15(3):712-20. PubMed PMID: 18163173. Epub 2007/12/29.
9. Bujko K, Sopylo R, Kepka L. Local excision after radio(chemo)therapy for rectal cancer: is it safe? Clin Oncol (R Coll Radiol). 2007 Nov;19(9):693-700. PubMed PMID: 17766096. Epub 2007/09/04.
10. Burger JW, de Graaf EJ, Doornebosch PG, Grunhagen DJ, Biermann K, de Wilt JH, et al. Local excision of rectal cancer after chemoradiation: feasibility depends on the primary stage. Int J Colorectal Dis. 2010 Sep;25(9):1141-2. PubMed PMID: 20217420. Pubmed Central PMCID: PMC2912719. Epub 2010/03/11.
11. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014 Mar 15;88(4):822-8. PubMed PMID: 24495589. Epub 2014/02/06.
12. Martin ST, Heneghan HM, Winter DC. Systematic review and meta-analysis of outcomes following pathological complete response to neoadjuvant chemoradiotherapy for rectal cancer. Br J Surg. 2012 Jul;99(7):918-28. PubMed PMID: 22362002. Epub 2012/03/01.
13. Pucciarelli S, De Paoli A, Guerrieri M, La Torre G, Maretto I, De Marchi F, et al. Local excision after preoperative chemoradiotherapy for rectal cancer: results of a multicenter phase II clinical trial. Dis Colon Rectum. 2013 Dec;56(12):1349-56. PubMed PMID: 24201388. Epub 2013/11/10.
14. Smart CJ, Korsgen S, Hill J, Speake D, Levy B, Steward M, et al. Multicentre study of short-course radiotherapy and transanal endoscopic microsurgery for early rectal cancer. Br J Surg. 2016 Jul;103(8):1069-75. PubMed PMID: 27146472. Epub 2016/05/06.

15. Bonjer HJ, Deijen CL, Abis GA, Cuesta MA, van der Pas MH, de Lange-de Klerk ES, et al. A randomized trial of laparoscopic versus open surgery for rectal cancer. N Engl J Med. 2015 Apr 2;372(14):1324-32. PubMed PMID: 25830422. Epub 2015/04/02.
16. Lange MM, Marijnen CA, Maas CP, Putter H, Rutten HJ, Stiggelbout AM, et al. Risk factors for sexual dysfunction after rectal cancer treatment. Eur J Cancer. 2009 Jun;45(9):1578-88. PubMed PMID: 19147343. Epub 2009/01/17.
17. Garcia-Aguilar J, Renfro LA, Chow OS, Shi Q, Carrero XW, Lynn PB, et al. Organ preservation for clinical T2N0 distal rectal cancer using neoadjuvant chemoradiotherapy and local excision (ACOSOG Z6041): results of an open-label, single-arm, multi-institutional, phase 2 trial. Lancet Oncol. 2015 Nov;16(15):1537-46. PubMed PMID: 26474521. Pubmed Central PMCID: PMC4984260. Epub 2015/10/18.
18. Verseveld M, de Graaf EJ, Verhoef C, van Meerten E, Punt CJ, de Hingh IH, et al. Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery (CARTS study). Br J Surg. 2015 Jun;102(7):853-60. PubMed PMID: 25847025. Epub 2015/04/08.
19. Welsh FK, Chandrakumaran K, John TG, Cresswell AB, Rees M. Propensity score-matched outcomes analysis of the liver-first approach for synchronous colorectal liver metastases. Br J Surg. 2016 Apr;103(5):600-6. PubMed PMID: 26864820. Epub 2016/02/13.
20. Sturesson C, Valdimarsson VT, Blomstrand E, Eriksson S, Nilsson JH, Syk I, et al. Liver-first strategy for synchronous colorectal liver metastases - an intention-to-treat analysis. HPB (Oxford). 2017 Jan;19(1):52-8. PubMed PMID: 27838252. Epub 2016/11/14.
21. Andres A, Toso C, Adam R, Barroso E, Hubert C, Capussotti L, et al. A survival analysis of the liver-first reversed management of advanced simultaneous colorectal liver metastases: a LiverMetSurvey-based study. Ann Surg. 2012 Nov;256(5):772-8; discussion 8-9. PubMed PMID: 23095621. Epub 2012/10/26.
22. Baltatzis M, Chan AK, Jegatheeswaran S, Mason JM, Siriwardena AK. Colorectal cancer with synchronous hepatic metastases: Systematic review of reports comparing synchronous surgery with sequential bowel-first or liver-first approaches. Eur J Surg Oncol. 2016 Feb;42(2):159-65. PubMed PMID: 26733368. Epub 2016/01/07.
23. Kelly ME, Spolverato G, Le GN, Mavros MN, Doyle F, Pawlik TM, et al. Synchronous colorectal liver metastasis: a network meta-analysis review comparing classical, combined, and liver-first surgical strategies. J Surg Oncol. 2015 Mar;111(3):341-51. PubMed PMID: 25363294. Epub 2014/11/05.
24. Siriwardena AK, Mason JM, Mullamitha S, Hancock HC, Jegatheeswaran S. Management of colorectal cancer presenting with synchronous liver metastases. Nat Rev Clin Oncol. 2014 Aug;11(8):446-59. PubMed PMID: 24889770. Epub 2014/06/04.
25. Yin Z, Liu C, Chen Y, Bai Y, Shang C, Yin R, et al. Timing of hepatectomy in resectable synchronous colorectal liver metastases (SCRLM): Simultaneous or delayed? Hepatology. 2013 Jun;57(6):2346-57. PubMed PMID: 23359206. Epub 2013/01/30.
26. Mentha G, Roth AD, Terraz S, Giostra E, Gervaz P, Andres A, et al. 'Liver first' approach in the treatment of colorectal cancer with synchronous liver metastases. Dig Surg. 2008;25(6):430-5. PubMed PMID: 19212115. Epub 2009/02/13.
27. Konopke R, Kersting S, Distler M, Dietrich J, Gastmeier J, Heller A, et al. Prognostic factors and evaluation of a clinical score for predicting survival after resection of colorectal liver metastases. Liver Int. 2009 Jan;29(1):89-102. PubMed PMID: 18673436. Epub 2008/08/05.
28. Nagashima I, Takada T, Matsuda K, Adachi M, Nagawa H, Muto T, et al. A new scoring system to classify patients with colorectal liver metastases: proposal of criteria to select candidates for he-

patic resection. J Hepatobiliary Pancreat Surg. 2004;11(2):79-83. PubMed PMID: 15127268. Epub 2004/05/06.

29. Nordlinger B, Guiguet M, Vaillant JC, Balladur P, Boudjema K, Bachellier P, et al. Surgical resection of colorectal carcinoma metastases to the liver. A prognostic scoring system to improve case selection, based on 1568 patients. Association Francaise de Chirurgie. Cancer. 1996 Apr 1;77(7):1254-62. PubMed PMID: 8608500. Epub 1996/04/01.
30. Cirocchi R, Trastulli S, Abraha I, Vettoretto N, Boselli C, Montedori A, et al. Non-resection versus resection for an asymptomatic primary tumour in patients with unresectable stage IV colorectal cancer. Cochrane Database Syst Rev. 2012 Aug 15(8):CD008997. PubMed PMID: 22895981. Epub 2012/08/17.
31. Clancy C, Burke JP, Barry M, Kalady MF, Calvin Coffey J. A meta-analysis to determine the effect of primary tumor resection for stage IV colorectal cancer with unresectable metastases on patient survival. Ann Surg Oncol. 2014 Nov;21(12):3900-8. PubMed PMID: 24849523. Epub 2014/05/23.
32. Chau I, Brown G, Cunningham D, Tait D, Wotherspoon A, Norman AR, 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 Feb 1;24(4):668-74. PubMed PMID: 16446339. Epub 2006/02/01.
33. Verhoef C, de Wilt JH, Burger JW, Verheul HM, Koopman M. Surgery of the primary in stage IV colorectal cancer with unresectable metastases. Eur J Cancer. 2011 Sep;47 Suppl 3:S61-6. PubMed PMID: 21944031. Epub 2011/09/29.
34. t Lam-Boer J, Van der Geest LG, Verhoef C, Elferink ME, Koopman M, de Wilt JH. Palliative resection of the primary tumor is associated with improved overall survival in incurable stage IV colorectal cancer: A nationwide population-based propensity-score adjusted study in the Netherlands. Int J Cancer. 2016 Nov 1;139(9):2082-94. PubMed PMID: 27342618. Epub 2016/06/28.
35. t Lam-Boer J, Mol L, Verhoef C, de Haan AF, Yilmaz M, Punt CJ, et al. The CAIRO4 study: the role of surgery of the primary tumour with few or absent symptoms in patients with synchronous unresectable metastases of colorectal cancer--a randomized phase III study of the Dutch Colorectal Cancer Group (DCCG). BMC Cancer. 2014 Oct 2;14:741. PubMed PMID: 25277170. Pubmed Central PMCID: PMC4196118. Epub 2014/10/04.
36. Vigano L, Capussotti L, Barroso E, Nuzzo G, Laurent C, Ijzermans JN, et al. Progression while receiving preoperative chemotherapy should not be an absolute contraindication to liver resection for colorectal metastases. Ann Surg Oncol. 2012 Sep;19(9):2786-96. PubMed PMID: 22622469. Epub 2012/05/25.

Chapter 8

Summary, general discussion and future perspectives

SUMMARY AND GENERAL DISCUSSION

This thesis contributes to the development and improvement of organ-preserving strategies in the treatment of rectal cancer. The multidisciplinary approach and 'tailor-made' treatment strategies have rapidly evolved since the early nineties [1-4]. Preservation of the rectum in the treatment of rectal cancer may improve the quality of life (QOL) reported after radical TME surgery and is gradually becoming the treatment of first choice in a specific subgroup of patients [5].

As a result of population screening for colorectal cancer, tumours and polyps are detected earlier. These polyps slowly change from benign to malignant. One of the stages of premalignancy is intramucosal carcinoma (IMC). The revised version of the Vienna criteria classifies polyps and provides treatment recommendations [6, 7]. The biological similarity between the IMC and polyps with high-grade dysplasia is the absence of connection with the lymphatics in the intermediate layer of the intestinal wall, the so-called lamina propria [8-12]. According the Vienna criteria, this condition classifies these abnormalities as benign. That seems logical, but the clinical evidence to support this classification is scarce. In **Chapter 2**, we demonstrated that IMC has the same risk of regrowth as benign polyps. Consequently, both entities can be safely treated with a rectal sparing strategy using transanal endoscopic microsurgery (TEM). This supports the classification of IMC as benign abnormalities.

Patients with selected early rectal tumours may be treated locally through the anus using TEM with low morbidity and mortality rates. TEM has been proven to be superior to non-endoscopic techniques, most likely owing to excellent visibility, leading to high-quality, radical, full-thickness rectal resection specimens [13-17]. TEM has the advantage of preserving the rectum and anorectal function, resulting in less complications and improved QOL compared with TME surgery. However, TEM is technically challenging and expensive because specialized equipment and instrumentation is required. As a result, TEM has never become widely incorporated. Nowadays, TEM has largely been replaced by transanal minimally invasive surgery (TAMIS). Unlike TEM, which uses a rigid rectoscope, TAMIS is performed using a flexible silicone port and laparoscopic instrumentation. TAMIS is easier to learn and requires less specialized equipment. QOL and functional outcomes after TAMIS are unknown. In **Chapter 3**, the functional outcomes in patients treated with TAMIS were compared with those in patients treated with conventional TEM surgery. There were no adverse effects of TAMIS on anorectal function. The general QOL improved after TAMIS, probably (also) as a result of removal of the tumour. After 6 months, the QOL of the TAMIS group was similar to that of the general population.

Further advances in the field of TAMIS are being achieved by the use of robotics. During robotic transanal surgery (RTS), multiple robotic arms are used to resect a rectal lesion transanally. In 2019, a retrospective study of 58 patients who underwent RTS was per-

formed. Negative resection margins were achieved in 94.8% of patients, and an early local recurrence rate of 5.5% was achieved within a year, with all patients proceeding to salvage surgery [18]. In non-robotic TAMIS, the percentage of negative margins is comparable (93%) [19].

If a suspected early carcinoma (clinical T1; clinical T1; cT1) is found, various treatment strategies can be applied. In **Chapter 4**, we examined the use of these strategies in the Netherlands between 2005 and 2018 using data from the Comprehensive Cancer Centre of the Netherlands (IKNL). During the incidence years, the absolute number of patients diagnosed with cT1 rectal cancer has increased from 540 patients in 2005–2009 to 1643 patients in 2015–2018, with a profound increase from 2014. This increase is most likely a result of the population screening for colorectal cancer in the Netherlands, which was introduced in 2014. Over the years, more patients without suspected regional lymph nodes, were treated by means of local excision. At the same time, less patients received (unjustified) neoadjuvant (chemo)radiotherapy. In addition, the accuracy of detection of pT1 tumours was found to be significantly lower in patients with suspected lymph node metastases than in patients without lymph node metastases. Over 45% of cT1N+ patients had pT2 tumours or higher, whereas 18.4% of the patients had tumours without suspected lymph nodes. This may have a biological explanation, as higher tumour stages harbour a greater metastatic potential [20, 21]. To improve discrimination between cT1 and cT2 tumours, endorectal ultrasound (ERUS) seems to be a useful and accurate method [22]. Three-dimensional ERUS may further improve staging accuracy [23]. However, these diagnostic modalities are not available in most Dutch centres.

As local excision became increasingly popular, indications for the applicability of LE seemed to expand beyond early-stage tumours. Consequences of this extension were investigated in the national population study described in **Chapter 5**. Results showed that LE without neoadjuvant treatment is an oncologically safe treatment strategy in pT1-2 tumours (pT1–2), with 5-year survival rates comparable with those after TME surgery. Patients undergoing completion TME (cTME) after LE had survival rates comparable with those of patients with pT2 tumours undergoing primary TME without neoadjuvant treatment [24]. In contrast, survival rates after LE for patients with a pT3 tumour were worse than those of patients who underwent cTME.

After local excision of a small early-stage (pT1) tumour with high-risk features (e.g. lymphatic invasion, budding, submucosal invasion ≥1 mm, and poor histological differentiation) or a low-risk pT2 tumour, completion TME surgery is standard of care, as 10–15% of these high-risk tumours harbour nodal metastases [20]. Completion TME has high treatment-related morbidity, and more preservative strategies may be feasible. The risk of nodal metastases and local and distant recurrence may be lowered by the administration of CRT, as CRT could lead to complete remission of regional lymph nodes and the surrounding area of the primary tumour that may harbour (micro)metastases. This strategy is under

investigation in the ongoing TESAR trial, in which patients with intermediate-risk pT1–2 rectal cancer (high-risk T1 tumours or low-risk T2 tumours) who underwent radical local excision are randomised between completion TME or adjuvant CRT [25]. This trial hypothesises that adjuvant chemoradiotherapy is non-inferior to TME in terms of local recurrence and superior in terms of treatment-related morbidity, functional outcome, and QOL.

In accordance with the Dutch guidelines, neoadjuvant chemoradiation is reserved for locally advanced rectal cancer (LARC; cT4, mesorectal fascia involvement, N2 disease, and/or suspicious extramesorectal lymph nodes) [26-29]. The incidence of lymph node metastases is lower after neoadjuvant CRT because CRT can sterilise tumour-containing lymph nodes [30, 31]. Moreover, CRT can cause downstaging or even complete remission of the rectal tumour itself. Complete response rates of 25% in LARC have been described, making these patients candidates for organ preservation. In patients with early rectal cancer, CR rates can even be as high as 44% [27, 32, 33]. These results have led to new treatment strategies in which rectal sparing surgery or even omission of surgery seems possible.

The CARTS study, described in **Chapter 6,** was one of the first prospective multicentre studies investigating the role of rectal sparing treatment with chemoradiation followed by local excision of tumour remnants in patients with early rectal cancer. Patients with cT3N0 distal rectal cancer were treated with chemoradiation. A (near) complete response rate was achieved in 55% of patients. Thus, TEM after neoadjuvant chemoradiotherapy may be equivalent to (laparoscopic) mesorectal excision in this patient group. However, chemotherapy-related toxicity is a concern as two patients in this study died as a result of this toxicity. Another concern is the postoperative toxicity after TEM in patients receiving chemoradiation, which is approximately five times higher than with primary TEM surgery (28% vs. 5.3%) [34, 35]. The third word of caution concerns (early) local recurrence (LR). LR developed mainly in patients who still had a pT2 tumour. According to the current guideline, a primary TME (without pretreatment) would suffice for these patients because perspectives might be worse and they may be unnecessarily exposed to the additional morbidity of chemoradiotherapy and TEM [36-38].

Trying to refrain from pelvic surgery and the accompanying morbidity, radiation therapy or chemoradiation are the two most promising strategies to induce downstaging. Several studies focused on neoadjuvant strategies in patients with early-stage (cT2N0M0) distal rectal cancer [39-41]. Short-course radiotherapy (SCRT) followed by TEM in patients with cT1-2N0 rectal cancer achieved high levels of organ preservation (70%), as demonstrated by the recently published TREC study [42]. However, the authors state that more precise data are required to determine oncological outcomes following different organ preservation treatment schedules. These data are expected to come from the ongoing STAR-TREC III study. This trial offers both strategies and compares these to TME, incorporating a patient preference model. Patients staged as ≤cT3bN0M0 may be included. Those who prefer organ preservation will be randomized 1:1 between chemoradiotherapy or SCRT. Depend-

ing on clinical response, patients enter an active surveillance regime and undergo TEM or TME. Oncological outcomes of cCR after (chemo)radiotherapy and rectum preservation is expected to be non-inferior to those of primary TME surgery and superior in terms of morbidity and function and QOL. However, one of the drawbacks of a rectal sparing approach with chemoradiotherapy for intermediate-stage rectal cancer is the potential for overtreatment.

For patients with locally advanced rectal cancer, the known pitfalls of poor compliance with postoperative treatment, unimproved incidence of distant metastasis, and the trend to postpone reassessment to enable organ preservation options are reasons to include systemic therapy prior to surgery: the total neoadjuvant therapy approach (TNT). An example of such an approach is the ***RAPIDO*** regimen in which patients with high-risk locally advanced rectal cancer received SCRT followed by 18 weeks of chemotherapy. The recently published results show an impressive pathological complete response rate of 28% [43]. Therefore, this strategy could contribute to organ preservation and probably even more so in patients with intermediate- or early-stage rectal cancer.

The 5-year results of the GRECCAR 2 trial, comparing local excision versus total mesorectal excision in T2T3N0–1 low rectal cancer treated with neoadjuvant chemoradiotherapy, reveal no difference in oncological outcomes. Thus, local excision may be proposed in selected patients having a small T2T3 low rectal cancer with a good clinical response after chemoradiotherapy [44].

The OPAXX study investigates how an organ-sparing treatment can still be used if a small tumour remains after standard pretreatment with (chemo)radiotherapy. There will be a lottery between 1) immediate additional internal radiation (contact therapy) after the initial magnetic resonance imaging (MRI) evaluation and 2) TAMIS surgery after an extra waiting period of several weeks if a small residual tumour remains [45].

In improving the likelihood of obtaining complete response rates, a promising strategy is the use of immunotherapy. Compared with chemotherapy, immunotherapy is believed to be less toxic, to induce fewer side effects, and to provide continuous protection against cancer owing to the immune system's memory, enabling longer-lasting remissions. Various studies with other tumour types have shown that administering immunotherapy at an earlier stage of the disease is more likely to be successful than treatment at an advanced stage [46-48].

The TARZAN trial is a study in which patients with resectable rectal cancer received radiotherapy, followed by neoadjuvant immunotherapy (bevacizumab and atezolizumab). Clinically complete and near-complete response rates were assessed 12 weeks after radiotherapy using MRI, digital rectal exam, and endoscopy with or without biopsies. Residual disease is defined as visible lesions at endoscopy and visible tumour at MRI [49]. Final results are awaited.

In the NICHE study, patients with early-stage ***colon cancer*** were administered neoadjuvant ipilimumab + nivolumab [46]. All patients underwent subsequent surgery. Pathological complete response was found in a stunning 60% (12/20) of the patients, provided they had a mismatch-repair-deficient tumour. This strategy might be suitable for patients with (early) rectal cancer but, to the best of our knowledge, has not been tested to date.

Patients with stage IV rectal cancer constitute an underexposed group of patients. The group of patients with stage IV cancer is pre-eminently a group in which rectum preservation should be considered, as these patients are at a high risk of disease progression and futile extensive pelvic surgery. In **Chapter 7**, we investigated the prognostic factors for the completion of the liver-first treatment and determined the number of patients who could not undergo TME surgery. The liver-first approach is treatment with preoperative systemic chemotherapy followed by hepatic resection for colorectal liver metastases and resection of the primary tumour as the last procedure. The rationale for treating the liver metastases first is that the postoperative morbidity of liver resections is generally low and patients with progressive disease can be spared the high morbidity of TME surgery. This study showed that more than a third of patients with rectal liver metastases could avoid extensive lower pelvic surgery. CEA >53.15 µg/L was associated with non-completion of the liver-first protocol. In 92% of patients who did not complete the liver-first protocol, a TME was not performed. Moreover, 10 of 90 (11%) patients who did undergo TME had a (near) complete response and thus could have been candidates for rectal sparing therapy.

FUTURE PERSPECTIVES

The question that demands to be answered is which strategy is the best for each individual patient. The various strategies that have been developed and will be further improved in the future will all have their advantages and disadvantages. It may be an utopia, but until we have developed strategies with the best of all worlds, that is, curing cancer while maintaining QOL, it is the duty and prerogative of physicians to guide their patients to make a well-informed decision, taking into account all aspects ranging from oncological safety to QOL, risks, benefits, and above all, the patients' preference. To meet patients' preferences and tailor treatment, future research should focus on response prediction and response evaluation, more effective (neo)adjuvant therapy and better understanding of patients' preferences.

It would be a major improvement to be able to predict treatment response before the start of neoadjuvant therapy. Especially for patients with primary resectable tumours, it may be of great value to tailor treatment and reduce unnecessary treatment-related morbidity. Good responders will be candidates for neoadjuvant therapy followed by an active surveillance strategy, whereas upfront surgery may be the optimal treatment for patients who will likely have no or poor response. Potential tools for accurate response prediction are biomarkers and radiomics (i.e. the combination of information from multiple modalities [MRI, functional MRI, and FDG-PET] and patient-derived organoids) [50, 51].

Options to improve effectiveness of neoadjuvant therapy are chemotherapy, immunotherapy, and radiotherapy. More intensive chemotherapy regimens likely lead to more treatment-related toxicity, whereas the effect on response rate is highly questionable. Therefore, focus should be on targeted therapies and dose escalation of radiotherapy. Immunotherapy has already proven its value in colon cancer, and its translation to rectal cancer will be made soon. However, the success of this therapy will be based on accurate and specific selection.

Strict surveillance is mandatory after organ preservation strategies to detect local recurrence (either intraluminal or nodal) at a resectable stage. Surveillance usually consists of MRI, endoscopy (with biopsies if needed), digital rectal exam (DRE), and computed tomography scan for distant metastases. Although the main goal of all rectum-preserving strategies is to refrain from potentially unnecessary major surgery, it is at least as important to preserve oncological safety. Patients in an active surveillance program should be discussed in dedicated multidisciplinary teams, and short- and long-term outcomes should be monitored carefully. This is done in the International Watch and Wait Database (IWWD), [52] in which outcomes after a Watch-and-Wait strategy are pooled in a prospective registry of individual patient data from expert centres from more than 15 countries.

During active surveillance after neoadjuvant therapy, the challenge is to detect regrowth as early as possible using an effective set of diagnostics. In addition to standard surveil-

lance modalities (such as MRI, CT, endoscopy, and DRE), biomarkers may be a promising instrument. Circulating tumour DNA (ctDNA) may be a diagnostic tool for the detection of minimal residual disease [48-50]. ctDNA is part of the total amount of small fragments of DNA in the blood, called cell-free DNA. These fragments are shed into the bloodstream from dying cells during cellular turnover or other forms of cell death [48-50]. ctDNA can be analysed in regular blood samples ('liquid biopsies'), making this a non-invasive approach to monitor disease and treatment response. In case of rectal sparing therapies, ctDNA may be a valuable addition to the armamentarium for detecting (early) local recurrence, apart from MRI, endoscopy with/without biopsies, and DRE. The current challenge lies in improving the sensitivity of ctDNA analyses to detect minimal residual disease. In the STAR-TREC III trial and NICHE trial mentioned before, the value of ctDNA will be established.

Ultimately, the success of the chosen therapy depends on the selection of the patient and their tumour. Development of decision aids to improve the understanding of what really matters to patients will help physicians to accommodate to patients' needs and improve the decision-making process. Patients' views and experiences may differ substantially from those of their physician(s) [53-56]. For example, in a study of the preferences of patients with colorectal cancer, it was found that most (63%) were willing to trade off a third of their remaining years of life to avoid a permanent stoma [57]. Remarkably, another study showed that QOL is similar in patients who have a colostomy (after abdomino-perineal resection) versus those with a coloanal anastomosis [58]. Better understanding of patients' treatment decisions will help physicians to tailor treatment to patients' needs and expectations. One of the instruments to gain insight into patients' preferences is the use of patient-related outcome measures (PROMs). PROMs are the results from questionnaires that evaluate different domains of QOL. Patients (or relatives) complete these questionnaires at various points in the care process and address, for example, pain, fatigue, emotional state, low anterior resection syndrome (LARS), and sexuality. PROMs could be used to develop clinical decision aids to support patients' decisions in the future.

CONCLUSION

This thesis examines the risks and benefits of rectum-preserving treatment of (premalignant) rectal neoplasia and contributes to knowledge required to guide the shared decision-making process. Future research should focus on improving the complete response rate, optimizing response prediction and assessment, and understanding patients' motivation to opt for or out of rectum-preserving strategies.

REFERENCES

1. Barina A, De Paoli A, Delrio P, Guerrieri M, Muratore A, Bianco F, et al. Rectal sparing approach after preoperative radio- and/or chemotherapy (RESARCH) in patients with rectal cancer: a multicentre observational study. Tech Coloproctol. 2017 Aug;21(8):633-40. PubMed PMID: 28755256.
2. Elferink MA, van Steenbergen LN, Krijnen P, Lemmens VE, Rutten HJ, Marijnen CA, et al. Marked improvements in survival of patients with rectal cancer in the Netherlands following changes in therapy, 1989-2006. Eur J Cancer. 2010 May;46(8):1421-9. PubMed PMID: 20172711. Epub 2010/02/23.
3. Habr-Gama A, Perez RO, Nadalin W, Sabbaga J, Ribeiro U, Jr., Silva e Sousa AH, Jr., et al. Operative versus nonoperative treatment for stage 0 distal rectal cancer following chemoradiation therapy: long-term results. Ann Surg. 2004 Oct;240(4):711-7; discussion 7-8. PubMed PMID: 15383798. Pubmed Central PMCID: PMC1356472. Epub 2004/09/24.
4. van Gijn W, Marijnen CA, Nagtegaal ID, Kranenbarg EM, Putter H, Wiggers T, 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 Jun;12(6):575-82. PubMed PMID: 21596621. Epub 2011/05/21.
5. Dattani M, Heald RJ, Goussous G, Broadhurst J, Sao Juliao GP, Habr-Gama A, et al. Oncological and Survival Outcomes in Watch and Wait Patients With a Clinical Complete Response After Neoadjuvant Chemoradiotherapy for Rectal Cancer: A Systematic Review and Pooled Analysis. Ann Surg. 2018 Dec;268(6):955-67. PubMed PMID: 29746338. Epub 2018/05/11.
6. Schlemper RJ, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, et al. The Vienna classification of gastrointestinal epithelial neoplasia. Gut. 2000 Aug;47(2):251-5. PubMed PMID: 10896917. Pubmed Central PMCID: PMC1728018. Epub 2000/07/18.
7. Dixon MF. Gastrointestinal epithelial neoplasia: Vienna revisited. Gut. 2002 Jul;51(1):130-1. PubMed PMID: 12077106. Pubmed Central PMCID: PMC1773259. Epub 2002/06/22.
8. Cooper HS, Patchefsky AS, Marks G. Adenomatous and carcinomatous changes within hyperplastic colonic epithelium. Dis Colon Rectum. 1979 Apr;22(3):152-6. PubMed PMID: 446245. Epub 1979/04/01.
9. Jass JR. Relation between metaplastic polyp and carcinoma of the colorectum. Lancet. 1983 Jan 1;1(8314-5):28-30. PubMed PMID: 6129371. Epub 1983/01/01.
10. Lane N. The precursor tissue of ordinary large bowel cancer. Cancer Res. 1976 Jul;36(7 PT 2):2669-72. PubMed PMID: 1277173. Epub 1976/07/01.
11. Rex DK, Ahnen DJ, Baron JA, Batts KP, Burke CA, Burt RW, et al. Serrated lesions of the colorectum: review and recommendations from an expert panel. Am J Gastroenterol. 2012 Sep;107(9):1315-29; quiz 4, 30. PubMed PMID: 22710576. Pubmed Central PMCID: PMC3629844. Epub 2012/06/20.
12. Sumner HW, Wasserman NF, McClain CJ. Giant hyperplastic polyposis of the colon. Dig Dis Sci. 1981 Jan;26(1):85-9. PubMed PMID: 7460710. Epub 1981/01/01.
13. Buess G, Kayser J. [Technique and indications for sphincter-saving transanal resection in rectal carcinoma]. Chirurg. 1996 Feb;67(2):121-8. PubMed PMID: 8881207. Epub 1996/02/01. Technik und Indikation zur sphinctererhaltenden transanalen Resektion beim Rectumcarcinom.
14. de Graaf EJ, Burger JW, van Ijsseldijk AL, Tetteroo GW, Dawson I, Hop WC. Transanal endoscopic microsurgery is superior to transanal excision of rectal adenomas. Colorectal Dis. 2011 Jul;13(7):762-7. PubMed PMID: 20345967. Epub 2010/03/30.
15. de Graaf EJ, Doornebosch PG, Stassen LP, Debets JM, Tetteroo GW, Hop WC. Transanal endoscopic microsurgery for rectal cancer. Eur J Cancer. 2002 May;38(7):904-10. PubMed PMID: 11978515. Epub 2002/04/30.

16. Bach SP, Hill J, Monson JR, Simson JN, Lane L, Merrie A, et al. A predictive model for local recurrence after transanal endoscopic microsurgery for rectal cancer. Br J Surg. 2009 Mar;96(3):280-90. PubMed PMID: 19224520. Epub 2009/02/19.
17. Cataldo PA, O'Brien S, Osler T. Transanal endoscopic microsurgery: a prospective evaluation of functional results. Dis Colon Rectum. 2005 Jul;48(7):1366-71. PubMed PMID: 15933798. Epub 2005/06/04.
18. Tomassi MJ, Taller J, Yuhan R, Ruan JH, Klaristenfeld DD. Robotic Transanal Minimally Invasive Surgery for the Excision of Rectal Neoplasia: Clinical Experience With 58 Consecutive Patients. Dis Colon Rectum. 2019 Mar;62(3):279-85. PubMed PMID: 30451744. Epub 2018/11/20.
19. Lee L, Burke JP, deBeche-Adams T, Nassif G, Martin-Perez B, Monson JRT, et al. Transanal Minimally Invasive Surgery for Local Excision of Benign and Malignant Rectal Neoplasia: Outcomes From 200 Consecutive Cases With Midterm Follow Up. Ann Surg. 2018 May;267(5):910-6. PubMed PMID: 28252517. Epub 2017/03/03.
20. Bosch SL, Nagtegaal ID. Predicting lymph node metastases in pT1 rectal cancer. Recent Results Cancer Res. 2014;203:15-21. PubMed PMID: 25102995.
21. Ricciardi R, Madoff RD, Rothenberger DA, Baxter NN. Population-based analyses of lymph node metastases in colorectal cancer. Clin Gastroenterol Hepatol. 2006 Dec;4(12):1522-7. PubMed PMID: 16979956. Epub 2006/09/19.
22. Boot J, Gomez-Munoz F, Beets-Tan RGH. Imaging of rectal cancer. Radiologe. 2019 Dec;59(Suppl 1):46-50. PubMed PMID: 31616956. Pubmed Central PMCID: PMC6914711. Epub 2019/10/17. Bildgebung des Rektumkarzinoms.
23. Schaffzin DM, Wong WD. Endorectal ultrasound in the preoperative evaluation of rectal cancer. Clin Colorectal Cancer. 2004 Jul;4(2):124-32. PubMed PMID: 15285819. Epub 2004/08/03.
24. Martijn H, Voogd AC, van de Poll-Franse LV, Repelaer van Driel OJ, Rutten HJ, Coebergh JW. Improved survival of patients with rectal cancer since 1980: a population-based study. Eur J Cancer. 2003 Sep;39(14):2073-9. PubMed PMID: 12957462. Epub 2003/09/06. eng.
25. Borstlap WA, Tanis PJ, Koedam TW, Marijnen CA, Cunningham C, Dekker E, et al. A multi-centred randomised trial of radical surgery versus adjuvant chemoradiotherapy after local excision for early rectal cancer. BMC Cancer. 2016 Jul 21;16:513. PubMed PMID: 27439975. Pubmed Central PMCID: PMC4955121. Epub 2016/07/22.
26. Araujo RO, Valadao M, Borges D, Linhares E, de Jesus JP, Ferreira CG, et al. Nonoperative management of rectal cancer after chemoradiation opposed to resection after complete clinical response. A comparative study. Eur J Surg Oncol. 2015 Nov;41(11):1456-63. PubMed PMID: 26362228. Epub 2015/09/13.
27. Maas M, Beets-Tan RG, Lambregts DM, Lammering G, Nelemans PJ, Engelen SM, et al. Wait-and-see policy for clinical complete responders after chemoradiation for rectal cancer. J Clin Oncol. 2011 Dec 10;29(35):4633-40. PubMed PMID: 22067400. Epub 2011/11/10.
28. Martens MH, Maas M, Heijnen LA, Lambregts DM, Leijtens JW, Stassen LP, et al. Long-term Outcome of an Organ Preservation Program After Neoadjuvant Treatment for Rectal Cancer. J Natl Cancer Inst. 2016 Dec;108(12). PubMed PMID: 27509881. Epub 2016/08/12.
29. Ayloor Seshadri R, Kondaveeti SS, Jayanand SB, John A, Rajendranath R, Arumugam V, et al. Complete clinical response to neoadjuvant chemoradiation in rectal cancers: can surgery be avoided? Hepatogastroenterology. 2013 May;60(123):410-4. PubMed PMID: 23635444. Epub 2013/05/03.
30. de Bruin AF, Nuyttens JJ, Ferenschild FT, Planting AS, Verhoef C, de Wilt JH. Preoperative chemoradiation with capecitabine in locally advanced rectal cancer. Neth J Med. 2008 Feb;66(2):71-6. PubMed PMID: 18292610. Epub 2008/02/23.

31. Sauer R, Becker H, Hohenberger W, Rodel C, Wittekind C, Fietkau R, et al. Preoperative versus postoperative chemoradiotherapy for rectal cancer. N Engl J Med. 2004 Oct 21;351(17):1731-40. PubMed PMID: 15496622. Epub 2004/10/22.
32. Garcia-Aguilar J, Shi Q, Thomas CR, Jr., Chan E, Cataldo P, Marcet J, et al. A phase II trial of neoadjuvant chemoradiation and local excision for T2N0 rectal cancer: preliminary results of the ACOSOG Z6041 trial. Ann Surg Oncol. 2012 Feb;19(2):384-91. PubMed PMID: 21755378. Pubmed Central PMCID: PMC5720824. Epub 2011/07/15.
33. Maas M, Nelemans PJ, Valentini V, Das P, Rodel C, Kuo LJ, 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 Sep;11(9):835-44. PubMed PMID: 20692872. Epub 2010/08/10.
34. Habr-Gama A, Gama-Rodrigues J, Sao Juliao GP, Proscurshim I, Sabbagh C, Lynn PB, et al. Local recurrence after complete clinical response and watch and wait in rectal cancer after neoadjuvant chemoradiation: impact of salvage therapy on local disease control. Int J Radiat Oncol Biol Phys. 2014 Mar 15;88(4):822-8. PubMed PMID: 24495589. Epub 2014/02/06.
35. Marks JH, Valsdottir EB, DeNittis A, Yarandi SS, Newman DA, Nweze I, et al. Transanal endoscopic microsurgery for the treatment of rectal cancer: comparison of wound complication rates with and without neoadjuvant radiation therapy. Surg Endosc. 2009 May;23(5):1081-7. PubMed PMID: 19263164. Epub 2009/03/06.
36. Madbouly KM, Remzi FH, Erkek BA, Senagore AJ, Baeslach CM, Khandwala F, et al. Recurrence after transanal excision of T1 rectal cancer: should we be concerned? Dis Colon Rectum. 2005 Apr;48(4):711-9; discussion 9-21. PubMed PMID: 15768186. Epub 2005/03/16.
37. Mahvi DA, Liu R, Grinstaff MW, Colson YL, Raut CP. Local Cancer Recurrence: The Realities, Challenges, and Opportunities for New Therapies. CA Cancer J Clin. 2018 Nov;68(6):488-505. PubMed PMID: 30328620. Pubmed Central PMCID: PMC6239861. Epub 2018/10/18.
38. Weiser MR, Landmann RG, Wong WD, Shia J, Guillem JG, Temple LK, et al. Surgical salvage of recurrent rectal cancer after transanal excision. Dis Colon Rectum. 2005 Jun;48(6):1169-75. PubMed PMID: 15793645. Epub 2005/03/29.
39. Habr-Gama A, Sao Juliao GP, Vailati BB, Sabbaga J, Aguilar PB, Fernandez LM, et al. Organ Preservation in cT2N0 Rectal Cancer After Neoadjuvant Chemoradiation Therapy: The Impact of Radiation Therapy Dose-escalation and Consolidation Chemotherapy. Ann Surg. 2019 Jan;269(1):102-7. PubMed PMID: 28742703. Epub 2017/07/26.
40. Lezoche E, Baldarelli M, Lezoche G, Paganini AM, Gesuita R, Guerrieri M. Randomized clinical trial of endoluminal locoregional resection versus laparoscopic total mesorectal excision for T2 rectal cancer after neoadjuvant therapy. Br J Surg. 2012 Sep;99(9):1211-8. PubMed PMID: 22864880. Epub 2012/08/07.
41. Stijns RCH, Tromp MR, Hugen N, de Wilt JHW. Advances in organ preserving strategies in rectal cancer patients. Eur J Surg Oncol. 2018 Feb;44(2):209-19. PubMed PMID: 29275912. Epub 2017/12/26.
42. Bach SP, Gilbert A, Brock K, Korsgen S, Geh I, Hill J, et al. Radical surgery versus organ preservation via short-course radiotherapy followed by transanal endoscopic microsurgery for early-stage rectal cancer (TREC): a randomised, open-label feasibility study. Lancet Gastroenterol Hepatol. 2021 Feb;6(2):92-105. PubMed PMID: 33308452. Pubmed Central PMCID: PMC7802515. Epub 2020/12/15.
43. Bahadoer RR, Dijkstra EA, van Etten B, Marijnen CAM, Putter H, Kranenbarg EM, 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 Jan;22(1):29-42. PubMed PMID: 33301740. Epub 2020/12/11.

44. Rullier E, Vendrely V, Asselineau J, Rouanet P, Tuech JJ, Valverde A, et al. Organ preservation with chemoradiotherapy plus local excision for rectal cancer: 5-year results of the GRECCAR 2 randomised trial. Lancet Gastroenterol Hepatol. 2020 May;5(5):465-74. PubMed PMID: 32043980. Epub 2020/02/12.
45. Beets. OPAXX. 2021.
46. Chalabi M, Fanchi LF, Dijkstra KK, Van den Berg JG, Aalbers AG, Sikorska K, et al. Neoadjuvant immunotherapy leads to pathological responses in MMR-proficient and MMR-deficient early-stage colon cancers. Nat Med. 2020 Apr;26(4):566-76. PubMed PMID: 32251400. Epub 2020/04/07.
47. O'Donnell JS, Hoefsmit EP, Smyth MJ, Blank CU, Teng MWL. The Promise of Neoadjuvant Immunotherapy and Surgery for Cancer Treatment. Clin Cancer Res. 2019 Oct 1;25(19):5743-51. PubMed PMID: 31040150. Epub 2019/05/02.
48. Powles T, Kockx M, Rodriguez-Vida A, Duran I, Crabb SJ, Van Der Heijden MS, et al. Clinical efficacy and biomarker analysis of neoadjuvant atezolizumab in operable urothelial carcinoma in the ABACUS trial. Nat Med. 2019 Nov;25(11):1706-14. PubMed PMID: 31686036. Epub 2019/11/07.
49. Belt vdM. Neoadjuvant Treatment in Rectal Cancer With Radiotherapy Followed by Atezolizumab and Bevacizumab (TARZAN); NCT04017455. 2019-.
50. Bodalal Z, Trebeschi S, Beets-Tan R. Radiomics: a critical step towards integrated healthcare. Insights Imaging. 2018 Dec;9(6):911-4. PubMed PMID: 30421396. Pubmed Central PMCID: PMC6269340. Epub 2018/11/14.
51. Bodalal Z, Trebeschi S, Nguyen-Kim TDL, Schats W, Beets-Tan R. Radiogenomics: bridging imaging and genomics. Abdom Radiol (NY). 2019 Jun;44(6):1960-84. PubMed PMID: 31049614. Epub 2019/05/03.
52. Beets GL, Figueiredo NL, Habr-Gama A, van de Velde CJ. A new paradigm for rectal cancer: Organ preservation: Introducing the International Watch & Wait Database (IWWD). Eur J Surg Oncol. 2015 Dec;41(12):1562-4. PubMed PMID: 26493223. Epub 2015/10/24.
53. Chewning B, Bylund CL, Shah B, Arora NK, Gueguen JA, Makoul G. Patient preferences for shared decisions: a systematic review. Patient Educ Couns. 2012 Jan;86(1):9-18. PubMed PMID: 21474265. Pubmed Central PMCID: PMC4530615. Epub 2011/04/09.
54. Godolphin W. The role of risk communication in shared decision making. BMJ. 2003 Sep 27;327(7417):692-3. PubMed PMID: 14512449. Pubmed Central PMCID: PMC200791. Epub 2003/09/27.
55. Morris AM. Shared Decision Making for Rectal Cancer Care: A Long Way Forward. Dis Colon Rectum. 2016 Oct;59(10):905-6. PubMed PMID: 27602920. Epub 2016/09/08.
56. van der Valk MJM, van der Sande ME, Toebes RE, Breukink SO, Broker MEE, Doornebosch PG, et al. Importance of patient reported and clinical outcomes for patients with locally advanced rectal cancer and their treating physicians. Do clinicians know what patients want? Eur J Surg Oncol. 2020 Sep;46(9):1634-41. PubMed PMID: 32336626. Epub 2020/04/28.
57. Harrison JD, Solomon MJ, Young JM, Meagher A, Butow P, Salkeld G, et al. Patient and physician preferences for surgical and adjuvant treatment options for rectal cancer. Arch Surg. 2008 Apr;143(4):389-94. PubMed PMID: 18427027. Epub 2008/04/23.
58. Kasparek MS, Hassan I, Cima RR, Larson DR, Gullerud RE, Wolff BG. Quality of life after coloanal anastomosis and abdominoperineal resection for distal rectal cancers: sphincter preservation vs quality of life. Colorectal Dis. 2011 Aug;13(8):872-7. PubMed PMID: 20545966. Epub 2010/06/16.

Chapter 9

Summary in Dutch;
Nederlandse samenvatting

Dit proefschrift bespreekt de voordelen en de risico's van endeldarm-sparende (***rectum-sparende***) behandelingen voor patiënten met (een voorloper stadium van) endeldarmkanker (***rectumcarcinoom***). Het doel van dit proefschrift is om bij te dragen aan het verbeteren van orgaan sparende strategieën bij de behandeling van patiënten met rectumcarcinoom en aan de gezamenlijke besluitvorming tussen arts en patiënt om de meest geschikte behandeling voor de patiënt te bepalen.

Door het bevolkingsonderzoek naar (endel)darmkanker, dat van start ging in 2014, wordt kanker vroeger opgespoord. Ook werden meer poliepen gevonden, die een voorloper kunnen zijn van uiteindelijke kanker. Deze poliepen veranderen langzaam van goedaardig naar kwaadaardig. Eén van de eerste stadia van beginnende kwaadaardigheid is het intramucosale carcinoom (***IMC***). De Vienna Classificatie stamt uit 2000 en beschrijft en classificeert onder andere darmpoliepen en welke behandeling daaraan verbonden zou moeten zijn. In 2013 verscheen een hernieuwde versie van de Vienna Classificatie.

De biologische overeenkomst tussen het IMC en poliepen met hooggradige dysplasie (poliepen met een sterk abnormaal groeipatroon), is de afwezigheid van verbinding met de lymfebanen in de tussengelegen laag van de darmwand, de zgn. lamina propria. Op grond van deze overeenkomst schaart de hernieuwde Vienna Classificatie deze afwijkingen onder de goedaardige afwijkingen. Dat lijkt logisch, maar het klinische bewijs om deze indeling te ondersteunen ontbrak. In **hoofdstuk 2** tonen we aan dat het IMC dezelfde risico's van hergroei heeft als goedaardige poliepen. Beiden kunnen dan ook veilig rectumsparend behandeld worden middels transanale endoscopische microchirurgie (TEM). De rationale van de indeling van de hernieuwde Vienna Classificatie om het IMC in te delen bij de goedaardige afwijkingen, kan dus worden gesteund.

Bij patiënten met een (zeer) vroege vorm van rectumcarcinoom of een voorloper daarvan, is plaatselijke verwijdering, oftewel lokale excisie (LE), een bewezen veilige behandeling. Deze rectumsparende behandeling heeft als voordeel dat de anorectale functie behouden blijft en het veel minder complicaties en een betere kwaliteit van leven geeft vergeleken met TME chirurgie (***Total Mesorectal Excision; TME chirurgie***).

Lokale excisie kan op verschillende manieren worden uitgevoerd, maar TEM is bewezen superieur boven niet-endoscopische technieken. Echter, TEM is technisch uitdagend en kostbaar omdat gespecialiseerde apparatuur en instrumentarium nodig zijn. Hierdoor is TEM niet breed geïncorporeerd geraakt. TEM is nu grotendeels vervangen door TAMIS: ***transanal minimally invasive surgery***. In tegenstelling tot TEM, waarbij gebruik gemaakt wordt van starre rectoscoop, wordt TAMIS uitgevoerd middels een flexibele siliconen poort en met laparoscopisch instrumentarium. TAMIS is even veilig als TEM, maar makkelijker te leren en er is minder gespecialiseerde apparatuur nodig. Echter, de kwaliteit van leven en

functionele resultaten bij patiënten die middels TAMIS werden behandeld waren nog niet onderzocht.

In **hoofdstuk 3** beschrijven we de resultaten van ons onderzoek naar de impact op de kwaliteit van leven en functionele resultaten bij patiënten die middels TAMIS werden behandeld. Deze resultaten warden vergeleken met die van conventionele TEM chirurgie. Er bleken geen nadelige gevolgen van TAMIS op de anorectale functie. De algemene kwaliteit van leven verbeterde na TAMIS, waarschijnlijk (ook) door het verwijderen van de tumor. Na 6 maanden was de kwaliteit van leven van de TAMIS patiënten gelijk aan die van de algemene populatie.

Wanneer een vermoedelijk vroegcarcinoom (***klinisch T1; clinical T1; cT1***) wordt gevonden, kunnen diverse behandelingsstrategieën worden ingezet. In **hoofdstuk 4** onderzochten we middels data van het Integraal Kankercentrum Nederland (IKNL) retrospectief de gebuikte strategieën bij cT1 rectumcarcinoom-patiënten in Nederland tussen 2005 – 2018 en of de behandelingen over de tijd veranderden. Gedurende de incidentiejaren is het absolute aantal patiënten gediagnosticeerd met cT1 rectumcarcinoom gestegen van 540 patiënten tussen de periode van 2005 – 2009 tot 1643 patiënten tussen 2015 – 2018, met een duidelijke toename vanaf 2014. Deze toename hangt zeer waarschijnlijk samen met de start van het bevolkingsonderzoek naar (endel)darmkanker in Nederland in 2014.

Over de jaren werden steeds meer patiënten, bij wie geen vermoeden bestond op uitzaaiingen naar de omgevende lymfeklieren, behandeld middels lokale excisie. Tegelijkertijd werden steeds minder mensen (onterecht) voorbehandeld met (chemo)radiotherapie. Doordat steeds minder patiënten voorbehandeld werden en steeds meer patiënten met LE behandeld werden zou men een toename kunnen verwachten van aanvullende (uitgebreide) rectumoperaties (***Total Mesorectal Excision; TME chirurgie***). Echter, ook het aantal aanvullende TME operaties nam significant af. Dit suggereert dat patiëntselectie en rectumsparende strategieën zijn verbeterd over de jaren.

Daarnaast onderzochten we hoe vaak een cT1 ook daadwerkelijk een pathologische T1 (pT1) tumor was. Deze accuratesse bleek significant lager te liggen bij patiënten met een, bij de preoperatieve diagnostiek, vermoeden op uitzaaiingen naar de omgevende lymfeklieren (***clinical Node positive; cN+***). In ruim 45% van deze cN+ patiënten bleek het tumorstadium hoger te zijn dan pT1. Van de patiënten zonder vermoedelijke lymfklieruitzaaiingen was dit in 18% het geval.

Lokale excisie werd toenemend populair en indicaties voor de toepasbaarheid van LE leken zich uit breiden voorbij de vroegcarcinomen van de endeldarm. Of deze uitbreiding terecht is werd in een nationale studie van de bevolking onderzocht en beschreven in **hoofdstuk 5.** Data van het Integraal Kankercentrum Nederland (IKNL) werd geraadpleegd om de overleving van patiënten na LE voor alle tumorstadia van rectumcarcinoom te on-

derzoeken en te vergelijken met TME chirurgie. We concludeerden dat LE in vroege stadia van rectumcarcinoom (pT1–2) zonder voorbehandeling een acceptabele en oncologisch veilige behandeling is, met een relatieve 5-jaars overleving vergelijkbaar met TME chirurgie. Patiënten die een aanvullende TME ondergingen hadden een vergelijkbare overleving met pT2 patiënten die een primaire TME zonder voorbehandeling ondergingen. Daarentegen bleek de relatieve overleving na LE voor patiënten met een pT3 tumor slechter te zijn, ook in vergelijking met die van patiënten die een (aanvullende) TME ondergingen.

Patiënten met gevorderd rectumcarcinoom worden volgens de Nederlandse richtlijnen preoperatief behandeld met chemoradiotherapie. Deze chemoradiotherapie kan resulteren in een volledige respons tot in 25% van de patiënten. Deze resultaten hebben geleid tot nieuwe behandelings- en rectumsparende strategieën, ook bij het vroeg stadium rectumcarcinoom. Zelfs het compleet achterwege laten van een operatie lijkt mogelijk.

Een van de eerste prospectieve multicentrische onderzoeken die de rol van een rectumsparende behandeling met chemoradiatie gevolgd door lokale excisie van het tumorresten bij patiënten met een vroeg stadium rectumcarcinoom, was de CARTS-studie, beschreven in **hoofdstuk 6**. Patiënten met een cT1-3N0 laaggelegen rectumcarcinoom werden behandeld met chemoradiatie, waarna de respons werd geëvalueerd. Het doel was om een (bijna) complete respons percentage van meer dan 30 procent te behalen en dit werd ruim overschreden, namelijk 55 procent. TEM na neoadjuvante chemoradiotherapie kan dus een waardig equivalent zijn van (laparoscopische) mesorectale excisie bij geselecteerde patiënten.

Chemoradiotherapie gerelateerde toxiciteit is echter een punt van zorg aangezien 2 patiënten in deze studie stierven als gevolg van deze toxiciteit. Een ander punt van zorg is de postoperatieve toxiciteit na TEM bij patiënten die chemoradiatie krijgen, die ongeveer 5 keer hoger is dan bij primaire TEM-chirurgie (28% versus 5,3%). Een derde waarschuwing betreft het (vroege) lokaal recidief (LR). LR ontwikkelde zich voornamelijk bij patiënten die toch nog een pT2 tumor bleken te hebben en daarom moet bij deze patiënten een completerende TME-operatie worden aanbevolen. Een van de nadelen van een rectumsparende benadering met chemoradiotherapie is de mogelijke overbehandeling. Bij deze patiënten zou volgens de huidige richtlijn namelijk een primaire TME (zonder voorbehandeling) volstaan hebben. Deze patiënten worden dus mogelijk onnodig blootgesteld aan de aanvullende morbiditeit van chemoradiotherapie en eventuele TEM.

Patiënten met een lokaal gevorderd rectumcarcinoom met gelijktijdige uitzaaiingen naar de lever (synchrone levermetastasen) kunnen worden behandeld volgens de liver-first benadering. Na systemische behandeling met chemotherapie, zonder ziekteprogressie bij re-stadiëring, wordt dan eerst de leveroperatie uitgevoerd. Na de leveroperatie worden de patiënten dan voorbehandeld voor de rectumtumor middels (chemo)radiotherapie. Na re-

stadiëring wordt als laatste stadium een operatie van de primaire rectumtumor uitgevoerd. De rationale om eerst de levermetastasen te behandelen, is omdat de postoperatieve morbiditeit van leverresecties over het algemeen laag is en patiënten met een progressieve ziekte de hoge morbiditeit van een lage bekkenoperatie kan worden bespaard. Echter, deze uitgebreide voorbehandeling met chemotherapie en (chemo)radiotherapie kan leiden tot een (bijna) complete respons van de rectumtumor.

Het is opmerkelijk dat bijna alle aandacht voor rectumsparende therapieën uitgaat naar patiënten met een vroeg stadium van endeldarmkanker, aangezien juist bij deze patiënten met een naar de lever uitgezaaid rectumcarcinoom een rectumsparende operatie of een watchful waiting protocol, waarbij patiënten intensief gecontroleerd worden, overwogen zou moeten worden om ze zinloze TME chirurgie te besparen. In **hoofdstuk 7** onderzochten we het volgende: bij hoeveel van deze patiënten een TME-operatie achterwege kon blijven en wat de voorspellende factoren voor het (niet) kunnen voltooien van deze intensieve liver-first behandeling zijn.

Deze studie heeft aangetoond dat meer dan een derde van de patiënten met rectale levermetastasen gespaard kon worden van uitgebreide rectumchirurgie. Bij patiënten die het liver-first-protocol niet voltooiden, was een TME uiteindelijk in 92% van de gevallen niet nodig of niet zinvol en bij 10 van de 90 (11%) patiënten die wel werden geopereerd middels TME bleek er sprake te zijn van een (bijna) complete respons en hadden dus in aanmerking kunnen komen voor rectumsparende therapieën.

Hoewel er wel een voorspeller voor het niet voltooien van het liver-first protocol werd gevonden, namelijk een CEA-niveau boven de 53.15 µg/L, kan dit niet worden gebruikt om patiënten uit te sluiten van het liver-first protocol, aangezien de meerderheid van de patiënten een resectie van zowel de primaire tumor als de levermetastase onderging met genezing als doel.

In **hoofdstuk 8** wordt een samenvatting gegeven van de voorgaande hoofdstukken, alsook een algemene discussie en toekomstperspectieven voor rectumsparende behandelingen van patiënten met rectumcarcinoom.

Appendices

LIST OF PUBLICATIONS

THIS THESIS

1. **Verseveld M**, Barendse RM, Dawson I, Vos EL, de Graaf EJR, Doornebosch PG
   Intramucosal carcinoma of the rectum can be safely treated with transanal endoscopic microsurgery; clinical support of the revised Vienna classification.
   Surgical Endoscopy 2014 nov; 28(11): 3210-5.
2. **Verseveld M**, Eelco JR de Graaf, Cornelis Verhoef, Esther van Meerten, Cornelis JA Punt, Ignace HJT de Hingh, Iris D Nagtegaal, Joost JME Nuyttens, Corrie AM Marijnen, Johannes HW de Wilt
   The CARTS study: Chemoradiation therapy for rectal cancer in the distal rectum followed by organ-sparing transanal endoscopic microsurgery.
   British Journal of Surgery 2015 Jun; 102(7): 853-60
3. **Verseveld M**, Renée M. Barendse, Martijn P. Gosselink, Cornelis Verhoef, Eelco J.R. de Graaf, Pascal G. Doornebosch
   Transanal Minimally Invasive Surgery; impact on quality of life and functional outcome.
   Surgical Endoscopy 2016 Mar; 30(3):1184-7
4. Nierop PMH, **Verseveld M**, Galjart B, Rothbarth J, Nuyttens JJME, van Meerten E, Burger JWA, Grünhagen DJ, Verhoef C
   The liver-first approach for locally advanced rectal cancer and synchronous liver metastases.
   European Journal of Surgical Oncology 2019 Apr; 45(4):591-596
5. **Verseveld M**, de Wilt JHW, Elferink MAG, de Graaf EJR, Verhoef C, Pouwels S, Doornebosch PG
   Survival after local excision for rectal cancer: a population-based overview of clinical practice and outcome
   Acta Oncologica 2019 Aug; 58(8):1163-1166
6. **Verseveld M**, Verver D, Noordman BJ, Pouwels S, Elferink MAG, de Graaf EJR, Verhoef C; Doornebosch PG, de Wilt JHW
   Treatment of clinical T1 rectal cancer in the Netherlands; a population-based overview of clinical practice
   *European Journal of Surgical Oncology 2021 Nov 13; S0748-7983(21)00787-3*9.

OTHER PUBLICATIONS

1. Topal B, Smelt HJM, Van Helden EV, Celik A, **Verseveld M**, Smeenk F, Pouwels S
   Utility of preoperative exercise therapy in reducing postoperative morbidity after surgery; a clinical overview of current evidence
   Expert Review of Cardiovascular Therapy 2019 Jun; 17(6):395-412
2. Hendriks S, **Verseveld M**, Boevé ER, Roomer R.
   Successful endoscopic treatment of a large impacted gallstone in the duodenum using laser lithotripsy, Bouveret's syndrome: A case report
   World Journal of Gastroenterology 2020 May 21;26(19):2458-2463
3. Jeroen W.A. Leijtens, Lisanne J.H. Smits, Thomas W.A. Koedam, Ricardo G. Orsini, Susanna M. van Aalten, **Maria Verseveld**, Pascal G. Doornebosch, Eelco J.R. de Graaf, Jurriaan B. Tuynman
   Long-term oncological outcomes after surgical local excision of T1 rectal cancer
   Manuscript accepted by Techniques in Coloproctology 2022
4. Daniel Bakker, Louis de Jong, Jesse van Buijtenen, **Maria Verseveld**
   Traumatic inguinal hernia after fall from truck on a broom
   Trauma Case Reports 2022 Jan; 39:100617
5. Hazen SM, Sluckin T, Beets G, Hompes R, Tanis P, Kusters M; Dutch Lateral Node Study Group, Aalbers AGJ, Aukema TS, van der Bilt JDW, den Boer FC, Boerma EG, van den Broek WT, Burger JWA, Consten ECJ, Crolla RMPH, Dekker JWT, Demirkiran A, Doornebosch PG, van Duyn EB, van Essen JA, Furnée EJB, van Geloven AAW, Gerhards MF, Grotenhuis BA, Fabry HFJ, Harlaar NJ, Hoff C, Holman FA, van der Hul RL, Kortekaas RTJ, Lamme B, Leijtens JWA, Lettinga T, Logeman F, Marinelli AWKS, El-Massoudi Y, van der Meij W, Melenhorst J, de Mey DJL, Mulder EJ, Neijenhuis PA, de Nes LCF, Nieuwenhuijzen GAP, Nonner J, Pereboom ITA, Polat F, Pultrum BB, Oosterling SJ, Richir MC, de Roos MAJ, Rothbarth J, Schasfoort RA, Sietses C, Spillenaar Bilgen EJ, Slooter GD, Talsma AK, Verberne CJ, Vermaas M, **Verseveld M**, Vogelaar FJ, van Vugt ST, Wegdam JA, van Wely BJ, Westerterp M, van Westreenen, HL, Wijsman JH, de Wilt JHW
   Current practices concerning the assessment and treatment of lateral lymph nodes in low rectal cancer: a survey among colorectal surgeons in The Netherlands
   Acta Chirurgica Belgium. 2021 Online ahead of print

PORTFOLIO

Name PhD student:	Mareille Verseveld, MD
Erasmus MC department:	Surgery, Division of Surgical Oncology
Research school:	Medicine
PhD period:	2014 – 2021
Promotors:	prof. dr. C. Verhoef, MD, PhD & prof. dr. J.W.H. de Wilt, MD, PhD
Copromotor:	dr. P.G. Doornebosch, MD, PhD

General Academic Skills

GCP WMO exam	2019

Oral Presentations

Masterclass gastrointestinal surgery, Otterlo, The Netherlands	2018
5th World Rectum Conference, Leiden, The Netherlands	2017
NVGIC congress (Alpine Summits) Hintertux, Austria	2015
2nd World Rectum Conference 2014, Leiden, The Netherlands	2014

Poster Presentations

United European Gastroenterology Week, Amsterdam, The Netherlands	2014
European Society of Coloproctology, Barcelona, Spain (2x)	2014

(Inter)national Conferences

40th European Society of Surgical Oncology congress, Lisbon, Portugal	2021
European Society of Coloproctology, Nice, France	2018
Masterclass gastrointestinal surgery, Otterlo, The Netherlands	2018
NVGIC, Ibiza, Spain	2017
European Colorectal Congress, St. Gallen, Switzerland	2017
5th World Rectum Conference, Leiden, The Netherlands	2017
Congress 5D's, Ermelo, The Netherlands	2016
ESSO Krakow, Poland	2016
NVGIC congress (Alpine Summits) Hintertux, Austria	2015
European Society of Coloproctology Barcelona, Spain	2014
ECCO Liverpool, United Kingdom	2014
2nd World Rectum Conference 2014, Leiden, The Netherlands	2014

Other

Chairman Wondcongres, Rotterdam, The Netherlands	2016

CURRICULUM VITAE

Maria Verseveld, Mareille, werd geboren op 21 augustus 1979 in Leiden. In 1996 behaalde zij haar HAVO diploma aan het Groene Hart Lyceum in Alphen aan den Rijn, waarna ze de opleiding tot operatieassistent volgde. Na haar diplomering als operatieassistent, het opheffen van haar deficiënties en afleggen van een colloquium doctum startte zij in 2001 met haar studie Geneeskunde in Leiden. Eind 2006 behaalde zij haar artsexamen.

Tijdens haar studie en coschappen bleef zij werkzaam als operatieassistente totdat zij in 2006 met haar eerste baan als ANIOS urologie startte in het Antoniushove Ziekenhuis in Leidschendam, tegenwoordig Haaglanden MC. Per 1 januari 2008 startte zij met haar opleiding tot uroloog in Leiden, destijds nog onder professor Jaap Zwartendijk. Haar chirurgische vooropleiding vond plaats in het toenmalige Zuider – en Clara ziekenhuis, tegenwoordig Maasstad Ziekenhuis, in Rotterdam bij toenmalige opleider Erwin van der Harst. Na haar chirurgische vooropleiding vervolgde zij haar opleiding urologie nog 1 jaar in Den Haag, maar besloot toch de overstap te maken naar de chirurgie.

Januari 2010 startte zij haar 3e jaar chirurgie in het IJsselland Ziekenhuis in Capelle aan den IJssel, onder opleider Imro Dawson. Onder begeleiding van Eelco de Graaf en Pascal Doornebosch zette zij haar eerste wetenschappelijke stappen. Haar differentiatie tot oncologisch en gastro-intestinaal chirurg volgde zij in “De Daniël”, oftewel het Erasmus MC Kankerinstituut in Rotterdam bij Pim Burger en professor Kees Verhoef en in het IJsselland Ziekenhuis in Capelle aan den IJssel.

Na het afronden van haar chirurgie opleiding per 1 januari 2015, volgde zij een fellowship colorectale en bariatrische chirurgie in het St Antonius ziekenhuis in Nieuwegein en was zij chèf de clinique in het Hofpoort ziekenhuis in Woerden. In oktober 2015 startte zij met haar fellowship colorectale oncologische chirurgie in het Catharina Ziekenhuis in Eindhoven bij professor Harm Rutten. Naast ruime ervaring op het gebied van (laparoscopisch) opereren, deed zij veel kennis op omtrent het locally advanced rectumcarcinoom.

In 2017 werd zij moeder van zoon Teun. In datzelfde jaar werd zij chèf de clinique in het Haaglanden MC in Den Haag totdat zij in september 2017 toetrad tot de vakgroep chirurgie van het Franciscus Gasthuis en Vlietland in Rotterdam / Schiedam. In 2018 trouwde zij met René Klaassen en in 2019 werd zij opnieuw moeder, van dochter Guus.

In het Franciscus Gasthuis en Vlietland zet zij zich met veel plezier en passie in voor patiënten met colorectale maligniteiten, patiënten met IBD, buikwandbreuken en melanoom. Zij levert een actieve bijdrage aan de opleiding van aankomende chirurgen, is PA- en fellow-opleider en geeft onderwijs aan verpleegkundigen en operatieassistenten. Tevens is en blijft zij bij meerdere studies en onderzoeken betrokken.

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Lieve Eelco, wat heb ik veel van jou geleerd. Vaak met een lach, soms met een grom, maar altijd met een ongekend vertrouwen. Wat heb ik genoten van onze samenwerking, onze gesprekken over van alles en het hebben van jou als leermeester. Rugbyspeler in hart en nieren, wijs en kundig chirurg, maar bovenal vader van Joris en echtgenoot van Tiny, wat een prachtig mens ben je! Voor mij ben je echt een voorbeeld geweest en nog! Oneindig veel dank voor al je wijze (levens)lessen!

Lieve Pascal, ik heb jou in mijn jaren als operatieassistente al mogen leren kennen. Het was het jaar 2000, Leiderdorp, Rijnland Ziekenhuis.. jij nog arts-assistent en ik nog deficiënties aan het wegpoetsen. Wij ontmoetten elkaar opnieuw in Capelle, wie had ooit gedacht dat jij mijn copromotor zou worden. En man... wat heb jij je ongelooflijk ingezet om mij te begeleiden en er soms ook doorheen te trekken. Dank voor je vertrouwen, je ongekende steun wat betreft van alles.. dank dank dank!

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Imro Dawson, opleider uit duizenden. Jouw wijze lessen en grappen klinken nog steeds na in mijn hoofd: “Wist je dat niet? Dat was een Capelli 31!!” als je weer een prachtige operatie-move maakte! En als ik iets wat minder handig deed: “Mareille… zo knipt een kapper..”, “Mareille.. dat is voor grappenmakers!” Inmiddels met pensioen, maar nog altijd volle betrokkenheid en interesse in jouw IJsvogeltjes! Dank, lieve Imro, voor je jarenlange en nog steeds durende steun!

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Kort, maar intens plezierig was mijn tijd in het HMC. Veel dank in het bijzonder aan Joost, Marieke, Marinke, Gijs, Andreas, Mireille en Wolter. Thank you for having me!

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