Long-term outcome of rectal cancer treatment

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CHAPTER 2

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

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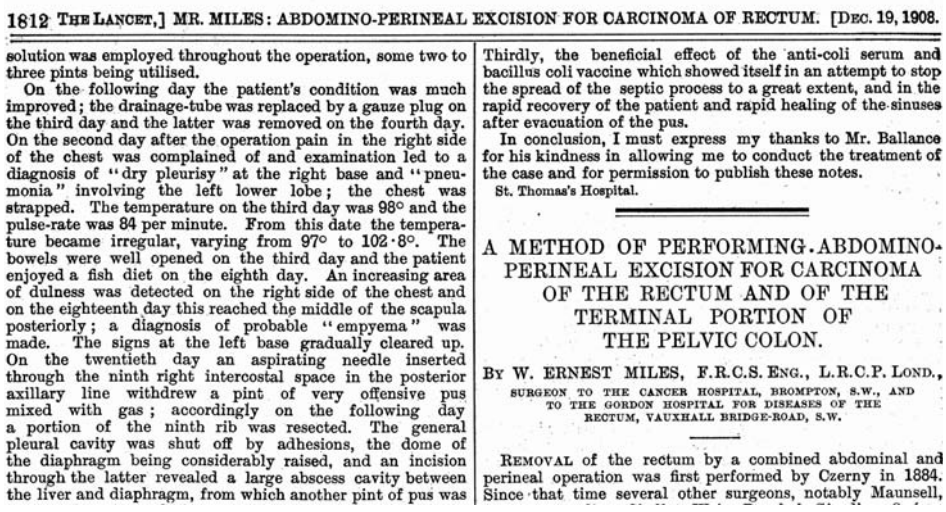
ABSTRACT

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.

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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

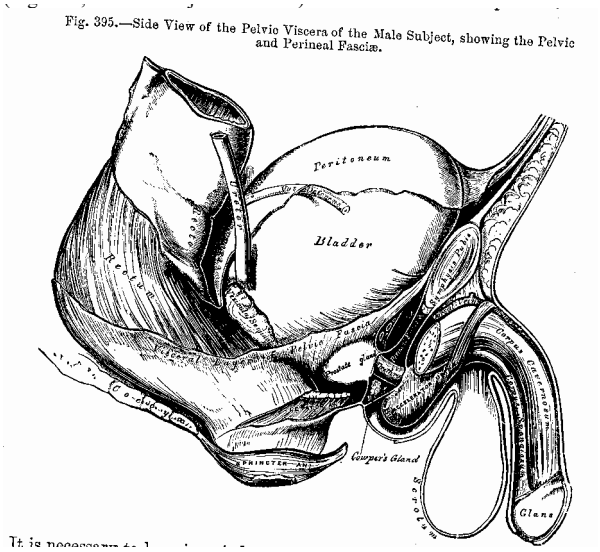

Figure 2. Illustration in Gray's Anatomy 1860, showing the extensive knowledge concerning pelvic fasciae in the 19th century.

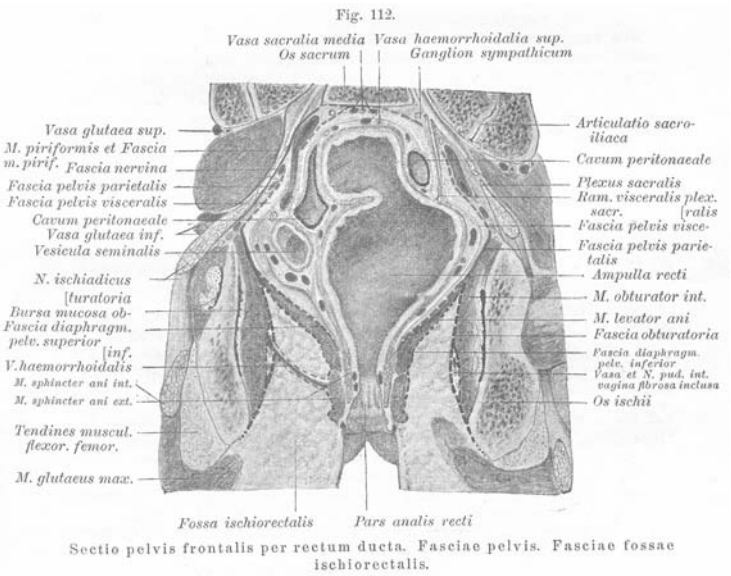

Figure 3. Anatomical illustration in Waldeyer's anatomical atlas (Das Becken 1899).

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

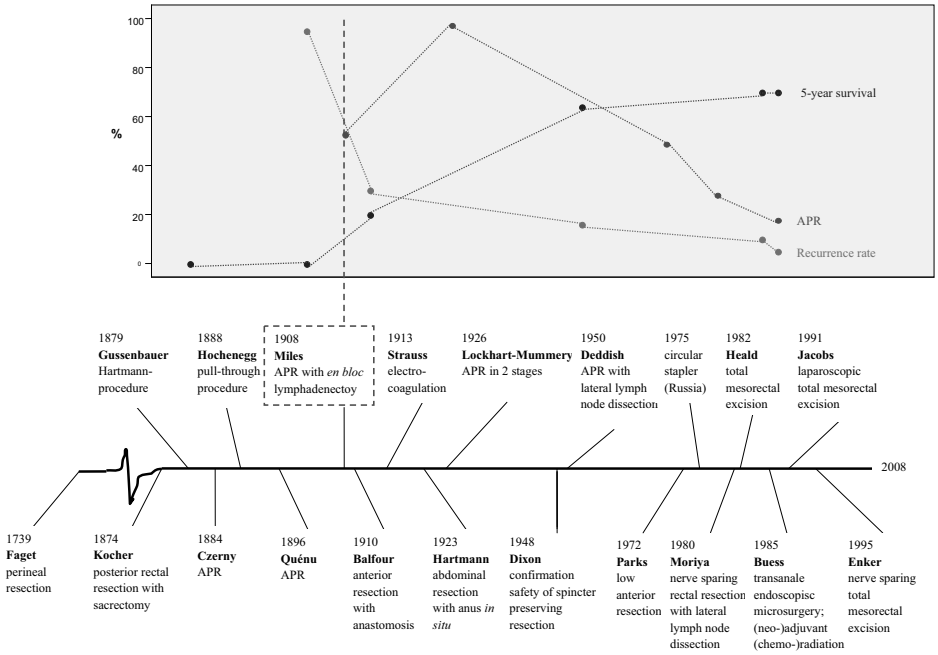

Figure 4. Timeline of important developments with respect to rectal cancer treatment also illustrating associated 5-year survival, recurrence rate and percentage of abdominoperineal resections (APR=abdominoperineal resection).

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

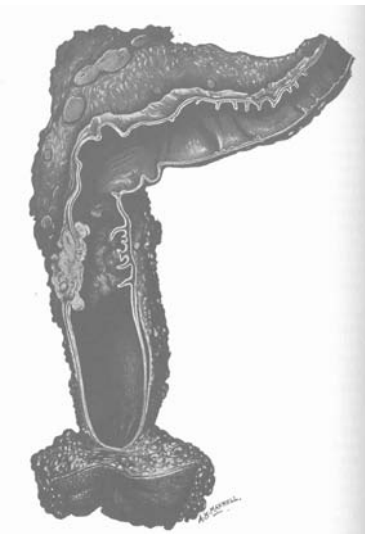

Figure 6. Specimen after Miles' abdominoperineal resection

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]

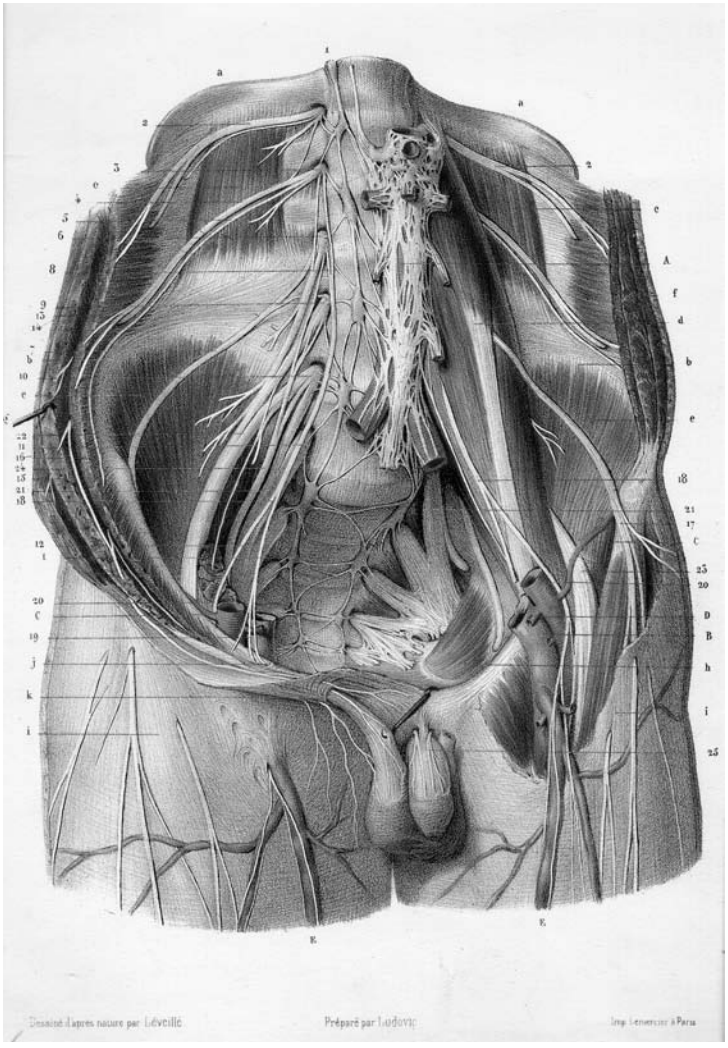

Figure 8. Anatomical illustration of the pelvic nerves (Neurologie. Hirschfeld, Ludovic en Leveille 1853)

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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