Long-term outcome of rectal cancer treatment

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Marilyne Lange

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Aan mijn ouders

CONTENTS

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.

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CHAPTER 2

One hundred years of curative surgery for rectal cancer: 1908-2008

Lange MM, Rutten HJ, van de Velde CJH.

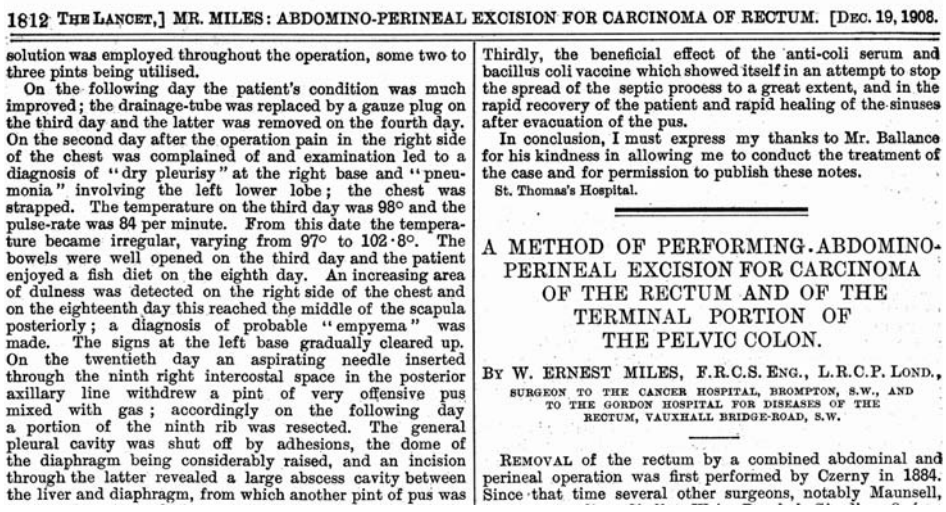
European Journal of Surgical Oncology. In press

ABSTRACT

In 1908, William Ernest Miles published his article in the Lancet, introducing the basis of modern rectal cancer surgery. He established the basis for curative cancer treatment by combining the knowledge of anatomy and biological behaviour with improved surgical options as a result of better anaesthesiological techniques. Miles' contribution comprised the introduction of the concept of lymphatic spread of cancer cells and his consequent radical surgical resection, removing all primary lymph nodes *en bloc*. Miles' concept has dominated the minds of surgeons throughout the 20th century and his abdominoperineal resection has been the gold standard for several decades. However, his concept of downward spread of rectal cancer was proven wrong, which initiated the historical shift from radical abdominoperineal resection to the use of sphincter saving surgery. Since the introduction of total mesorectal excision, abdominoperineal excision has been performed in only a minority of patients. Further improvement in surgical technique consisted of autonomic nerve preservation, improving functional outcome. From a historical overview, it can be concluded that the management of rectal cancer has been progressed tremendously over the past 100 years, mainly because of an increased understanding of the pathology and natural history of the disease, which has been initiated by Miles.

INTRODUCTION

In 1908, William Ernest Miles published his article in the Lancet, introducing the basis of modern rectal cancer surgery (Figure 1).[1] He established the basis for curative cancer treatment by combining the knowledge of anatomy and biological behaviour with improved surgical options as a result of better anaesthesiological techniques. Nineteenth-century anatomists have provided the basis for surgical dissection within anatomically defined planes (Figure 2). Waldeyer's anatomical atlas (Das Becken 1899) is still an important reference book (Figure 3).[2] At that time, anaesthesiology was greatly improved by the introduction of combined spinal and gas anaesthesia, enabling laparotomy under muscle relaxation. Joseph Lister developed surgical antisepsis to a level it was safe to perform a laparotomy without the increased risk of peritonitis. Miles' contribution comprised the introduction of the concept of lymphatic spread of cancer cells and his consequent surgical resection, removing all primary lymph nodes *en bloc*. The world-wide establishment of Miles' abdominoperineal amputation of the rectum meant the acknowledgement of the fact that cancer surgery should be based on anatomical and biological principles. These principles, only slightly adjusted, are still applied nowadays as much as 100 years ago. The influence of Miles and the evolving understanding of the natural history of the disease on the development of rectal cancer treatment in the past century will be discussed in the following historical overview (Figure 4).



1812 THE LANCET,] MR. MILES: ABDOMINO-PERINEAL EXCISION FOR CARCINOMA OF RECTUM. [DEC. 19, 1908.

solution was employed throughout the operation, some two to three pints being utilised.

On the following day the patient's condition was much improved; the drainage-tube was replaced by a gauze plug on the third day and the latter was removed on the fourth day. On the second day after the operation pain in the right side of the chest was complained of and examination led to a diagnosis of "dry pleurisy" at the right base and "pneumonia" involving the left lower lobe; the chest was strapped. The temperature on the third day was 98° and the pulse-rate was 84 per minute. From this date the temperature became irregular, varying from 97° to 102·8°. The bowels were well opened on the third day and the patient enjoyed a fish diet on the eighth day. An increasing area of dulness was detected on the right side of the chest and on the eighteenth day this reached the middle of the scapula posteriorly; a diagnosis of probable "empyema" was made. The signs at the left base gradually cleared up. On the twentieth day an aspirating needle inserted through the ninth right intercostal space in the posterior axillary line withdrew a pint of very offensive pus mixed with gas; accordingly on the following day a portion of the ninth rib was resected. The general pleural cavity was shut off by adhesions, the dome of the diaphragm being considerably raised, and an incision through the latter revealed a large abscess cavity between the liver and diaphragm, from which another pint of pus was

Thirdly, the beneficial effect of the anti-coli serum and bacillus coli vaccine which showed itself in an attempt to stop the spread of the septic process to a great extent, and in the rapid recovery of the patient and rapid healing of the sinuses after evacuation of the pus.

In conclusion, I must express my thanks to Mr. Ballance for his kindness in allowing me to conduct the treatment of the case and for permission to publish these notes.

St. Thomas's Hospital.

A METHOD OF PERFORMING ABDOMINO-PERINEAL EXCISION FOR CARCINOMA OF THE RECTUM AND OF THE TERMINAL PORTION OF THE PELVIC COLON.

BY W. ERNEST MILES, F.R.C.S. ENG., L.R.C.P. LOND.,

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REMOVAL of the rectum by a combined abdominal and perineal operation was first performed by Czerny in 1884. Since that time several other surgeons, notably Maunsell,

Figure 1. Original publication of W.E. Miles in the Lancet in 1908

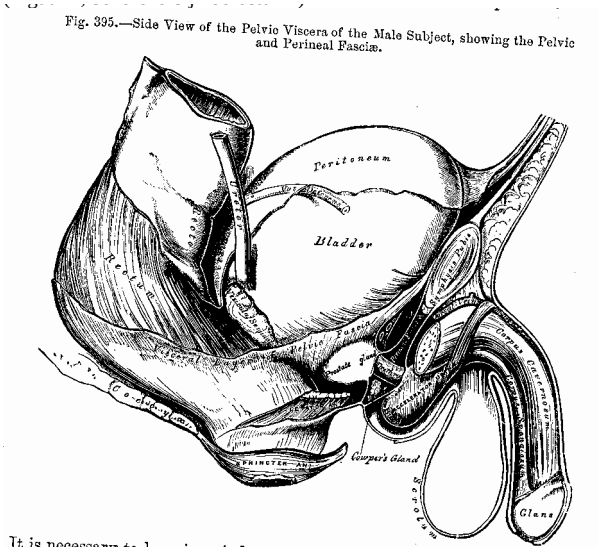

Figure 2. Illustration in Gray's Anatomy 1860, showing the extensive knowledge concerning pelvic fasciae in the 19th century.

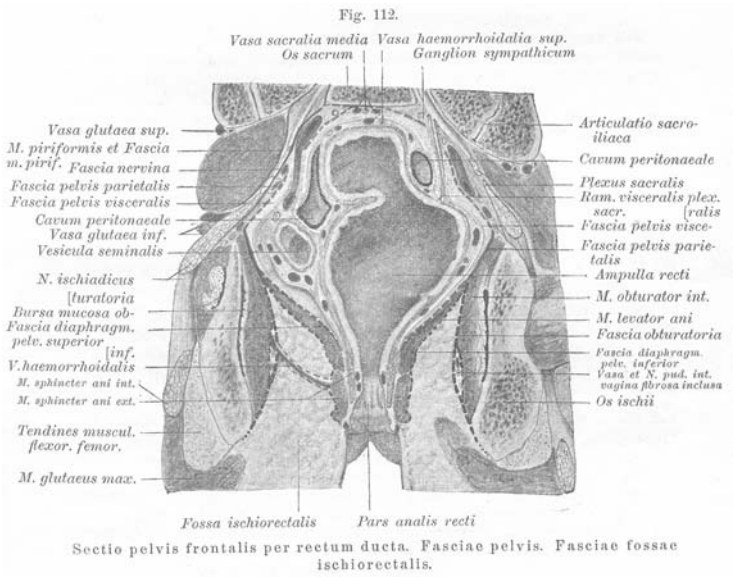

Figure 3. Anatomical illustration in Waldeyer's anatomical atlas (Das Becken 1899).

PERINEAL AND SACRAL RESECTION

Rectal resection was not performed until the early 19th century. Up to then defunctioning colostomy, as described by Amussat, was the only procedure used for the palliation of obstructive rectal cancer.[3] In the early eighteen hundreds, French

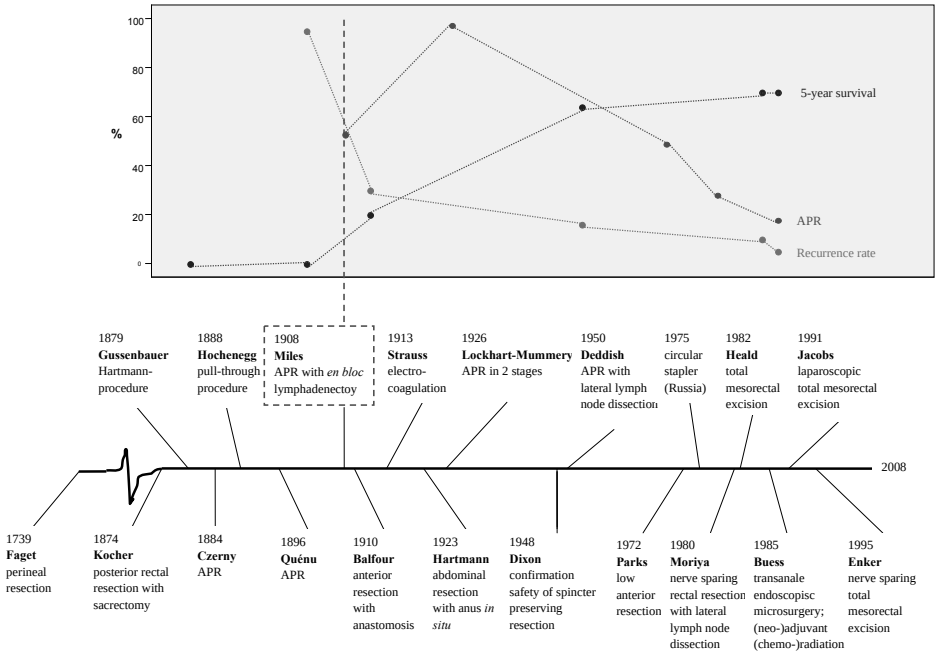

Figure 4. Timeline of important developments with respect to rectal cancer treatment also illustrating associated 5-year survival, recurrence rate and percentage of abdominoperineal resections (APR=abdominoperineal resection).

surgeons had begun to develop a bolder approach by aiming at direct ablation of the lesion through a perineal approach and with construction of a colostomy. The first perineal resection was probably performed accidentally by Jean Faget in 1739 and was carried out for the sequels of perforated rectal cancer presenting as a bilateral ischiorectal abcess.[4] Jacques Lisfranc performed the first perineal resection for a case of uncomplicated rectal cancer in 1826 by removing only a few centimetres of the distal rectum.[5] In 1874, the Swiss surgeon Theodor Kocher introduced the transsacral resection with coccygectomy, which was further extended by Paul Kraske to facilitate the operative exposure.[6,7] The main problem of the perineal and sacral approaches remained the limited exposure of the surgical field making it almost impossible to remove the tumour radically. Another problem was the construction of a sacral anus, which was difficult to manage for the patient. Rarely, a variant of the sacral resection is still performed in case of a small distal rectal tumour, through the so-called parasacral approach of York-Mason, dividing and subsequently restoring the sphincter complex.[8] However, this technique has been replaced by transanal endoscopic procedures.

ABDOMINAL RESECTION (HARTMANN PROCEDURE)

The mortality rate after perineal resection was mainly caused by peritonitis. Therefore, disruption of the peritoneum was considered a major surgical complication which should be avoided in rectal surgery. Two important developments at the turn of the 19th century enabled performing a laparotomy. First, the development of combined spinal and gas anaesthesia, facilitated laparotomy with muscle relaxation, making the complicated anatomy of the small pelvis accessible to the surgeon. Secondly, Joseph Lister showed how to apply surgical principles of asepsis. Together with Goodyear, he invented the sterile surgical glove. In 1879 the first abdominal resection of a proximal tumour with intraperitoneal closure of the distal rectum was performed by Carl Gussenbauer.[9] This method was strongly propagated by the French surgeon Henri Hartmann (Hôtel Dieu, Paris) for high-lying rectal cancer because peroperative blood loss was very limited, as the anus and pelvic floor were left *in situ*. The so-called Hartmann procedure is still performed for emergency or palliative procedures and in rare cases for curative resection, but above all it is standard practice for acute perforated diverticulitis, never meant as such by Hartmann himself.

ABDOMINOPERINEAL RESECTION (APR)

Miles received his medical education at St. Bartholomew Hospital in London and had been licensed to practice medicine in 1891 (Figure 5). He was a pupil of Harrison Cripps, known for his work on rectal pathology published in 1884.[10] Cripps was awarded the Jacksonian Prize by the Royal College of Surgeons in 1874 for his monograph on rectal cancer. Despite the cautious attitude towards perineal resection in England, because of the extremely high morbidity and mortality rates of continental surgeons, Cripps introduced rectal cancer surgery through perineal approach in England.

By the end of the 19th century, as light microscopy had been available for more than 100 years, the cellular basis of disease was commonly accepted. The etiology of cancer was less understood. Constitutionalists believed that metastases were multifocal, *de novo* developments of cancer. Cripps dissociated himself from this philosophy and described metastases as disseminations of the primary tumour through the blood or lymph vessels. Miles developed this interpretation further.

From 1899 to 1906, Miles performed 57 perineal resections. Of these patients 54 (95 percent) had early recurrences. Miles carried out *post mortem* examination and found recurrences in the pelvic peritoneum, in the mesocolon and in the lymph

Figure 5. W.E. Miles

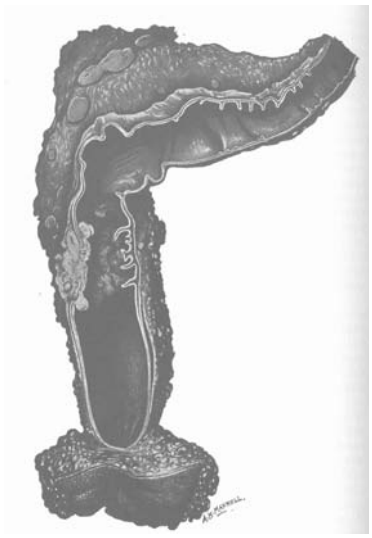

Figure 6. Specimen after Miles' abdominoperineal resection

nodes situated at the bifurcation of the left common iliac artery. Subsequently, he considered that spread occurred, particularly in the lymphatics, in all directions ("cylindrical concept") and that involved lymph nodes were responsible for the development of locally recurrent disease. Consequently, he developed *en bloc* resection of rectal cancer with associated lymph nodes through a combined abdominal and perineal approach: the APR was born. Removal of the rectum by a combined abdominal and perineal operation had been performed before (1884) by Vincent Czerny. He was forced to utilise this combined approach due to complications during sacral resection of a proximal tumour. However, the patient did not survive the procedure. Adding laparotomy to the perineal approach enabled resection of proximal lymph nodes and high-lying tumours. The wider abdominal access allowed Miles to bring the anatomical knowledge of the pelvic fasciae and spaces into practice and to perform an "anatomically correct" resection (Figure 6). Miles' revolutionary principles included (1) the necessity of an abdominal anus, which was much more manageable than a sacral artificial anus, (2) resection of the rectum and the sigmoid, as its blood supply is contained in the zone of upward spread, (3) resection of the mesorectum, (4) removal of the group of lymph nodes situated over the bifurcation of the common iliac artery, and lastly (5) wide perineal part of the operation with resection of the levator ani muscle so that the lateral and downward zones of spread could be effectively extirpated. In 1908, Miles introduced his technique, converting the R2 into a curative R0 resection for the first time. In 1923 Miles reported a recurrence rate of 29.5 percent.[11] The mortality rate of the first series of patients, for the most

part caused by blood loss and infectious complications (no blood transfusion and antibiotics available) was 31 percent. This reduced to 10 percent just before World War Two as a result of overall improvement in anaesthesia, patient care, patient selection, operability and other clinical modalities. Due to its mutilating nature, this operation was invariably associated with urogenital dysfunction. In the beginning, several surgeons other then Miles performed the procedure in two stages in order to limit blood loss, first constructing a colostomy and mobilising the rectum through a laparotomy. After several weeks the rectum would be resected through a perineal approach. Other surgeons, like Quénu and Lloyd-Davies, preferred to carry out APR in one stage, preferably by a simultaneous operating abdominal and perineal team in order to speed up the procedure. Until World War Two the technique of Lockhart-Mummery was more popular in the United States.[9] Lockhart-Mummery initially used the sigmoid to construct a stoma and after several weeks he resected the rectum through a perineal approach. The English pathologist Cuthbert Dukes (Dukes classification for colorectal tumours) compared this operation with that of Miles and concluded that considerably less lymph nodes were resected.[12]

The apical group of lymph nodes, near the origin of the inferior mesenteric artery, was left *in situ* by Miles, as he advocated ligation of the vascular supply below the left colic artery. Moynihan proposed high ligation at the take-off of the inferior mesenteric artery from the aorta in order to resect the apical group of lymph nodes too.[13] This controversy has not been resolved yet.

SPHINCTER PRESERVATION

Miles' APR gained widespread approval and became the gold standard for rectal cancer, irrespective of tumour height. The main disadvantage was the necessity of a permanent colostomy. In 1910, the American surgeon Donald Balfour described a technique of anterior resection through an abdominal approach with the construction of a primary end-to-end anastomosis.[14] This was really in continuation with the 'Durchzug'-procedure (pull-through technique) after Hochenegg (1888), in which the anorectal stump was everted, stripped of its mucosa and returned to its natural position. The distal colon was then drawn through the denuded anorectum and sutured to the anal verge.[15] Despite the maintenance of bowel continuity, this technique never gained wide acceptance due to the high mortality rate caused by anastomotic leakage. Moreover, William Mayo stated that this operation would not be radical enough.[16] However, Dukes demonstrated that downward and lateral spread from rectal cancer was overestimated by Miles as it was unusual unless the cancer was advanced and lymphatics along the superior vessels were blocked by metastases.[12] The safety of

sphincter saving surgery was established by Claude Dixon in 1948 when he reported the results of 400 patients with a mortality rate of 2.6 percent and a five-year survival of 64 percent.[17,18] Anterior resection came to be the accepted treatment for cancer in the middle or upper third of the rectum, although this approach was not applicable for cancers of the lower third (distal 5 cm).

It was generally thought that an adequate resection required a margin of normal tissue 5 cm distal to the lower edge of the tumour. However, contrary to Miles' belief concerning all three dimensions of spread, anatomico-pathological studies showed that the majority of lymph nodes were found either parallel to or proximal to the level of the primary rectal tumour.[19] Subsequent analyses demonstrated that distal margins of 2 cm did not compromise survival or local control and that Miles had overestimated the incidence of distal spread.[20] This observation provided the rationale for further developments in surgical technique that facilitated sphincter preservation even for tumours of the distal rectum that did not directly invade the anal sphincter. The better understanding of what constitutes an adequate distal margin initiated the historical shift from radical APR to the use of sphincter saving techniques in the late 1970s. At that time, with the recognition of the importance of mechanical bowel preparation and antibiotics, the stage was set for the use of circular stapling devices, first conceived by the Russians and introduced by Steichen and Ravitch in the United States.[21] Circular stapling devices facilitated the technical possibility of low rectal anastomosis reducing the risk of anastomotic leakage. In addition, several pioneers have contributed to the advancement of sphincter saving procedures.

In 1972 Alan Parks described an important modification of the pull-through technique: the construction of a coloanal anastomosis through the dilated anal canal.[22] In 1986 Lazorthes *et al*. and Parc *et al*. proposed creation of a colonic reservoir combined with coloanal anastomosis to compensate for the loss of reservoir in the neorectum.[23,24] The benefits of a J-pouch relative to a straight coloanal anastomosis included decreased stool frequency, urgency and nocturnal bowel movements.[25] After the acceptance of preoperative radiotherapy in rectal cancer treatment, the risk of leakage of the anastomosis created within the irradiated field remained a great concern (10-25 percent).[26] In this respect, at present a temporary defunctioning ileostoma is constructed in most cases.

TOTAL MESORECTAL EXCISION (TME)

Interest in lateral tumour spread from primary rectal cancer was renewed by Phil Quirke in 1986.[27] Phil Quirke identified that there was a high positive predictive value of circumferential margin involvement for the subsequent development of

Figure 7. Blunt dissection before the introduction of "total mesorectal excision"

locally recurrent cancer and poor survival. The conventional resection technique consisted of blunt dissection, which failed to clear the pelvis of mesorectal disease and resulted in an increased risk of positive lateral margins.[28] Subsequently, Heald developed a resection technique with embryologically defined surgical planes. He recognized that the midline hindgut (rectum) and its mesorectum were embryologically derived together as a single unit. In 1982 he introduced the "total mesorectal excision" (TME) technique, which involved *en bloc* resection of the tumour and the mesorectal tissue to the level of the levator muscles through sharp dissection in the avascular plane between the mesorectum and surrounding tissues under direct vision. Hida supported the assertion that the principal field of spread is contained within the mesorectum. His work confirmed that rectal cancer is a supralevator compartment disease and that Miles' "cylindrical concept" was wrong.[29] The TME technique resulted in a significant decrease in positive lateral margins.[30] Sharp dissection reduced the risk of excessive peroperative blood loss and postoperative functional disorders (Figure 7).[31,32] The TME technique resulted in reproducible specimens for pathological examination, decreased local recurrence rates significantly (from 12-20 to 4 percent) and allowed ultralow resections with coloanal anastomosis to be accepted as appropriate operations.[33] These radical reconstructive operations allowed APR to be relegated to use in only a minority of patients (15 percent), mainly those with direct sphincter invasion and/or pre-existing faecal incontinence.[34] Sphincter preservation became possible in even more patients thanks to tumour downstaging after neoadjuvant (chemo-)radiotherapy.[35-37] This approach has become the gold standard in the Western World, in contrast with Japan, where an operation also removing lateral lymph nodes outside the mesorectum has been developed.

LATERAL LYMPH NODE DISSECTION

Lateral lymph node dissection as part of rectal cancer treatment was structurally promoted since 1950 by Deddish, despite high rates of urogenital dysfunction.[9] Stearns and Bacon investigated and confirmed lateral spread of rectal cancer and practiced rectal cancer resection with lateral lymph node dissection as well.[38,39] Later on, this technique was revived in Japan, improving local control and survival.[40,41] Outcomes were comparable after TME combined with neoadjuvant radiotherapy.[42,43] Radical resection with lateral lymph node dissection has been generally abandoned in the West, because of the low incidence of lateral pelvic node involvement and the consideration that lateral node involvement may represent systemic, incurable disease.[44,45] Additionally, lateral lymph node dissection was associated with more blood loss, longer operating time and autonomic nerve damage, causing urogenital dysfunction in the majority of patients.[45,46] Furthermore, the use of preoperative irradiation is considered to take care of involved lateral nodes.

NERVE PRESERVING RECTAL RESECTION

Damage to the pelvic autonomic nerve system was long thought to be an inevitable part of radical surgery for rectal cancer. However, encouraged by improved cure rates of oncologic treatment, more and 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. Hojo and Moriya developed new resection techniques, allowing preservation of the autonomic innervation of urogenital organs (hypogastric nerves, inferior hypogastric plexus and pelvic splanchnic nerves; Figure 8).[47-49] Subsequently, the American surgeon Enker combined the nerve preserving principle with the TME technique, resulting in intact urogenital function in almost 90 percent of his patients without compromising oncologic outcome.[50,51] Moriya demonstrated in a prospective study of 47 patients in the Netherlands the feasibility and safety of the nerve sparing technique.[52] Surgical training programmes spread the technique of TME with nerve preservation world-wide, however urogenital dysfunction, as well as faecal incontinence, due to surgical nerve damage is still a major problem.[31,53-56]

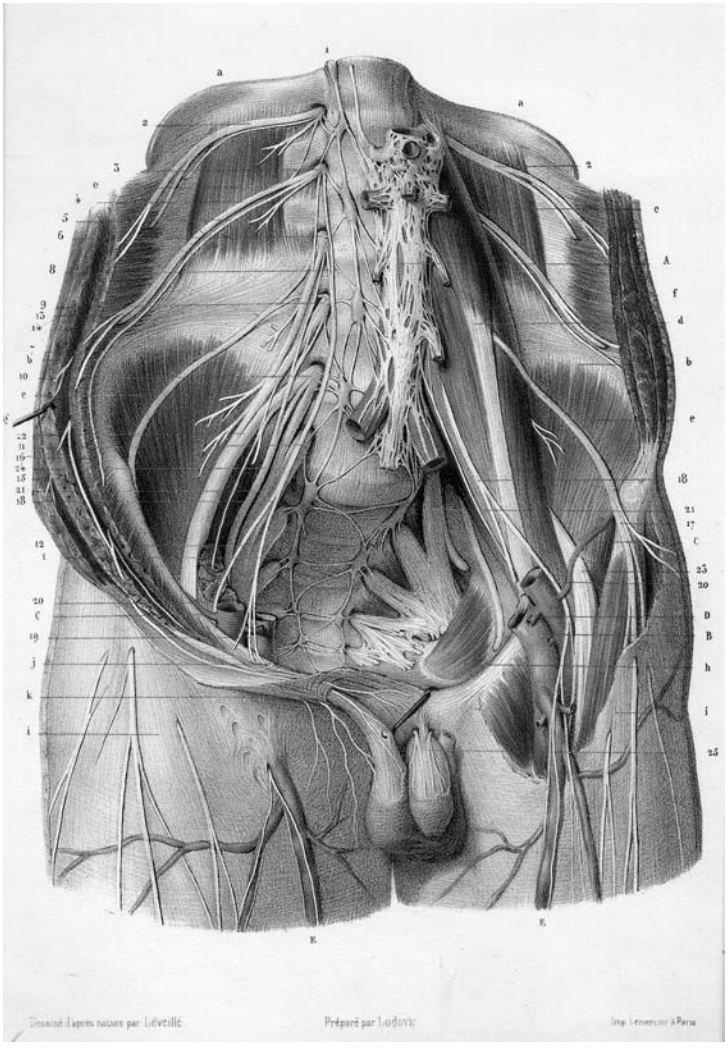

Figure 8. Anatomical illustration of the pelvic nerves (Neurologie. Hirschfeld, Ludovic en Leveille 1853)

THE FUTURE

Although at present the primary treatment of rectal cancer still is surgical resection, the role of neoadjuvant (chemo-)radiotherapy is becoming increasingly important. The first time rectal cancer was successfully treated with radiotherapy was in 1914 by Symons.[57] The past decade has shown that preoperative radiotherapy should be standard procedure in rectal cancer treatment, especially on the basis of the Dutch TME trial.[58] The combination of neoadjuvant radiotherapy with TME resulted in significantly improved local control. On the other hand, despite the reduced recurrence

rate, radiotherapy does not improve long-term survival after TME, but significantly increases the risk of functional problems.[59,60] Adequate patient selection enables an individualised treatment strategy, preventing under- and overtreatment, which reduces (disease-free) survival and quality of life, respectively. Preoperative imaging with CT is used to identify extrapelvic metastases, whereas MRI/EUS is used for evaluating locoregional disease. The evaluation of regional lymph node involvement remains relatively inaccurate.[61] Currently, new imaging modalities are developed and molecular biomarkers are identified to predict prognosis, making patient tailored treatment possible soon.

Furthermore, minimally invasive techniques are becoming increasingly important in rectal cancer surgery. Laparoscopic rectal resection, firstly reported by Jacobs in 1991, results in reduced peroperative blood loss and shorter recovery compared to open TME.[62] However, until now, no differences have been found in long-term oncologic and functional outcome, but findings from large ongoing trials should be awaited.[63] Current challenge in rectal cancer treatment is rectum saving therapy, thus avoiding the morbidity associated with major resectional treatment. A concern of rectum saving treatment is the possibility of residual tumour cells in lymph nodes or at the tumour site, which might cause local recurrence. However, it has been shown that patients with complete response after neoadjuvant chemoradiotherapy have little chance of persisting tumour cells.[64] Transanal endoscopic microsurgery (TEM) was introduced by Buess in 1983 and was in fact a continuation of the local electrocoagulation technique, developed by Strauss in 1913 and later only used for palliation.[15,65] This technique implies local excision and has resulted in promising findings in the treatment of early rectal cancer. Habr-Gama has aimed to omit surgery completely from rectal cancer treatment.[66] Patients with complete clinical response after chemoradiotherapy were closely observed and not operated on. This study has shown promising results. However, long-term follow-up of prospectively conceived multicentre data concerning safety and functional outcome of rectum saving approaches is needed.

CONCLUSION

Rectal cancer treatment has progressed tremendously over the past 100 years. Results have not really been altered by extremely expensive modern add-ons, but mainly by an increased understanding of the pathology and natural history of the disease. Miles initiated this as he established the focus of attention to the importance of local tumour spread and lymph node involvement in curative rectal cancer treatment. His concept has dominated the minds of surgeons throughout the 20th century. Although

Miles was not the first to excise cancer of the rectum, nor even the first to do so by a combined abdominoperineal approach, his name has become forever synonymously associated with this combined and now synchronous procedure. However, Miles' concept concerning distal spread of rectal cancer has been proven wrong, which initiated the historical shift to sphincter saving procedures. The acknowledgement of the importance of embryology in defining surgical planes has lead to the introduction of TME which is the gold standard nowadays. Although today APR is performed in only a minority of patients, wider perineal and pelvic floor resections for low rectal cancers have regained interest again, from which it may be concluded that Miles is influencing rectal cancer surgery as much as he did 100 years ago.[67]

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CHAPTER 3

Level of arterial ligation in rectal cancer surgery: low tie preferred over high tie. A review

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ABSTRACT

Consensus does not exist on the level of arterial ligation in rectal cancer surgery. From oncologic considerations, many surgeons apply high tie arterial ligation (level of inferior mesenteric artery). Other strategies include ligation at the level of the superior rectal artery, just caudally to the origin of the left colic artery (low tie), and ligation at a level without any intraoperative definition of the inferior mesenteric or superior rectal arteries.

Publications concerning the level of ligation in rectal cancer surgery were systematically reviewed. Twenty-three articles that evaluated oncologic outcome (n=14), anastomotic circulation (n=5), autonomous innervation (n=5), and tension on the anastomosis/anastomotic leakage (n=2) matched our selection criteria and were systematically reviewed. There is insufficient evidence to support high tie as the technique of choice. Furthermore, high tie has been proven to decrease perfusion and innervation of the proximal limb. It is concluded that neither the high tie strategy nor the low tie strategy is evidence based and that low tie is anatomically less invasive with respect to circulation and autonomous innervation of the proximal limb of anastomosis. As a consequence, in rectal cancer surgery low tie should be the preferred method.

INTRODUCTION

The most important prognostic factor for survival after rectal cancer surgery is represented by both distant metastasis and lymph node involvement. With respect to lymph node involvement, in 1908 Miles developed the abdominoperineal resection procedure for rectal cancer, incorporating transabdominal removal of lymphatic tissue. Believing that the route of lymphatic drainage of the rectum would follow its arterial supply, he recommended division of the superior rectal artery (SRA) just distally to the origin of the left colic artery (LCA; low tie; Figure 1), with subsequent *en bloc* excision of nodes and bowel below.[1] Within the same year Moynihan first proposed resection of the inferior mesenteric artery (IMA) at its origin (high tie; Figure 1), including the apical group of lymph nodes within the resection.[2] During subsequent years, the high tie principle was further advocated by several authors.[3–7] However, according to the National Cancer Institute of the United States of America, an appropriate proximal lymphatic resection for rectal cancer without clinical evident lymph node disease is provided by the removal of the blood supply and lymphatics up to the level of the origin of the primary feeding vessel.[8] For rectal cancer this is at the origin of SRA (low tie), which is immediately distal to the offspring of LCA. However, the key report on which this guideline is based is represented by the study by Rouffet *et al.*[9] which is a trial on colon, not rectal, carcinoma. Actually, the level at which the artery is ligated in operations for rectal cancer varies greatly, depending

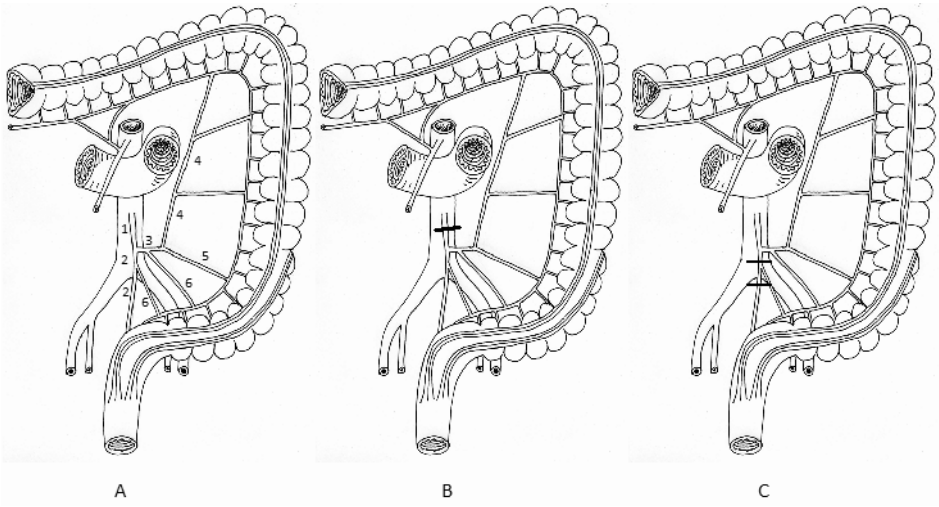

Figure 1. Anatomic graph of vascular ligation techniques A. Inferior mesenteric artery (1), superior rectal artery (2), left colic artery (3), ascending limb (4), descending limb of the left colic artery (5), sigmoid arteries (6). B. High tie. C. Low tie, cranially or caudally to the origin of the sigmoid artery (if present), but always caudally to the origin of the left colic artery.

largely on the surgeon.[4,10–16] In daily practice only a minority of surgeons dissect the origin of LCA to estimate the level of arterial ligation with respect to IMA and SRA with certainty. Furthermore, in most publications on high tie and low tie, SRA is incorrectly denominated as IMA caudally to the origin of LCA. After Lanz and Wachsmuth the artery caudally to the origin of LCA is denominated SRA and not IMA.[17] Most authors use the term "high tie" for every type of ligation of IMA at all levels of the 1-cm to 7-cm long artery, including "flush" ligation of IMA at its very origin at the aorta.

The choice of the level of arterial ligation in rectal cancer surgery can be based on three considerations: oncologic, anatomic, and technical. This article systematically reviews the evidence of possible benefits of high tie and low tie ligation techniques regarding these three different considerations.

METHODS

A comprehensive literature search was conducted using PubMed and Cochrane database. The following terms were used: high ligation, high tie, low tie, and low ligation. In addition the terms IMA, SRA, or LCA were used in combination with colorectal cancer, rectal cancer, lymph node, circulation, flow, stump pressure, function, autonomous, nerve, and tension. We also hand searched references.

The publication time window was from 1980 to 2007. Studies were included for this review if it concerned a randomised, controlled trial or a cohort study (prospective/retrospective) that evaluated adult patients who underwent rectal resection with high tie or low tie or an anatomic study, describing the location of the autonomous nerve supply in relation with ligation technique. Review articles, letters, comments, conference proceedings, and case reports were not selected for this review. With respect to oncologic considerations outcomes of interest were survival, disease recurrence, and incidence of positive lymph nodes at the root of IMA. With respect to anatomic considerations outcomes of interest for effect on anastomotic circulation were tissue blood flow, tissue oxygen tension, and anastomotic leakage, and for effect on autonomous innervation were bowel and urogenital dysfunction and location of nerve supply in relation with the root of IMA. With respect to technical considerations outcomes of interest were length of the proximal limb, tension on the anastomosis, and anastomotic leakage. An assessment of the quality of the included studies was conducted according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.

RESULTS

No randomised, clinical trials comparing high tie and low tie were found.

In total 23 studies were selected for the three categories as follows:

1. Oncologic considerations: studies that concerned the influence of the level of arterial ligation on cancer prognosis and/or the incidence of lymph node metastasis at the root of IMA. In total 14 studies were selected (Table 1): 7 studies that compared high tie and low tie[13–16,18–20]; and 7 noncomparative studies.[21–27]
2. Anatomic considerations: studies that concerned the influence of the level of arterial ligation on anastomotic circulation (2A) and studies that concerned the influence of the level of arterial ligation on autonomous function (2B).
    1. In total five studies were selected that concerned the influence of the level of arterial ligation on anastomotic circulation and/or anastomotic leakage rate (Table 2): two studies that compared high tie and low tie[18,28]; and three noncomparative studies.[29–31]
    2. In total five studies that concerned the influence of the level of arterial ligation on autonomous innervation were selected (Table 3): one study that compared high tie and low tie[32]; and four noncomparative studies.[33–36]
3. Technical considerations: studies that concerned the influence of the level of arterial ligation on the length of the proximal limb of anastomosis. In total two studies were found, which are mentioned in Table 1 (Corder *et al.*[18] and Pezim and Nicholls[14]). Both studies compared anastomotic leakage rates between high tie and low tie and found no significant difference.

DISCUSSION

Oncologic considerations

Lymph node involvement is a major prognostic factor for survival after rectal cancer surgery. The high tie technique includes the apical group of lymph nodes at the root of IMA within the resection. However, the incidence of metastatic lymph nodes at the origin of IMA has been reported to be relatively low in several studies, ranging from 0.3 to 8.6 percent.[14,20,22,23,25–27] Furthermore, Kanemitsu *et al.*[24] found no nodal metastases at the origin of IMA in patients with pT1 rectal tumours. This study suggested that low tie might be sufficient for pT1 sigmoid or rectal cancers. According to these findings, high tie might be beneficial only for patients with nodepositive disease. However, even in the case of nodepositive disease, it may be true that once the tumour has involved in these high lymph nodes, it has probably spread beyond. In

Table 1. Overview of included studies concerning oncologic considerations of the level of arterial ligation

Study	Level of evidence	Design	N	Tumour location	Procedure	Outcome measure	Results
Uehara *et al*. (2007)[20]	2b	Retrospective cohort	285	Rectum	High or low tie	Five-year survival; incidence of LN+	No significant difference;1.9%
Kanemitsu *et al*. (2006)[24]	2b	Retrospective cohort	1 188	Colon and rectum	High tie	Incidence of LN+	1.7%
Kawamura *et al*. (2005)[25]	2b	Retrospective cohort	121	Rectosigmoid	High tie	Incidence of LN+	0.0% (only pT1 tumours)
Fazio *et al*. (2004)[19]	2b	Retrospective cohort	458	Rectum	High or low tie	Survival	No significant difference
Steup *et al*. (2002)[27]	2b	Retrospective cohort	605	Rectum	High tie	Incidence of LN+	0.3%
Kawamura *et al*. (2000)[13]	2b	Retrospective cohort	511	Colon and rectum	High or low tie	Disease-free survival	No significant difference
Hida *et al*. (1998)[23]	2b	Retrospective cohort	198	Rectum	High tie	Incidence of LN+	8.6%
Adachi *et al*. (1998)[21]	2b	Retrospective cohort	172	Rectosigmoid	High tie	Incidence of LN+	0.7%
Slanetz et al. (1997)[15]	2b	Retrospective cohort	2409	Rectum	High or low tie	Five-year survival	Only stage-specific difference
Leggeri *et al*. (1994)[26]	2b	Retrospective cohort	252	Rectum	High tie	Incidence of LN+	4.0%
Corder *et al*. (1992)[18]	2b	Retrospective cohort	143	Rectum	High or low tie	Survival; recurrence	No significant differences
Dworak *et al*. (1991)[22]	2b	Retrospective cohort	424	Rectum	High tie	Incidence of LN+	1.0%
Surtees *et al*. (1990)[16]	2b	Retrospective cohort	250	Rectum	High or low tie	Survival rate	No significant difference
Pezim and Nicholls (1984)[14]	2b	Retrospective cohort	1 370	Rectosigmoid	High or low tie	Five-year survival	No significant difference

LN+ = positive lymph node at the root of inferior mesenteric artery.

Table 2. Overview of studies concerning the influence of the level of arterial ligation on anastomotic circulation (IMA = inferior mesenteric artery)

Study	Level of evidence	Design	N	Procedure	Outcome measure	Results
Seike *et al*. (2007)[31]	2b	Prospective cohort	96	Rectal cancer resection with high tie	Tissue blood flow	Significant blood flow reduction after high techniques; high blood flow reduction in older, male patients
Dworkin *et al*. (1996)[29]	2b	Prospective cohort	26	Rectosigmoid resection	Tissue blood flow	Significant blood flow reduction after IMA ligation
Hall *et al*. (1995)[28]	2b	Prospective cohort	62	Colorectal resection with high or low tie	Tissue oxygen tension	No significant difference; tissue oxygen tension of sigmoid not adequate after both techniques
Kashiwagi *et al*. (1994)[30]	2b	Prospective cohort	13	IMA clamping	Tissue blood flow	No significant reduction
Corder *et al*. (1992)[18]	2b	Retrospective cohort	143	Rectal resection with high or low tie	Anastomotic leakage rate	No significant differences

this respect a factor could be represented by the generally poor prognosis of patients with rectal cancer with more than five involved lymph nodes who, if included in studies with high ligation, might obscure its value. Moreover, alternate lymphatic routes may frustrate attempts at tumour control by vascular ligation, regardless of the level of the tie. Tumours of the upper third of the rectum may drain along lymphatic channels that follow the portal vein and may be responsible for isolated lymphatic metastases within the hepatoduodenal ligament.[37] In the lower third of the rectum, drainage may occur laterally to the iliac nodes *via* lymphatics within the lateral ligaments.[38]

Three retrospective cohort studies on high tie reported advantageous results with significant five-year and ten-year survival data for the very limited groups of patients with positive lymph nodes at IMA.[23,24,26] We found the number of studies comparing high tie with low tie to be limited. All but one of these studies did not find any survival benefit after high tie in rectal cancer surgery.[13–16,18–20] Only Slanetz and Grimson[15] reported a stage-specific survival benefit of high tie in a retrospective study of 1 107 patients treated with high tie with extensive resection of mesenteric lymph drainage

Table 3. Overview of studies concerning the influence of the level of arterial ligation on autonomous innervations (IMA = inferior mesenteric artery)

Study	Level of evidence	Design	N	Procedure	Outcome measure	Results
Liang *et al*. (2007)[34]	2b	Prospective cohort	98	D3-resection (high tie)	Urogenital function	75.5% bladder and 91.7% sexual dysfunction
Sato *et al*. (2003)[32]	2b	Retrospective cohort	132	Rectal resection with high or low tie	Bowel function	High tie resulted in worse bowel function
Zhang *et al*. (2006)[36]	5	Anatomic study	16	Exploration inferior mesenteric plexus in cadavers	Location inferior mesenteric plexus	Inferior mesenteric plexus was never located at the root of IMA
Nano *et al*. (2004)[35]	5	Anatomic study	42	Exploration of left paraortic trunk in cadavers and patients undergoing rectal resection	Location left paraortic trunk	Left paraortic trunk was never located at the root of IMA
Hoer *et al*. (2000)[33]	5	Anatomic study	12	Isolation of inferior mesenteric plexus in cadavers	Location inferior mesenteric plexus	Inferior mesenteric plexus is invariably located at the root of IMA

and 1 154 treated with low tie. However, this study did not eliminate the stage migration phenomenon, which may arise as a result of more accurate staging because of more extensive lymphadenectomy. Therefore, a proportion of patients might be assigned to a more advanced stage than would otherwise be the case, although their prognosis is the same. If this has occurred, the overall results in each stage would have improved and the proportion of patients in more advanced stages would have increased.[39]

Previous reports state that the number of harvested lymph nodes correlates significantly with long-term results in patients with colorectal carcinoma, advocating the importance of pathologic examination of 12 or more nodes.[40,41] Limited lymph node dissection with preservation of IMA may result in a decreased number of harvested nodes. However, increasing the number of nodes by dissection of distant free nodes is considered to have no clinical impact.[42]

Most studies concerning high tie *vs.* low tie took place before the introduction of total mesorectal excision (TME) and neoadjuvant treatment for rectal cancer. Neoadjuvant treatment also has the potential to sterilise microscopic metastases in

nodes at the origin of IMA, undermining the rationale of high tie even more.[43] On the other hand, preoperative radiotherapy did not seem to prevent distant metastasis in the Dutch TME trial.[44] Possible benefit of high tie in combination with current surgical techniques and neoadjuvant treatment procedures needs to be investigated. In conclusion, assuming that reports on high tie procedures really reflect anatomically correct high tie dissections, there might be a small proportion of patients profiting from high tie. However, the amount and level of evidence for high tie is considered to be too modest for standardisation of ligation of IMA.

Anatomic considerations

Perfusion of the proximal limb of anastomosis or perfusion of colostomy.
Consensus exists on the necessity of well-perfused anastomotic limbs. However, factors jeopardizing anastomotic circulation are not well known.

The low tie technique allows for adequate blood supply to the colon proximally to the anastomosis, whereas after high tie vascularisation of the distal colon and sigmoid depends completely on the middle colic and marginal arteries.[23,35] The marginal artery arising from the middle colic artery is thought to be adequate for sustaining the viability of the remaining colon.[45,46] However, despite most studies support this hypothesis, from preoperative measurements Dworkin *et al.* and Seike *et al*. concluded that high tie significantly reduces perfusion of the proximal limb.[14,18,28,29,31] Furthermore, because in many patients a decrease in systemic blood pressure occurs during the recovery phase after surgery, it is not excluded that in some cases pressure in the marginal artery is insufficient to maintain adequate blood flow to the colon limb despite the inherent tendency of “auto-regulation” in its vascular bed.[47] In correspondence with colon ischemia as a complication of IMA ligation in aorta surgery, especially in older patients with atherosclerotic vessels, ligation of IMA might result in hypoperfusion of the proximal limb.[31,48] In addition, in some patients deficits of the marginal artery might exist at the splenic flexure.[48] Kashiwagi *et al*.[30] reported on the necessity of a larger sigmoid resection in rectal carcinoma surgery when IMA was ligated. Consequently, mobilisation of the splenic flexure would always be necessary.

Despite evidence for a decreased perfusion of the proximal limb after high tie exists, it can be concluded that until now the benefit of low tie concerning perfusion of the anastomosis has not been proven but it might be present in patients with atherosclerotic disease.

Autonomous innervation

Preservation of the autonomous nervous system is important to prevent urogenital and anorectal dysfunction.[49] The paraortic trunks originate from the mesenteric plexus and descend along the aorta to join together and form the superior hypogastric plexus. If these are cut, ejaculation disorders and urinary incontinence may occur.[50] Therefore, in high tie it is important to identify the safest point of ligation of IMA to avoid autonomous nerve damage during surgery of rectal cancer. In the literature, disagreement exists concerning the relationship between the origin and the course of IMA and the autonomous nerve supply. Two anatomic studies conclude that the origin of IMA is the only safe point of ligation, whereas another found that the inferior mesenteric plexus forms a dense network around IMA to a distance of 5 cm from the aorta, suggesting that high tie leads to damage of the sympathetic nerves.[33,35,51] Two studies evaluated autonomic function after rectal resection. Liang *et al*.[34] reported urogenital dysfunction in the majority of patients after high tie. Sato *et al*.[32] compared patients who underwent rectal cancer resection before the implementation of low tie with patients who were treated after this implementation at the specific institution. Patients treated with high tie reported worse bowel function. Ligation of IMA at its origin disrupts the descending autonomic fibres and consequently leads to a long denervated colon segment, causing defecatory dysfunction.[52] However, until now insufficient evidence exists about whether low tie has a better prognosis with regard to autonomic function.

Technical considerations

Length of the proximal limb of anastomosis.

Apart from ischemia, tension on the anastomosis is thought to increase the risk of anastomotic leakage.[23,35,53] Some authors state that high tie often is indispensable to guarantee a tension-free anastomosis in low anterior resection.[35,53,54] With this technique the proximal limb is not withheld by an intact LCA-IMA-aorta axis.

However, a tension-free anastomosis also can be achieved in low tie resections by cutting the descending branch of LCA.[18] To our knowledge, there are no studies that evaluate the effect of different ligation techniques on anastomotic tension. The aforementioned publications of Pezim and Nicholls[14] and Corder *et al*.[18] suggest that critical length of the proximal limb is not an issue in low tie strategy. In addition, splenic flexure mobilisation is not indicated routinely.[55]

Conclusions

Since Miles and Moynihan respectively proposed low tie and high tie techniques for rectal carcinoma surgery in the same year (1908), until now the level of arterial ligation has been debated. The lack of prospective, randomised, clinical trials with sufficient follow-up in combination with an inconsistent methodology can be held responsible for this lack of consensus. In addition it is uncertain whether precise peroperative evaluation of anatomy has always been correct in the available studies that describe high tie and/or low tie ligation. High tie, because it has regained new interest in laparoscopy by its presumed advantage of easily creating mesenteric windows, is still advocated by many.[51,54,56–59] However, from our review there is insufficient evidence to support high tie as the technique of choice. Although the anatomic disadvantage of high tie concerning impaired perfusion and innervation of the proximal colon limb has not been proven sufficiently with regard to anastomotic leakage and bowel dysfunction until now, low tie is anatomically less invasive and is preferable to high tie in rectal cancer surgery.

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CHAPTER 4

Risk factors for sexual dysfunction after rectal cancer treatment

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ABSTRACT

Background
Sexual dysfunction (SD) is a common and distressing complication of rectal cancer treatment. This study aimed to identify risk factors for long-term male and female SD.

Methods
Between 1996 and 1999, patients with resectable rectal cancer were randomised to total mesorectal excision (TME) with or without preoperative radiotherapy (PRT). Questionnaires concerning SD were completed preoperatively and at 3, 6, 12, 18 and 24 months postoperatively. Possible risk factors, including patients' demographics, tumour characteristics, PRT and surgical factors were investigated.

Results
Of preoperative sexually active patients 15.2 percent of men (59/388) and 13.7 percent of women (19/138) never indicated to be sexually active after treatment, which was related to age>65 years and in male patients also to anastomotic leakage.

Increase of general SD, erectile dysfunction and ejaculatory problems was reported by 76.4, 79.8 and 72.2 percent of male patients, respectively. Risk factors were nerve damage, blood loss, anastomotic leakage, PRT and the presence of a stoma. In female patients increase of general SD, dyspareunia and vaginal dryness was reported by 61.5, 59.1 and 56.6 percent, respectively. This was associated with PRT and the presence of a stoma.

Conclusion
Sexual dysfunction is a frequent and serious problem after treatment for rectal cancer. Associated risk factors demonstrate that it can be mainly attributed to surgical (nerve) damage with an additional effect of PRT. Therefore, patients should be informed preoperatively and education of surgeons in pelvic neuroanatomy and crucial anatomical dissection planes may provide the key to improvement of functional outcome.

INTRODUCTION

The past two decades have witnessed substantial improvement in survival from rectal cancer as a result of earlier diagnosis, improved efficiency and use of radiotherapy and advances in surgical techniques such as total mesorectal excision (TME)[1,2]. Total mesorectal excision is defined as "a sharp dissection under clear vision between the parietal and visceral planes of the pelvic fascia, removing the mesorectum contained within an intact endovisceral fascia"[1-3]. The practice of TME in rectal cancer treatment improved autonomous nerve preservation substantially. Subsequently, the rates of sexual dysfunction (SD) were reduced[4-6]. However, SD after rectal cancer treatment is still a frequent and distressing complication[7-9]. There is a suggestion that sexual function is impaired by radiotherapy, but function can also be affected by surgery alone[6,8,10,11]. It is difficult to identify the contribution of each treatment component in the development of SD. There is a general lack of large, prospective studies concerning long-term SD after rectal cancer treatment, especially in female patients. In order to gain insight in the etiology of SD after rectal cancer treatment, we prospectively investigated which treatment factors contributed to the development of long-term male and female SD in a large multicentre trial in which all patients had been treated by TME surgery and had been randomised for yes/no preoperative radiotherapy (PRT).

METHODS

Study population and treatment

From January 1996 to December 1999, 1 861 patients with histologically proven adenocarcinoma of the rectum and without evidence of distant metastases were randomised to receive PRT followed by TME or TME alone in a large, international, multicentre trial. Details of the TME trial have been described elsewhere[12]. Patients assigned to PRT received a total dose of 25 Gy in five fractions over 5 to 7 days. Surgery had to take place within 10 days of the start of PRT. All patients underwent surgery according to the TME principles, as advocated by Heald[13]. Participating surgeons attended workshops and symposiums, saw instructional videotapes and were monitored by specially trained instructor surgeons. At each hospital, the first five total mesorectal excisions were supervised by an instructor surgeon[14]. Informed consent was obtained from all patients before randomisation and was separately obtained for the quality-of-life study. Health-related quality of life was evaluated in Dutch patients only (n=1 530). Patients with any recurrence during the period of

evaluation were excluded to avoid confounding due to symptoms caused by disease recurrence.

Measures

Patients were asked to fill out questionnaires before treatment and at 3, 6, 12, 18 and 24 months after surgery. Patients who failed to return two consecutive questionnaires were considered as withdrawn from the study and did not receive further questionnaires. For the different time points, the following time windows were defined: 1.5 to 4.5 (3 months), 4.5 to 9 months (6 months), 9 to 15 (12 months), 15 to 21 (18 months) and 21 to 27 (24 months). Patients with a missing preoperative form were not analysed, however patients with a missing form at a certain time point after treatment were still included in the other time points.

The questionnaire evaluated sexual activity and included several items concerning sexual functioning. Responses were given on four-point scales ranging from "not at all" to "very much". Items within a scale were summed and linearly transformed to fit a range from 0 to 100, with lower scores representing better levels of functioning. The questionnaire consisted of one general SD scale (three items: interest, pleasure, satisfaction; Cronbach's α for females = 0.88 and for males = 0.85); for females a scale on dyspareunia (two items: $\alpha = 0.87$) and an item on vaginal dryness were also included, and for males a scale on erectile dysfunction (three items: $\alpha = 0.98$) and one on ejaculatory problems (two items: $\alpha = 0.86$) were included.

Statistics

Male and female patients were analysed separately. Only patients who were sexually active before rectal cancer treatment were evaluated. Sexual activity after rectal cancer treatment was assessed and associated factors were identified with univariate and multivariable regression analysis.

Furthermore, postoperative deterioration of sexual functioning was evaluated. To do this, relative dysfunction scores were obtained by subtracting the baseline-score (preoperative score) from the score at each subsequent time-point. For each patient the mean postoperative relative scores with respect to general SD and to erectile dysfunction and ejaculatory problems or to dyspareunia and vaginal dryness were calculated. In this way, even patients who only filled in one postoperative questionnaire could be evaluated. Scores ranging from 0-10, 10-20 and >20 were considered as minor, moderate and severe deterioration respectively[17]. Analysed risk factors were gender, age, body mass index (BMI), tumour stage, PRT, resection type (low anterior or abdominoperineal resection), level of anastomosis, resection of an ad-

ditional organ, excessive peroperative blood loss (>1 500 ml), surgical damage to the superior hypogastric plexus, hypogastric nerves and/or pelvic plexus (as mentioned in the surgery report), definitive or temporary stoma and anastomotic leakage. The influence of these variables was examined in univariate and multivariable regression analysis. $P \leq 0.05$ was considered statistically significant.

In order to produce figures indicating the development of dysfunction over time, linear mixed models with random patient intercepts and time (categoric) and the specific risk factor as fixed factors were used to obtain estimates of each of the scheduled time points, to account for random drop-out. In a previous study, it was shown that it was not necessary to incorporate non-ignorable drop-out[16].

RESULTS

Study population

Of the 1 530 Dutch patients, patients were excluded from analysis for the following reasons: ineligible at randomisation (n=50), no operation (n=37), in-hospital deaths (n=52), no informed consent for quality-of-life study (n=89) and no quality-of-life forms returned (n=30). In addition, 282 patients had a local or distant recurrence within the first two years, leaving 990 patients. Patient and treatment characteristics are listed in Table 1.

Sexual activity

Before treatment, 79.2 percent of male (388/490) and 51.7 percent of female patients (138/267) were sexually active. Univariate and multivariable regression analysis could not identify any clinical or pathological contributing factor correlating with absence of sexual activity other than age >65 years, female gender and not having a partner ($p<0.001$, RR=0.16, $p<0.001$, RR=0.27 and $p<0.001$, RR=0.12, respectively).

Of the male patients sexually active before treatment, 31.5 percent indicated not to be sexually active at three months after surgery. This percentage remained more or less stable over time (28.5 percent at two years). However, only 59 male patients (15.2 percent) never indicated to be sexually active after treatment. Risk factors associated with never being sexually active were age >65 years ($p=0.002$, RR=0.40) and anastomotic leakage ($p=0.008$, RR=0.31). In contrast, of the female patients sexually active before treatment, 32.5 percent indicated not to be sexually active at three months but this decreased to 18.4 at two years after rectal cancer treatment. Only 19

Table 1. Patient and treatment characteristics (continuous variables: median (minimum, maximum); categorical variables: number of patients (%))

Age (years) (n=990)	64.0 (26, 92)
Gender (n=990)	
Male	625 (63.1)
Female	365 (36.9)
Body Mass Index (kg/m^2; n=784)	25.4 (16.9, 53.1)
Tumour location (n=157)	
Anterior	79 (50.3)
Posterior	78 (49.7)
Tumour size (cm; n=979)	4.0 (0, 13.0)
Tumour stage	
T0-T1	88 (8.9)
T2	388 (39.2)
T3	493 (49.8)
T4	21 (2.1)
Preoperative radiotherapy (n=990)	497 (50.3)
Type of resection (n=990)	
Low anterior resection	657 (66.4)
Abdominoperineal resection	293 (29.6)
Hartmann	40 (4.0)
Resection additional organ (n=990)	185 (18.7)
Peroperative blood loss (ml; n=971)	1000 (20, 15000)
Anastomotic height of LAR (cm; n=607)	5.5 (0, 14.0)
Anastomotic leakage after LAR (n=657)	66 (10.0)
Temporary/definitive stoma (n=950)	725 (73.2)

female patients (13.7 percent) never indicated to be sexually active after treatment. This was associated with increased age (p=0.041, RR=0.35).

Male sexual functioning

As stated in the methods section, only patients who indicated to be sexually active preoperatively were included in the analysis of sexual functioning (388 male and 138 female patients).

Both in male and female patients general sexual functioning deteriorated postoperatively and remained worse over time for male, but improved for female patients (Figure 1). Seventy-six percent (275/360) of male patients reported either newly developed general SD or aggravation of pre-existent general SD after rectal

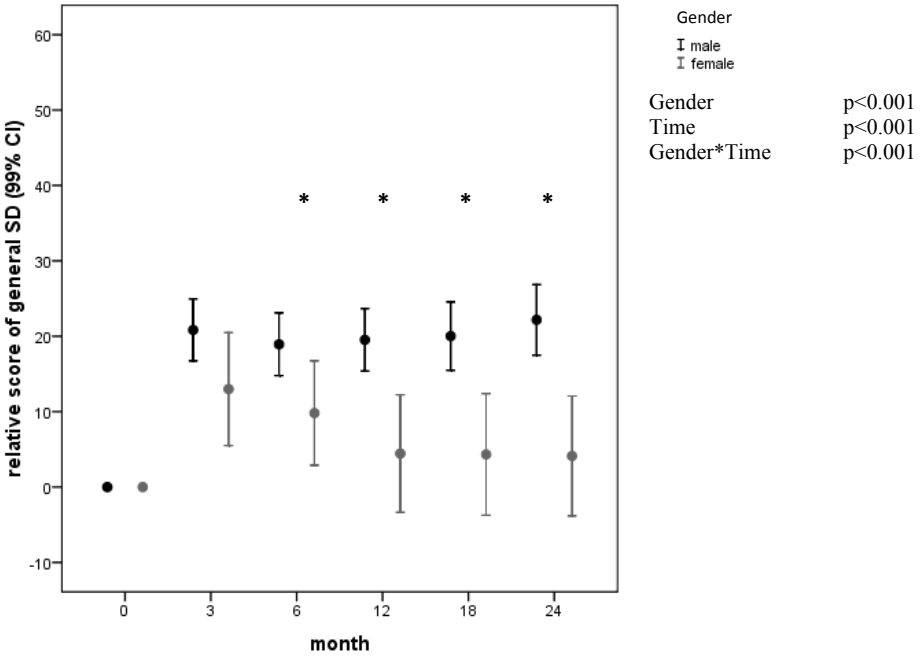


Figure 1. Linear mixed models analysis of relative general sexual dysfunction scores in male and female patients. Ninety-nine confidence intervals are displayed on the y-axis. An asterisk indicates a significant difference ($p<0.001$) at a specific time-point. (SD=sexual dysfunction; CI=confidence interval)

cancer treatment, of whom 59.3 percent (163/275) had a mean relative score of more than 20 points, indicating severe deterioration. The mean postoperative increase in general SD score was 20.2 (standard error [SE]=1.5) and was significantly associated with PRT, excessive peroperative blood loss, anastomotic leakage and temporary/definitive stoma in univariate regression analysis (Table 2). However, in multivariable analysis only PRT and temporary/definitive stoma remained significant risk factors ($p=0.003$, mean difference=8.53, SE=2.9 and $p=0.019$, mean difference=8.97, SE=3.5, respectively; Figure 2a). Postoperative erectile dysfunction developed or worsened in 79.8 percent (257/322) of patients compared to the pre-treatment situation. Of these patients 71.2 percent (183/257) had a mean relative score of more than 20 points. The mean postoperative increase in erectile dysfunction score was 31.3 (SE=1.9) and was significantly associated with age>65 years, nerve damage, resection type, excessive peroperative blood loss, temporary/definitive stoma and anastomotic leakage in univariate regression analysis. However, in multivariable analysis only excessive peroperative blood loss and anastomotic leakage remained significant risk factors ($p=0.033$, mean difference=13.6, SE=4.2 and $p=0.034$, mean difference=14.5, SE=7.2, respectively; Table 2; Figure 2b). Ejaculatory problems de-

Table 2. Results of univariate and multivariable regression analysis of the influence of patient and treatment related factors on the mean relative scores of general sexual dysfunction, erectile dysfunction en ejaculatory problems in male patients. (SD=sexual dysfunction, N=number of patients, SE=standard error, LAR=low anterior resection, APR=abdominoperineal resection, uni=univariate analysis, multi=multivariable analysis)

	General SD					Erectile dysfunction					Ejaculatory problems				
Risk factors	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi
Age				0.343					0.089	0.298				0.559	
≤65 years	243	21.16	1.76			225	33.39	2.25			220	31.14	2.37		
>65 years	117	18.23	2.55			97	26.51	3.24			86	28.57	3.53		
Body Mass Index				0.381					0.228					0.258	
≤30 kg/m²	266	20.58	1.70			245	30.29	2.13			232	30.49	2.31		
>30 kg/m²	22	15.07	7.42			17	40.44	8.94			14	41.47	9.71		
Tumour stage				0.233					0.929					0.466	
I	41	24.00	3.47			39	31.29	5.20			36	34.96	5.59		
II	136	20.60	2.51			120	31.92	3.17			117	31.37	3.23		
III	179	19.60	2.02			159	31.14	2.58			149	28.86	2.84		
IV	4	-5.00	11.12			4	20.63	19.26			4	19.69	16.82		
Preoperative radiotherapy				0.003	0.003				0.108					0.024	0.026
no	185	16.06	2.06			170	28.50	2.59			162	26.22	2.68		
yes	175	24.59	1.98			152	34.47	2.63			144	35.14	2.87		
Resection type				0.233					0.037	0.129				0.920	
LAR	233	18.96	1.69			210	28.04	2.21			204	30.52	2.47		
APR	116	22.72	2.91			102	36.41	3.52			93	30.08	3.47		

Risk factors	General SD					Erectile dysfunction					Ejaculatory problems				
	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi
Level of anastomosis				0.398					0.230					0.244	
≤4.0 cm	155	22.83	2.34			140	33.85	2.78			130	26.98	2.87		
4.0-7.0 cm	85	18.19	3.06			74	32.57	3.93			74	33.56	4.46		
>7.0 cm	71	19.27	2.59			67	25.49	4.09			63	34.78	4.38		
Resection additional organ				0.554					0.531					0.523	
no	321	19.91	1.55			288	30.92	1.95			273	30.86	2.10		
yes	39	22.66	3.85			34	34.71	5.93			33	26.79	5.72		
Excessive blood loss				0.058	0.148				0.001	0.033				0.510	
no	256	18.46	1.69			233	27.82	2.17			222	29.68	2.32		
yes	97	24.66	2.85			83	41.42	3.58			79	32.68	3.99		
Nerve damage				0.637					0.038	0.175				0.007	0.011
no	264	19.88	1.65			237	28.85	2.14			223	27.10	2.19		
yes	93	21.45	3.07			82	37.67	3.72			80	39.17	4.23		
Temporary/definitive stoma				0.012	0.019				0.019	0.262				0.839	
no	78	13.24	2.13			74	22.83	3.65			69	29.64	4.19		
yes	271	22.21	1.79			238	33.24	2.18			228	30.61	2.30		
Anastomotic leakage				0.031	0.076				0.043	0.034				0.022	0.043
no	332	19.30	1.46			299	30.28	1.89			284	29.17	2.02		
yes	28	30.95	6.59			23	44.82	7.86			22	46.56	7.90		

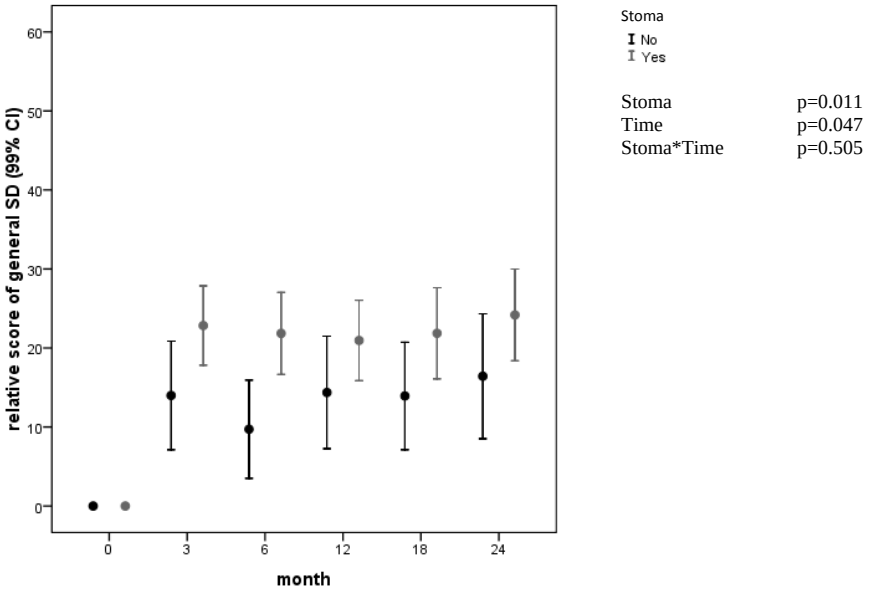
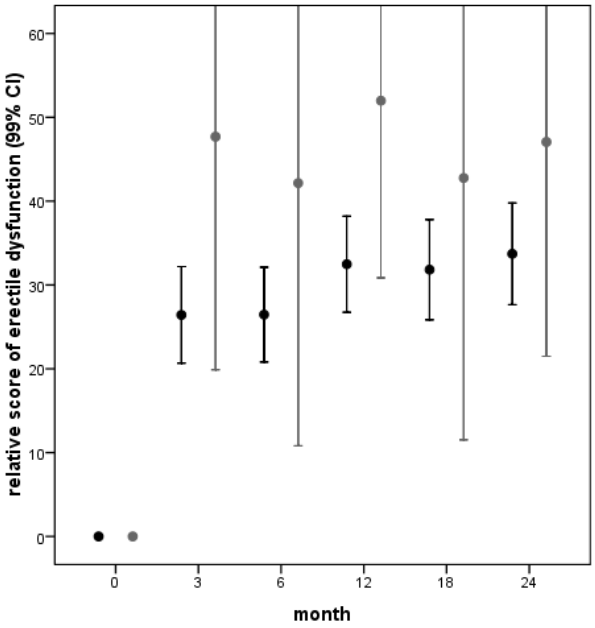


Figure 2. Linear mixed models analysis of a) relative general sexual dysfunction scores in male patients with or without a temporary/definitive colostoma, b) relative erectile dysfunction in male patients with or without excessive peroperative blood loss and with or without anastomotic leakage and c) relative ejaculatory problems in male patients with or without nerve damage and with or without anastomotic leakage. Ninety-nine confidence intervals are displayed on the y-axis. An asterisk indicates a significant difference ($p<0.001$) at a specific time-point. (SD=sexual dysfunction; CI=confidence interval)

veloped or worsened postoperatively in 72.2 percent (221/306) of patients, of whom 67.4 percent (149/221) had a mean relative score of more than 20 points. The mean postoperative increase in ejaculatory problem score was 30.4 (SE=2.0) and was significantly associated with PRT (p=0.026, mean difference=8.92, SE=3.9), autonomic nerve damage (p=0.011, mean difference=12.07, SE=4.4) and anastomotic leakage (p=0.043, mean difference=17.39, SE=7.6; Table 2; Figure 2c).

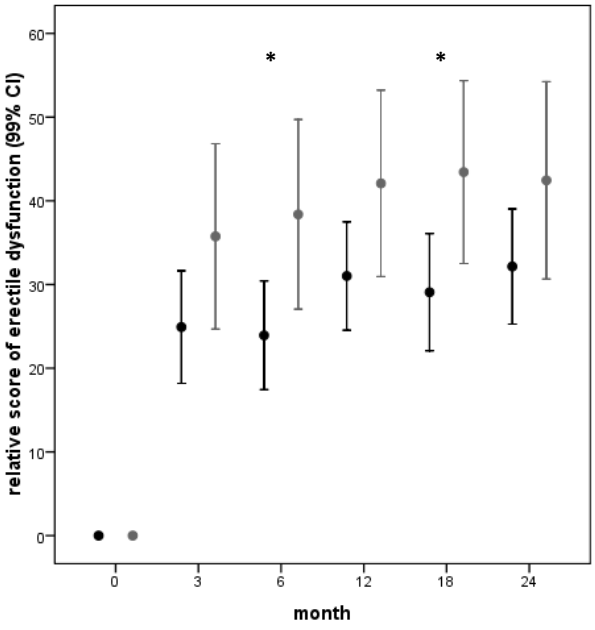
Female sexual functioning

Sixty-two percent (72/117) of female patients reported either newly developed general SD or aggravation of pre-existent SD after rectal cancer treatment, of whom 45.8 percent (33/72) had a mean relative score of more than 20 points. The mean postoperative increase in general SD score was 8.2 (SE=2.5). Preoperative radiotherapy was the only significant risk factor (p=0.033, mean difference=10.5, SE=4.9; Table 3). Postoperative dyspareunia developed or worsened compared to the pre-treatment situation in 59.1 percent (65/110) of patients, of whom 44.6 percent



Anastomotic leakage
no
yes

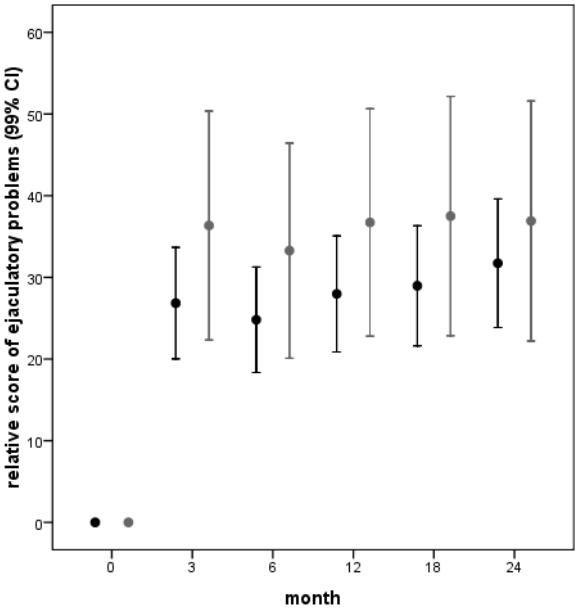
Anastomotic leak	p=0.051
Time	p=0.010
Leak*Time	p=0.507



Blood loss
<= 1500 ml
> 1500 ml

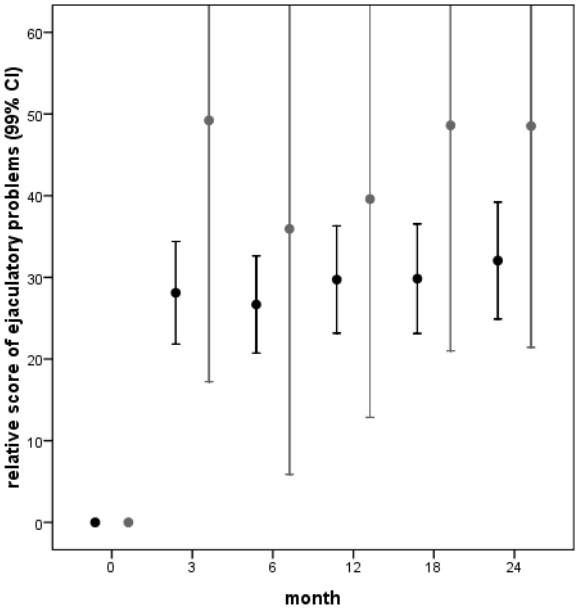
Blood	p=0.002
Time	p=0.001
Blood*Time	p=0.626

b.



Nerve damage
No
Yes

Nerve damage	p=0.011
Time	p=0.465
Nerve damage*Time	p=0.769



Anastomotic leakage
no
yes

Anastomotic leak	p=0.035
Time	p=0.070
Leak*Time	p=0.212

c.

(29/65) had a mean relative score of more than 20 points. The mean postoperative increase in dyspareunia score was 12.3 (SE=2.5) and was only associated with the presence of a temporary or definitive colostoma (p=0.051, mean difference=11.3, SE=5.7; Table 3; Figure 3a). Vaginal dryness developed or worsened postoperatively in 56.6 percent (60/106) of patients. Sixty-two percent (37/60) of these patients had a mean relative score of more than 20 points. The mean postoperative increase in vaginal dryness score was 13.4 (SE=2.5) and was only associated with the presence of a stoma (p=0.063, mean difference=10.8, SE=5.7; Table 3; Figure 3b).

DISCUSSION

In light of improved prognosis of rectal cancer quality of life has become an increasingly important criterion. Policy makers have insisted on including assessment of quality of life in clinical trials. However, quality of life is influenced by the ability to adapt to unfortunate conditions and it has been shown that it does not reflect poor functional outcome.[11] The present study evaluated the development of long-term sexual morbidity in a large randomised multicentre trial. To our knowledge there are no other studies available in which sexual morbidity has been evaluated prospectively on such a large scale in both male and female patients.

Prospective questionnaires were used in order to prevent under-reporting. However, SD might still have been underreported for example out of shame. Furthermore, assessment of female SD remains a difficulty as simple endpoints equivalent to potency and ejaculation are not available and sexual intercourse often remains techniqually possible, even if SD is present. In addition, the questionnaires were not validated. At the time the Dutch TME trial was conducted, validated questionnaires concerning specific sexual problems were not available yet, such as the recently developed module CR29 of QLQ-C30. It should also be noted that the used mean relative scores do not account for a possible time-effect. However, this is justified since the linear mixed models showed no time effect of surgical factors.

The clinical importance of SD after rectal cancer treatment is demonstrated by this study as the majority of the patients was sexually active (526 of 757 patients). The majority of patients reported deterioration of sexual functioning after rectal cancer treatment. Sexual dysfunction after rectal cancer treatment is a multidimensional problem. Reduced self-image, fatique, loss of independence, depression, and changes in interpersonal relationships might harm sexual function. In this study, the presence of a temporary or definitive colostoma was associated with SD in female patients,

probably indicating its psychological role in the development of SD. Decreased arousal due to the presence of a colostoma may result in reduced lubrication and dyspareunia, which were also related to each other (data not shown).[17] In addition to psychological factors, physical factors can play a role. Pelvic organ dysfunction after rectal cancer treatment occurs frequently and surgical damage to the pelvic autonomic nerves is believed to be an important cause[5,18-20]. Damage to the superior hypogastric plexus and hypogastric nerves could lead to disturbed ejaculation[21]. Disruption of the pelvic splanchnic nerves or the pelvic plexus could lead to erectile dysfunction. In the present study, the main predictive factor of increased ejaculatory problems was peroperative autonomic nerve damage. However, erectile dysfunction was only associated with peroperative blood loss and anastomotic leakage and not with nerve damage. With respect to autonomic nerve damage, surgeons most commonly indicated "total preservation" or "unclear" in the surgery report. Therefore, nerve damage was probably underreported and excessive peroperative blood loss may be a surrogate parameter for surgical nerve damage. Use of diathermic coagulation to secure haemostasis may cause nerve damage, especially if it is used improperly and in proximity to the pelvic plexus. Moreover, excessive blood loss hinders vision deep in the pelvis, making nerve sparing virtually impossible[6]. Anastomotic leakage as an important risk factor may be explained by its association with extensive inflammation, which may cause damage to the nerves and seminal vesicles. Theoretically, damage to the superior hypogastric plexus in women could lead to impaired lubrication and disruption of the pelvic splanchnic nerves or the pelvic plexus could cause diminished labia-swelling response. However, this was not supported by the present study. In female patients nerve preservation is less difficult than in the narrow conically shaped male pelvis, which could explain why SD was more common in male than in female patients. Moreover, in women sexual function may be primarily mediated by the sexual centres in the cerebrum and by impulses carried by the pudendal nerves.

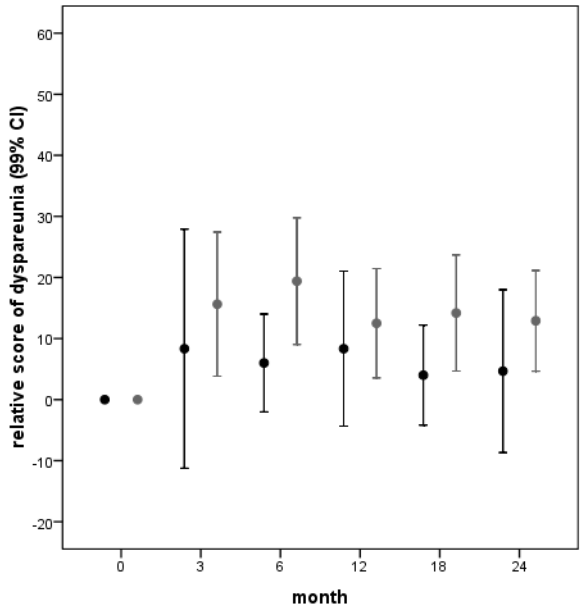
A well known surgical risk factor for SD is abdominoperineal resection, especially with respect to erectile dysfunction in male patients[7,18,22,23]. Avulsion of the pelvic splanchnic nerves from their sacral roots might occur following a tear of the presacral parietal fascia during the perineal phase of this procedure[22]. In the present study abdominoperineal resection resulted in increased erectile dysfunction. However, this effect did not remain significant after correcting for peroperative blood loss, which was increased during abdominoperineal resection compared to low anterior resection (data not shown).

In addition to surgical damage, it is known that PRT is associated with long-term functional morbidity[7,8,10,11,24]. The cause of radiotherapy-related SD is multifacto-

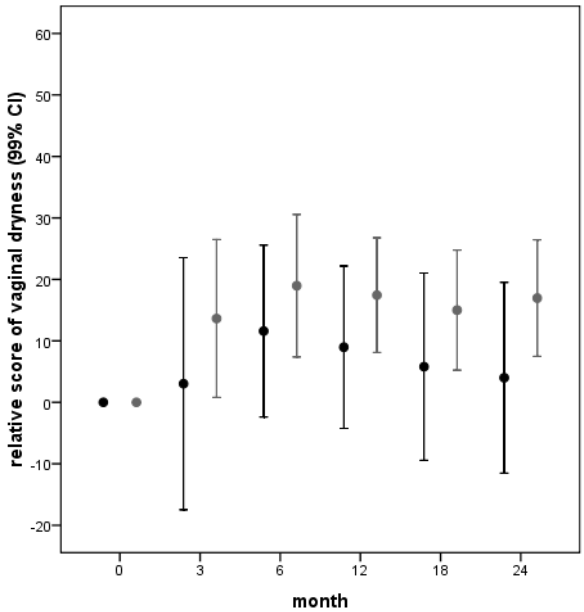
Table 3. Results of univariate and multivariable regression analysis of the influence of patient and treatment related factors on the mean relative scores of general sexual dysfunction, dyspareunia and vaginal dryness in female patients. (SD=sexual dysfunction, N=number of patients, SE=standard error, LAR=low anterior resection, APR=abdominoperineal resection, uni=univariate analysis, multi=multivariable analysis)

	General SD					Dyspareunia					Vaginal dryness				
Risk factors	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi
Age				0.673					0.140					0.694	
≤65 years	92	7.69	2.91			88	14.19	2.85			84	13.95	2.81		
>65 years	25	10.25	4.45			22	4.85	5.23			22	4.83	5.97		
Body Mass Index				0.363					0.676					0.972	
≤30 kg/m²	81	8.03	3.06			75	13.97	3.00			71	13.91	3.17		
>30 kg/m²	13	15.67	8.52			12	17.34	7.07			12	13.61	9.72		
Tumour stage				0.622					0.788					0.624	
I	9	12.66	7.86			8	9.72	5.98			7	0.95	15.27		
II	51	4.80	4.10			45	9.75	3.71			45	14.12	3.18		
III	52	11.17	3.57			53	15.03	4.07			50	14.20	4.03		
IV	5	4.86	4.29			4	10.42	7.89			4	17.92	8.75		
Preoperative radiotherapy				0.033	0.033				0.845					0.384	
no	62	3.30	3.33			59	11.86	3.58			55	11.29	3.24		
yes	55	13.80	3.57			51	12.85	3.57			51	15.74	3.97		
Resection type				0.584					0.293					0.431	
LAR	89	8.64	2.86			82	10.76	2.92			79	12.22	2.97		
APR	26	5.38	4.96			26	17.12	5,44			25	17.00	5.21		

Risk factors	General SD					Dyspareunia					Vaginal dryness				
	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi	N	relative score	SE	p-value uni	p-value multi
Level of anastomosis				0.438					0.557					0.325	
≤4.0 cm	62	11.13	2.80			58	10.81	3.91			55	9.10	3.96		
4.0-7.0 cm	27	5.20	4.37			26	9.86	4.38			25	17.93	4.13		
>7.0 cm	16	3.69	9.94			14	19.07	7.02			14	15.24	3.43		
Resection additional organ				0.184					0.558					0.591	
no	86	6.26	2.98			81	11.43	3.06			77	12.59	3.07		
yes	31	13.73	4.23			29	14.81	4.38			29	15.67	4.51		
Excessive blood loss				0.488					0.404					0.475	
no	96	7.27	2.81			90	13.01	2.86			87	14.14	3.00		
yes	20	11.87	5.18			19	7.41	5.31			18	9.26	3.64		
Nerve damage				0.222					0.788					0.527	
no	89	6.60	3.05			82	12.04	2.81			80	14.15	2.88		
yes	27	13.82	3.62			27	13.63	5.82			25	10.33	5.56		
Temporary/definitive stoma				0.930					0.051	0.051				0.063	0.063
no	32	7.55	4.01			29	4.01	3.96			28	5.48	4.38		
yes	83	8.04	3.07			79	15.33	3.15			76	16.28	3.09		
Anastomotic leakage				0.123					0.662					0.434	
no	111	9.13	2.32			104	12.59	2.59			100	13.92	2.55		
yes	6	-8.19	22.53			6	7.69	12.46			6	5.28	15.41		



a.



b.

Figure 3. Linear mixed models analysis of a) relative dyspareunia scores and b) relative vaginal dryness scores in female patients with or without a temporary/definitive colostoma. Ninety-nine confidence intervals are displayed on the y-axis. (CI=confidence interval)

rial, involving fibrosis, vascular toxicity, neurotoxicity and psychological factors[25]. Radiation damage to the cavernous arteries may result in impotence and the seminal vesicles may stop functioning after irradiation, resulting in ejaculatory problems.[25,26] However, in the present study PRT was not an independent risk factor for erectile dysfunction or ejaculatory problems. Furthermore, the effect of PRT on the dysfunction scales running to 100 was less than ten points, while postoperative scores were approximately 20 points higher than preoperative scores. Therefore, despite the additional effect of PRT, SD seems to be mainly caused by surgery. It is difficult to influence surgical factors, except for nerve damage. Expert studies have shown that autonomic nerve preservation is achievable, but their results have not been reproduced in larger studies[6,19]. Because exact identification of the autonomic nerves can be difficult, the use of a nerve stimulating device could possibly facilitate preservation of the pelvic autonomic nerves during TME[27]. Also high volume hospitals and surgeons may have better results.

In conclusion, we believe that education and training of surgeons in pelvic neuroanatomy and crucial anatomical dissection planes is the key to improvement of functional outcome.

In addition, any doctor treating rectal cancer patients should be aware that many are sexually active and inform their patients about the possible negative sexual consequences of treatment. At present, there is an ongoing project investigating to what extent patients and oncologists believe that patients should also participate in decision making regarding therapy. During follow-up doctors should be aware that patients might experience substantial distress from SD and suggest possible therapies[28].

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CHAPTER 5

Urinary dysfunction after rectal cancer treatment is mainly caused by surgery

Lange MM, Maas CP, Marijnen CAM, Wiggers T, Rutten HJ, Klein Kranenbarg E, van de Velde CJH.

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ABSTRACT

Background
Urinary dysfunction (UD) is common after rectal cancer treatment, but the contribution of each treatment component (surgery and radiotherapy) to its development remains unclear. This study aimed to evaluate UD during 5 years after total mesorectal excision (TME) and to investigate the influence of preoperative radiotherapy (PRT) and surgical factors.

Methods
Patients with operable rectal cancer were randomised to TME with or without PRT. Questionnaires concerning UD were completed by 785 patients before and at several time points after surgery. Possible risk factors, including PRT, demographics, tumour location, and type and extent of resection, were investigated by multivariable regression analysis.

Results
Long-term incontinence was reported by 38.1 percent of patients, of whom 72.0 percent had normal preoperative function. Preoperative incontinence (relative risk (RR) 2.75, $p=0.001$) and female sex (RR 2.77, $p<0.001$) were independent risk factors. Long-term difficulty in bladder emptying was reported by 30.6 percent of patients, of whom 65.0 percent had normal preoperative function. Preoperative difficulty in bladder emptying (RR 2.94, $p<0.001$), peroperative blood loss (RR 1.73, $p<0.028$) and autonomic nerve damage (RR 2.82, $p=0.024$) were independent risk factors. PRT was not associated with UD.

Conclusion
UD is a significant clinical problem after rectal cancer treatment and is not related to PRT, but rather to surgical nerve damage.

INTRODUCTION

The past two decades have witnessed substantial improvement in survival from rectal cancer resulting from earlier diagnosis, improved efficiency and delivery of radiotherapy, and advances in surgical techniques such as total mesorectal excision (TME)[1,2]. In the light of improved prognosis the quality of functional outcome has become increasingly important. As a consequence, an increasing number of studies have focused on postoperative urinary, sexual and anorectal dysfunction. Currently, the rate of urinary dysfunction (UD) after rectal cancer surgery ranges from 30 to 70 percent[3-6].

The contribution of each treatment component (surgery and radiotherapy) to the development of UD remains unclear. Damage to the pelvic autonomic nerve system, either as a result of surgery or radiotherapy, might be involved. Damage to the superior hypogastric plexus and the hypogastric nerves causes reduced bladder capacity, and may result in urge incontinence. Damage to the sacral splanchnic nerves may lead to overflow incontinence and urinary retention, and difficulty in bladder emptying[7]. Bilateral surgical disruption of the inferior hypogastric plexus has been shown clinically to lead to devastating UD[8].

A plane of dissection around the mesorectum is required in TME for rectal cancer, in an attempt to avoid nerve disruption. However, despite this, clinical studies show that this operation is associated with 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[3,9]. Clinical data from large prospective studies on the contribution of surgical nerve damage to UD after TME are, however, lacking.

There is no consensus about the role of preoperative radiotherapy (PRT) in the development of UD after rectal cancer treatment either[4,9-12]. Other possible risk factors have also been investigated in previous studies, with contradictory results concerning the influence of age[9,12,13], sex[5,9,14,15], tumour height[14-16], tumour size[12,15] and type of resection[4,5,9,12,16-18]. Interpretation of results is difficult because of differences in definitions of types of UD and their assessment. The number of patients and length of follow-up in these studies were limited. Moreover, the influence of the risk factors was often evaluated without distinguishing between incontinence and difficulty in bladder emptying, although these problems may have a different etiology.

The aim of the present study was to evaluate UD in both the short and long term, and to examine the influence of PRT and surgical factors separately on long-term incontinence and difficulty in bladder emptying after TME.

METHODS

The database of the Dutch TME trial was used. This international multicentre trial investigated the efficacy of short-term PRT in patients with rectal cancer treated with TME. From January 1996 to December 1999, 1 861 patients with histologically proven adenocarcinoma of the rectum and without evidence of distant metastases were included in the trial, and randomised to receive PRT followed by TME or TME alone. Patients were eligible for randomisation when the tumour was clinically resectable and located 15 cm or less from the anal verge. Details of the Dutch TME trial have been described elsewhere[19]. Only Dutch patients who underwent low anterior resection or abdominoperineal resection, and participated in the quality-of-life study[19,20] and in the study of long-term side-effects of PRT[21], were selected for the present analysis. Patients with any recurrence during the period of evaluation were excluded to avoid confounding due to symptoms caused by disease recurrence.

Treatment

Patients assigned to PRT received a total dose of 25 Gy in five fractions over 5-7 days. The clinical target volume included the primary tumour and the mesentery with vascular supply, containing the perirectal, presacral and internal iliac nodes. The recommended upper border was at the level of the promontory. The perineum was included if abdominoperineal resection was planned, whereas the lower border was 3 cm above the anal verge if the planned operation was low anterior resection. Surgery had to take place within 10 days of the start of PRT. All patients underwent surgery according to the TME principles, as advocated by Heald[22]. Participating surgeons attended workshops and symposiums, watched instructional videotapes, and were monitored by specially trained instructor surgeons. At each hospital, the first five TMEs were supervised by an instructor surgeon[23]. Autonomic nerve preservation was mentioned in the surgery report as either total preservation, damage to the superior hypogastric plexus, one or both hypogastric nerves, one or both sides of the inferior hypogastric plexus or the splanchnic nerves, or unclear whether nerves were preserved (autonomic nerves not identified).

Outcome measures

For the quality-of-life study, questionnaires, including questions on incontinence and difficulty in bladder emptying, were sent to patients before surgery and at 3, 6, 12, 18 and 24 months after TME[20]. The time frame of these questions was the past week.

Responses were given on a four-point severity scale, with options 'not at all', 'a little', 'quite a bit' and 'very much'.

For the study investigating long-term side-effects of PRT, only patients without recurrent disease who responded to the previous forms were sent a questionnaire at a median of 5 years after TME[21]. In this study the time frame of the questions was the past 3 months. The presence of urinary incontinence was indicated on a five-point scale, with options 'not at all', 'less than once a week', 'once a week', 'a few times a week' and 'every day'. The frequency of difficulty in bladder emptying was indicated on a six-point scale with options 'no, not at all', 'less than one in five times', 'less than half of times, 'in half of times', 'in more than half of times' and 'yes, almost always'.

For the evaluation of changes in UD over 5 years, scales for both urinary incontinence and difficulty in bladder emptying were transformed into three-point scales: 'no dysfunction' (corresponding to the answer 'not at all'), 'moderate dysfunction' (corresponding to: 'a little', 'less than once a week', 'once a week', 'a few times a week', 'less than one in five times', 'less than half of times') and 'severe dysfunction' (corresponding to 'quite a bit', 'very much', 'every day', 'in more than half of times' and 'yes, almost always').

For univariate and multivariable logistic regression analyses, answers were transformed into a binary outcome measure (absence *versus* presence of incontinence and difficulty in emptying the bladder, irrespective of severity or frequency), to allow for differences in questionnaire design.

Statistical analysis

Data were analysed with the statistical software SPSS® version 12.0 for Windows® (SPSS, Chicago, Illinois, USA). Differences in percentages of patients with UD at two time points were analysed with the McNemar test. The influence of the predictor variables on the risk of UD 5 years after TME was calculated using univariate logistic regression analysis. To examine the independent influence of these variables, all variables associated with UD with $p<0.100$ in the univariate regression analysis were included in a multiple logistic regression analysis. $P\leq0.050$ was considered statistically significant. At all times incontinence and difficulty in bladder emptying were analysed separately.

RESULTS

Of a total of 1 530 Dutch patients, 542 were excluded from analysis for the following reasons: ineligible at randomisation (50), did not have surgery (37), died in hospital (52), did not provide informed consent for the quality-of-life study (89), did not return quality-of-life forms (30), and developed local or distant recurrence (284).

Table 1. Patient and treatment characteristics (continuous variables: median (minimum, maximum); categorical variables: number of patients (%); SHP=superior hypogastric plexus; HN=hypogastric nerves)

Age (years) (n=785)	64.0 (26, 92)
Gender (n=785)	
Male	499 (63.6)
Female	286 (36.4)
Body Mass Index (kg/m^2; n=629)	25.3 (16.9, 53.1)
Child delivery (♀; n=283)	242 (85.5)
Tumour location (n=131)	
Anterior	66 (50.4)
Posterior	65 (49.6)
Tumour size (cm; n=775)	4.0 (0, 13.0)
TNM (n=696)	
0/I	270 (38.8)
II	200 (28.7)
III	226 (32.5)
Tumour height (cm; n=775)	7.0 (0, 18.0)
Preoperative radiotherapy (n=785)	373 (47.5)
Type of resection (n=785)	
Low anterior resection	532 (67.8)
Abdominoperineal resection	223 (28.4)
Hartmann	30 (3.8)
Anastomotic height of LAR (cm; n=511)	5.5 (0, 14.0)
Resection additional organ (n=785)	144 (18.3)
Peroperative blood loss (ml; n=771)	1000 (50, 15000)
Autonomic nerve damage as reported by surgeons (n=777)	
Total preservation	580 (74.6)
SHP and/or HN	69 (8.9)
Pelvic plexus/splanchnic nerves	44 (5.7)
Unclear	84 (10.8)

Of 988 remaining patients, pretreatment forms were missing for 203 because they were completed after the start of PRT (53) or after surgery (67), were not dated (25) or were not completed at all (58). The preoperative response rate was 79.5 percent. Patient and treatment characteristics of the 785 patients who remained assessable are listed in Table 1.

Response rates to the postoperative forms varied between 82.2 and 89.6 percent[20,21]. Questionnaires concerning long-term side-effects of PRT were completed between 3.3 and 7.4 years after TME. Because the percentages of patients with incontinence and those with difficulty in bladder emptying did not differ significantly within this interval (F=0.17, p=0.680 and F=1.80, p=0.181 respectively), all these patients were grouped together and considered as five-year follow-up patients.

Incontinence

Some 130 (16.7 percent) of 780 patients reported incontinence before surgery, of whom 29 (22.6 percent) experienced an aggravation of symptoms after TME. Three months after TME the proportion of patients with incontinence was increased to 25.8 percent (McNemar χ^2=34.16, 1 d.f., p<0.001). A further increase was observed until 5 years after TME when 38.1 percent reported incontinence (McNemar χ^2=23.94, 1 d.f., p<0.001), of whom 72.0 percent had normal preoperative function. At that time the severity of dysfunction in patients with incontinence was also increased (McNemar χ^2=14.70, 1

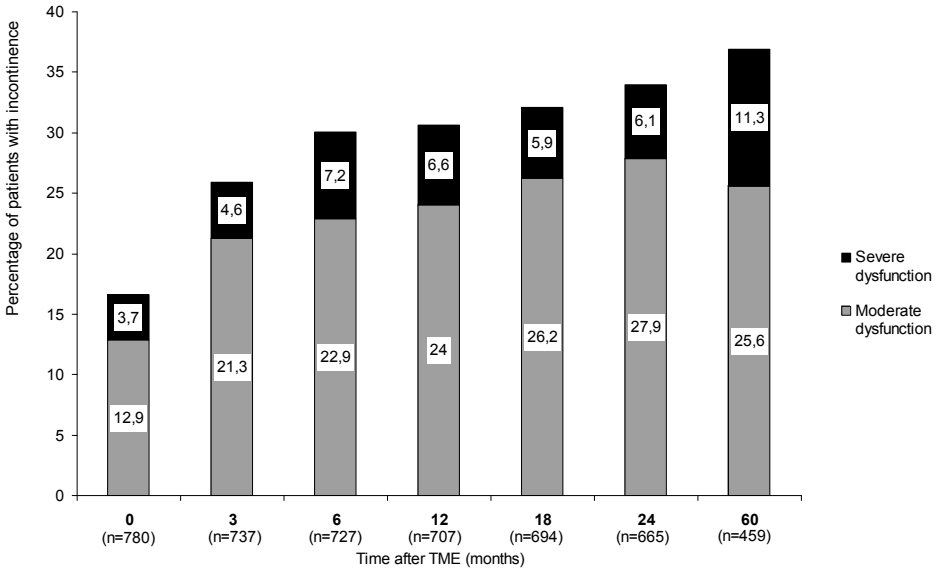

Figure 1. Percentage of patients with incontinence with time after total mesorectal excision (TME)

d.f., p<0.001); 30.7 percent reported severe incontinence at 5 years compared with 17.8 percent at 3 months after TME. Figure 1 shows the percentages of patients with moderate or severe incontinence before and over the first 5 years after TME.

Of 447 patients who reported on the severity of incontinence at 5 years, 385 had no incontinence before TME; 126 (32.7 percent) of these developed long-term incontinence after treatment, of whom 93 (73.8 percent) reported moderate and 33 (26.2 percent) reported severe incontinence 5 years after TME. In 63.9 percent incontinence that first developed by 3 months after TME persisted for 5 years. In the univariate regression analysis, preoperative incontinence, age above 65 years and female sex were associated with an increased risk of incontinence. No other risk factors for incontinence, including PRT and type of resection, could be identified (Table 2). In addition, body mass index above 30 kg/m2 (relative risk (RR) 1.69, p=0.141) childbirth (analysed in women only; RR 1.19, p=0.698) and posterior *versus* anterior tumour location (RR 0.86, p=0.756) did not increase the risk of urinary incontinence significantly. In the multivariable regression analysis, only preoperative incontinence (RR 2.75, p=0.001) and female sex (RR 2.77, p<0.001) remained predictive variables for urinary incontinence at 5 years after TME. Increased age was not a significant independent risk factor (RR 1.39, p=0.118). Except for preoperative dysfunction as a risk factor, the results were similar for patients with newly developed incontinence after treatment (data not shown).

Difficulty in bladder emptying

Before operation 176 (22.5 percent) of 782 patients reported difficulty in bladder emptying, of whom 11 (6.0 percent) experienced an aggravation of symptoms after TME. Three months after TME the proportion of patients with difficulty in bladder emptying was increased significantly to 36.0 percent (McNemar χ^2=46.05, 1 d.f., p<0.001). A significant decrease up to 18 months (McNemar χ^2=7.31, 1 d.f., p=0.007) and a subsequent stabilization occurred, resulting in 30.6 percent of patients with difficulty in bladder emptying 5 years after TME, of whom 65.0 percent had normal preoperative function. Long-term improvement in the severity of dysfunction was especially apparent in patients with severe difficulty in bladder emptying after TME. Figure 2 shows the percentages of patients with difficulty in bladder emptying before and over the first 5 years after TME.

Of 445 patients who answered the question concerning bladder emptying at 5 years, 351 patients had normal preoperative function; 90 (25.6 percent) of these developed long-term difficulty after treatment, of whom 79 (88.0 percent) reported moderate and 11 (12.0 percent) reported severe dysfunction 5 years after TME. In the univariate regression analysis, increased risk in difficulty in bladder emptying

Table 2. Regression analysis with urine incontinence at five years after TME as outcome variable (RR=Relative Risk; CI=confidence interval; SHP=superior hypogastric plexus; HN=hypogastric nerves)

	Patients with incontinence (%)	RR (95% CI)	p-value	p-value (multivariable analysis)
Age (n=459)				
<65 years	33.3 (90 of 270)			
≥65 years	45.0 (85 of 189)	1.64 (1.12-2.40)	0.012	0.118
Gender (n=459)				
Male	29.2 (84 of 288)			
Female	53.2 (91 of 171)	2.76 (1.86-4.09)	<0.001	<0.001
Preoperative incontinence (n=455)				
No	33.8 (132 of 391)			
Yes	62.5 (40 of 64)	3.27 (1.89-5.66)	<0.001	0.001
Tumour size (n=454)				
<4.0 cm	38.5 (102 of 365)			
≥4.0 cm	37.0 (70 of 189)	0.94 (0.64-1.38)	0.753	
TNM (n=459)				
0/I	40.2 (86 of 214)			
II	35.4 (45 of 127)	0.82 (0.52-1.29)	0.383	
III	37.3 (44 of 118)	0.89 (0.56-1.41)	0.885	
Tumour height (n=441)				
<5.0 cm	35.9 (61 of 170)			
5.0-10.0 cm	38.8 (81 of 209)	1.13 (0.74-1.72)	0.565	
≥10.0 cm	45.2 (28 of 62)	1.47 (0.82-2.66)	0.200	
Preoperative radiotherapy (n=459)				
No	37.6 (88 of 234)			
Yes	38.7 (87 of 225)	1.04 (0.72-1.53)	0.815	
Type of resection (n=459)				
Low anterior resection	39.7 (123 of 310)			
Abdominoperineal resection	33.1 (44 of 133)	0.75 (0.49-1.15)	0.190	
Hartmann	50.0 (8 of 16)	1.52 (0.56-4.16)	0.414	
Anastomotic height of LAR (n=300)				
<4.0 cm	39.8 (41 of 103)			
4.0-7.0 cm	44.4 (52 of 117)	1.21 (0.71-2.07)	0.487	
≥7.0 cm	28.8 (23 of 80)	0.61 (0.33-1.14)	0.121	
Resection additional organ (n=459)				
No	36.6 (138 of 377)			
Yes	45.1 (37 of 82)	1.42 (0.88-2.31)	0.151	
Peroperative blood loss (n=451)				
<1500 ml	38.3 (132 of 345)			
≥1500 ml	38.7 (41 of 106)	1.02 (0.65-1.59)	0.938	
Autonomic nerve damage (n=455)				
Total preservation	38.1 (133 of 349)			
SHP and/or HN	38.5 (15 of 39)	1.02 (0.51-2.00)	0.966	
Pelvic plexus/splanchnic nerves	36.4 (8 of 22)	0.93 (0.38-2.27)	0.870	
Unclear	37.8 (17 of 45)	0.99 (0.52-1.87)	0.966	

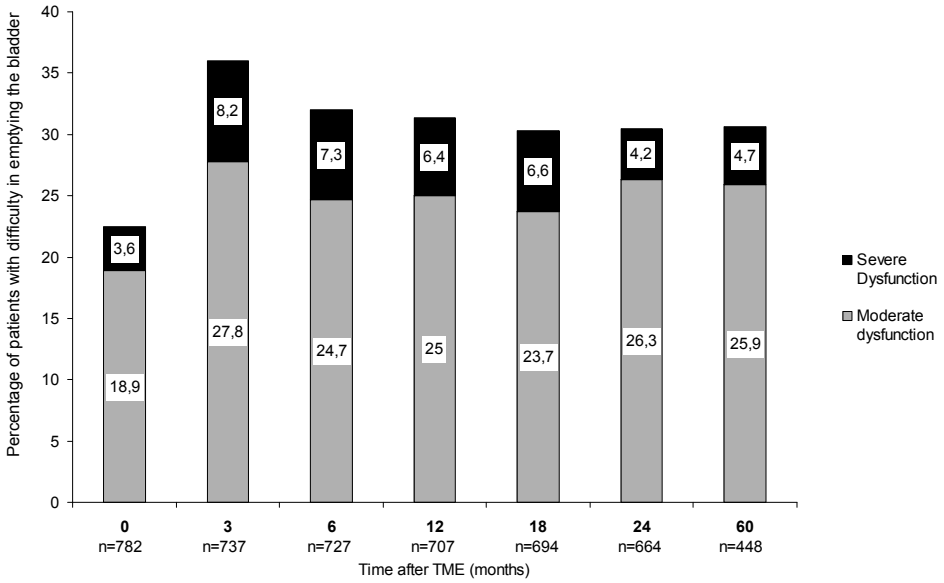

Figure 2. Percentage of patients with difficulty in emptying the bladder with time after total mesorectal excision (TME)

5 years after TME was associated with preoperative difficulty in bladder emptying, excessive peroperative blood loss (at least 1 500 ml), and surgical damage to one or both sides of the inferior hypogastric plexus and/or the splanchnic nerves. No significant effect of PRT was observed (Table 3). In addition, body mass index above 30 kg/m^2 (RR 0.79, p=0.549), childbirth (analysed in women only; RR 2.72, p=0.121) and posterior *versus* anterior tumour location (RR 0.67, p=0.411) did not increase the risk of difficulty in bladder emptying significantly. In the multivariable regression analysis, preoperative difficulty in bladder emptying (RR 2.94, p<0.001), excessive peroperative blood loss (RR 1.73, p=0.028) and autonomic nerve damage (RR 2.82, p=0.024) remained significant predictors. Except for preoperative dysfunction as a risk factor, the results were similar for patients with newly developed difficulty in bladder emptying after TME (data not shown).

DISCUSSION

This five-year follow-up study has shown that new development and aggravation of UD occurs frequently after rectal cancer treatment. Urinary incontinence was associated with preoperative incontinence and female sex. Risk factors for difficulty in bladder emptying were preoperative difficulty in bladder emptying, peroperative blood loss and autonomic nerve damage. PRT did not increase the risk of UD.

Table 3. Regression analysis with difficulties in bladder emptying at five years after TME as outcome variable (RR=Relative Risk; SHP=superior hypogastric plexus; HN=hypogastric nerves)

	Patients with incontinence (%)	RR (95% CI)	p-value	p-value (multivariable analysis)
Age (n=448)				
<65 years	30.9 (83 of 269)			
≥65 years	30.2 (54 of 179)	0.97 (0.64-1.46)	0.877	
Gender (n=448)				
Male	33.1 (92 of 278)			
Female	26.5 (45 of 170)	0.73 (0.48-1.11)	0.141	
Preoperative problems in bladder emptying (n=445)				
No	25.6 (90 of 351)			
Yes	48.9 (46 of 94)	2.78 (1.74-4.45)	<0.001	<0.001
Tumour size (n=443)				
<4.0 cm	30.6 (79 of 258)			
≥4.0 cm	30.3 (56 of 185)	0.98 (0.65-1.48)	0.937	
TNM (n=448)				
0/I	32.4 (68 of 210)			
II	26.4 (33 of 125)	0.75 (0.46-1.23)	0.249	
III	31.9 (36 of 113)	0.98 (0.60-1.59)	0.924	
Tumour height (n=430)				
<5.0 cm	31.3 (52 of 166)			
5.0-10.0 cm	29.4 (60 of 204)	0.91 (0.59-1.43)	0.690	
≥10.0 cm	33.3 (20 of 60)	1.10 (0.58-2.06)	0.775	
Preoperative radiotherapy (n=448)				
No	33.8 (77 of 228)			
Yes	27.3 (60 of 220)	0.74 (0.49-1.10)	0.136	
Type of resection (n=448)				
Low anterior resection	29.4 (89 of 303)			
Abdominoperineal resection	31.8 (41 of 129)	1.12 (0.72-1.75)	0.617	
Hartmann	43.8 (7 of 16)	1.87 (0.68-5.18)	0.228	
Anastomotic height of LAR (n=293)				
<4.0 cm	30.4 (31 of 102)			
4.0-7.0 cm	31.5 (35 of 111)	1.06 (0.59-1.89)	0.857	
≥7.0 cm	37.5 (30 of 80)	1.37 (0.74-2.55)	0.314	
Resection additional organ (n=448)				
No	30.7 (113 of 368)			
Yes	30.0 (24 of 80)	0.97 (0.57-1.64)	0.901	
Peroperative blood loss (n=440)				
<1500 ml	28.4 (95 of 335)			
≥1500 ml	39.0 (41 of 105)	1.62 (1.02-2.56)	0.040	<0.001
Autonomic nerve damage (n=444)				0.024
Total preservation	26.8 (91 of 340)			
SHP and/or HN	35.9 (14 of 39)	1.53 (0.76-3.08)	0.230	
Pelvic plexus/splanchnic nerves	54.5 (12 of 22)	3.28 (1.37-7.86)	0.008	
Unclear	44.2 (19 of 43)	2.17 (1.13-4.14)	0.019	

This is the largest study to investigate potential risk factors for UD, distinguishing between urinary incontinence and difficulty in bladder emptying, longitudinally over 5 years after TME. The prevalence of UD in the present study is comparable to published data[3-6,8-10,12,16].

Several studies have shown that damage to the autonomic nerves results in UD[5,14,17,24]. The pelvic autonomic nerves are essential for normal urinary function. During urine storage, the sympathetic nervous system plays a major role. Preganglionic neurones in the upper lumbar spinal cord excite sympathetic neurones in the inferior mesenteric ganglia through the superior hypogastric plexus, hypogastric nerves and pelvic ganglia via the sacral splanchnic nerves. This causes contraction of smooth muscle in the trigone and urethra, which is coordinated with contraction of the external urethral sphincter. These various neural pathways continue to be activated until bladder pressure is sufficient to trigger a micturition reflex.

The parasympathetic nervous system plays a dominant role during voiding. Activation of sacral preganglionic neurones excites parasympathetic ganglionic neurones in the pelvic splanchnic nerves and inferior hypogastric plexus. This causes contraction of the detrusor muscle and relaxation of the urethra, with coordinated inhibition of nerve activity to the external urethral sphincter[25]. Therefore, damage to the parasympathetic sacral splanchnic nerves and inferior hypogastric plexus may lead to difficulty in bladder emptying, as demonstrated in the present study. The risk of difficulty in bladder emptying after TME was significantly increased if there was surgical damage to the sacral splanchnic nerves and inferior hypogastric plexus, which was recorded by the surgeon in 44 (5.7 percent) of 777 patients.

A correlation between long-term urinary incontinence and autonomic nerve damage was not demonstrated. The reason for this might be that surgical disruption of the autonomic nerves only leads to significant incontinence when most of the pelvic autonomic nerves are seriously damaged. One-sided preservation of the inferior hypogastric plexus only has been shown clinically to result in acceptable urinary continence[3,8]. The incidence of bilateral surgical disruption of the inferior hypogastric plexus is not known. Surgeons are often unable to verify whether bilateral damage has occurred, but it is not expected to occur frequently during a TME procedure[9].

Even with accurate neuroanatomical knowledge, pelvic autonomic nerve sparing surgery can be very difficult. Individual differences in the running patterns of the nerves and variation in the volumes of nerve fibres in each region of the pelvis hamper appropriate identification of structures. The use of a nerve stimulating device might facilitate preservation of the pelvic autonomic nerves during TME. The efficacy of a nerve stimulator in assisting intraoperative identification of the autonomic nerves during TME and objectively confirming nerve preservation after proctectomy was tested by da Silva and colleagues[26] in 29 men. Intraoperative visualisation of

the hypogastric nerves was possible in 19 of 26 patients. The nerve stimulator successfully identified the nerves in six of the seven remaining patients and confirmed preservation of the hypogastric nerves in 27 of 29 patients after proctectomy. The ultimate role of this device during TME requires further evaluation.

New anatomical views could also enhance autonomic nerve sparing during TME. In a recent publication, a Japanese group meticulously investigated the fascial structures posterolateral to the rectum. They identified a prehypogastric nerve fascia between the fascia propria of the rectum and the parietal presacral fascia. Sharp dissection in front of the prehypogastric nerve fascia seemed to lead the plane precisely between the hypogastric nerves, pelvic plexus and proper rectal fascia which borders the mesorectum. In contrast, although the loose areolar space between the presacral parietal fascia and the visceral fascia (mesorectal fascia) is easily identified during classical TME dissection, some surgeons follow the presacral parietal fascia and not the mesorectal fascia. Especially laterally this fascia divides in several compartments containing the ureter and the autonomic nerves. However, it is not identified easily and, once in the wrong plane, the nerves can be severed[27].

In the present study excessive peroperative blood loss was significantly associated with nerve damage (data not shown). Diathermic coagulation and use of numerous sutures to secure haemostasis may cause nerve damage. Moreover, excessive blood loss hinders vision deep in the pelvis, making nerve sparing virtually impossible[3,5]. Excessive peroperative blood loss was also an independent risk factor for difficulty in bladder emptying, which might be explained by impaired tissue healing or may be due to the possibility that nerve damage was underreported.

The decrease in number of patients with difficulty in bladder emptying after 3 months might be explained by postoperative inflammatory changes in the paravesical tissues, which heal with time, and the possible resolution of partial nerve damage within the first 3-6 months after surgery, resulting in functional improvement and even complete recovery[13].

Difficulty in bladder emptying may result in overflow incontinence[28]. Indeed, difficulty in bladder emptying was significantly associated with urinary incontinence 3 months after TME (data not shown). Long-term urinary incontinence after TME was not associated with difficulty in bladder emptying in this study (data not shown), because the number of patients with urinary incontinence increased during the 5 years after TME, probably owing to ageing of the patient group with a concomitant risk of urge and stress incontinence[29]. The present study has shown that newly developed incontinence shortly after TME is a predictor of long-term incontinence. It might therefore be worth proposing a pelvic floor and bladder training programme to those who develop incontinence after TME[30].

A surgical factor contributing to the development of long-term urinary incontinence after TME might be surgical disruption of the innervation of the levator ani muscles. According to renewed anatomical insights, the levator ani muscles, which are essential to urinary continence ('hammock' hypothesis)[31], are not innervated by the pudendal nerves, but receive their motor innervation from a separate nerve, which runs on the surface of the levator ani muscle. During surgical dissection deep within the pelvis, this nerve might be disrupted[32]. A weak pelvic floor resulting in loss of support to urethral and bladder neck can contribute to loss of sphincter tone and therefore incontinence[31,33]. During the TME trial this anatomical insight was not acknowledged and was therefore not considered. In this respect an increased incidence of urinary incontinence might be expected after abdominoperineal resection with implicit (partial) resection of the levator ani muscles. This is not shown by the present results, but is in accordance with several earlier studies[16,18]. The present study is possibly biased owing to exclusion of patients with recurrence (relatively more patients with advanced tumours and those treated with abdominoperineal resection). Such patients, especially those treated with abdominoperineal resection, indeed reported more (severe) urinary incontinence 3 months after surgery (data not shown).

There was an increased risk of new development of incontinence after TME in women in this study. According to Ulmsten[31], support to the urethral and bladder neck is regulated by surrounding structures, the most important being the pubourethral-vesical ligaments, suburethral vaginal wall, levator plate, pubococcygeus muscles and connective tissue. These components can compensate for each other in case of inappropriate function. In postmenopausal women many of these structures might already be impaired because the function of many structures involved in preserving continence is influenced by oestrogen receptors[31]. Additional changed anatomical relationships between the bladder, urethra and pelvic floor, and possibly damage to the innervation of the levator ani muscles during TME, would further impair the continence mechanism and lead to incontinence.

Urinary dysfunction has been reported after radiotherapy for cancer of the pelvic organs[34,35]. Depending on the dose and irradiation field, radiotherapy may cause fibrosis in the bladder and the urethral sphincters[35]. However, there is no consensus in the literature about the contribution of radiotherapy to the development of UD after rectal cancer treatment. Only one of the published studies randomised for PRT. Pollack and colleagues[4] recently reported an increased risk of UD after rectal cancer treatment in irradiated patients compared with those who had TME alone. However, only 139 patients were evaluated. Analysis of data from 785 patients in the Dutch trial of TME with or without radiotherapy, which was designed primarily to detect the effect and consequences of PRT, has demonstrated that PRT does not contribute

to the development of UD after rectal cancer treatment when surgical factors are taken into account.

In conclusion, a substantial proportion of patients with rectal cancer suffer from long-term UD. It is a significant clinical problem after treatment for primary rectal cancer. Difficulty in bladder emptying is related to surgical damage to the autonomic nerves. Because no influence of PRT was found, surgery also seems to play an important role in the development of urinary incontinence. Special attention to the pelvic autonomic nerves and a more careful surgical approach are required.

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CHAPTER 6

Risk factors for faecal incontinence after rectal cancer treatment

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ABSTRACT

Background
Low anterior resection (LAR) may result in faecal incontinence. This study aimed to identify risk factors for long-term faecal incontinence after total mesorectal excision (TME) with or without preoperative radiotherapy (PRT).

Methods
Between 1996 and 1999, patients with operable rectal cancer were randomised to TME with or without PRT. Eligible patients who underwent LAR were studied retrospectively at 2 years (399 patients) and 5 years (339 patients) after TME.

Results
At 5 years after surgery faecal incontinence was reported by 61.5 percent of patients who had PRT and 38.8 percent of those who did not ($p<0.001$). Excessive blood loss and height of the tumour were associated with long-term faecal incontinence, but only in patients treated with PRT.

Conclusion
Faecal incontinence is likely to occur after PRT and TME, especially when the perineum is irradiated.

INTRODUCTION

Local recurrence is a major problem in the treatment of rectal cancer. A significant improvement in local control has been achieved by the introduction of preoperative radiotherapy (PRT)[1,2] and improved surgical techniques, including total mesorectal excision (TME)[3-9]. TME is defined as 'a sharp dissection under clear vision between the parietal and visceral planes of the pelvic fascia, removing the mesorectum (the fatty tissue surrounding the rectal wall) contained within an intact endovisceral fascia'[3]. The understanding that distal resection margins of 1-2 cm are adequate[10] resulted in an increased number of patients being treated with low anterior resection (LAR)[7,11,12].

Compared with abdominoperineal resection (APR), LAR has the advantage of preserving normal anal continence, provided that adequate function is ensured[13]. However, poor functional outcome is often reported, with several studies demonstrating that one-third of patients experience faecal incontinence after LAR[12,14,15]. Even worse outcomes are reported by patients treated with PRT[16-18]. Although restorative surgery is generally thought to result in a better quality of life (QoL), faecal incontinence is a major problem. Abdominoperineal resection might, therefore, be a more satisfactory option than LAR in selected patients[11,19,20]. Risk factors should be identified that can be used to select patients likely to become incontinent. Previous studies generally agree that PRT is such a risk factor[16-18], but differ with respect to the influence of other variables[7,12,13,19,21-35].

The aim of the present study was to investigate risk factors for long-term faecal incontinence in the Dutch TME trial[2]. This trial included over 900 patients treated with LAR and provided information on incontinence in both the short and long term. Demographic, tumour-specific and treatment-related variables were selected from the literature, in addition to factors that may have led to nerve damage during surgery.

METHODS

Data were obtained from the database of the Dutch TME trial[2]. This international multicentre trial investigated the efficacy of short-term PRT in patients with rectal cancer treated with TME. Between January 1996 and December 1999, 1 861 patients with histologically proven adenocarcinoma of the rectum and without evidence of distant metastases were included in the trial and randomised to undergo TME alone or preceded by PRT. Patients were eligible for randomisation if the tumour was clinically resectable and located 15 cm or less from the anal verge. Only patients who

underwent LAR and participated in the QoL study[16,17] or in the study on long-term side-effects of PRT[16,17] were selected for this analysis. Patients with recurrence during the period of evaluation were excluded to avoid this potential confounding variable.

Treatment

Patients assigned to PRT received a total dose of 25 Gy in five fractions over 5-7 days. The target volume included the primary tumour, and perirectal, presacral and internal iliac nodes. The perineum was included if APR was planned; otherwise the lower border was 3 cm above the anal verge. Surgery took place within 10 days of the start of PRT.

Outcome measures

Patients completed a questionnaire for the QoL study[16], including a question on faecal incontinence 3, 6, 12, 18 and 24 months after operation. Responses were given on a four-point severity scale, ranging from 'not at all' to 'very much'. In the study investigating long-term side-effects of PRT[17] (a median of 5 years after surgery), the frequency of faecal incontinence was indicated on a four-point scale ranging from 'never' to 'always (every day)'. To minimise differences in questionnaires, answers were transformed into a binary outcome measure (absence *versus* presence of incontinence, irrespective of severity or frequency) for the univariate and multivariable logistic regression analyses.

The database did not contain information on anastomotic height, so this was estimated by subtracting the distal margin from the distance of the tumour to the anal verge (tumour height). The distal margin was evaluated on the macroscopic specimen after surgery. If the distal margin was equal to or larger than the estimated tumour height, patients were considered to have an ultralow anastomosis (height of anastomosis 0 cm). Anastomotic height, ranging from 0 to 12.5 (median 5.5) cm, was divided into quartiles for the analysis outlined here.

Statistical analysis

Data were analysed with SPSS® version 12.0 for Windows® (SPSS, Chicago, Illinois, USA). The influence of the predictor variables on the risk of incontinence 2 and 5 years after surgery was calculated using univariate logistic regression analysis. To examine any independent influence, all variables associated with faecal incontinence ($p<0.100$ in the univariate regression analysis) were entered into a multiple logistic

regression analysis. P≤0.050 was considered statistically significant. Patients treated with and without PRT were analysed separately.

RESULTS

Of the 1 530 Dutch patients, 924 eligible patients underwent LAR. Of these, 371 patients were excluded owing to in-hospital death (34), lack of informed consent for the QoL study (85), or local or distant recurrence (252). At 2 years after surgery 460 correctly completed questionnaires were received. This number was 385 at 5 years after randomisation owing to intercurrent deaths and non-compliance. Because of the presence of a stoma the question on incontinence was answered by 399 and 339 patients at 2 and 5 years respectively.

Faecal incontinence

Questionnaires concerning long-term side-effects of PRT were completed between 3.3 and 7.4 years after LAR. The percentage of patients with incontinence did not change significantly within this interval (F=0.46, p=0.499), so a median follow-up of 5 years was used in the following analyses. Figure 1 shows the proportions of patients with incontinence over time. From 3 to 24 months, the percentage of patients with incontinence declined significantly in both those treated with PRT (Wilcoxon's

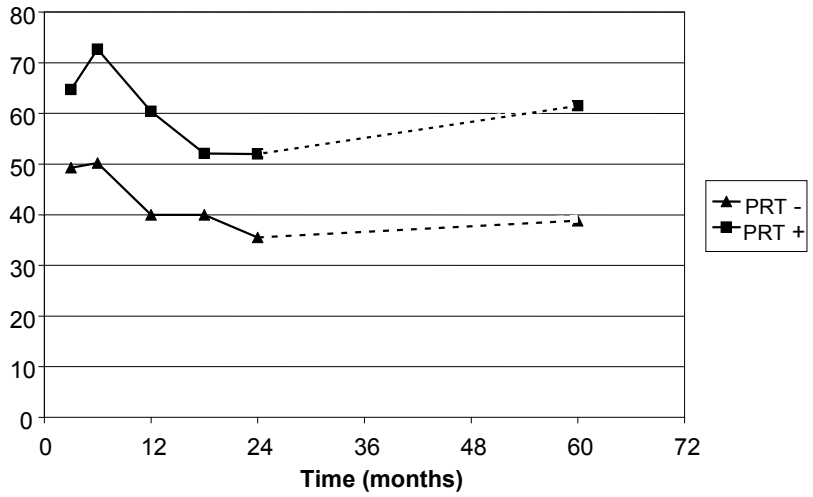

Figure 1. Percentage of patients with faecal incontinence after rectal cancer surgery with (PRT+) or without preoperative radiotherapy (PRT-). Dashed portion of curves is based on only one questionnaire for each patient, obtained between 3.3 and 7.4 years after LAR.

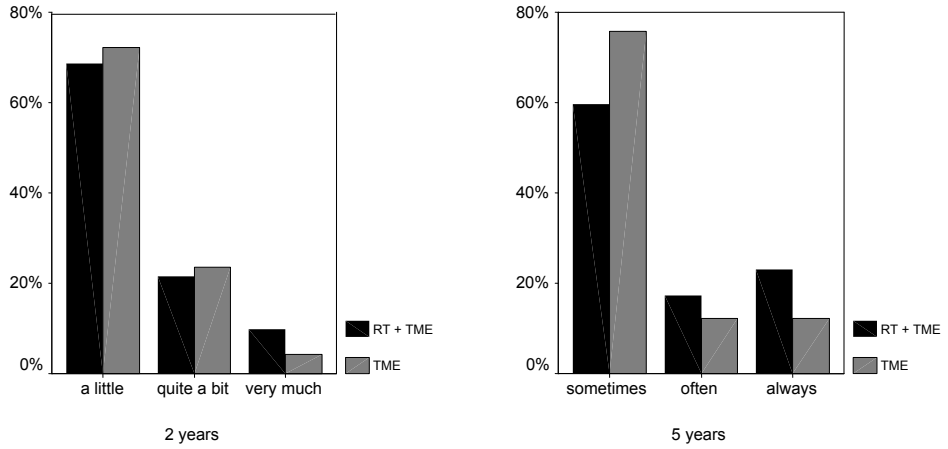

Figure 2. a) Severity of faecal incontinence at 2 years and b) frequency at 5 years after rectal cancer surgery with or without preoperative radiotherapy

Z=-2.12, p=0.034) and those who did not receive PRT (*Z*=-2.54, p=0.011). At 24 months 102 (52.0 percent) of the 196 patients treated with PRT and 72 (35.5 percent) of 203 without PRT reported incontinence (p=0.001, χ^2 test). Between 24 months and 5 years the percentage of patients with incontinence increased significantly in the PRT group (*Z*=-2.04, p=0.041), but not in the group without PRT (*Z*=-1.33, p=0.182). At 5 years 104 (61.5 percent) of 169 patients treated with PRT and 66 (38.8 percent) of 170 who did not receive PRT reported faecal incontinence (p<0.001).

Within the group of patients with incontinence, the severity at 2 years was comparable in the groups treated with and without PRT (χ^2=0.334, p=0.933) (Figure 2a). Most patients reported a little faecal incontinence (68.6 and 72.2 percent among patients who did and did not have PRT respectively). At 5 years after surgery, incontinent patients with PRT reported a higher frequency of faecal incontinence than patients without PRT (χ^2= 4.711, p=0.030) (Figure 2b).

Risk factors

The influence of potential risk factors on long-term faecal incontinence was first analysed for the total patient group. Because multivariable regression analysis showed an interaction effect between PRT and excessive peroperative blood loss (more than 1 400 ml) (p=0.001), it was decided to investigate the risk factors for the groups with and without PRT separately. The results of the univariate regression analysis are shown in Table 1.

Table 1. Analysis of risk factors for faecal incontinence 2 and 5 years after surgery with or without preoperative radiotherapy. (RR=relative risk; BMI=body mass index; TNM=tumour node metastasis. *Logistic regression analysis.)

	Radiotherapy						No radiotherapy					
	2 years			5 years			2 years			5 years		
	Incontinent	RR	p*	Incontinent	RR	p*	Incontinent	RR	p*	Incontinent	RR	p*
Age		1.01	0.618		1.00	0.947		1.02	0.292		1.00	0.907
Sex												
V	37 of 74	1.00		41 of 67	1.00		29 of 90	1.00		25 of 76	1.00	
M	62 of 122	1.14	0.656	63 of 102	1.02	0.941	43 of 113	1.29	0.389	41 of 94	1.58	0.155
Childbirth												
Yes	33 of 63	1.00		34 of 57	1.00		26 of 74	1.00		19 of 60	1.00	
No	3 of 8	0.55	0.433	5 of 8	1.13	0.878	3 of 12	0.62	0.494	5 of 12	1.54	0.530
BMI												
< 25	28 of 62	1.00		32 of 54	1.00		24 of 76	1.00		29 of 65	1.00	
≥ 25	49 of 90	1.45	0.261	48 of 79	1.07	0.862	35 of 92	1.33	0.383	31 of 80	0.79	0.476
TNM			0.500			0.708			0.612			0.313
0/I	52 of 96	1.00		53 of 83	1.00		31 of 83	1.00		25 of 70	1.00	
II	21 of 46	0.70	0.327	25 of 40	0.94	0.884	18 of 61	0.71	0.343	18 of 52	0.95	0.900
III	29 of 54	1.07	0.843	26 of 46	0.74	0.413	23 of 59	0.98	0.956	23 of 48	1.66	0.186
Tumour height			0.201			**0.009**			0.722			0.519
< 5 cm	22 of 33	1.00		23 of 26	1.00		14 of 41	1.00		11 of 31	1.00	
5-10 cm	57 of 115	0.49	0.086	63 of 105	0.20	**0.011**	47 of 125	1.16	0.691	43 of 103	1.30	0.534
≥ 10 cm	23 of 47	0.48	0.118	18 of 38	0.12	**0.002**	11 of 36	0.85	0.737	11 of 35	0.83	0.727
Anastomotic height			**0.052**			0.075			0.597			0.491
< 4.0 cm	30 of 54	1.00		35 of 48	1.00		27 of 66	1.00		20 of 51	1.00	
4.0–5.5 cm	26 of 41	1.39	0.441	26 of 39	0.74	0.527	13 of 32	0.99	0.979	14 of 28	1.55	0.356
5.5–7.5 cm	14 of 41	0.42	**0.040**	18 of 36	0.37	**0.033**	18 of 47	0.90	0.780	15 of 42	0.86	0.729
≥ 7.5 cm	25 of 44	1.05	0.900	18 of 36	0.37	**0.033**	12 of 42	0.58	0.195	11 of 35	0.71	0.461

	Radiotherapy						No radiotherapy					
	2 years			5 years			2 years			5 years		
	Incontinent	RR	p*	Incontinent	RR	p*	Incontinent	RR	p*	Incontinent	RR	p*
Surgery duration												
< 170 min	46 of 91	1.00		54 of 85	1.00		46 of 118	1.00		36 of 98	1.00	
≥ 170 min	56 of 105	1.12	0.697	50 of 84	0.84	0.593	26 of 85	0.69	0.218	30 of 72	1.23	0.515
Blood loss												
< 1400 ml	63 of 136	1.00		65 of 118	1.00		60 of 160	1.00		56 of 136	1.00	
≥ 1400 ml	39 of 59	2.26	**0.012**	39 of 50	2.89	**0.006**	12 of 40	0.71	0.378	10 of 30	0.71	0.428
Pouch												
No	75 of 142	1.00		76 of 120	1.00		58 of 148	1.00		49 of 124	1.00	
Yes	26 of 53	0.86	0.640	27 of 48	0.74	0.395	14 of 54	0.54	0.084	17 of 46	0.90	0.761
Temporary stoma												
No	36 of 72	1.00		37 of 65	1.00		26 of 79	1.00		26 of 75	1.00	
Yes	64 of 122	1.10	0.741	65 of 102	1.33	0.380	44 of 119	1.20	0.558	39 of 93	1.36	0.337
Anastomotic leak												
No	95 of 186	1.00		99 of 160	1.00		64 of 187	1.00		60 of 159	1.00	
Yes	7 of 10	2.24	0.254	5 of 9	0.77	0.705	8 of 16	1.92	0.212	6 of 11	1.98	0.276
Overall complications												
No	47 of 98	1.00		51 of 86	1.00		39 of 117	1.00		42 of 101	1.00	
Yes	55 of 98	1.39	0.253	53 of 83	1.21	0.543	33 of 86	1.25	0.459	24 of 69	0.75	0.372

Patients treated without preoperative radiotherapy

In patients who did not have PRT no variable significantly influenced incontinence risk at 2 or 5 years.

Patients treated preoperative radiotherapy

Excessive blood loss (upper quartile of more than 1 400 ml) was more common in patients who received PRT than in those who did not (p=0.014). In patients treated with PRT, excessive blood loss was a risk factor for incontinence at both 2 years (relative risk 2.26, p=0.012) and 5 years (relative risk 2.89, p=0.006). Level of anastomosis was not significantly associated with faecal incontinence at 2 years (p=0.052) or 5 years (p=0.075). However, patients with an anastomotic level closer than 4.0 cm from the anal verge reported significantly more incontinence than patients with an anastomotic level between 5.5 and 7.5 cm from the anal verge at 2 years (p=0.040) and at 5 years (p=0.033). Low tumour height also increased the risk of incontinence, but only at 5 years (p=0.009); 23 of 26 patients with a tumour within 5 cm from the anal verge had incontinence compared with 63 of 105 and 18 of 38 patients with a tumour 5-10 cm (p=0.011) or more than 10 cm (p=0.002) from the anal verge respectively.

In the multivariable regression analysis, excessive blood loss and anastomotic height were included as input variables to predict incontinence at 2 years in patients with PRT. Excessive blood loss remained a significant predictor (relative risk 2.32, p=0.015), but anastomotic height did not (p=0.081). In the prediction of incontinence at 5 years after TME, excessive blood loss, anastomotic height and tumour height would be included (p<0.100 in the univariate analysis). However, because anastomotic height was calculated from tumour height, only one of these variables could be included in the multivariable regression analysis[36]. Therefore, the analysis was performed twice: first with excessive blood loss and anastomotic height as input variables, and then with excessive blood loss and tumour height as input variables (Table 2). Excessive blood loss was a significant independent variable (p=0.011) and tumour height also remained a significant predictor (p=0.013), but not anastomotic height (p=0.070).

When treating low tumours, inclusion of the anal sphincter in the radiation field cannot always be avoided. Responses from patients with an anastomosis below the median of 5.5 cm were evaluated to determine the influence of sphincter irradiation on incontinence. In 21 (22 percent) of 94 patients the perineum, and consequently the sphincter, was included in the radiation field. Within this group 16 of 21 patients reported incontinence at 2 years after TME compared with 40 of 73 patients whose sphincter was not specifically included in the radiation field (relative risk 2.64,

Table 2. Results of multivariable analyses of risk factors for faecal incontinence. (RR=relative risk; *Logistic regression analysis)

	RR	p*
Analysis 1		
Blood loss		
< 1400 ml	1.00	
≥ 1400 ml	3.24	0.005
Anastomotic height		0.070
< 4.0 cm	1.00	
4.0 – 5.5 cm	0.71	0.467
5.5 – 7.5 cm	0.38	0.045
≥ 7.5 cm	0.33	0.020
Analysis 2		
Blood loss		
< 1400 ml	1.00	
≥ 1400 ml	2.75	0.011
Tumour height		0.013
< 5.0 cm	1.00	
5.0 – 10.0 cm	0.21	0.016
≥ 10.0 cm	0.13	0.003

p=0.085). Respective figures at 5 years were 14 of 15 *versus* 47 of 72 (relative risk 7.45, p=0.059).

DISCUSSION

This study identified tumour height and excessive blood loss as independent predictors of faecal incontinence after LAR with TME in patients who had PRT, whereas no risk factors were found in patients who did not receive PRT.

Faecal incontinence may be defined as involuntary rectal evacuation[37]. This may range from inadvertent gas release to minor soiling or complete escape of rectal contents. The present study analysed the influence of potential risk factors on the risk of incontinence, irrespective of its severity. However, slight impairment of continence may be more acceptable to patients than a permanent stoma. The clinical relevance of the present cut-off point (absence *versus* presence of incontinence) is therefore limited. It should also be noted that the measurement of tumour height by endoscopy or digital rectal examination, and thus the calculation of anastomotic height, are not very accurate. However, the present examination of potential risk factors in a relatively large study population followed for up to 5 years after surgery provides useful information.

Faecal incontinence after LAR has already been reported in the Dutch TME trial, especially among patients treated with PRT[16,17]. Some 38.8 percent of patients who had TME alone and 61.5 percent of those treated with surgery and PRT were incontinent at 5 years. This was in agreement with other studies, generally reporting incontinence in about half of patients[14-19]. However, only 9 percent of patients treated with long-term PRT (45 Gy over 5 weeks) had incontinence[38]. This discrepancy may be attributed to physician reporting of incontinence in the latter study. Meanwhile faecal incontinence may have been overreported in the present study if responders had more problems than non-responders. This should not affect the influence of possible risk factors as long as proportional risks are relatively consistent, as described.

No consensus was achieved in previous studies on the influence of most potential risk factors[7,12,13,19,21-35]. However, most agree that the risk of incontinence is not influenced by the construction of a temporary stoma[19,21,22] or increased age[7,19,21,22,24,26]. It is surprising that the influence of age cannot be demonstrated in patients with rectal cancer, because incontinence is strongly associated with senescence in the general population[37]. Furthermore, previous investigators[32-35] found that reconstruction with a colonic J-pouch (which compensates for the loss of rectal reservoir) was associated with a lower incidence of incontinence than reconstruction with a straight anastomosis. This was not apparent in the present study, possibly because of the relatively small number of patients with a colonic J-pouch (28.1 percent).

In previous publications a low anastomotic height increased the risk of incontinence in patients treated with PRT[19,21,24,27]. These studies evaluated anastomotic level (and not tumour height) as a risk factor for incontinence. Both were evaluated here because the two variables have a different influence on the underlying mechanisms of incontinence: tumour height determines the lower border of the radiation field, whereas anastomotic height determines the length of residual rectum. At 5 years tumour height was more predictive than anastomotic height, suggesting that the site of irradiation is more important than rectal length. However, incontinence is multifactorial[37] and it is challenging to separate these metrics based on distance alone. The rectum acts as a reservoir and the smaller neorectum has a lower capacity and smaller tolerated volumes[39]. Fibrosis due to PRT diminishes compliance of the residual rectum. The anal sphincters keep the anal canal closed in a resting state[37]. Radiotherapy may disrupt the myenteric plexus of the internal anal sphincter[39], compromising the rectoinhibitory reflex and resting anal pressures[18,37]. PRT is known to damage the internal sphincter after several years[40]. However, early problems may arise as a result of damage to the innervation of the pelvic floor muscles. The levator ani muscles, essential to continence, receive their motor innervation from a nerve that runs on the surface[41]. During dissection deep within the pelvis, this nerve might

be disrupted. Furthermore, transection of the inferior mesenteric artery at its origin (high tie) might disrupt autonomic nerve fibres[42].

The results of this study may contribute to a better understanding of incontinence following rectal cancer surgery, and may facilitate the decision to perform a LAR or create a permanent stoma. Treating all rectal cancers with PRT would result in some degree of overtreatment[18], so patient selection for PRT is necessary.

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CHAPTER 7

Faecal and urinary incontinence after multimodality treatment for rectal cancer

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DESCRIPTION OF THE CASE

A 67-year-old woman reported to experience frequent bowel movements during a control check-up after rectal cancer treatment. Five years before, she was treated for stage I-disease (T2N0M0), located 5 cm from the anal verge. The treatment consisted of short-course pelvic radiotherapy (5x5 Gy) followed by low anterior resection (LAR) with straight colorectal anastomosis. No postoperative complications had occurred, and a temporary colostomy had been constructed, which was reversed after 4 months. The woman had no previous medical history.

On questioning, she reported to have suffered from rectal urgency symptoms ever since the colostomy was reversed. These symptoms were quite acceptable, especially because she assumed them to be temporary. However, it became worse over time and urgency developed into involuntary stool leakage, requiring wearing a protective pad constantly. Furthermore, she indicated to experience urine loss, especially during coughing, laughing or lifting. She stated that voiding and defaecation were fully normal before her treatment for rectal cancer.

ARE INCONTINENCE PROBLEMS AFTER RECTAL CANCER TREATMENT COMMON?

Faecal incontinence after rectal cancer treatment occurs frequently, affecting almost half of patients with normal preoperative functioning.[1] This may range from inadvertent gas release to minor soiling or complete escape of rectal contents. These symptoms are often described as “anterior resection syndrome”.[2] Long-term urinary incontinence develops in almost one third of patients and combined urinary and faecal incontinence occurs in 14 percent of patients with normal preoperative function.[3,4] Figure 1 shows the incidence of faecal and urinary incontinence during five years after rectal cancer treatment. Incontinence problems lead to avoidance of certain activities, such as long-distance travel by car or plane, during which bathroom facilities may not be immediately available. Additionally, sexual dysfunction is a frequent and distressing complication of rectal cancer treatment. Male patients may experience ejaculatory problems and impotence. Female patients may suffer from dyspareunia and vaginal dryness.[5] Poor functional outcome of rectal cancer treatment is a major problem since bowel and urinary dysfunction can have a negative impact on a patient’s physical, psychological, social and emotional functioning, as well as the patient’s overall well-being.[6]

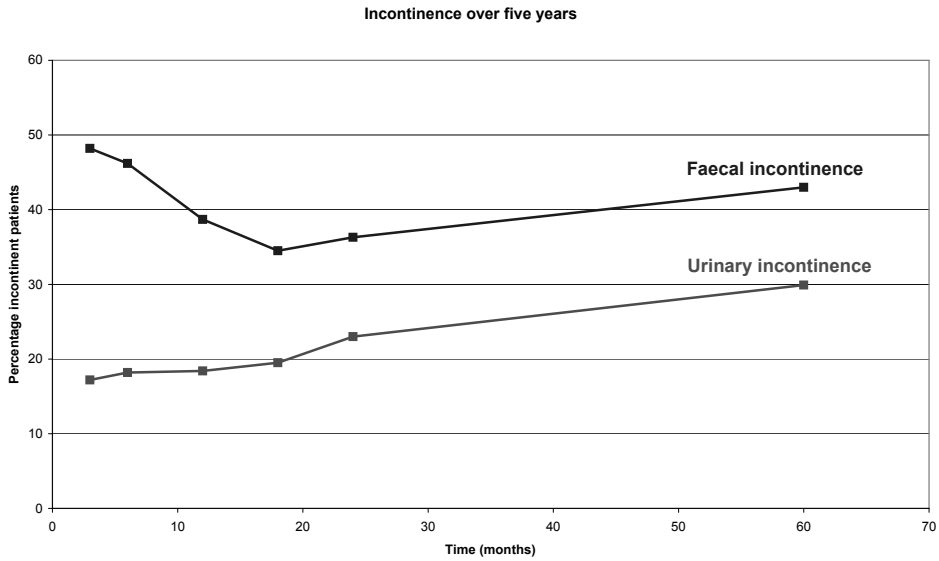

Figure 1. Percentage of faecal and urinary incontinence after rectal cancer treatment reported by patients without preoperative faecal or urinary incontinence who participated in the Dutch TME trial.

WHAT COULD HAVE CAUSED HER INCONTINENCE PROBLEMS?

Faecal incontinence is usually the result of failure of more than one component of the continence mechanism. The rectum, the anal sphincters and the pelvic floor muscles are essential in the maintenance of faecal continence.[7] First of all, the rectum acts as a reservoir to store stool. A smaller neorectum after LAR has a lower capacity causing a decrease in maximum tolerated volumes. Furthermore, the anal canal contains a rich network of nerve endings sensitive to pain, temperature and touch, which is used to differentiate solid or liquid stool from flatus, and allows for selective passage of flatus. Patients with a small neorectum after resection of a low lying tumour, as was the case in the present patient, are therefore at increased risk for faecal incontinence. Moreover, in this patient's case, rectal cancer resection was preceded by pelvic radiotherapy, which is known to increase the risk of faecal incontinence.[8] Radiotherapy diminishes compliance of the rectum due to fibrosis, resulting in a reduced reservoir function. Radiotherapy induced fibrosis of the myenteric plexus of the internal anal sphincter can prevent adequate closure of the anal canal in a resting state. In addition, faecal incontinence after rectal cancer treatment has been reported to be caused by impaired pelvic floor movement, i.e. a disturbed change in anorectal angle due to a dysfunctional levator ani muscle.[9] According to renewed anatomical insight, the levator ani muscle is not innervated by the pudendal nerve, but receives its innervation from a separate nerve, which runs on the surface of the pelvic floor

(a three-dimensional reconstruction of the levator ani nerve can be obtained online in a recent publication in Journal of Clinical Oncology[4]). During surgical dissection deep within the pelvis, especially in case of a low lying tumour, this nerve might be disrupted.[4]

Urinary incontinence after rectal cancer treatment may consist of urge, overflow and/or stress incontinence. Urge incontinence may result from a reduced bladder capacity due to surgical disruption of the sympathetic nerve supply (the hypogastric nerves and the pelvic plexus).[10] Overflow incontinence may be caused by surgical damage to the sacral splanchnic nerves, resulting in bladder emptying problems (Figure 2). However, the present patient suffers from involuntary urine loss during increased abdominal pressure, which is a sign of urinary stress incontinence. Stress urinary incontinence may result from impaired support to the urethra and bladder

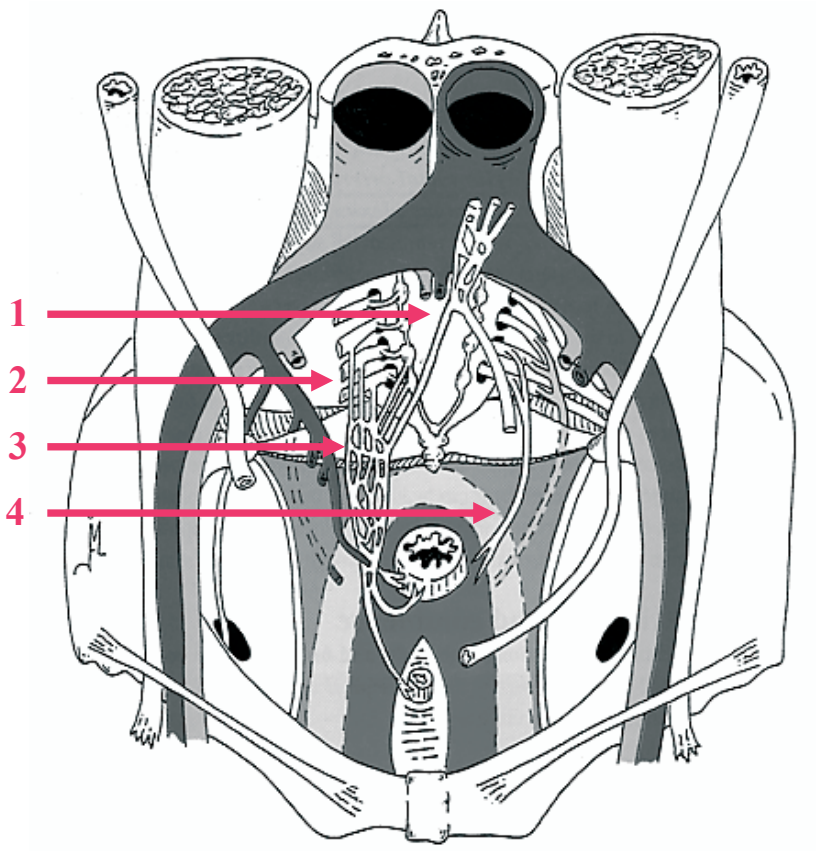

Figure 2. Anatomical graph of the pelvic floor and the autonomic nerves (1: hypogastric nerves; 2: pelvic splanchnic nerves; 3: pelvic plexus; 4: levator ani nerve. Adapted from: Lange JF (2002) Surgical anatomy of the abdomen. Maarssen (Netherlands): Elsevier. p. 178.)

neck. This support is regulated by surrounding structures, the most important being the pubourethral-vesical ligaments, the suburethral vaginal wall, the levator plate, the pubococcygeus muscles and the connective tissue. These components can compensate for each other in case of inappropriate function. In postmenopausal female patients many of these structures are impaired because the function of many structures involved in preserving continence is influenced by oestrogen receptors. Additional changed anatomical relations between bladder, urethra and pelvic floor, and possibly damage to the innervation of the levator ani muscles during LAR would further impair the continence mechanism and lead to urinary incontinence.[11]

WHAT COULD HAVE CAUSED THE WORSENING OF SYMPTOMS OVER TIME?

Improvement in anorectal function usually occurs over 6 to 12 months, which correlates with expansion in the reservoir capacity of the neorectum. Postoperative assessment of function after one year has shown that many patients achieve continence to solid stool but that control of minor staining, flatus, and stool frequency is more variable.[12] However, worsening of faecal incontinence over time is typically seen in patients treated with pelvic radiotherapy (Figure 3). This may be explained by the fact that vascular damage is a long-term effect of radiotherapy, compromising the

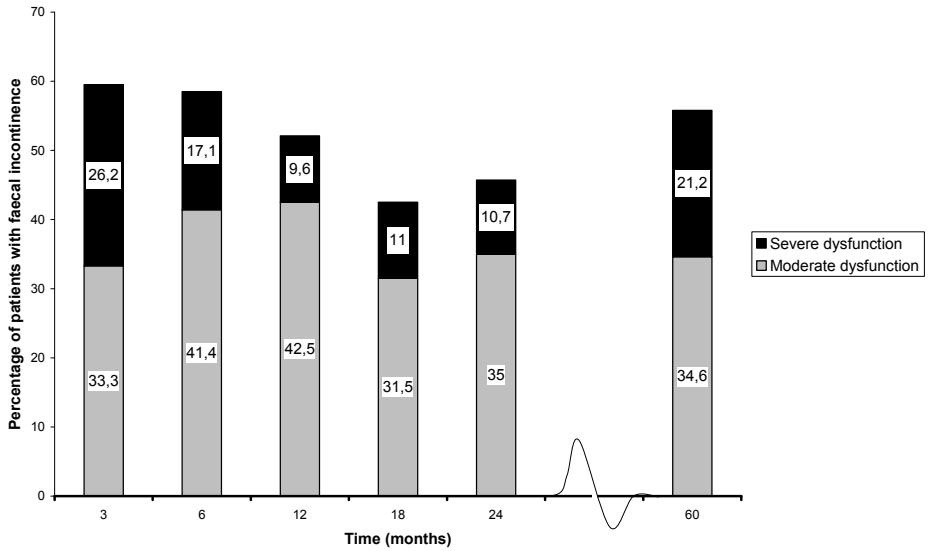

Figure 3. Incidence of moderate and severe faecal incontinence reported by patients who participated in the Dutch TME trial and were treated with preoperative radiotherapy. Only patients without preoperative dysfunction were included in this diagram.

endovascular cushions filling the 7-8 mm gap within the internal sphincter ring, which contribute to continence at rest.[13]

Worsening of urinary incontinence over time could be due to ageing and laxity of the pelvic floor musculature with concomitant risk of increased stress incontinence.

HOW COULD INCONTINENCE PROBLEMS HAVE BEEN PREVENTED?

First, functional problems after rectal cancer surgery might have been prevented by special attention to nerve preservation. Despite the fact that the current rectal resection technique, described by total mesorectal excision, permits preservation of the innervation of the pelvic organs, nerve sparing surgery can be difficult. Differences among individuals in the running patterns of the nerves and variation in the volumes of nerve fibres in each region of the pelvis hamper appropriate identification of structures. Especially during excessive peroperative blood loss, nerves are at risk due to diathermic coagulation and numerous sutures to secure hemostasis. To avoid excessive bleeding and accidental nerve disruption during surgery, it is important to adhere to the surgical plane and reduce the use of blunt dissection. Also, the use of a nerve stimulating device may facilitate preservation of the pelvic autonomic nerves during pelvic dissection.[14]

It is difficult to prevent radiotherapy induced bowel dysfunction, as radiotherapy is considered an important part of rectal cancer treatment, decreasing the risk of local recurrence.[15,16] However, treating all rectal cancer patients with radiotherapy can result in substantial overtreatment. Therefore, it is of great importance to identify patients with low risk of local recurrence in which radiotherapy is redundant.[16] Currently, new imaging modalities are developed and molecular biomarkers are being identified to predict prognosis, making patient tailored treatment possible soon.

An alternative to avoid faecal incontinence after rectal cancer treatment is to construct a permanent stoma by abdominoperineal resection instead of sphincter preservation by LAR. Traditionally, the construction of a stoma has been regarded as an unfavourable outcome, as Quality of Life (QoL) of stoma patients is believed to be inferior compared to non-stoma patients. However, recent studies have shown that QoL after abdominoperineal resection may not be as bad as once believed and may be equal after LAR.[17] Moreover, LAR patients with a low anastomosis have been reported to have a worse QoL compared to stoma patients, due to poor functional outcome.[18] Obviously, cultural, social, religious and sociodemographic factors influence how patients assess their QoL with a permanent stoma. In selected cases, abdominoperineal resection might be a more satisfactory option than LAR.

WHAT TREATMENT MODALITIES ARE AVAILABLE?

Standards of management of patients with incontinence problems after rectal cancer treatment are still lacking. Many treatments are available, however there is not enough evidence to support the effectiveness of any of them. First of all, conservative measures aimed at symptomatic control (e.g. dietary regiments, absorbent pads and pharmacotherapy including hormonal manipulation, constipating agents and enemas) may be tried. Colonic irrigation in the morning in order to clean the colon from faeces has been shown to reduce symptoms.[19] The present patient was offered colonic irrigation. During a control check-up one year later, she reported a beneficial effect of colonic irrigation, improving the quality of her life.

Alternatively, there are a number of interventions aimed at correcting the underlying cause, including both non-surgical and surgical techniques. Non-surgical procedures include biofeedback and pelvic floor muscle training. Biofeedback therapy, showing patients how to use the pelvic floor muscles properly, is often recommended and may consist of rectal sensitivity, strength and coordination training.[20] Pelvic floor muscle training improves pelvic floor support. It is regarded as the first line treatment for urinary incontinence and used to improve faecal incontinence. Pelvic floor muscle training may be of limited use in patients in which the innervation of the pelvic floor has been damaged during surgery.

If conservative management fails, surgical intervention may be considered. First, appropriate assessment should be carried out for characterisation of the underlying cause. Anorectal physiology can be evaluated with manometry, and mechanical damage to the sphincter muscle can be detected with endoanal ultrasound. If the sphincter is intact, sacral nerve stimulation in which electrodes are inserted through the sacral foramina under general anaesthetic for stimulation of the sacral nerves may be effective for both urinary and faecal incontinence. Several studies have shown promising results, however experience with sacral nerve stimulation for faecal incontinence following rectal resection is still limited.[21] In case of a sphincter muscle defect, an artificial bowel sphincter can be constructed. This would not be an option in the present case as severe complications after artificial bowel sphincter construction in a radiation-injured anorectum have been reported.[22] The construction of a colostomy is considered an option when all else has failed, but is also associated with a significant rate of complications in irradiated patients.[23] Uncertainty remains whether any surgical intervention does more good than harm.

DISCUSSION

Incontinence problems after rectal cancer treatment are common and can have a major impact on QoL. Nevertheless, it often remains undiscussed in clinical practice. Patients should be informed preoperatively about the possible development anorectal and urogenital dysfunction and the increased risk in case of a low tumour and radiotherapy. The different surgical options, LAR and abdominoperineal resection, and their potential outcomes should be discussed with the patient, as the individual preference of the patient is of great importance in this.[24] Educating patients on the modern stoma care may reduce ill-informed hesitations towards a permanent stoma by patients. At present, there is an ongoing project concerning the perceived costs and benefits of preoperative radiotherapy in rectal cancer treatment and investigating to what extent patients and oncologists believe that patients should also participate in decision making regarding preoperative radiotherapy.

Postoperatively, evaluation of the patients' functional outcome should be standard procedure at every follow-up appointment. Patients are not likely to bring up incontinence problems themselves out of shame or because they don't relate it to rectal cancer treatment, especially if incontinence problems occur several years after treatment. Available therapies, primarily conservative regiments, should be proposed if needed.

Although the exact etiology of incontinence problems after multimodality treatment of rectal cancer is unknown, specific technical aspects of the surgical procedure play a major role. Special attention to pelvic autonomic nerves, sharp dissection, adhering to the surgical plane and reducing the use of blunt dissection may lower the risk of urinary and faecal incontinence.[4] Furthermore, to prevent overtreatment with radiotherapy, a tailor-made approach for every rectal cancer patient that is based on preoperative prediction of the risk for local recurrence seems to be favourable. Currently, new imaging modalities are developed and molecular biomarkers are identified to predict prognosis, making patient tailored treatment possible soon.[25,26] This will reduce the number of patients with poor functional outcome after rectal cancer treatment.

KEY LEARNING POINTS

- Incontinence problems after rectal cancer treatment are common and can have a major impact on QoL.
- Patients should be informed about the surgical options, LAR and abdominoperineal resection, and about their potential outcomes.

- Surgical nerve damage may play a major role in the development of faecal and urinary incontinence, with an additional effect of radiotherapy.
- Faecal incontinence can worsen over time in case of radiotherapy.
- Several non-surgical and surgical therapies of incontinence problems are available; conservative therapies should be the first line choice.

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CHAPTER 8

Causes of faecal and urinary incontinence after total mesorectal excision for rectal cancer based on cadaveric surgery

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ABSTRACT

Background
Total mesorectal excision (TME) for rectal cancer may result in anorectal and urogenital dysfunction. We aimed to study possible nerve disruption during TME and its consequences for functional outcome. Because the levator ani muscle plays an important role in both urinary and faecal continence, an explanation could be peroperative damage of the nerve supply to the levator ani muscle.

Methods
Total mesorectal excision was performed on cadaver pelves. Subsequently, the anatomy of the pelvic floor innervations and its relation to the pelvic autonomic innervation and the mesorectum were studied. Additionally, data from the Dutch TME trial were analysed to relate anorectal and urinary dysfunction to possible nerve damage during TME procedure.

Results
Cadaver TME surgery demonstrated that, especially in low tumours, the pelvic floor innervation can be damaged. Furthermore, the origin of the levator ani nerve was located in close proximity of the origin of the pelvic splanchnic nerves. Analysis of the TME trial data showed that newly developed urinary and faecal incontinence was present in 33.7 percent and 38.8 percent of patients, respectively. Both types of incontinence were significantly associated with each other ($p=0.027$). Low anastomosis was significantly associated with urinary incontinence ($p=0.049$). One third of the patients with newly developed urinary and faecal incontinence also reported difficulty in bladder emptying, for which excessive peroperative blood loss was a significant risk factor.

Conclusion
Peroperative damage to the pelvic floor innervation could contribute to faecal and urinary incontinence after TME, especially in case of a low anastomosis or damage to the pelvic splanchnic nerves.

INTRODUCTION

The past two decades have witnessed substantial improvement in survival from rectal cancer, resulting from earlier diagnosis, improved efficiency and delivery of radiotherapy, and advances in surgical techniques, such as total mesorectal excision (TME).

The TME procedure removes the rectum with its primary lymphovascular field of drainage as an intact package. Under direct vision along pre-existing embryologically determined planes, sharp dissection divides the mesorectal fascia (ie, the visceral fascia surrounding the mesorectum) from the pelvic parietal fascia overlying the pelvic floor, thereby preserving the autonomic nerves required for maintenance of urogenital function.[1-3]

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.[3,4] Surgical damage to the pelvic autonomic nerves is believed to be an important cause of urinary dysfunction.[5-7] The pelvic parasympathetic supply (pelvic splanchnic nerves or nervi erigentes) arises from sacral nerves S2 to S4, whereas the sympathetic supply is by the hypogastric nerves. Together, these parasympathetic and sympathetic nerves form the autonomic nerve plexus of the small pelvis (pelvic plexus or inferior hypogastric plexus). The pelvic plexus is a coarse and flat meshwork that is situated laterally to the pelvic organs and supplies the rectum, uterus, vagina, vestibular bulbs, clitoris, bladder, urethra, penis, and prostate.[8,9] Because of their location, disruption of the pelvic plexus and the pelvic splanchnic nerves may occur frequently during dissection of the lateral planes of the mesorectum deep in the pelvis.[10] Parasympathetic injury (pelvic splanchnic nerves or pelvic plexus) produces a hypo- or acontractile bladder with decreased sensation, causing difficulty in bladder emptying.[5,8] The prevalence of faecal incontinence after low anterior resection with preoperative radiotherapy (PRT) is reported to be as high as 60 percent, and even without PRT, to be as high as 40 percent.[11-13] Damage to the pudendal nerve has been suggested as a cause of faecal incontinence after rectal cancer treatment.[14] Common knowledge among clinicians is that the pudendal nerve innervates the levator ani muscle, which is a striated muscular diaphragm that closes the pelvic cavity. The levator ani muscle is the main pelvic floor muscle and is a crucial component of the urinary and faecal continence system.[15-17] Recent studies have re-emphasised the existence of a separate nerve to the levator ani (the levator ani nerve [LAN]), which arises from sacral nerves S3 and/or S4, separately from the pudendal nerve. The nerve is mentioned in various anatomy textbooks[18,19] but is still not clearly illustrated in others.[20,21] The LAN approaches the levator ani muscle from within the pelvis on the superior surface of the pelvic floor, which makes ac-

cidental disruption of the nerve during pelvic surgical interventions conceivable.[22-24] This is in contrast with the pudendal nerve, which runs inferior to the pelvic floor muscles and has only a minor contribution to the levator ani muscle innervation.[25] We hypothesised that surgical disruption of the LAN during TME could play a role in the etiology of faecal and urinary incontinence after TME. We aimed to study possible nerve disruption during the TME procedure as a cause of postoperative anorectal and urinary dysfunction. To do this, we performed TME on cadaver pelves and studied the anatomy of the levator ani muscle innervation and its relation to the pelvic autonomic innervation and the mesorectum. Subsequently, data from the Dutch TME trial were analysed to relate anorectal and urinary dysfunction to possible peroperative nerve damage.[26]

METHODS

Anatomy and cadaver surgery

Ten pelves of male cadavers (age range: 67 to 91 years) without signs of pelvic surgery were dissected as described elsewhere[24] to investigate and quantify the topographical anatomy of the LANs and the pelvic splanchnic nerves and the relation to the mesorectal fascia. Total mesorectal excision was performed on one midsagittally transected right male hemipelvis, two complete male pelves, and one complete female pelvis by an experienced colorectal surgeon (B.A.B.). The procedure was performed as it would be in a patient with a low rectal tumour with an indication for a low anterior resection. The rectum was removed according to the TME principles.[27] The pelvic splanchnic nerves and the LAN were subsequently dissected with special reference to relations between the nerves and the rectum, the parietal pelvic fascia, and the mesorectal fascia.

Dutch TME trial database

Data were obtained from the database of the Dutch TME trial.[26] Between January 1996 and December 1999, 1 861 patients with histologically proven adenocarcinoma of the rectum and without evidence of distant metastases were included in the trial and randomly assigned to undergo TME alone or preceded by PRT. All patients underwent surgery according to the TME principles, as advocated by Heald.[27] Only patients who underwent low anterior resection and participated in the quality-of-life study or in the study on long-term functional outcome were selected for this analysis.[13,28]

Outcome measures

Faecal and urinary incontinence and difficulty in bladder emptying were evaluated preoperatively and at 5 years after TME.[13,28] To determine whether preoperative dysfunction should be taken into account, the influence of preoperative dysfunction on faecal and urinary incontinence and difficulty in bladder emptying was evaluated. Newly developed combined faecal and urinary incontinence was assumed to result from pelvic floor dysfunction, as this was the most probable causative factor of both dysfunctions. Therefore, to evaluate to what extent incontinence could be explained by dysfunction of the pelvic floor, faecal and urinary incontinence were related to each other. Subsequently, to estimate the risk of simultaneous damage to the LAN in case of damage to the pelvic splanchnic nerves, faecal and urinary incontinence were related to difficulty in bladder emptying.

Statistical Analysis

Data were analysed with SPSS version 14.0 for Windows (SPSS, Chicago, IL). The influence of the predictor variables on the risk of the different types of dysfunction after TME was calculated using univariate logistic regression analysis. To examine any independent influence, all variables associated with the specific type of dysfunction ($p=0.100$ in the univariate regression analysis) were entered into a multivariable logistic regression analysis. $P=0.05$ was considered statistically significant.

RESULTS

Anatomy and cadaver surgery

On macroscopical dissection, we found the LAN to originate from sacral nerves S3 and/or S4. The nerve was macroscopically detectable in all pelves. During its course on the surface of the coccygeus and levator ani muscle, the LAN runs 4 cm (95% CI, 4 to 5.5 cm) lateral to the midsagittal plane at the level of the ischial spine, 4.5 cm (95% CI, 4 to 5.5 cm) lateral to the tip of the coccyx, and 9 mm (95% CI, 0 to 14 mm) caudal to the ischial spine. In all cases, the nerve was situated underneath the pelvic parietal fascia, which covers the levator ani muscle. When the mesorectum was dissected in the surgical plane between the mesorectal fascia and the pelvic parietal fascia and subsequently lifted, the origin of the pelvic splanchnic nerves and the LAN presented themselves as joint sacral branches. The pelvic splanchnic nerves, whose origin from the sacral nerve plexus lies underneath the pelvic parietal fascia,

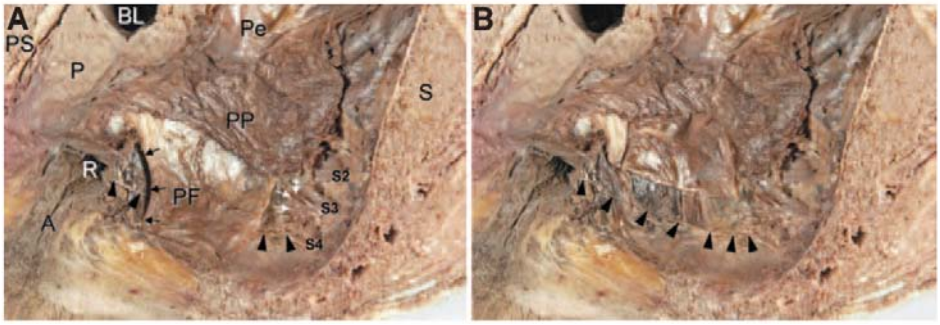

Figure 1. Total mesorectal excision (TME) on an adult male pelvis. The pelvis was midsagittally transected after TME. Note that the parietal fascia was removed from the surface of the levator ani muscle during the TME procedure (black arrows show the cut border). The part of the parietal fascia that covered the sacral origin of the levator ani nerve and pelvic splanchnic nerves was removed during dissection to visualise the nerves. The most distal part of the levator ani nerve was disrupted during TME in this pelvis (not visible). (A) Medial view of the right hemi pelvis with part of the parietal fascia still covering the levator ani nerve. (B) Medial view of the right hemi pelvis. The parietal fascia, covering the nerves, is now flipped sideways to fully reveal the levator ani nerve. A, anus; BL, bladder; P, prostate; Pe, peritoneum; PF, parietal fascia; PP, pelvic plexus; PS, pubic symphysis; R, rectum; S, sacrum; S2, S3, S4, sacral nerves S1 to S3.

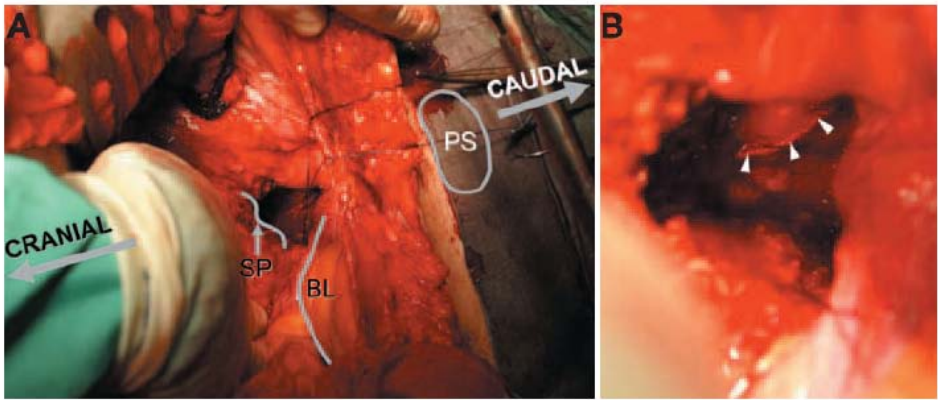

Figure 2. The levator ani nerve in vivo during total mesorectal excision. (A) Overview. (B) Detail of the levator ani nerve (white arrowheads). BL, urinary bladder; PS, pubic symphysis; SP, sacral promontory.

run in a separate fascial sheath to reach the pelvic plexus that is situated lateral to the rectum, tangentially to the lateral surface of the mesorectal fascia. The LAN does not run in this fascial sheath, but continues solitary toward the pelvic floor muscles underneath the lateral pelvic parietal fascia. Dissection of the LAN in the pelves after TME showed a similar anatomic composition. The plane of surgical dissection during TME is between the visceral fascia of the mesorectum and the parietal fascia. At the most distal part of the rectum, approximately 2 cm cranial from the entrance

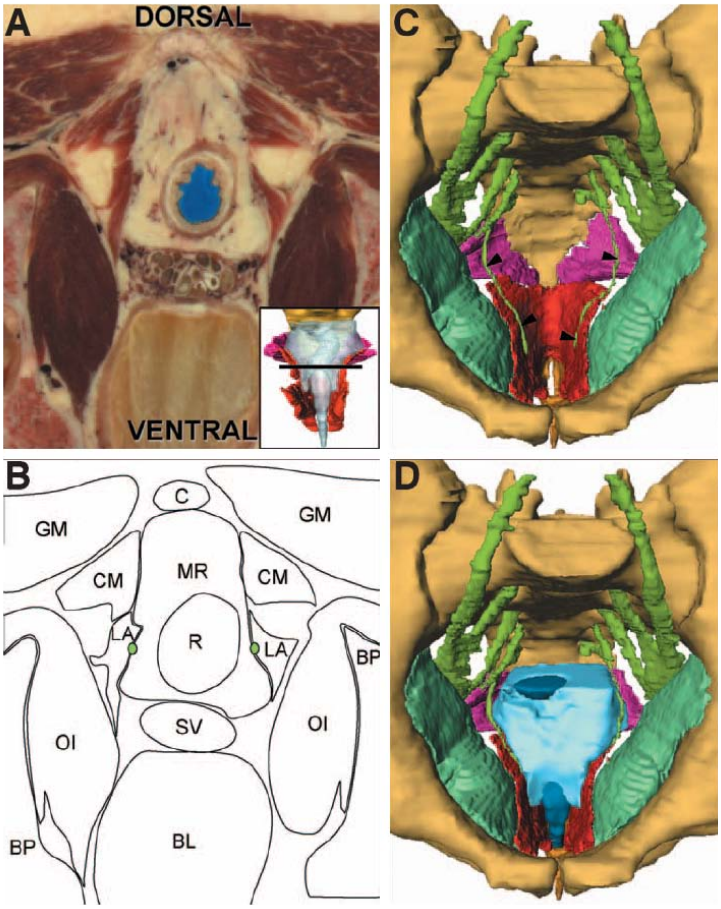

Figure 3. Anatomic relation of the mesorectum and the levator ani nerve in the adult male. (A) Transverse section through the male pelvis. The level of the section is illustrated in the inset. (B) Schematic overview of the structures shown in part A. The green circles represent the approximate position of the levator ani nerves. (C, D) Three-dimensional reconstruction of the same adult pelvis as in part A with (D) and without (C) the mesorectum. The levator ani muscle (red), coccygeus muscle (pink), obturator internus muscle (mint green), rectum (blue), mesorectum (light blue), sacral nerve plexus (light green) are reconstructed from serial sections. Because the levator ani nerve (light green, arrowheads in C) was not identifiable in the serial sections, it was illustrated with information from our dissection studies. Note the close relation of the mesorectum to the levator ani nerves. BL, urinary bladder; BP, bony pelvis; C, coccyx; CM, coccygeus muscle; GM, gluteus maximus muscle; LA, levator ani muscle; MR, mesorectum; OI, obturator internus muscle; R, rectum; SV, seminal vesicle.

of the rectum through the levator ani muscle, the mesorectal fascia and the parietal fascia become inseparable. Therefore, the parietal fascia must be removed from the surface of the pelvic floor muscles to preserve the mesorectal package. At this point, the LAN is in close proximity of the surgical dissection plane. In one male pelvis, the LAN was disrupted unilaterally at this level during the TME procedure. In the

pelvis where the LAN was disrupted, Figure 1 shows the close relation between the surgical dissection plane and the nerve in the lowest part of the dissection. Figure 2 shows the LAN in vivo during TME. Figure 3 illustrates the close relation between the LAN and the mesorectum.

Dutch TME trial database

Of the 1 530 Dutch patients, patients were excluded from analysis for the following reasons: ineligible at randomisation (n=50), no operation (n=37), in-hospital death (n=52), no informed consent for the quality-of-life study (n=89), no quality-of-life forms returned (n=30), no low anterior resection (n=456), and missing pretreatment form (n=165). Consequently, 651 patients remained assessable for analysis. However, not all questions were answered by every patient in the returned questionnaires, resulting in 649, 647, and 649 assessable patients concerning faecal incontinence, urinary incontinence, and difficulty in bladder emptying, respectively.

Pre- and postoperative dysfunctions

Faecal incontinence was reported by 269 (41.4 percent) of 649 patients preoperatively and by 134 (48.7 percent) of 275 patients 5 years after rectal cancer treatment (p=0.001; relative risk=3.16). Of patients with normal preoperative function, 38.8 percent (69 of 178 patients) had newly developed faecal incontinence after rectal cancer treatment.

Urinary incontinence was reported by 110 (17.0 percent) of 647 patients preoperatively and by 123 (39.5 percent) of 311 patients 5 years after rectal cancer treatment (p<0.001; relative risk= 4.19). Of patients with normal preoperative function, 33.7 percent (88 of 261 patients) had newly developed urinary incontinence after rectal cancer treatment. Of patients with newly developed faecal incontinence, 36.5 percent (23 of 63 patients) also reported newly developed urinary incontinence (p=0.027; relative risk=2.21). Fourteen percent (23 of 160) of patients with normal preoperative function reported both faecal and urinary incontinence after rectal cancer treatment.

Difficulty in bladder emptying was reported by 144 (22.2 percent) of 649 patients preoperatively and by 89 (29.3 percent) of 304 patients 5 years after rectal cancer treatment (p=0.001; relative risk=3.02). Of patients with normal preoperative function, 24.3 percent (59 of 243 patients) had newly developed difficulty in bladder emptying after rectal cancer treatment. Of patients with newly developed faecal and urinary incontinence, 38.8 percent (7 of 18 patients) also reported difficulty in bladder emptying (p=0.044; relative risk=2.34).

Risk factors

Table 1 lists the results of the univariate logistic regression analysis of risk factors for faecal and urinary incontinence and difficulty in bladder emptying. In the multivariable analysis of faecal incontinence (Table 2), PRT, low anastomotic height, tumour

Table 1. Logistic regression analyses of risk factors for faecal and urinary incontinence and difficulty in bladder emptying after rectal cancer treatment (RR=relative risk)

	Faecal incontinence			Urinary incontinence			Difficulty in bladder emptying		
	Proportion with dysfunction	RR	p-value	Proportion with dysfunction	RR	p-value	Proportion with dysfunction	RR	p-value
Gender									
male	80 of 160	1.00		54 of 181	1.00		54 of 175	1.00	
female	54 of 115	0.89	0.618	69 of 130	2.66	<0.001	35 of 129	0.83	0.481
Age									
<65	80 of 168	1.00		60 of 188	1.00		53 of 188	1.00	
≥65	65 of 107	1.12	0.645	63 of 123	2.24	0.001	36 of 116	1.15	0.597
Preoperative dysfunction									
no	69 of 178	1.00		88 of 261	1.00		59 of 243	1.00	
yes	64 of 96	3.16	<0.001	32 of 47	4.19	<0.001	29 of 59	3.02	<0.001
Radiotherapy									
no	56 of 143	1.00		60 of 159	1.00		49 of 155	1.00	
yes	78 of 132	2.24	0.001	63 of 152	1.17	0.856	40 of 149	0.79	0.362
Posterior tumour location									
no	54 of 103	1.00		48 of 120	1.00		26 of 114	1.00	
yes	11 of 31	0.50	0.101	13 of 137	0.81	0.596	10 of 38	1.21	0.660
Tumour size (cm)									
<4.0	84 of 159	1.00		72 of 183	1.00		53 of 178	1.00	
≥4.0	48 of 114	0.65	0.081	50 of 125	1.03	0.908	35 of 123	0.94	0.805
Blood loss (ml)									
<1500	109 of 225	1.00		102 of 252	1.00		67 of 246	1.00	
≥1500	25 of 46	1.27	0.466	20 of 55	0.84	0.573	22 of 54	1.84	0.051
Anastomotic height (cm)									
<6.0	75 of 142	1.00		75 of 164	1.00		46 of 158	1.00	
≥6.0	42 of 102	0.63	0.073	34 of 108	0.55	0.020	36 of 107	1.24	0.434
Anastomotic leakage									
no	126 of 258	1.00		114 of 280	1.00		82 of 274	1.00	
yes	8 of 17	0.931	0.887	9 of 31	0.596	0.211	7 of 30	0.713	0.453

Table 2. Multivariable regression analyses of risk factors for faecal and urinary incontinence and difficulty in bladder emptying after rectal cancer treatment (RR=relative risk)

	Faecal incontinence		Urinary incontinence		Difficulty in bladder emptying	
	RR	p-value	RR	p-value	RR	p-value
Preoperative dysfunction	3.48	<0.001	2.44	0.017	3.15	<0.001
Female gender			2.34	0.001		
Age ≥65			1.96	0.014		
Tumour size ≥4.0cm	1.57	0.113				
Radiotherapy	2.25	0.004				
Blood loss ≥1500ml					1.95	0.038
Anastomotic height <6.0cm	1.62	0.089	1.72	0.049		

size ($p<0.100$ in the univariate analysis), and preoperative faecal incontinence were included as input variables to predict faecal incontinence after rectal cancer treatment. In the multivariable analysis, PRT ($p=0.004$; relative risk=2.25) and preoperative faecal incontinence ($p=0.001$; relative risk=3.48) remained significant predictors. In the multivariable analysis of urinary incontinence (Table 2), female gender ($p=0.001$; relative risk=2.34), age ($p=0.014$; relative risk=1.96), preoperative urinary incontinence ($p=0.017$; relative risk=2.44), and low anastomotic height ($p=0.049$; relative risk=1.72) remained significant predictors. In the multivariable analysis of difficulty in bladder emptying (Table 2), preoperative dysfunction ($p<0.001$; relative risk=3.15) and excessive peroperative blood loss ($p=0.038$; relative risk=1.95) remained significant risk factors.

DISCUSSION

The present study aimed to evaluate nerve disruption during TME as a cause of poor functional outcome by using anatomic and clinical data, with special attention to LAN and incontinence.

Fourteen percent of patients newly developed combined faecal and urinary incontinence after TME and, therefore, probably had a dysfunctional pelvic floor. As the cadaver surgery study revealed, the nerve supply to the pelvic floor, by means of the LAN, lies in the field of operation and can be disrupted during TME. From the anatomic findings, it can be predicted that especially during TME for low tumours, where the parietal fascia of the levator ani muscle is entered, the LAN is at risk. Indeed, our TME database analysis demonstrates that an anastomotic level less than 6 cm increased the risk of (combined) faecal and urinary incontinence significantly.

Additionally, in other studies, low anastomotic level, next to PRT, is considered to be the most important risk factor for faecal incontinence.[11,29,30] We found that the anatomic origin of the LAN was closely related to the origin of the pelvic splanchnic nerves. From this, it can be predicted that improper surgical dissection or excessive manipulation of the mesorectum hold a risk of combined disruption of the LAN and the pelvic splanchnic nerves. In one third of patients, newly developed faecal and urinary incontinence was accompanied by newly developed difficulty in bladder emptying. This would imply that in one third of patients, in whom the LAN was disrupted, simultaneous disruption of the LAN and pelvic splanchnic nerves occurred at the sacral origin.

The TME dissection plane along the parietal presacral fascia is likely to mislead the surgeon and result in injury to the pelvic splanchnic nerves and/or pelvic plexus because the parietal presacral fascia divides into several laminae lining or enclosing these nerves. In addition, when an incorrect plane is followed, the sacral venous plexus, which lies in close proximity of the pelvic splanchnic nerves, may be damaged, resulting in excessive blood loss.[31] Indeed, excessive peroperative blood loss was significantly associated with difficulty in bladder emptying in our study. Diathermic coagulation and numerous sutures to secure hemostasis may cause nerve damage. Moreover, excessive blood loss hinders sight deep in the pelvis, making nerve sparing virtually impossible.[3,32] An increased risk of nerve damage and poor functional outcome in case of a posteriorly located tumour would be expected. However, this is not supported in the present study. Apparently, surgical damage during TME does not depend on characteristics of the tumour but only on specific aspects of the surgical technique used.

Faecal incontinence is multifactorial.[33] The rectum acts as a reservoir, and the smaller neorectum after TME has a lower capacity and smaller tolerated volume.[34] Furthermore, PRT is known to increase the risk of faecal incontinence, which is also supported by the present study.[11,35] Radiotherapy diminishes compliance of the residual rectum because of fibrosis and may disrupt the myenteric plexus of the internal anal sphincter, compromising the rectoinhibitory reflex and resting anal pressures.[33,34] In addition, faecal incontinence after rectal cancer treatment has been reported to be caused mainly by impaired pelvic floor movement (ie, a disturbed change in anorectal angle resulting from a dysfunctional puborectalis muscle).[36]

Urinary incontinence after TME is multifactorial as well. Unfortunately, the questionnaires did not differentiate between urge, overflow, and stress incontinence. Damage to the sympathetic nerve supply (the hypogastric nerves and the pelvic plexus) causes a reduced bladder capacity and may result in urge incontinence.[5] However, one-sided preservation of the pelvic plexus has been clinically shown to result in acceptable urinary continence.[3,37] Surgeons are often unable to verify whether

bilateral damage has occurred, but it is not expected to occur frequently during a TME procedure.[4] Damage to the sacral splanchnic nerves may lead to difficulty in bladder emptying and overflow incontinence.[5] However, urinary incontinence was not significantly related to difficulty in bladder emptying in this study (data not shown). Therefore, we assume that the reported urinary incontinence was mainly stress incontinence. Stress incontinence may also result from impaired support to the urethra and bladder neck.[38] As for faecal incontinence, a dysfunctional pelvic floor has been suggested as an important cause of urinary incontinence.[15-17] This is supported by our results, as faecal and urinary incontinence were occurring simultaneously in a significant number of patients.

In conclusion, the results of our study lead us to state that, especially in patients with low rectal tumours, the risk of LAN disruption is substantial, which could contribute to an increased risk of urinary and faecal incontinence after TME, as indicated by our clinical data. Accidental disruption of the LAN during a surgically difficult procedure could be a factor that has been neglected thus far. The results of our surgical study imply that a correctly performed posterior dissection of the mesorectum would not disrupt the LAN, because the plane of posterior dissection in a TME procedure is between the pelvic parietal fascia and the mesorectal fascia. However, the surgical margin is so small that any deviation from this surgical plane easily results in disruption of the nerve. Adhering to the surgical plane, reducing the use of blunt dissection, and improving rectal retraction may lower the risk of LAN disruption during distal resection. Surgeons that perform TME should be aware of the anatomy of the LAN to avoid disrupting it. A nerve sparing TME should mean not only sparing the pelvic autonomic nerves, but sparing the LAN as well. The challenge is now to assess puborectalis function in patients suffering from faecal incontinence after TME, to actually see whether the puborectalis muscle is denervated. Further studies on faecal incontinence after TME should therefore include clinical assessment of pelvic floor denervation (ie, puborectalis muscle atrophy) in patients who suffer from faecal incontinence after TME.

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CHAPTER 9

Leukocyte depletion of perioperative blood transfusion does not affect long-term survival and recurrence in gastrointestinal cancer patients

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Submitted

ABSTRACT

Background
Perioperative red blood cell (RBC) transfusions are reported to be associated with poor prognosis in cancer surgery. Allogeneic leukocytes are assumed to play a causal role. The present study evaluates the long-term effect of leukocyte depletion of RBC transfusions in gastrointestinal (GI) cancer patients.

Methods
The Tactic-study was a multicentre randomised controlled trial evaluating short-term benefits of leukocyte depleted (LD) *versus* non-LD RBC transfusions. For the present study, five-year survival and cancer recurrence of GI cancer patients included in the Tactic-study were evaluated (n=512).

Results
Eighty-nine percent of patients had a primary tumour and in 79.9 percent of patients surgery was with curative intent. Two hundred and forty-three patients received perioperative RBC transfusion, receiving a median of three units. The five-year survival rate of patients with any type of GI cancer was 50.8 percent in the LD group and 45.8 percent in the non-LD group with a recurrence rate of 32.9 percent in the LD group and 34.3 percent in de non-LD group (p=0.19 and p=0.86, respectively). Disease-free survival was 60.0 percent in the LD group and 56.6 percent in the non-LD group (p=0.48).

Conclusion
Leukocyte depletion is not associated with better long-term survival and lower cancer recurrence in GI cancer patients.

INTRODUCTION

On the basis of the immunomodulatory effect of allogeneic blood transfusion improving renal allograft survival, in 1981 Gantt raised the question whether the effect of transfusion-associated immunomodulation (TRIM) might also be associated with an increased risk of cancer recurrence in patients undergoing resection of a malignancy.[1,2] This hypothesis was based on the premise that, if allogeneic blood transfusion down-regulates the host's immune surveillance that targets malignant cells, the receipt of allogeneic blood transfusion might enhance tumour growth.

Since 1981 more than 150 clinical studies have examined the association of perioperative allogeneic blood transfusion with cancer recurrence.[3] Most of these were observational studies comparing patients who did or did not receive transfusions and produced contradictive results.[4-7]

Since allogeneic leukocytes may play a key role in the TRIM effect, leukocyte depletion could be effective in inhibiting TRIM.[8] Many randomised controlled trials (RCTs) investigated a role of leukocytes in blood products on postoperative infections.[9-12] However, only two RCTs have been conducted to evaluate a role of allogeneic leukocyte on cancer surveillance.[9,13,14] In a third RCT, the Tactic-study (Transfusion Associated Complications=Transfusion Induced Complications?) which included gastrointestinal (GI) cancer patients, leukocyte-depleted (LD) red blood cell (RBC) transfusions resulted in a reduced in-hospital mortality. Given the scarcity of data on the effect of leukocyte containing transfusions on cancer and the ongoing risk of recurrence up to five years after surgery, a follow-up of this trial to five years was performed to evaluate the long-term effects on cancer recurrence and survival.[12]

METHODS

The Tactic-study was conducted between June 2000 and December 2001 at 19 Dutch hospitals. Twelve hundred patients were randomised to LD or non-LD RBC transfusion. Details of the design of the study, patient intake and outcome have been described previously.[12] In the original Tactic-study 560 patients who were operated for a GI malignancy were included. However, in 48 of the patients benign instead of malignant disease was found during surgery. Because the present study concerns oncologic outcome, only those patients were selected with confirmed GI malignancy after surgery (n=512). Gastrointestinal procedures included resections of the stomach, oesophagus, liver, colon, rectum, pancreas or isolated liver perfusions (Table 1). Units of RBC concentrates with the buffy coat removed contained up to $8x10^8$ white blood cells/unit, whereas in RBC filtered before storage the maximum

count was $<10^6$ white blood cells/unit. Both RBC products were plasmareduced and reconstituted with SAG-M.

Outcome measures

New outcome measures were formulated: overall survival (OS), disease-free survival (DFS) and local or distant recurrence since the date of surgery. With respect to DFS, an event was defined as local or distant recurrence of disease or death due to any cause, whichever occurred first.

Data collection

Pre- and peroperative characteristics of the patients had been systematically recorded.[12] For the long-term follow-up clinical data were collected five years after surgery from medical records in each hospital. Subsequently, questionnaires were sent to the general practitioner for each patient to complete the data collection. In case of missing survival data, the regional Comprehensive Cancer Centre was addressed. All medical data were entered in a database by number. Neither the identity of the patient nor the randomisation group were stored in the main database. The actual randomisation was provided only at the final analysis.

Statistical analysis

Univariate comparison of baseline qualitative variables was performed by χ^2 test; for quantitative parameters *t* test or Mann-Whitney U test were used. To analyse the influence of leukocyte depletion on the outcome measures Kaplan-Meier curves were calculated and differences between survival curves were assessed with the log rank test. Patients with missing data were included until the time point at which data were missing. Patients who were lost to follow-up before five years postoperatively were censored from five-year survival and recurrence analyses. Patients treated without curative intent were excluded from DFS and recurrence analyses. Both intention-to-treat analysis and analysis according to transfusion were performed, however, as these resulted in similar findings, only results of the intention-to-treat analysis are shown.

Combined analysis

In addition, a combined analysis was performed with a previous multicentre RCT, the CRAB-study (Cancer Recurrence And Blood Transfusion). The CRAB-study

had been conducted between 1987 and 1990 including patients with primary colorectal cancer undergoing surgery with curative intent (n=698).[9] In 2001 a five-year follow-up of these patients has been reported.[14] This study had a comparable study design with the Tactic-study and blood products used from 1986 throughout 2001 were virtually similar. A subgroup of the Tactic-study group, who met the criteria of the CRAB-study (surgery with curative intent for primary colorectal cancer) was selected (n=277). To evaluate whether combined analysis was justified these CRAB- and Tactic- subgroups were analysed separately. Subsequently, analyses of OS, DFS and recurrence rates were repeated in the combined study-group (n=975). Furthermore, an observational analysis was done comparing the prognosis of transfused patients with that of non-transfused patients. Variables with a $p<0.10$ were included in a Cox regression analysis, conducted to correct for confounding factors. $p\leq0.05$ was considered statistically significant.

RESULTS

Study population

The mean age at surgery was 65.3 years. Eighty-nine percent of patients had a primary tumour and in 79.9 percent of patients surgery was with curative intent. Two hundred and sixty-nine patients did not receive any RBC transfusion, leaving 243 patients for analysis according to transfusion. In patients who received RBC transfusion on average 4.9 units were transfused. Patient and treatment characteristics are listed in Table 1. The mean follow-up was ±70 months.

Overall survival

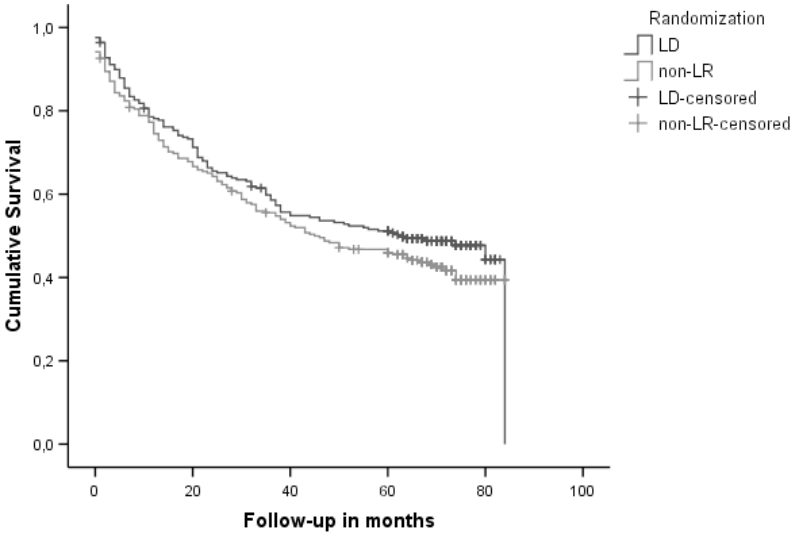
In OS analysis 504 patients were included. No significant difference between both randomisation arms was found (p=0.19, hazard ratio=0.85; Figure 1). Five-year OS was 50.8 percent in the LD group and 45.8 percent in the non-LD group (11 patients, 4 in LD and 7 in non-LD group, lost to follow-up within five years after surgery).

Disease-free survival and recurrence

In the analyses of DFS and recurrence rate 341 patients were included. No significant difference between both randomisation arms was found (p=0.48, hazard ratio=0.89 and p=0.86, hazard ratio=0.97, respectively; Figure 2). Five-year DFS was 60.0 percent in the LD group and 56.6 percent in the non-LD group (5 patients, 2 in LD and

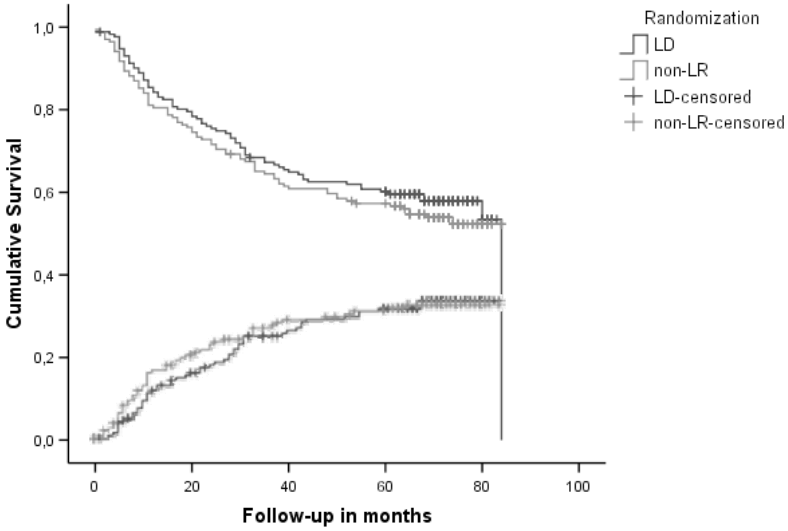
Table 1. Clinical data of the 512 patients with gastrointestinal cancer in the Tactic-study. The separate column at the right shows data of the 243 transfused patients only. (LD=leukocyte depleted ; continuous: median (interquartile range); categorical: n (%); *LD versus non-LD)

	All patients (n=512)			Transfused patients (n=243)		
	LD (n=252)	non-LD (n=260)	*p-value	LD (n=114)	non-LD (n=129)	*p-value
Age (years; n=512)	66 (57, 73)	67 (57, 75)	0.16	67 (59, 74)	68 (59, 77)	0.21
Gender (n=512)			0.83			0.97
Male	145 (57.5)	152 (58.5)		66 (57.9)	75 (58.1)	
female	107 (42.5)	108 (41.5)		48 (42.1)	54 (41.9)	
BMI (kg/m^2; n=153)	25.3 (22.3, 27.8)	24.9 (22.8, 27.6)	0.48	25.0 (20.9, 28.6)	25.1 (22.9, 27.2)	0.42
Indication primary tumour (n=473)	214 (90.3)	208 (88.1)	0.45	92 (87.6)	93 (86.1)	0.75
Tumour location (n=422)			0.62			0.52
Oesophagus	14 (6.5)	14 (6.7)		6 (6.5)	7 (7.5)	
Stomach	18 (8.4)	14 (6.7)		7 (7.6)	4 (4.3)	
Liver	0 (0)	2 (1.0)		0 (0)	1 (1.1)	
Pancreas	15 (7.0)	11 (5.3)		10 (10.9)	6 (6.5)	
Small intestine	3 (1.4)	2 (1.0)		3 (3.3)	1 (1.1)	
Colorectal	164 (76.6)	162 (77.9)		66 (71.7)	72 (77.4)	
Kidney	0 (0)	1 (0.5)		0 (0)	1 (1.1)	
Mesenterial lymph nodes	0 (0)	1 (0.5)		0 (0)	1 (1.1)	
Retroperitoneal liposarcoma	0 (0)	1 (0.5)		0 (0)	1 (1.1)	
Tumour stage (n=335)			0.16			0.10
I	42 (25.0)	29 (17.4)		20 (29.0)	11 (14.5)	
II	44 (26.2)	56 (33.5)		18 (26.1)	29 (38.2)	
III	50 (29.8)	57 (34.1)		18 (26.1)	25 (32.9)	
IV	32 (19.0)	25 (15.0)		13 (18.8)	11 (14.5)	
Indication recurrence (n=473)	23 (9.7)	28 (11.9)	0.45	13 (12.4)	15 (13.9)	0.75
Location (n=51)						0.81
Locoregional	6 (26.1)	8 (28.6)	0.84	4 (30.8)	4 (26.7)	
Distant	17 (73.9)	20 (71.4)		9 (69.2)	11 (73.3)	
(neo)adjuvant therapy (n=256)	71 (54.2)	59 (47.2)	0.26	38 (65.5)	27 (45.0)	0.025
Curative intention (n=439)	177 (79.7)	173 (79.7)	1.00	76 (79.2)	78 (80.4)	0.83
Tumour free resection margin (n=280)	129 (90.2)	128 (93.4)	0.33	55 (88.7)	63 (96.9)	0.071
Peroperative blood loss (ml; n=474)	700 (300, 1315)	750 (300, 1456)	0.75	1290 (600, 2313)	1175 (700, 2000)	0.75
Number of transfused units (n=512)	0 (0, 2)	0 (0, 3)	0.48	3 (2, 6)	3 (2, 5)	0.84



Number at risk					
Overall survival					
LD	248	180	135	124	14
non-LD	256	172	133	114	12

Figure 1. Overall survival of 504 patients who were allocated to leukocyte depleted or to non-leukocyte depleted blood product in the Tactic-study.



Number at risk					
LD	172	136	111	102	13
non-LD	169	128	103	94	11

Figure 2. Disease-free survival (illustrated by the two upper curves) and recurrence (illustrated by the two lower curves) of 341 patients who were allocated to leukocyte depleted or non-leukocyte depleted blood product in the Tactic-study.

3 in non-LD group, lost to follow-up within five years after surgery). The mean time to recurrence was 22 months. In the LD-group 32.9 percent of patients developed a recurrence compared to 34.3 percent in the non-LD group (46 patients, 20 in LD and 26 in non-LD group, lost to follow-up within five years after surgery).

Combined analysis for recurrence of colorectal cancer after curative surgery

The combined analysis consisted of 277 patients of the Tactic-study and 698 patients of the CRAB-study, who underwent curative surgery for primary colorectal cancer. Both subgroups were homogenous (Figure 3). Patient and treatment characteristics of the combined study-group are listed in Table 2. The mean follow-up of the patients in the combined study-group was ±76 months. In OS analysis 975 patients were included and no significant difference between both randomisation groups was found (p=0.94, hazard ratio=0.99). In both groups five-year OS was 64.9 percent

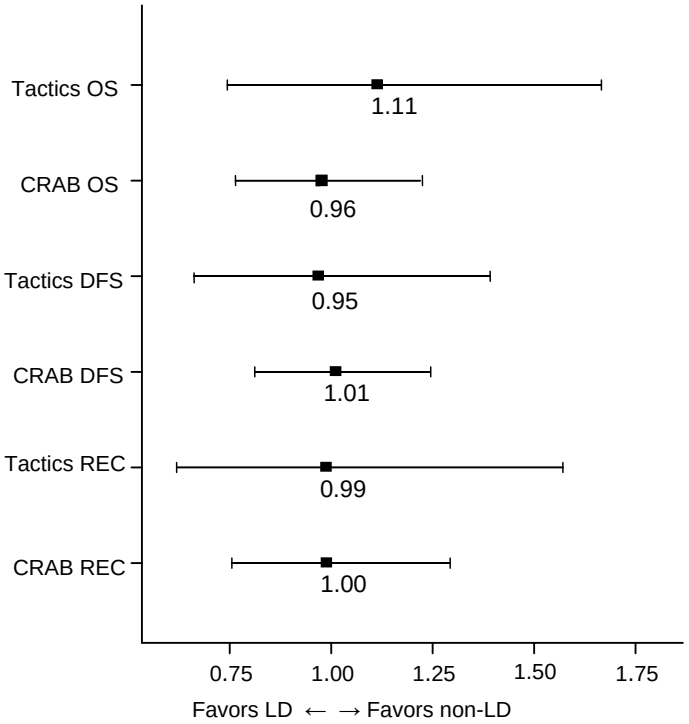


Figure 3. The Tactic-subgroup study and the CRAB-study showing homogenous results with respect to the association of leukocyte depletion with five-year overall survival (OS), disease-free survival (DFS) and recurrence (REC) in patients who underwent surgery with curative intent for a primary colorectal malignancy. For each study the hazard ratio is given as calculated from intention-to-treat analysis. Each hazard ratio is surrounded by its 95% confidence interval.

Table 2. Clinical data of the combined group of 975 patients with primary colorectal cancer operated with curative intent in the Tactic-study (n=277) and the CRAB-study (n=698). The separate column at the right shows data of the 576 transfused patients only. (LD=leukocyte reduced; continuous: median (interquartile range); categorical: n (%); *LD versus non-LD)

	All patients (n=975)			Transfused patients (n=576)		
	LD (n=479)	non-LD (n=496)	*p-value	LD (n=275)	non-LD (n=301)	*p-value
Age (years; n=975)	68 (60, 75)	67 (59, 76)	0.80	69 (61, 76)	69 (60, 77)	0.63
Gender (n=975)			0.71			0.63
Male	254 (53.0)	257 (51.8)		137 (49.8)	156 (51.8)	
female	225 (47.0)	239 (48.2)		138 (50.2)	145 (48.2)	
Tumour stage (n=693)			0.24			0.76
I	62 (18.1)	55 (15.7)		30 (15.2)	33 (15.5)	
II	169 (49.3)	186 (53.1)		103 (52.0)	112 (52.6)	
III	103 (30.0)	106 (30.3)		62 (31.3)	67 (31.5)	
IV	9 (2.6)	3 (0.9)		3 (1.5)	1 (0.5)	
(neo)adjuvant therapy (n=853)	58 (13.8)	48 (11.1)	0.23	30 (12.0)	23 (8.5)	0.18
Peroperative blood loss (ml; n=963)	500 (200, 1000)	500 (200, 1000)	0.85	800 (400, 1500)	700 (250, 1300)	0.24
Number of transfused units (n=734)	2 (0.4)	2 (0.4)	0.38	4 (2, 6)	3 (2, 5)	0.11

(37 patients, 17 in LD and 20 in non-LD group, lost to follow-up within five years after surgery). In analyses of DFS and recurrence rate 970 patients were included showing no significant difference between both randomisation arms (p=0.92, hazard ratio=0.99 and p=0.94, hazard ratio 0.99, respectively). Five-year DFS was 58.9 percent in the LD group and 59.3 percent in the non-LD group (29 patients, 13 in LD and 16 in non-LD group, lost to follow-up within five years after surgery). In the LD group 32.2 percent of patients developed a recurrence *versus* 33.1 percent in the non-LD group (151 patients, 74 in LD and 77 in non-LD group, lost to follow-up within five years after surgery).

Red blood cell transfusion

Observational analysis of the combined study-group showed worse OS, DFS and recurrence rates in patients who received RBC transfusions (59.5 percent, 54.2 percent and 36.2 percent, respectively) compared to patients who did not receive any perioperative RBC transfusion (72.7 percent, 66.1 percent and 26.5 percent, respectively). Even after correcting for gender, tumour stage and age in multivariable analysis, RBC transfusion remained a significant risk factor (Table 3).

Table 3. Multivariable analysis of overall survival, disease-free survival and recurrence in the combined analysis of patients who underwent surgery with curative intent for a primary colorectal malignancy. (HR=hazard ratio; CI=confidence interval; LD=leukocyte depletion; RBC=red blood cell; *age was not included in the analysis of recurrence rate, as it was not a significant factor in univariate analysis (p=0.80, hazard ratio=1.00); **number of patients is too small for analysis)

	Overall survival			Disease-free survival			Recurrence		
	p-value	HR	95% CI	p-value	HR	95% CI	p-value	HR	95% CI
LD	0.60	0.94	0.74 – 1.20	0.56	0.94	0.75 – 1.17	0.73	0.95	0.72 – 1.26
RBC transfusion	0.003	1.48	1.14 – 1.91	0.022	1.32	1.04 – 1.67	0.055	1.33	0.99 – 1.78
male gender	0.019	1.34	1.05 – 1.72	0.002	2.43	1.13 – 1.79	0.018	1.41	1.06 – 1.87
age	<0.001	1.04	1.03 – 1.05	<0.001	1.03	1.02 – 1.04	*		
stage	<0.001			<0.001			<0.001		
I									
II	0.34	1.22	0.82 – 1.82	0.51	1.13	0.79 – 1.62	0.89	0.97	1.54
III	<0.001	2.83	1.89 – 4.25	<0.001	2.72	1.89 – 3.90	<0.001	3.31	5.16
IV	0.019	2.88	1.19 – 7.00	0.78	1.18	0.36 – 3.84	**		

DISCUSSION

The presence of allogeneic leukocytes in transfusion products is presumed to impair response against cancer.[8] However, only two RCTs addressed this presumption.[13,14] Patients operated for various types of GI cancer in the Tactic-study, receiving LD RBC transfusions had shown a lower in-hospital mortality (4 percent *versus* 8 percent).[12] The follow-up study however showed that there was no long-term beneficial effect of leukocyte depletion of perioperative RBC transfusion on the prognosis of (GI) cancer patients.

The present analysis of the Tactic-study, comprising all types of GI cancer, showed no significant differences in five-year OS and DFS in patients receiving LD transfusions compared to patients receiving non-LD transfusion. In the combined analyses with the CRAB study, addressing the question of recurrence in patients with colorectal cancer after intentionally curative surgery, the two trial arms showed similar results with respect to five-year OS, DFS and recurrence rate.

The Tactic- and the CRAB-study compared prestorage leukocyte depletion, by filtration of buffy-coat depleted RBCs, eliminating release of breakdown products of leukocytes that could mediate TRIM.[15,16] The absence of any effect of leukocyte depletion in our study may on one hand be explained by lack of antigenicity of

colorectal cancer, not capable to elicit host immunity.[17] On the other hand, specific constituants of allogeneic blood, not related to residual contaminating leukocytes may mediate the TRIM effect. Next to allogeneic leukocytes, allogeneic platelets, plasma and substances that accumulate in erythrocyte components during storage have all been implicated in the pathogenesis of TRIM.[3]

The differences in outcome between transfused and non-transfused patients have been reproduced in the present study. However, important other risk factors reflecting clinical status, such as invasion of tumour into lymph or blood vessels, were not assessed and could not be included in the analysis. The better clinical status of patients not requiring blood transfusions, make it unjust to ascribe differences solely to the transfusion status of the patients. An increased recurrence rate in transfused patients, either allogeneic or autologous, compared to patients who had not required a transfusion, has been discussed before, concluding that this was due to the (confounding) circumstances that necessitated transfusions.[18] In 468 patients with rectal cancer, Bentzen *et al*. revealed that well-established prognostic factors accounted for the worsened prognosis in transfused patients, not transfusion as such, and that patients receiving RBC transfusion performed as expected from their clinicopathological characteristics.[19]

Irrespective of a possible effect of RBC transfusion, the present study shows that, despite the short-term benefits, leukocyte depletion does not improve long-term outcome of GI cancer patients.

The United Kingdom, Ireland, Portugal, France, Canada, Scandinavia and The Netherlands have implemented universal leukocyte depletion of all transfused cellular blood components as precautionary action. Some countries based their decision on the hypothesis that this practice would prevent the theoretical risk of transmission by transfusion of the agent of variant Creutzfeldt-Jakob disease, while others on the hypothesis that this practice would reduce the number of transfusion complications like fever, viral transmission, alloimmunisation, cancer recurrence and mortality.[20] There is no reason with respect to cancer recurrence or long-term (disease-free) survival to use LD RBC in GI cancer patients instead of simple buffy-coat removal as program of transfusion. This may be important for those countries that have not yet implemented universal leukocyte depletion.

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CHAPTER 10

Discussion and future perspectives

Curative rectal cancer treatment has been performed for more than 100 years. It was initiated by Miles, who established the focus of attention on the importance of local tumour spread and lymph node involvement. In 1908 he introduced radical tumour resection by abdominoperineal resection (APR). In the subsequent century rectal cancer treatment has tremendously progressed. Rectal cancer surgery turned from destructive amputative surgery to restorative surgery by changing surgical technique from conventional blunt dissection to total mesorectal excision (TME) with sharp dissection.[1] Sharp dissection in the avascular plane between the mesorectum and surrounding tissues led to improved overall survival (from 48 percent to >60 percent), reduced local recurrence rates (from >20 percent to <10 percent), higher incidence of sphincter preservation and reduced peroperative blood loss and autonomic nerve damage.[2-5] The addition of radiotherapy further improved outcome of rectal cancer treatment. In the Dutch TME trial five-year local recurrence risk of patients undergoing a macroscopically complete local resection was significantly reduced in case of short-course preoperative radiotherapy (PRT; 5x5 Gy over 5 days) compared to patients undergoing surgery alone (5.6 *versus* 10.9 percent; $p<0.001$).[6] However, PRT was shown to be ineffective in case of incomplete tumour resection.[7] Involvement of the circumferential resection margin (CRM) remained the most important prognostic factor.[8] Reducing the risk of CRM involvement was recognized to be a matter of team work. Standardised pathological examination of the surgical specimen has become an important tool to evaluate surgical quality and provide feedback to the individual surgeon. Furthermore, the MERCURY-study group demonstrated that high-resolution magnetic resonance imaging (MRI) is accurate in predicting whether the CRM will be affected by tumour.[9] In that case, radiation and medical oncologists decrease tumour burden by administering prolonged chemoradiotherapy (CRT), increasing the likelihood that the surgeon can perform a radical (R0) resection. Burton *et al*. showed that multidisciplinary team discussion of MRI and implementation of a preoperative treatment strategy result in significantly reduced positive CRM rates in rectal cancer patients.[10] In this manner rectal cancer treatment has evolved into a multidisciplinary treatment with standardised surgical, pathological and radiotherapeutical procedures.

Today rectal cancer treatment continues to develop explicitly. First of all, an increasing role of adjuvant chemotherapy is to be expected. In contrast to the amazing achievements with respect to locoregional control, the rates of distant metastasis have not changed since the early eighties.[11] Distant metastases are accountable for mortality and frequently occur, regardless of radiotherapy (25.8 percent *versus* 28.3 percent).[4] Adjuvant chemotherapy might approach micrometastatic disease early, trying to control it and by this, curing more patients and prolonging survival over

locoregional therapies alone. The development of effective adjuvant chemotherapy for rectal cancer is a priority issue. In the past adding adjuvant chemotherapy to long-course PRT (45-55 Gy in 1.8 Gy fractions over 4-6 weeks) has been proven to be ineffective for improving survival of rectal cancer patients, however this was in the era of conventional surgery.[12] In the more recent EORTC 22921 and FFCD 9203 trials, adjuvant chemotherapy did not improve survival either.[13,14] Furthermore, in the Polish study survival of patients treated with long-course CRT was similar to survival in patients treated with short-course PRT only.[15] However, in these studies surgical quality control was not performed. Currently, the SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus TME) trial randomises stage II/III rectal cancer patients who have had 5x5 Gy plus TME between oral capecitabine and observation.

Another purpose of chemotherapy in the multimodality approach of rectal cancer is enhancing the efficacy of radiation. Due to the modulating effect of chemotherapy on tumour cells and therefore increased sensitivity for radiation damage, CRT was expected to be superior to radiotherapy alone with respect to local control. Buijko *et al*. reported similar local recurrence rates in patients treated with short-course PRT compared to patients treated with long-course CRT.[15] However, the addition of chemotherapy to long-course PRT in the EORTC 22921 and FFCD 9203 trials resulted in a significant reduction of local recurrence rates.[13,14] Furthermore, higher rates of tumour eradication (pathologic complete response, pCR) were found. The sterilisation effect of CRT would significantly reduce the risk of lymph node metastases, which may reach rates over 13 percent even in T1 rectal cancer.[16] Therefore, patients with early rectal cancer after neoadjuvant treatment (ypT1 and ypT2) might be considered candidates for local excision by means of transanal endoscopic microsurgery (TEM), which has shown disappointing local recurrence rates of 15-30 percent in patients treated without neoadjuvant treatment.[17] In case of pCR, which has been reported in 10–30 percent of patients treated with preoperative CRT, surgery might even be omitted.[18,19] Rutten *et al*. recently stated that treatments that keep surgical trauma to a minimum and optimise the use of radiotherapy might be more suitable for elderly patients with diminished physiological reserves and comorbid conditions.[20] The development of rectum saving treatment is further encouraged by our finding that surgery is the main cause of functional morbidity after rectal cancer treatment. However, discrepancy exists between clinical complete response (cCR) and pCR.[21] In case of cCR cancer cells are found in 40-75 percent of postoperative specimens.[18,21-24] Moreover, following preoperative CRT, the incidence of residual mesorectal lymph node involvement remains significant.[25] Nevertheless, the study of Habr-Gama *et al*. in which patients with sustained cCR were managed by observation alone has shown excellent results.[26] However, results of patients with cCR who did

not receive surgical treatment and developed a recurrence within one year were not provided. Furthermore, as local recurrences after CRT tend to occur late, follow-up was too short. Therefore, long-term follow-up of prospectively conceived multicentre data concerning safety and functional outcome are needed.

The overall aim of clinical research in rectal cancer should be to develop a range of multidisciplinary treatment strategies that can be tailored to the requirements of individual patients, taking into consideration disease factors and patient factors, such as the presence of comorbidities and risks of suffering treatment-related complications. Improved imaging techniques and translational research are required for the identification of patients groups which will gain the maximum benefit from each treatment option. Magnetic resonance imaging with lymph node specific contrast enhancement may be the most promising modality for distinguishing between the lower risk N0 rectal cancer patients, for whom TEM or TME might suffice and higher risk N1 and N2 rectal cancer patients, which should be treated with PRT followed by TME. New MRI contrast agents, like ultrasmall superparamagnetic iron oxide (USPIO) and MS 325 may help radiologists to solve the problem of lymph node identification in the near future.[27] A cohort study in which 322 patients were stratified into different treatment groups after USPIO-MRI has shown promising results (95 percent complete resections). Furthermore, translational research will contribute to tailored treatment based on individual tumour profiles in the near future. Genomics and proteomics enable identification of biomarkers which may be used to predict prognosis and response to treatment. For example, local recurrence can be predicted by detection of tumour apoptosis-levels through measurements of caspase-3 activity.[28] Research on cancer biology and the discovery of a number of molecular pathways has also led to the development of molecular targeted treatments. Bevacizumab, the monoclonal antibody targeting the vascular endothelial growth factor, as well as cetuximab, which is a monoclonal antibody against epidermal growth factor receptor, have recently been approved to be used against advanced colorectal cancer. The optimal use of these agents, as well as their combined administration, are currently the focus of several ongoing studies.[29]

In the progress of rectal cancer treatment during the upcoming century, surgeons will remain the key characters. Several aspects of surgical performance are to be improved. Firstly, anastomotic leakage remains a frequently reported complication after low anterior resection (LAR) and is associated with postoperative mortality and increased recurrence rates.[30] At present, temporary defunctioning stomas are often created as it has recently been shown to limit the consequences of anastomotic leakage.[31] However, den Dulk *et al*. showed that a substantial proportion of these stomas are never reversed (19 percent).[32] Therefore, the chance of stoma reversal

should be estimated preoperatively and an individualized decision should be made on resection type by counterbalancing the possible loss of quality of life (QoL) in case of a definitive colostoma created during APR, which depends on the patient's preferences and socio-demographical characteristics, with the patient's comorbidity, which might limit successful reversal of a temporary stoma after LAR. Furthermore, vascular ligation technique might influence anastomotic healing. Although data are not conclusive, Chapter 2 suggests that high tie ligation, which is the most popular technique, might be less preferable than low tie ligation.[33] However, a change of practice is unlikely to occur. As anastomotic leakage will probably remain a problem in the upcoming decades, it is important to control the consequences in case anastomotic leakage occurs. Currently, a standardised postoperative surveillance is being introduced in The Netherlands to reduce delay in the diagnosis of anastomotic leakage and mortality.[34]

Secondly, APR resection technique needs to be improved. At present, APR is associated with worse local control and a 10 percent reduction in overall survival.[35-37] Positive CRM rates are 26.5 percent after APR *versus* 12.6 percent after LAR ($p<0.001$), which indicates that the quality of the surgical procedure is a crucial factor contributing to the poor results after APR.[36] In this respect preoperative CRT is suggested. Chemoradiotherapy and delayed surgery has been shown to downstage and downsize tumours.[23,38] However, downstaging and downsizing are not the only contributors to free CRM. In the EORTC 22921 trial, it was shown that no significant difference in CRM involvement was obtained after preoperative CRT despite an impact on tumour stage and size.[39] Therefore, improvement in surgical technique remains necessary to reduce CRM involvement. Wider perineal and pelvic floor resections for low rectal cancers will improve results after APR in the upcoming decade.[35,36,40]

Upgrading surgical performance also implies reducing variability among surgeons. Total mesorectal excision is a difficult and technically demanding operation and the skills of the surgeon are of major importance in achieving good results.[41] Surgical trainee programmes can have a major impact. The national Scandinavian and Dutch surgical initiatives have shown lasting effects of training of surgeons in resection technique.[34] Also case volume appears to be related to variability in patient outcome.[41] In order to improve results in the future all patients should be offered cure by a well educated, multidisciplinary team in high-volume centres. In addition, CRM involvement should be determined in daily practice as it is an important parameter of outcome and essential for feedback to the individual surgeon.[41] A recent study evaluating the rate of reported CRM in the pathology report, found an increase from 37 to 70 percent after feedback to the regional pathology working group.[42] This illustrates the importance of registration to assess and improve quality of rectal cancer treat-

ment. From January 1st 2009 a Multidisciplinary Quality Assurance Program will be started under the initiative of the European Society of Surgical Oncology (ESSO) implicating outcomes registry which will enable assessment of structure and process of care, identification and implementation of best practices and subsequent confirmation of improvement of rectal cancer treatment. In this manner, reliable treatment evaluation becomes within reach for individual centres and individual surgeons. In case of suboptimal performance, treating teams can be encouraged either to improve their treatment results by seeking additional training or to stop treating rectal cancer patients. This will reduce variability and contribute to improved clinical outcome. When counterbalancing this against expensive chemotherapy regimens and universal leukocyte depletion of transfused blood products, both beneficial to only a minority of patients, one has to conclude that upgrading the surgical performance is cheap and definitely cost effective.[43,44]

Given the increasing number of treatment alternatives in rectal cancer treatment, it will become increasingly important to accurately capture the impact of different treatment regimens on QoL. This would help in making difficult decisions, in which modest changes in survival or local control must be balanced against effects on QoL, from chemotherapy and radiotherapy toxicities to permanent colostomies. Understanding the impact of various treatment alternatives on postoperative QoL will help to choose a plan optimising both oncologic outcome and function. Therefore, QoL is now regarded as a key measurement in assessing outcomes of interventions.[45,46] However, as patients adjust to the functional changes after having survived cancer, their perception of QoL might shift and might not accurately reflect postoperative functional differences.[46-49] Interestingly, QoL of rectal cancer patients is comparable to that of the same aged general population, despite significant problems with respect to anorectal and urogenital functioning.[46,50-52] Therefore, QoL measurements, such as the EORTC C-30 and CR-38 are not suitable to detect functional differences and thus to determine the optimal treatment strategy.[53,54] More data concerning specific organ dysfunction before and after rectal cancer treatment are required. This may help patients set realistic expectations for their postoperative life. More realistic expectations may, in turn, help patients to adapt to functional alterations postoperatively, resulting in a better QoL. Next to informing patients, it has been suggested that patients need to be involved in treatment decision making. Especially when a patient presents with a serious illness, different treatment options exist, the gains of treatment should be weighed against possible adverse effects, or outcomes are uncertain, patient involvement is required.[55] This is supported by the fact that both individual patients and individual oncologists greatly vary in their perception of how tumour control, survival and functional outcome should be weighed in decid-

ing upon the most preferable treatment.[56,57] At present, patients are often informed through internet and prefer a more active role in decision making. However, there is considerable evidence suggesting that patients do not wish to be involved in decisions regarding their own care and instead prefer a more paternalistic approach in which their physicians make the decisions for them.[58] An ongoing project is investigating to what extent patients and oncologists believe that patients should also participate in decision making regarding therapy.

To adequately balance benefits and costs of each treatment alternative and to elucidate etiology for prevention and treatment of postoperative organ dysfunction, systematic registration of preoperative and long-term postoperative pelvic organ dysfunction is needed. In this respect the Dutch TME trial has been exceptional. This study, which was a surgical initiative conducted by the Dutch Colorectal Cancer Group (DCCG) organised rectal cancer treatment for the first time and realised specialisation of surgeons in TME surgery and nerve preservation and pathologists in assessment of the quality of resected specimens. High compliance of patients, radiotherapists, surgeons and pathologists has generated a unique set of long-term data, among which different aspects of QoL. Through the current thesis the Dutch TME trial has provided insight in the incidence and etiology of long-term pelvic organ dysfunction after rectal cancer treatment. Poor functional outcome appears to occur commonly: about one third of patients reported urinary dysfunction, half of patients suffered from faecal incontinence and more than half of patients experienced deterioration of sexual functioning. Significant adverse effects of short-course PRT on long-term anorectal and urogenital functioning were observed, which is supported by the Stockholm trials.[52,65,68] This has resulted in criticism against short-course PRT. However, reliable data concerning late side-effects of other regimens are lacking. In a study of Buijko *et al*. short-course PRT was compared with preoperative CRT and no increased toxicity was observed after short-course PRT.[15] Furthermore, the addition of chemotherapy might result in even more dysfunction, as it has been shown to induce nerve damage.[72] Long-term functional outcome of long-course CRT should be evaluated extensively.

In this thesis, it has been shown that despite the additional effect of PRT, anorectal dysfunction seems to be mainly caused by surgical damage, as even without PRT faecal incontinence occurs in 40 percent of patients.[50,73] In addition, in Chapter 4 we found only a minor effect of PRT on sexual dysfunction . Moreover, no contribution of PRT in the development of urinary dysfunction was shown in Chapter 5.[51] Therefore we conclude that pelvic organ dysfunction is mainly caused by surgical factors. First of all, surgical resection of rectal cancer inevitably results in a decrease in maximum tolerated volumes, as the neorectum has a relatively low capacity.[71] Moreover, the rich network of nerve endings to the anal canal, sensitive to pain, temperature and

touch differentiating solid or liquid stool from flatus and allowing selective passage is removed. This also explains why patients with a small neorectum after resection of a distal tumour are at increased risk of faecal incontinence. Other surgical factors influencing functional outcome, which were identified in our study, include anastomotic leakage and excessive peroperative blood loss. Inflammation and haemostasis by diathermic coagulation and numerous sutures may cause nerve damage. Surgical nerve disruption during dissection is also believed to be a cause of pelvic organ dysfunction.[74-76] Some authors support the idea that specific identification of the pelvic autonomic nerves is not essential during TME surgery.[77] By following the concept of the TME procedure, the pelvic autonomic nerves would be automatically preserved. However, the data presented in this thesis do suggest that avoiding pelvic autonomic nerve damage during TME surgery might be more troublesome than it seems. In a quarter of the cases the surgeon stated that the pelvic autonomic nerves had or might have been disrupted. We found an association between damage to the parasympathetic nerves (pelvic splanchnic nerves and inferior hypogastric plexus) and difficulty in bladder emptying in addition to an association between damage to the sympathetic nerves (superior hypogastric plexus and hypogastric nerves) and ejaculatory dysfunction.[51] The parasympathetic nerves may be disrupted during deep dissection of the lateral planes. The sympathetic nerves are at risk during presacral and ventrolateral dissection of the mesorectum. Regarding the dysfunction rates, it seems probable that the surgeons have underreported nerve damage. Moreover, damage to the levator ani nerve was not reported, as this nerve was not addressed at during the Dutch TME trial. However, the levator ani nerve is responsible for the innervation of the main body of the pelvic floor muscle, which is of major importance for the urinary and faecal continence system.[78,79] The levator ani nerve has been neglected so far, but we have shown this nerve might be involved in the etiology of incontinence after rectal cancer treatment. It is interesting that such a new concept can be developed after rectal resection has been performed for more than 100 years. Although the levator ani nerve has been illustrated in detail as early as in the 19th century (Hirschfield), in current anatomy textbooks it is hardly ever mentioned. Anatomy, as well as surgery, is still developing, and cooperation of anatomists and surgeons may be an effective tool for further progress in the future. Besides the superior and inferior hypogastric plexuses, the hypogastric and pelvic splanchnic nerves, the levator ani nerve also would not be disrupted during a correctly performed TME. However the surgical 'margin' is so small that any deviation from the surgical plane easily results in nerve damage. Differences among individuals in the running patterns of the nerves and variations in the volumes of nerve fibres in each region of the pelvis make appropriate identification difficult. Especially when excessive peroperative blood loss hinders sight in the pelvis, in most cases due to disruption of

the presacral venous plexus, nerve sparing is virtually impossible.[63,64,80] The use of a nerve stimulating device might facilitate preservation of the pelvic autonomic nerves during TME in the future.[81] Data concerning nerve disruption during laparoscopic TME should be awaited. Theoretically, the magnified view of the pelvis afforded by the laparoscope might facilitate nerve identification and thus prevent nerve injury.

In conclusion, this thesis indicates that nerve preservation during rectal cancer surgery needs to be more emphasised in daily practice. In this respect systematic registration of identified crucial structures (superior and inferior hypogastric plexuses, hypogastric and pelvic splanchnic nerves, levator ani nerve) during surgery is needed. Additionally, structured education in pelvic neuroanatomy and training as a prerequisite for certification as a rectal cancer surgeon, would be the key to improvement of functional outcome.

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SUMMARY

CHAPTER 1

In The Netherlands about 2 500 new cases of rectal cancer are diagnosed each year. Approximately 75 percent is considered surgical resectable and will be treated with total mesorectal excision (TME), which removes the complete mesorectum through sharp dissection of pre-existing embryologically determined planes, allowing the preservation of the pelvic autonomic nerves. The Dutch TME trial showed the benefit of adding preoperative radiotherapy (PRT) to TME on local control, which is considered standard treatment in Europe. Most patients undergo low anterior resection (LAR), which preserves the sphincter. However, anastomotic leakage is a frequent (5-26 percent) and dangerous complication of LAR. Also, faecal incontinence may occur which can have a major impact on quality of life. In this respect, consensus does not exist concerning the benefit of sphincter preservation *versus* definitive colostomy after abdominoperineal resection (APR).

There is a general lack of large prospective studies concerning long-term functional morbidity after rectal cancer treatment. Anorectal and urogenital dysfunction have been reported, but the etiology remains unclear. Surgical disruption of the pelvic nerve system and radiation damage might be involved. The aim of the current thesis was to evaluate long-term results of rectal cancer treatment, specifically focusing on the etiology of long-term morbidity.

CHAPTER 2

This chapter is a historical overview describing the impact of Miles on the development of rectal cancer treatment. One hundred years ago he introduced the basis of modern rectal cancer surgery by establishing the importance of lymphatic spread of cancer cells. He developed a radical APR, removing all primary lymph nodes *en bloc*. Miles' concept has dominated the minds of surgeons throughout the 20th century and his surgical technique has been the gold standard for several decades. However, when a distal margin of two centimetres was proven to be safe and circular staplers were developed, a shift took place from radical APR to the use of sphincter saving surgery. Since the introduction of TME, APR has been performed in only a minority of patients. Further improvement in surgical technique consisted of autonomic nerve preservation, improving functional outcome. From a historical overview, it can be concluded that the management of rectal cancer has been progressed tremendously

over the past hundred years, mainly because of an increased understanding of the pathology and natural history of the disease, which has been initiated by Miles.

CHAPTER 3

Ever since Miles and Moynihan proposed low tie (ligation at the level of the superior rectal artery) and high tie technique (ligation at the level of the inferior mesenteric artery), respectively, in the beginning of the 20th century, the level of central arterial ligation has been under debate. The choice of central ligation can be based on three considerations: oncologic, anatomic and technical. This chapter systematically reviews the evidence of possible benefits of both ligation techniques regarding these three different considerations. From a literature review it is concluded that neither the high tie nor the low tie strategy is evidence based and that low tie is anatomically less invasive with respect to circulation and autonomous innervation of the proximal limb of anastomosis. As a consequence, in rectal cancer surgery low tie should be the preferred method.

CHAPTER 4

In order to gain insight in the etiology of sexual dysfunction of rectal cancer treatment, long-term sexual dysfunction was evaluated in the Dutch TME trial, in which patients with resectable rectal cancer were randomised to TME with or without PRT. A questionnaire study allowed male and female patients to report general sexual dysfunction, erectile dysfunction (♂), ejaculatory problems (♂), dyspareunia (♀) and vaginal dryness (♀). Most patients were sexually active before rectal cancer treatment (526 of 757 patients). Of preoperative sexually active patients 15.2 percent of men and 13.7 percent of women never indicated to be sexually active after treatment, which was related to age>65 years and in male patients also to anastomotic leakage. Of the patients who were sexually active preoperatively, the majority reported deterioration of sexual functioning after rectal cancer treatment. In male patients this was associated with autonomic nerve damage, excessive peroperative blood loss, anastomotic leakage, PRT and the presence of a temporary or definitive colostomy. The presence of a colostomy and PRT were risk factors in female patients. From these results it can be concluded that sexual dysfunction is a frequent and serious problem after treatment for rectal cancer, which can be mainly attributed to surgical (nerve) damage with an additional effect of PRT.

CHAPTER 5

Urinary dysfunction (UD) after rectal cancer treatment is a common problem, of which the contributing factors are unclear. To evaluate UD during five years after TME and to identify contributing factors, 785 patients of the Dutch TME trial were analysed. Long-term incontinence was reported by 38.1 percent of patients of whom 72.0 percent had normal preoperative function. Preoperative incontinence and female gender were independent risk factors ($p=0.001$, RR=2.75 and $p<0.001$, RR=2.77, respectively). Long-term difficulty in bladder emptying was reported by 30.6 percent of patients of whom 65.0 percent had normal preoperative function. Preoperative difficulty in bladder emptying ($p<0.001$, RR=2.94), peroperative blood loss ($p=0.028$, RR=1.73) and autonomic nerve damage ($p=0.024$, RR=2.82) were independent risk factors. Preoperative radiotherapy was not associated with UD. From this chapter it can be concluded that UD is a significant clinical problem after rectal cancer treatment and is not related to PRT but rather to surgical nerve damage.

CHAPTER 6

Low anterior resection results in faecal incontinence in a large number of patients. This chapter reports on risk factors associated with long-term faecal incontinence in the Dutch TME trial.

Faecal incontinence was reported by 39 percent of patients without PRT and 62 percent of patients with PRT at five years after TME. Preoperative radiotherapy was associated with increased incontinence in both a quantitative and qualitative way. Only in patients treated with TME and PRT excessive peroperative blood loss, tumour and anastomotic height were associated with long-term faecal incontinence. If the perineum was included in the radiotherapy field and a low anastomosis was constructed, faecal incontinence occurred in 14 out of 15 patients. Therefore, patients with distal tumours should be warned that faecal incontinence is likely to occur after PRT, especially when the perineum is irradiated. In these patients APR might be preferable.

CHAPTER 7

This chapter presents a female patient suffering from combined faecal and urinary incontinence five years after rectal cancer treatment. Based on the literature, several aspects are discussed, such as incidence, etiology, progression over time, prevention and treatment of incontinence. Key learning points from this chapter include:

- Incontinence problems after rectal cancer treatment are common and can have a major impact on quality of life.
- Patients should be informed about the surgical options, LAR and APR, and about their potential outcomes.
- Surgical nerve damage may play a major role in the development of faecal and urinary incontinence, with an additional effect of radiotherapy.
- Faecal incontinence can worsen over time in case of radiotherapy.
- Several non-surgical and surgical therapies of incontinence problems are available; conservative therapies should be the first line choice.

CHAPTER 8

In this chapter anatomical and clinical findings are reported concerning the possible role of levator ani nerve disruption in the development of faecal and urinary incontinence after TME. Cadaver TME surgery demonstrated that, especially in low tumours, the pelvic floor innervation can be damaged. Furthermore, the origin of the levator ani nerve was located in close proximity of the origin of the pelvic splanchnic nerves. Analysis of the TME trial data showed that newly developed urinary and faecal incontinence was present in 33.7 percent and 38.8 percent of patients, respectively. Both types of incontinence were significantly associated with each other ($p=0.027$). Low anastomosis was significantly associated with urinary incontinence ($p=0.049$). One third of the patients with newly developed urinary and faecal incontinence also reported difficulty in bladder emptying, for which excessive peroperative blood loss was a significant risk factor. It is concluded that peroperative damage to the levator ani nerve, which is at risk in case of a low anastomosis or in case of damage to the pelvic splanchnic nerves, could be a factor that has been neglected so far.

Together with the results in Chapter 4, 5 and 6, these results indicate that patients should be informed preoperatively about functional outcome and that education of surgeons in pelvic neuroanatomy and crucial anatomical dissection planes may provide the key to improvement of functional outcome.

CHAPTER 9

Perioperative red blood cell (RBC) transfusions are reported to be associated with poor prognosis in cancer surgery and allogeneic leukocytes in RBC transfusions are assumed to play a causal role. This chapter reports the results of a randomised controlled trial comparing leukocyte depleted (LD) and non-leukocyte depleted red

blood cell transfusion in gastrointestinal cancer patients (n=512). Also a combined analysis with a similar randomised controlled trial, in which only colorectal cancer patients treated with curative intent were included, was performed (n=975). The five-year survival rate of patients with any type of gastrointestinal cancer was 50.8 percent in the LD group and 45.8 percent in the non-LD group with a recurrence rate of 32.9 percent in the LD group and 34.3 percent in de non-LD group (p=0.19 and p=0.86, respectively). The combined analysis of colorectal cancer patients revealed no difference in long-term survival (64.9 percent in both groups) and recurrence rates (32.2 percent *versus* 33.1 percent) between the two transfusion arms (p=0.94 and p=0.94, respectively). From these results it can be concluded that in patients with gastrointestinal cancer, leukocyte depletion is not associated with better long-term survival and lower cancer recurrence.

CHAPTER 10

Rectal cancer treatment has tremendously progressed in the past 100 years. Improvement of surgical technique has been the key factor in this progression. Further improvement of local control has been established by the addition of radiotherapy. Nowadays, rectal cancer treatment is a multidisciplinary treatment with standardised surgical, pathological and radiotherapeutical procedures.

Rectal cancer treatment continues to develop explicitly. First of all, an increasing role of chemotherapy is to be expected. On one hand to approach micrometastatic disease early, trying to control it and by this, curing more patients and prolonging survival. This is currently under investigation (SCRIPT study). On the other hand chemotherapy is added to enhance the efficacy of radiation. The sterilisation effect of chemoradiotherapy has led to the development of rectum saving treatments. Local excision of early rectal cancer with transanal endoscopic microsurgery (TEM) and neoadjuvant chemoradiation therapy alone in case of complete clinical response have shown promising results. However, long-term follow-up of prospectively conceived multicentre data concerning safety and functional outcome are needed.

The overall aim of clinical research in rectal cancer should be to develop a range of multidisciplinary treatment strategies that can be tailored to the requirements of individual patients. Improved imaging techniques and translational research are required for the identification of patient groups which will gain the maximum benefit from each treatment option.

Especially surgical performance is to be improved in the upcoming century. The risk of anastomotic leakage, positive resection margins (especially during abdominoperineal resections) and surgical variability should be reduced. Currently, the

European CanCer Organisation (ECCO) is organising a Multidisciplinary Quality Assurance Program which enables assessment of structure and process of care, identification and implementation of best practices and subsequent confirmation of improvement of rectal cancer treatment. In addition, giving the increasing number of treatment alternatives in rectal cancer treatment, it will become increasingly important to accurately capture the impact of different treatment regimens on quality of life. Registration of specific organ dysfunction before and after rectal cancer treatment is required. In this respect the Dutch TME trial has been exceptional. Through the current thesis it has provided insight in the incidence and etiology of long-term pelvic organ dysfunction after rectal cancer treatment. Poor functional outcome appears to occur commonly and to be mainly caused by surgical (nerve) damage. According to our results, the levator ani nerve, which has been neglected so far, might be involved. In this respect systematic registration of identified crucial structures (superior and inferior hypogastric plexuses, hypogastric and pelvic splanchnic nerves, levator ani nerve) during surgery is needed. Additionally, structured education in pelvic neuroanatomy and training as a prerequisite for certification as a rectal cancer surgeon, would be the key to improvement of functional outcome.

NEDERLANDSE SAMENVATTING

HOOFDSTUK 1

Ieder jaar worden in Nederland ongeveer 2 500 nieuwe gevallen van rectumcarcinoom gediagnosticeerd. Vijfenzeventig procent van de rectumcarcinomen is resectabel en wordt verwijderd met behulp van totale mesorectale excisie (TME). Deze operatie is een *en bloc* resectie van de primaire tumor met het mesorectum door middel van scherpe dissectie in het circumferentiele, avasculaire vlak tussen de viscerale en parietale fascie van het rectum, waarbij de autonome pelviene zenuwen gespaard kunnen worden. De Nederlandse TME-studie heeft uitgewezen dat preoperatieve radiotherapie (PRT) vast onderdeel van de behandeling van het rectumcarcinoom dient te zijn omdat het resulteert in een significant verbeterde lokale controle. De meerderheid van de patiënten met rectumcarcinoom wordt behandeld met een lage anterieure resectie (LAR), waarbij de sfincter wordt gespaard. Naadlekkage is een veelvoorkomende (5-26 procent) en ernstige complicatie van LAR. Bovendien kan faecale incontinentie ontstaan, wat een aanzienlijke impact kan hebben op de kwaliteit van leven. In dit opzicht ontbreekt consensus met betrekking tot het voordeel van behoud van de sfincter *versus* een definitief colostoma zoals bij een abdominoperineale resectie (APR) wordt aangelegd. Het aantal grote prospectieve studies betreffende lange termijn-functionele morbiditeit na behandeling van het rectumcarcinoom is beperkt. Anorectale en urogenitale disfuncties zijn veelvoorkomende problemen, maar de etiologie is vooralsnog onbekend. Chirurgische zenuwschade en schade door bestraling zouden een rol kunnen spelen. Dit proefschrift richt zich op de lange termijn-resultaten van behandeling van het rectumcarcinoom en in het bijzonder op de etiologie van lange termijn-morbiditeit.

HOOFDSTUK 2

Dit hoofdstuk bevat een historisch overzicht waarin de invloed van Miles op de ontwikkelingen in de behandeling van het rectumcarcinoom wordt beschreven. Honderd jaar geleden introduceerde Miles het concept van lymfogene metastasering en zijn daarop toegesneden operatie met *en bloc* resectie van het rectumcarcinoom en de primaire lymfeklierstations. Deze radicale APR werd vervolgens wereldwijd ingevoerd als gouden standaard voor een groot deel van de 20e eeuw. Maar de bevinding dat een distale marge van slechts twee centimeter adequaat was en de ontwikkeling van automatische circulaire staplers luidden de historische verschuiving van

APR naar sfinctersparende chirurgie in. Na de introductie van TME, waarbij het recidiefpercentage tot ongeveer vijf procent daalde, werd APR veel minder frequent (15 procent) uitgevoerd. Verdere verbeteringen betroffen onder andere de ontwikkeling van zenuwsparende technieken. Uit dit historische overzicht kan geconcludeerd worden dat er in de afgelopen eeuw op het gebied van de behandeling van het rectumcarcinoom een enorme vooruitgang geboekt is. Dit is vooral te danken aan verbeterde chirurgie op basis van toegenomen pathologische en biologische kennis, geïnitieerd door Miles.

HOOFDSTUK 3

Sinds Miles en Moynihan respectievelijk low tie- (ligatie ter hoogte van de a. rectalis superior) en high tie-techniek (ligatie ter hoogte van de a. mesenterica inferior) voorstelden, ontbreekt consensus met betrekking tot het niveau van de vasculaire ligatie bij rectumresectie. Bij de keuze tussen beide ligatietechnieken spelen oncologische, anatomische en technische aspecten een rol. Dit hoofdstuk is een systematische review van de literatuur betreffende eventuele voordelen van beide technieken met betrekking tot deze aspecten. Hoewel van beide ligatietechnieken het oncologische, anatomische of technische voordeel nooit voldoende is aangetoond, verdient de low tie-techniek de voorkeur omdat deze minder invasief is met betrekking tot de bloedvoorziening en innervatie van de aanvoerende colonlis.

HOOFDSTUK 4

Dit hoofdstuk rapporteert de resultaten van een studie naar seksuele disfunctie op de lange termijn na behandeling van rectumcarcinoom. Gegevens van patiënten uit de Nederlandse TME-studie, waarbij werd gerandomiseerd voor TME met of zonder PRT werden geanalyseerd. Preoperatief en tot twee jaar postoperatief werden vragenlijsten ingevuld met onder andere vragen over seksuele activiteit, algemeen seksueel functioneren, erectiele disfunctie (♂), ejaculatiestoornissen (♂), dyspareunie (♀) en lubricatiestoornissen (♀). Voor behandeling van het rectumcarcinoom waren de meeste patiënten seksueel actief (526 van de 757 patiënten). Van de patiënten die voor TME seksueel actief waren, rapporteerde de meerderheid verslechtering van het seksueel functioneren sinds de behandeling van het rectumcarcinoom. Bij mannen was dit gerelateerd aan autonome zenuwschade, excessief peroperatief bloedverlies, naadlekkage, PRT en de aanwezigheid van een tijdelijk of definitief

stoma. De aanwezigheid van een stoma en PRT waren risicofactoren bij vrouwelijke patiënten. Uit deze resultaten blijkt dat seksuele dysfunctie na behandeling van het rectumcarcinoom een veelvoorkomend probleem is en voornamelijk te wijten is aan chirurgische (zenuw-) schade, met een additioneel effect van PRT.

HOOFDSTUK 5

Ook mictieproblemen kunnen ontstaan na behandeling van het rectumcarcinoom. Om mictieproblemen tot vijf jaar na TME te evalueren en etiologische factoren te identificeren werden gegevens van 785 patiënten uit de Nederlandse TME-studie geanalyseerd. Vijf jaar na TME gaf 38.1 procent van de patiënten aan incontinent te zijn voor urine, waarvan 72.0 procent preoperatief geen incontinentieklachten had. Preoperatieve incontinentie en vrouwelijk geslacht waren onafhankelijke risicofactoren (respectievelijk $p=0.001$, RR=2.75 en $p<0.001$, RR=2.77). Bemoeilijkte blaaslediging werd gerapporteerd door 30.5 procent van de patiënten, van wie 65.0 procent een normale preoperatieve functie had. Preoperatieve bemoeilijkte blaaslediging ($p<0.001$, RR=2.94), excessief peroperatief bloedverlies ($p=0.028$, RR=1.73) en autonome zenuwschade ($p=0.024$, RR=2.82) waren onafhankelijk risicofactoren. Mictieproblemen waren niet gerelateerd aan PRT. Hieruit kan geconcludeerd worden dat mictieproblematiek een significant klinisch probleem is na behandeling van het rectumcarcinoom en niet gerelateerd is aan PRT maar aan chirurgische zenuwschade.

HOOFDSTUK 6

Na LAR is een groot deel van de patiënten incontinent voor faeces. Dit hoofdstuk rapporteert de resultaten van een studie waarbij risicofactoren voor faecale incontinentie werden geïdentificeerd in de Nederlandse TME-studie. Vijf jaar na TME gaf 39 procent van de onbestraalde en 62 procent van de bestraalde patiënten aan faecaal incontinent te zijn. Faecale incontinentie was zowel kwalitatief als kwantitatief gerelateerd aan PRT. Alleen in bestraalde patiënten waren excessief peroperatief bloedverlies, tumor- en naadhoogte significante risicofactoren voor faecale incontinentie. Veertien van de 15 patiënten van wie het perineum in het bestralingsveld had gelegen werden incontinent voor faeces. Patiënten met een distale tumor zouden daarom preoperatief geïnformeerd moeten worden over het risico op het ontwikkelen van faecale incontinentie na PRT. Als bestraling van het perineum onvermijdelijk is, verdient APR de voorkeur.

HOOFDSTUK 7

In dit hoofdstuk wordt aan de hand van een casus het probleem van gecombineerde faecale en urine incontinentie op de lange termijn na behandeling van het rectumcarcinoom besproken. Op basis van de literatuur wordt op verschillende aspecten ingegaan, waaronder incidentie, etiologie, verloop, preventie en behandeling van incontinentie.

De belangrijkste leerpunten van dit hoofdstuk:

- Incontinentie problemen na behandeling van het rectumcarcinoom komen veel voor en kunnen een grote impact hebben op de kwaliteit van leven.
- Patiënten zouden preoperatief geïnformeerd moeten worden over de chirurgische opties, LAR en APR, en over de mogelijke uitkomsten.
- Chirurgische zenuwschade speelt mogelijk een grote rol bij het ontstaan van faecale en urine incontinentie, met een additioneel effect van PRT.
- Faecale incontinentie kan gedurende vijf jaar na TME verergeren in geval van PRT.
- Verschillende niet-chirurgische en chirurgische behandelingen van incontinentie zijn beschikbaar; in de eerste lijn zijn conservatieve therapieën het meest geschikt

HOOFDSTUK 8

Dit hoofdstuk evalueert aan de hand van een anatomische en klinische studie de mogelijke rol van chirurgische beschadiging van de n. levator ani bij het ontstaan van faecale en urine incontinentie na TME. Uit gesimuleerde TME-operaties op bekkenpreparaten bleek dat deze zenuw beschadigd kan worden, vooral bij het aanleggen van een lage naad. Bovendien bleek de origo van de n. levator ani ter hoogte van S3-4 samen met de origo van de nn. splanchnici pelvici te verlopen. Analyse van de TME database toonde aan dat faecale en urine-incontinentie in respectievelijk 33.7 procent en 38.8 procent van patiënten zonder preoperatieve klachten ontstond. Beide vormen van incontinentie waren significant aan elkaar gerelateerd ($p=0.027$). Een lage naad was een significante risicofactor voor urine incontinentie ($p=0.049$). Een derde van de patiënten met het incontinentiesyndroom rapporteerde tevens bemoeilijkte blaaslediging, waarvoor excessief peroperatief bloedverlies een significante risicofactor was. Geconcludeerd kan worden dat vooral in patiënten met een laag rectumcarcinoom het risico op beschadiging van de n. levator ani aanzienlijk is, hetgeen zou kunnen bijdragen aan een verhoogd risico op faecale en urine

incontinentie na TME. Ook gecombineerde schade van de n. levator ani en de nn. splanchnici pelvici lijkt reëel.

Samen met hoofdstuk 4,5 en 6 geven deze resultaten aan dat patiënten preoperatief geïnformeerd moeten worden over functionele morbiditeit en dat chirurgisch onderwijs in de neuroanatomie van het kleine bekken en in de cruciale anatomische snijvlakken de functionele uitkomsten zouden kunnen verbeteren.

HOOFDSTUK 9

Verschillende studies hebben aangetoond dat perioperatieve bloedtransfusie een belangrijke risicofactor is met betrekking tot recidief en overleving bij oncologische patiënten. Allogene leukocyten in getransfundeerde erytrocytenconcentraten (RBC) worden hiervoor verantwoordelijk gehouden. Dit hoofdstuk beschrijft de resultaten van een gerandomiseerde studie naar de lange termijn-effecten van RBC-transfusie met of zonder leukocytenfiltratie op het optreden van recidief en op de overleving bij patiënten met een gastro-intestinale maligniteit (n=512). Daarnaast is een gecombineerde analyse uitgevoerd met een vergelijkbare gerandomiseerde studie, waarin uitsluitend patiënten met een resectabele primaire colorectale maligniteit waren geïncludeerd (n=975). De vijfjaars-overleving van patiënten met een gastro-intestinaal carcinoom was 50.8 procent in de gefiltreerde groep en 45.8 procent in de ongefiltreerde groep, met een recidiefpercentage van 32.9 procent in de gefiltreerde en 34.3 procent in de ongefiltreerde groep (respectievelijk p=0.19 en p=0.86). Ook in de gecombineerde analyse werd geen verschil gevonden in vijfjaars-overleving (64.9 procent in beide groepen) en recidiefpercentage (32.2 procent *versus* 33.1 procent) tussen beide transfusiearmen. Geconcludeerd kan worden dat leukocytenfiltratie niet resulteert in een betere lange termijn-overleving en lagere recidiefkans in patiënten met een gastro-intestinale maligniteit.

HOOFDSTUK 10

De behandeling voor rectumcarcinoom is sterk verbeterd in de afgelopen 100 jaar. Dit is vooral te danken aan vooruitgang van de chirurgische techniek. Ook de toevoeging van radiotherapie heeft de lokale controle positief beïnvloed. De behandeling voor rectumcarcinoom is ontwikkeld tot een multidisciplinaire behandeling met gestandaardiseerde chirurgische, pathologische en radiotherapeutische procedures.

Ook nu nog is de behandeling voor rectumcarcinoom nadrukkelijk in beweging. Ten eerste zal chemotherapie steeds belangrijker worden. Aan de ene kant zou

chemotherapie micrometastases in een vroeg stadium kunnen behandelen en daarmee meer patiënten genezen en de overleving verlengen. Dit wordt momenteel onderzocht in de SCRIPT (Simply Capecitabine in Rectal Cancer after Irradiation Plus TME) –studie. Aan de andere kant, wordt chemotherapie toegevoegd aan radiotherapie om het effect te versterken. Het steriliserende effect van chemoradiotherapie heeft geleid tot de ontwikkeling van rectumsparende behandelingen. Locale excisie van vroeg-stadium tumoren met transanale endoscopische microchirurgie en neoadjuvante chemoradiatie zónder chirurgische resectie in geval van complete klinische remissie heeft geleid tot veelbelovende resultaten. Deze behandelingen zijn vooralsnog erg omstreden en de veiligheid en functionele uitkomsten zullen bevestigd moeten worden aan de hand van prospectief verkregen multicenter lange-termijn gegevens.

Het uiteindelijke doel van klinisch onderzoek naar de behandeling van het rectumcarcinoom is het ontwikkelen van een spectrum van multidisciplinaire behandelingsstrategieën voor een “therapie op maat”. Beeldvormingstechnieken worden verbeterd en biomarkers worden geïdentificeerd om prognose en respons op behandeling te kunnen voorspellen.

Maar vooral op het gebied van chirurgie zijn verbeteringen te verwachten. Het risico op naadlekkage, positieve resectiemarges en de chirurgische variabiliteit moeten verminderd worden. Op dit moment organiseert de European CanCer Organisation (ECCO) een multidisciplinair “quality assurance programme” waardoor het mogelijk wordt de structuur en processen in de zorg vast te stellen, best practices te bepalen en te implementeren en vervolgens verbetering van behandeling voor rectumcarcinoom te bevestigen. Verder zal, gezien het groeiende aantal behandelingsstrategieën, het steeds belangrijker worden de impact van de behandelingen op de kwaliteit van leven te bepalen. Registratie van specifieke functionele stoornissen voor en na behandeling van het rectumcarcinoom is noodzakelijk. In dit opzicht is de Nederlandse TME-studie uniek geweest. Middels dit proefschrift heeft het inzicht gebracht in de incidentie en etiologie van lange-termijn anorectale en urogenitale stoornissen na behandeling van het rectumcarcinoom. Functionele problemen blijken vaak voor te komen en voornamelijk veroorzaakt te worden door chirurgische (zenuw-)schade. Onze resultaten hebben laten zien dat de n. levator ani, een zenuw die tot nu toe weinig aandacht heeft gekregen, mogelijk een rol speelt. Systematische registratie van de identificatie van cruciale structuren (plexus hypogastricus superior en inferior, nn. hypogastrici en pelvici splanchnici, n. levator ani) zou deel uit moeten maken van het operatieplan. Verder zou gestructureerde educatie en training in de neuroanatomie van het bekken als een vereiste voor certificering als rectumchirurg de sleutel zijn voor een verbetering van de functionele resultaten.

CURRICULUM VITAE

The author of this thesis was born on December 18th, 1983 in Uccle, Belgium. She grew up in Rotterdam and graduated from Johannes Calvijn Gymnasium *cum laude* in 2002. In the same year she started medical school at the University of Leiden. As a student she conducted research at the Department of Surgery of the Leiden University Medical Centre (Prof. dr. C.J.H. van de Velde) in 2006. This research project brought a lot of inspiration and she continued working on "long-term outcome of rectal cancer treatment" until December, 2008. The results of this research are presented in the current thesis. Currently, Marilyne is continuing her medical training at the University of Amsterdam.

NAWOORD

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