Long-term outcome of rectal cancer treatment

Lange, M.M.

CHAPTER 1

General introduction and outline

EPIDEMIOLOGY

Colorectal cancer is the third most frequent cancer diagnosed in men (after lung and prostate cancer) and the second most frequent cancer diagnosed in women (after breast cancer).[1] About 10 000 new cases are diagnosed in The Netherlands each year, of which approximately 25 percent are located in the rectum.[2] The incidence rate is increasing. This is mainly due to earlier detection and increasing age of the population, as the highest incidence of rectal cancer is found in the sixth and seventh decade. Five-year survival rate of rectal cancer is about 60 percent and depends to a large extent on the Tumour Node Metastases (TNM) stage at diagnosis.

PRETREATMENT STAGING

The TNM staging system is the gold standard for prognostication of rectal cancer relying on the morphological and histopathological appearance of the tumour.[3] Classification into stages with distinct clinical courses enables the clinicians to define treatment. Preoperative imaging with computed tomography (CT) is used to identify extrapelvic metastases, whereas magnetic resonance imaging (MRI) and endorectal ultrasound (EUS) is used for staging and evaluating locoregional disease. The evaluation of regional lymph node involvement remains relatively inaccurate. In addition, MRI is used for visualising the mesorectal fascia and predicting if negative surgical margins can be achieved. In that case the tumour is considered surgically resectable for cure, which comprises approximately 75 percent.[4]

SURGICAL TREATMENT

Surgical resection with total mesorectal excision (TME) is the predominant treatment option for rectal cancer. Resection of rectal cancer is relatively difficult due to the close relation of the rectum to the surrounding structures and the narrow access in the deep pelvis. Direct view of the operative field is difficult during deep dissection, explaining why rectal resection for cancer remains one of the operations in elective abdominal surgery that most frequently requires perioperative blood transfusions.[5] A reduction of blood transfusion has been accomplished especially by sharp dissection in the avascular plane between the mesorectum and the surrounding tissues, which is implicated in the TME technique.[6] Furthermore, the assumed increased risk of morbidity and mortality has led to a critical attitude towards blood transfusion.

In addition, universal leukocyte depletion has been implemented in order to prevent transfusion induced morbidity, which will be further discussed in Chapter 9.[7]

Anatomically, the rectum extends from the anal verge for about 12-15 cm, where it curves anteriorly and merges into the sigmoid. Circumferentially the rectum is surrounded by fatty and connective tissue, which is known as the mesorectum. Starting at the sacral promontory, the mesorectum being most pronounced at the dorsal site of the rectum diminishes below the rectosacral fascia around the levator ani muscles at the end of the distal third of the rectum. The mesorectum frequently contains microscopic tumour deposits, resulting from radial spread of the tumour. The concept of lymphatic spread and the importance of the removal of the mesorectal tissue had already been established by Miles in 1908.[8] Miles' impact on the development of rectal cancer treatment will be discussed in Chapter 2. The aim of TME, which was popularised by Heald in 1979, is complete removal of the mesorectum through sharp dissection along pre-existing embryologically determined planes, allowing the preservation of the pelvic autonomic nerves.[9] This technique has become the gold standard, however routine TME in rectal cancer at all levels has been challenged in view of increased risk of anastomotic leakage.[10] The extent of distal tumour spread in the mesorectum after multimodality treatment is currently under discussion. Partial mesorectal excision might be more appropriate for upper rectal cancer.

The TME technique results in reproducible specimens for pathological examination. The pathologist determines the quality of the resected specimen by assessment of resection margins. Studies of Quirke *et al*. have shown that, rather than the distal and proximal margin, the circumferential resection margin (CRM) is of importance for prediction of prognosis.[11] The CRM is considered positive when tumour tissue approaches the resection margin within one millimetre, increasing the risk of local recurrence significantly.[12] The development of the TME technique has led to a reduced risk of positive CRM and a significant decrease of local recurrence rates from (12-20 to 4 percent).[13] For determination of the nodal status also the number of involved lymph nodes is determined during pathological examination. Excision of a minimum of 10 lymph nodes is recommended for determining a negative nodal status.[14]

LOW ANTERIOR RESECTION *VERSUS* ABDOMINOPERINEAL RESECTION

The introduction of TME, the understanding that distal resection margins of 1-2 cm are adequate and the possibility of tumour downsizing allowed abdominoperineal resection (APR) to be relegated to use only in a minority of patients.[15-19] Sphincter

preservation by low anterior resection (LAR) is currently the gold standard. Traditionally, the construction of a colostomy, which is implicated in APR, has been regarded as an unfavourable outcome, as quality of life of patients with a colostomy is believed to be inferior to patients without a colostomy. However, recent studies have shown that quality of life after APR may be not as bad as once believed and may be equal or worse after LAR due to faecal incontinence, which occurs frequently after restorative surgery.[20-26]

Furthermore, the rise in sphincter saving procedures might contribute to an increase of anastomotic failure. Anastomotic leakage is a frequently reported complication after LAR (5-26 percent) and is associated with high morbidity and mortality rates.[2,5,6] A defunctioning stoma reduces the risk of clinically relevant anastomotic leakage.[27] Furthermore, the construction of a tension free anastomosis with good blood supply is of major importance and may be influenced by the level of arterial ligation during TME, which will be further discussed in Chapter 3.[28-30]

(NEO-)ADJUVANT THERAPY

Short-course preoperative radiotherapy (PRT; 5x5 Gy) increased both local control and overall survival in the Swedish Rectal Cancer Trial.[31,32] However, in this trial, surgery consisted of conventional resection, which implies blunt dissection of the rectal fascia, resulting in incomplete removal of the mesorectal tissue. To evaluate the benefits of PRT followed by TME surgery, the Dutch Colorectal Cancer Group conducted the Dutch TME trial. This was a nationwide clinical randomised controlled trial comparing PRT and TME surgery with TME surgery alone. From January 1996 till December 1999 1 861 patients where randomised. Standardisation and quality control of surgery, radiotherapy and pathology were achieved by means of a monitoring committee of specially trained instructor surgeons, a panel of supervising pathologists and study coordinators for surgery, radiotherapy and pathology. Results showed no effect on survival but a reduced local recurrence rate after short-course PRT, which has become the most common type of treatment in Europe.[33] However, long-course PRT (45-55 Gy in 1.8 Gy fractions over 4-6 weeks) combined with chemotherapy is also frequently used.[34] In case of locally advanced tumours with a threatened or involved CRM, this treatment regimen facilitates resection by downsizing the tumour.[35] A randomised phase III study (Stockholm III) is presently ongoing, comparing long-course PRT and short-course PRT with immediate or delayed surgery.

FUNCTIONAL OUTCOME

Until recently research in rectal cancer treatment has mainly focused on local recurrence and survival rates. However, not only improved tumour control should play a role in the debate concerning rectal cancer treatment, but also morbidity. In addition to faecal incontinence, urinary and sexual dysfunctions are frequent and distressing complications of rectal cancer treatment.[36-38] It is suggested that pelvic organ function is impaired by radiotherapy, but function can also be affected by surgery alone.[22,39,40] Damage to the pelvic nerve system might be involved.[36,41] Damage to the autonomic innervation of the pelvic organs was long thought to be an inevitable part of radical surgery for rectal cancer. However, encouraged by improved cure rates of oncologic treatment, more research changed its focus of attention from eradication of the tumour only, towards combining cure with quality of life of patients after treatment. The surgical concept of nerve identification and preservation was initiated in Japan, where resection techniques were developed which allowed preservation of the autonomic innervation of the pelvic organs (hypogastric nerves, inferior hypogastric plexus and pelvic splanchnic nerves).[42] The American surgeon Enker combined the nerve preserving principle with the TME technique, resulting in intact urogenital function in almost 90 percent of patients, without compromising oncologic outcome.[43] Moriya confirmed the feasibility and safety of the nerve sparing technique in a prospective study of 47 patients in the Netherlands.[44] Surgical training programmes spread the technique of TME with nerve preservation world-wide. However, despite this, clinical studies report a high incidence of pelvic organ dysfunction and the good functional results achieved by expert rectal surgeons have not yet been reproduced in larger studies.[22,38,45] The contribution of each treatment component in the development of anorectal and urogenital dysfunction remains unclear. There is a general lack of large prospective studies concerning long-term functional morbidity after multimodality treatment for rectal cancer, especially with respect to female sexual functioning. The Dutch TME trial was the first trial in which long-term functional outcome was documented extensively, which will be the main focus of the current thesis.

OUTLINE

The aim of this thesis was to evaluate long-term results of rectal cancer treatment, specifically focusing on the etiology of long-term morbidity.

Chapter 2 is a historical overview describing the impact of Miles, who introduced radical APR, on the development of rectal cancer treatment. With respect to arterial

ligation during rectal cancer surgery, Miles recommended division of the superior rectal artery just distally to the origin of the left colic artery (low tie).[8] Moynihan was the first who advocated resection of the inferior mesenteric artery at its origin (high tie).[46] The level of ligation has been suggested to be associated with oncologic and functional outcome.[47,48] Currently, consensus does not exist and the level at which the arterial supply is ligated during rectal cancer surgery varies greatly, depending largely on the surgeon.[49] **Chapter 3** systematically reviews the evidence of benefits of both ligation techniques.

Chapter 4, Chapter 5 and **Chapter 6** evaluate long-term sexual dysfunction, urinary dysfunction and faecal incontinence after rectal cancer treatment, respectively. In order to gain insight into the etiology, risk factors associated with poor functional outcome were identified in the database of the Dutch TME trial. **Chapter 7** presents a hypothetical patient with incontinence problems after rectal cancer surgery and discusses the incidence, etiology and available treatment modalities. Incontinence problems may be caused by surgical damage to the innervation of the pelvic floor muscles, which are a crucial component of the urinary and faecal continence system.[50,51] **Chapter 8** combines anatomical findings and analysis of clinical data to evaluate nerve disruption during TME as a cause of poor functional outcome, with special attention to the pelvic floor innervation and incontinence.

Excessive blood loss during rectal cancer surgery is associated with surgical nerve disruption, resulting in functional morbidity, but also with blood transfusion, increasing the risk of short-term morbidity.[45,52-54] Moreover, blood transfusions are reported to be associated with poor cancer prognosis.[55] The presence of allogeneic leukocytes in transfusion products is presumed to impair response against cancer.[56] **Chapter 9** reports the long-term recurrence and survival rates of a randomised controlled trial comparing leukocyte depleted and non-leukocyte depleted red blood cell transfusion in gastrointestinal cancer patients.

Chapter 10 provides a discussion of the data presented in this thesis.

REFERENCE LIST

1. Zampino MG, Labianca R, Beretta G et al. Rectal cancer. Crit Rev Oncol Hematol 2004; 51: 121-43.
2. Association of Comprehensive Cancer Centres. Utrecht, The Netherlands. [August 2008 last accessed].
3. Sobin LH. TNM, sixth edition: new developments in general concepts and rules. Semin Surg Oncol 2003; 21: 19-22.
4. Lahaye MJ, Engelen SM, Nelemans PJ et al. Imaging for predicting the risk factors--the circumferential resection margin and nodal disease--of local recurrence in rectal cancer: a meta-analysis. Semin Ultrasound CT MR 2005; 26: 259-68.
5. Benoist S, Panis Y, Pannegeon V, Alves A, Valleur P. Predictive factors for perioperative blood transfusions in rectal resection for cancer: A multivariate analysis of a group of 212 patients. Surgery 2001; 129: 433-9.
6. Mynster T, Nielsen HJ, Harling H, Bulow S. Blood loss and transfusion after total mesorectal excision and conventional rectal cancer surgery. Colorectal Dis 2004; 6: 452-7.
7. Murphy MF. Potential clinical benefits and cost savings of universal leucocyte-depletion of blood components. Transfus Sci 1998; 19: 343-6.
8. Miles WE. A method of performing abdominoperineal excision for carcinoma of the rectum and of the terminal portion of the pelvic colon. Lancet 1908; 2: 1812-3.
9. Heald RJ. A new approach to rectal cancer. Br J Hosp Med 1979; 22: 277-81.
10. Law WL, Chu KW. Anterior resection for rectal cancer with mesorectal excision: a prospective evaluation of 622 patients. Ann Surg 2004; 240: 260-8.
11. Quirke P, Durdey P, Dixon MF, Williams NS. Local recurrence of rectal adenocarcinoma due to inadequate surgical resection. Histopathological study of lateral tumour spread and surgical excision. Lancet 1986; 2: 996-9.
12. Adam IJ, Mohamdee MO, Martin IG et al. Role of circumferential margin involvement in the local recurrence of rectal cancer. Lancet 1994; 344: 707-11.
13. Heald RJ. Rectal cancer: the surgical options. Eur J Cancer 1995; 31A: 1189-92.
14. Cserni G, Vinh-Hung V, Burzykowski T. Is there a minimum number of lymph nodes that should be histologically assessed for a reliable nodal staging of T3N0M0 colorectal carcinomas? J Surg Oncol 2002; 81: 63-9.
15. Engel AF, Oomen JL, Eijsbouts QA, Cuesta MA, van de Velde CJ. Nationwide decline in annual numbers of abdomino-perineal resections: effect of a successful national trial? Colorectal Dis 2003; 5: 180-4.
16. Guren MG, Eriksen MT, Wiig JN et al. Quality of life and functional outcome following anterior or abdominoperineal resection for rectal cancer. Eur J Surg Oncol 2005; 31: 735-42.
17. Heald RJ, Smedh RK, Kald A, Sexton R, Moran BJ. Abdominoperineal excision of the rectum--an endangered operation. Norman Nigro Lectureship. Dis Colon Rectum 1997; 40: 747-51.
18. Karanjia ND, Schache DJ, North WR, Heald RJ. 'Close shave' in anterior resection. Br J Surg 1990; 77: 510-2.
19. Rasmussen OO, Petersen IK, Christiansen J. Anorectal function following low anterior resection. Colorectal Dis 2003; 5: 258-61.

20. Bretagnol F, Troubat H, Laurent C, Zerbib F, Saric J, Rullier E. Long-term functional results after sphincter-saving resection for rectal cancer. Gastroenterol Clin Biol 2004; 28: 155-9.
21. Grumann MM, Noack EM, Hoffmann IA, Schlag PM. Comparison of quality of life in patients undergoing abdominoperineal extirpation or anterior resection for rectal cancer. Ann Surg 2001; 233: 149-56.
22. Marijnen CA, van de Velde CJ, Putter H et al. Impact of short-term preoperative radiotherapy on health-related quality of life and sexual functioning in primary rectal cancer: report of a multicenter randomized trial. J Clin Oncol 2005; 23: 1847-58.
23. Ortiz H, Armendariz P. Anterior resection: do the patients perceive any clinical benefit? Int J Colorectal Dis 1996; 11: 191-5.
24. Pachler J, Wille-Jorgensen P. Quality of life after rectal resection for cancer, with or without permanent colostomy. Cochrane Database Syst Rev 2005; CD004323.
25. Peeters KC, van de Velde CJ, Leer JW et al. Late side effects of short-course preoperative radiotherapy combined with total mesorectal excision for rectal cancer: increased bowel dysfunction in irradiated patients--a Dutch colorectal cancer group study. J Clin Oncol 2005; 23: 6199-206.
26. Williamson ME, Lewis WG, Finan PJ, Miller AS, Holdsworth PJ, Johnston D. Recovery of physiologic and clinical function after low anterior resection of the rectum for carcinoma: myth or reality? Dis Colon Rectum 1995; 38: 411-8.
27. Matthiessen P, Hallbook O, Rutegard J, Simert G, Sjodahl R. Defunctioning stoma reduces symptomatic anastomotic leakage after low anterior resection of the rectum for cancer: a randomized multicenter trial. Ann Surg 2007; 246: 207-14.
28. Bruch HP, Schwandner O, Schiedeck TH, Roblick UJ. Actual standards and controversies on operative technique and lymph-node dissection in colorectal cancer. Langenbecks Arch Surg 1999; 384: 167-75.
29. Hida J, Yasutomi M, Maruyama T et al. Indication for using high ligation of the inferior mesenteric artery in rectal cancer surgery. Examination of nodal metastases by the clearing method. Dis Colon Rectum 1998; 41: 984-7.
30. Nano M, Dal Corso H, Ferronato M et al. Ligation of the inferior mesenteric artery in the surgery of rectal cancer: anatomical considerations. Dig Surg 2004; 21: 123-6.
31. Improved survival with preoperative radiotherapy in resectable rectal cancer. Swedish Rectal Cancer Trial. N Engl J Med 1997; 336: 980-7.
32. Folkesson J, Birgisson H, Pahlman L, Cedermark B, Glimelius B, Gunnarsson U. Swedish Rectal Cancer Trial: long lasting benefits from radiotherapy on survival and local recurrence rate. J Clin Oncol 2005; 23: 5644-50.
33. Kapiteijn E, Marijnen CA, Nagtegaal ID et al. Preoperative radiotherapy combined with total mesorectal excision for resectable rectal cancer. N Engl J Med 2001; 345: 638-46.
34. Bosset JF, Collette L, Calais G et al. Chemotherapy with preoperative radiotherapy in rectal cancer. N Engl J Med 2006; 355: 1114-23.
35. Mohiuddin M, Regine WF, Marks GJ, Marks JW. High-dose preoperative radiation and the challenge of sphincter-preservation surgery for cancer of the distal 2 cm of the rectum. Int J Radiat Oncol Biol Phys 1998; 40: 569-74.
36. Moriya Y. Function preservation in rectal cancer surgery. Int J Clin Oncol 2006; 11: 339-43.
37. Pollack J, Holm T, Cedermark B et al. Late adverse effects of short-course preoperative radiotherapy in rectal cancer. Br J Surg 2006; 93: 1519-25.

38. Vironen JH, Kairaluoma M, Aalto AM, Kellokumpu IH. Impact of functional results on quality of life after rectal cancer surgery. Dis Colon Rectum 2006; 49: 568-78.
39. Bonnel C, Parc YR, Pocard M et al. Effects of preoperative radiotherapy for primary resectable rectal adenocarcinoma on male sexual and urinary function. Dis Colon Rectum 2002; 45: 934-9.
40. Nesbakken A, Nygaard K, Bull-Njaa T, Carlsen E, Eri LM. Bladder and sexual dysfunction after mesorectal excision for rectal cancer. Br J Surg 2000; 87: 206-10.
41. Rees PM, Fowler CJ, Maas CP. Sexual function in men and women with neurological disorders. Lancet 2007; 369: 512-25.
42. Hojo K, Vernava AM, III, Sugihara K, Katumata K. Preservation of urine voiding and sexual function after rectal cancer surgery. Dis Colon Rectum 1991; 34: 532-9.
43. Enker WE. Potency, cure, and local control in the operative treatment of rectal cancer. Arch Surg 1992; 127: 1396-401.
44. Maas CP, Moriya Y, Steup WH, Klein KE, van de Velde CJ. A prospective study on radical and nerve-preserving surgery for rectal cancer in the Netherlands. Eur J Surg Oncol 2000; 26: 751-7.
45. Junginger T, Kneist W, Heintz A. Influence of identification and preservation of pelvic autonomic nerves in rectal cancer surgery on bladder dysfunction after total mesorectal excision. Dis Colon Rectum 2003; 46: 621-8.
46. Moynihan BGA. The surgical treatment of cancer of the sigmoid flexure and rectum. Surg Gynecol Obstet 1908; 463.
47. Deddish MR. Abdominopelvic lymphnode dissection in cancer of the rectum and distal colon. Cancer 1951; 4: 1364-6.
48. Koda K, Saito N, Seike K, Shimizu K, Kosugi C, Miyazaki M. Denervation of the neorectum as a potential cause of defecatory disorder following low anterior resection for rectal cancer. Dis Colon Rectum 2005; 48: 210-7.
49. Surtees P, Ritchie JK, Phillips RK. High versus low ligation of the inferior mesenteric artery in rectal cancer. Br J Surg 1990; 77: 618-21.
50. Ashton-Miller JA, DeLancey JO. Functional anatomy of the female pelvic floor. Ann N Y Acad Sci 2007; 1101: 266-96.
51. Madoff RD, Parker SC, Varma MG, Lowry AC. Faecal incontinence in adults. Lancet 2004; 364: 621-32.
52. Jensen LS, Kissmeyer-Nielsen P, Wolff B, Qvist N. Randomised comparison of leucocyte-depleted versus buffy-coat-poor blood transfusion and complications after colorectal surgery. Lancet 1996; 348: 841-5.
53. Tartter PI. Perioperative blood transfusion and colorectal cancer recurrence: a review. J Surg Oncol 1988; 39: 197-200.
54. van Hilten JA, van de Watering LM, van Bockel JH et al. Effects of transfusion with red cells filtered to remove leucocytes: randomised controlled trial in patients undergoing major surgery. BMJ 2004; 328: 1281.
55. Gantt CL. Red blood cells for cancer patients. Lancet 1981; 2: 363.
56. Miller JP, Mintz PD. The use of leukocyte-reduced blood components. Hematol Oncol Clin North Am 1995; 9: 69-90.