Walter E. Longo
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Editors

Modern Management of Cancer of the Rectum

Second Edition

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To Janice, Ashleigh, William
Mary Frances and Matthew
And
Frank, Mary Lou
Frankie, Peter and Christine

– Walter E. Longo

To my wonderful children
Maya and Alok
Of whom I am the proudest

– Vikram B. Reddy

To Monica for her immense patience

– Riccardo A. Audisio

Foreword

Since the last edition of *Modern Management of Cancer of the Rectum,* there has been great progress in all matters to do with rectal cancer. Much has come from formal systematic prospective clinical research based on evermore refined preoperative staging and changes in management strategies, including developments in chemoradiotherapy and surgery. Genetic analysis has demonstrated that large-bowel cancer is at least three diseases. The blank genetic picture of 30 years ago is gradually being filled in by an extraordinary amount of new information. Preoperative staging has achieved a high degree of accuracy, which can predict the histopathological examination of the excised specimen in most cases. This has changed the management strategy regarding the integration of chemoradiotherapy with surgery, whether major or local. Treatment has been opened up dramatically through chemoradiotherapy as primary treatment, by which patients experiencing a complete response are followed without surgery or undergo local excision at the site of the primary tumour. This approach still needs validation, and there are now several prospective studies examining this question.

There is much focus in the book on the identification of risk factors which determine the cancer-specific outcome of patients with rectal cancer. These include preoperative staging of lymph nodes before and after chemoradiotherapy, which is still one of the most important factors influencing multidisciplinary management. The book deals with all forms of treatment, from that aimed with curative intent to the management of palliative disease. All types of treatment of colorectal cancer are considered, including any form of chemoradiotherapy and the newly applied brachytherapy. The numerous operations for rectal cancer are also dealt with in detail, with equivalence given to local and radical procedures. The growing interest in the treatment of pelvic recurrence and metastatic disease receives considerable attention. There are chapters on follow-up, rare colorectal tumours, revisional surgery and quality of life after treatment. Further chapters include discussion of the technique focussing on restorative resection, lateral-node dissection and laparoscopic, compared with robotic, surgery.

Modern Management of Cancer of the Rectum deals with every aspect of rectal cancer. Its overall view is delivered by an internationally recognised panel of experts, all of whom are leaders in their field. The referencing is excellent, supplying a bibliography including classical publications leading on to an invaluable list of modern citations. The book is well laid out, with

excellent tables and illustrations. As a statement of the present position regarding all aspects of rectal cancer, it is an up-to-date account by experts.

London, UK

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Preface to the Second Edition

The premise of the second edition of *Modern Management of Cancer of the Rectum* is a revision and update of a gradually changing field, in which the surgeon, medical oncologist, and radiation oncologist cannot function without the others. In the 13 years since the last edition, several advances in medical oncology and surgical techniques have changed the management of rectal cancer, and every chapter of this edition reflects these changes, while adding new ones about the burden of disease, relevant anatomy, role of laparoscopy and robotics, anorectal reconstruction, and remedial surgery. We hope that this book will become an important reference material for the newest data regarding rectal cancer and its management. Expert authors from all around the world have dedicated their precious time to create outstanding chapters on all aspects of the management of rectal cancer.

We trust that this book will provide practicing surgeons, surgeons in training, oncologists, radiation oncologists, and all others who diagnose and treat this malignancy with up-to-date information that will ultimately allow for a better management of each of our patients.

In producing this book, we would like to acknowledge our mentors for their inspiration and teaching, our patients who made us want to persevere in our advancements, our students so that they may be better than us, and our families for their support and understanding. We would like to acknowledge our utmost appreciation and gratitude to our authors, to our publishers, and to Joni Fraser at Springer for making this book possible.

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The Evolving Treatment of Rectal Cancer

1

Jorge L. Reguero and Walter E. Longo

Abstract

Rectal cancer treatment has advanced in nearly 300 years from a hopeless, morbid outcome to potentially curative treatments with constant improvement in quality of life. This chapter briefly outlines and reviews the historical evolution of the treatment of adenocarcinoma of the rectum. The earliest procedures were mostly palliative with the first proposed resections for rectal cancer appearing in the eighteenth century. Extirpative procedures utilizing the perineal, vaginal and sacral approaches prevailed until Miles' abdominoperineal resection in 1908 revolutionized the principles for a correct oncological resection. In time, the focus of interest shifted towards less radical procedures centered on the restoration of intestinal continuity. Later on, sphincter preservation procedures and pouch surgery emerged in an attempt to achieve better functional outcomes. Heald's total mesorectal excision proposed in the 1980s represented another milestone in the treatment of rectal cancer by significantly reducing local recurrence rates. Over recent years, combined multimodality therapy and the development of laparoscopic surgery have brought major advancements to the field. In the twenty-first century, the limits of rectal cancer treatment continue to be pushed with surgery still representing the primary form of therapy for optimal oncologic and functional results.

Keywords

Rectal cancer • Transsacral • Kraske • Perineal approach • Lockhart-Mummery • Miles • Abdominoperineal • Heald

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Introduction

The treatment of cancer of the rectum is historically among one of the most debated for years. This has been due to constant technical challenges, the development of novel therapies such as

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neoadjuvant therapy, emerging technologies and the concern with quality of life. Many of the surgical advances in surgery have come in conjunction with sentinel milestones in medicine itself such as antisepsis, anesthesia, blood banking, critical care, microscopy, diagnostic imaging, emerging surgical technology, pharmacology, energy delivery and genetics. Regardless, the evolution of rectal cancer treatment has gone from a hopeless, morbid outcome to potentially curative treatments that are very well tolerated, with shorter hospital stays and a favorable quality of life.

The principal form of treatment for rectal cancer early on, as well as today, has been attempted surgical removal of the tumor. Many of the early treatments were unrecorded and it is difficult to give credit to every individual who contributed to the management of this disease. Other treatments evolved simultaneously so an exact chronologic review would be misleading. Once considered an incurable disease, initial attempts at treatment were often palliative, and mortality resulting from the treatment was often close to 100 %, with extremely consequential morbidity.

This chapter will briefly outline and review the historical evolution of the treatment of adenocarcinoma of the rectum. Details of procedures and outcomes of many historical landmarks such as the abdominoperineal resection, restorative procedures, local therapy, minimally invasive, robotic procedures and adjuvant therapy, among others, are found in the subsequent specific chapters contained within this textbook and from the original articles quoted.

Origins of Rectal Cancer Treatment

John of Arderne is credited with first recognizing the signs and symptoms of rectal cancer in 1376 [1]. Although there appeared to be some rudimentary understanding of its natural history, no form of excisional surgery was performed for nearly another 400 years.

The earliest procedures were mostly palliative. Giovanni Morgani first proposed resection of the rectum in the eighteenth century [2]. Treating rectal cancers by some form of extirpative procedure had not been considered until then. In 1739, Jean Faget of France made history by first attempting a rectal resection [3]. He believed to be draining an ischio-rectal abscess but instead a perforated rectal cancer was encountered. Faget resected the rectum, leaving the patient with a sacral anus and a disastrous functional outcome.

The use of colostomy as a diverting procedure has been reported since ancient times and it played an early role in the management of rectal cancer. In 1776, Henry Pillmore of Rouen, France, performed the first colostomy in an adult for an obstructing "annular scirrhous" carcinoma though the patient eventually did not survive [4]. Colostomy achieved an important role when a French surgeon by the name of Amussat urged that it be the routine procedure for obstructing rectal cancer [5].

Early Extirpative Procedures: Perineal, Sacral and Vaginal Approaches

Jacques Lisfranc is credited for performing the first successful excision of a rectal tumor in 1826 [1]. Within 7 years, he performed nine additional perineal or posterior resections, of which five were considered successful [2]. These were performed without anesthesia or hemostasis. The patients were asked to bear down, the rectum was everted and a limited rectal amputation then performed. This would result in an incontinent perineal anus. Most patients would not leave the hospital and succumbed to hemorrhage and sepsis. The pain was unbearable, local recurrence was common and functional outcome dismal.

Anesthesia and antisepsis advances spurred a significant development of new techniques in the following decades. In 1873, Aristide Verneuil modified Lisfranc's perineal resection and removed the coccyx to allow for better exposure and a more radical excision [6]. The conventional perineal approach had resulted in poor exposure of the upper rectum up to that point. In 1876, Theodore Kocher pioneered the transsacral

resection with coccygectomy to excise the rectum and anastomose the colon to the anus [3, 7]. Around the same time, Paul Kraske had developed his own technique to remove the rectum, which he presented in 1885 at the Congress of the German Society of Surgery [1, 2]. He removed the coccyx and part of the left wing of the sacrum and preserved the anus and sphincters to allow for a potential anastomosis. Restoring intestinal continuity via the sacral approach was often problematic due to tension on the upper segment and inadequate blood supply. In general, the perineal and sacral approaches provided limited exposure, precluding radical resection of the tumors.

Others experimented with transvaginal resection of rectal tumors. These techniques are, at present, of historical value. Norton reported in 1889 the excision of a tumor of the anterior rectal wall not involving the vagina. The sphincter muscles were resected along with the rectum. In 1890, MacArthur was unable to mobilize the bowel enough to bring it to the skin while operating on a patient with recurrent rectal cancer. He, therefore, sutured it to the upper vagina. Byford reported in 1896 a singular method in which the vagina was used to replace the excised portion of the rectum. The proximal and distal portions were sutured to different portions of the vagina and the vaginal opening was closed [8].

Nearly 100 years after Lisfranc initial perineal resection, Lockhart-Mummery from St Mark's Hospital in London revised the technique so it would allow for a relatively safer operation [9]. He would first perform a permanent loop colostomy and determine if the tumor was resectable. A week to 10 days later the perineal stage would take place. Removal of the coccyx with the patient in semi-prone position would allow for rectal and anal mobilization; the peritoneum was then opened and as much bowel as possible was pulled down and resected. In 1926, he reported a series of 200 patients in which an 8.5 % mortality was noted, much lower than that of the abdominoperineal resection at the time. A 50 %, 5-year survival without recurrence was observed, though it is said that he rejected about 50 % of his cases that were deemed unresectable [8, 9]. This posterior excision, as it was called, remained popular until the 1940s. The main drawback was that it left the superior lymphatics unresected; therefore, it was not an adequate cancer operation nor was it applicable for upper rectal tumors.

A small variant of the sacral resection, the York-Mason modification of the Kraske procedure, has been used to resect small distal rectal tumors through a presacral approach [10]. This technique of dividing and subsequently restoring the anal sphincter is rarely used anymore and has been replaced by either transanal procedures or ultralow resections with coloanal anastomosis.

Emergence of the Abdominoperineal Resection

Early attempts at abdominal resection of tumors were experimental and performed with little attention to oncological principles. Carl Gussen bauer, an assistant to Billroth, performed the first abdominal resection of a rectal tumor with intraperitoneal closure of the distal rectum [11]. The first reported case combining abdominal and perineal approaches was performed by Vincenz Czerny in Germany [9]. In 1884, he was unable to remove a rectal cancer using a posterior perineal approach alone and decided to complete the extirpation through the abdomen by turning his patient supine. In 1904, Charles Mayo [8] first presented his technique of abdominoperineal resection (APR) at a meeting in Portland, Oregon, stressing the importance of resecting the lymphatics above the rectum, as high as the sacral promontory. The sigmoid colon was divided at that level and the inferior mesenteric artery transected as high as possible.

The problem of local recurrence was evident among surgeons at the time, including Sir William Ernest Miles. He had been a pupil of Harrison Cripps, who was well known for his work on rectal cancer and the introduction of the perineal approach in England [2, 7]. Miles had witnessed local recurrences within the pelvis in 54 of 57 of his patients excised by this mean [12]. He analyzed postmortem dissections and realized a more radical excision was needed, based on a

better and new understanding of the perirectal lymphatic spread.

In 1908, Miles described a modification of Czerny's operation and emphasized the downward, upward, and lateral spreads of the cancer, with the upward being the most important in his opinion [13, 14]. He considered even the most talented surgeons were unable to completely excise the mesorectal lymph nodes proximal to the tumor via the perineal approach. His operation started by creating a loop colostomy and dividing the bowel 2 in. below it. The distal bowel was mobilized until it could be pushed down into the pelvis and the peritoneum could be closed over it. The patient was then positioned in the right semi-prone position, the coccyx resected and the excision completed from the perineal approach. The procedure was based on five principles including resection of the rectosigmoid and its blood supply, resection of the mesorectum, removal of lymph nodes over the bifurcation of the common iliac artery, wide perineal resection including removal of the levator ani muscle and creation of an abdominal colostomy. Although his original series of 12 patients found 42 % mortality [14], seven survivors were tumor free in 1 year. In subsequent years, he was able to further reduce the mortality associated with the procedure as well as the overall recurrence rate, making the APR the standard of care for rectal tumors. Miles not only revolutionized the principles for a correct oncological resection of rectal cancers, but his approach was a landmark operation in the history of large bowel surgery.

The English pathologist Cuthbert Dukes published in 1930 that there was no significant difference between perineal and abdominoperineal operations for Stages A and B rectal cancer (negative lymph nodes, invasion into or through the bowel wall respectively); but the Miles operation was superior for Stage C (lymph node positives), because the perineal approach would leave the superior lymphatics unresected. This finding validated Miles pathologic premises [12, 15].

Several modifications of the abdominoperineal procedure popularized by Miles emerged in the following years. In 1915, Daniel Fiske Jones proposed a two-stage procedure consisting of an initial abdominal portion followed by a perineal stage 5–7 days later under spinal anesthesia [1]. Jones considered this would decrease sepsis and he reported a mortality of 18 % in 16 patients. Gabriel, a disciple of Lockhart-Mummery, proposed in 1934 a further modification of the APR designated as a perineoabdominal excision [16]. He performed a one-stage procedure starting with a perineal excision, then turning the patient supine and mobilizing the colon through an abdominal incision. Gabriel demonstrated a significant improvement in 5-year survival figures, 30 % vs 17.9 %, for those patients found to have positive lymph nodes via a perineoabdominal excision versus the perineal approach favored by his mentor.

As others emphasized the safety of a two-stage procedure, it was not until 1938 that the one-stage procedure originally described by Miles became commonplace. There was not longer the need to reposition the patient after Sir Hugh Devine introduced the adjustable leg rests in 1937, so the operation could be performed in the lithotomy-Trendelenburg position [2]. Oswald Lloyd Davies was the first to perform a synchronous combined radical abdominoperineal resection in the lithotomy-Trendelenburg position with two teams working simultaneously [1, 2]. The speed and efficiency of the procedure vastly improved with the two-team approach. By the 1960s, the Lloyd Davies technique was the most commonly performed excisional procedure for rectal cancer with a marked reduction in mortality.

Advent of Restorative Procedures

With Miles' operation and principles of resection well established, the focus of interest shifted towards new procedures centered on the restoration of intestinal continuity. The abdominoperineal resection was not only considered too radical by some surgeons but it submitted patients to a permanent colostomy and frequent genitourinary dysfunction.

Some of these techniques had originated in the late nineteenth century. The first documented

attempt at restoration of intestinal continuity for rectal cancer is attributed to Reybard of Lyon when he performed a partial sigmoid resection for a colonic growth with immediate anastomosis of the ends [17]. In 1888, the "Durchzug" procedure (pull-through technique) was described by Hochenegg, in which the anorectal stump was everted, stripped of its mucosa and returned to its natural position followed by the distal colon drawn through the denuded rectum and sutured to the anal verge [7]. Despite achieving bowel continuity, this technique was not widely accepted due to the high mortality resulting from anastomotic leaks.

In 1892, Widenham Maunsell of New Zealand described a method for anastomosing the sigmoid colon to the anus [1, 17]. After dividing the anal sphincters in the posterior midline, the rectosigmoid was mobilized through the abdomen and invaginated out through the expanded anus. The tumor was resected and the two ends of the bowel anastomosed. Robert Weir, from Columbia University, New York, later modified this technique in 1901 [8]. Weir mobilized the rectosigmoid through the abdomen in similar fashion; but in contrast to Maunsell, he transected it 3 in. from the anus and pulled out the lower rectum from the perineum using an assistant. The upper bowel was dragged down through the lumen of the exteriorized everted rectum and anastomosed to it.

Babcock and Bacon offered a new procedure in 1939 and 1945 respectively, the delayed union and amputation technique, that basically involved removing the lining of the anal canal and bringing down the mobilized colon through it, leaving about 50 cm outside the body [9]. The previously divided anal sphincters were then sutured to the protruding colon and the excess intestine was removed after 2–3 weeks. With the temporary perineal colostomy, a proximal diversion was unnecessary. Bacon reported lower incidence of male impotence and fecal incontinence than with the APR, and yet similar cancer specific survival rates [9, 15]. In 1961, Turnbull and Cuthbertson from the Cleveland Clinic described their technique, a two-stage abdominoanal pull-through procedure [15, 17]. The rectum was resected, the colon pulled out through the everted rectal stump and the rectum sutured to the seromuscular layer of the protruding colon. Ten days later, and to the patient's relief, the bowel was finally excised above the dentate line and the end-to-end anastomoses performed.

During the second half of the twentieth century, restoration of intestinal continuity by means of primary anastomosis evolved through the abdominosacral resection championed by Localio [18]. He placed the patient in the right lateral position with the hips flexed, thus avoiding the need for repositioning between the abdominal and sacral portions of the procedure. The abdominal incision was made above the left inguinal ligament, the resection was completed from the sacral approach and a primary anastomosis performed with a 4–5 cm distal stump [8, 18].

Sphincter Preservation and Pouch Surgery

Many surgeons were in disagreement with Miles' oncologic principle regarding downward lymphatic spread as an important pathway for rectal cancer propagation. By preserving the sphincters a radical downward resection could be avoided and therefore better functional outcomes would be achieved.

In 1910, the American surgeon Donald Balfour described a technique of anterior resection through an abdominal approach with the construction of an end-to-end anastomosis between the rectum and the sigmoid colon [2, 8]. In this setting he utilized a "tube support" for the anastomosis after accidentally injuring the sigmoid colon during a procedure. He later suggested his operation could have a role in cancer resections. This technique never gained widespread acceptance due to the high mortality rate related to anastomotic leaks.

The French surgeon Henri Hartmann offered an alternative operation for the treatment of cancer of the middle to upper rectum. In 1921 he described an anterior resection without end anastomosis for high rectal lesions [3]. After resecting the involved segment and its mesentery, the rectum was inverted and left in place.

This procedure succeeded in removing the tumor with establishment of a colostomy and avoided the perineal dissection. It was associated with less blood loss and lower mortality than the abdominoperineal resection. The main disadvantage was the necessity of a permanent colostomy. The Hartmann's resection is frequently applied today in the initial management of complicated sigmoid diverticulitis.

Experience with sphincter preservation multiplied after surgeons returned to practice from World War II. In 1948 Claude Dixon of the Mayo Clinic shifted the focus of rectal cancer surgery from the abdominoperineal resection to sphincter sparing procedures with the reintroduction of the anterior resection [7, 19]. The safety of his approach was confirmed when he reported the results of 400 patients with a mortality rate of 2.6 % and a 5-year survival of 64 %. His operation was designed either as a three-stage procedure when a colostomy was created before resection or as a two-stage procedure with a colostomy created at the time of resection and a hand-sewn anastomosis, using one row of sutures posteriorly and two rows anteriorly. Anterior resection came to be accepted as the standard of care for cancer of the upper and middle third of the rectum, although this approach was not applicable for cancers of the lower third (distal 5 cm). Experience with proximal rectal cancers led to the use of this technique on more distal tumors. The low anterior resection (LAR) was distinguished from high resections by an extraperitoneal rectal anastomosis and was initially associated with more complications.

One of the biggest developments in the evolution of sphincter-saving procedures was a better understanding of distal margins of tumor resection. In 1951, Goligher, Dukes and Bussey had established a safe oncological margin of 5 cm [2, 15]. Interestingly, only 2 % of tumors in 1,500 specimens reviewed spread more than 2 cm. This "safe margin" was quickly challenged in 1953 when Quer proposed a 2.5 cm distal margin after discovering spread greater than 1.5 cm in only one of 89 specimens [2]. Pollett and Nichols found further evidence for a safe distal margin of 2 cm [20]. They published in 1983 the analysis of 334 rectal cancer specimens with different distal margins of <2 cm, 2–5 cm and >5 cm, where they discovered no survival difference over 5 years. The knowledge that distal margins of 2 cm did not compromise survival or local control provided the rationale for further developments in surgical technique in the late 1970s. This permitted sphincter preservation for tumors of the distal rectum that did not invade the anal sphincter mechanism. In more recent years, Moore analyzed patients undergoing a restorative procedure with distal margins <1 cm or >1 cm and found no difference in oncologic outcome [21].

In 1972, Sir Alan Parks described an important modification of the pull-through technique that allowed for sphincter preservation even in low-lying tumors without compromising oncologic results [22]. The entire rectum was mobilized in a low anterior or abdominoperineal resection, and the colon was anastomosed to the anorectum through the dilated anal canal, avoiding the potentially damaging eversion required in previous pull-through procedures. In his series, all 76 patients underwent restoration of bowel continuity, ten patients developed pelvic sepsis but there were no deaths and only 50 % reported good functional outcomes [23].

The development of surgical staplers constituted another breakthrough for sphincter preservation surgery. In 1975, Fain first described his experience with the Soviet designed circular stapling apparatus for rectal cancer anastomosis [24]. Mark Ravitch, an American pediatric surgeon, capitalized on this finding and introduced circular stapling devices in the United States, facilitating technical success of low pelvic anastomosis [9]. In 1977, the circular stapler enabled the creation of low colorectal or coloanal anastomosis without increased leak rates when compared to hand-sewn anastomosis [15].

Furthermore, to avoid a colostomy in surgery for very low rectal cancer, intersphincteric resection (ISR) with coloanal anastomosis was developed in the 1980s. This procedure includes removing all or part of the internal sphincter and restoring bowel continuity for rectal cancers involving or located next to the anal canal [9]. Due to the catastrophic potential consequences of

anastomotic leak in these low anastomoses, especially in the setting of an irradiated field, a defunctioning stoma is performed in most cases. A recent systematic review of the technique revealed acceptable oncologic outcomes but often-imperfect functional results [25].

One of the main drawbacks to the low colorectal or coloanal anastomosis that were being performed with increasing frequency was the poor functional outcome, with fecal urgency, soiling and incontinence following the loss of the rectal reservoir. In 1986, Lazorthes and Parc proposed the creation of a colonic reservoir combined with the coloanal anastomosis to compensate for the loss of reservoir in the neorectum [26, 27]. The colonic J-pouch showed short and long term functional improvements over straight anastomosis and fewer anastomotic leaks. Fazio [28] championed the coloplasty as an alternative to colonic J-pouch reservoir in an effort to improve reservoir capacity and decrease morbidity, especially in the setting of inadequate colonic length, diverticular disease or when the colonic J-pouch would not fit into a narrow pelvis. Pouch surgery has continued to evolve to present times with standardization of technical aspects and refinements in construction to achieve better functional outcomes.

Total Mesorectal Excision and Autonomic Nerve Preservation

From the establishment of the anterior resection by Dixon in the 1940s to the 1970s, the blunt or manual presacral pelvic dissection for rectal cancer constituted the technique of choice. This type of dissection risked violation of the mesorectum along undefined planes, leaving residual cancer-containing mesorectum within the pelvis. Worldwide, 5-year survival rates of only 45–50 % for all curable stages were reported at the time and local recurrence rates of 30–40 % were expected [12].

Quirke revealed on his study that more than a quarter of specimens had positive lateral wall margins with 85 % developing local pelvic recurrence [29]. It was Quirke, in 1986, who brought forward the importance of lateral tumor spread of primary rectal cancer. He also identified the fact that inadequate circumferential resection margin led to the development of locally recurrent rectal cancer and was associated with poor survival. This brought to the forefront the importance of sharp dissection in the pelvis, replacing the conventional resection technique of blunt dissection.

Heald recognized that the midline hindgut (rectum) and its mesorectum were embryologically derived together [30]. In 1982, he introduced the concept of "total mesorectal excision" (TME) technique, which involved sharp en bloc resection of the tumor and mesorectal tissue to the level of the levator muscles. Later, Hida supported with his work the rationale for TME by demonstrating that the principal field of lymphatic spread is contained within the mesorectum [31]. He confirmed the fact that rectal cancer is a disease of the supralevator compartment and that Miles' cylindrical concept was wrong. The TME technique by sharp dissection in the avascular plane between the mesorectum and surrounding tissues reduced the risk of excessive blood loss, decreased local recurrences from 12 to 20 % to less than 4 % and allowed for ultralow resections with coloanal anastomosis [32]. Heald achieved disease-free survival rates of 80 and 78 % at 5 and 10 years respectively. The TME technique continued to be easily reproduced with similar survival rates; it has relegated the radical APR to very few patients, representing another milestone in the treatment of rectal cancer [15].

Now that cure rates had increased and disease free survival was on the rise, the focus of attention shifted towards improving quality of life for patients after treatment. Damage to the pelvic autonomic nerves was felt to be inevitable part of the radical surgery for rectal cancer. In Japan, Tsuchiya, Hojo and Moriya pioneered the concept of nerve identification and preservation [2, 7]. New resection techniques allowed preservation of the hypogastric nerves, inferior hypogastric plexus and pelvic splanchnic nerves and with that, preservation of the autonomic innervation of the urogenital organs. Postoperative sexual and urinary dysfunctions

were subsequently reduced from more than 50 % to 10–28 % [15]. In America, Warren Enker combined the nerve preserving principle with the TME technique resulting in intact urogenital function in 90 % of patients with intact oncologic results [7]. Moriya demonstrated on his Dutch series of 47 patients how nerve preservation did not compromise the radical nature of mesorectal excision [33].

Combined Multimodality Therapy

Since the early 1900s, radiation therapy (RT) has had a major role in the treatment of rectal cancer. In 1914, Symonds first reported the use of radium bromide in a patient with rectal cancer achieving complete regression of the tumor [7, 12]. For the next 60 years postoperative pelvic RT was used mainly as a mean to decrease the incidence of pelvic recurrence over surgery alone, but did not show any improvement in overall survival [15]. George Binkley, the first Chief of the Rectal Service at Memorial Sloan-Kettering Cancer Center, introduced multimodality RT in the 1920s. Originally intended for non-surgical candidates, significant tumor regression was observed in patients receiving radiation that went on to have resection, prompting Binkley to recognize the value of radiation as an adjuvant treatment [12]. It was precisely at Memorial Sloan-Kettering where Stearns, Deddish and Quan observed that resected, lymph node positive patients with preoperative RT, had a higher 5-year survival than patients without preoperative radiation concluding that preoperative radiation would be useful in patients with locally advanced rectal cancer. The past few years have confirmed that preoperative RT should be the standard in rectal cancer, based on several large trials. In 2001, the Dutch Colorectal Cancer Group showed significantly better local recurrence rates for RT plus TME versus TME alone, 2.4 and 8.2 % respectively [34]. Overall survivals at 2 years were not different. Preoperative RT has since been shown to downstage and reduce the bulk of the primary tumor, rendering sphincter saving procedures possible [15].

In 2004, Sauer, from the German Rectal Cancer Study Group, compared preoperative and postoperative chemoradiation therapy in locally advanced rectal cancer patients, showing improved local control with less toxicity in the preoperative group [35]. It is precisely the use of combined modality therapies (CMT) in recent years that has achieved the greatest reduction in local failure when compared to RT alone (50 %), and improvement in survival rates (10 %) [15]. Neoadjuvant chemoradiation treatment has improved sphincter conservation and in conjunction with TME offers a reduction in the incidence of local recurrence; but this occurs at the expense of long-term compromise of sexual and bowel function outcomes. Multimodality treatment of rectal cancer, with the combination of radiation therapy, chemotherapy, and surgery has become the preferred approach to locally advanced rectal cancer.

Other Forms of Therapy: Local Treatments and Transanal Excision

Transanal excision through an operating proctoscope or by dilating the anus and using retractors has been advocated by surgeons for the occasional small, exophytic, movable and well-differentiated lesion [17]. However, in the first half of the twentieth century, local treatment of rectal cancers was really a necessity spurred by the high mortality of the extirpative procedures in vogue.

Concerns about seeding viable tumor cells prompted electrocoagulation to be the preferred treatment. Strauss advocated electrocoagulation in 1935 for palliation in poor-risk patients with carcinoma of the rectum, and in those patients with extensive lesions, although his indications were gradually broadened to include almost all stages of carcinoma of the rectum [8]. His results appeared to have little impact until Madden and Kandalaft, and subsequently Crile and Turnbull

reported more favorable outcomes in 1967 and 1972 respectively [17].

Cryosurgery has been utilized by Gage and Fritsch for palliation of symptoms in patients with inoperable rectal cancers. Disadvantages of this technique include hemorrhage, discharge of necrotic tissue and malodorous secretions. Endocavitary radiation was championed by Papillon in 1973 as an alternative to surgery for potentially curable lesions [15]. It involved delivery of high radiation doses using a special device inserted through a large diameter proctoscope. Total dose was anywhere from 8,000 to 15,000 rads over a 4–10 week period at a dose of 1,000–2,000 rads per session. These were highly selected patients who met with a 70 % 5-year cure and 10–15 % local recurrence rate [17].

Local excision is an alternative, less invasive approach to early rectal cancer; but, from the oncologic standpoint, it results in closer resection margins and it does not allow for sampling of lymph nodes [36]. Adequate methods of local staging utilizing either intrarectal ultrasound or pelvic MRI have allowed a small group of patients with distal rectal tumors to be candidates for a transanal local excision. Emerging technology allowing improved exposure has made transanal approaches more feasible. Transanal endoscopic microsurgery (TEM) was first introduced in 1983, allowing for resection of adenomas and early rectal carcinomas not suitable for local or colonoscopic excision, and that would otherwise require major surgery [37]. It permitted full-thickness excision and closure of the rectal defect of lesions as proximal as the pelvic brim. There is still much controversy about the long-term results and indications.

The Emergence of Minimally Invasive Procedures

Over the past 20 years, the development of laparoscopic surgery brought a major advancement in the treatment of colorectal cancer. Laparoscopic surgery of the colon was first reported in 1991 [38]. At present, its benefit to patients with colon cancer has been well established by numerous randomized studies. The procedure results in earlier recovery of bowel function, reduced blood loss, less postoperative pain and decreased length of hospitalization when compared to open colectomy. Despite this success in colon cancer treatment, the use of laparoscopic resection requires careful consideration to oncologic principles and functional outcomes. Also, the consequences of conversion to an open procedure need to be considered. The United Kingdom Medical Research Council trial of conventional versus laparoscopic assisted surgery in colorectal cancer (CLASSIC) reported a conversion rate of 34 % in rectal cancer surgery with comparable complication rates and no difference in 3 year overall survival, disease free survival and recurrence rates [39].

With laparoscopic surgery for colon cancer recognized as oncologically equivalent to conventional open surgery, could the same be said of laparoscopic surgery for rectal cancer? One of the major concerns is whether or not a good total mesorectal excision can be achieved. With the information provided on laparoscopic rectal cancer surgery from various centers, a few large multicenter trials have been initiated. In the United States, the American College of Surgeons Oncology Group trial (ACOSOG-Z6051) is a phase III prospective randomized trial comparing laparoscopic assisted resection with open resection for rectal cancer. The trial began in August 2008 is currently nearing completion. A second major randomized trial, the COLOR II, is conducted in Europe [40]. Current evidence suggests that laparoscopic rectal cancer resection benefits patients with earlier return of bowel function, reduced blood loss and shorter hospital stay. There is little data to make any conclusions on the effect of laparoscopic resection for rectal cancer on genitourinary function. In general, laparoscopic rectal cancer resection is now considered safe and feasible but only experienced, trained surgeons should practice it. Robotic-assisted surgery for rectal cancer has demonstrated good short term and midterm outcomes; this technique

has been performed with acceptable morbidity and a low rate of positive circumferential resection margin with effective local control.

Surgery for Locally Recurrent Disease

Though the incidence of loco-regional recurrence after primary resection has been substantially reduced with optimized surgery and adjuvant therapy, local failure rates are still significant. It is common knowledge that the choice of surgical therapy for salvage of these patients depends on the initial procedure performed as well as the location of the tumor. If initially a restorative procedure was performed, an APR is often required; a re-restorative procedure could be possible but often frowned upon.

In current series, about half of recurrences are limited to the pelvis, thus a significant number of patients can be considered for curative re-excision. Involvement of both anterior and posterior pelvic structures is usually managed by pelvic exenteration, first described by Brunschwig in the 1960s [41]. His results were characterized by high mortality and poor survival. Involvement of the sacrum requires a more radical procedure such as the abdominosacral resection popularized as a two-stage procedure by Wanebo [42]. Today, because of routine use of neoadjuvant therapy, the understanding of the principles of TME and optimized surgery, local recurrence rates have substantially decreased. Over the last 20 years, especially with the ability of intraoperative radiotherapy, survival has improved and morbidity is less, though the operations remain technically challenging.

Future Perspectives

In the twenty-first century, the limits of rectal cancer treatment continue to be pushed. Rectum saving therapy, avoiding the morbidity associated with major resection treatment, has been touted. Chemoradiation utilized in the preoperative setting was readily accepted and moreover, refinement in techniques of energy delivery, and improvements in chemo-sensitizers resulted in an increased number of "complete responders". As some of these patients may be looking at a large pelvic procedure with no residual tumor in the specimen, Habr-Gamma aimed to omit surgery completely from rectal cancer treatment [43]. Her series, as well as others', showed promising results; however, long-term data is not complete.

The practice of robotic rectal cancer resection is on the rise. Efforts are directed to further investigate its role in long-term outcomes.

Although recurrent rectal cancer is somewhat less frequent than in the past, future techniques to salvage patients both following minimal access and radical procedures will be an important hurdle. It is apparent today that personalized medicine and genomics will be a large part of medical care. As the genetics of those likely to respond or not to various therapies continues to be elucidated, surgeons will need to collaborate with geneticists, radiation oncologists and medical oncologists in a multidisciplinary fashion. Until proven otherwise, surgery will continue to be the primary form of therapy for optimal oncologic and functional results. Fortunately, the goals of complete removal of the tumor with anal sphincter preservation, decreased treatment morbidity with relatively normal postoperative bowel and pelvic function and high curative rates have been met.

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Epidemiology and Burden of Rectal Cancer

2

David E. Beck

Abstract

Rectal cancer is common and is associated with a significant economic burden. The incidence of rectal cancer has geographical variation based on access to care and risk factors. Causal factors such as the patient's age, personal history of inflammatory bowel disease, cancer or polyps and family history of cancer are not modifiable. However, the Western style of diet, limited physical activity and the use of alcohol and tobacco have been causally associated with the development of colorectal cancer and can be altered. Fortunately, the vast majority of cases and deaths from colorectal cancer can be prevented by applying existing knowledge about cancer prevention. Appropriate dietary changes, regular physical activity and maintenance of healthy weight, together with targeted screening programs and early therapeutic intervention could, in time, substantially reduce the morbidity and mortality associated with colorectal cancer.

Keywords

Rectal cancer • Etiology • Epidemiology • Economics • Prevention • Risk factors

Incidence of Rectal Cancer

Colorectal cancer is the third most common cancer and a major cause of morbidity and mortality throughout the world [1–3]. Rectal cancer accounts for about one-third of this disease burden, but data on rectal cancer is often combined with colon cancer making accurate numbers difficult to obtain. It is estimated that there will be 40,000 cases of rectal cancer in the US in 2014 with a slight male predominance [4, 5].

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Geographical Variations

Worldwide, colorectal cancer represents 9.4 % of all cancers in men and 10.1 % in women. There is significant world wide geographic variability in

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incidence and mortality. Countries with the highest incidence rates include Australia, New Zealand, Canada, the United States and parts of Northern Europe, and those with the lowest risk include China, India and parts of Africa and South America [1, 6]. The incidence rate varies up to 10-fold between countries and ranges from more than 40 per 100,000 people in the United States, Australia and New Zealand and Western Europe to less than 5 per 100,000 in Africa and some parts of Asia [1, 2, 6]. These incidence rates however, may be susceptible to ascertainment bias if there is a higher degree of underreporting in developing countries with the lower rates of colorectal cancer.

Temporal Trends

In addition to geographical differences in colorectal cancer incidence, the incidence rates are changing. In parts of Northern and Western Europe, the incidence appears stable while it is decreasing in the United States [7, 8]. In other high-income countries that have recently made the transition from a relatively low-income economy, such as Japan, Singapore, and eastern European, the incidence is increasing rapidly and has at least doubled in many since the mid-1970s [9, 10].

In the United States, male and female colorectal cancer incidence rates declined from the mid-1980s to the mid-1990s, followed by a short period of stabilization, and from 1998 to 2005 incidence rates declined an average of 2.8 % per year for males and 2.2 % per year among females [8]. These decreases in colorectal cancer incidence have been largely attributed to screening programs that may have improved the detection of precancerous polyps [11]. However, although national incidence rates have declined slightly over the last decade, the burden of disease remains high, and disproportionate within demographic subpopulations. For instance, before the 1980s, incidence rates for white males were higher than for black males and approximately equal for black and white females. Since that time, incidence rates have been higher for men than women, and higher among blacks than in whites [12].

Mortality Rates and Trends

Worldwide mortality attributable to colorectal cancer is approximately half that of the incidence. In the United States, colorectal cancer is the second leading cause of deaths among cancers that affect both men and women [11–13]. It was estimated that approximately 49,380 people from the United States would die of the colorectal cancer in 2011 and more than a third will be due to rectal cancer [14].

In North America, New Zealand, Australia, and Western Europe, mortality from colorectal cancer in both men and women has declined significantly [15]. However, in some parts of Eastern Europe, mortality has been increasing by 5–15 % every 5 years [7]. In the United States, deaths from colorectal cancer have decreased significantly by 4.3 % per year from 2002 to 2005 [8]. Current trends in mortality statistics from many of the developed countries are encouraging. However, incidence rated may be more appropriate indicator of trends in disease occurrence. Colorectal cancer incidence is unaffected by changes in treatment and survival, although it has been shown to be influenced by improved diagnostic techniques and screening programs [12].

Cancer Survival and Prognosis

Colorectal cancer survival is highly dependent upon stage of disease at diagnosis, and typically ranges from 90 % 5-year survival for localized cancers; to 70 % for regional and 10 % for metastatic cancer [11, 16]. In general, the earlier the stage at diagnosis, the higher chance of survival.

Since the 1960s, survival for colorectal cancer has increased substantially for all stages [11]. The relative improvement in 5-year survival over this period and survival has been better in countries with high life-expectancy and good access to modern specialized health care. However, enormous disparities in colorectal cancer survival exist globally and even within regions [3, 5, 9]. This variation is not easily explained, but most of the marked global and regional disparity in survival is likely due to differences in access to diagnostic and treatment services [7]. In the United

States, the 5-year survival for colorectal cancer improved in the period 1995–2000 by more than 10 % for both males and females, from 52 to 63 % in females and from 50 to 64 % in males [11]. The increase in survival during this period was not uniform among racial groups, however, and was reduced among non-whites compared with whites [9, 10, 16].

Non-modifiable Risk Factors

Several risk factors are associated with the incidence of colorectal cancer. Those that an individual cannot control include age and hereditary factors.

Age

The likelihood of colorectal cancer diagnosis increases after the age of 40 and rises sharply after age 50 [2, 16]. More than 90 % of colorectal cancer cases occur in people aged 50 or older and the incidence rate is more than 50 times higher in persons aged 60–79 years than in those younger than 40 years [16–18]. However, colorectal cancer appears to be increasing among younger persons and in fact, in the United States, colorectal cancer is now one of the ten most commonly diagnosed cancers among men and women aged 20–49 years [12, 19, 20].

Personal History of Adenomatous Polyps

Neoplastic polyps of the colorectum, namely tubular and villous adenomas, are precursor lesions of colorectal cancer [8]. Nearly 95 % of sporadic colorectal cancers develop from these adenomas [18]. The lifetime risk of developing a colorectal adenoma is nearly 19 % in the US population [2, 3]. An individual with a history of adenomas has a much higher risk of developing colorectal cancer than individuals with no previous history of adenomas [21]. A long latency period, estimated at 5–10 years, is usually required for the development of malignancy from adenomas [21, 22]. Detection and removal of an adenoma prior to malignant transformation may reduce the risk of colorectal cancer [23]. However, a history of adenomatous polyps or localized carcinoma is associated with an increased development of metachronous colorectal cancer [21].

Personal History of Inflammatory Bowel Disease

Inflammatory bowel disease (IBD, ulcerative colitis and Crohn's disease) increase an individual's overall risk of developing colorectal cancer [17]. The extent and duration of disease are associated with increased risk which has been estimated between 4 and 20 fold [7]. Therefore, regardless of age, individuals with IBD are highly encouraged to be screened for colorectal cancer on a more frequent basis.

Family History of Colorectal Cancer or Adenomatous Polyps

While the majority of colorectal cancers occur in persons without a family history or a predisposing illness, up to 20 % of people who develop colorectal cancer have family history of colorectal cancer [2, 24]. People with a history of colorectal cancer or adenomatous polyps in one or more first-degree relatives are at increased risk. It is higher in people with a stronger family history, such as a history of colorectal cancer or adenomatous polyps in any first-degree relative younger than age 60; or a history of colorectal cancer or adenomatous polyps in two or more first-degree relatives at any age [25]. The increased risk is most likely due to inherited genes, shared environmental factors, or some combination of these.

Inherited Genetic Risk

Approximately 5–10 % of colorectal cancers are a consequence of recognized hereditary conditions [9]. The most common inherited conditions are familial adenomatous polyposis (FAP) and

hereditary non-polyposis colorectal cancer (HNPCC). HNPCC is associated with mutations in genes involved in the DNA repair pathway, namely the *MLH1* and *MSH2* genes [2, 26]. FAP is caused by mutations in a the tumor suppressor gene the *APC* gene [6].

HNPCC may account for about 2–6 % of colorectal cancers and the lifetime risk of colorectal cancer in people with the recognized HNPCC-related mutations may be as high as 70–80 % and the average age at diagnosis is the mid-40s [2, 17, 27, 28]. *MLH1* and *MSH2* mutations are also associated with an increased relative risk of a number of other cancers, including several extracolonic malignancies (cancer of the uterus, stomach, small bowel, pancreas, kidney and ureter) [2]. FAP accounts for less than 1 % of all colorectal cancer cases [2, 17, 22]. While individuals with HNPCC develop only a few adenomas, people with FAP characteristically develop hundreds of polyps, usually at a relatively young age. One or more these adenomas typically undergoes malignant transformation as early as age 20 [22]. By age 40, almost all people with this disorder will have developed cancer if the colon is not removed [2, 17]. *APC*-associated polyposis conditions are inherited in an autosomal dominant manner. Approximately 75–80 % of individuals with *APC*-associated polyposis conditions have an affected parent.

Environmental Risk Factors

Colorectal cancer is widely considered to be an environmental disease, with "environmental" defined broadly to include a wide range of often ill-defined cultural, social, and lifestyle factors. As such, a large proportion of colorectal cases are theoretically preventable [5, 29]. Some of the evidence of environmental risk comes from studies of migrants and their offspring. Migrants moving from low risk to high risk countries, experience incidence rates that increase toward those typical of the population of the host country [7, 29]. Colorectal cancer incidence in the offspring of Japanese migrants to the US now approaches or surpasses that in the white population, and is three or four times higher than among the Japanese in Japan [2, 5]. Apart from migration, other geographical factors such as living in urban areas increases the incidence of colorectal cancer. In fact, urban residence is a stronger predictor of risk than location of birth [7]. This excess incidence in urban areas is more apparent among men and less apparent for rectal cancer [5].

Nutritional Practices

Diet strongly influences the risk of colorectal cancer, and changes in food habits might reduce up to 70 % of this cancer burden [30]. Diets high in fat, especially animal fat, are a major risk factor for colorectal cancer [5, 7]. The implication of fat as a possible etiologic factor, is linked to the concept of the typical Western diet, which favours the development of a bacterial flora capable of degrading bile salts to potentially carcinogenic *N*-nitroso compounds [31]. High meat consumption has also been implicated in the development of colorectal cancer [31, 32]. The positive association with meat consumption is stronger for colon cancer than rectal cancer [31]. Potential underlying mechanisms for a positive association of red meat consumption includes the presence of heme iron in red meat [32, 33, 35]. In addition, meats cooked at high temperatures produce heterocyclic amines and polycyclic aromatic hydrocarbons both of which are believed to have carcinogenic properties [32, 34]. In addition, some studies suggest that diets low in fruits and vegetables increase the risk of colorectal cancer [17]. Differences in dietary fiber may be also responsible for the geographical differences in the colorectal incidence rates [7]. Increased intake of dietary fiber may dilute fecal content, increase fecal bulk, and reduce transit time [2].

Physical Activity and Obesity

Several lifestyle-related factors have been linked to colorectal cancer. Two modifiable and interrelated risk factors, physical inactivity and excess body weight, are reported to account for about a fourth to a third of colorectal cancers [2, 5, 21, 34, 36]. Sustained moderate physical activity

raises the metabolic rate and increases maximal oxygen uptake [21]. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity, as well as reducing blood pressure and insulin resistance [35]. In addition, physical activity increases gut motility [2]. The lack of physical activity in daily routines also can be attributed to the increased incidence of obesity in men and women, another factor associated with colorectal cancer [21, 37]. Several biological correlates of being overweight or obese, notably increased circulating estrogens and decreased insulin sensitivity, are believed to influence cancer risk, and are particularly associated with excess abdominal adiposity independently of overall body adiposity [21]. However, the increased risk associated with overweight and obesity does not seem to result merely from increased energy intake; it may reflect differences in metabolic efficiency [21].

Cigarette Smoking

The association between tobacco cigarette smoking and lung cancer is well established, but smoking also is extremely harmful to the colon and rectum. Evidence suggests that 12 % of colorectal cancer deaths are attributed to smoking [38]. The carcinogens found in tobacco increase cancer growth in the colon and rectum, and increase the risk of being diagnosed with this cancer [17]. Cigarette smoking is important for both formation and growth rate of adenomatous polyps, the recognized precursor lesions of colorectal cancer [39]. Larger polyps found in the colon and rectum were associated with long-term smoking. Evidence also demonstrates an earlier average age of onset incidence of colorectal cancer among men and women who smoke cigarettes [38, 40].

Heavy Alcohol Consumption

As with smoking, the regular consumption of alcohol may be associated with increased risk of developing colorectal cancer. Alcohol consumption is a factor in the onset of colorectal cancer at a younger age as well as a disproportionate increase of tumors in the distal colon [38, 40]. Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic [41]. There is also an interaction with smoking [38]. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol [41]. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells [41]. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species [41]. Lastly, high consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis [2].

Economics and Financial Issues

Rectal cancer is common and is expensive to treat. This economic burden is challenging to quantify and some of the following observations may not be applicable outside of a fee for service health system. Emotionally receiving a diagnosis of cancer is stressful for the patient, family and health care team. In addition to the emotional impact, treatment of rectal cancer is associated with time and financial issues. The time associated with different aspects of treatment are estimated in Table 2.1 and can total 39–60 weeks.

Obtaining data on the costs associated with rectal cancer treatment is difficult. In the United States charge data is available but cost data is significantly more difficult to obtain. Using SEER-Medicare data from 1996 to 2002 Lang and associates estimated that lifetime excess costs at $26,500 for rectal cancer patients [42]. Huag and colleagues using health insurance data from Germany on patients diagnosed with rectal cancer between 2007 and 2010 calculated the mean incremental annualized coast to range $25,000 to $45,000 [43]. Additional charge estimates for aspects of rectal cancer treatment are also listed in Table 2.1 and average $72,000 to $75,000. Traditionally, charges have varied from 30 to 50 % of collectable fees which approximate costs. Finally, the time lost from work or other activities is an opportunity cost that is real but almost impossible to value.

Table 2.1 Burden of rectal cancer

Activity	Time	Cost/charges
Diagnosis	1–2 weeks	$500
Staging	2 weeks CT scan, MRI, U/S	$3,000
Consults/MDT	1 week	$500
Radiotherapy	Short course : 5 days Long course : 5 weeks of therapy and 6–10 weeks for tumor resolution	$2,000 $5,000
Initial surgery	Hospital 6 days Recovery 2 weeks	Surgeon's fee $1,800 Hospital charge : $25,000
Stomal closure	6–8 weeks Hospital : 2–3 days Recovery : 2 weeks	Surgeon's fee $500 Hospital charge : $8,000
Chemotherapy, adjuvant	6 months	$40,000
Total	39–60 weeks	$72,800–$75,800

Conclusion

Rectal cancer is common and several factors considered to be causally associated with the development of colorectal cancer. For instance, the risk of colorectal cancer is clearly increased by a Western diet. Genes responsible for the most common forms of inherited colorectal cancer have also been identified. Fortunately, the vast majority of cases and deaths from colorectal cancer can be prevented by applying existing knowledge about cancer prevention. Appropriate dietary changes, regular physical activity and maintenance of healthy weight, together with targeted screening programs and early therapeutic intervention could, in time, substantially reduce the morbidity and mortality associated with colorectal cancer.

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Anatomy and Physiology of the Rectum and Anus

3

Mike Chadwick

Abstract

An understanding of the physiology and structure of rectum and anus, their related structures within the pelvis, and their embryological origins, is important when considering rectal cancer surgery in terms of precise dissection in anatomical planes, oncological clearance and functional impact for the patient. This includes sphincter preservation with restoration of gastrointestinal continuity, as well as preservation of urinary and sexual function. It is by a deeper understanding of pelvic anatomy and embryology that due to the proximity of pelvic structures damage and potential for functional compromise may be avoided when planning and carrying out rectal cancer treatment strategies. This chapter gives an overview of pelvic anatomy and physiology with specific reference to the operative technical considerations but also underpins the principles by which pre-operative staging assessment and adjuvant treatment are conducted in the overall management of rectal cancer.

Keywords

Anatomy • Rectum • Mesorectal • Fascia • Pelvic • Cancer

Introduction

To understand the principles of anatomy and physiology of the rectum and anus and the rationale for surgical treatments for the management of rectal cancer one needs to understand the structure of the alimentary tract as a whole as well as its embryology. It is then, by a deeper understanding of pelvic anatomy and embryology, that damage due to the proximity of pelvic structures and potential for functional compromise

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may be avoided when planning and carrying out rectal cancer treatment strategies.

Structural Overview

The gut tube is composed of an inner mucosal layer, supported throughout its length by a submucosal layer made up of connective tissue, blood and lymphatic vessels, secretor-motor nerve fibres and smooth muscle – the muscularis mucosae. Centrifugal to this layer lie two layers of circular and longitudinal smooth muscle with interdigitations of the intrinsic nerve supply of the gut – the myenteric plexi of Meissner and Auerbach. The outer layer of the gut tube is the closely applied fascial tissue known as serosa.

The blood supply, venous and lymphatic drainage of the gut is arranged in mesenteries. The vessels are surrounded and supported by areolar tissue and fat encased in very thin fascia. These mesenteries are, to a greater or lesser extent, shortened or lengthened according to the functional regions of the gut. Where mobility or expansion is required for a given section of the alimentary tract the gut tube and its mesentery are completely covered in peritoneum. This is why the stomach, first part of duodenum, the entirety of the small intestine, transverse and sigmoid colon are considered "peritoneal". They have long mobile mesenteries and have the potential to volve. The lower oesophagus, second third and fourth part of the duodenum, ascending and descending colon and upper rectum and their mesenteries are simply covered on their ventral surface by peritoneum and thus referred to as retroperitoneal portions of the gut. They have relatively shorter mesenteries and can never volve. These portions of the gut tube have come to lie in their "normal" positions as a result of embryological rotation of the gut.

Embryological Overview

The alimentary tract is a continuous tube, passing though the body cavity. It derives its origin from the endoderm of the embryological tri-laminar disc. The middle embryological layer, or mesoderm, provides the origin of the blood supply and lymphatic drainage of the gut (the mesenteries) encased within fascial layers and covered in peritoneum as well as the skeletal muscles encasing the abdomen and pelvis. The remaining embryological layer, the ectoderm, provides the origin of the skin of the lips and the sensate area of the anus and anal canal as far as the dentate line as well as the extrinsic autonomic nerve supply to the gut. Thus the gut tube provides a portal from one end of the ectoderm to another. The gut tube is divided functionally and anatomically into foregut – mouth to second part of duodenum, midgut – second part of duodenum to distal transverse colon, and hindgut – distal transverse colon to upper anal canal. Whilst the foregut is responsible for digestion of foodstuff, and the midgut for absorption and assimilation of derived nutrients and electrolytes, the hindgut is chiefly responsible for conservation of water by reabsorption. There are corresponding lymphovascular supplies taking origin from the coeliac axis, superior and inferior mesenteric arterial roots respectively. (At the extremes of the alimentary tract the mouth, tongue, pharynx and upper oesophagus are supplied by branches of the carotid arteries; the anus and lowermost rectum are supplied by branches of the pudendal arteries.) The gut tube develops within a coelomic cavity whose lining becomes the peritoneum.

Embryology of the Anorectum

The anorectum dorsally is linked ventrally to the ureters, allantois and Wolffian/Mullerian ducts (the embryological origin of the urinary bladder, gynaecological/andrological tracts), opening into a sac termed the cloaca. A urorectal septum of mesodermal tissue separates the allantois from the hindgut (see Fig. 3.1). A primordial external pouch, the proctodaeum, is initially lined with ectoderm which, fused with the endoderm of the cloaca, becomes elongated and divided by the urorectal septum. This septum will become the rectovaginal septum in the female and Denonvilliers' fascia in the male.

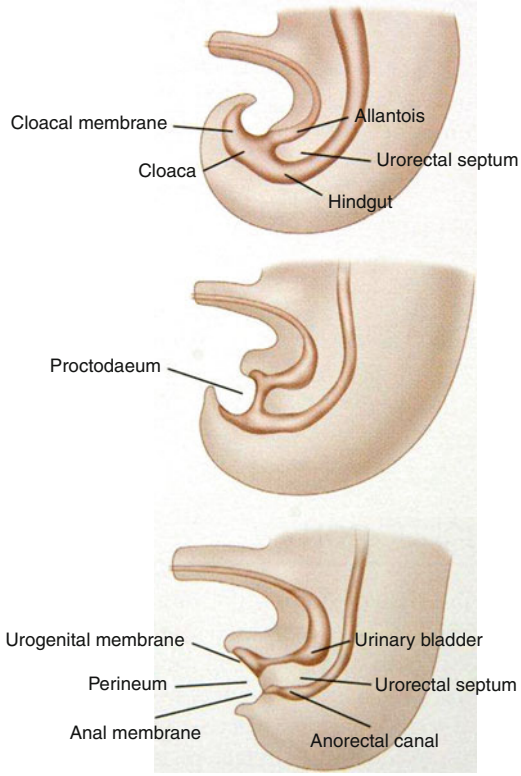

Fig. 3.1 Embryonal development of the cloaca (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 2. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

At this point the urorectal septum and proctodeal membrane become the perineal body and overlying skin and the now separated anterior and posterior portions of proctodaeum, fused with cloacal endoderm, become the urogenital membrane and anal membrane respectively. These membranes indent and become the urogenital sinus and anorectal canal at about the seventh week of gestation. The anorectal membrane perforates by degeneration leaving a differentiation gradient from rectal columnar epithelium through to squamous keratinised epithelium within the anal canal. This corresponds to the region of mucosa just above the dentate line.

The embryology of the urogenital sinus and ventral attachments to the cloaca account for the proximity of the genital structures, and their neurovascular supply, to the anorectum – in particular the posterior vaginal wall in the female and seminal vesicles and prostate in the male. It is therefore important to understand the embryology and anatomy of these structures when considering the need for oncologically beneficial surgery and its potential effects on sexual and urinary function.

Oncological principles regarding rectal cancer surgery derive from the fact that the blood supply and lymphatic drainage of almost the entire rectum are visceral, via the superior rectal artery, and associated lymphatics, from the hindgut originator vessel, the inferior mesenteric artery. The lymphovascular supply is encased, as are all mesenteries, in a fascial layer. In the case of the mesorectum this capsule is termed the mesorectal fascia and constitutes part of the endopelvic fascia. The mesorectal fascia separates the visceral rectum from the somatic pelvis but also from the fascial septum of the genital organs – the rectovaginal septum in females and Denonvilliers fascia in males.

Anatomy of the Rectum

The rectum is the last absorptive and propulsive part of the gastrointestinal tract and bridges the last 15–20 cm of gut from sacral promontory to anal orifice, its mesentery wrapped in mesorectal fascia, lying anterior to the sacral concavity, superior to the anal hiatus of the pelvic floor muscles, posterior to the rectovaginal septum vagina and uterus/ Denonvilliers' fascia, prostate seminal vesicles and bladder. The anal canal lies at a dorsal angle of 90–100° to the rectum due to tonic contraction of the puborectalis muscle of the pelvic floor. This is known as the anorectal angle.

The rectum can be divided functionally and anatomically into two parts: the upper part being mainly propulsive and sharing a similar diameter to the sigmoid above; the lower part, being mainly for storage, is dilated, sometimes considerably, to form the rectal ampulla. The rectum is recognisably different from the colon at surgery due to the absence of appendices epiploicae and the diffusion of longitudinal muscle bands (teniae coli) to form a continuous longitudinal smooth muscle layer.

The upper two thirds of the anterior rectal wall are covered by peritoneum. The rest of the rectum and its mesorectal package are retro/extraperitoneal. The pelvic peritoneum covering the rectum thickens and reflects laterally and anteriorly to cover the ureters, endopelvic fasciae, posterior bladder and seminal vesicles and prostate in the male (the rectovesical pouch). The pelvic peritoneum covers the uterus and fallopian tubes (the broad ligament), posterior cervix and posterior vaginal fornix in the female (rectouterine pouch of Douglas). It is continuous with the parietal peritoneum of the anterior abdominal wall.

Blood Supply to the Rectum

The visceral blood supply to the rectum is from the inferior mesenteric artery via the superior rectal artery dividing into mesorectal branches and comprises at least 80 % of the rectal blood supply. The mesorectal branches further ramify from posterior to lateral and anteriorly perforating the muscle layers of the rectal wall to supply the muscles, submucosa and mucosa. They descend in the muscle and submucosal layers towards the upper anal canal.

These mesorectal arteries anastomose at capillary level with supply from the middle rectal arteries which are branches of the internal iliac arteries to supply that portion of the rectum passing through the pelvic floor. They are inconsistently present and are only bilaterally detectable as distinct vessels in 10 % of individuals. They pass with rectal branches of the inferior hypogastric nerve plexi in fascial condensations commonly, but not universally, recognised as the "lateral ligaments".

Below the pelvic floor the remainder of the blood supply to the anorectum is from the superior haemorrhoidal (also known as the inferior rectal) arteries which, passing through the ischioanal space, are branches of the internal pudendal arteries which pass through Alcock's canal, themselves branches of the internal iliac arteries. Thus there is a connection between visceral and somatic blood supplies – inferior mesenteric and internal iliac.

Venous Drainage of the Rectum

Via multiple veins within the mesorectum most blood drains to the inferior mesenteric vein (IMV) which drains into the splenic vein behind the pancreas. The IMV is seen within the descending colonic mesentery passing behind the pancreas at the level of the ligament of Treitz at the duodenojejunal flexure. The blood then enters the portal venous system and it is thought that hepatic metastases arise by haematogenous spread via this route.

There is a rich network of venous connections within the mesorectum, however, and some of the rectal blood supply also drains via the inferior rectal veins to the internal iliac veins. It is thought that via this route distant extrahepatic metastases (e.g. lung) arise by haematogenous spread.

Operative Significance

The inferior mesenteric artery is divided close to its origin from the aorta at curative rectal cancer surgery taking care to avoid damaging the hypogastric nerve plexus. This often results in taking the ascending left colic branch which supplies the descending colon and anastomoses variably with the marginal artery from the distal branches of the middle colic arteries supplying the transverse colon, whose origin is the superior mesenteric artery (SMA). Once the specimen is resected the residual colon to be anastomosed to the anorectum at the pelvic floor can therefore be considered a pedicled flap, whose sole blood supply is then the marginal artery.

The IMV can cause significant tethering of the colonic pedicle if not divided high near the ligament of Trietz. This manoeuvre is important in ensuring a tension free coloanal anastomosis.

It is thanks to the multiplicity of blood supply to the lowermost anorectal muscle and mucosa that coloanal anastomoses are possible. Thus marginal arterial supply from the SMA meets pudendal arterial supply from the internal iliac arteries to perfuse the healing anastomosis.

Lymphatic Drainage of the Rectum

Lymphatic drainage of the rectum is mainly in a cranial direction from the submucosa to mesorectal lymph nodes to inferior mesenteric lymph nodes and then para-aortic nodes. Thus typical patterns of lymph node involvement present themselves in cases of rectal cancer. However given the presence or absence of middle rectal vessels drainage to lateral pelvic sidewall or internal iliac nodes is also possible. Thus lateral pelvic lymph node metastases may also occur but tend to happen with more locally advanced mid to lower rectal cancers which have breached the circumferential mesorectal fascial margin.

Nerve Supply to the Rectum

The rectum is neurally supplied by the autonomic nervous system. This comprises an intrinsic (myenteric & submucosal) and extrinsic sympathetic and parasympathetic system. The intrinsic system consists of a network of nerve plexi and ganglia supplying the mucosa, submucosa and all muscle layers of the rectum. Responsive to stretch and chemical stimuli, the intrinsic system is chiefly responsible for motility, secretion, absorption, perception and immune function. These nerve plexi are linked to the central nervous system by autonomic sympathetic and parasympathetic nerves via ganglia to spinal visceral afferents.

The sympathetic nerves reach the rectum via the superior sympathetic pre-aortic, and inferior mesenteric plexi which condense to form the hypogastric bundle which then divides below the aortic bifurcation anterior to the sacral promontory into right and left hypogastric nerves. These then course laterally in the pelvis and join spinal parasympathetic nerves (pelvic splanchnic nerves), which exit the sacral foramina with sacral nerves 2, 3 and 4, to form the inferior hypogastric plexi, branches of which form the rectal plexus to supply the rectum on each lateral side through the aforementioned fascial condensations known as the lateral ligaments. The inferior hypogastric plexus then continues anteriorly as a condensation within neurovascular bundles to supply the urinary bladder and cavernous nerves of sexual function.

Fascial Layers of the Pelvis

The pelvis and its contents can be thought of as a series of concentric and eccentric fascial layers and spaces rather like an onion/shallot in which another eccentric allium has grown. Working from outside to in, the bony pelvis is covered in periosteum, a musculoaponeurotic layer including the iliopsoas, obturators, piriformis and pelvic floor muscles, nerve roots, somatic nerves of the lumbar and sacral plexi, and blood vessels including the iliac vessels and their branches. Anterior to the sacrum this layer is known as the pre-sacral space which contains areolar tissue and significant presacral veins which can be easily damaged causing massive haemorrhage without careful dissection in the correct plane.

This layer is then encased in the parietal pelvic fascia. Anterior to the sacral concavity this is known as presacral fascia. Laterally below the level of the peritoneal reflection this fascia invaginates centrally on either side toward the mesorectum to allow the passage of the rectal nerve plexi and middle rectal arteries (if present) to supply the rectal wall. The posterior and anterior leaves of these fascial invaginations condense with the neurovascular bundles to form the "lateral ligaments" also described as rectal pedicles or "T junctions" (Fig. 3.2). They offer no support mechanism merely a conduit for neurovascular supply.

Inferiorly the parietal pelvic fascia thickens over the pelvic floor musculature and is known as Waldeyer's fascia (Fig. 3.3). Anterior to the rectum and posterior to the urogenital organs the parietal fascia overlies the perineal body and anterior and posterior leaflets of this fascia rise together fused between urogenital organs and anterior rectum forming a rectogenital septum to reach the most caudal portion of the peritoneum – the pouch of Douglas/rectovesical pouch. It continues laterally and is continuous with the lateral aspects of the presacral fascia. This condensation

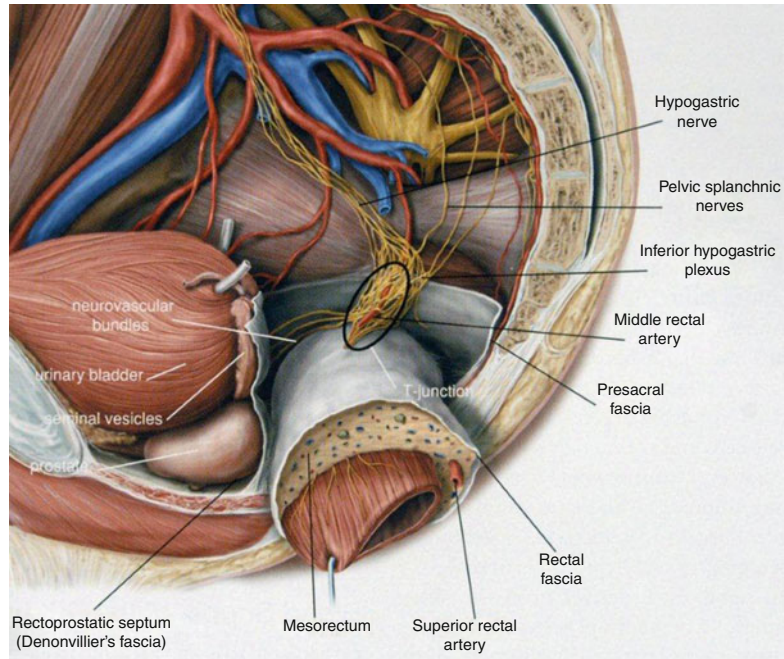

Fig. 3.2 Perirectal spaces, sagittal section of male pelvis, left view. The rectum and the surrounding mesorectum are pushed towards the contralateral side to illustrate the course of the autonomic pelvic nerves along the pelvic wall (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 2. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

of fascia is of considerable density in its upper portions and can clearly be seen in two layers (Fig. 3.3) with the magnified views obtained at laparoscopic and robotic surgery, and histopathologically. However, inferiorly it is less distinct in the male and appears to fuse with the prostatic capsule. It is the embryological urorectal septum or rectogenital septum in the adult and as described before constitutes the rectovaginal septum in the female and Denonvilliers' fascia in the male. (It can be severely damaged and rendered vestigial in females after childbirth. This contributes to the formation of rectocoeles.) It effectively divides the pelvis into anterior and posterior (anterior/middle and posterior in females) compartments from now on.

Posterior Compartment

Outer Layer 1 is the retrorectal space which contains the hypogastric nerves, inferior hypogastric plexi (and middle rectal vessels if present). These extrinsic autonomic nerves therefore all lie between peritoneum, parietal presacral fascia and mesorectal fascia covered by a flimsy fascial sheath (pre-hypogastric nerve fascia). This layer also contains the inferior posterolateral pelvic portions of the ureters and gonadal vessels.

Middle Layer 2 is the endopelvic visceral fascia of the rectum or mesorectal fascia. The mesorectum is wrapped around by the mesorectal fascia which is considerably more substantial posteriorly where under tension at surgery it can lead to the appearance of bilateral bulges.

It fuses with the parietal fascia at the lateral ligaments and at the level of S4 with Waldeyer's fascia as it passes through the pelvic floor.

Inner layer 3 is the mesorectum and rectum itself.

Anterior Compartment

Outer Layer 1 contains the anterior pelvic portions of the ureters and gonadal vessels and vasa deferentia.

Middle Layer 2 is the endopelvic visceral fasciae of the urogenital organs. The fasciae are generally thin and flimsy. They include ureteric sheaths and gonadal vessel sheaths, perivesical fascia, and fascia overlying the prostate and

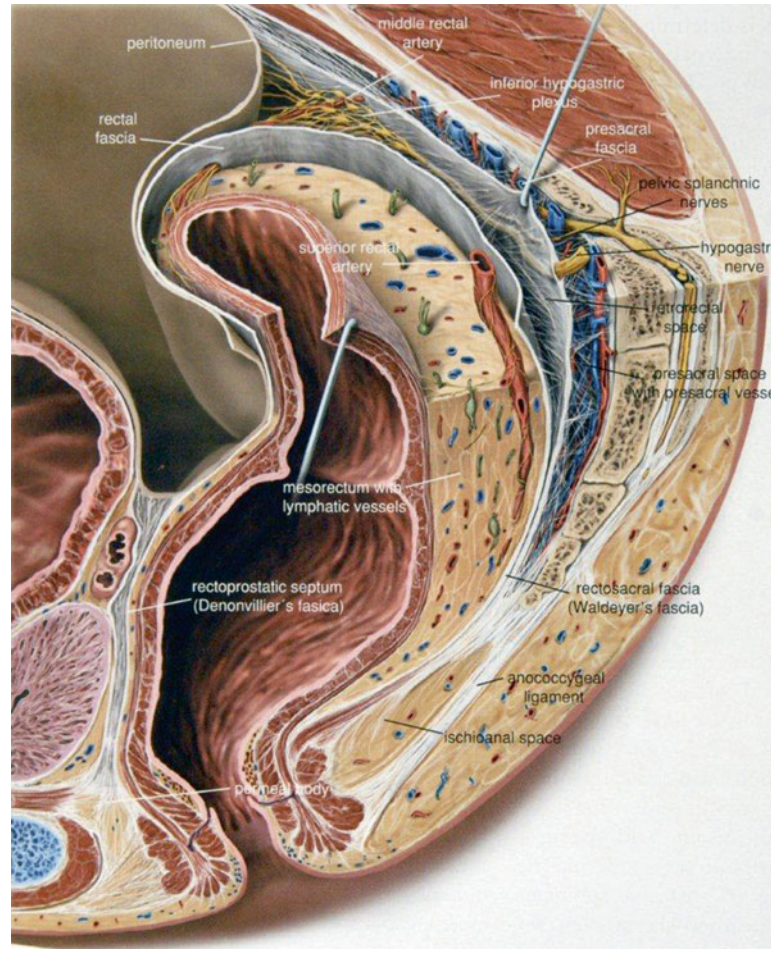

Fig. 3.3 Perirectal fascia, mediosagittal section of male pelvis, left view. The endopelvic mesorectal fascia and parietal pelvic presacral fascia are highlighted to illustrate the perirectal mesorectum and retrorectal and presacral spaces (planes). Of note the retrorectal space ("mesorectal plane") is free of blood vessels and nerves and corresponds to the correct surgical plane for rectal mobilisation during total mesorectal excision (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 2. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

seminal vesicles and vasa deferentia in the male, and vagina, cervix and uterus in the female. pelvic urogenital organs and related blood vessels.

Inner layer 3 contains the aforementioned urogenital organs.

The central lining layer of the pelvis is the pelvic peritoneum as described above.

Oncological and Functional Significance of the Mesorectal Fascia

It has been demonstrated that the quality of the resected specimen (intactness of the mesorectal fascia) and lack of tumour involvement of the circumferential resection margin are independent prognostic markers for local recurrence after rectal cancer resection. Thus a clear understanding and recognition of the mesorectal fascia and the surgically distinct avascular plane around it is essential for producing a complete specimen removal with an intact fascia for the success of surgery as the primary curative treatment for rectal cancer. Remaining in the correct plane between the mesorectum and parietal pelvic fascia and rectogenital septum facilitates identification of, and reduces the likelihood of damage to, the neurovascular structures important in maintaining normal urogenital function. These are therefore the principles by which the total mesorectal excision (TME) was popularised.

Tumours which lie within 1 mm of the mesorectal fascia are considered "circumferential resection margin-positive" so even with an optimal surgically resected specimen there is a high risk for local recurrence in these cases. It has

also been shown that high resolution preoperative imaging in the form of MRI has helped to predict a threatened CRM by recognition of the mesorectal fascia and the proximity of such tumours. In these cases, as part of a multidisciplinary appraisal, selective neoadjuvant treatment in the form of chemoradiotherapy may be offered to patients to improve their risk of local recurrence.

Anatomy of the Anus

The rectal ampulla narrows at the level of the pelvic floor at the anorectal junction and becomes the upper anal canal which extends caudally and posteriorly towards the anal orifice. The anal canal is on average 3.5–5 cm long.

Anal Mucosa

The columnar mucosa of the rectum becomes stratified squamous and non-keratinised within the anal canal (anoderm) from the dentate line, and then keratinised at the anal verge. The anoderm is devoid of glands and hair. The dentate line marks the transitional zone where endoderm/cloacal lining meets ectoderm/proctodeal lining and this explains the sensate nature of the lower anal canal and relatively asensate upper anal canal. It is also therefore the region where visceral and somatic blood and lymphatic supplies merge. Above the dentate line lie 8–12 vertical folds of Morgagni which contain terminal branches of the superior rectal artery. Between these folds lie pockets/crypts or anal valves and it is the alternating pattern of folds and crypts that give rise to the teeth-like appearance of the "dentate" line (also known as the pectinate line). The skin of the anal verge is of a darker pigment than the surrounding perianal skin and appears radially folded due to the underlying corrugator ani muscle. The skin has all normal glandular elements present including sweat, apocrine and sebaceous glands. The blood supply is from the inferior rectal/haemorrhoidal arteries, branches of the pudendal arteries.

The anal mucosa is supported by submucosa, and two rings of smooth and striated muscle constituting the internal and external anal sphincters respectively, which act as a unit known as the anal sphincter complex.

Anal Submucosa

Connective tissue and vascular channels form a network at the anorectal junction which extends to the dentate line forming the haemorrhoidal cushions. These act as valves and are important in continence of flatus and mucus. The arterial supply is from the superior rectal artery and venous drainage is via channels which perforate the internal anal sphincter and drain to the external haemorrhoidal venous plexus. This therefore means that with normal resting tonic contraction of the internal anal sphincter, the haemorrhoidal cushions are engorged providing flatal/mucous continence. When the sphincter relaxes before defaecation the complexes drain to the external venous haemorrhoidal plexus reducing the volume of anorectal tissue, facilitating the passage of stool.

Anal Sphincter Complex

The internal anal sphincter is composed of circular smooth muscle derived from the lowermost circular muscle of the rectum. It is shorter than the external sphincter and is closely applied to the overlying anoderm below the dentate line. Above the dentate line the submucosal haemorrhoidal complexes separate it from the mucosa within and just above the anal canal. The subcutaneous part of the external anal sphincter overlies the internal sphincter creating an intersphincteric groove at the anal verge.

The longitudinal smooth muscle fibres of the lowermost rectal wall also descend between the internal and external sphincters and fuse with fibres of the puborectalis muscle to form conjoint longitudinal muscle fibres which, after diverging, insert centrally into the perianal skin (the

corrugator ani muscle), and peripherally into superficial perineal fascia – the floor of the ischioanal space, separating it from the subcutaneous perianal space.

The external anal sphincter is attached to the internal anal sphincter by the connective tissue and longitudinal muscle fibres within the interpshincteric plane. It forms an elliptical cylinder up to 15 mm thick composed of mainly slow-twitch type 1, striated muscle fibres enabling prolonged contraction and basal tone. It is divided axially by septa at three levels.

The uppermost level is at the anorectal ring and the fibres coalesce with the puborectalis muscle. It is this attachment which allows changes in the anorectal angle upon puborectalis contraction during defaecation. This upper part is less well developed anteriorly in females – a normal finding on endoanal ultrasound. The appearance of this segment should not be confused with scarring as evidence of previous obstetric injury.

The middle, more superficial, segment is firmly attached to the anococcygeal ligament posteriorly and perineal body anteriorly. The most distal subcutaneous portion of the sphincter surrounds the anal orifice and extends deep to the perianal skin below the most caudal border of the internal anal sphincter (Fig. 3.4).

The Pelvic Floor

The pelvic floor comprises a musculofibrous system of parietal pelvic fascia (previously discussed), a pelvic diaphragm and a urogenital diaphragm.

The pelvic diaphragm or "levator ani complex" (Fig. 3.5) consists of striated paired muscles (left and right coccygei, iliococcygei, pubococcygei) and the puborectalis muscle. Shaped like a part-flattened funnel the muscles descend and fuse with the external anal sphincter. Pubococcygeus acts like a hammock. Some of the fibres of each pubococcygeus decussate to blend with longitudinal rectal wall fibres as they pass through the pelvic floor to form the conjoint longitudinal muscle. Puborectalis acts as a sling and pulls the anal canal toward the pubis. This has the action of reducing the anorectal angle, necessary for initiating defaecation. The muscles are poorly developed in a female compared with a male which allows for childbirth but risks functional evacuatory problems later in life.

The urogenital diaphragm (Fig. 3.6) is a musculofibrous plate extending from the inferior aspect of the pubis bilaterally to the perineal body and consists of the deep and superficial transversus perinei muscles and smooth muscle fibres bordering the anal and urogenital hiatus, created by a

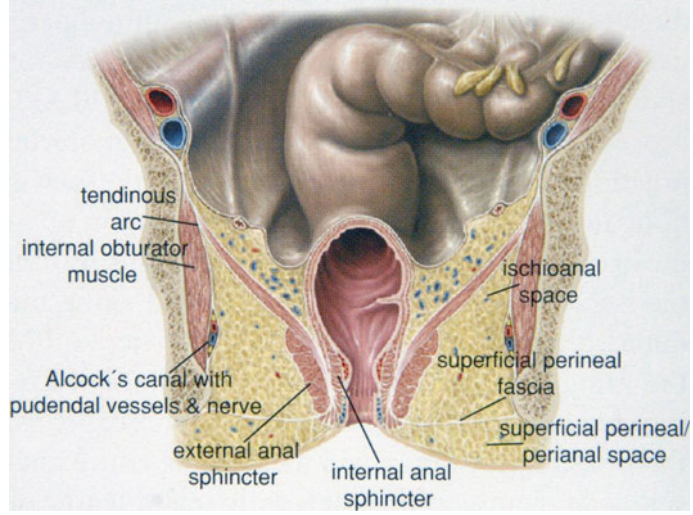

Fig. 3.4 Rectum, anal canal and pelvic floor, frontal section, anterior view. The levator ani muscle originates at the tendineus arc on both sides and forms the funnel shaped pelvic diaphragm extending down to the external anal sphincter. The triangular space delimited by the levator ani muscle, the internal obturator muscle and the superficial perineal fascia corresponds to the ischioanal space. The main pudendal nerve branch and internal pudendal blood vessels are ensheathed by a duplication of the obturator fascia (Adcock's canal) (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 2. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

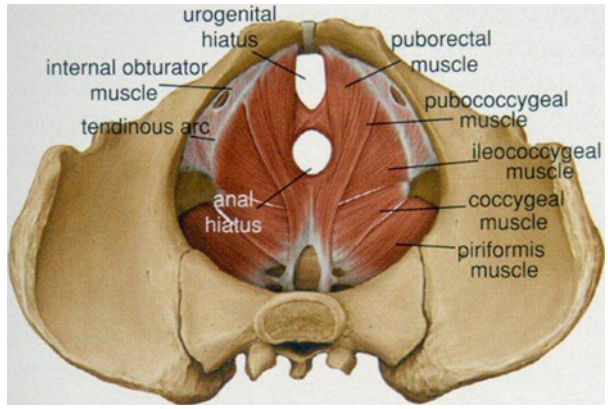

Fig. 3.5 Pelvic floor, cranial view. The pelvic diaphragm is formed by the levator ani muscle composed of the puborectal muscle, pubococcygeal muscles and iliococcygeal muscles. Most of the levator ani muscle originates from the tendineus arc ("white line"), which corresponds to a condensed connective tissue line of the obturator fascia. The puborectal sling forms a midline gap for the urethra and vagina (urogenital hiatus) and the anal canal (anal hiatus). The coccygeal muscles extend from the ischial spines to the lateral margins of the coccyx following the course of the sacrospinal ligaments (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 1. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

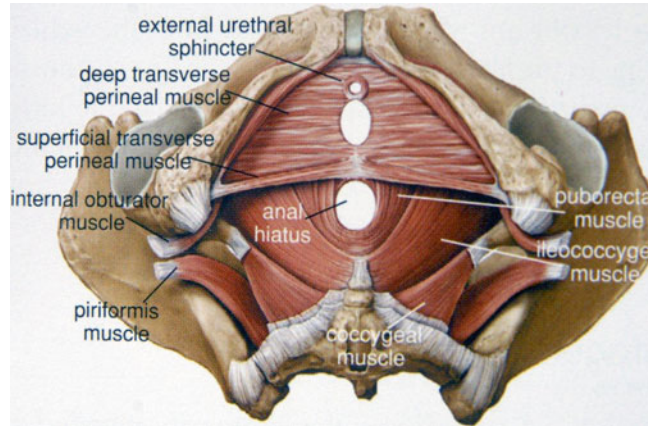

Fig. 3.6 Female pelvic floor and urogenital diaphragm, caudal view. The urogenital hiatus of the pelvic diaphragm is covered caudally by the urogenital diaphragm composed of the deep and superficial transverse perinei muscles (Reproduced from Schunke M, et al. Promethius LernAtlas der Anatomie, vol. 1. 3rd ed. Stuttgart: Thieme Publ.; 2012, with permission)

midline gap in the levator ani muscles of the pelvic diaphragm. Most anteriorly is a urethral opening surrounded by the external urethral sphincter linked in men to the anterior external anal sphincter by smooth muscle fibres of the "rectourethralis"; in females, posterior to the urethral hiatus, a vaginal hiatus also is present bounded laterally by smooth muscle fibres of "rectovaginalis".

Nerve Supply

The pelvic and urogenital diaphragms are innervated by motor efferents of sacral nerves S2, S3 and S4 either directly or via the pudendal nerves which also carry all somatosensory input from the perineal region and the ectodermal lower anal canal up to the dentate line.

Direct sacral nerves supply motor function to the upper fibres of the pelvic diaphragm/levator ani. Providing the surgeon is in the plane between mesorectal fascia and parietal pelvic fascia during rectal cancer surgery the direct sacral nerves to the pelvic floor should not be injured.

Pudendal nerves, taking origin from sacral nerve roots S2, S3 and S4, initially travel out of the pelvis with the sciatic nerves via the greater sciatic foramina. They then re-enter the pelvis

around the sacrospinous ligaments at the level of the ischial spines, through the lesser sciatic foramina, below the levator ani in fascial sheaths (Alcock's canals) with internal pudendal vessels on each side. Multiple branches pass anteriorly through the ischioanal space to supply the anal sphincter and lower fibres of levator ani and sensation to anoderm, perineum, scrotum/labia. Dorsal penile/clitoral nerve branches then travel above the urogenital, below the pelvic diaphragms to supply the cavernous bodies. Terminal branches innervate the prostate in the male and vaginal mucosa in the female having intermingled with the autonomic neurovascular bundles from within the pelvis finally to supply the urinary sphincter mechanism.

The surgeon is mindful of these nerve branches with particularly low parts of rectal dissection and especially when considering abdominoperineal excisions.

The Perineum

The perineum is composed of the ischioanal space, superficial perineal space and perineal body.

The ischioanal space lies below and lateral to the "funnelled" levators, surrounds the anal sphincter complex and extends inferiorly to the superficial perineal fascia which forms a septum linking the ischial tuberosities with the longitudinal muscle fibres of the intersphincteric space and inferior border of the external anal sphincter. Laterally it is bound by the obturator interni. It is divided posterioinferiorly in the midline by the anococcygeal ligament. It is filled with areolar tissue and fat.

Branches of the pudendal vessels and nerves run in this space to supply the various structures described above. Lymphatic drainage is to the deep inguinal lymph nodes. This is why locally advanced low rectal adenocarcinoma and anal carcinoma may also present with inguinal lymph node metastases as well as mesorectal, inferior mesenteric, para-aortic and internal iliac node involvement.

The subcutaneous perineal space comprises the fatty tissue and fibrous septae between the superficial perineal fascia and the perianal skin.

The perineal body is the thickening of connective tissue where there is a common insertion of a posterior attachment from the anterior corrugator ani, superficial transversus perinei, the external anal sphincter, anorectal ring and central fibres of the puborectalis along with smooth muscle fibres of rectourethralis most medially and, bulbospongiosus anteriorly. Superiorly the perineal body is attached to parietal pelvic fascial covering forming the lowermost extent of rectogenital septum thus linking the perineal body to the pelvic peritoneal reflection (Pouch of Douglas in the Female). The rectourethralis is said to mark the level of the lowermost border of the rectogenital septum.

Operative Significance

Knowledge of the anatomy of this region is important when considering abdominoperineal excision of the rectum (APER) for very low rectal cancer. The perineal part of the dissection must allow complete resection of the anal sphincter complex and the low rectal tumour by taking a cylinder of perianal fatty tissue through the ischioanal space, avoiding pudendal nerve damage, and taking the levators close to their origin at the arcus tendineus to avoid "waisting" or narrowing toward the low rectal tumour. As previously discussed the risk of local tumour recurrence is high if the circumferential margins of the specimen are involved with tumour. Thus has been popularised the extralevator abdominoperineal excision (ELAPE) for low rectal cancer.

The proximity of the bulbospongiosus to the anterior part of the external anal sphincter, due to crossover of fibres (rectourethralis smooth muscle) at the perineal body and therefore there being no discernible dissection plane, makes it particularly challenging to achieve adequate oncological resection whist preserving urinary and ejaculatory function in the male during APER. Careful dissection posterior to the transversus perinei is considered the best approach to avoid damage to

the urethra and urethral sphincter complex and its nerve supply.

Defecatory Physiology of the Rectum and Anus

The anorectum and pelvic floor are under neural influence from visceral autonomic and somatic nerve supplies. Their motor nerve cell bodies originate in Onuf's nuclei within the conus medullaris of the spinal cord at the neurological level of S2-S4. Corticospinal tract nerves synapse to allow central nervous system control. The pudendal and sacral nerves supply the pelvic floor, as described above.

Muscular Function

The pelvic floor muscles display tonic activity on electromyographic testing in the resting state. Muscle fibre recruitment is increased as abdominal pressure increases either voluntarily or with sneezing/coughing. However with straining the pelvic floor muscles are seen to relax. This enables defaecation by a combination of voluntary straining to create a pelvic expulsive force to supplement the rectal emptying, propulsive force generated by contraction of circular and longitudinal smooth muscle of the rectal wall under the influence of the parasympathetic splanchnic nerves. Defaecation is normally preceded by colonic mass movement under the influence of parasympathetic neurotransmitters such as acetyl choline and hormones (e.g. cholecystokinin, gastrin). These agents also reduce salt and water absorption. Conversely secretormotor activity is reduced and absorption of sodium, chloride and water is increased under the influence of neurotransmitters dopamine and noradrenaline, and hormones glucagon, VIP, encephalin, somatostatin. Sleep appears to inhibit colonic contraction which dramatically increases on waking and feeding (the gastrocolic reflex).

In the normal faecally continent state, the internal anal sphincter contributes to the majority (70 %) of the resting tone of the anus. The external sphincter contributes a smaller proportion of resting tone but is most active in reflex contraction at times of increased abdominal pressure such as when exercising, sneezing or coughing. A voluntary component of squeeze pressure is also an important function of the external sphincter. This voluntary force is also contributed to by contraction of the puborectalis. A pressure wave generated in the rectal wall can be overridden and even reversed by voluntary contraction of the EAS and pelvic floor. This enables the patient to defer defaecation. Indeed involuntary phasic, short segment, reverse-peristaltic contractions can be observed in the distal rectum every 1–2 h. This is thought to contribute to continence. Short clusters of rectal wall contractions can also be observed whose significance is unknown.

The EAS, being composed of mainly slow twitch fibres, whilst having relatively low pressure tonal contraction, is incapable of sustained high pressure contraction beyond about 30 s and fatigues easily. Resting tone in the normal males is on average higher than in females due to increased length and bulk of the sphincter complex in men. Similarly voluntary squeeze pressures are considerably (30–50 %) higher. Average functional sphincter length in men is 4 cm whereas it is about 3.5 cm in women. Typical values for sphincter tonal resting pressure are around 70 mmHg for men and 65 mmHg for women with maximum squeeze pressures typically around 190 and 140 mmHg respectively (Rao et al. 1999).

Recto-Anal Inhibitory Reflex (RAIR)

The EAS is forced to relax during defaecation and straining but also due to the recto-anal inhibitory reflex (RAIR). Rectal distension beyond a certain threshold causes a reflex relaxation of the internal anal sphincter (IAS). This allows the rectal contents to be "sampled" to discriminate its consistency and necessity to be evacuated. This reflex can be measured by manometry of the anal sphincter in response to a rapidly inflated rectal balloon. Normal response is defined as a transient

Table 3.1 Normative values for rectal balloon sensation testing

Sensitivity	Sex	First constant sensation (ml)	Desire to defaecate (ml)	Maximum tolerated volume (ml)
Normal	Male	40–110	70–190	140–270
	Female	20–70	60–160	90–270
Hyposensitivity	Male	>160	>230	>315
	Female	>120	>210	>325
Hypersensitivity	Male		<70	<140
	Female		<60	<90

From Gladman MA, Scott SM, Chan CL, Williams NS, Lunniss PJ. Rectal hyposensitivity: prevalence and clinical impact in patients with intractable constipation and faecal incontinence. Dis Colon Rectum. 2003;46(2):238–46; Chan CL, Scott SM, Williams NS, Lunniss PJ. Rectal hypersensitivity worsens stool frequency, urgency and lifestyle in patients with urge faecal incontinence. Dis Colon Rectum. 2005;48(1):134–40

25 % drop in resting anal tone. This reflex is absent in congenital aganglionoses (e.g. Hirschprung's disease) and acquired conditions such as systemic sclerosis. Disorders of pudendal nerve conduction or rectal disorders of structural collapse (e.g. intussusception, mucosal prolapse) can also lead to complex patterns of faecal incontinence, obstructive defaecation and RAIR failure (non-relaxation/anismus).

Anorectal Sensation

The rectal mucosa and wall have little in the way of sensory determination except distension (stretch). Rectal balloon distension testing has been used to define normal, hyposensitive and hypersensitivity in the rectum. With incremental rises in volume of an inflating balloon within the rectal ampulla different measurements can be taken e.g. first constant sensation (minimum volume perceived by the patient); desire to defaecate volume (threshold volume where a desire to defaecate is experienced); maximum tolerated volume (volume at which patient experiences overwhelming desire to defaecate due to discomfort). These measurements are also possible in patients who have had a proctectomy and coloanal anastomosis suggesting that stretch of the pelvic floor and colonic wall also play a part in sensation. Typical values are shown in Table 3.1.

Sensation of distension is a function of rectal wall compliance, extrinsic afferent nerve integrity and complex central processing of perception and behavioural pattern. Therefore balloon distension testing only provides a guide to the sensitivity of the rectal wall in response to stretch. It cannot measure factors extrinsic to the rectum involved in its function.

Rectal Cancer Management Implications

In rectal cancer surgery where the whole rectum is removed and coloanal anastomosis is performed one can expect reduced thresholds for sensation of desire to defaecate and reduced maximum tolerated volumes due to the relative non-distensibility of colon as compared with the rectal ampulla. It is for this reason that modifications in continuity restorative technique have created the "colopouch"-anal anastomosis. The effective doubling of "neorectal" volume is designed to improve defaecatory quality of life in terms of frequency, urgency, stool consistency and volume. The true benefit of these techniques has not been conclusively proven.

Neoadjuvant radiotherapy, certain adjuvant chemotherapy (e.g. oxaliplatin) and surgery can all have a deleterious effect on nerve function and therefore may contribute to postoperative faecal continence problems. The use of per-anal stapling devices to achieve low colo-anal anastomoses can also disrupt the sphincter and the valve effect of the haemorrhoidal cushions and mucosa. When selecting patients for sphincter-sparing surgery in

the treatment of rectal cancer it is important that the surgeon and the patient are aware of the patient's pre-existing sphincter function and quality of life and the potential risks of deterioration. Therefore in some cases where pre-existing anal sphincter dysfunction is present it may be better to select a permanent colostomy from the outset and offer the patient a "TME Hartmann".

Conclusion

An understanding of the physiology and structure of rectum and anus, their related structures within the pelvis, and their embryological origins, is important when considering rectal cancer surgery in terms of precise dissection in anatomical planes, oncological clearance and functional impact for the patient. This includes sphincter preservation with restoration of gastrointestinal continuity and preservation of urinary and sexual function. This chapter gives an overview of pelvic anatomy and physiology with specific reference to the operative technical considerations but also underpins the principles by which preoperative staging assessment and adjuvant treatment are conducted in the overall management of rectal cancer.

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Pathology and Staging of Rectal Cancer

4

Xuchen Zhang and Dhanpat Jain

Abstract

Treatment of rectal cancer requires multidisciplinary collaboration. Proper reporting and staging of rectal cancer specimens is indispensable for the management of rectal cancer. The work of pathologist over the years has substantially changed from merely providing an initial diagnosis and pathological staging to detailed evaluation of prognostic factors and molecular markers that optimize treatment, as well as evaluate treatment response. Currently, the AJCC TNM staging system is the most accepted staging system worldwide. It is necessary to adopt standard protocols for uniform staging and reporting of rectal cancer.

Keywords

Rectal cancer • Total mesorectal excision • Circumferential resection margin • TNM staging • Pathology

Introduction

Colorectal cancer (CRC) is the third most prevalent cancer and third most common cause of cancer death in the United States [1]. Rectal cancer accounts for approximately 40 % of CRCs [1]. Successful multimodal treatment of rectal cancer requires accurate diagnosis and staging, which guides optimal treatment strategies [2]. Preoperative staging is performed using endorectal ultrasound and MRI, however, staging after neoadjuvant therapy becomes less reliable by imaging studies because of post-therapeutic changes, such as fibrosis, edema, inflammation, and necrosis and pathologic analysis is considered the gold standard [3]. In such cases it is imperative that a thorough pathologic examination is performed for accurate assessment of treatment response and prognostication. Thus, the role of pathologists in the management of rectal cancer is not only to confirm the diagnosis of cancer, but also to stage the disease and provide prognostic information [4]. In addition, pathologists are increasingly asked to provide information regarding various molecular markers such as status of

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microsatellite instability (MSI), mutations of K-RAS, B-RAF, PI3KCA, PTEN and other biomarkers that have prognostic and therapeutic implications. This chapter addresses how best to handle of resection specimens for rectal cancer.

Rectal Cancer Specimen Handling

Surgical resection remains the most effective therapy for rectal cancer and meticulous gross examination of the resected specimen is critical and of prognostic significance. A variety of surgical approaches, depending on the location and extent of disease, are used to treat primary rectal cancers, including localized excisions (polypectomy, transanal excision, and transanal endoscopic microsurgery [TEM]), and more invasive procedures involving total mesorectal excision (TME) [5]. Handling of these specimens varies and herein is discussed in detail.

Transanal Excision/Transanal Endoscopic Microsurgery (TEM)

Transanal excision is recommended for small (<3 cm) and low grade (well to moderately differentiated) early-stage rectal cancers (T1N0). Localized tumors that extend into the muscularis propria (T2N0), can also be successfully treated by TEM involving a full-thickness excision performed perpendicularly through the bowel wall into the perirectal fat. Local excision can also be offered as a palliative measure to address local disease in patients with advanced lesions (T3 or above, N1 or above) who are unable to safely tolerate a major abdominal surgery [5, 6].

Ideally, transanal excision or TEM specimens should be received as a single piece of oriented tissue (Fig. 4.1), however, fragmented piecemeal excisions are often carried out. If the specimen is removed in one piece, the surgeon may orient it and pin it on a cork/wax board before immersing it in the fixative. The base of the excision (deep margin) should be inked and pathologists should assess the adequacy of local excision, which is difficult in fragmented specimens. Interaction with surgeon may facilitate specimen handling when its orientation or nature is in doubt.

Mesorectal Excisions

Patients with rectal cancer who are not candidates for local surgery are treated with a transabdominal resection [5, 7]. In transabdominal resections, TME is recommended. A TME involves an "en bloc" removal of the rectum together with the mesorectum, including associated vascular and lymphatic structures, fatty tissue, and the mesorectal fascia. For lesions in the mid to upper rectum, an anterior resection (AR) extends 4–5 cm below the distal edge of the tumor, followed by creation of a colorectal anastomosis or colostomy. An abdominoperineal resection (APR) is performed when the tumor directly involves the anal sphincter or levator muscles, or when a margin-negative resection of the tumor would result in loss of anal sphincter function and incontinence. An APR involves "en bloc" resection of the rectosigmoid, rectum, and anus, and the surrounding mesentery, mesorectum, and perianal soft tissue [5]. Complete removal of the mesorectum (TME) is important as it contains most of the involved LNs and tumor deposits [7]. In rectal cancer, one of the most important margins is the margin around the mesorectum – circumferential resection margin (CRM). Positive CRM correlates with increased local recurrence rates and decreased survival [8].

It is best to examine the resection specimen in the fresh state as well as following fixation. Surgeons are discouraged from opening the specimen before the pathological gross evaluation unless absolutely necessary, as this may hinder proper assessment of the circumferential resection margins. Prior to opening the specimen, the prosector should identify and differentially ink the serosal and non-peritonealized surfaces and identify the lowest level of peritoneal reflection. It should be emphasized that the entire non-peritonealized surface forms the CRM, which the surgeon has to dissect or cut to detach the bowel

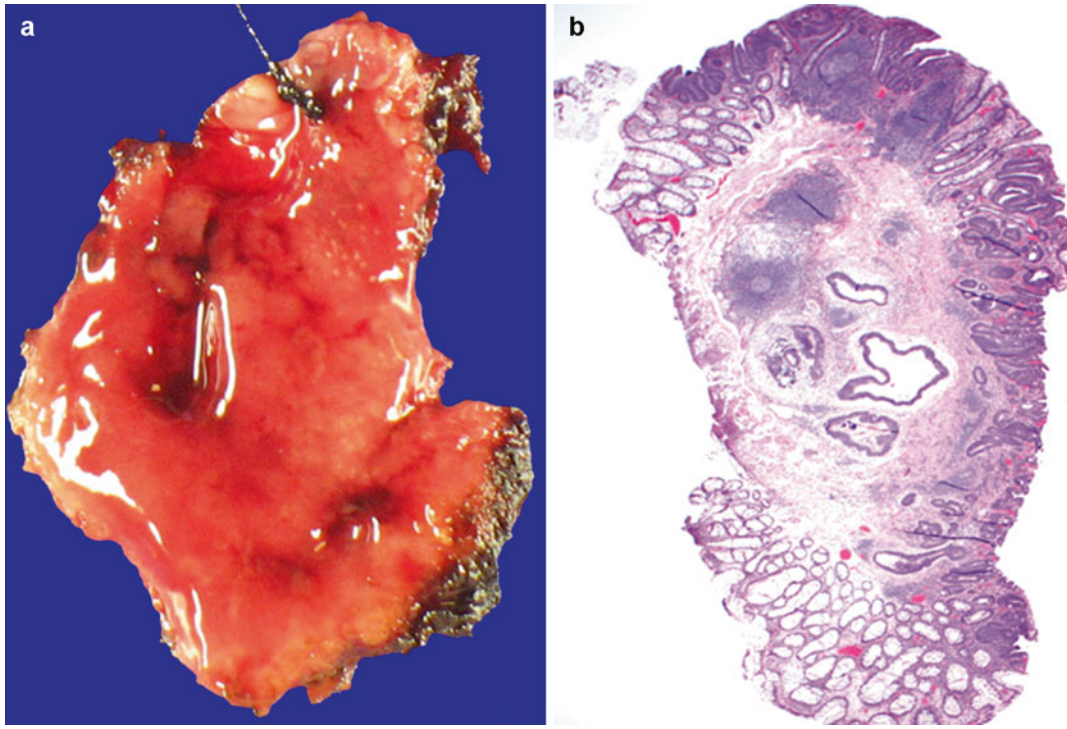


Fig. 4.1 Transanal excision of early-stage rectal adenocarcinoma. (**a**) A single piece of transanal excision specimen with a suture denoting the proximal end. (**b**) Section shows a well-differentiated adenocarcinoma invades into submucosa arising from a tubular adenoma (Hematoxylin and eosin stain). Evaluation of intact well-oriented section allows assessment of the lateral mucosal and deep margins, which are negative as shown here

from the retroperitoneum. The demarcation of rectum from sigmoid varies and different criteria are applied by anatomist, radiologist, gastroenterologist and pathologist, however, from a oncologic standpoint the tumor location in relation to the peritoneal reflection forms an important landmark. Lower 2/3rd of the rectum lacks any serosal covering, and hence the entire circumferential surface is CRM, while upper 1/3rd or less is partly covered by serosa. During the gross examination one should note the type of operation performed, length of bowel resected, location of tumor with respect to peritoneal reflection, completeness of mesorectal excision, any significant peritoneal pathology (e.g., tumor perforation), tumor configuration, distance of tumor from all resection margins, etc. The quality of surgery of the levator/sphincter area around the anal canal below the mesorectum should also be separately assessed in APR specimens

Accurate assessment of the mesorectum is critical and predicts both local recurrences and distant metastasis. Total mesorectal excision (TME) has been suggested to reduce local tumor recurrence by 10–20 % in various studies [9, 10]. Mesorectal resection can be scored as complete, partially (nearly) complete or incomplete (Fig. 4.2). Complete is defined as intact bulky mesorectum with a smooth surface with only minor irregularities of the mesorectal surface, no surface defects greater than 5 mm in depth, no coning towards the distal margin of the specimen, and smooth appearing CRM on transverse sectioning. Nearly (partially) complete is defined as moderate mesorectal buck, irregularity of the mesorectal surface with defects greater than 5 mm, but none extending to the muscularis propria, and no visibility of the muscularis propria except at the site of insertion of the levator ani muscles. Incomplete is defined as little mesorectal

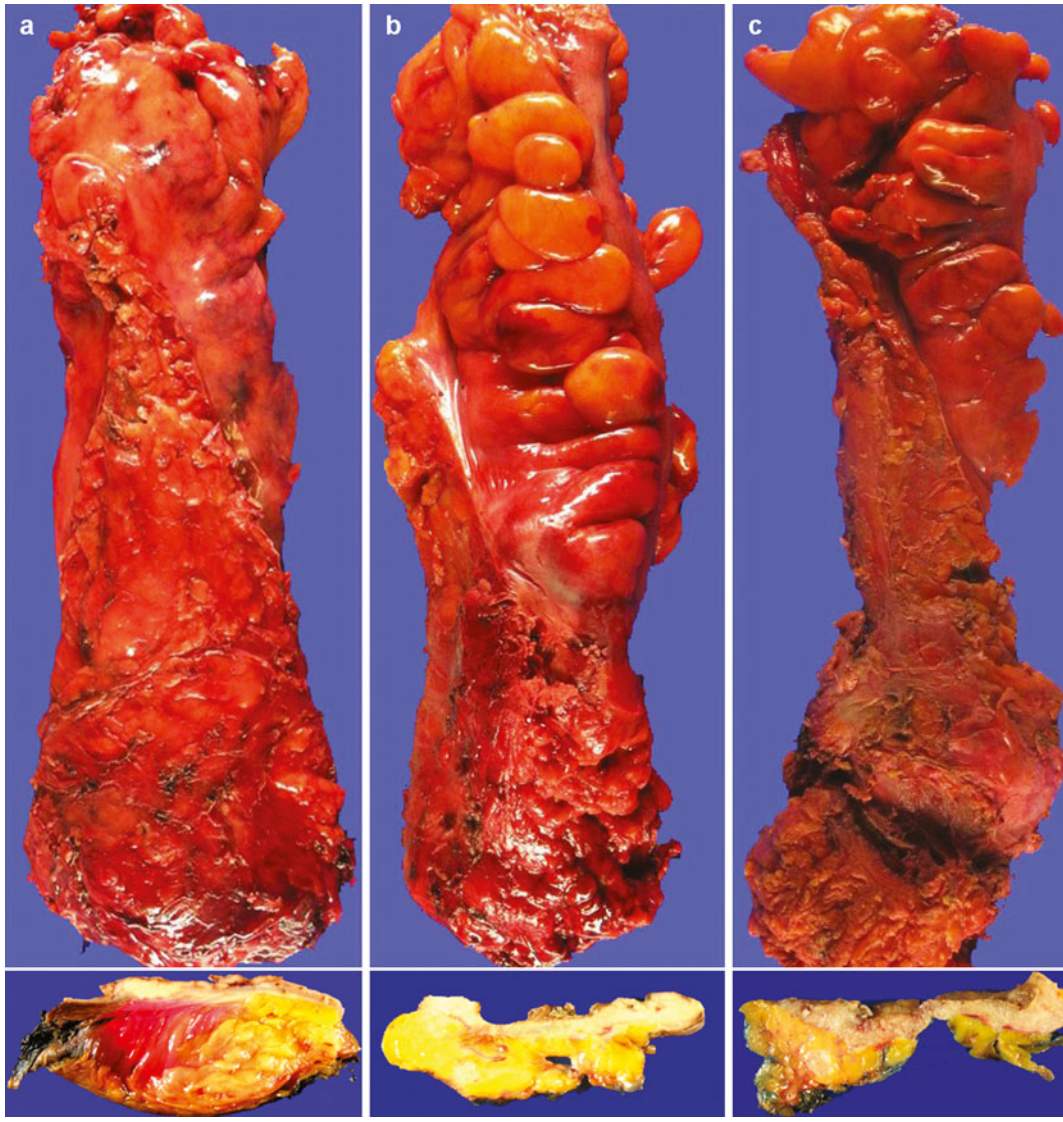


Fig. 4.2 Gross assessment of mesorectal excision in fresh resection specimens as seen in an intact unopened specimen from outside. The *inset* below each photograph shows a representative cross-section of the formalin-fixed specimen showing the rectal cancer and the mesorectum. (**a**) Complete mesorectal excision showing smooth mesorectal surface with only minor irregularities; (**b**) A specimen showing partially (nearly) complete mesorectal excision with irregularity of the mesorectum much deeper than 5 mm; (**c**) A specimen showing incomplete mesorectal excision showing defects in the mesorectum down to the muscularis propria and >5 mm

bulk, defects in the mesorectum extending to the muscularis propria, and an irregular appearing circumferential margin after transverse sectioning. Of note, the entire specimen is scored according to the worst involved area.

The proximal and distal resection margins can be evaluated by either longitudinal sections perpendicular to the margin or en face sections parallel to the margin. The distance from the tumor edge to the closest resection margin(s) should be noted, particularly for low anterior resections. For these cases, a 2 cm long distal resection margin is considered desirable; for T1 and T2 tumors, a 1 cm long margin may be sufficient. Anastomotic

recurrences are rare when the distance to the closest resection margin is ≥5 cm [11].

There are no universally accepted guidelines as to how the specimen should be processed, particularly for evaluation of TMEs. Some advocate fixing the specimen by inflation with formalin and then serially slicing the entire specimen transversely, which allows the best way to examine the full circumference of the specimen. However, this process requires longer fixation time, which prolongs the turnaround time. Some suggest that the specimen can be opened similar to large bowel tumors along the border opposite to the tumor, after inking the external surfaces. Following fixation, slices are made at 1 cm intervals and sequentially evaluated. Others make a compromise between these methods by opening both ends along the anterior margin and leaving segment containing the tumor intact. If the tumor segment is longer than 1 or 2 cm, a formalin-soaked gauze or paper can be threaded into the lumen to facilitate fixation. Subsequently the tumor-containing segment can be serially sectioned to yield complete transverse slices. When there is no identifiable tumor especially after neoadjuvant therapy, review of any prior images and palpation the mucosa by inserting a finger into the lumen is helpful. One should carefully open the specimen looking for a scar or shallow ulcer indicating the likely tumor site. For fixation, the opened specimen is ideally pinned to a cork/wax board and immersed in formalin overnight (about 12–24 h).

There is no consensus on the number of sections that should be submitted from the tumor; however, it has been suggested that a minimum of 5 sections are required to detect LVI in most cases [12, 13]. The College of American Pathologist (CAP) also recommends at least 3, and optimally 5 sections should be submitted from the tumor [14]. In general, tumors <3 cm in size should be entirely submitted. For larger tumors, some follow the 1 section/cm rule, merely by convention rather than any evidence based data. If possible, at least one section should also be taken across the direction of the vascular supply close to the tumor to facilitate assessment of venous invasion. At least two sections should be submitted from where the tumor is closet to the peritoneum. Peritoneal involvement may be grossly suspected from areas of serosal pallor, retraction or puckering; however, some cases are only detected microscopically. Conversely, peritumoral fibrosis and inflammation can often simulate peritoneal invasion, and microscopic confirmation is always necessary. If the tumor has an adenomatous edge, appropriate sections should be taken to demonstrate it.

The remaining uninvolved mucosa should be carefully inspected and sections should be submitted from any mucosal bumps, polyps, or abnormalities. Representative random sections should also be taken to ensure there is no unsuspected underlying disease (e.g., inflammatory bowel disease). Although it is traditional to take sections of the proximal and distal resection margins, unless tumor extends close (within 2 cm) to one of the margins, this is of little value. However, poorly differentiated tumors may extend primarily in the submucosa and sometimes spread discontinuously via lymphovascular channels leading to positive margins.

Lymph Node Dissection

A careful search for lymph nodes (LNs) forms an important and sometimes the most painful and time-consuming aspect of handling rectal cancer specimens. The number of retrieved LNs appears to vary with age and gender of the patient, tumor grade, tumor site, specimen type, prior therapy and immune status of the patient. Lymph node size is a poor guide to the presence of metastasis in CRC, with metastases often found in small LNs (<5 mm in diameter), hence a diligent search for LNs is required. All grossly negative or equivocal LNs should be submitted for histological examination. Grossly positive LNs may be partially submitted for microscopic confirmation of the metastasis. Most LNs are found in posterior and lateral quadrants of the mesorectum at the level of the tumor and immediately above, less commonly in the anterior mesorectum [15]. There is no universal agreement on the minimum number of required LNs. The minimum number

to accurately stage nodal status and predict patient survival with stage II rectal cancer varies from 10 to 23 LNs amongst studies [16–18]. The 7th edition AJCC staging manual and the CAP recommend evaluating 10–14 LNs in CRC resections in patients without neoadjuvant therapy [11, 19], while examination of at least 12 LNs has been proposed by the National Comprehensive Cancer Network (NCCN) clinical practice guidelines for rectal cancer and endorsed by the National Quality Forum and the Commission on Cancer [5, 20]. However, by no means do these guidelines imply that pathologists should stop searching for LNs once 12 have been identified. If fewer nodes are found, reexamining the specimen for additional LNs should be considered with or without visual enhancement techniques [11]. Visual enhancement techniques such as fat clearing solutions [21], methylene blue-assisted LN dissection [22], and acetone elution with subsequent compression of adipose tissue ("acetone compression") [23] result in dramatically increased LN counts compared to conventional dissection. However, data are insufficient to recommend routine use of these ancillary techniques and practices vary markedly across labs, even within the same region [8, 11].

Use of neoadjuvant therapy in rectal cancer often leads to atrophy of the lymphoid tissue and reduces LN yield. The mean number of LNs retrieved from rectal cancers treated with neoadjuvant therapy is significantly less than that from those treated by surgery alone [24]. When 12 LNs were considered sufficient for staging, only 20 % of rectal cancers treated with neoadjuvant therapy had adequate LN sampling in stage II tumors in one study [24]. To date, the number of LNs needed to accurately stage neoadjuvant-treated cases is unknown, though a minimum of 12 LNs is still recommended. Studies show the number of retrieved LNs is affected by degree of treatment response and the number of LNs should not be used as a surrogate for adequacy of oncologic resection after neoadjuvant therapy for rectal cancer [25, 26]. Visual enhancement techniques facilitate the detection of LNs, however, their utility in the setting of neoadjuvant therapy remains unclear [5, 23]. Nonetheless, great care must be taken to retrieve LNs in any setting for optimal staging and prognostication.

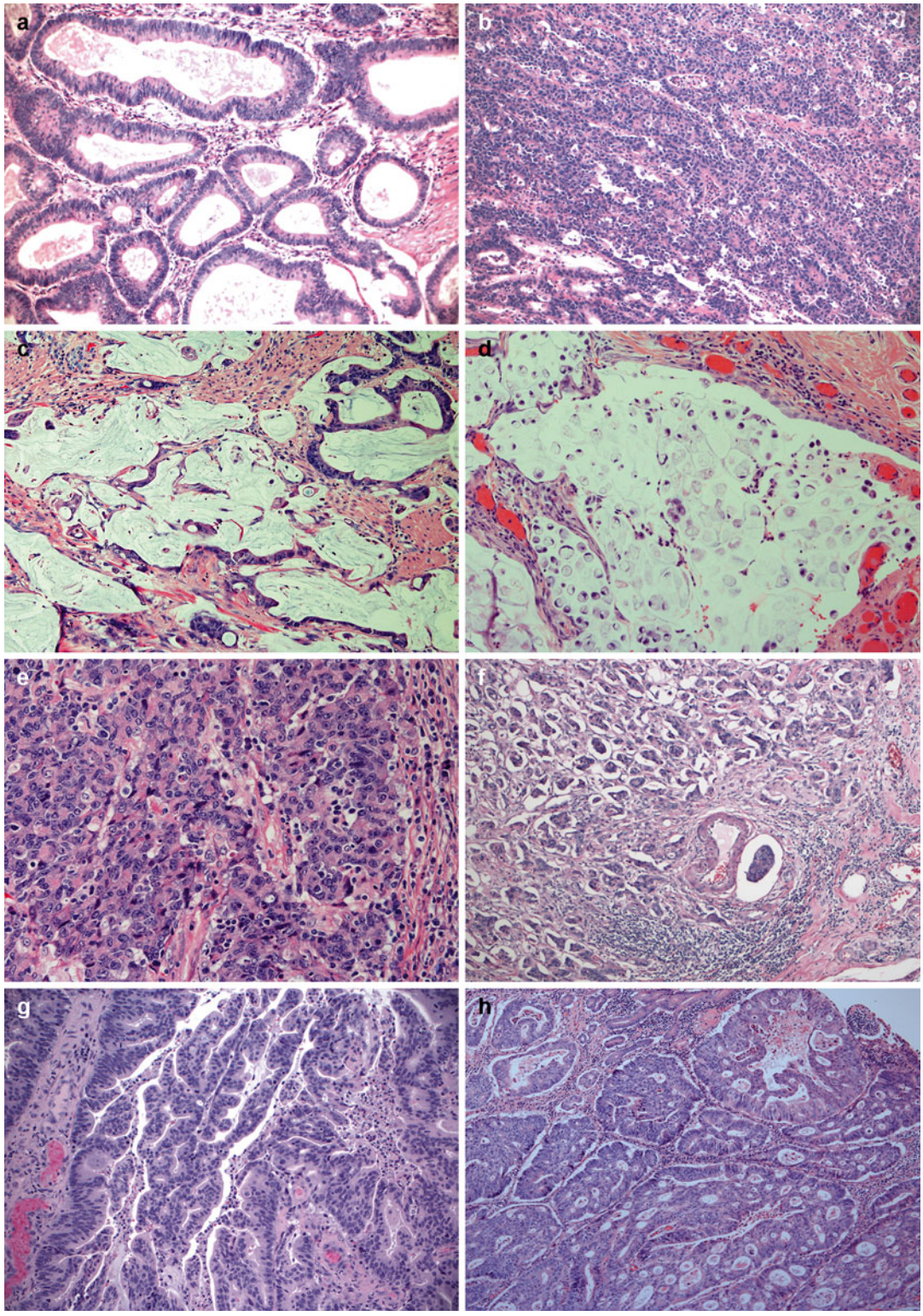
In addition to absolute number of LNs examined, the ratio of positive LNs is an independent prognostic indicator for patients with CRC, irrespective of number of LNs examined. However, large prospective studies are needed to determine if this should be added to the current staging systems [27, 28].

Histological Features of Rectal Cancer and Their Prognostic/Predictive Significance

Histologic Types

Most primary rectal cancers are adenocarcinomas, of which most are conventional gland-forming tumors (Fig. 4.3a, b). However, some special types need to be addressed as they exhibit different behavior and/or molecular phenotype. The special histopathologic sub-types of CRC recognized over

Fig. 4.3 Histologic types of rectal carcinomas. (**a**) Conventional well-differentiated (Low-grade) adenocarcinoma showing well-formed glands (glandular structures in >95 % of the tumor); (**b**) Conventional poorly-differentiated (High-grade) adenocarcinoma (glands around 5–50 % of the tumor); (**c**) Mucinous adenocarcinoma showing large amount of extracellular mucin and tumor cells that often surround these mucin pool and are often low grade; (**d**) Signet-ring cell carcinoma showing poorly cohesive tumor cells containing single, large mucin vacuoles in their cytoplasm; (**e**) Medullary carcinoma showing solid sheets of tumor cells with many tumor infiltrating lymphocytes; (**f**) Micropapillary adenocarcinoma showing small clusters of tumor cells within stromal spaces mimicking vascular channels; (**g**) Serrated adenocarcinoma showing small papillary epithelial tufts (serrated/corkscrew glandular features); (**h**) Cribriform comedo-type adenocarcinoma showing glands with a comedo-like pattern and bridging of cells across the lumens filling with necrotic debris. Hematoxylin and eosin stain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the years include (a) mucinous adenocarcinoma: more than 50 % of the lesion is composed of pools of extracellular mucin (Fig. 4.3c); (b) signet-ring cell carcinoma: more than 50 % of tumor cells with prominent intracytoplasmic mucin, typically with displacement and molding of the nucleus (Fig. 4.3d); (c) medullary carcinoma: sheets of malignant cells with vesicular nuclei, prominent nucleoli and abundant cytoplasm exhibiting prominent infiltration by intraepithelial lymphocytes (Fig. 4.3e); (d) adenosquamous carcinoma: tumors show features of both squamous cell carcinoma and adenocarcinoma, either as separate areas within the tumor or admixed; (e) spindle cell carcinoma: a biphasic carcinoma with a spindle-cell sarcomatoid component in which the tumor cells are at least focally immunoreactive for keratins; and (f) undifferentiated carcinoma: tumors lack morphological, immunohistochemical, and molecular biological evidence of differentiation beyond that of an epithelial tumor and have variable histological features [29]. Micropapillary, serrated and cribriform comedo-type adenocarcinomas have been introduced as new distinct histological subtypes of CRC in the new WHO classification [29]. Micropapillary adenocarcinoma shows small clusters of tumor cells within retracted stromal spaces mimicking vascular channels (Fig. 4.3f). Micropapillary adenocarcinoma can be present in combination with other types in variable amounts. Although it is unclear how much of this component is significant, recognition of any micropapillary component, should be reported, as it imparts a significantly worse prognosis and a high incidence of LN metastasis [30]. Serrated adenocarcinoma shows architecture similar to serrated polyps and is believed to arise via serrated pathway of CRC (Fig. 4.3g). The tumors may show MSI-low, MSI-high or have K-RAS or B-RAF mutations, amongst other distinct molecular changes [31, 32]. Cribriform comedo-type adenocarcinoma shows extensive large cribriform glands with central necrosis analogous to breast adenocarcinomas (Fig. 4.3h), and is usually microsatellite stable with CpG island hypermethylation [33].

Other types of primary carcinoma such as clear cell carcinoma, choriocarcinoma-like carcinoma, large cell or small cell neuroendocrine carcinoma and hepatoid adenocarcinoma do occur in the rectum, but are uncommon. Squamous cell carcinomas are mostly seen as an extension from an anal primary, however, rarely these can be rectal primaries.

Tumor Grading

Adenocarcinomas are graded predominantly based on the extent of glandular appearance. Despite a significant degree of interobserver variability, histologic grade has repeatedly been shown to be an important stage-independent prognostic parameter. Specifically, it has been demonstrated that high tumor grade is an adverse prognostic factor. While traditionally 3- or 4-tiered grading systems: grade 1 (well-differentiated, lesions exhibit glandular structures in >95 % of the tumor) (Fig. 4.3a); grade 2 (moderately differentiated, adenocarcinoma has 50–95 % glands); grade 3 (poorly differentiated, adenocarcinoma has 5–50 % glands) and grade 4 (undifferentiated, < 5 % of tumor with glandular differentiation) have been used, the WHO classification now divides, these into low-grade (well and moderately differentiated adenocarcinomas) (Fig. 4.3b) and high-grade (poorly differentiated and undifferentiated adenocarcinomas) tumors [29]. Studies using the new 2-tiered grading stratification system suggest it is relatively simple, and more reproducibile, while maintaining its prognostic significance. Now CAP also recommends the 2-tiered grading system for grading CRC [34].

In practice, the weakness of the glandular-based grading system is that the estimation of the degree of gland formation is subjective that leads to significant interobserver variability, and ultimately limits the prognostic significance of the histological grade. Furthermore, grade should be established based upon the least differentiated component in heterogeneous tumors; however, the size of such a component has not been specified in any of the systems used in current practice. A proposal that takes into account the extent of poorly differentiated component, defined as a tumor area with no glandular formation, has been proposed recently [35]. Grade 3 was applied to

tumors for which the poorly differentiated component fully occupied the microscopic field of an X40 objective lens. For tumors having a smaller component, cancer clusters composed of at least 5 cells, but not forming glands, were counted in the microscopic field of an X4 objective lens where the clusters were the most common. Tumors with less than 10 clusters were classified as grade 1 and those with more than 10 clusters were classified as grade 2. Grade 1 tumors demonstrated 99.3 % cancer-related 5-year survival; grade 2, 86.0 %; and grade 3, 68.9 %, independent of pT and pN stage [35]. Additional studies demonstrated that this tumor grading system based on counting poorly differentiated cell clusters provided significant prognostic information with regards to progression-free survival and was more reproducible than the conventional grading system [36].

Invasive Growth Pattern and Lymphocytic Infiltration

Despite interobserver variability and absence of specific definition and diagnostic criteria, the nature of the advancing tumor margin and degree of lymphocytic infiltrate have been shown to be powerful prognostic indicators in rectal cancer. The majority of rectal cancers show a well- or moderately well-circumscribed (so-called "expanding") margin. An infiltrative margin, however, is frequently associated with perineural and lymphovascular invasion and confers worse prognosis [37, 38]. As stated above, the recently recognized micropapillary pattern and/or tumor budding, which are often present at the invasive front, are also associated with poor prognosis [39].

Lymphocytic infiltration including tumor-infiltrating lymphocytes (TIL), peritumoral lymphocytes and peritumoral lymphoid aggregates in CRCs has long been considered as an indicator of host immune response to tumor cells, and some studies show a better prognosis in their presence irrespective of the MSI status. Recent studies have shown that lymphocytic infiltration, especially CD3+ T cells or FOXP3+ regulatory T cells along the tumor invasive border or within the tumor stroma, and tumor-infiltrating CD8+ lymphocytes in the cancer cell nests are related to longer survival, early tumor stage, expanding growth pattern and lower levels of LVI in patients with CRC [40, 41]. The peritumoral lymphoid aggregates have been named as Crohn's-like reaction because it resembles inflammatory response in Crohn's disease [42]. Recently, TILs and to a lesser extent Crohn's-like reaction have gained attention because of their association with MSI-H status in most cases [43].

Microsatellite Instability-High Morphology

Identification of microsatellite instability-high (MSI-H) colorectal tumors is important, as DNA mismatch repair deficiency may serve as a prognostic marker of patient outcome, predict response to chemotherapy, and serve as a screening tool for Lynch syndrome. These tumors are commonly located in the right colon, however, they also can be seen in left side with approximately 8 % of rectosigmoid junctional and rectal cancers being MSI-H [44]. MSI-H left-sided and right-sided CRCs [45] have similar histologic features including TILs (Fig. 4.4a), Crohn's-like lymphocytic reaction (Fig. 4.4b), mucinous/signet-ring differentiation, and/or a medullary growth pattern. These histologic features have a high predictive value for MSI-H; however, a significant portion of patients with Lynch Syndrome or sporadic MSI-H colorectal cancer will be missed if testing for MSI is solely based on tumor morphology or patient's clinical/family history. Hence, recently universal testing for MSI has been advocated in all newly diagnosed CRCs regardless of patient's clinical/family history and tumor morphology [46].

Tumor Budding

Tumor budding is described as the presence of detached single cells or clusters of up to 4 or 5 cells (Fig. 4.5a, b) along the invasive tumor front [47]. In contrast to the tumor border configuration

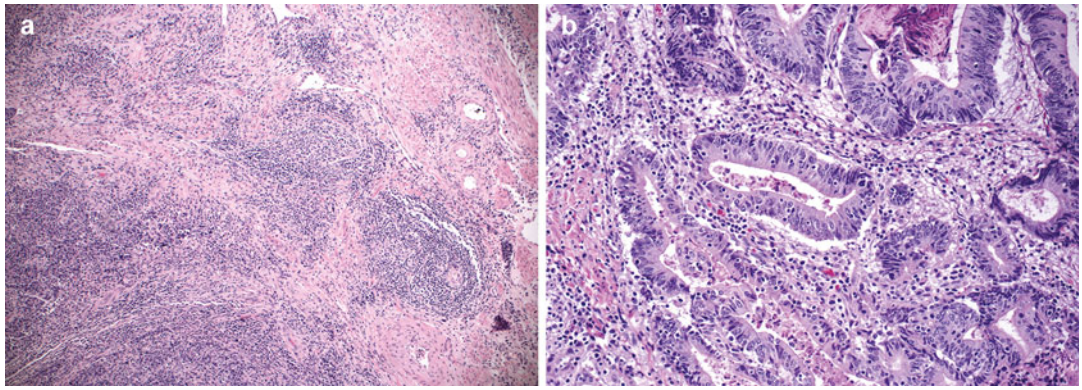

Fig. 4.4 Rectal adenocarcinoma showing with features associated with high microsatellite instability. (**a**) Adenocarcinoma with Crohn's-like lymphocytic reaction; (**b**) Adenocarcinoma with many intratumoral lymphocytic infiltration (Hematoxylin and eosin stain)

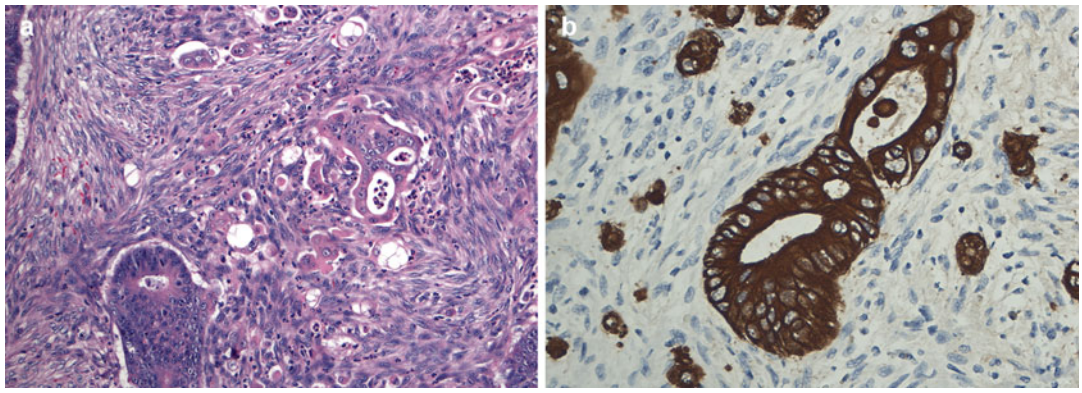

Fig. 4.5 Tumor budding. (**a**) Infiltrating single tumor cells or clusters of up to 5 tumor cells seen surrounding well formed moderately differentiated glandular structures present at the invasive front of the adenocarcinoma (Hematoxylin and eosin stain); (**b**) Tumor budding highlighted by cytokeratin immunostain which shows many more tumor cells that are difficult to appreciated on hematoxylin and eosin stain

(infiltrative or pushing pattern), tumor budding is best identified at high magnification, although one can suspect its presence by the typical cellular myofibroblastic response around the advancing edge of the tumor at low magnification that is typically seen in low grade tumors with pushing borders. This phenomenon has been suggested to represent epithelial–mesenchymal transition, thus increasing the migratory capacity, metalloproteinase expression, and resistance to apoptotic signals, corresponding to a more aggressive biological behavior [48, 49]. Tumor budding scores based on 10 high-power field evaluation show excellent inter-observer agreement and high-grade budding (>10 buds across 10 high-power fields) has been shown to be associated with a higher tumor grade, higher TNM stage, LVI, infiltrating tumor border and reduced survival [50]. Although tumor budding is independently associated with LN and distant metastases, and shorter disease-free and overall survival [51, 52], it is not yet universally reported by pathologists due to the absence of consensus criteria for assessment and cut-off values.

Lymphatic and Venous Invasion

Vascular invasion is currently an independent prognostic factor in CRC influencing disease

progression and survival [14]. The vascular system consists of arterial, venous and lymphatic vessels, however, it is not always possible to distinguish lymphatic channels from capillary-type vessels, because both are small, thin-walled structures. Theoretically, these two types of invasions should lead to different consequences: lymphatic invasion should be predictive of LN metastasis, whereas vascular invasion should be the source of systemic or hepatic metastases. Use of lymphatic endothelial markers, such as podoplanin (D2-40) or lymphatic endothelial hyaluronan receptor (LYVE-1) as well as capillary endothelial markers, such as CD31 or CD34 can distinguish between lymphatic and capillary vessels. However, these are not routinely used in practice. Thus, the presence of small vessel tumor invasion is best reported as lymphovascular invasion (LVI) or angiolymphatic invasion [53]. The AJCC staging manual (7th edition) combined lymphatic and venous invasion into LVI and recommends reporting its presence or absence in CRCs. Large vessel invasion, in particular of extramural venous invasion, has been shown to be an independent powerful indicator of unfavorable outcome and increased risk of synchronous or metachronous distant, especially liver metastasis; however, there are significant interobserver and interinstitutional variations in their recognition due to lack of standard guidelines [53–56].

Perineural Invasion

Perineural invasion (PN) is an often under-reported high-risk pathologic feature in rectal cancer with a widely varying detection rate from 9 to 42 % [57]. It has a similar impact as LVI and should be reported as a prognostic (site-specific) factor, although it does not affect the tumor staging [5, 19]. A 3-tiered grading system (Pn0, no perineural invasion; Pn1a, intramural perineural invasion; Pn1b, extramural perineural invasion) proposed by the Japanese Society for Cancer of the Colon and Rectum (JSCCR) showed 5-year disease-free survival as 88 %, 70 %, and 48 %, respectively, independent of T or N stage [58]. However, most current systems just report the presence or absence of PN.

Tumor Deposits

Tumor deposits (TD) are nodules of tumor present in the pericolonic/perirectal fat that lack recognizable lymphoid tissue. While we have been fixated with the notion that these likely represent nodal metastases with complete replacement of the nodal architecture by the tumor, studies suggest that these may also represent venous invasion, perineural invasion, discontinuous spread of tumor or the advancing edge of the tumor, each with different prognostic implication [59]. TDs have been shown to be associated with reduced disease-free and overall survival [60]. The interpretation of TDs which first appeared in the 5th edition AJCC staging system in 1997 has changed many times over the years. In the current 7th edition, TDs are considered as such recognizing their varied nature. Their number should be recorded in the pathologic report, and they are classified as pN1c in the absence of unequivocal LN metastases, regardless of the pT category; however, once nodal metastasis are identified, the final staging is performed as per the nodal counts (pN1-2). Equating them to LN metastasis likely underestimate their prognostic impact; we expect that this will be addressed in subsequent staging schemes [61].

With regards to rectal cancer it should be noted that neoadjuvant therapy may create residual tumor islands separate from the main tumor mass, which when located in perirectal fat are difficult to differentiate from true TDs. Since these islands are often the remains of advanced-stage tumors, their presence indicates that tumor regression has taken place, which can be linked to a better prognosis. Therefore, some advocate omitting TD terminology after neoadjuvant therapy, and simply to consider such residual islands in the ypT3 category [62].

Serosal (Peritoneal) Involvement

Although the rectum is mostly extraperitoneal, the upper third is variably covered by peritoneum; as such, tumors occurring in upper rectum can potentially involve the serosa and be staged as pT4a. Serosal involvement is an independent

prognostic factor in rectal cancer predicting a poor prognosis and should not be confused with CRM involvement [63]. Serosal involvement (T4a) implies a higher risk for intraperitoneal tumor spread and necessitates systemic chemotherapy, whereas positive circumferential margin often indicates increased risk of local recurrence and necessitates treatment modalities that can improve local control, including radiotherapy [64]. Visceral peritoneal involvement is often underestimated and can be easily missed without thorough sampling and/or sectioning and requires careful examination. Data suggest that presence of inflammatory reaction, mesothelial hyperplasia, and/or serosal erosion/ulceration when the tumor is present very close to the serosal surface (<1 mm) is sufficient to indicate serosal involvement and one need not wait to see free tumor cells on the serosal surface [11].

The colorectal serosa is formed by a mesothelial layer supported by a basement membrane containing elastic lamina. Use of elastin stain to demonstrate breach of the peritoneal elastic lamina has also been suggested to serve as evidence of possible serosal involvement [65, 66]. However, the lack of demonstrable peritoneal elastic lamina in all CRCs and the inconsistent sensitivity of the elastic staining reagents limit its wide acceptance in routine practice.

Circumferential (Radial) Resection Margin (CRM)

The CRM represents the adventitial soft tissue margin closest to the deepest penetration of tumor and is created surgically by blunt or sharp dissection of the retroperitoneum [11]. Multivariate analysis has suggested that CRM involvement is a critical factor in predicting cancer-specific survival, local recurrence, and distant metastasis in rectal cancer [4, 67, 68]. A positive CRM in rectal cancer increases the risk of recurrence by 3.5-fold and doubles the risk of death from disease [67]. The distance between the closest leading edge of the tumor and the CRM should be measured and recorded in mm in the report/staging form in all rectal carcinomas

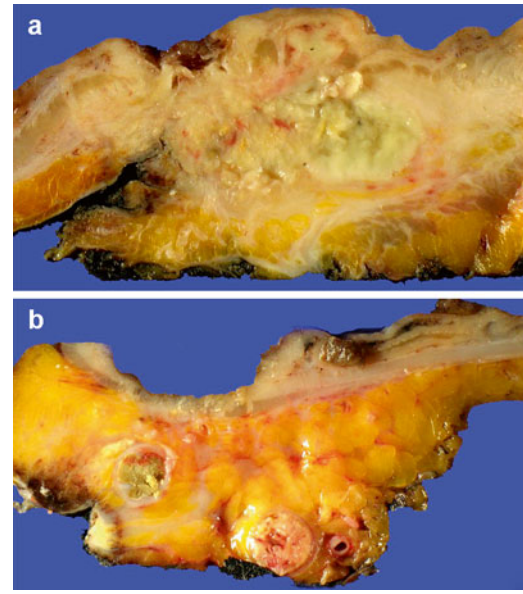

Fig. 4.6 Assessment of circumferential resection margin (CRM) involvement. (**a**) Slicing through tumor and mesorectum showing tumor within mesorectal fat with negative CRM. This patient had been treated with neoadjuvant therapy. (**b**) Slicing through tumor and mesorectum showing CRM focally involved by tumor and a tumor deposit present at the CRM

[19]. A positive CRM is defined as tumor ≤1 mm from the margin, because local recurrence rates are similar from 0 to 1 mm (Fig. 4.6). This assessment includes both tumor within a LN and direct tumor extension. A positive CRM secondary to LN metastasis in some studies has been associated with lower recurrence rates than that by direct extension [9, 69]. Thus, if CRM positivity is based solely on intranodal tumor, it should be stated in the pathologic report.

Involvement of the CRM in a patient after therapy with curative intent (e.g., surgical resection for cure) is designated under R classification [19]: R0 for complete tumor resection with all negative margins; R1 for microscopic positive margin and R2 for gross residual tumor. As mentioned above, grading of the completeness of the TME based on gross examination, however, is not assigned any category in the AJCC TNM system and the practice in various pathology laboratories is inconsistent. Of note, the CAP has now omitted the documentation of R category in pathologic reporting of CRCs.

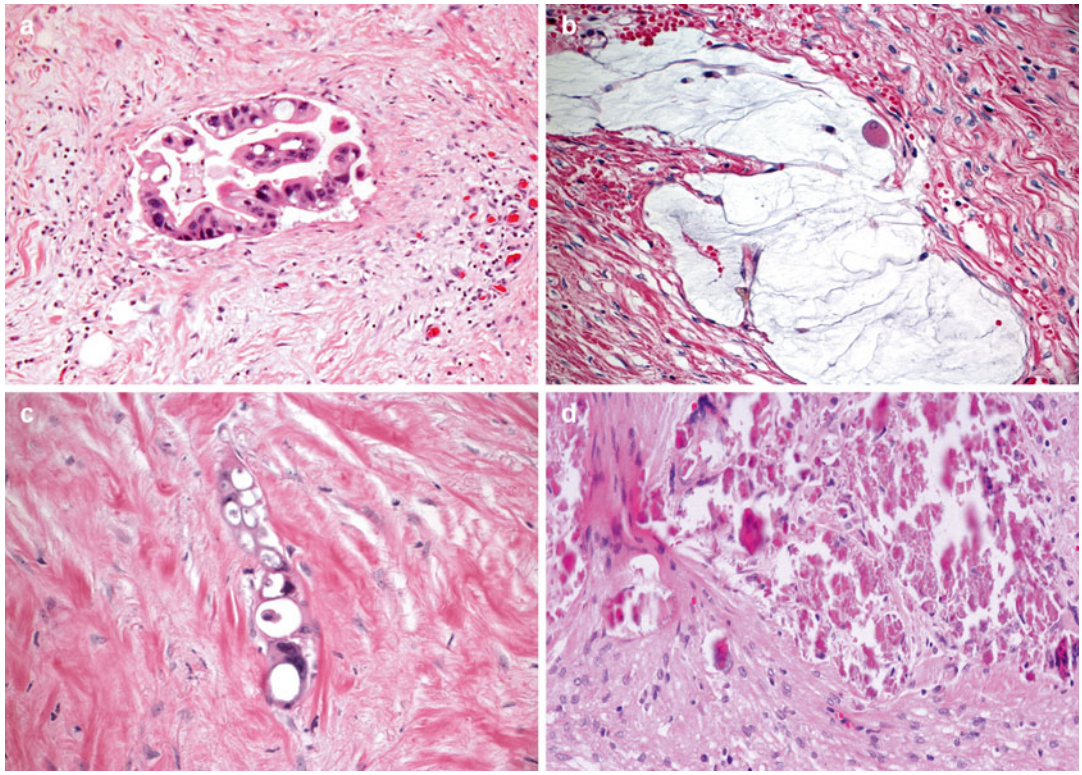

Fig. 4.7 Common morphologic patterns of rectal carcinoma with neoadjuvent therapy effect. (**a**) Cytoplasmic eosinophilia and vacuoles in the tumor cells; (**b**) accellular mucin pool; (**c**) Stromal fibrosis with residual tumors cells showing coarse cytoplasmic vacuoles and hyperchomatic nuclei; (**d**) Tumor necrosis and stromal fibrosis (Hematoxylin and eosin stain)

Neoadjuvant Therapy Effect

Multimodality therapy has been successfully implemented in the treatment of locally advanced rectal cancers and increasing numbers of patients now receive pre-operative neoadjuvant therapy. The extent of tumor response to the neoadjuvant therapy has the strongest prognostic impact in the treated rectal cancers. The 7th edition AJCC Cancer Staging Manual [19], the CAP [11] and the NCCN rectal cancer guidelines [5] require comment on neoadjuvant treatment effect that should be reported as: 0 (complete response) – no viable cancer cells; 1 (moderate response) – single cells or small groups of cancer cells; 2 (minimal response) – residual cancer outgrown by fibrosis and finally 3 (poor response) – extensive residual cancer or minimal or no tumor kill. Of note, tumor regression should be assessed only in the primary tumor, LN metastases should not be included in the assessment.

Some tumors show little or no response to neoadjuvant therapy, however, microscopically a variety of morphological changes are often seen after neoadjuvant therapy and need to be recognized (Fig. 4.7a–d). The residual cells may show therapy induced nuclear pleomorphism, increased cytoplasmic eosinophilia and vacuoles, and degenerative changes. Some cases may show presence of neuroendocrine cells, admixed with or without an adenocarcinoma component, and it is speculated that these cells are chemoresistant and hence survive. Significance of residual endocrine cells post chemoradiation has been studied only in few studies which suggest they have no added adverse prognostic impact beyond that dictated by stage of residual tumor [70]. Sometimes mucin pools with or without associated tumor

cells are seen. While mucin pools associated with viable appearing tumor cells are staged as per the deepest invasion of the tumor or mucin, evidence suggests that acellular mucin pools present in the bowel wall or LNs behave similar to when no residual tumor is identified [71]. Therefore, acellular mucin pools in specimens from patient receiving neoadjuvant therapy are considered as complete eradication of tumor. A variety of other secondary changes are seen that include stromal fibrosis, inflammatory cell infiltration, calcification and foreign body giant cell reaction which by themselves have no prognostic implication.

The Staging of Rectal Cancer

Dukes Staging System

Pathologic tumor staging remains the fundamental guide for prognostication and treatment decision in managing rectal cancer. Significant improvements have been made in the staging system since the classical proposal introduced by Dukes in 1932 [72]. The original 1932 Dukes classification was based on the extent of disease, as evaluated by the degree of tumor infiltration through the bowel wall, and the presence or absence of LN involvement [72]. Dukes' A, B, C staging system underwent several subsequent revisions and modifications by Dukes himself as well as other investigators, and it used to be the most popular CRC staging system (Table 4.1). Although Dukes' staging was a simple, reproducible and widely recognized staging system, it did not take into account the extent of LN involvement, tumor grade, and other pathologic features of tumors. Also there was lack of incorporation of clinical information as well as difficulty in comparing one clinical trial to another due to various versions of Dukes' classification. The Dukes' staging system has largely been replaced by the more detailed AJCC/International Union Against Cancer (UICC) Tumor-Node-Metastasis (TNM) system.

Table 4.1 Dukes staging of colorectal cancer

Stage	Description
A	Growth of primary tumour does not penetrate beyond muscularis propria; no nodal metastases
B	Growth of primary tumour extends beyond muscularis propria; no nodal metastases
C1	Lymph node metastases present but apical node(s) free of tumour
C2	Metastases within apical lymoh node(s)

TNM Staging System

The TNM staging system of the AJCC/UICC has gained popularity over the years and is nowadays the standard staging system for cancers including CRCs [73]. The TNM staging system describes the anatomic tumor extent. It is well known that the best estimation of prognosis in rectal cancer is related to the anatomic extent of disease determined by pathologic examination of the resection specimens. The TNM staging system has the ability to separately classify the individual tumor (T), lymph node (N), and metastatic (M) elements and then group them into different stages. Revisions of TNM staging are made periodically in response to newly acquired clinical data and improved understanding of cancer biology and factors affecting prognosis. Despite some criticisms, periodic update is one factor that makes the AJCC/UICC TNM staging system the most clinically useful staging system and accounts for its worldwide use [74].

TNM Descriptors

Staging is performed at various points in the care of cancer patients, such as pretreatment or "clinical stage", post-surgical or "pathologic" stage, post-treatment stage or cancers identified at autopsy. Prefixes such as "c", "p", "y", "r" and "a" are used to denote the nature of staging. The "c" prefix indicates clinical (pretreatment) stage which is usually determined by imaging techniques carried out at diagnosis before treatment or when pathologic classification is not possible. The "p" refers to the pathologic determination of the TNM as opposed to the clinical one. Pathologic classification is based on gross and

microscopic examination of the resection specimen of a previously untreated primary tumor. Assignment of pT requires a resection of the primary tumor or an excision biopsy adequate to evaluate the highest pT category, pN entails removal of nodes adequate to validate LN metastasis, and pM implies microscopic examination of distant lesions. The "y" is used for those cancers that received neoadjuvant pretreatment. The ycTNM or ypTNM categorizes the extent of tumor actually present at the time of that examination. The "r" indicates a retreatment or recurrent tumor after a disease-free interval and is recorded as rcTNM or rpTNM.

The "a" prefix is used to stage cancers that recognized only at postmortem.

Of note, a TNM stage grouping can be constructed using a combination of clinically derived and pathologically derived data (e.g., pT1cN0cM0), when pathologic data are not readily available.

T Category Considerations

Tumor extent is classified as Tis, T1, T2, T3 and T4 in rectal cancers and it appears that the prognosis worsens with deeper invasion into the bowel wall, even within a given layer, e.g. submucosa, muscularis propria or perirectal soft tissues (Table 4.2). Unlike other organs, carcinoma in situ (pTis) in the colon and rectum is defined as "cancer cells confined within the glandular basement membrane (intraepithelial) or mucosal lamina propria (intramucosal) with no extension into the submucosa" [19]. The staging of carcinomas with lamina propria invasion (intramucosal carcinoma) similar to "carcinoma in situ" is unique to large bowel. The rationale is that the potential of LN metastasis with intramucosal CRC is virtually nil, and lack or sparse lymphatics in lamina propria is believed to be responsible for this phenomenon, although studies show that lymphatic channels are present in the colorectal lamina propria [75]. Tumors are also capable of inducing formation of neo-lymphatics as demonstrated by lymphatic emboli in rare cases of intramucosal carcinoma. However, we would warn caution when staging poorly differentiated and aggressive forms of CRC such as signet ring type or micropapillary type as Tis, especially when involving the deep mucosa [76].

Tumor extension through muscularis mucosae into the submucosa is classified as pT1. The frequency of LN metastasis is 6–12 % in pT1 tumors and it relates to the depth of invasion [77]. To evaluate the depth of submucosal invasion, classification according to vertical invasive level between muscularis mucosae and muscularis

Table 4.2 AJCC cancer staging for colon and rectal carcinomas

Primary tumor (T)	
Tx	Primary tumor cannot be assessed
T0	No evidence of primary tumor
Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
T1	Tumor invades submucosa
T2	Tumor invades muscularis propria
T3	Tumor invades through the muscularis propria into pericolorectal tissues
T4a	Tumor penetrates to the surface of the visceral peritoneum
T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in 1–3 regional lymph nodes
N1a	Metastasis in one regional lymph node
N1b	Metastasis in 2–3 regional lymph nodes
N1c	Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolic or perirectal tissues without regional nodal metastasis
N2	Metastasis in 4 or more regional lymph nodes
N2a	Metastasis in 4–6 regional lymph nodes
N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	
M0	No distant metastasis
M1	Distant metastasis
M1a	Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node)
M1b	Metastases in more than one organ/site or the peritoneum

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propria into three categories (sm1, upper third; sm2, middle third; sm3; lower third of submucosal layer) has been used with rates of LN metastasis being 2, 8 and 23 % respectively [78]. Measurement of depth of submucosal invasion is also proposed in the JSCCR guideline for the treatment of CRC [79]. The JSCCR criteria for identifying curable pT1 CRC after endoscopic resection is as follows: differentiated adenocarcinoma, no LVI, submucosal invasion depth <1,000 μm and low-grade tumor budding. Resection with LN dissection is recommended when the pT1 tumor is poorly differentiated adenocarcinoma, with high-grade tumor budding, LVI or depth of invasion >1,000 μm [79]. However, other studies demonstrated that high-grade tumor budding, poorly differentiated adenocarcinoma and LVI, irrespective of depth of submucosal invasion, predicted LN metastasis [80, 81]. Furthermore, the prognosis of pT1 rectal carcinoma resected by endoscopic resection or local excision is >90 %, even if LN metastasis is present, and the prognosis after curative resection does not differ significantly between patients with and without LN metastasis [82]. Currently, the depth of submucosal invasion is not incorporated in the AJCC TNM staging system.

Tumor extension into the muscularis propria is classified as pT2. The incidence of regional LN metastases ranges from 24.3 to 29.7 % in pT2 rectal cancer [83]. Sub-classification of pT2 tumors by depth of invasion into pT2a (infiltration of the inner circumferential layer) and pT2b (infiltration of the outer longitudinal layer) has been investigated and showed higher risk of LN metastasis in pT2b than that pT2a tumors [84]. However, other study did not reveal any significant difference in tumor grade, LVI, LN involvement or prognosis between pT2a and pT2b tumors [85]. Currently, the clinical significance of sub-classification of pT2 rectal cancers is unclear.

Tumor extension through the muscularis propria into pericolorectal tissues is classified as pT3. Of note, invasion of the external sphincter is classified as pT3, whereas invasion of the levator ani muscle is classified as pT4. Some have advocated that the depth of soft tissue invasion in pT3 tumors should be reported based on the studies that more deeply invasive tumors were associated with a worst outcome [85–87]. The sub-classification of pT3 rectal cancer has been performed according to the depth of soft tissue invasion by using a 4-tiered (pT3a: 1 mm, pT3b: 1–5 mm, pT3c: 5–15 mm, pT3d: >15 mm) [85, 86] or 2-tiered (<4 mm/>4 mm; <5 mm/>5 mm; <6 mm/>6 mm) stratifications [87–89]. Further prospective studies to determine the reliability and validity of one widely accepted cut-off value and standardized method of assessment of invasion depth are warranted. Currently, pT3 sub-classification is not recommended by the CAP and the AJCC staging system.

Tumor invasion of other organs or structures includes invasion of other segments of colorectum by way of the serosa is classified as pT4. The division of pT4 into pT4a and pT4b was introduced in the 6th edition AJCC staging manual: pT4a refers tumors invading adjacent structures or organs and pT4b refers tumors involving visceral peritoneum. However, the definitions of pT4a versus pT4b were reversed in the 7th edition AJCC staging manual [19]. This change was based mainly on analyses of the Surveillance, Epidemiology and End Results survival data (SEER) suggesting a better survival rate in patients with pT4a than those with pT4b tumors [90, 91]. While this may sound rational, further studies are required to determine the optimal sub-staging of pT4 CRCs [92].

N Category Considerations

Invasion in regional LNs is classified as N0, N1 and N2 (Table 4.2). For rectal cancer regional LNs include perirectal, sigmoid mesenteric, inferior mesenteric, lateral sacral, presacral, internal iliac, sacral promontory, superior rectal, middle rectal, inferior rectal LNs. Of note, metastasis to non-regional LNs such as external iliac or common iliac nodes is classified as distant metastasis and designated as M1. In the 7th edition AJCC staging manual, pN1c refers to TDs without regional nodal metastasis [19]. However, the significance of TDs (see above) and their role in

stage is still evolving. Nevertheless, attempt should be made to document the number and features of such TDs in addition to using the designation pN1c, as that will serve as data for future analysis.

Sentinel lymph node (SLN) mapping has been used in a variety of cancers however, its role in rectal cancer remains controversial, though some have advocated that it should be considered in every patient diagnosed with rectal cancer without clinical evidence of LN involvement or metastatic disease [93, 94]. The lymphatic drainage in rectal cancer is not sufficiently "orderly and sequential" to apply SLN evaluation with frequent skip or aberrant metastases. In addition, studies show that "upstaging" of LNs by SLN mapping only changed the staging in 1 % of patients with CRC and its clinical significance remains unclear [95–97]. Hence, involvement of a SLN in rectal cancer does not change the extent of the resection and SLN mapping in rectal cancer is still investigational [5].

The prognostic significance of micrometastasis and isolated tumor cells (ITC) has been studied in a variety of cancers including CRC [98]. Micrometastasis is defined as a metastasis measuring >0.2 mm and ≤2.0 mm in diameter and is designated as pN1 (mic) in LNs or M1 (mic) at distant sites. ITC is defined as single tumor cells or small clusters of tumor cells measuring ≤0.2 mm in diameter, usually found by special techniques such as immunohistochemical staining and designated as pN0 (i+). It should be noted that ITC identified on H&E stain are annotated similar to ITC seen on immunohistochemical stains. In contrast to micrometastasis, ITC are currently considered as pN0, though recent systematic review and meta-analysis show decreased survival in patients who had evidence of ITC in regional nodes [98]. Of note, special/ancillary techniques such as multiple tissue levels, immunohistochemistry, or polymerase chain reaction to detect ITC are not recommended in routine clinical practice for regional LN examination however when identified, these should be clearly mentioned in the pathologic report.

M Category Considerations

Metastasis to any nonregional LN or metastasis to any distant organ or tissue is categorized as M1 disease (Table 4.2). Metastasis confined to one organ or site (e.g., liver, lung, ovary, nonregional node) is classified as pM1a, whereas metastases in more than one organ/site or the peritoneum is classified as pM1b. MX category has been eliminated from the 7th edition AJCC staging system, since pathologist often does not have the information to assign M. Accordingly, the CAP also has dropped the M component [11].

Of note, cases with a biopsy of a possible metastatic site that shows ITC such as circulating tumor cells or disseminated tumor cells, or bone marrow micrometastases detected by immunohistochemistry or molecular techniques are also classified as cM0 (i+) to denote the uncertain prognostic significance of these findings and to classify the stage group according to the T and N and M0.

Anatomic Stage/Prognostic Groups

In contrast to the 6th edition, the 7th edition AJCC staging manual has renamed the "Anatomic Stages" to "Anatomic Stages/Prognostic Groups" to highlight the increasing role of non-anatomic factors [19]. Rectal cancers are grouped into stages I, II, III and IV. Different groups have been expanded into subsets (e.g., stage II into stage IIA, IIB and IIC) for more refined prognostic information (Table 4.3).

Site-Specific Prognostic Factors and Molecular Markers

Seven new prognostic factors that are clinically significant have been included in the 7th edition AJCC staging manual, in addition to the prior notation of serum CEA levels [19]. The new site-specific factors include: TDs, tumor regression grade, CRM, MSI and PN and their importance in rectal cancer has been discussed above. Discovery of prognostic and therapeutic

Table 4.3 Anatomic stage/prognostic groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2a	M0
	T1-T2	N2b	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

biomarkers at a molecular level remains one of the most exciting developments in the era of personalized medicine. While there has been an explosion of our knowledge with regards to the molecular pathology of CRC, very few molecular markers have been validated for clinical use so far; however, there are many that seem promising and are likely to find clinical application in the near future. A detailed discussion of molecular pathology is beyond the scope of this chapter and only few pertinent issues are discussed. Two new molecular prognostic factors included in the 7th edition AJCC are K-RAS mutation and 18q loss of heterozygosity (LOH) [19]. K-RAS mutation is associated with lack of response to treatment with monoclonal antibodies against the epidermal growth factor receptor (EGFR) in patients with metastatic CRC. While clinical guidelines for K-RAS mutational analysis are evolving, current provisional recommendations from the American Society of Clinical Oncology are that all patients with stage IV CRC who are candidates for anti-EGFR therapy should have their tumor tested for K-RAS mutations [99]. Although the loss of 18q LOH is considered a prognostic marker, its value in guiding clinical management is controversial. Of note, currently neither of the prognostic factors is required for staging, though their prognostic and predictive values have been acknowledged. The significance of MSI has already been discussed above and is now routinely tested in most centers.

In addition to the above mentioned prognostic (site-specific) factors, molecular profiling, including B-RAF, PIK3CA, PTEN, N-RAS and other relevant biomarkers has been recommended for optimal selection of targeted therapies, particularly anti-EGFR targeted therapies [100]. Both the RAS-RAF-mitogen activated protein kinase (MAPK) pathway and the phosphoinositide 3-kinase (PI3K)-PTEN-AKT pathway are involved in EGFR signaling [100]. Mutations in PIK3CA lead to loss of PTEN expression. PTEN gene expression and PIK3CA mutations have been shown to be associated with a shorter progression-free survival and overall survival, and are predictors of clinical benefit to anti-EGFR antibody therapy in patients with KRAS wild-type metastatic CRC [101]. Recently, the CAP provided template to be used for reporting results of these biomarker testing of specimens from patients with CRC [102]. Similar to other prognostic factors, these biomarkers are not part of the TNM staging system, but it is recommended that they should be recorded, if available [19].

Summary

Current treatment of rectal cancer requires a multidisciplinary collaboration. As outlined in this chapter, pathological gross and microscopic examination and proper reporting and staging of rectal cancer specimen are indispensable part of the management of rectal cancer. Currently, the AJCC TNM staging system is the most widely accepted staging system worldwide. It is necessary to adopt standard protocols for uniform staging and reporting of rectal cancer. The findings of underlying molecular pathways have deepened our knowledge in understanding the pathogenesis and made it possible to facilitate targeted/personalized therapy in rectal cancers. In this context, the work of pathologist has changed substantially from merely making the initial diagnosis to further evaluation of pathological risk factors and molecular changes to optimize and evaluate the effectiveness of treatment.

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Genetics, Screening, and Chemoprevention

5

Samantha J. Quade and Paul E. Wise

Abstract

The last few decades have seen tremendous advances in the understanding of human genetics, especially since the sequencing of the human genome in 2003. With rectal cancer, as with all cancers, genetics is at the center of its etiology, whether it is associated with an inherited syndrome or a somatic mutation from environmental or other oncogenic factors. Understanding the genetics of cancer has improved the understanding of all aspects of oncology and cancer biology, such as cancer progression and spread, cancer prevention, and cancer treatment, especially considering "personalized medicine" that allows an individual's cancer "genetic signature" to be used to tailor therapy. Unlike the surgical treatment of rectal cancer addressed in this textbook, there is little unique to rectal cancer relative to colon cancer when discussing cancer genetics and cancer biology. Instead, most of the research and advances in this field have focused on both colon and rectal cancer (CRC) based on their indistinguishable genetic signature [1], and therefore this chapter will focus on the genetics of CRC with particular attention to the impact of genetics on cancer development as well as cancer outcomes and chemotherapeutic treatment. Additionally, CRC screening and chemoprevention options, critical for early detection and prevention efforts and also not often specific to rectal cancer, will be addressed.

Keywords

Rectal cancer genetics • Colorectal cancer genetics • Colon cancer genetics • Colorectal cancer screening • Colorectal cancer prevention

Introduction

The last few decades have seen tremendous advances in the understanding of human genetics, especially since the sequencing of the human genome in 2003. With rectal cancer, as with all

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cancers, genetics is at the center of its etiology, whether it is associated with an inherited syndrome or a somatic mutation from environmental or other oncogenic factors. Understanding the genetics of cancer has improved the understanding of all aspects of oncology and cancer biology, such as cancer progression and spread, cancer prevention, and cancer treatment, especially considering "personalized medicine" that allows an individual's cancer "genetic signature" to be used to tailor therapy. Unlike the surgical treatment of rectal cancer addressed in this textbook, there is little unique to rectal cancer relative to colon cancer when discussing cancer genetics and cancer biology. Instead, most of the research and advances in this field have focused on both colon and rectal cancer (CRC) based on their indistinguishable genetic signature, and therefore this chapter will focus on the genetics of CRC with particular attention to the impact of genetics on cancer development as well as cancer outcomes and chemotherapeutic treatment. Additionally, CRC screening and chemoprevention options, critical for early detection and prevention efforts and also not often specific to rectal cancer, will be addressed.

Genetics of Colorectal Cancer

Central to our understanding of CRC biology are the cellular genetic alterations that lead to the development of cancer, whether those alterations are related to a hereditary germline mutation or an acquired (also known as somatic) gene mutation. Normal colonic cell maturation begins in the base of the colonic crypts with normal proliferation, differentiation, and eventual cell death occurring along the wall of the crypts and being mediated by a number of gene types including proto-oncogenes that mediate cellular proliferation and tumor suppressor genes that mediate cellular differentiation and programmed cell death (or apoptosis). The neoplastic process at a cellular level can be thought of simply as a single cell developing clonal expansion and uncontrolled cell growth, either through increasing cell division (primarily through dysfunction of the proto-oncogenes leading them to be termed "oncogenes") or by abnormal differentiation or through inhibition of programmed cell death (e.g., inhibition of normal apoptosis by tumor suppressor genes) [2]. Because oncogenes result from gene mutations that lead to activation of the proto-oncogenes, only a single allelic mutation is required to show the effect. Examples of oncogenes involved in colorectal carcinogenesis includes *KRAS*, *c-Myc*, and *BRAF*. Tumor suppressor genes on the other hand, because they require inactivation to lead to carcinogenesis, require "two-hits" or biallelic mutations (or "loss of heterozygosity" or LOH) to have a negative impact on cellular differentiation or apoptosis. Examples of these genes involved in CRC include *APC*, *p53*, *SMAD*, and *DCC*. Due to the burgeoning volume of genetic information identified with today's sequencing and microarray technology as now being associated with CRC, this chapter will not attempt to address every gene implicated in tumorigenesis, just those most frequently identified and those with the greatest implications to therapy.

Many of the above-mentioned tumor suppressor and oncogenes are central to the initial model of colorectal carcinogenesis that was first proposed by Fearon and Vogelstein in 1990 in which genetic alterations were linked with histologic changes that showed how normal colorectal mucosa could develop a benign adenoma and eventually progress to invasive adenocarcinoma (Fig. 5.1) [3]. This early model, still thought to be the primary genetic etiology for the development of most sporadic CRCs, has been supplemented with the recognition of other CRC molecular pathways such as the "serrated pathway" to colorectal carcinogenesis [4]. While somatic mutations in these genes, which cannot be passed down in the germline to offspring, account for the majority of CRCs, mutations in these classes of genes can occur more rarely in the germline as well. This results in a hereditary predisposition to CRC, including syndromes such as familial adenomatous polyposis (FAP) related to mutations in *APC* or juvenile polyposis syndrome related to mutations in *SMAD* or *BMPR1A* [5].

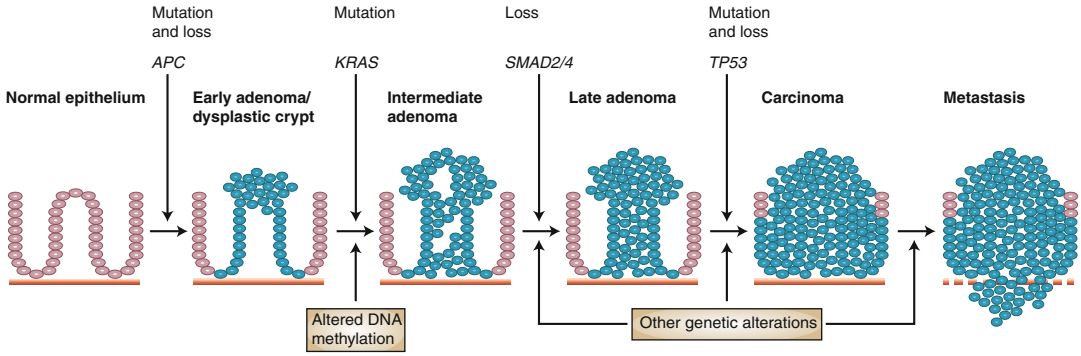

Fig. 5.1 Schematic of the adenoma-to-carcinoma sequence in the development of colorectal cancer. The primary genes that are mutated related to each step are indicated (See text for abbreviations and descriptions of the genes) (Adapted from Davies et al. [110]. With permission from Macmillan Publishers Ltd)

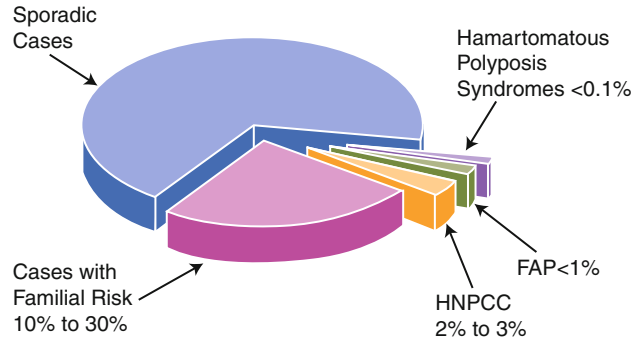

Fig. 5.2 Graph depicting the percentages of colorectal cancer patients that are considered to have sporadic, familial, and hereditary etiologies for their cancers (Reprinted from Burt [111]. With permission from Elsevier)

These hereditary mutations are usually acquired by being passed down from parents but can also occur sporadically in the germline as well. These hereditary conditions account for a small percentage of incident CRCs (approximately 5 %), whereas sporadic CRCs related to somatic gene mutations are the most common (approximately 70 %), and "familial" CRCs, likely related to more low risk genetic polymorphisms, make up approximately 25 % of incident CRCs (Fig. 5.2).

A third path for tumorigenesis is via DNA repair genes. These genes include mismatch repair (MMR) genes (e.g., *MLH1*, *MSH2*, etc.) as well as nucleotide- and base-excision repair genes (e.g., *MYH*). These genes are responsible for repair of DNA replication mistakes occurring during cellular division or those induced by exposure to environmental mutagens. If these genes are inactivated, DNA replication errors that routinely occur in every one in 1,000 DNA base pairings during cellular division are allowed to propagate through the daughter cell lines, with risks of subsequent alterations in other critical genes increasing (including proto-oncogenes or tumor suppression genes), leading to increased risk of cancer development [3]. Mutations in these types of genes can also be germline mutations, having been linked with inherited CRC syndromes such as hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome. More commonly than through germline mutations, carcinogenesis can occur through somatic mutations of these genes (as well as tumor suppressor genes), but gene inactivation can also occur through hypermethylation "silencing" of these genes' promoter regions, much like through the serrated pathway, which is known as an epigenetic phenomenon since the DNA itself is not mutated.

Oncogenes

When proto-oncogenes, which regulate cellular proliferation and differentiation, become mutated, they may become oncogenes producing unregulated transcription or growth factors. This can occur through a number of mechanisms including missense mutations (point mutations leading to an amino acid change altering gene expression or protein function), chromosome rearrangement (altering gene expression or protein function), or through gene amplification (copy number increase of a portion of a chromosome leading to increase in gene expression). Oncogenes behave such that a mutation in one of the two alleles is sufficient to produce activation and phenotypic expression of the mutated gene. Oncogenes implicated in sporadic CRC include *RAS* genes, *c-Myc*, and *BRAF*.

RAS Family

The *RAS* oncogene family includes three cellular variants Harvey- RAS (*HRAS*), Kirsten-RAS (*KRAS)* and Neuroblastoma-RAS (*NRAS*). *KRAS* is the most commonly mutated gene in CRC from the *RAS* family and lies on the short arm of chromosome 12 (12p), encoding for a guanosine triphosphatase (GTPase) protein involved in the transduction of growth and differentiation signals through the serine protein BRAF (see below) [6]. When mutated and activated, *KRAS* results in cellular overgrowth and dysplasia, likely as an early event in tumorigenesis, usually found after the initial *APC* mutation in CRC development (Fig. 5.1). *KRAS* mutations are present in about 50 % of CRC and colonic adenomas ≥1 cm compared with only 9 % of adenomas <1 cm, suggesting that in a proportion of CRCs, RAS activation is an early promoter rather than an initiator of tumorigenesis [7]. *KRAS* has also been implicated in the process of tumor invasion and metastasis. A study conducted comparing genetic and epigenetic changes in primary metastatic and non-metastatic CRC found that *KRAS* mutations were significantly associated with metastatic tumors [8].

Importantly, if particular *KRAS* mutations are present in CRC, there appears to be an impact on the targeted response of epidermal growth factor receptor (EGFR) agents such as cetuximab and panitumumab [9]. These monoclonal antibodies to EGFR are thought to work through binding of the agents leading to internalization of the receptor and blockage of downstream *KRAS* signalling. It is believed that *KRAS* mutations leading to a constitutively active protein (>90 % of the *KRAS* mutations, located on codons 12 and 13 in exon 2 of the gene) will negate the effects of the EGFR agent [10]. This has been confirmed in clinical studies. Karapetis, et al. analyzed 394 out of 572 patients with CRC who were randomly assigned to receive cetuximab plus best supportive care or best supportive care alone with the effectiveness of cetuximab being significantly associated with *KRAS* mutation status (P = 0.01). Patients with wild-type *KRAS* tumors showed significantly improved survival (median survival: 9.5 vs 4.8 months) with treatment with cetuximab compared with supportive care alone whereas patients with a mutated *KRAS* showed no difference to those who received supportive care alone with respect to overall survival or progression free survival [9]. This finding has been confirmed by meta-analyses of multiple studies on EGFR agents and *KRAS* status [11, 12] as well as recent trials [13, 14]. A number of European and North American Oncology Societies have recommended that all patients with metastatic CRC who are being considered for anti-EGFR therapy have their cancer tested in an accredited lab for *KRAS* mutations as standard of care [10].

NRAS, a membrane protein very homologous with *KRAS*, is found on chromosome 1 and is mutated in approximately 3–5 % of CRCs [10]. Mutations in this gene are often mutually exclusive from those in *KRAS* [15]. In a European Consortium trial with cetuximab, in *KRAS* non-mutated patients, *NRAS* mutants had a significantly lower response rate (7.7 % vs. 38.1 %; OR, 0.14; p = 0.013) than did *NRAS* wild types, and a trend for shorter progression free and overall survival [10]. Similarly, a 2013 study reviewing outcomes from 1,060 patients who had both *KRAS*

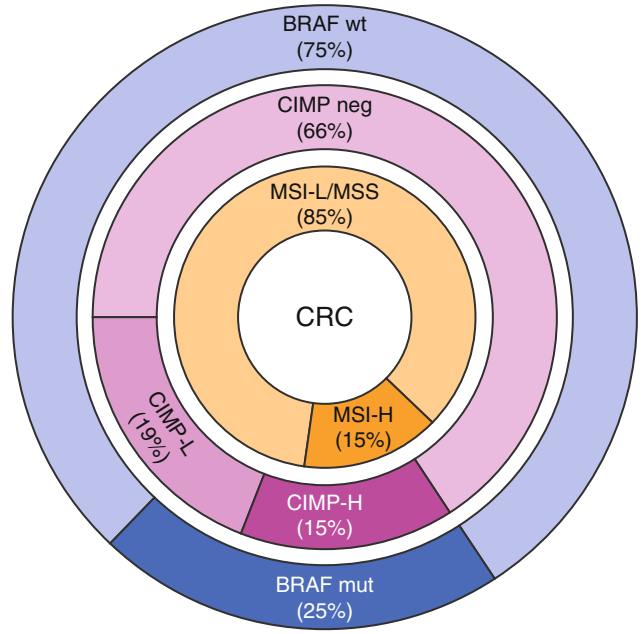

Fig. 5.3 Molecular etiologies of colorectal cancer which can be characterized by the presence or absence of microsatellite instability (MSI), the CpG island methylator phenotype (CIMP), or BRAF mutation status (wild type [wt] or mutant [mut]). MSI and CIMP are characterized as "high" (MSI-H and CIMP-H, respectively) and "low" (MSI-L and CIMP-L, respectively) (From Boland and Goel [112]. With permission from Oxford University Press)

and *NRAS* testing of their tumor showed worse outcomes (response rate and survival) with the use of panitumumab in the setting of any *RAS* mutation versus wild type tumors with the same chemotherapeutic regimen. The authors of this study concluded that anti-EGFR agents "…have no value in patients with metastatic colorectal cancer and mutated *RAS*" [14]. The results of these studies have impacted treatment guidelines such that many organizations advocate *KRAS* and *NRAS* (and possibly *BRAF*, if needed) testing of all metastatic tumors due to the impact of the results on treatment regimens [16].

c-Myc

The proto-oncogene *c-Myc* located on chromosome 8 has been associated with a number of cell functions including production of a transcription factor linked with cellular functions such as differentiation and apoptosis as well as tumor angiogenesis [17]. While the gene is most frequently linked with Burkitt's lymphoma, it is clearly involved in CRC tumorigenesis and has shown overexpression in the majority of CRCs. While it has not been used to direct therapeutics like the *RAS* genes have, *c-Myc* overexpressing CRCs have shown better survival, although this advantage appears to be negated in the presence of a mutant *p53* gene [18].

BRAF

BRAF is a signal transduction gene on chromosome 7q34 involved in the MAP kinase cellular pathways (associated with RAS) that impact cell division, proliferation, and apoptosis. *BRAF* is mutated in 5 % of sporadic "adenoma to carcinoma" CRCs but up to 25 % of all CRCs (Fig. 5.3). Approximately 90 % of the time the *BRAF* mutation is in the form of a substitution at nucleotide 1799 leading to valine (V) being substituted for by glutamate (E) at codon 600 (referred to as "V600E") which leads to a ten times more active BRAF protein than normal [19]. As noted above, *BRAF* mutations are often mutually exclusive of *KRAS* and *NRAS* mutations, and *BRAF* is less frequently found mutated when a CRC is associated with *p53* and *APC* mutations, suggesting that *BRAF* mutations may be part of a different CRC tumorigenesis pathway [1]. This pathway is often thought to be

related to epigenetic silencing of *MLH1* due to hypermethylation of its promoter region leading to a sporadic microsatellite instability high (MSI-H, see below) CRC developing via the CpG island methylator phenotype (CIMP) mechanism also known as the "serrated pathway" described by Jass. In fact, the odds ratio of an association between CIMP and a *BRAF* mutation in CRC is greater than 200 [20]. CRCs associated with *BRAF* mutations and the CIMP-high (CIMP-H) pathway are more often in older women, right side of the colon, and associated with smoking [21]. BRAF mutations are found in 40–87 % of sporadic MSI-H CRCs [22], but the order of molecular events leading to MSI-H and/or CIMP-H CRCs has not been completely defined when associated with *BRAF* mutations [21]. When a *BRAF* mutation is noted in association with an MSI-H CRC, the tumor is more likely to be a sporadic CIMP-H CRC as opposed to related to the hereditary condition Lynch syndrome caused by a germline MMR gene mutation, and therefore *BRAF* mutation testing can be used to determine the need for further MMR germline testing [19, 23]. *BRAF* testing is also indicated in CRCs that are *KRAS* and *NRAS* wild type if the patient is being considered for anti-EGFR therapy, as discussed above. Finally, the presence of a *BRAF* mutation in the setting of a microsatellite stable CRC (as opposed to MSI-H) is a poor prognostic indicator, although this does not yet inform therapy recommendations at the present time [19].

Tumor Suppressor Genes

This class of genes inhibits abnormal cell growth by slowing the cell cycle to allow for DNA repair and promote apoptosis when repair is no longer possible. They are recessive genes, meaning that both alleles must be lost or mutated for the gene to be inactive and phenotypically expressed. This inactivation can occur through a number of mechanisms including deletion or mutations that impact protein structure or function (nonsense mutations that lead to a truncated, nonfunctional protein, frameshift mutations that lead to translation of a different protein, or splice site mutations which leave introns present in the RNA that then translate an incorrect protein product). Tumor suppressor genes that play a role in CRC include *APC*, *DCC*, and *p53*.

Adenomatous Polyposis Coli (*APC*)

The *APC* gene is located on the long arm of chromosome 5 (5q) [24]. It encodes a protein that has multiple functional domains that mediate oligomerization as well as binding of a variety of intracellular proteins including β-catenin, ϒ-catenin, glycogen synthase kinase (GSK)-3β, Axin, tubulin, EB1 and hDLG [25]. Mutant, truncated APC proteins lack at least one type of β-catenin binding repeat. The APC protein is located in the basolateral membrane in the colorectal epithelial cells, and as the cells migrate up through the crypt columns, expression increases [26]. In colorectal mucosal cells, damage to the APC protein complex results in increased levels of free cellular β-catenin. Two important functions of β-catenin include cellular adhesion and cell signaling. Therefore, with a dysfunctional truncated protein related to the *APC* gene mutation, whether sporadic or germline, β-catenin accumulates in the nucleus and induces gene overexpression through aberrant cell signalling (via the Wingless [Wg] and Wnt signaling pathways first described in Drosphilia and mice) and increased cell proliferation. Additionally, since binding of β-catenin to cadherins (important for cell-to-cell adhesion) and to the APC protein is mutually exclusive [25], the cytoplasmic accumulation of β-catenin due to the presence of a dysfunctional non-binding APC protein enhances cell-to-cell adhesion and limits cell migration. This results in the balance of cellular turnover shifting from the lower proliferative compartment of the crypt to the upper villi, which is greatly impaired, leading to the accumulation of the hyperproliferating cells [27]. In addition, the truncated APC protein acts through the Wnt/β-catenin/Axin signalling pathway to alter apoptosis and cell cycle control which drives neoplastic cell proliferation further leading to the formation of an adenomatous, pre-cancerous polyp [4].

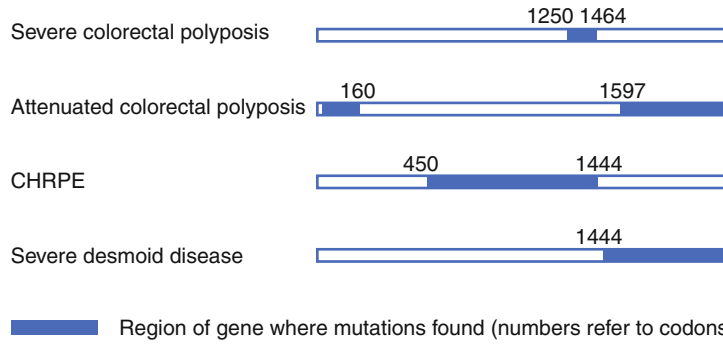

Fig. 5.4 Schematic of the APC gene to show some of the genotype-phenotype correlations noted in familial adenomatous polyposis (FAP) (From Beck et al. [113]. With kind permission from Springer Science + Business Media, Figure 37.3)

Germline mutations in *APC* result in FAP or one of its variants such as attenuated FAP (aFAP) or Turcot syndrome [28–32]. "Classic" FAP is an autosomal dominant disease that is associated with <1 % of all incident CRCs and leads to carpeting of the colon and rectum with hundreds to thousands of adenomatous polyps. When germline mutations occur in the *APC* gene, there is a very high phenotypic penetrance with 90–100 % of mutation carriers ultimately developing FAP. An individual with FAP has one mutated copy of the *APC* gene, and a subsequent somatic inactivation of the second wild type copy of the gene in a colonic epithelial cell leads to polyp initiation as discussed above [33]. In "classic" FAP, polyps usually start developing in adolescence, and if the colon is left intact, CRC will develop at an average age of 39 years [34–36]. In contrast, aFAP (also linked with the *MYH* base-excision repair gene and presenting as an autosomal recessive condition) is defined by fewer than 100 colorectal adenomas with polyp onset usually in the mid-30s and CRC developing on average by the mid-50s. Varied clinical presentations can be dependent on the location of the mutation within the *APC* gene [37]. Mutations that are proximal to codon 1249 or distal to codon 1465 (at the 3′ and 5′ ends of the *APC* gene) usually lead to the aFAP phenotype, whereas mutations between codons 1250 and 1330 (especially 1309 and 1328, which have been associated with higher rates of rectal cancer) lead to more extensive polyposis.

Extracolonic malignancies also occur in FAP including hepatoblastoma in children, papillary thyroid cancer, duodenal and gastric carcinomas, and ampullary and pancreatic carcinomas, as well as benign disorders such as dermoid cysts, desmoid tumors, osteomas, supernumerary teeth, and congenital hypertrophy of the retinal pigment epithelium (CHRPE). These extracolonic manifestations are often also related to the *APC* mutation site (Fig. 5.4). For example, CHRPE is found primarily in patients with mutations located between exons 9 and 15. Turcot syndrome is associated with FAP and medulloblastoma of the central nervous system when related to an *APC* gene mutation, but it has also been associated with Lynch syndrome (the hereditary condition related to germline MMR gene mutations) [34–36].

Genetic testing for FAP should first involve genetic counseling to ensure proper assessment for determination of the appropriateness of testing and to ensure that the patients and their families understand the implications of testing. Approximately 25–30 % of FAP patients will be related to *de novo* germline mutations, meaning that the parents of the affected patient do not carry the gene mutation or manifest the disease phenotypically. Mutation detection during testing depends on the phenotypic manifestations of FAP. In a study of over 7,000 patients with varying degrees of adenomatous polyposis, gene testing for *APC* and *MYH* were conducted with 80 % of those with "classic" FAP (>1,000 polyps) showing a pathogenic *APC* mutation and 2 % showing a biallelic *MYH* mutation. In contrast, those patients with between 20 and 99 adenomas had an APC mutation only 10 % of the time and a biallelic *MYH* mutation 7 % of the time [38]. Genetic testing other members of the family can be facilitated if the initially diagnosed affected proband has an abnormal test, allowing

for mutation-specific testing of those at-risk as opposed to need for full gene sequencing [39]. Having abnormal genetic testing or being at high risk without undergoing genetic testing (e.g., child of an FAP patient) will require a lifetime of surveillance beginning with a flexible sigmoidoscopy or colonoscopy at age 10–15 years and then every 12 months thereafter, as well as an upper endoscopy starting as age 20 years (or before colectomy) and occurring every 1–4 years to assess for gastric, periampullary and duodenal adenomas [40, 41]. For patients who have or may have aFAP, surveillance should consist of a full colonoscopy starting in the late teens and every 2–3 years thereafter secondary to the predominance of right sided colonic tumors, and upper endoscopy is also advised starting at age 25–30 years [41]. The National Comprehensive Cancer Network has advised that all of these "…patients be managed by physicians or centers with expertise in FAP" [41].

Because of the CRC risk related to these conditions, total abdominal colectomy and ileorectal anastomosis (IRA) or total proctocolectomy (TPC) and either end ileostomy or restoration of intestinal continuity through an ileal pouch anal anastomosis (IPAA) is advised for patients with FAP and aFAP. The timing of the operation is dependent on the phenotypic manifestations (e.g., development of CRC or high grade dysplasia, etc.) as well as symptoms of the disease (e.g., bleeding) as well as the maturity and understanding of the patient, but the ideal time is thought to be during the late teens or early 20s.

Operative choice for FAP or aFAP is based on the patient's phenotype (e.g., presence of cancer, rectal polyp number greater than 20, etc.) as well as their baseline health and continence status. Concerns about desmoid development (higher in women and after operations, especially in those with a family history of desmoids) and sexual function and fecundity (ability to become pregnant) may impact the decision of the operative approach as well. Concerns about rectal cancer and rectal polyp development impact operative choice as well. A Dutch Polyposis Registry study tried to assess the appropriate operative choice for FAP patients based on genotype by tracking those patients having undergone an IRA who were grouped based on the site of their *APC* gene mutation as an indicator of their polyposis phenotype. Rectal cancer risks ranged from 3 to 8 % in the rectal remnant and need for proctectomy during 20 years of follow-up ranged from 10 to 74 % depending on the initial phenotype, suggesting that more aggressive genotypes would benefit from TPC at the time of their initial operation [42]. An IPAA does not completely eliminate the risk of distal polyps or cancer issues, unfortunately, and therefore FAP patients that undergo IPAA require continued rectal remnant and pouch surveillance. A French group assessed adenoma development after IPAA for FAP with the risk of developing adenomas at 5, 10, and 15 years being 7, 35 and 75 %, respectively. No invasive carcinomas were noted. Interestingly, they did not find a correlation between adenoma development and the site of the *APC* mutation [43]. Also, a Dutch study on 254 patients after IPAA for FAP showed the cumulative risk of developing an adenoma in the pouch at 10 years to be 45 % with 12 % developing an advanced adenoma and 2 % developing carcinoma [44]. Therefore, depending on the polyp burden, pouchoscopy is recommended every 1–3 years after IPAA and proctoscopy every 6–12 months after IRA [41]. Chemoprevention options for FAP are discussed below.

p53

The *p53* gene is located on the short arm of chromosome 17p [45]. It functions as the gatekeeper by slowing the cell cycle to allow for DNA repair after damage by ultraviolet light, radiation or chemotherapy [6]. Inactivation of p53, found in 70 % of CRC cases and as many as half of all carcinomas in humans, occurs late in the tumorigenic sequence. Therefore, *p53* gene mutation is likely to be a limiting factor for the malignant transformation of precancerous cells in the LOH pathway. If a *p53* mutation is identified in CRC it has potentially both prognostic and therapeutic significance. Most studies show a significantly lower survival rate for patients with *p53* negative

tumors compared with those with non mutated (wild type) *p53* [46].

Deleted in Colon Cancer (*DCC*)

The *DCC* gene is located on the long arm of chromosome 18 (18q) [47] and codes for a transmembrane protein involved in cell-to-cell adhesion. It has been hypothesized that inactivation of the *DCC* gene and the resulting absence of the DCC protein may enhance the metastatic potential of CRC. DCC protein expression may also have prognostic significance and DCC-positive Stage II and III CRC were found to have statistically significant overall survival when compared with those with DCC negative cancers [48]. Studies are still ongoing as to the prognostic significance of *DCC* in CRC.

Mismatch Repair

The MMR genes are responsible for correcting incorrect nucleotide base pairings or small nucleotide insertions or deletions that occur routinely during DNA replication [49, 50]. These genes include *MSH2* (mutS homolog 2), *MSH6* (human mutS homolog 6), *MLH1*(mutL homolog 1), and *PMS2* (post meiotic segregation 2), amongst others. When a patient has one mutated MMR gene, the normal allele is able to produce the proteins needed for DNA repair functions; but when the normal remaining gene undergoes a "second hit" mutation, the MMR proteins fail to form or function appropriately. If MMR errors subsequently occur in the replication of an oncogene or tumor suppressor gene, neoplasia may result.

Cancers due to a MMR gene mutation are associated with an MSI-H phenotype. Microsatellites are short, tandemly repeated DNA base sequences that are scattered throughout the genome, some being located near significant protein-encoding genes. When there is lack of one of the functional MMR proteins, there can be variability in these repeats which leads to MSI [51]. MSI is highly sensitive for Lynch syndrome, the hereditary CRC syndrome associated with an MMR germline mutation. Almost 90 % of CRCs from patients with Lynch syndrome are MSI-H while MSI is found in up to 15 % of sporadic CRCs [52, 53]. MSI-H CRCs, whether sporadic or related to Lynch syndrome, tend to occur in the proximal colon, have a greater mucinous component, contain lymphocytic infiltration, and are more often poorly differentiated [54]. These criteria were incorporated into the Bethesda and revised-Bethesda criteria (Table 5.1) which have been utilized to determine which CRCs warrant testing for MSI to then determine whether further genetic testing for Lynch syndrome might be warranted (see below).

The condition often considered synonymous with Lynch syndrome is known as "HNPCC" or hereditary nonpolyposis colorectal cancer, which describes patients who fit clinical criteria that were originally developed to identify high risk patients for research studies (Amsterdam I and II criteria) (Table 5.2). Both HNPCC and Lynch syndrome are autosomal dominant

Table 5.1 Revised Bethesda criteria for testing colorectal cancer for microsatellite instability (MSI)

Patients who meet Amsterdam criteria (Table 5.2)
Colorectal cancer diagnosed in a patient below age 50 years
Presence of synchronous and/or metachronous colorectal or other HNPCC-associated tumors (endometrial, stomach, small bowel, ovarian, pancreas, ureter and renal pelvis, biliary tract, and brain (usually glioblastoma) tumors, sebaceous gland adenomas and keratoacanthomas, and carcinoma of the small bowel), regardless of patient age
Colorectal cancer with "MSI histology" (tumor infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed in a patient who is less than 60 years of age

Table 5.2 Amsterdam II criteria for hereditary nonpolyposis colorectal cancer (HNPCC)

≥3 relatives with an associated cancer (colorectal cancer, or cancer of the endometrium, small intestine, ureter or renal pelvis), one should be a first-degree relative of the other two
≥2 successive generations affected
≥1 relative diagnosed before age 50 years
FAP has been ruled out

disorders that are caused by germline mutations in the MMR genes. They account for 3–6 % of all incident CRCs, and patients with the condition are also at increased risk for extracolonic malignancies such as endometrial, genitourinary, central nervous system, biliary, and ovarian cancers, amongst others [55]. These patients often have early onset CRC (average age 42 years) with a high risk of synchronous (5–20 %) and metachronous (10–50 %) CRC [56]. Mutations in *MLH1* are implicated in 32 % of Lynch syndrome cases, *MSH2* mutations in 39 % of cases, *MSH6* in 15 % of cases and *PMS2* mutations in 14 % of cases [57]. The estimated penetrance of MMR gene mutations can be high, with anywhere from 30 to 80 % of MMR gene mutation carriers developing CRC and 20–60 % developing endometrial cancer. As in FAP, genotype-phenotype correlations have also been determined for Lynch syndrome. For example, Weber, et al. demonstrated that kindreds with *MLH1* mutations had a higher incidence of rectal cancer and fewer extracolonic manifestations when compared with those with *MSH2* mutations [54].

Individuals with a germline MMR gene mutation or family history fulfilling HNPCC criteria should have a colonoscopy every 1–2 years starting between the ages 20 and 25 years and every year after age 40 years. A prospective trial screening 22 Lynch syndrome families demonstrated a significant 63 % decrease in the development of CRC from 11.9 to 4.5 % in those who underwent surveillance colonoscopy or barium enema plus sigmoidoscopy every 3 years compared to those who underwent no screening [58]. Studies have shown that appropriate screening of Lynch syndrome patients improves mortality rates as well [59]. The timing of screening initiation may be adjusted depending on the underlying genotype, especially with *MSH6* and *PSM2* mutation patients developing CRC later in life on average versus *MLH1* and *MSH2* patients [41].

Surgical options for colon cancer in the setting of Lynch syndrome include a segmental colectomy versus total abdominal colectomy with IRA (due to the risk of metachronous cancer). Three separate studies (two from single institutions and one from the multi-institutional Colon Cancer Family Registry (CCFR)) showed that more extended colon resections to treat CRC in HNPCC or Lynch syndrome patients lead to significantly decreased metachronous cancer rates, even when compliance was appropriate with post-operative screening protocols [60–62]. This has also been found when assessing the treatment of patients with Lynch syndrome and rectal cancer, which is the presenting index cancer in approximately 15 % of these patients [63]. One single institution study of HNPCC patients who initially presented with rectal cancer showed a greater than 50 % rate of metachronous advanced adenomas or colon cancers at a median of 6 years after proctectomy [64]. A CCFR study of 79 Lynch syndrome patients with an index rectal cancer who underwent proctectomy showed risks of metachronous colon cancer of 19 % at 10 years, 47 % at 20 years, and 69 % at 30 years [65]. Authors of both studies concluded that HNPCC/Lynch syndrome patients should be considered for TPC and IPAA at the time of index rectal cancer treatment.

Similar to FAP, the genetic testing for Lynch syndrome must start with genetic counseling and familial assessment. There are a number of algorithms utilized to determine which patients with CRC should be tested for Lynch syndrome. The Bethesda Guidelines (Table 5.1) were established in 1996 to help identify which CRC patients to consider for further Lynch syndrome testing via MSI testing [66]. Because of the inaccuracy of family histories and studies showing a close to 50 % miss rate for Lynch syndrome using clinical criteria alone [67], universal screening of all CRCs was recommended by some national organizations, whether through MSI testing or use of immunohistochemistry assessment of tumor MMR proteins [68]. Attempting to identify the best Lynch syndrome screening strategy for CRCs, one study of over 10,000 patients assessed the sensitivity and specificity of universal screening (sensitivity, 100 %; specificity, 93.0 %) versus Bethesda guidelines (sensitivity, 87.8 %; specificity, 97.5 %). Meanwhile, a strategy known as Jerusalem criteria (screen all CRC patients 70

years old or younger) showed sensitivity of 85.4 % and specificity of 96.7 % while a strategy based on Jerusalem criteria as well as screening those over 70 years fulfilling the Bethesda guidelines showed sensitivity of 95.1 % and specificity of 95.5 % with the latter option missing almost 5 % of Lynch syndrome cases but resulting in 35 % fewer cases undergoing unnecessary MMR testing [69]. Regardless of strategy, institutions are recommended to identify a means to screen CRCs for Lynch syndrome. As mentioned above, *BRAF* or hypermethylation testing should also be considered as part of the screening strategy to rule out an epigenetic CRC etiology [23].

Colorectal Cancer Screening

Since the introduction of nationwide CRC screening efforts in the United States, the death rate related to the disease has been slowly declining. Since 1998, CRC-related mortality rates have decreased by 3 % per year in men and by 2.3 % per year in women (American Cancer Society). This has been attributed to a number of factors, including the effect of screening identifying more early, treatable CRCs as well as even preventing the initial development of CRC through removal of adenomas endoscopically. This reduction is likely also related to reduced exposure to CRC risk factors in the general population as well as improving treatment modalities for CRC and rectal cancer alike [70].

Unlike other screening programs which aim to just identify cancers early enough in their development such that they are curable (e.g. mammography for breast cancer, prostate specific antigen screening for prostate cancer, etc.), screening for CRC can both find early, treatable CRCs as well as prevent these cancers from developing in the first place through removal of their adenoma precursors [71]. These precursors especially include those polyps at highest risk for malignant degeneration including advanced adenomas (adenomas $\geq$10 mm in size, those with high grade dysplasia, and/or those with a villous component) [72]. Because screening the entire population for CRC is not possible or cost-effective, the available screening modalities are recommended based on their efficacy as well as stratifying patients into average, intermediate or moderate risk, and high-risk categories. These designations help determine the best modality of screening as well as the age of initiation of screening and the appropriate screening intervals.

Those who are considered average risk for CRC, which includes 70–80 % of all patients eligible for screening, are those who are 50 years and older, asymptomatic, and without other risk factors such as family or personal history of colorectal neoplasia. Moderate/intermediate risk accounts for 15–20 % of the eligible screening population and includes those with a family history of CRC or adenomas diagnosed at age $<$ 60 years in one or more first degree relatives (parent, sibling or child) or two first degree relatives at any age. Personal history of CRC or adenomatous polyps also puts patients in a moderate risk category. High risk (5–10 % of all those eligible for CRC screening) includes those with a known family history of FAP, HNPCC/Lynch syndrome or other inherited CRC syndrome or a personal history of inflammatory bowel disease (IBD) including Crohn's colitis or ulcerative colitis. Most of the recommendations below are from The Colorectal Cancer Screening and Surveillance recommendations of the U.S. Multisociety Task Force on Colorectal Cancer [73]. Tables 5.3 and 5.4 show the summary recommendations.

Average Risk

The average risk patient has a range of options for screening which have been shown to be cost-effective and reduce mortality. The two primary categories of screening techniques include: stool tests that primarily detect cancer (includes tests for occult blood or exfoliated DNA) and structural tests of the colon and rectum that detect polyps and cancer (which includes flexible sigmoidoscopy, colonoscopy, double contrast barium enema (DCBE) and computed tomographic colonography (CTC)) [73].

The stool tests available include fecal occult blood tests (FOBT), fecal immunochemical tests

Table 5.3 Guidelines for screening for the early detection of colorectal cancer and adenomas for average-risk women and men aged 50 years and older

The following options are acceptable choices for colorectal cancer screening in average adults beginning at age 50 years, Since each of the following tests has Inherent characteristics related to prevent on potential, accuracy, costs, and potential harms, individuals should have an opportunity to make an informed decision when choosing one of the following options		
In the opinion of the guidelines development committee, *colon cancer prevention* should be the primary goal of colorectal cancer screening. Tests that are designed to detect both early cancer and adenomatous polyps should be encouraged if resources are available and patients are willing to undergo an invasive test		
Test	**Interval**	**Key issues for informed decisions**
Tests that detect adenomatous polyps and cancer		
FSIG with insertion in 40 cm or to splenic flexure	Every 5 years	Complete or partial bowel prep is required Sedation usually is not used, so there may be some discomfort during the procedure The protective effect of sigmoidoscopy is primarily limited to the portion of the colon examined Patients should understand that positive findings on sigmoidoscopy usually result in a referral for colonoscopy
Colonoscopy	Every 10 years	Complete bowel prep is required Conscious sedation is used in most centers; patients will miss a day of work and will need a chaperone for transportation from the facility Risks include perforation and bleeding, which are rare but potentially serious; most of the risk is associated with polypectomy
DCBE	Every 5 years	Complete bowel prep is required If patients have one or more polyps ≥6 mm, colonoscopy will be recommended; follow-up colonoscopy will require complete bowel prep Risks of DCBE are low, rare cases of perforation have been reported
CTC	Every 5 years	Complete bowel prep is required If patients have one or more polyps ≥6 mm, colonoscopy will be recommenced; if same day colonoscopy It not available, a second complete bowel prep will be required before colonoscopy Risks of CTC are low; rare cases of perforation have been reported Extracolonic abnormalities may be identified on CTC that could require further evaluation
Tests that primarily detect cancer		
gFOBT with high sensitively for cancer	Annual	Depending on manufacturer's recommendations, two to three stool samples collected at home are needed to complete testing, a single sample of stool gathered during a digital exam in the clinical settling is not an acceptable stool test and should not be done
FIT with high sensitivity for cancer	Annual	Positive test are associated with an increased risk of colon cancer and advanced neoplasia; colonoscopy should be recommended if the test results are positive If the test is negative, it should be repeated annually Patients should understand that one-time testing is likely to be ineffective
sDNA with high sensitivity for cancer	Interval uncertain	An adequate stool sample must be obtained and packaged with appropriate preservative agents for shipping to the laboratory The unit cost of the currently available test is significantly higher than other forms of stool testing If the test is positive, colonoscopy will be recommended If the test is negative, the appropriate interval for a repeat test is uncertain

From Levin et al. [114]
Abbreviations: *FSIG* flexible sigmoidoscopy, *DCBE* double-contrast barium enema, *CTC* computed tomography colonography, *gFOBT* guaiac-based fecal occult blood test, *FIT* fecal immunochemical test, *sDNA* stool DNA test

Table 5.4 Guidelines for screening and surveillance for the early detection of colorectal adenomas and cancer in individuals at increased risk or at high risk

Risk category	Age to begin	Recommendation	Comment
Increased risk—patients with history of polyps at prior colonoscopy			
Patients with small rectal hyperplastic polyps [1]	–	Colonoscopy or other screening options at intervals recommended for average-risk individuals	An exception is patients with a hyperplastic polyposis syndrome. They are at increased risk for adenomas and colorectal cancer and need to be identified for more intensive follow up
Patients with 1 or 2 small tubular adenomas with low-grade dysplasia [1]	5 years 10 years after the initial polypectomy	Colonoscopy	The precise timing within this interval should be based on other clinical factors (such as prior colonoscopy findings, family history, and the preferences of the patient and judgment of the physician)
Patients with 3–10 adenomas or 1 adenoma >1 cm or any adenoma with villious features or high-grade dysplasisa [19]	3 years after the initial polypectomy	Colonoscopy	Adenomas must have been completely removed. If the follow-up colonoscopy is normal or shows only 1 or 2 small, tubular adenomas with low-grade dysplasia, then the interval for the subsequent examination should be 5 years
Patients with >10 adenomas on as single examination [1]	<3 years after the initial polypectomy	Colonoscopy	Consider the possibility of an underlying familial syndrome
Patients with sessile adenomas that are removed piecemeal [22]	2–6 months to verify complete removal	Colonoscopy	Once complete removal has been established, subsequent surveillance needs to be individualized based on the endoscopist's judgment. Completeness of removal should be based on both endoscopic and pathologic assessments
Increased risk—patients with colorectal cancer			
Patients with colon and rectal cancer should undergo high-quality perioperative clearing [19]	3–6 months after cancer resection, if no unreasectable metastases are found during surgery; alternatively, colonoscopy can be performed intra-operatively	Colonoscopy	In the case of nonobstructing tumors, this can be done by preoperative colonoscopy. In the case of obstructing colon cancers, CTC with intravenous contrast or DCBE can be used to detect neoplasms in the proximal colon
Patients undergoing curative resection for colon or rectal cancer [2]	1 year after the resection (or 1 year following the performance of the colonoscopy that was performed to clear the colon of synchronous disease)	Colonoscopy	This colonoscopy at 1 year is in addition to the perioperative colonoscopy for synchronous tumors. If the examination performed at 1 year is normal, then the interval before the next subsequent examination should be 3 years. If that colonoscopy is normal, then the interval before the next subsequent examination should be 5 years. Following the examination at 1 year, the intervals before subsequent examinations may be shortened if there is evidence of HNPCC or if adenoma findings warrant earlier colonoscopy. Periodic examination of the rectum for the purpose of identifying local recurrence, usually performed at 3- to 6-months intervals for the first 2 or 3 years, may be considered after low-anterior resection of rectal cancer

(continued)

Table 5.4 (continued)

Risk category	Age to begin	Recommendation	Comment
Increased risk—patients with a family history			
Either colorectal cancer or adenomatous polyps in a first-degree relative before age 60 years or in 2 or more first-degree relatives at any age [18]	Age 40 years or 10 years before the youngest case in the immediate family	Colonoscopy	Every 5 years
Either colorectal cancer or adenomatous polyps in a first-degree relative ≥60 year or in 2 second-degree relatives with colorectal cancer [18]	Age 40 years	Screening options at intervals recommended for average-risk individuals	Screening should begin at an earlier age, but individuals may choose to be screened with any recommended form of testing
High risk			
Genetic diagnosis of FAP or suspected FAP without genetic testing evidence [18]	Aged 10–12 years	Annual FSIG to determine if the individual is expressing the genetic abnormality and counseling to consider genetic testing.	If the genetic test is positive, colectomy should be considered.
Genetic or clinical diagnosis of HNPCC or individuals at increased risk of HNPCC [18]	Aged 20–25 years or 10 years before the youngest case in the immediate family	Colonoscopy every 1–2 years and counseling to consider genetic testing	Genetic testing for HNPCC should be offered to first-degree relatives of persons with a known inherited MMR gene mutation. It should also be offered when the family mutation is not already known, but 1 of the first 3 of the modified Bethesda Criteria is present
Inflammatory bowel disease [18], chronic ulcerative colitis, and Crohn's colitis	Cancer risk begins to be significant 8 years after the onset of pancolitis 12–15 years after the onset of left-sided colitis	Colonoscopy with biopsies for dysplasia	Every 1–2 years; these patients are best referred to a cancer with experience in the surveillance and management of inflammatory bowel disease

From Levin et al. [114]
Abbreviations: *FSIG* flexible sigmoidoscopy, *DCBE* double-contrast barium enema, *CTC* computed tomographic colonoscopy, *FAP* familial adenomatous polyposis, *HNPCC* hereditary nonpolyposis colon cancer, *MMR* mismatch repair

(FIT), and stool DNA (sDNA). Yearly FOBT can be performed by a number of available methods and requires two samples from three consecutive stools, but multiple surveys have shown poor adherence and understanding of these guidelines (only 26 % of physicians followed them correctly). There are different fecal occult blood tests available, and while they fail to detect many small precancerous lesions [74], there are four large randomized, controlled studies demonstrating a significant decrease in CRC mortality with the use of FOBT [75–78]. A positive FOBT must be followed up with a colonoscopy to be effective as a screening method and to reduce mortality. A trial comparing FOBT versus fecal DNA for CRC screening in an average risk population showed that the DNA panel detected 40.8 % of subjects with CRCs plus adenomas with high

grade dysplasia while FOBT only detected 14 % ($P < 0.001$) [79].

Flexible sigmoidoscopy has been shown to lead to a decrease in distal colon cancer mortality as high as 80 % (45 % for all CRCs), but does not show a reduction in deaths from more proximal cancers. The effectiveness of FOBT was compared to sigmoidoscopy in an average risk population through a Cochrane Review of nine studies comparing 338,467 subjects randomized to screening versus 405,919 controls. When compared to no screening, CRC mortality was lower with flexible sigmoidoscopy (relative risk 0.72; 95 % CI 0.65–0.79) and FOBT (relative risk 0.86; 95 % CI 0.8–0.92). Indirect comparison of the two screening methods, the relative risk of dying from CRC, was 0.85 for flexible sigmoidoscopy compared to FOBT [80].

Alternatives to FOBT and sigmoidoscopy include DCBE every 5 years. Johnson, et al. at Mayo Clinic compared CTC with DCBE for detection of colorectal polyps. CTC detected 56–79 % of polyps >10 mm compared to 39–56 % for DCBE with relative specificity for polyps >10 mm from 96 to 99 % with CTC and 99–100 % for DCBE [81]. Of note, anything found on CTC or DCBE should be followed up by colonoscopy to be efficacious.

Colonoscopy is the only screening modality to provide both diagnostic and therapeutic intervention if a polyp is detected. Colonoscopy remains the gold standard for evaluation and is dependent on the endoscopist's skill for detecting and removing polyps. Colonoscopy decreases the risk of CRC incidence by 76–90 % and has been show to decrease CRC mortality. In 2012 The National Polyp Study published their long-term data with follow-up time as long as 23 years showing a 53 % reduction in mortality with colonoscopy [82]. Downsides of colonoscopy include risk of perforation and bleeding, risks of sedation, need for bowel preparation, risk of missed lesions (at least 6 % for lesions ≥10 mm), and overall cost (time lost from work in addition to procedural costs, etc.). A clear, complete colonoscopy in an average risk patient should be adequate for screening and performed every 10 years. This has been endorsed by many professional groups as the preferred ("gold standard") screening method.

Newer screening modalities such as chromoendoscopy or dye-spray endoscopy, narrow band imaging, magnification endoscopy, and pill colonoscopy have not been established as effective means for surveillance or screening for average risk patients and are not equivalent in the hands of all providers. Further studies as these technologies evolve will establish their role both in screening as well as for surveillance after endoscopic or surgical polypectomy or cancer resections. They are only considered adjunctive at this time by most surgical and medical societies and warrant further study.

Moderate Risk

Moderate risk patients include those with a family history of CRC in one or more first degree relatives or adenomas diagnosed at age < 60 years, or two first degree relatives at any age, or those patients with a personal history of CRC or adenomatous polyps. Individuals with primary or multiple secondary relatives affected by CRC or adenomas should be screened at the age of 40 years or 10 years before the youngest case in the family, whichever is earliest. Colonoscopy is considered the screening tool of choice in these patients because of its high sensitivity and ability to remove precursor lesions.

The recommendations from the updated joint guidelines of the American Cancer Society and the US multi-Society Task Force on CRC in 2008 determine evidence-based surveillance recommendations for patients after polypectomy and previous curative resection for CRC [73]. Patients with previous CRC should have a complete colonoscopy at or within 6 months of their original diagnosis due to the 3–5 % incidence of synchronous cancers. After resection of a colon cancer, they should have a 1 year colonoscopy followed by a 3 year and then every 5 year follow-up colonoscopies if the results are normal.

Follow-up for rectal cancer is less well established, but recommendations from major societies include follow up colonoscopy in 1 year after

resection with or without a 6 month post-resection sigmoidoscopy due to the 2–30 % local recurrence rates. There are, however, no prospective trials of rectal cancer patients to assess the appropriate follow-up interval or establish survival benefits for post-resection surveillance. The general recommendations therefore, are otherwise similar to those for surveillance after colon cancer resection. Those rectal cancer patients who did not have a total mesorectal excision or did not receive radiation therapy for locally advanced rectal cancer should have a sigmoidoscopy every 3–6 months for the first 2–3 years after resection.

Patients with adenomas are at increased risk for metachronous neoplasia and have been shown to have a decreased incidence of subsequent cancer with follow-up surveillance. Patients with one to two <10 mm tubular adenomas should have a repeat in 5–10 years, depending on personal and family history. Patients with ≥10 mm adenomas, villous adenomas, high grade dysplasia or cancer in a completely resected polyp, or patients with 3–10 adenomas all completely removed should have a repeat colonoscopy in 3 years, assuming a complete colonoscopy in a well-prepped colon. If they have >10 polyps, or an incomplete or poorly prepared colon, they should have a repeat in <3 years. After the follow-up colonoscopy for these conditions, a repeat every 5 years is warranted if the repeat is normal. Patients with large, sessile adenomas that are resected piecemeal should undergo repeat in 2–6 months, then every 5 years thereafter if normal, based on clinical judgment. Most patients with hyperplastic polyps, except those with serrated polyposis, are considered average risk depending on family and personal history otherwise and should continue routine screening.

Increased Risk

Patients with increased risk of CRC include those with hereditary CRC syndromes and IBD. FAP patients and their family members at risk should all be offered genetic testing and counseling by trained individuals. Initial screening with colonoscopy or sigmoidoscopy is recommended at age 10–15 years for at-risk patients with a positive genetic test or no testing done/available, followed by yearly sigmoidoscopy or colonoscopy if genetic testing is positive. If genetic testing is not done, they should be endoscoped yearly until age 24 years, then every 2 years until age 34, then every 3 years until age 44, then every 3–5 years thereafter if no polyps are found (or consider every 5 years doing colonoscopy starting at age 20 if there is likelihood of attenuated FAP). If genetic testing does not show a mutation in a family with a known mutation, they can be screened as average risk [41]. If no mutation is found, some would recommend sigmoidoscopy or colonoscopy every 7–10 years due to the concern for a false negative genetic test until age 40, then every 5 years thereafter.

For HNPCC/Lynch syndrome patients and their at-risk relatives, colonoscopy should be performed every 1–2 years starting at age 20–25 years old (or 2–5 years younger than the youngest affected relative at the time of their diagnosis if diagnosed before age 25) and then annually starting at age 40. These screening recommendations have been impacted by recent genotype-phenotype data for Lynch syndrome. For example, patients with an *MSH6* or *PMS2* mutation are recommended to start their first colonoscopy at age 25–30 (or 2–5 years younger than the first CRC in the family if their age was under 30 years) [41]. Other screening tests (e.g., yearly urinalysis, consideration of endometrial biopsies, etc.) are recommended for these patients due to the high risk of extracolonic cancers, but these will not be outlined here and are recommended on a case by case basis.

IBD affecting the colon (Crohn's or ulcerative colitis) leads to an increased risk of cancer based on the extent of colonic involvement, duration of disease, family history of cancer, age at IBD onset, history of sclerosing cholangitis, and/or presence of backwash ileitis. There are no prospective studies confirming the efficacy of surveillance colonoscopy on colitis patients, but retrospective studies have shown mortality reductions from cancer in these patients undergoing appropriate surveillance, although some data are

conflicting [83, 84]. It is recommended that colonoscopy be performed every 1–2 years starting 8–10 years after the diagnosis for those with extensive colitis and 12–15 years after the diagnosis for left sided colitis [73], and biopsies should be obtained every 10 cm in four quadrants (minimum of 32 biopsies) as the cancers in IBD are usually flat and may be difficult to discern visually.

Chemoprevention

While CRC screening modalities, especially colonoscopy, have shown efficacy in preventing CRC development, they are not without risks or cost. Means to prevent CRC with lower cost and risks have lead to focusing on the use of chemoprevention agents as a potential option. Chemoprevention is the use of natural or synthetic chemical agents to inhibit or reverse CRC tumorigenesis. These agents are not used to treat invasive carcinoma, and therefore the main goal in their use is to block the initiation of, or progression through, carcinogenesis, both in low, intermediate, and high risk individuals.

Folate

Folate, the naturally-occurring form of the water-soluble B vitamin found in vegetables, fruits, and beans, or folic acid, which is the synthetic supplement added to foods, is controversial as a chemopreventative agent for CRC. Folate plays an essential role in one-carbon metabolism as a carrier of single-carbon units, including participation in DNA methylation and DNA biosynthesis [85]. Two large observational studies examining the association between folate and the risk of CRC tumorigenesis where conducted as part of the Nurses Health Study and Health Professionals follow-up study which included patients with a total of 2,299 CRCs and 5,655 colorectal adenomas. The results demonstrated an association between total folate intake 12–16 years before diagnosis and a lower risk of CRC (RR 0.69, CI: 0.51–0.94, >800 mcg vs. <250 mcg folate/day). Long and short-term intake of folate was associated with lower risk of colorectal adenoma with a strong association with intake 4–8 years before diagnosis. The regular use of a multivitamins with folate for >15 years was associated with a lower risk of CRC. No adverse effects of folate were noted in this study [86]. Despite the apparent preventative effect of folate in those large observational studies, when folic acid was studied in larger prospective trials in low and intermediate risk populations, there was no statistically significant decrease in adenoma or CRC incidence, although follow-up times were thought to be potentially too short (7 years or less) [87]. Some trials have suggested that folate may inhibit early adenoma formation but may facilitate progression of early lesions to more advanced lesions, although this has not been confirmed [88]. Given that there were essentially no noted increases in adverse events in the folic acid groups in the prospective studies reviewed, some institutions still recommend the use of folate as a potential chemopreventative agent for CRC. One trial in intermediate risk patients (www.clinicaltrials.gov, NCT00512850 with 672 patients in follow up) and one trial in low risk patients (NCT02066688, recruiting 2,400 patients starting in 2013, includes calcium and vitamin D) are ongoing. There are no data available on the effectiveness of folic acid or folate in high risk populations.

Vitamin B6 (Pyridoxine)

Vitamin B6 or pyridoxine, a water-soluble vitamin found primarily in fortified cereals, starchy vegetables, beef, and poultry, contains the active coenzyme pyridoxal 5′ phosphate (PLP) that is involved in enzymatic reactions. A function of pyridoxine involves the transfer of one-carbon groups for DNA synthesis and methylation. It has been hypothesized that low vitamin B6 levels may increase the risk of CRC secondary to defective DNA synthesis, repair and methylation [89]. A meta-analysis of prospective cohort studies assessing the association of vitamin B6 intake and blood levels of PLP and the risk of CRC assessed the results of nine studies on vitamin B6 intake and

four studies on blood levels of PLP with over 6,000 CRC cases included. The pooled relative risk of CRC for the highest versus the lowest amounts of vitamin B6 intake and blood PLP levels was 0.90 (95 % CI: 0.75–1.07) and 0.52 (95 % CI: 0.38–0.71), respectively. When excluding one study that biased the results, the remaining eight studies yielded a pooled relative risk of 0.80 (95 % CI: 0.69–0.92) when comparing high vs. low categories of vitamin B6 intake. The risk of CRC decreased by 49 % for every 100-pmol/mL increase in blood PLP levels. The authors concluded that "…blood PLP levels are inversely associated with risk of CRC…" and that there "…was no significant association between vitamin B6 intake and CRC risk" [90]. Another more recent review suggests that assessments of timing of vitamin B6 intake as well as assessment of confounders and interactions with other agents are warranted, but they confirm that pooled data from two prospective trials did not show an impact of vitamin B6 supplementation on CRC incidence [91].

Calcium and Vitamin D

Calcium is involved in cellular signalling and is thought to impact carcinogenesis by binding fatty and bile acids within the lumen of the colon which inhibits the fat-induced hyperproliferation of the colonic epithelium as well as promotes cellular differentiation and apoptosis. This has been thought to be particularly impactful in tumors with *RAS* mutations [88]. Vitamin D has also been shown to inhibit cellular proliferation as well as promote cellular differentiation and apoptosis, and cancer rates have been shown to be higher in patients with lower vitamin D levels [92]. Calcium has been associated with a reduced risk of adenoma formation in patients with intermediate risk, but with no reduction in advanced adenoma formation or CRC in these groups. In terms of high risk patients, one small study on 28 FAP patients did not show a difference in 6 months of follow-up on the number or progression of rectal polyps [87]. When looking at average risk populations, a randomized, double blinded, placebo-controlled study included post-menopausal women from 40 Women's Health Initiative centers and compared over 18,000 women who received elemental calcium and vitamin D twice daily with over 18,000 matched women who received placebo. The incidence of invasive CRC did not differ significantly between the groups after 7 years of follow-up [93]. Similarly, a community-based prospective, randomized, placebo-controlled trial of over 1,100 women showed an overall decrease in their secondary endpoint of all cancer incidence over 4 years of follow up, but the data with CRC was limited due to only two incident CRCs in the placebo group and one in the calcium and calcium + vitamin D groups [92]. No major adverse effects of calcium or vitamin D were reported in the literature related to use for CRC chemoprevention [87]. There is a prospective trial assessing calcium and vitamin D efficacy in CRC prevention, as noted above (www.clinicaltrials.gov, NCT02066688).

Aspirin

Aspirin reduces the incidence or growth rate of several cancers in animal models, mediated by inhibition of the cyclo-oxygenase enzymes and reduced production of prostaglandins and other inflammatory mediators. In a metaanalysis reviewing eight trials, over 25,000 patients treated with daily aspirin for 5 years or longer showed a reduced risk of incident CRC. The benefit was unrelated to the aspirin dose (75 mg and upward). The benefit was apparent only after 5 years follow up with all cancers, the hazard ratio being 0.66 (95 % CI: 0.50–0.87) and 0.46 (95 % CI: 0.27–0.77) for all gastrointestinal cancers, with $P = 0.003$ [94]. Aspirin use as a chemopreventative has been assessed in high risk patients, including FAP and Lynch syndrome. The CAPP1 trial assessed 133 patients with genotypically confirmed FAP on 1 year of 600 mg of aspirin versus placebo and showed a decrease in the size of the largest polyp but showed no change in polyp number with the use of aspirin and did not report data on CRC incidence [87]. The CAPP2 trial assessed MMR gene mutation

carriers who were randomly assigned in a two by two factorial design to 600 mg of aspirin or aspirin placebo or 30 g of resistant starch or starch placebo for up to 4 years. Of over 860 participants, 48 developed 53 primary CRCs (18 of 427 assigned to aspirin and 30 of 434 to aspirin placebo). The authors concluded that 600 mg of aspirin taken daily for a mean of 25 months statistically reduced the incidence of CRC in Lynch syndrome [95]. A new trial that is currently recruiting (CAPP3) will assess dose response for aspirin (100, 300, and 600 mg) as a chemopreventative in patients with Lynch syndrome [96]. For intermediate risk patients (prior adenoma or CRC), a meta-analysis showed a statistically significant decrease in further adenoma formation with the use of aspirin (21 % reduction in the relative risk of recurrence of an adenoma of any type [RR 0.79, 95 % CI 0.68–0.92, p = 0.002]), but no significant decrease in advanced adenomas or CRC [87]. A number of other studies have shown that use of aspirin in patients with prior CRC reduces the risk of cancer-related mortality significantly, especially in cancers expressing cyclo-oxygenase (COX)-2 [97]. Many of the data on average risk patients and the effect of aspirin on CRC incidence reduction are from pooled data from cardiovascular trials which showed a 34 % reduction in 20-year CRC mortality after 5 years, while other trials have shown a time- and dose-dependent effect on CRC risk reduction [98]. There is little data on the impact of aspirin use on the incidence of adenomas or advanced adenomas in the average risk population [87]. Side-effects of gastrointestinal upset and bleeding have been reported with the use of aspirin.

Sulindac, DFMO and Other NSAIDs

Difluoromethylornithine (DFMO) and the nonsteroidal anti-inflammatory drug (NSAID) sulindac have both demonstrated inhibition of intestinal and colorectal carcinogenesis, even more so when combined. The mechanisms are unclear, but DFMO is an ornithine decarboxylase inhibitor that effects polyamines and reduces folate-dependent metabolites. The mechanism is unclear as to how NSAIDs affect carcinogenesis as well, but it is thought to be related to their prostaglandin regulation. Relative risk reduction for NSAIDs is in the 0.6–0.7 range in most studies assessing CRC and adenoma incidence, but there have been concerns about gastrointestinal bleeding risks associated with these medications [99]. In patients with a previous history of adenomas who received oral DFMO and 150 mg of sulindac daily for 3 years showed lower polyp recurrence versus placebo (12.3 % vs. 41.1 %, respectively, $P < 0.001$) [100]. In patients with FAP, early studies showed promise with the use of sulindac and polyp reduction, although cancer incidence was not impacted. A subsequent randomized, double blinded study was performed on genotypically confirmed patients with an *APC* mutation but who were phenotypically unaffected. After receiving either sulindac orally twice a day versus placebo for 48 months there was no significant difference in the mean number or size of polyps [101]. There are ongoing studies assessing the impact of DFMO and sulindac in FAP.

Cyclooxygenase (COX)-2 inhibitors have shown promise in colorectal carcinogenesis prevention. Celecoxib, a selective COX-2 inhibitor, has been shown to reduce adenoma incidence, but the concern over cardiac risks have forced the U.S. Preventive Services Task Force to not recommend the use of celecoxib for adenoma prevention in average risk individuals [99]. Celecoxib has been studied in higher risk patients such as those with FAP. A double blinded, placebo controlled study on 77 FAP patients treated with celecoxib (100 or 400 mg twice per day) vs. placebo for 6 months showed a 30 % and 15 % reduction in polyp burden, respectively, vs. placebo without concerning side effects [102]. Despite this, while the agent was initially approved by the FDA as an adjunct for chemoprevention in FAP, that approval was withdrawn in 2012.

Hormone Therapy

The effects of postmenopausal hormone therapy have been published as part of the Women's Health Initiative on over 16,000 postmenopausal

women who were randomly assigned to a combination of conjugated estrogen plus medroxyprogesterone acetate daily or placebo showing a significantly reduced hazard ratio (HR 0.56, 95 % CI: 0.38–0.81; P = 0.003), although the few CRCs diagnosed were at a more advanced stage of disease [103]. There is some evidence that hormone therapy may have no effect or a negative effect in terms of rectal cancer [104]. Hormone therapy is not recommended in the prevention of CRC.

Statins

The role of statins in the prevention of CRC has been evaluated as a secondary endpoint in large clinical trials assessing the safety of statin therapy in cardiovascular outcomes. Statins work through HMG-CoA reductase, which has been shown to be overexpressed in CRC cells, and statins have been shown to induce apoptosis in cancer cell lines *in vitro* [105, 106]. A population-based study was undertaken on almost 2,000 patients having had a diagnosis of CRC in Northern Israel between 1998 and 2004 who were matched to just over 2,000 healthy controls. A structured interview was conducted with self-reports of statin use and prescription records. Statin use for at least 5 years was associated with a 47 % relative risk reduction for CRC after adjustment for other risk factors [107]. Studies are ongoing to assess statin prevention efficacy after CRC resections.

Antioxidants

Dietary antioxidants such as β-carotene, vitamin A, vitamin C, vitamin E and selenium have been touted as possible cancer preventative supplements because they may fight free radicals that may cause oxidative stress and DNA damage leading to gastrointestinal disease and CRC [108]. A meta-analysis was performed reviewing all randomized clinical trials comparing antioxidant supplements with placebo or no intervention on the proposed prevention of colorectal adenomas and subsequent CRC. Eight randomized trials with 17,620 participants were included in the analysis. Neither fixed effect nor randomized effect model analysis showed statistically significant effects of supplementation with β-carotene, vitamins A, C, E or selenium alone or in combination. There was no significant difference between the intervention groups regarding adverse events including mortality [109].

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6 The Role of Imaging in the Diagnosis and Staging of Primary and Recurrent Rectal Cancer

Manish Chand, Svetlana Balyasnikova, and Gina Brown

Abstract

Accurate pre-operative imaging is a central part of treatment decision making in the modern management of rectal cancer. The increasing use of neoadjuvant chemoradiation necessitates the identification of specific prognostic factors such as tumour penetration, nodal status, extramural venous invasion and most importantly, the relationship of the tumour edge to the circumferential resection margin. MRI has been the most accurate modality in the local staging of rectal cancer both pre-operatively, and to measure treatment response. Recurrent cancer usually requires a more tailored approach and also needs detailed imaging of the extent of disease. A compartment based system has been shown to aid surgical planning leading to improved outcomes.

Keywords

Rectal cancer • MRI • Staging • Neoadjuvant chemoradiation • Chemotherapy • TNM • Recurrence

Introduction

Imaging has become an integral component of rectal cancer management for both primary and recurrent tumours. As our understanding of tumour behaviour has increased, accurate identification of specific tumour-related features is essential to be able to offer patients optimal treatment. Although histopathology remains the so-called 'Gold Standard' for final tumour staging and for treatment decisions involving the use of adjuvant therapy, pre-operative treatment decisions are almost exclusively based on the results of baseline imaging. Furthermore, as most patients present with locally advanced disease which will require neoadjuvant therapy, the role of imaging in detecting and then monitoring the predictive and prognostic factors that will influence survival outcomes become all the more important.

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The importance of accurate imaging is also being recognised in recurrent rectal cancer. These patients are more complex in their presentation, and tumour may extend well beyond fascial planes into surrounding structures. The treatment planning, particularly for surgery, is challenging and the more detailed the pre-operative information the more successful the outcomes. Recently, imaging-based risk stratification determined by which anatomical compartments are involved has been shown to predict for clinical and survival outcomes [1, 2].

Imaging modalities have two distinct roles in staging disease. In primary tumours they must be able to determine the extent of local spread as well as detect any distant disease. A combination of modalities is usually used to give a final staging result. Magnetic resonance imaging (MRI) is the optimal modality for assessing local disease spread and is the choice investigation in the UK and Europe – the rationale behind this is discussed later. Endoanal ultrasound (EAUS) is more commonly used for early cancers in which local resectional procedures may be more appropriate than radical surgery. There is little discussion regarding the use of computerised tomography (CT) for staging distant disease as a first line investigation. However if there is any ambiguity in the diagnoses of distant lesions, positron emission tomography (PET) may be used for detection and MRI for delineation and characterisation. For recurrent disease, a more tailored approach may be taken to determine overall tumour burden which may involve a combination of imaging modalities [3, 4].

Optimal Local Staging – Why MRI?

MRI has become the optimal modality for the local staging of primary tumours. There are several advantages over alternative techniques such as EAUS and CT. But to fully understand why MRI is considered superior to EAUS or CT, it is necessary to place this in the context of neoadjuvant treatment decisions and local policies.

Pre-operative therapy in the form of short- or long-course radiotherapy with concomitant chemotherapy is given to tumours with the aim to reduce the risk of local recurrence. Pre-operative chemoradiotherapy has been shown to improve local recurrence rates in locally advanced disease [5–8]. Tumours can be risk-stratified depending on the presence of specific features and characteristics. Of these, proximity of the tumour edge to the circumferential resection margin (CRM) is the most important determinant of local recurrence [9, 10] – the outermost boundary of the mesorectum which forms the resection lines for the surgeon in total mesorectal excision (TME) surgery [11, 12].

Progressive units have sought to be more selective in their use of pre-operative chemoradiotherapy balancing the proposed survival benefits with that of the not insignificant morbidity associated with neoadjuvant treatment. Those units whose practise is to offer all but the most low-risk of patients pre-operative CRT are less likely to insist on identification of those tumour characteristics which directly influence disease recurrence as they will base their adjuvant treatment decisions on the final pathology staging following surgery. When adopting a more selective policy it is essential to identify the key features which risk-stratify patients – increasing tumour penetration into the mesorectum; vascular invasion and the CRM. For example, evidence of nodal disease may not necessarily mean that patients need pre-operative therapy if there are no other adverse features and surgery is successfully undertaken using the principles of total mesorectal excision (TME). If the only high-risk feature is mesorectal nodal disease the benefit of pre-operative treatment is only marginal if the plane of surgery is adequate [13, 14].

The biggest advantage of MRI over EAUS is that it can accurately and reproducibly identify the CRM (Fig. 6.1) [15–19]. In addition is accurate in detecting penetration into the mesorectum, venous invasion and superior than all modalities for nodal disease [20–23]. So the benefits of MRI for local staging are only truly realised in units where a more selective policy is adopted with regards to pre-operative treatment. These units

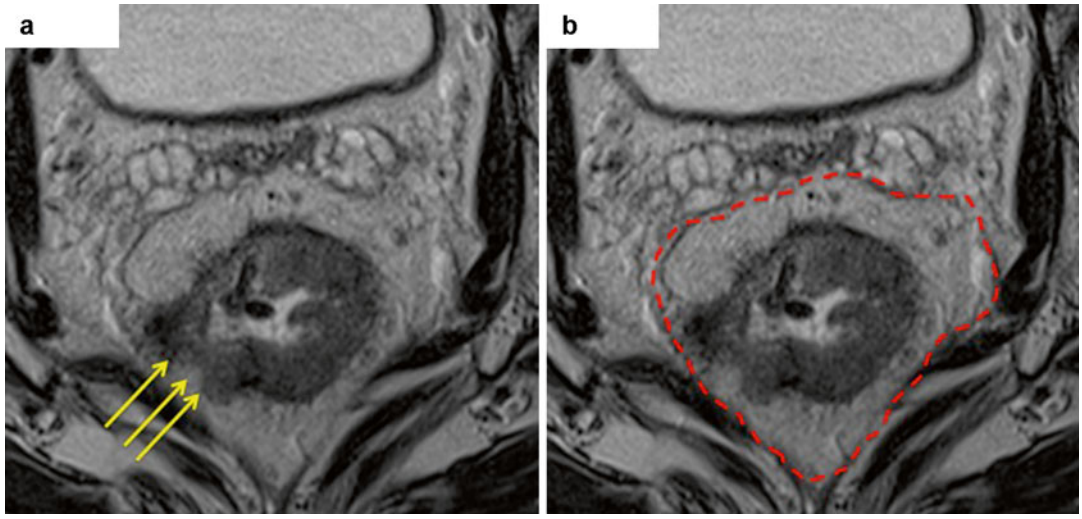

Fig. 6.1 Mid rectal annular tumour spreads beyond the muscularis propria up to 8 mm (**a**- *yellow arrows*). Mesorectal fascia (**b** – *red line*, which defines the mesorectum) is involved by direct spread of tumour (distance from the tumuor tomesorectal fascia is less than 1 mm – CRM +)

also use MRI to assess treatment response following CRT, which is another benefit. It can help predict prognosis through degrees of downstaging of the individual adverse features – a restaging and thus risk-stratification of disease after neoadjuvant therapy [24–26].

The staging of recurrent disease is more complex. The prognostic factors which influence survival outcomes in primary disease do not fully apply. Other considerations, mainly the extent and pattern of local recurrence are most important in treatment planning and to accurately delineate the extent of disease a combination of imaging modalities may be used [27].

Imaging-Based Risk-Stratification

As mentioned above, not all patients require preoperative treatment – this is determined by accurate risk-stratification. Depending on the local policy, risk-stratification will be based on the identification of specific features. Stratification can take place on initial presentation whereby traditional prognostic factors based on histopathological studies in primary tumours are used as a basis – tumour depth (T-stage), nodal disease (N-stage), extramural venous invasion (EMVI). Further stratification can be performed following CRT however the influence on traditional prognostic factors is unclear in this situation.

Tumours which exhibit evidence on initial staging of CRM involvement, tumour penetration beyond 5 mm into the mesorectum (T3c), venous invasion, N2 disease are considered high-risk and will routinely be offered neo-adjuvant treatment. These features are accurately identified on serial MRI and have been shown to correlate well with pathology and overall survival outcomes [28–33].

MRI Technique

For optimal results using MRI it is essential to adhere to specific technical criteria [34, 35]. This includes correct field of view (FOV), field alignment and sequences. Incorrect use of any of these technical considerations can results in under- or over-staging of disease and consequently suboptimal management. For example, using an inadequate FOV can make accurate delineation of the important anatomical structures difficult.

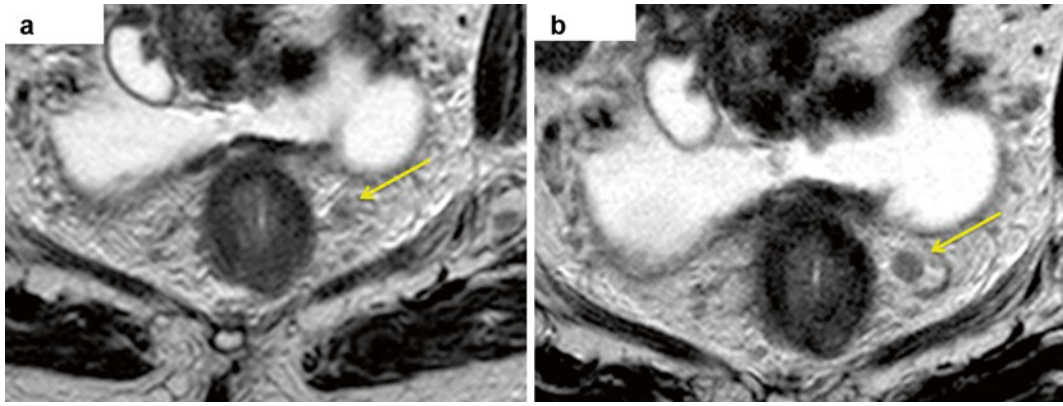

Fig. 6.2 Differences in FOV for imaging nodal disease. (**a**) Shows 22 cm × 22 cm FOV and consequent poor quality of image (lymph nodes are difficult to assess – *yellow arrow*). This is much improved in (**b**) where the FOV is 16 cm × 16 cm. The nodal anatomy is clearly visible with particular respect to the nodal border and signal characteristic (*yellow arrow*)

Using correct FOV also affects the voxel size. If the voxel size is increased, resolution is lost and morphological characteristics become less obvious. Incorrect FOV is the most common error that leads to poor-quality images. Figure 6.2a shows the MRI of a patient with a prominent node in the mesorectum. Distinguishing whether this is a malignant or benign node is challenging if the resolution is poor and in this example it is difficult to adequately visualise the nodal architecture – FOV is 22 cm × 22 cm. In Fig. 6.2b, the correct FOV is used (16 × 16 cm) and it is much more straightforward to delineate the nodal anatomy.

Another common mistake which results in inaccurate staging is incorrect field alignment. Sequences must be taken in the correct plane with respect to the long axis of the rectum. Typical images are taken in 3 mm slices. Figure 6.3 shows the correct field alignment based on the MERCURY protocol [20, 36]. If the field is incorrect, the tumour edge is inaccurately identified.

Initial localization images in the coronal and sagittal planes are needed to plan further high-resolution images. The first series are T2-weighted sagittal, turbo spin-echo sequences from one pelvic sidewall to the other enable identification of the tumour. The second series consists of large-field-of- view axial sections of the whole pelvis. The third series consists of the high-resolution images that are T2-weighted thin-section axial images through the rectal cancer and adjacent tissues.

Prognostic Factors in Primary Rectal Cancer

Accurate identification of the important prognostic factors is the main role of MRI in the local staging of disease. The following section describes the evidence for these factors and the accuracy of detection.

Tumour Depth

The progression of disease and characteristic spread of rectal cancer is through the layers of the bowel wall. The micro-structure of the bowel wall can be identified on MRI which fits with the traditional TNM staging system [37]. Spread of tumour through the bowel into the surrounding mesorectum and beyond is associated with worsening prognosis. The risk of recurrence for T1, T2 and T3 tumours independent of lymph node involvement are in the order of 5, 10, and 25 %, respectively. However there is a distinct cut-off in terms of prognosis relating to the depth of

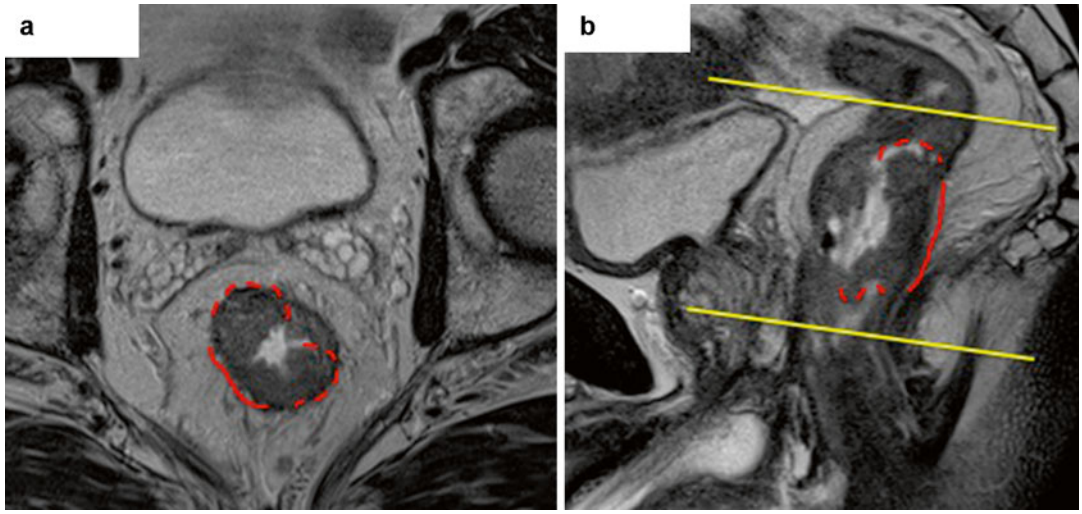

Fig. 6.3 Correct alignment of MRI field. This is perpendicular to the long axis of the rectum and commonly mistaken resulting in under- or overstaging of disease. Axial (**a**) scans should be taken perpendicular to the rectal wall on sagittal image (**b**) s at the level of invading tumour border (*continuous red line*) which is a distance between raised rolled edges (where submucosal layer is preserved – *dashed red line*)

penetration. Tumours which only minimally extend into the mesorectum and those which are confined to the bowel wall are considered to be 'good prognosis' or 'low-risk' cancers. These can be managed with primary surgery providing there are no other adverse features.

Accurate assessment of this relies on the identification of the layers of the bowel wall which is accurately accomplished by both MRI and EAUS. EAUS may be more useful for T1 and T2 tumours where accurate identification of the mesorectal fascia has less importance. EAUS has increased accuracy for defining the detail of the bowel wall structure which is particularly useful when planning mucosal resection or transanal excision. Sensitivity and specificity for T1 cancers is 87.8 and 98.3 %, respectively [38]. As transanal endoscopic microsurgery (TEMS) and endoscopic submucosal resections become more popular, greater detail of the bowel wall is essential to select appropriate patients.

MRI can readily identify the layers of mucosa and muscle through distinct signal characteristics. T2-weighted images are particularly useful for this. The mucosal layer is seen as a very fine line of low signal intensity overlying the much thicker and higher signal of the submucosa. Outside this the muscularis propria can be seen as a duel-layer representing the inner circular and the outer longitudinal muscle layers. The latter has a typically irregular appearance due to vessels traversing the rectal wall. The perirectal fat is identified as a high signal with signal void areas surrounding the relatively low signal intensity of the muscularis. This is all enveloped by the fine layer of low signal intensity representing the mesorectal fascia.

To understand the prognostic relevance of spread into the mesorectum it is important to appreciate its unique nature. The rectum is the only part of the gastrointestinal tract which is intimately surrounded by a distinct mesentery containing lymphovascular structures. This fatty layer can be readily seen in-vivo although it is not so easily identifiable in the cadaver. The outermost boundary is defined by the mesorectal fascia (MRF) which demarcates the CRM during surgical excision. The CRM acts an oncological barrier to tumour spread. However increasing penetration into the mesorectum (T3 disease) is associated with increasing rates of disease recurrence [39–45].

Cawthorn, Merkel and Willett were the first to report on this heterogeneity within T3 tumours.

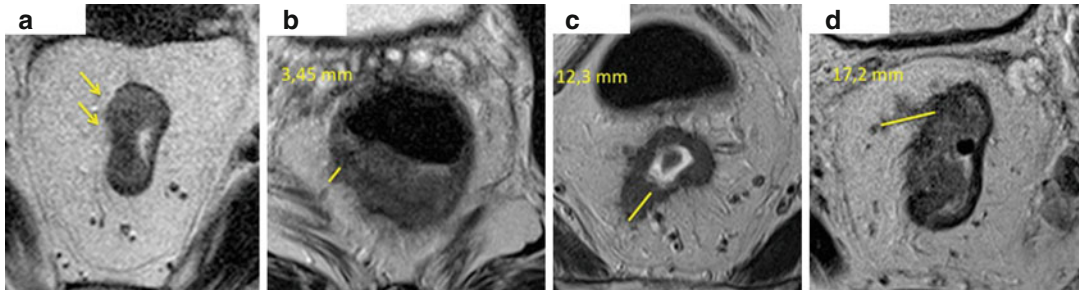

Fig. 6.4 T3 sub-classification based on penetration into the mesorectum. T3a (**a**) –initial tumour spread into the mesorectum (1 mm – *yellow arrows*), the muscularis propria is not preserved. T3b (**b**) – tumour spread beyond the muscularis measures 3 mm (*yellow line*).T3c (**c**) – tumour spread measures 12 mm. T3d (**d**) – tumour spread is more then 15 mm (17 mm)

Cawthorn reported 5 year survival to be 55 % with tumour penetration less than 4 mm into the mesorectum compared to 25 % when more than 4 mm [40]. Merkel studied patient's survival characteristics with T3 tumours and used a cut-off of 5 mm. Those patients with extramural spread of more than 5 mm had 5 years survival rate of 54 % compared with 85 % for those patients whose tumours had extramural spread of less than 5 mm [46]. These results were independent of lymph node involvement. These early studies highlight the importance of accurate measurement of tumour penetration into the mesorectum and those tumours with a worse prognosis, namely T3c and T3d. Therefore the distinction between T2 and T3 tumours with less than 5 mm mesorectal spread – T3a and T3b; becomes irrelevant as these patients will have minimal benefit from CRT. This has led to the sub-staging of T3 tumours which has been adopted by the UICC TNM classification since 1993 (Fig. 6.4).

More recently, the prognostic importance of T3 substage has been recognised following CRT. Merkel et al. studied the prognostic impact on survival outcomes for patients with T3a and T3b tumours (ypT3a/b) [47]. They found that ypT3 subclassification was an independent prognostic factor for disease-free, observed and cancer-related survival [48]. ymrT3 subclassification has also been found to predict prognosis in terms of overall and disease-free survival with local recurrence rates to be less than 4 % in the MRI-predicted 'good tumours' [28].

MRI has been shown as the optimal modality for identifying the CRM and mesorectum. In addition to being able to detect the depth of tumour spread into the mesorectum to within 1 mm it can also identify the tumour edge with similar detail. . It has been shown to be able to identify potential tumour at the CRM to within 1 mm [19, 23, 49, 50]. Pathologists recognise a clear margin for tumour excision to be 1 mm. If tumour is seen within 1 mm of the CRM, it is said to be a 'positive margin' or 'R1 resection'. In the MERCURY Study, a total of 349 patients underwent pre-operative MRI assessment followed by TME surgery were predicted to have clear margins. 327 (94 %) patients were subsequently found to have clear margins on histopathology [20]. This gave a specificity of 92 %. Taylor et al. have shown that rates of local recurrence decreased from 53 % with tumour less than 1 mm from the potential CRM to less than 8 % when the tumour distance from the mesorectal fascia was between 1 and 5 mm [49, 51]. A measured distance of 5 mm on MRI has been shown to strongly correlate with negative CRM on histology, which led to patients being offered chemoradiotherapy when tumours are within 5 mm of the mesorectal fascia. However, this results in substantial overt-treatment of patients with safe margins.

Nodal Disease – N Staging

The importance of solitary lymph node involvement in rectal cancer is now being challenged with respect to its risk of local recurrence [52]. Traditional teaching has suggested that malignant

mesorectal lymph nodes are associated with local recurrence thus patients should be offered radiation therapy. The results of MRC CR07 trial seemed to give this further credence however these results did not account for sub-optimal surgery [14]. TME is the accepted surgical technique for rectal cancer and should be considered the single-most important factor in reducing local recurrence in the last century. Historical trials included patients who had undergone a wide variation of quality in their surgery and when the results of CR07 are taken with respect to which plane of resection was used, the story is rather different. The actual benefit for patients who have undergone TME surgery is less than 4 %. Therefore in the current modern era of rectal cancer management where high-quality precision surgery is the expected norm, it does not make sense to put patients through an intensive radiotherapy regime with minimal benefit. This is not to say that nodal disease does not have a bearing on metastatic disease but this can be treated with adjuvant systemic therapy rather than local radiotherapy. One must also remember that whilst neoadjuvant treatment improves local recurrence rates, it has no effect on overall survival.

Yet despite this, and whilst nodal involvement remains a consideration for units, correct technique and staging of nodes is paramount to avoid unnecessary treatment. The same basic technical principle apply but the criteria used to distinguish benign from malignant nodes is equally important. There has been a predilection for using size criteria when determining the nature of mesorectal nodes; that is, the larger the node, the more likely it will be malignant. There has been no robust trial evidence behind this or pathological correlation. A study which matched nodes from in vivo and specimen MRIs with pathology specimens showed that there was no useful size cut-off for predicting nodal status [53]. Further, a histological survey of over 12,000 lymph nodes in rectal cancer showed considerable size overlap between normal or reactive nodes and those containing metastases [54]. A perceived limitation of MRI is the lack of accuracy and ability to detect nodes smaller than 3 mm. Yet this may not be as clinically relevant as first appears. Only 2 % of nodes which are malignant were of this size [53].

More important than size is nodal border and the tumour signal within the node. when a high resolution MRI technique is used, it is easier to evaluate lymph node architecture and has enabled new criteria for lymph node involvement to be developed. Tumour infiltration into lymph nodes leads to characteristics radiological features which can be readily identified on MRI (Fig. 6.5). Tumour leads to capsular disruption causing the nodal border to become irregular as opposed to the more rounded border of benign nodes. A very small number of lymph nodes with a smooth bordered contour (<6 %) have been shown to be malignant whilst those demonstrating irregular outline are malignant in over 90 % of cases. Mixed signal intensity occurs due to the heterogeneity of the tumour and necrosis within the node. When using the signal characteristics and border outline together, the sensitivity is much improved. Using features of nodal border, contour and differing signal characteristics the sensitivity and specificity increases to 85 and 97 %, respectively. Endoanal ultrasound (EAUS) does not predict lymph node involvement any better. Indeed sensitivity and specificity for detection of cancerous lymph nodes in rectal cancer is 73.2 and 75.8 %, respectively [55] although more likely to be accurate in the more proximal parts of the rectum. Swollen reactive nodes, small blood vessels and even local structure such as the seminal vesicles may mimic malignant nodes.

Using the same criteria as above with T2-weighted MRI, lymph nodes can be accurately identified following neoadjuvant treatment. Koh et al. prospectively evaluated the MR staging of lymph nodes before and after chemoradiotherapy and compared this with histopathological analysis to demonstrate significant correlation between post-treatment MR assessment and histopathology of nodal disease [56].

Extramural Venous Invasion – EMVI

The prognostic effect of vascular invasion has been suspected for several decades however there has been huge variability in practice with regards to treatment decisions. Over recent years, there has been a refinement in the definition of vascular

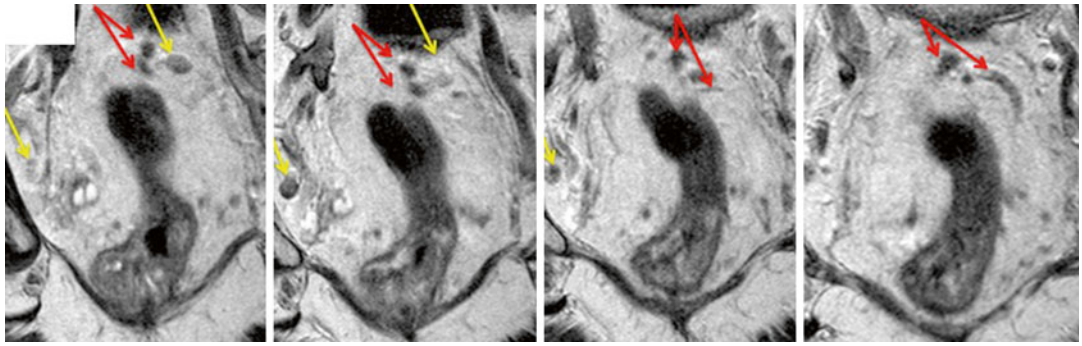

Fig. 6.5 MRI showing mesorectal nodes. Both mesorectal and pelvic nodes are round/oval structures (*yellow arrows*), that usually seen on not more than 2–3 consecutive images. The operator must scroll through images so not to confuse them with vessels (*red arrows*)

invasion in respect to colorectal cancer and, in particular, rectal cancer. This has been based on seminal work by Talbot in 1980 who demonstrated the importance of distinguishing extramural from intramural venous invasion [57, 58]. Extramural venous invasion (EMVI) is defined by evidence of tumour cells or, in the case of the radiological definition, tumour signal in the vasculature outside the muscularis propria. This means that it is found in more locally advanced tumour – T3 and T4 disease.

One of the main reasons behind the variability in treatment decisions when EMVI is present must be due to the heterogeneity in the literature. The historical studies which have been the basis of much of our current understanding in rectal cancer have used a variety of definitions in the methodology for sampling and analysis. In addition, there has been little detail in the techniques used for detection which has ultimately resulted in a wide range in prevalence [59–62]. Standardisation in reporting techniques have made data reporting in both pathology and radiology more accurate as EMVI is specifically sought [35, 63, 64].

The use of radiological detection of EMVI has helped drive its prognostic importance. It is considered in the MRI reporting sets of almost all prospective trials involving rectal cancer. EMVI has been investigated in patients undergoing primary surgery and in those which have undergone pre-operative treatment. One study investigated the rate of detection of EMVI on MRI (mrEMVI) compared with so-called Gold standard of pathology detection from the assessment of resection specimens [19]. Eighteen patients had large vessel EMVI visible on H and E stain. Fifteen of these 18 cases found mrEMVI. However more subtle involvement of tumour within smaller vessels was not resolved on MRI.

The radiological characteristics have been previously described (Fig. 6.6) [65]. To accurately identify EMVI on MRI, it is imperative to have a sound understanding and appreciation of the vasculature around the rectum. This can help distinguish venous disease from nodal deposits and it is necessary to 'chase' the signal along the length of the vessel through multiple images. Veins around the rectum are recognised on T2-weighted images as serpiginous or tortuous linear structures. Differentiating between larger and smaller vessels can be difficult and requires a combination of signal characteristics and morphology. The larger, named vessels such as the superior and middle rectal veins appear with anatomical consistency which helps in confident identification. Ideal assessment of mrEMVI must include the following: pattern of tumour margin (extension into small veins may produce a nodular border); location of tumour relative to major vessels; vessel calibre (tumour causes vessel expansion and increase in tumour signal in the lumen); and vessel border. Smaller venules can be seen perforating the normal outer rectal wall and produce a low to intermediate signal intensity in tubular structures on T2-weighted images.

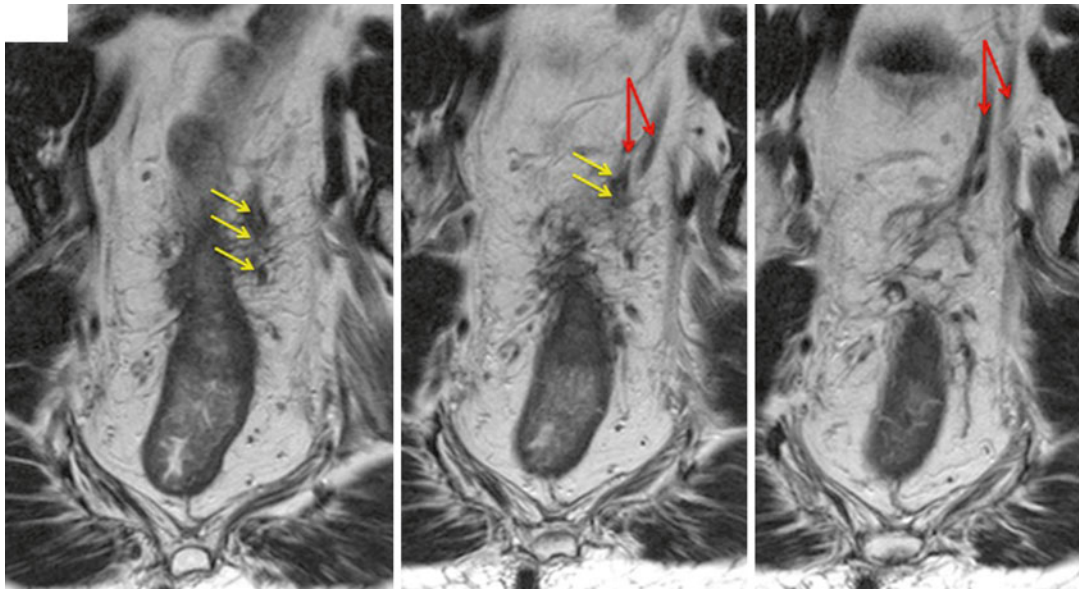

Fig. 6.6 EMVI shown in locally advanced tumour. The tumour signal can be seen extending into the veins and expanding it (*red arrows*) outside the bowel wall. This is characteristic of venous invasion. However, the operator must follow the signal through several images to ensure venous disease rather than nodal spread (*yellow arrows*)

Using the radiological characteristics, Smith et al. offered a scoring system to stratify the degree of venous invasion. A study of 142 patients investigated the accuracy of detection and prognostic relevance of mrEMVI [66]. Patients included in the study undergoing either primary TME-surgery (n = 94) or neo-adjuvant therapy followed by surgery (n = 48). The incidence of mrEMVI was initially 39.4 % but fell to 24.1 % for those patients who were re-imaged following pre-operative treatment – indicating a degree of 'down-staging'. Recurrence free survival at 3 years was compared between mr- and histology-detected EMVI and reported as 35 and 34 %, respectively. Recurrence-free survival when EMVI was not present was 73.8 and 74.1 % respectively.

More recently, the effect of pre-operative chemoradiotherapy (CRT) on mrEMVI has been examined. Using the same radiological criteria as described above, EMVI can be re-assessed following CRT (Fig. 6.7). The radiological detection of EMVI using MRI has been compared with pathology-detected EMVI in patients following pre-operative treatment with long-course chemoradiotherapy [yu/chand/patel]. There has been concern by pathologists that the fibrosis which occurs following radiotherapy makes detection more difficult [67, 68]. This issue has been cited by some with respect to MRI identification of prognostic factors following CRT, however there reproducibility and accuracy of detection once appropriate training has been undertaken as reflected in the consistency of reporting within large collaborative studies such as MERCURY. A recent study has shown the advantage of using MRI rather than pathology for detecting EMVI after CRT (ymrEMVI versus ypEMVI) [33]. In the cohort of 188 patients, EMVI was detected in 99 patients after CRT when MRI criteria was used. On final pathology staging, only 36 patients were identified with EMVI. This would indicate that either MRI was over-estimating or pathology under-estimating EMVI. Yet this survival analysis revealed that by using either technique, evidence of EMVI led to worse disease-free survival at 3 years. This implied that ymrEMVI is either a unique prognostic phenomenon which is not directly comparable to ypEMVI or that ymrEMVI is more accurate in detecting EMVI following CRT.

EMVI can also be graded with a MRI-based tumour regression score. mrEMVI status has been

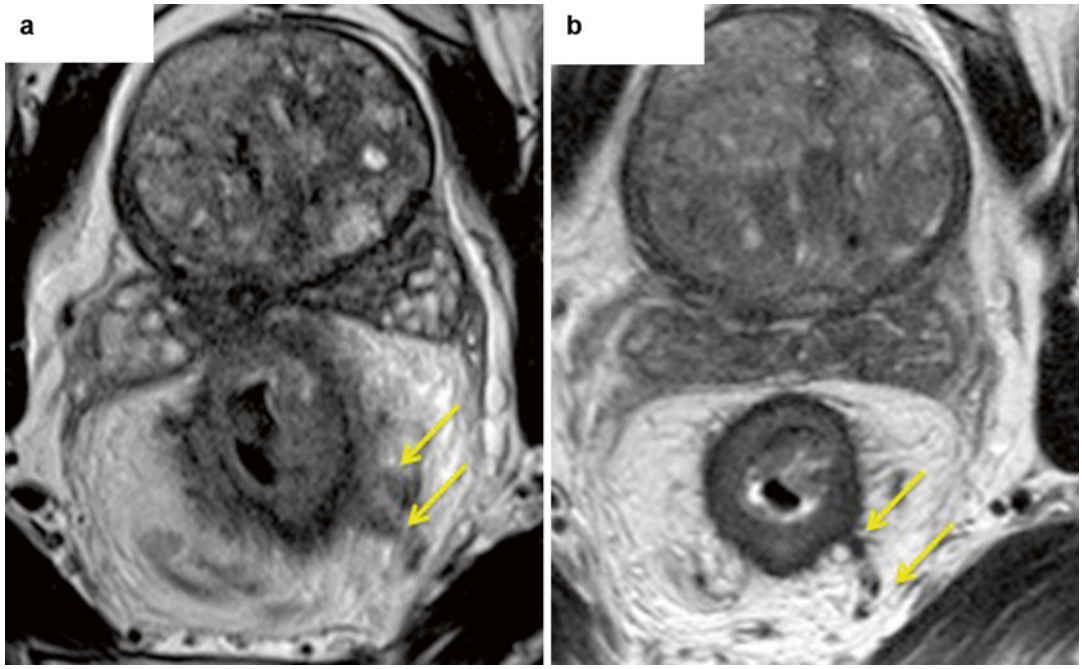

Fig. 6.7 Radiological features of mrEMVI after chemoradiotherapy (ymrEMVI). Fibrosis can be seen in the veins outside the bowel wall. Mid rectal annular tumour. Before CRT (**a**) – a gross expansion of extramural veins in present (*yellow arrows*), post CRT (**b**) – vein have the normal diameter with low signal intensity within them (*yellow arrows*), suggestive of fibrosis

shown to convert following CRT, that is, patients who are initially diagnosed with mrEMVI positive status can become mrEMVI negative [69]. This is accompanied with an improvement in disease-free survival. The degree of improvement in EMVI following CRT can be linked with a respective improvement in survival outcomes. In one study, where mrEMVI had regressed by 50 % of more the 3-year DFS was 87.8 % with a recurrence rate of only 9 %. Those patients that showed less than 50 % fibrosis had 3-year DFS 45.8 % with 44 % recurrence rate. This equated to a hazard ratio of 5.75. This introduces the concept of mrEMVI as an imaging biomarker [70].

In the context of post-CRT prognosis, there is a lack of robust prospective evidence to demonstrate which factors may be considered the most relevant. We continue to rely on the historical studies of patients that had undergone primary surgery and, in some cases, oncologically inadequate surgery with poor resection planes achieved. Recently, EMVI has been shown to confer a worse prognosis in terms of disease-free survival in rectal cancer patients who have undergone pre-operative long-course CRT than nodal disease. A study which examined the survival outcomes of patients with stage II and III disease found that patients with stage II disease and MRI evidence of EMVI had similar outcomes to those patients with stage III disease. Further, patients with stage III tumours had worse disease-free survival when there was evidence of EMVI [71].

Current multicentre studies such as BACCHUS (Bevacizumab And Combination Chemotherapy in rectal cancer Until Surgery) and MARVEL (Molecular And Radiological EValuation of Extramural venous invasion in RectaL Cancer) may help further understand the true importance of EMVI.

Height of Tumour

The position of height of a rectal cancer is measured from the anal verge. Although there are

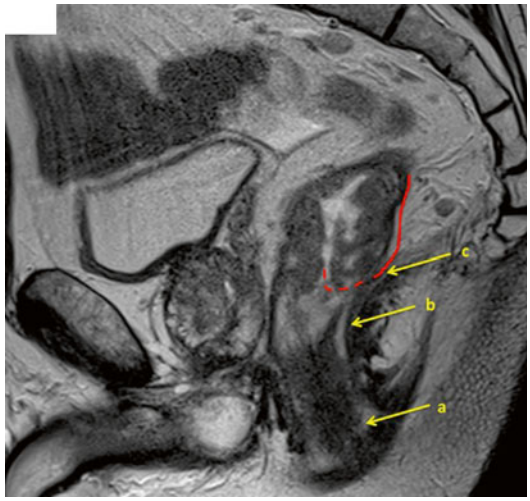

Fig. 6.8 Height of tumour on MRI. The length must be measured using *straight lines* from the anal verge and using the correct field alignment perpendicular to the long axis of the rectum. Measurement of the tumour distance from the anal verge: *a* – lower most level of subcutaneous portion of external sphincter, *b*- level of the puborectalis sling, *c*- distal edge of the tumour. *a–c* distance from the distal edge of the invading border (*continuous red line*) not the rolled age (*dashed line*) to the anal verge (*a–c*), distance from the distal edge of the tumour to the top of the puborectalis sling (*b–c*)

differing definitions of the exact length of the rectum it is the importance of 'low tumours' which must be considered. Tumours found within the distal 6 cm are classified as "low" rectal cancers. Low tumours are associated with local recurrence and anastomotic leak following surgery [72].

Height can be assessed clinically with the 'educated finger', rigid sigmoidoscopy or MRI. Whilst surgeons quite rightly place great emphasis on the clinical use of per rectal examination or sigmoidoscopy, MRI can provide objective and functional measurements which are reproducible. MRI-height is based on relating the tumour to consistent anatomical structures (Fig. 6.8) [73, 74]. The level of the tumour has implications on surgical planning and may be the difference between performing an anterior resection or abdomino-perineal resection, or deciding to create a defunctioning stoma. Axial images on MRI can clearly demonstrate the level and longitudinal spread of the tumour. However, correct field alignment is imperative and taking images through a plane which is not exactly 90° to the long axis of the rectum and over- or under-call tumour height.

Specific Challenges Associated with Recurrent Rectal Cancer

Recurrent disease has its own specific set of challenges. A recent consensus statement from the Beyond TME Collaborative which consisted of a worldwide panel of recognised, multidisciplinary experts in rectal cancer attempted to clarify definitions, treatment guidelines relating to locally advanced rectal cancers and recurrent disease [75]. To diagnose recurrent disease they recommended, "*Where tissue biopsy is not possible or is negative, serial enlargement of a lesion accompanied by either positive positron emission tomography (PET)–computed tomography (CT) or rising carcinoembryonic antigen (CEA) level and specialist multidisciplinary team (MDT) opinion suggestive of malignancy can be accepted for diagnosis*".

Whilst extra-pelvic disease can be detected using a combination of modalities most commonly starting with CT, identification and the extent of spread of local disease is best diagnosed using MRI [76–78]. It can accurately detect local invasion into surrounding structures [79], which is an important part of risk stratification. Local recurrences are defined as disease relapse within the pelvis and this may include anastomotic recurrence as well as deposits in close proximity. It can be seen in up to 15 % of cases [80]. Certain factors are associated with local recurrence including a positive resection margin (R1/R2), tumour height, anastomotic leak. However, a significant number of recurrences have no obvious precipitating factor.

Prognosis of these patients is poor and variable. Both these concerns have led to recent calls to centralise the management of such cases. A multidisciplinary, expert team with experience in managing recurrent disease are best positioned to provide optimal standards of care and thus improve prognosis. This has been highlighted in the recent 'Beyond TME' Consensus Statement. And central to this document was the premise of accurate imaging to define the extent of disease relating it to compartments of the pelvis. Such

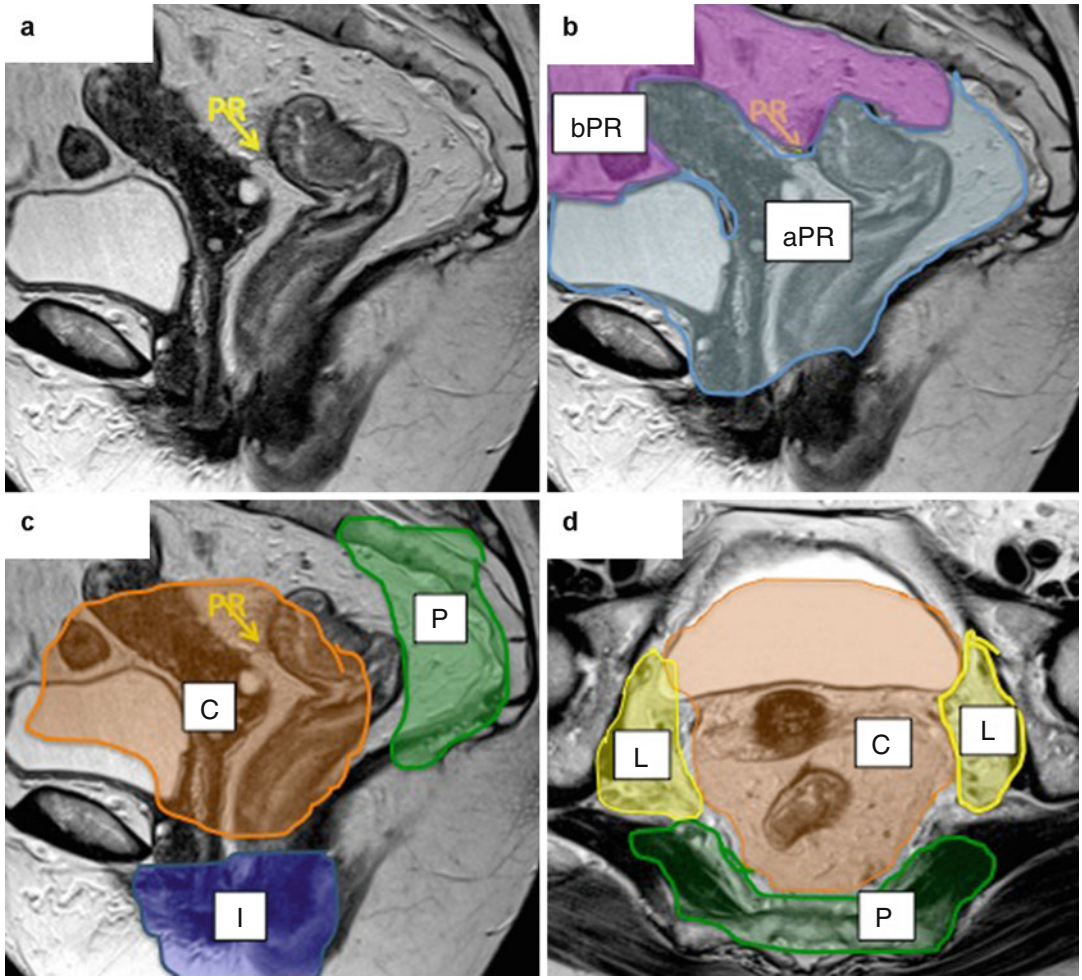

Fig. 6.9 The pelvis can be divided into seven compartments: (**a**) – peritoneal reflection (*PR*); (**b**) – above PR (*aPR*), below PR (*bPR*); (**c**, **d**) – central (*C*), posterior (*P*), lateral (*L*), inferior (*I*)

pre-operative staging is essential to plan the most appropriate surgical procedure to ensure oncologically successful surgery. The prognosis of patients with R0 resections are comparable to primary disease in suitably selected patients and much improved over those with R1 and R2 [81].

Imaging of the pelvis for recurrent disease has been the basis of classifications systems when planning treatment. The Memorial Sloan Kettering classification involves defining the recurrence as axial, anterior, posterior, or lateral (1). Prognosis can be correlated with which 'compartment' is affected with the lateral compartment being associated with the worst outcomes. A more recent classification system based on fascial boundaries and anatomical planes has been proposed which involves seven compartments (Fig. 6.9) (2). The diagnostic accuracy of this classification has been examined in patients undergoing exenteration surgery for recurrent disease. The accuracy of MRI to correctly predict the extent of disease and therefore most appropriate surgical strategy was high (sensitivity >93 % in all but the lateral compartment (89 %) and specificity above 82 %).

Conclusion

The role of imaging in staging of rectal cancer has become essential in offering patients optimal treatment. The improvement in resolution and technique has meant that great detail can be seen by radiologists which in turn influence

management strategies. The universal acceptance of a standardised surgical technique in TME has allowed clinicians, through the forum of the multidisciplinary team, to plan surgical treatment in a safe and effective manner. If tumour-related features with known adverse outcomes can be pre-operatively treated with chemoradiotherpy, surgery is likely to result in improved outcomes and low risk of local recurrence. Furthermore, if traditional excision margins remain at risk following pre-operative therapy, more radical surgery can be planned with MRI affording important anatomical detail.

The use of MRI in recurrent disease is now becoming more apparent. It has led to the use of staging systems based on anatomical compartments being developed which can predict surgical and survival outcomes. This is invaluable when planning radical, exenteration-type surgery.

It is likely that MRI will become more widespread as teaching and experience amongst radiologists continues to develop. This will hopefully lead to better patient outcomes as oncologists and surgeons can plan the most appropriate treatment for patients.

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The Surgeon's Perspective on Neoadjuvant Chemoradiation for Rectal Cancer

7

Rhodri J. Codd and Peter M. Sagar

Abstract

Pre-operative chemo-radiation has become standard practice in the treatment of patients with locally advanced rectal cancer. Indeed, in much of Europe and in the United States, pre-operative chemoradiation has been recommended as a standard of care for patients with clinical stage II and stage III rectal cancer. However, management philosophies for rectal cancer have evolved independently in different countries, with a number of varying approaches developing worldwide. The aim of this chapter is to review current practice and to provide an algorithm for the management of such patients.

Keywords

Rectal cancer • Chemo-radiation • Down-staging • Pathological response • Complete response

Introduction

Rectal cancer surgery was historically associated with a high rate of local recurrence and often a need for a permanent stoma. In an effort to achieve an R0 resection and to preserve the anal sphincter, pre-operative chemo-radiation became the treatment of choice for patients with locally advanced rectal cancer. In much of Europe and in the United States, pre-operative chemoradiation has been recommended as a standard of care for patients with clinical stage II and stage III rectal cancer [1]. However, management philosophies for rectal cancer have evolved independently in different countries, with a number of varying approaches developing worldwide.

Surgery for rectal cancer has evolved significantly over recent years. Traditionally, blunt dissection of the rectum was advocated for rectal cancer and this resulted in high rates of local recurrence. Bill Heald from Basingstoke (UK) identified the failings of this imprecise technique and recognized that, by the use of meticulous sharp dissection under direct vision, the rectum, along with its entire mesentery, could be removed as an intact unit [2, 3]. Total mesorectal excision (TME) resulted in a

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significant reduction in lateral margin positivity and very low local recurrence rates and was also associated with a significant reduction in pelvic nerve damage and bladder and sexual dysfunction post-operatively. By the use of this technique, he was able to achieve a local recurrence rates of 6 % with fewer than 10 % of the cohort receiving pre-operative chemoradiation [4]. Similar excellent results have been replicated elsewhere with the application of high quality surgery [5–9], thus highlighting the importance of this surgical development and bringing into question the routine use of neoadjuvant chemoradiation.

More recently, it has been recognized that despite a full TME dissection, patients with low rectal cancer requiring abdomino-perineal resection (APR) have a higher circumferential resection margin (CRM) involvement rate, a higher local recurrence rate, and a poorer prognosis than those treated with anterior resection [10]. CRM involvement in patients undergoing traditional APR for low rectal cancer is often due to the removal of insufficient tissue at the level of the insertion of the levator ani muscles and relative wasting of the specimen at this level. More radical removal of a cylindrical specimen via an extra-levator abdominoperineal resection (ELAPR) has resulted in improved oncological outcomes. In particular, local recurrence rates are reduced [11, 12].

Many surgeons, impressed with the results of TME and ELAPR, remain sceptical about the value of routine neoadjuvant chemoradiation with particular concern about long-term morbidity. It is believed that low local recurrence rates can be achieved with high quality surgery alone [13]. It has been suggested by some that radiotherapy should not be used to compensate for poor quality surgery for rectal cancer. Instead, efforts should be made to improve the overall quality of surgery so that fewer patients require radiotherapy [13, 14]. High quality surgery and its associated improved outcomes may be associated with a more selective approach to the use of neoadjuvant chemoradiation by multidisciplinary teams. Each individual patient with rectal cancer should be carefully assessed and discussed in a forum (multidisciplinary meeting) with the aid of good quality imaging prior to making decisions regarding the need for neoadjuvant treatment.

Who Should Receive Chemoradiation?

The work of Quirke et al. [15] demonstrated that the presence of microscopic tumour cells within 1 mm of the CRM (or lateral margin) is associated with an increased rate of local recurrence and subsequent poor survival. Modern imaging, particularly MR imaging can accurately predict the risk of CRM involvement and therefore the risk for the surgeon of failing to achieve an R0 resection. The MERCURY study group were able to demonstrate that MR imaging and post-operative histopathology assessments of tumor spread were considered equivalent to within 0.5 mm [16]. This modality has been shown to accurately identify the depth of invasion of the cancer and in the low rectum can predict the involvement of the levator ani muscles and the inter-sphincteric plane. The height of the tumour and its length can also be measured but unfortunately, as with other imaging modalities, prediction of lymph node status remains inaccurate. High quality MR imaging combined with surgical clinical assessment can allow multi-disciplinary teams to predict those patients who will benefit from chemoradiation and those patients who should undergo primary surgery.

Important factors to consider when selecting patients for neo-adjuvant chemoradiation include the height of the tumor and the site of the tumor. Low and anteriorly based cancers confer a higher risk of margin involvement and therefore local recurrence, whereas posteriorly based tumors and tumors of the upper and mid rectum are associated with a lower risk of CRM positivity [17]. Often, an examination under anaesthetic combined with the MRI findings can allow a precise assessment of these characteristics. Other factors that are associated with local recurrence include T4 cancers, evidence of extramural

vascular invasion or perineural invasion and evidence of nodal involvement [17]. A review of the available histology and imaging can identify these characteristics.

Patient factors such as the sex of the patient and their BMI (Body Mass Index) are also important. Surgery for a low, anteriorly based rectal cancer in an obese male with a narrow pelvis is significantly more challenging when compared with similar pathology in a slim female with a gynecoid pelvis. Surgeons may have a lower threshold for neoadjuvant treatment in the former type of patient when compared with the latter in order to reduce the risk of local recurrence.

Multi-disciplinary teams should carefully consider individual patients and their pathology prior to embarking on neoadjuvant treatment or recommending primary surgery. At the extreme ends of the spectrum of disease, decision-making can be easier. T1, T2 and T3a cancers of the upper or mid-rectum without evidence of nodal involvement or EMVI may be treated with primary surgery whereas neo-adjuvant treatment is advised when the CRM is threatened or if the sphincters are threatened or involved.

Pathology of an intermediate nature has to be carefully considered by each MDT and throughout the world individual preferences will vary considerably. The National Institute for Health and Care Excellence (NICE) in the United Kingdom defines these intermediate lesions as either T3b tumors where the margins are not threatened, suspicious lymph nodes not threatening the CRM and evidence of EMVI [18]. The presence of these factors can influence decision making of the MDT, but at present there are no established evidence-based recommendations. Further research is necessary in order to establish the role for neoadjuvant chemoradiation in this intermediate group of patients.

Tumor Downstaging and Sphincter Preservation

Significant tumor downstaging can be achieved by the use of chemo-radiation [19–21]. A large proportion of tumors will regress and up to 25 % will achieve a pathological complete response [20, 21]. One must remain aware that a small proportion of rectal cancers will fail to respond to chemoradiation and will actually progress despite this treatment. This group of non-responders should be identified in a timely manner, as earlier surgery will be beneficial.

In those who do achieve a good response to chemoradiation and in whom there is tumor downstaging (Figs. 7.1 and 7.2), it is our practice to surgically treat patients based on their

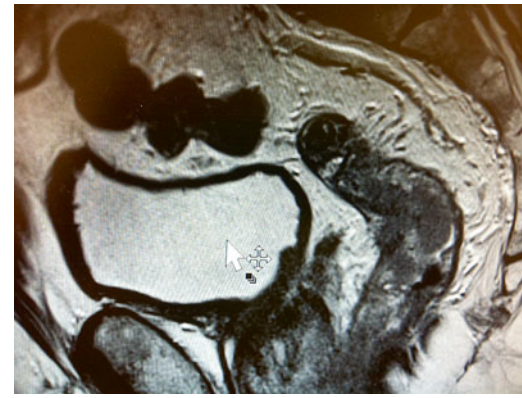

Fig. 7.1 This MR image shows a T3N1V1 mid rectal tumour with a potentially involved circumferential margin. There is a plaque of high signal intensity in the presacral space. The patient subsequently underwent long course chemoradiotherapy

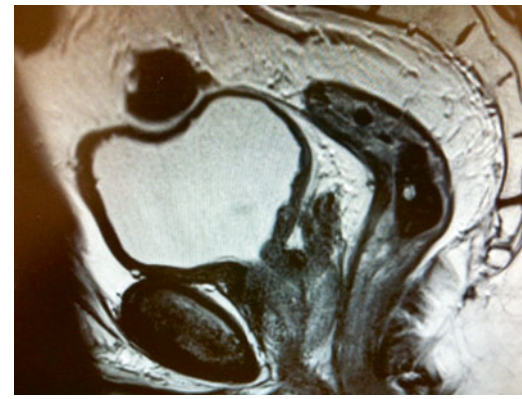

Fig. 7.2 This is an MR image post long course chemoradiotherapy. There has been a good response with the previously involved nodes no longer evident. The changes in the presacral region have disappeared. Histopathology of the subsequently resected specimen reported ypT1N0V0 R0 Mandard tumour regression grade 2

pre-chemoradiation MRI scan. For instance, should adjacent viscera be involved on the pre-treatment MRI but be clear of tumor on the post-treatment scan we would advocate multi-visceral surgery in order to avoid leaving residual microscopic tumor cells and thus the risk of locoregional recurrence. Similarly, should the sphincters be threatened on the pre-treatment scan but be clear on the post-treatment MRI it is our preference to offer an abdominoperineal resection for the same reasons. In addition it can be notoriously difficult to differentiate post-radiotherapy fibrosis from residual disease on MRI. In which case we would prefer to confirm this histologically.

Tumor downstaging as a result of chemoradiation may be utilized in order to achieve sphincter preservation in those with low rectal cancer threatening the sphincter complex. However, current evidence for this specific role is not clear and the use of chemoradiation in order to achieve this goal remains controversial [22]. It is our practice, as we have already stated, to treat patients according to their original pre-treatment MRI images. We would therefore not use neoadjuvant treatment for the purpose improving our rate of sphincter preservation.

It is important to recognize that some rectal cancers behave biologically very differently to others. Clinicians treating rectal cancer should aim to identify those patients who respond to neoadjuvant treatment and perhaps more importantly the small proportion who will progress despite this therapy and require early surgery. Over recent years, there has been a focus on trying to identify prognostic molecular biomarkers in rectal cancer in an attempt to predict response to chemoradiation. It is hoped that in the future therapies can be tailored to the tumor biology of each individual patient [1]. However a present we do not have this luxury and must use existing clinical and radiological tools to define the extent of tumor response to neoadjuvant treatment.

Monitoring tumor response to neoadjuvant treatment can be challenging. Size and shape-based criteria can be lacking in accuracy when trying to discriminate between responders and non-responders [23, 24]. One of the most accurate tools for monitoring response is the MRI defined tumor regression grade, which appears to be able to predict long-term outcomes in terms of local recurrence and 5-year survival [25]. Sequential imaging with this modality has the advantage of being able to quantify response to chemoradiation and may be used to predict the appropriate timing of surgery based on level of response.

Interval Between Completion of Neo-adjuvant Treatment and Surgery

The timing of surgery post neo-adjuvant treatment remains an area for further research effort. Currently the only randomized trial to tackle this question is the Lyon R90-01 trial published in 1999 [26]. This study included over 200 patients with rectal cancer who were randomized to surgery either within 2 weeks of completing their radiotherapy or surgery between 6 and 8 weeks of completing treatment. The group who underwent surgery following a longer interval (6–8 weeks) had significantly more clinical tumor response and tumor downstaging when compared with those who received surgery within 2 weeks of radiotherapy. These findings have influenced standard US and UK practice and until recently it has remained routine to wait between 6 and 8 weeks post neo-adjuvant treatment before proceeding with surgery. More recently however this standard interval has been challenged as it appears that waiting for longer than 8 weeks may allow a higher degree of tumor necrosis and regression.

Surgeons from the Cleveland Clinic have studied a cohort of over 240 patients and identified a significantly better pathological complete response (pCR) rate in those waiting over 8 weeks between completing neo-adjuvant treatment and undergoing surgery [27]. Multivariate analysis revealed time-interval between completion of treatment and surgery to be the only predictor of pCR. A follow-up study determined that waiting for over 8-weeks was safe and was not associated with higher peri-operative mor-

bidity or mortality. This longer time-interval was associated with a lower 3-year local recurrence rate [28].

A study from Nottingham in the UK looked at tumor regression related to neo-adjuvant treatment and calculated the tumor-halving time for rectal cancer to be 14 days [29]. These findings were based on the tumor volume difference between pre-treatment CT imaging and post-operative histopathology measurements. It was estimated that from beginning neoadjuvant treatment it would take an average sized tumor 20-weeks to regress fully, based on these findings. One must remain aware however that each individual patient will respond differently to chemoradiation. Some may respond far quicker whilst others will fail to respond at all and may even progress despite neoadjuvant therapy.

There is a prospective trial that is currently recruiting and is being run by the Royal Marsden NHS Foundation Trust in London. The primary aim of this study is to identify whether waiting 12 weeks from completion of chemoradiotherapy results in greater tumor downstaging or tumor regression when compared with an interval of 6 weeks. Secondary outcome measures will include the proportion of patients undergoing sphincter-saving surgery and the peri-operative morbidity and mortality rates. There is also another prospective study called "A trial looking at surgery following treatment for rectal cancer (STARRCAT)" which is also recruiting and is also comparing intervals of 6 and 12 weeks. The aims of this study however are to assess surgical difficulty and complexity when surgery is delayed and also to evaluate patient experience and the side-effects of treatment. The results of these studies may help to ascertain the optimum time-interval between completion of chemo-radiotherapy and surgery.

Clinical and Pathological Complete Response

Significant downstaging of rectal cancers will occur in a substantial proportion of patients treated with neo-adjuvant chemoradiation, and in some cases the tumor will be entirely sterilized. Some studies have reported that up to 25 % of patients will have a pathological complete response (pCR) following this form of treatment [19–21]. pCR is defined as the complete absence of adenocarcinoma cells within the surgical specimen when examined by a histopathologist (i.e. stage: ypT0 N0).

A pooled analysis of individual patient data from 27 existing articles suggested that those patients who achieve a pCR had significantly better 5-year disease free survival rates when compared with those who failed to achieve such a good response [30]. A systematic review and meta-analysis of existing evidence including a total of 3,363 patients with either stage II or stage III rectal cancer and with a mean follow up of 55.5 months identified significantly better outcomes in patients who achieved a pCR when compared with those who only achieved an incomplete response [31]. Those with a pCR where approximately four times less likely to develop local recurrence and also over four times less likely to develop distant disease. They were more than four-times more likely to be disease free at 5 years and had a 3.3 fold overall survival advantage when compared with incomplete or non-responders. The findings of this meta-analysis suggest that following pCR the risk of local recurrence at a mean follow-up of 55.5 months is 0.7 %. If this is the case, then pCR following neoadjuvant chemoradiation virtually eradicates the risk of local recurrence. pCR was shown to be associated with an overall 5-year survival rate of 90.2 % and a disease free survival rate of 87 %. These results are comparable to those following an R0 resection for stage I rectal cancer [31]. One should be aware however, that the majority of the studies included in this analysis are retrospective case-series and that there is currently no level 1 evidence to support these findings. Despite this it seems logical to expect patients who respond well to chemoradiation and then undergo surgery to remove the rectum to do better than patients who fail to respond so well to neoadjuvant treatment.

There are many different approaches to the management of patients who achieve a pCR post

neoadjuvant treatment throughout the world. There are some who would recommend less radical surgery for selected patients with pCR, thus avoiding the need for an anterior resection or AP resection of the rectum. There are reported series of transanal excision and the use of transanal endoscopic microsurgery (TEMS) to excise the scars left behind post neoadjuvant treatment in patients who appear to have achieved a clinical complete response (cCR) to treatment [32–35]. Unfortunately, as with much of the data relating to patients with a pCR, many of these reports are from small case-series and much of the data has been gathered retrospectively. There is currently no high level evidence to support this practice.

There are also advocates of an expectant ("watch and wait" or "wait and see") approach to the management of patients who achieve a cCR post neoadjuvant treatment. In particular, Habr-Gama and her colleagues from Sao Paulo in Brazil have published widely with regards to this approach [36–41]. Their approach includes intensive clinical, radiological and endoscopic follow-up post neoadjuvant treatment. In those patients deemed to have achieved a cCR, defined as the absence of clinically detectable residual tumor, an expectant (non-operative) approach is adopted. Conversely, those who are assessed and have failed to achieve a cCR are recommended to undergo rectal resection.

The appeal of an expectant approach to the management of patients with rectal cancer who undergo a cCR following neo-adjuvant therapy is understandable. Those in question are usually patients with low rectal cancer who would normally require significant pelvic surgery in the form of a low anterior resection or AP excision. Surgery of this type carries with it a risk of morbidity and mortality, with potential long-term side effects in terms of bowel, urinary and sexual dysfunction and a significant change of a temporary or permanent stoma. Avoiding these potential hazards can be understandably appealing to patients and their surgeons. However the longer-term uncertainties associated with the "watch and wait" approach must also be considered.

There are a number of unanswered questions associated with the approach of Habr-Gama and her colleagues, reflected in the fact that this strategy has not been adopted more widely in the field of colorectal surgery. One needs to clarify what constitutes a cCR and how accurately does this predict a pCR. Habr-Gama and her colleagues recognize the difficulty related to defining what constitutes a cCR and the imprecision and variation of this definition between different authors [42]. Currently, there is no standardized definition of what constitutes a cCR.

In a paper from 2010, Habr-Gama and colleagues have listed a number of observed clinical and endoscopic findings in patients who frequently have a cCR [42]. Subtle features such as whitening of the mucosa, telangiectasia at the site of the tumor and a loss of pliability of the rectal wall harboring the scar are thought to predict a cCR. Conversely, ulceration, a palpable nodule or stenosis at the site of the previous tumor are thought to predict an incomplete clinical response and the need for definitive surgery. Biopsies are thought by Habr-Gama to be of limited clinical value [43]. Whereas positron emission tomography/computed tomography (PET/CT) performed at 12 weeks post neoadjuvant treatment is considered a useful modality in the assessment and diagnosis of residual disease [44].

In a Dutch series where a "watch and wait" approach was adopted, cCR was defined according to a number of strict criteria. These included the clinical absence of palpable or visible disease, the absence of suspicious lymph nodes at MRI, no disease or a small scar or ulcer at endoscopy and negative biopsies from the scar. Only if all of these criteria were met, was the patient considered to have achieved a cCR [45]. Currently, it seems that there is no widespread consensus amongst colorectal surgeons as to the definition of a cCR. Indeed when members of the Association of Coloproctology of Great Britain and Ireland were sent a questionnaire on the subject, they replied with over 70 different combinations of investigations and imaging modalities to define a cCR [46]. At present there is a need for greater clarity and standardization of the definition of a cCR, before more widespread adoption of this management strategy can be recommended.

There is also a potential for patients with an apparent cCR to harbor disease within their lymph nodes. Up to 17 % of patients will have no intraluminal evidence of residual disease and at pathology no mural evidence of cancer (ypT0) but will harbor cancer cells within the lymph nodes [47]. Conversely, there will be some patients (8.3 % according to Habr-Gama et al. [37]) who clinically appear to have evidence of residual disease who in fact pathologically will have achieved a pCR. Clinically, endoscopically and radiologically predicting pCR remains challenging at best and even in the hands of very experienced surgeons with patients undergoing intensive follow-up it remains fraught with difficulty. Future advances in radiology, biochemistry and molecular biology may enable more accurate prediction of pCR in those with a cCR and may eventually obviate the need for radical surgery and its potential morbidity in this group of patients [31].

At present, the "watch and wait" strategy remains experimental. In addition to the points already discussed, there are concerns regarding limitations of many of the reporting studies. The majority of these studies are small retrospective series with insufficiently long and rigorous follow-up. There have been concerns raised regarding the fact that up to 20 % of patients with an apparent cCR will fail non-operative treatment within the first year and will require salvage surgery [1]. There is a lack of data specifically relating to these failures, their management and their eventual outcome. There is also a lack of data relating to quality of life and functional outcomes of patients undergoing non-operative treatment post neo-adjuvant treatment. Well-designed, prospective observational studies have been recommended to answer some of the questions regarding this expectant management approach [48].

Well-designed, prospective trials attempting to resolve some of these unanswered questions are already in progress. There is a study sponsored by the Royal Marsden NHS Foundation Trust (NCT01047969) that is recruiting patients currently and is aiming to assess the safety of omission of surgery following neo-adjuvant treatment. The primary outcome measures are to estimate the percentage of patients who can safely omit surgery, (defined as the percentage of patients at 2 years after the end of chemoradiation who have not had surgery and who are in cCR) and to prove the safety of deferred surgery, (as measured by the percentage of patients who have local failure at 2 years), where local failure is defined as positive margin status of resected tumor or surgically unsalvageable disease. Unfortunately, definitive results from this study are unlikely to be available before 2019. A Danish study is also currently recruiting patients in order to answer similar questions regarding the policy of "watchful waiting" (NCT00952926). This prospective study aims to calculate the frequency of local recurrence, the frequency of distant metastases and the overall 5-year survival in patients treated non-operatively following a cCR.

We would recommend awaiting the findings of these prospective trials before adopting a "watch and wait" approach in those with a cCR. This does not mean that a non-operative approach following neo-adjuvant therapy can never be adopted. There may be the exceptional case where an expectant management approach is preferable. For instance in a frail, unfit patient who has achieved a cCR and in whom the risks of surgery outweigh the potential benefits. In this type of case, a non-operative strategy may be discussed at MDT and with the patient and their family. However in general, and in view of the current level of available evidence the widespread adoption of a "watch and wait" policy in those achieving a cCR cannot be justified.

Side Effects and Surgical Implications of Neoadjuvant Chemoradiation

The reduced risk of local recurrence associated with the use of neoadjuvant chemoradiation is offset somewhat by its potential short-term and long-term complications. From a surgeons perspective, one will be familiar with the intraoperative effects of radiotherapy on pelvic tissues. This treatment can affect the pliability of

tissues and make dissection along recognized tissue planes more challenging. There is also a tendency for greater intra-operative haemorrhage in those who have received neoadjuvant treatment [49]. There is also thought to be a higher risk of anastomotic leakage following neoadjuvant chemoradiation, which should be remembered when considering decisions regarding restorative surgery and in decisions regarding the use of a defunctioning ileostomy [49, 50].

The early post-operative complications of neo-adjuvant chemo-radiation include a higher rate of wound infection, wound dehiscence, anastomotic leakage, thrombosis and bowel obstruction [49]. Wound breakdown can be particularly problematic for those patients who have undergone an abdomino-perineal excision of the rectum post neo-adjuvant treatment. The perineal wound is prone to impaired healing in those who have received pelvic radiotherapy. The Medical Research Council CR07 trial which compared preoperative radiotherapy with selective postoperative chemo-radiotherapy identified a substantial increase in the rate of delayed perineal wound healing in those who had undergone an AP resection for rectal cancer following pre-operative radiotherapy (36 %) compared with those who received adjuvant treatment alone (22 %) [51]. Some wounds may have failed to heal up to a year or more post-surgery [52]. The potentially higher peri-operative risks associated with chemo-radiation should be considered by clinicians and explained to patients, in order for them to make an informed decision about whether to receive neo-adjuvant treatment or not.

Chemo-radiation is also associated with acute toxicity in a substantial proportion of patients. A Cochrane review comparing pre-operative chemoradiation versus radiation alone identified an incidence of grade 3 or grade 4 acute treatment related toxicity 14.9 % of patients treated with chemoradiation and a rate of 5.1 % in those treated with radiotherapy alone [53]. Grade 3 toxicity indicates that intervention other than medications is necessary to treat the side effect whereas grade 4 toxicity involves hospitalization for treatment of the problem. The EORTC study observed either grade 3 or grade 4 toxicity in 7.4 % of the patients treated with radiotherapy alone and in 13.9 % of patients who underwent neoadjuvant chemoradiation [54]. Similar findings were observed in a Polish trial comparing the effects of short course radiotherapy versus long-course chemoradiation with grade 3 or 4 toxicity occurring in 18.2 % of those receiving chemoradiation compared with 3.2 % of those receiving radiotherapy alone [55].

Acute toxicity is observed significantly more frequently in those receiving neo-adjuvant chemo-radiation when compared with those receiving similar doses of radiotherapy alone [54, 55]. Acute treatment-related toxicity may cause interruptions in neo-adjuvant therapy and in some patients may result in them failing to complete the course of therapy. This significant potential for toxicity associated with neo-adjuvant therapies must be considered by multidisciplinary panels and should be explained and discussed thoroughly with patients. Accurate pre-treatment staging is essential in order to ensure that only appropriate patients are considered for this potentially morbid pre-operative therapy.

Aside from these early complications, chemo-radiation may also be associated with late toxicity. Late toxicity includes anorectal, urinary and sexual dysfunction. These side effects may significantly affect the daily routine of a patient and their overall quality of life [49]. Follow-up data from the randomized controlled trials looking at neo-adjuvant chemo-radiation is limited with regards to long-term functional outcomes. A follow-up study from the Dutch group comparing the late side effects of short course radiation in those undergoing total mesorectal excision for rectal cancer with a median follow-up of 5.1 years, identified a significantly higher rate of bowel dysfunction in those receiving pre-operative radiotherapy when compared with surgery alone. The irradiated patients reported increased rates of faecal incontinence (62 % vs 38 %; $p<0.001$), pad wearing due to incontinence (56 % vs 33 %; $p<0.001$), per-anal blood

loss (11 % vs 3 %; $p<0.004$), and per-anal mucus loss (27 % vs 15 %; $p<0.005$). Their general satisfaction with bowel function was significantly lower than those who underwent surgery alone and the impact of this bowel dysfunction on their daily activities was greater [56]. Long-term data focusing on quality of life and function from RCT's looking at long-course chemo-radiation is still awaited [57].

Data from non-randomized trials point towards the potential for long-term functional problems and the impact on quality of life in patients treated with pelvic irradiation. In a study conducted in Oxford (United Kingdom), questionnaires were completed by over 400 patients who had previously undergone pre-operative radiotherapy for a combination of pelvic cancers including rectal cancer. Issues with bowel, urinary and sexual function were relatively common amongst these patients, with bowel urgency reported in 59 % of females and 45 % of males; urinary urgency reported in 49 % of females and 46 % of males and sexual dysfunction reported in 24 % of females and 54 % of males. The frequency of these functional problems was similar in those who had received radiotherapy between 1 and 5 years previously and also in those who had received treatment between 6 and 11 years previously. This study therefore highlighted the potential chronicity of these late side effects. As one would expect, the severity of the symptoms was linked to poorer overall quality of life and to a higher rate of depression [58].

A systematic review and meta-analysis focusing on the long-term functional impact of chemo-radiation was recently performed and published by Swiss and German authors [49]. This review searched for all studies reporting on the long-term functional effects in patients who had received neo-adjuvant chemo-radiation for rectal cancer. The focus of the study was on long-term sexual, urinary and anorectal function. Twenty-five appropriate studies and 6,548 patients were included in the analysis. Post-treatment follow-up ranged in length from between 3 and 6 months post stoma closure to 5.1 years post-operatively. This systematic review and meta-analysis revealed a significant difference in long-term anorectal function between those that were treated with neo-adjuvant chemo-radiation followed by resectional surgery when compared with resectional surgery alone. Rates of stool incontinence were significantly higher in irradiated patients (RR =1.67, CI = 1.36–2.05, $p<0.0001$) and manometric results including mean resting pressure and maximum squeeze pressures were significantly worse in this group of patients. There were no significant differences in sexual or urinary function between the two groups. Methodological quality of the included studies was low and there was a high degree of heterogeneity, highlighting the need for more robust evidence. Despite this, currently available evidence suggests the potential for long-term anorectal dysfunction in those treated with pre-operative chemo-radiation and this should be discussed thoroughly with patients prior to commencing therapy.

Conclusion

As surgeons, we must work together with other members of the multi-disciplinary team in order to ensure patients are made aware of the relative merits and the potential negative effects of pre-operative chemoradiation. This therapy has proven benefits in appropriately staged patients, with a reduction in local recurrence rates, even in those who receive optimal surgery [57]. However, this benefit must be balanced against the potential treatment related complications that have been discussed throughout this book chapter. These complications indicate the need for highly accurate pre-operative tumor staging in order to minimize the number of patients receiving unnecessary chemoradiation. Patients must also be involved in the decision-making process and should be fully counselled by clinicians in order to ensure that they are aware of the potential benefits and the side effects of neoadjuvant treatment. Finally, a strategy for the use of chemo-radiation in rectal cancer is provided as an algorithm in Fig. 7.3.

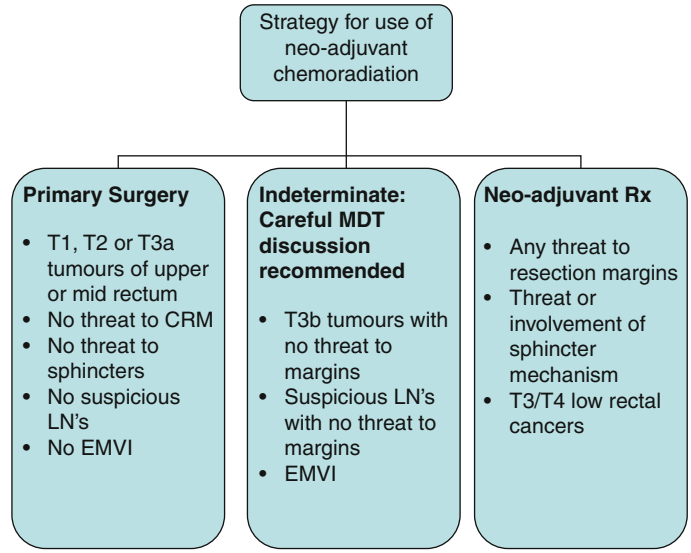

Fig. 7.3 A strategy for the use of neo-adjuvant therapy for rectal cancer

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Contact X-Ray Brachytherapy for Rectal Cancer

8

Arthur Sun Myint, Jean-Pierre Gerard, and Robert J. Myerson

Abstract

Over the past century, surgery has been the mainstay of rectal cancer management and will remain so for the foreseeable future. However, surgical mortality and morbidity is high, especially for the elderly patients. The population is ageing globally, the effect being more pronounced in Western countries. It is important to avoid extirpative surgery, especially in elderly patients, to deter surgical harm. National bowel cancer screening programmes around the world have helped to diagnose rectal cancer in its early stages. It is important to treat the early stages of the disease differently from the more advanced stages. Most protocols are bias heavily towards surgical management for rectal tumors. National and international consensus guidelines do not take into consideration the advancing age of the general population and recommend surgery as the gold standard of care. There is an urgent need to consider alternative treatment options that avoid extirpative surgery and stoma in the early stages of rectal cancer in the elderly.

Keywords

Contact X-rays • Brachytherapy • Papillon • Early rectal cancer • Dose response • High dose superficial X-rays • Complete clinical response

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Introduction

The number of cases diagnosed with early rectal cancer was low in the past, but there is evidence that this figure has increased in the past few years. The main reason is due to a number of Western countries starting national bowel cancer screening using faecal occult blood testing and flexible sigmoidoscopy. It is envisaged that the percentage of cases diagnosed with Dukes A

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will increase from 8 to 60 % over time [1]. It is therefore important for healthcare providers to be aware of this fact and to personalize the treatment options. Tailoring the treatment for early-stage rectal cancer will avoid over-treatment with policies laid down traditionally to cater for more advanced rectal cancers. Current colorectal guidelines recommend surgery as the gold standard of care in rectal cancer. Total mesorectal excision (TME) is necessary for mid- and upper-rectal cancer. For low-rectal cancer, abdomino-perineal excision (APER) is preferred even for early-stage disease. However, mortality and morbidity is high, especially in elderly patients, numbers of whom are increasing worldwide. The clinicians involved should consider alternative treatment options to minimize harm caused by the accepted standard of care. Contact X-ray brachytherapy is a minimally invasive treatment with no mortality and very little morbidity. It uses low-energy X-rays (50 kV) that penetrate only a few millimeters, incurring minimal damage to normal tissues surrounding the tumour. The use of low energy X-rays also means that the wall of the treatment rectoscope effectively shields all but the visualized portion of the rectum. If there is any residual tumour at the end of the treatment, surgery can then be carried out. The extent of surgery depends on the extent of the residual disease. Small residual disease of less than 2 cm can be treated by local excision. Bulky residual disease can be treated by more radical surgery, accepting the calculated surgical risk in a small number of non responders. Case selection is important for a successful outcome.

Case Selection

Inclusion Criteria

1. Malignant mobile exophytic rectal cancer confined to the bowel wall (cT1 or cT2).
2. Well to moderately differentiated adeno carcinoma.
3. No evidence of suspicious lymph node involvement.
4. No evidence of distant metastases.
5. Tumours situated within 12 cm of anal verge.
6. Patients agreeing to long-term follow-up.

Exclusion Criteria

1. Deeply ulcerative fixed rectal adenocarcinoma (advanced cT3 and cT4).
2. Bulky tumours involving more than half the circumference of the bowel wall
3. Poorly differentiated rectal carcinoma
4. Lympho-vascular invasion.

Contact X-ray brachytherapy (CBX), often called Papillon contact radiotherapy, was named after Professor Papillon from Lyon, who popularized this technique for rectal cancer treatment. The technique use 50 kV X-rays to deliver a high dose of low-energy X-rays directly onto the tumour, with a rapid dose fall-off. This can be delivered using an orthovoltage machine (Ariane, Derby) or with electronic brachytherapy (Xoft [Axxent], CA). The principle of contact X-ray brachytherapy is to deliver a high dose (30 Gy) of radiation to a small volume (5–10 cc) with low-energy radiation (50 kV) that has limited penetration (60 % at 5 mm, 38 % at 10 mm for 30 mm applicator). The treatment is given at 2-weekly intervals. X-ray contact brachytherapy shaves off the exophytic malignant sessile polyp layer by layer with each treatment, resulting in downsizing of tumour centripetally in all directions with regression to the point of original tumour (Fig. 8.1). There is now increasing evidence from histological specimens from operated patients that there is accompanying down-staging from advance stage tumour (cT3) to early stage (ypT0-ypT1) in good responders to radiation, which translates to improve local control and disease-free survival [2]. During these 2-week intervals the normal tissues recover. There could be a small amount of superficial mucosal ulceration at the site of the original cancer, but this usually heals after 3–6 months. It is important not to biopsy this area, as the histological findings can be difficult to interpret even by an experience pathologist. If there is a small residual tumour it can continue to regress

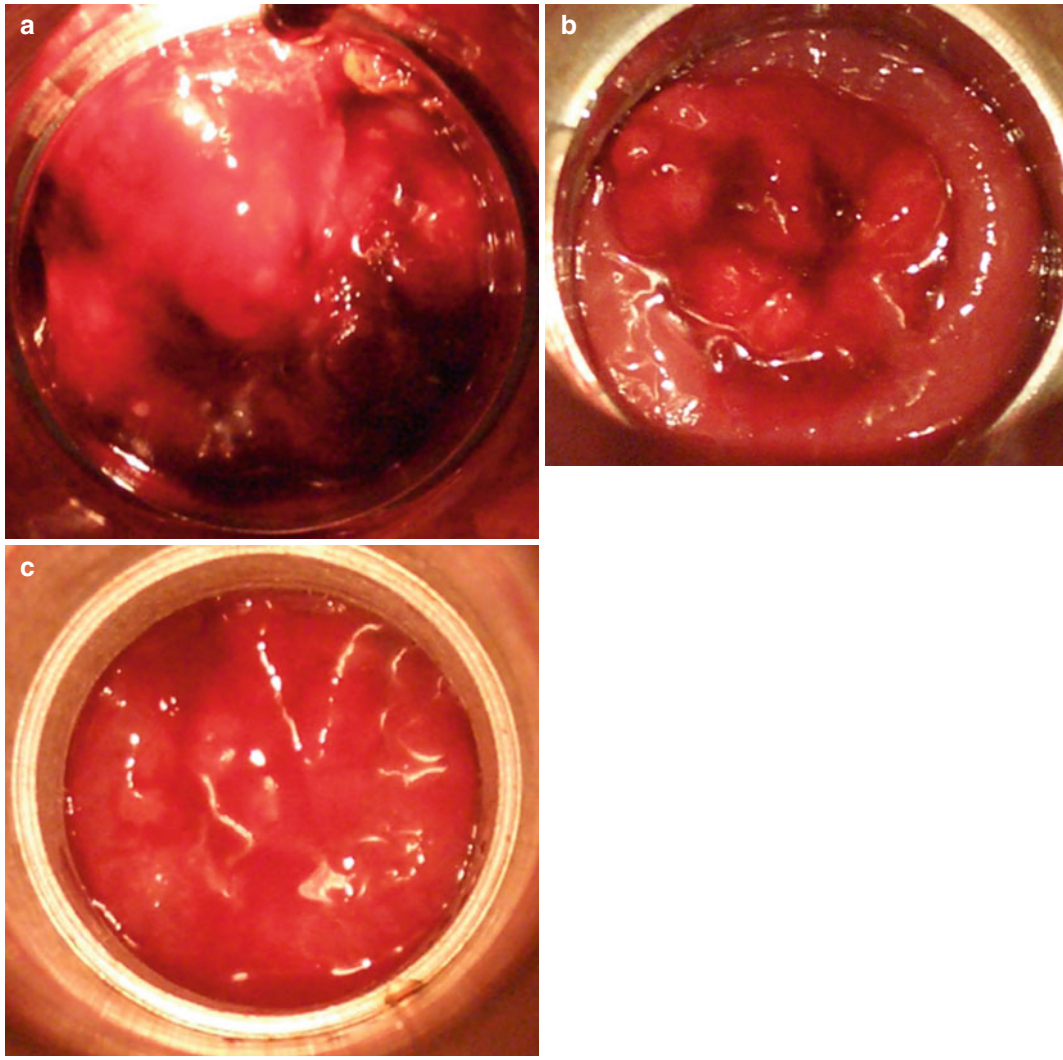

Fig. 8.1 (**a**) Pretreatment (day 0) T2N0M0; (**b**) Post treatment (day 14); (**c**) Post treatment (day 28) after 2 fractions, showing good response (good responder)

and eventually become a small superficial fibrotic scar (Fig. 8.2). This area can readily be detected on the MRI scans, supplemented by diffusion weighted images, which need to be interpreted by an experience radiologist. In case of uncertainty, regular 3-monthly serial endoscopic examinations, digital rectal examination (in palpable tumours) and imaging will help to clarify the resolving scar from a residual cancer which tends to grow back during this period. In the majority of cases with recurrence, the regrowth of cancer is usually slow after radiation. However, it is important to follow these patients up closely and regularly to detect any subtle changes and to arrange timely investigations as necessary.

Investigations

Case selection is important for successful outcomes and initial staging is very important. All cases should be discussed at the colorectal MDT meeting. Complex cases should be discussed at

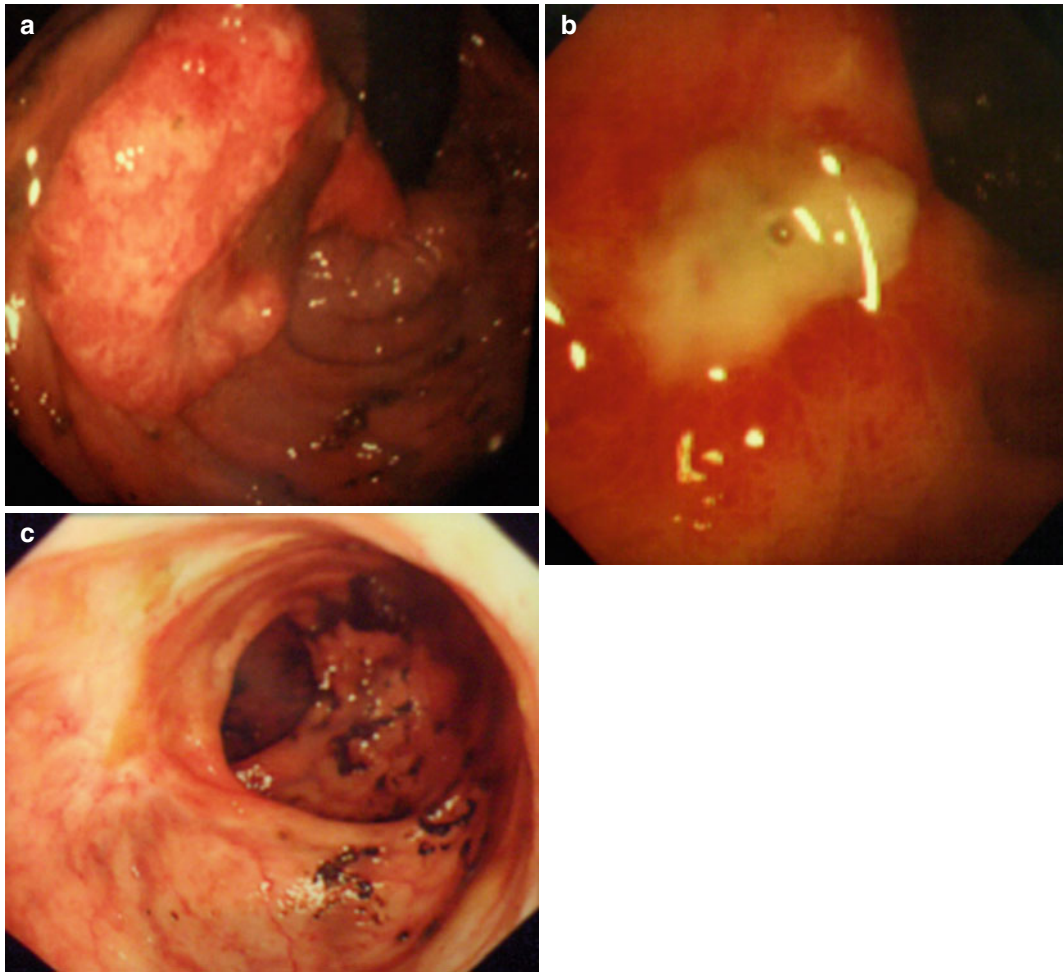

Fig. 8.2 (**a**) Malignant rectal cancer T3N1M0; (**b**) Post treatment ulcer; (**c**) Post treatment healed scar (10 years)

the specialist early rectal cancer MDT, because the issues involved can be difficult. Patients should be inform about the consensus of opinion from the experts. However, the final management decision rests with the patient, therefore they should be well-informed. Help should be available to clarify matters and their decision must not be obtained under duress. Endoscopy with biopsy to establish histological diagnosis is mandatory. Histology should confirm the invasive malignancy and it is also important to exclude any adverse histopathologic prognostic features that may be a relative contraindication for local treatment. Poorly differentiate adenocarcinoma and the presences of lympho-vascular involvement are the two most important features. In some cases, the decision to treat or not to treat is complex, and enough time should be allowed to come to mutual agreement. All patients should have baseline high-resolution MRI [3], contrast enhanced CT scan of chest, abdomen and pelvis. Intra-anal ultrasound (EUS) if available is useful to differentiate early tumours T1 from T2 but it is important to understand that this distinction is not always clear-cut. A PET/ CT scan is not routinely done as part of initial investigations. If the tumour marker CEA is high at diagnosis, it is useful to monitor response and to detect recurrences during follow-up assessments.

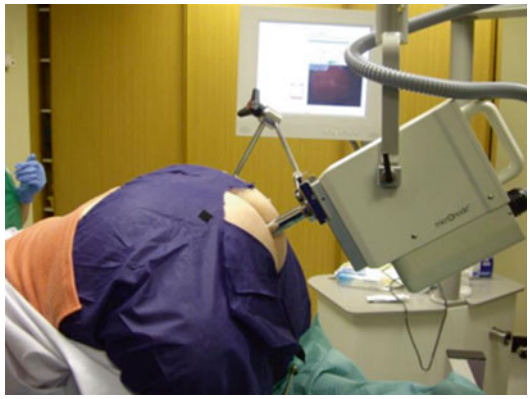

Fig. 8.3 Treatment position for contact X-ray brachytherapy

Preparation of Patient

X-ray contact brachytherapy can be carried out as a day patient procedure. The patient stays on a low-residue diet for 3–5 days before treatment. On the day of treatment a micro-enema is given per rectum half an hour before treatment. This clears the bowel, which helps to identify the tumour margins accurately. The patient is generally treated in prone jack-knife position, which helps to open the rectal lumen (Fig. 8.3), but sometimes in lithotomy position can be useful for low posterior cancers. Techniques to inflate the rectum for better visualization of the tumour have been developed and will help for centres starting with this facility. Local anesthetic gel (Instillagel®) is applied around the anus to numb the area and ease any discomfort. In addition, glyceryl trinitrate (Rectogesic®) or a similar preparation can be applied to relax the muscles around the anus. This will help to ease the discomfort when inserting the rectal applicator.

Treatment Protocol

There are three sizes of rectal applicator, 30, 25 and 22 mm, and the choice depends on the size of the tumour. If the rectal cancer is less than 30 mm, the treatment can start with contact X-ray brachytherapy. For larger tumors, external beam chemoradiotherapy 45 Gy in 25 fractions over 5 weeks (EBCRT) with capecitabine 825 mg/m^2 is used initially to downsize the tumour. In elderly patients with compromise renal function the dose can be modified. For those who are not fit for chemotherapy, because of cardiac problems or poor renal function, short course radiotherapy (SCRT) 25 Gy in 5 fractions over 5 days can be used instead. However, there is evidence from the Trans-Tasman Radiation Oncology Group trial (01.04) that long course CRT will downsize and downstage the tumour much more effectively, with pCR 15 % vs. 1 % in favor of long course for more advanced T3 rectal cancers [4]. Even after short course and delay, the regression of tumour can be quite slow. A contact X-ray brachytherapy boost can follow EBCRT within 2–4 weeks to improve local control. A randomised trial called OPERA (**O**rgan **P**reservation for op**E**rable **R**ectal **A**denocarcinoma) is being set up to evaluate this hypothesis. The dose of contact X-ray brachytherapy is usually 30 Gy per fraction in three fractions given every 2 weeks. Although the physical dose delivered is 30 Gy, the radiobiological effect (RBE) of orthovoltage low-energy X-rays is much higher at 1.4–1.6, so the equivalent dose effect (EQD) is increase to the dose range above 40 Gy per fraction. This dose is delivered in just over 1 min, where normally with external beam the equivalent radiation dose is delivered in 4–5 weeks. As a result of this dose intensity, the cancer-cell kill effect has a very steep slope. The dose of external beam radiotherapy 45 Gy and contact X-ray brachytherapy of 90 Gy, giving a total dose of 135 Gy delivered, however, this dose is radiobiologically equivalent to 160 Gy. This seems a very high dose but it has little effect on the normal surrounding tissues, as most of the dose is applied directly onto the surface of the tumour and not on the normal surrounding tissues beneath it. The tumour is shaved off layer by layer with each application of X-ray brachytherapy, until it regresses completely (Fig. 8.1).

Possible Side Effects

The side effects were reviewed on 100 patients, treated with the new Papillon RT 50 machine at Clatterbridge from 2009 to 2010. There were 69

males. The median age of patients was 72 years (range 33–99). Elderly and unfit patients had radical RT (n = 43), post-op (n = 39), pre-op (n = 5) and palliative (n = 13). The Papillon dose was 60 Gy in 2 fractions over 2 weeks (post-op) and the radical group had 90 Gy in three fractions over 4 weeks following EBCRT or SCRT 25 Gy in 5 fractions over 5 days. The main toxicity was bleeding, occurring in 26 % of patients. Fifteen patients had mild bleeding and five had G3 bleeding requiring Argon plasma coagulation. No patients needed blood transfusions or defunctioning stoma to control their bleeding. Two patients developed rectal pain following treatment. Both had very low-rectal tumors just above the dentate line. One needed immediate salvage surgery for residual tumour, the other patient's symptoms settled with conservative treatment after 8 weeks. There were no fistulas or strictures caused by the new contact machine. There was no 30 days mortality related to contact radiotherapy [5].

Follow-Up

Patients who achieve a complete clinical response following contact X-ray brachytherapy are followed up similarly to those in the watch and wait group following chemoradiation [6]. As most of the recurrences are in the first 2 years, intensity of follow-up is concentrated around this time. One needs to be mindful of the extra anxiety caused to patients during this period and the extra cost of the investigations offered. Patients should be reviewed every 3 months in the first 2 years and 6 monthly up to 5 years. Digital rectal examination (DRE) and endoscopy is carried out as part of the examination during these visits. It is important that one or two experience observers review the patients regularly, as there could be some subtle mucosa changes that need to be observed closely without a biopsy. Experience centres advocating the 'watch and wait policy' advice not to biopsy these lesions, as the histology are difficult even for the most experience pathologists to interpret [6]. The area of biopsy may not be representative of the status of the tumour, as there could be a geographical miss. The ulceration caused by a deep biopsy may not heal, and there could be persistent pain and bleeding from this area. In addition, it makes the interpretation of mucosal changes difficult in the future. If persistent mucosal abnormality is causing concern, the whole area should be excised using transanal endoscopic mucosal resection (TEMS) to obtain an accurate histology, including full thickness of the muscle to assess the histology fully (Fig. 8.4) [7]. The majority (61 %) of mucosal abnormalities do not harbor invasive malignancy apart from low- to high-grade dysplasia, which does not require major surgical resection [8]. However, if there is suspicion of bulky residual disease either from MRI, endoscopy or digital examination, provided that the patient is fit and agreeable to surgery, immediate salvage surgery should be offered. High-resolution MRI scans should be carried out with diffusion weighting imaging (if available) every 3 months in the first 2 years and 6-monthly in the third year. CT scanning should be carried out at 6-monthly intervals in the first 3 years. The timing for these investigations is still not internationally agreed, and as more centres gain experience with the 'watch and wait' policy some consensus on follow-up policy can be agreed at the international meetings that are now held regularly every year. The risk of recurrence is low after 3 years but follow up should continue 6-monthly up to 5 years at least. Recurrences beyond 5 years are very rare, and if patients agree to longer term follow up and local healthcare systems permit this, they should be follow up for 10 years.

Evidence of Efficacy for Contact X-Ray Brachytherapy

Contact X-ray brachytherapy has been around for more than 80 years. Initial treatment was carried out in Berlin with a 50 kV machine made by Siemens. Chaoul treated more than 100 patients, many of them with unresectable rectal tumors. Primary healing occurred in 62 patients and 30 patients were cured at follow-up of 4–17 years [9]. In 1946, Lamarque and Gros from Montpellier laid down the guidelines for contact radiotherapy.

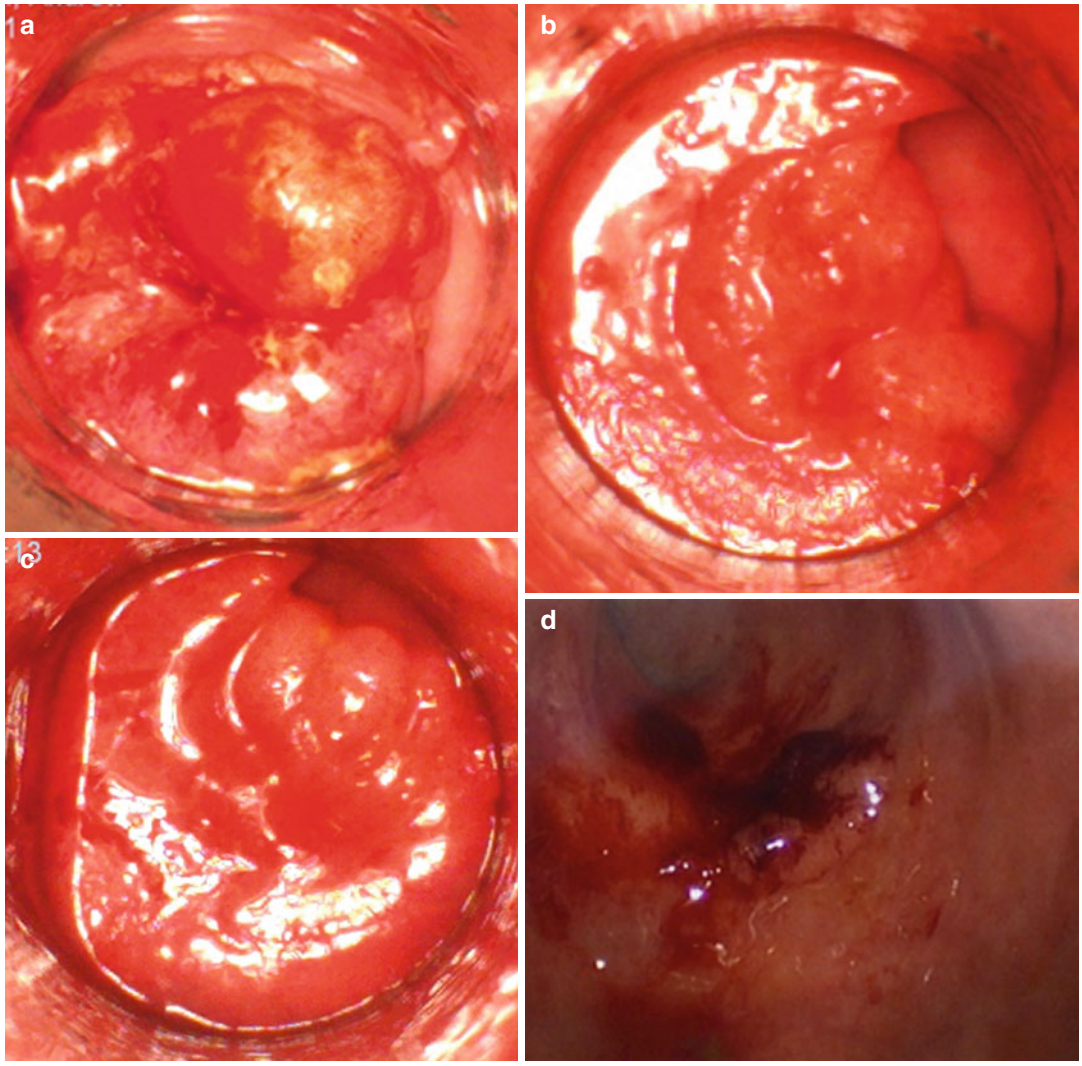

Fig. 8.4 (**a**) Pretreatment (day 0) 07/06/12; (**b**) Post treatment day 14 (20/06/12); (**c**) post treatment day 28 (05/07/12); (**d**) Possible recurrence 14 months later. Had TEMS (14/11/13) Histology –TVA with low grade dysplasia, no invasive malignancy

They conducted a study of histological changes and observed early signs of cytoplasmic and nuclear degeneration a few hours after contact radiotherapy and increasing during the next few days. They showed that bowel epithelium can be destroyed by a single dose of 40 Gy but the regeneration was complete 1 month later. They reported on a series of 116 patients with rectal cancer treated by contact radiotherapy. Cure rates at 5 years even for advanced inoperable tumour were 20 % [10]. These were remarkable results, because in that era adenocarcinoma of the rectum was thought to be radioresistant. Papillon started the contact radiotherapy facility using a 50 kV Phillips machine in Lyon in the early 1950s. He reported on 312 patients with T1 rectal cancer treated by contact X-ray brachytherapy alone from 1951 to 1987 with a 5-year survival of 74 %. There were only 9 local recurrences and 7.7 % of cases died from cancer-related causes. The remaining non-cancerous deaths were related to advancing age with co-existing medical problems. For more

advanced cases T2 or T3, Papillon used external beam radiotherapy, 39 Gy in 13 fractions over 17 days. This was followed by contact X-ray brachytherapy and iridium implant boost. This regime was used in 67 patients (median age 74 years) and they were followed up for more than 5 years. At 5 years the survival was 59.7 %. Of the 40 patients who were alive and well, 39 had normal anal function and only one had undergone APER for local failure. Among the 8 patients who died of cancer, 3 had distant metastases and 5 had pelvic failures. Eighteen patients (26.8 %) died from intercurrent disease due to poor general condition of patients [11]. Papillon observed a relationship between the size of tumour and the chance of cure. Five year survival rate was 80 % for lesions 3 cm or less and for larger tumours was only 61.5 %. The configuration of the tumour seems to have less prognostic significance than the size of the lesion. However, distant metastases occurred twice as frequently for ulcerative tumours. In 1980, Sischy from Highland Hospital in Rochester (New York) reported a series of successfully treated limited rectal carcinomas by contact radiotherapy in the USA. Of 74 patients treated for cure, only 4 had local failure. Seventy patients followed up for at least 18 months were alive and well and free of disease (94 %) [12]. Myerson and his colleagues from Washington University, St Louis, reported on 199 patients treated from 1980 to 1995. They found that the most important factors for local control (Multivariate analysis) were the use of external beam radiotherapy ($P<0.001$), prior removal of macroscopic disease ($P=0.001$) and mobility on palpation ($P=0.009$). Endocavitary treatment was very well tolerated. Of 199 cases, 19 (9.5 %) had minor transitory tennesmus or bleed, managed conservatively. The only grade 3 or 4 morbidities occurred in those patients who needed salvage surgery for tumour recurrence. In the update of their series to 2004, they had 59 T1 lesions identified. Forty of these 59 cases underwent local excision of all macroscopic disease before radiation. With radiation all but 3 (who had a history of prior pelvic radiation for other malignancy) received a combination of external beam (usually 20 Gy in 5 fractions over 5 days) followed 6–8 weeks later by endocavitary radiotherapy. There were only 3 failures and only one (1.8 %) in the 56 who received external beam radiotherapy. The difference between this cohort and the experience reported from others using local excision without contact radiotherapy was highly significant (55/59 vs. 106/129 [$P=0.003$]) [13]. Gerard reported on 101 patients with T1/T2 tumour treated with contact radiotherapy between 1977 and 1993. There were only 10 % local failures, with 83 % overall survival at 5 years [14]. He further reported on 63 patients with T2 and T3 tumour and a median age of 72 years treated between 1986 and 1998. Twenty-six were poor surgical risk patients, 15 refused permanent stoma and 22 who were fit for surgery agreed to radiotherapy to avoid a permanent stoma. Clinical staging was done in 57 patients. Forty patients had T2 tumour and 23 had T3 tumour. Patients were offered combined modality treatment with EBRT (39 Gy in 13 fractions over 17 days) and contact radiotherapy boost (80 Gy in 3 fractions over 3 weeks). At median follow-up of 54 months, local control was achieved in 65 % and 86 % after salvage surgery for residual disease. Primary control rates and 5-year overall survival (patients <80 years) were 80 and 86 % for T2 disease. The respective figures for patients with T3 disease was 61 and 52 %. No severe grade 3 toxicity requiring colostomy was observed. Anorectal function was good in 92 % of patients. Rectal bleeding and bowel urgency were the most common long-term side effects. Two prognostic factors were found to be important. The tumour response after two fractions on day 21 and T stage of the tumour were found to be significant factors [15]. Gerard went further to conduct the only randomised trial (Lyon 96–02) to evaluate the role of contact radiotherapy in improving sphincter preservation for T2-T3 distal rectal cancer. Between 1996 and 2001, 88 patients were randomised between EBRT (36 Gy/13/17 days) and EBRT preceded by contact (Papillon) boost. Sphincter preservation was achieved in 76 %, compared to 44 % in the experimental group [16]. Much higher complete clinical responses (24 % vs. 2 %) and pCR or near-complete sterilization (57 % vs. 34 %) were observed in the contact boost arm compared to the standard arm. These results were maintained in Gerard's

recent update after 10 years' follow-up [17]. He is proposing that the OPERA trial should reproduce these results, but organ preservation with local control at 2 years will be the primary endpoint rather than sphincter preservation. Later he moved to Nice and updated his results for patients treated in Nice with contact X-ray brachytherapy from 2002 to 2009 [18]. The more recent update of his results up to 2009 using the new Papillon (Ariane) has shown further improvement due to better case selection with 90 % of patients achieving complete clinical response (cCR) and only 10 % had local recurrence ([19].

In 1992, a team from Clatterbridge visited Lyon and introduced contact radiotherapy in their country. The first facility in the UK was set up in 1993 and nearly 800 patients have been treated with contact X-ray brachytherapy as part of their treatment. In 2009, a new RT 50 machine made by a British company (Ariane) was made available for clinical use and approximately 500 patients out of the whole cohort were treated with this new machine. Analysis of the original cohort was done on four groups [20].

1. Surgery alone (TEMS)
2. Surgery (TEMS) followed by post-operative radiotherapy
3. Pre-operative chemoradiotherapy followed by local excision (TEMS)
4. Radical radiotherapy alone.

Trans-anal endoscopic microsurgery (TEMS) alone was used for all small malignant polyps with negative resection margins and no adverse features (Group 1 [n = 13]). If the resection margins were close (<1 mm) or histology showed any adverse features e.g. poorly differentiated tumour or lympho-vascular invasion or more advanced tumour (pT2), immediate salvage surgery was offered. If the patient refused surgery or was a high anesthetic-risk patient, post-operative chemoradiotherapy 45 Gy in 25 fraction over 5 weeks or its radiobiological equivalent dose/fraction was offered, followed by contact X-ray brachytherapy boost giving a further 60 Gy in 2 fractions over 2 weeks (Group 2 [n = 25]). Patients with low-rectal cancer who were averse to permanent stoma or not keen on extirpative surgery were offered pre-operative EBRT (45 Gy/25#/5 weeks) followed by contact X-ray brachytherapy in good responders (>50 % regression) of primary tumour. The dose of contact X-ray brachytherapy was 80 Gy in 3 fractions given over 4 weeks (Group 3 [n = 33]). In cases with complete clinical response, a watch policy was adopted. If there was minimal residual disease <20 mm, TEMS was offered to obtain a histological diagnosis. If there was no response to contact X-ray brachytherapy, immediate salvage surgery was offered. The final group consisted of patients not fit for salvage surgery for residual disease due to incomplete response following treatment. For these patients we continued to adopt a watch policy (Group 4 [n = 29]). The analysis of the initial first 100 patients was similar to reported results from other centres with Papillon facilities. These patients were treated between 1992 and 2002. At median follow-up of 33 months (range 3–120 months) local recurrence occurred in 10 patients (10 %). In the whole group three patients (5.6 %) with local recurrence had T1 and five patients (17 %) had T2 tumors. Six patients had salvage surgery (60 %) and one refused surgery although the recurrence was operable. Cancer-specific survival was 96 % after salvage surgery and overall survival was 77 %, reflecting the fact that the majority of patients were elderly with co-existing medical problems from which they finally succumbed [20]. In the second extended cohort of 220 patients from Clatterbridge, 24 (11 %) had persistent disease after combined modality treatment. Twenty-one (21/24) had immediate surgery and 19 (90 %) were cured. Three patients were not fit for salvage surgery and died of their cancer. Of 196 patients who were disease-free, 11 (5.5 %) developed local recurrence and 7 had delayed salvage surgery, 6 of these patients were cured (86 %). Seven (3.5 %) patients had distant relapse and two (1 %) had both local and distant relapse. Overall salvage rate of all recurrences was 30/44 (68 %). Overall cure rate after salvage surgery was 202/220 (92 %) [21]. These results were encouraging, considering that the majority of these patients are elderly and medically compromised.

Salvage for Residual Disease, Re-growths or Recurrences

If there is residual disease following completion of treatment at 12 weeks it is recommended that one should continue to observe the patients up for to 24 weeks, provided there is no progression of the residual disease. If the disease persists at 24 weeks, it is high unlikely that the disease will regress beyond this period, and immediate salvage surgery should be carried out. Reported from Clatterbridge in their second cohort, 24 of 220 (11 %) patients needed immediate salvage surgery [21]. In most cases the disease continues to regress during these 24 weeks but sometimes there can be a regrowth if there is residual viable cancer. If recurrence occurs, this is usually within the first 12 months. Immediate salvage surgery should be carried out for this. If the disease relapses after 12 months, it is regarded as a true recurrence and delayed salvage surgery is indicated. In the cohort of patients treated at Clatterbridge, 68 % of local recurrences could be salvaged in this way. The remaining patients either refused surgery or were too unfit for salvage surgery [7]. Reports from the São Paulo group experienced 28/90 (31 %) local recurrences, and salvage surgery was possible in 26 (93 %). All local recurrences were detected by clinical/endoscopic assessment and none were detected by radiological imaging alone [22]. There appeared to be a higher number of local recurrences in the São Paulo group compared to the cohort treated at Clatterbridge. It is likely that contact X-ray boost given following EBCRT played a significant role in reducing local recurrences. This hypothesis will be evaluated in OPERA, which is a randomised trial comparing chemoradiotherapy alone against EBCRT followed by contact X-ray brachytherapy boost. There were additional reports on the 'watch and wait' policy for clinical complete responders after CRT for rectal cancer from the Maastricht group, which supported the concept of a successful approach with the 'watch and wait' policy [23].

Radiation Dose Escalation to Improve Outcomes

It is well established that there is a dose response relationship in rectal cancer. Evidence from radiation dose escalation studies shows that higher doses of radiation improve local control. However, dose escalation using external beam radiation alone will cause unacceptable toxicity for normal surrounding tissues. This limits the dose of radiation that can be escalated, as shown in the dose escalation study from the Princess Margaret Hospital [24]. Most radiotherapy regimes use a small boost field to primary tumour following 45 Gy in 25 fractions over 5 weeks. This is given either as a concomitant boost or following the completion of the initial phase of large field treatment. The dose of radiation boost varies from 5.4 Gy in 3 fractions to 9 Gy in 5 fractions over 1 week, which is not a sufficient dose to sterilize the residual cancer in the majority of cases. Only in 20–30 % of cases there is no residual disease (ypT0). Therefore, other forms of radiation boost have been investigated. The Danish HDR brachytherapy boost trial evaluated the role of brachytherapy boost using 10 Gy in two fractions against no further boost following a chemoradiation dose of 50.4 Gy in 28 fractions over 6 weeks in locally advanced resectable T3 and T4 rectal cancer below 10 cm from the anal verge. The rate of response (TRG+2) for T3 was 29 % vs. 44 % in favor of boost ($p=0.04$) and the R0 resection rate was 99 % vs. 90 ($p=0.03$). However, there was no significant pCR between the two arms, which was the main end-point. Although this was a negative trial for HDR brachytherapy boost, the dose given was inadequate [25]. Further analysis of radiation dose response models for locally advanced rectal cancer after chemoradiotherapy suggested a highly significant dose response relationship ($P=0.002$). For complete response (TRG1), the dose response parameter was $D_{50TRG1}=92$ Gy (95 % CI 79.3–144.9 Gy) and for major response (TRG1-2) $D_{50TRG1-2}=72$ Gy (CI 65.3–94 Gy). Tumour size and N category both had a significant effect on the dose response relationship. It is highly

unlikely that external beam alone could deliver either 72 Gy for major response or 95 Gy to achieve a complete pathological response [26]. Dutch investigators are evaluating the response to dose escalation using brachytherapy with multiple fractions of 5, 6, 7 and 8 Gy in HIBERT trial. Initial results suggested 7 Gy in 3 fractions appears to be safe. The long term clinical outcomes have not been reported yet. Canadian investigators use 10 Gy in 3 fractions. However, toxicity seems to be the dose limiting factor. It is clear from a number of single institute best-practice results that a dose escalation of up to 130–160 Gy was possible without undue major toxicity to normal surrounding tissues and this can only be achieved by X-ray brachytherapy. The results from CONTEM observational studies are awaited with interest.

Rectal Brachytherapy for Radiation Dose Escalation

There are three types of rectal brachytherapy:
1. X-ray contact brachytherapy
2. HDR rectal brachytherapy
3. Interstitial implants

X-Ray Contact Brachytherapy

This technique uses low-energy X-rays (50 kV), so has fewer problems with shielding for radiation protection. It is suitable for non-infiltrating exophytic small (<3 cm) rectal cancer confined to the bowel wall. It is used as a fractionated course, usually 3–4 fractions every 2 weeks. Dose and fractionation is well established and the results have been validated in many centres around the world.

HDR Rectal Brachytherapy

Also known as intra-luminal brachytherapy, this system uses either radioactive Ir^{132} or $cobalt^{60}$ and because the energy of the source is high there are problems with radiation protection. This is suitable for more infiltrative /ulcerative rectal cancers that have penetrated well beyond the confines of the bowel wall. The commercially available multi-channel rectal applicator OncoSmart® (Elekta) is used. Alternatively, a single-channel rectal/vaginal applicator with or without central shielding (Elekta)/ Eckert & Ziegler (Bebig) can be used as a single fraction boost or fractionated (usually 2–3 fractions). The dose and fractionation are still under investigation. There is no established isoeffect dose data to reproduce the equipoise effect with X-ray contact brachytherapy. Centres planning to start rectal brachytherapy should have both systems to cater for different stages, configuration (ulcerative/infiltrative) and sizes of rectal cancer.

Interstitial Implants

These are used for more infiltrative residual rectal cancers following external beam radiotherapy, or in those tumours that have extended into the anal canal and are not suitable for contact X-ray brachytherapy or intra-luminal brachytherapy. Iridium, originally used for interstitial implants, has now been replaced by HDR systems. Needles are implanted under GA or spinal anesthesia in theatre. Fractionated treatment is given over 24 h. Dose is usually between 5–7 Gy per fraction, given in three fractions.

Discussion

In the past decade, increasing use of pre-operative chemoradiotherapy for advanced rectal cancer has improved local control and this has become the standard of care [27]. The majority of patients who are fit for surgery have had resection of the primary together with the regional lymph nodes. Total mesorectal excision for upper- and mid-rectal cancer became the gold standard of care at the turn of this century [28]. However, abdomino-perineal excision (APER) is still recommended even for very early stage small rectal cancers.

Following pre-operative chemoradiotherapy there is no residual cancer (ypT0) in the histological specimens in about 15–20 % of cases [29]. At the same time, realization of harm from surgery, especially for elderly patients, is highlighted in a number of publications [30]. In addition, well-informed patients are not keen to have a stoma, even a temporary one, and have started to question the need for extirpative surgery when informed that no residual tumour can be seen on post-treatment scans. Endoscopy is not routinely carried out as part of the assessment following pre-operative chemoradiotherapy. There will be a demand and need to offer this, when a post-treatment MRI scan shows no evidence of residual tumour [2]. In 1991, the surgical group from São Paulo started deferring surgery if no residual tumour was detected following chemoradiotherapy [6, 22]. A number of publications followed from this group and others to support this approach [23]. At Lisbon in February 2014, an international surgical meeting, 'When Not to Operate', highlighted this approach and there was general consensus among the surgeons to adopt this approach for suitable patients.

The concept of non-surgical treatment is not new. This approach was started by contact X-ray brachytherapy before World War Two by the German group [9] and popularized by Papillon from Lyon for medically unfit patients or those with advanced rectal cancer [11]. Rectal adenocarcinoma was thought to be radio-resistant at that time. However, when the results from advanced cancers were encouraging, other elderly patients with operable cancer were offered this treatment. Obviously the results were better for early cancers, and many elderly patients were spared extirpative surgery and the prospect of a permanent stoma. There were few centres around the world with contact X-ray facilities and the practice did not expand as much as it should have. Firstly, there were only a small number of patients suitable for this type of treatment and, secondly, in the mid-1980s the Phillips Company stopped the production of 50 kV machine as it moved more towards development of diagnostic scans. Thirdly, technological advances led to the development of other endoscopic techniques such as endoscopic resection (EMR/ ESD), and these became competing treatment options for polyps. However, EMR is not suitable for invasive malignancy, because underlying muscle is not removed for proper histological assessment. Moreover, development of innovative surgical techniques such as TEMS, TEO and TAMIS competes for T1 small rectal cancers [31]. However, general anesthesia is still necessary for these procedures and so they are not suitable for high anesthetic risk patients. In the mid-1990s a British company (Ariane) together with a team from Clatterbridge and Prof Gerard from Nice collaborated to develop a new robust contact X-ray brachytherapy machine. This stimulated a revival of interest in contact X-ray brachytherapy and now there are several centres around the world with this new contact X-ray brachytherapy facility [19]. In 2006, an international interest group known as ICONE (International Contact Radiotherapy Network) was set up in Nice. This group held annual meetings and efforts were made to set up a randomised trial known as OPERA (**O**rgan **P**reservation in op**E**rable **R**ectal **A**denocarcinoma). The results from this trial will strengthen the role of contact X-ray brachytherapy in rectal cancer.

Conclusion

Local treatment of rectal carcinoma is still controversial. However, there is increasing interest in the approach that avoids extirpative surgery with a permanent stoma. Moreover, increasing numbers of patients of patients are now being diagnosed with early low-rectal cancer through national bowel cancer screening [1] and we need a robust protocol on how best to manage them. The standard of care for early low-rectal cancer is APER and this is clearly unacceptable for early stage small low-rectal cancers [32]. For elderly patients, extirpative surgery has increased mortality and morbidity and should be avoided [30]. Most patients would prefer not to have a stoma if given the choice. Moreover, the financial burden on healthcare providers worldwide is mounting, as patients live longer because of the excellent medical care they receive. If there is residual cancer

following contact X-ray brachytherapy and external beam radiotherapy, immediate salvage surgery can be carried out without compromising their chance of cure. Cost-savings for healthcare providers from this strategy cannot be ignored in this era of austerity measures. Most importantly, the patients' quality of life will improve if they can avoid extirpative surgery, a stoma and few weeks stay in hospital away from their loved ones. Patients should have the choice to avoid surgery if they wish. For elderly patients or high surgical risk patients, contact X-ray brachytherapy should be considered as an alternative treatment option for early small low-rectal cancers.

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Local Excision of Rectal Cancer

9

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Abstract

Transanal Local Excision has become a very useful surgical tool for the management of selected cases of rectal cancer due to its low postoperative morbidity and minimal functional consequences. However, the considerably high local recurrence rates led to the introduction of preoperative therapies. Neoadjuvant chemoradiation therapy has been considered the preferred alternative in this setting and may result in significant rates of tumor regression allowing the procedure to be offered to a significant proportion of cases. On the other hand, this multimodality approach may also determine increased postoperative morbidity. In addition, completion or salvage total mesorectal excision in the case of local recurrence or the presence of unfavorable pathological features may also be a challenging task. Finally, accurate selection criteria for this minimally invasive approach are still lacking and may be influenced by baseline staging, post-treatment staging and final pathology information. Ultimately, selection of patients for this treatment modality remains a significant challenge for colorectal surgeons. In the present chapter, the rationale, surgical technique and outcomes of transanal local excision are detailed both after surgery alone or in the setting of multimodality therapy.

Keywords

Transanal Local Excision • Rectal Cancer • Transanal Endoscopic Microsurgery (TEM) • Neoadjuvant Chemoradiation • Minimally invasive surgery

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Introduction

Transanal local excision has been considered an interesting alternative for the management of selected rectal cancers for many decades. The possibility of removing rectal tumors through the anus avoiding entry into the abdomen and the complexity of working in the confines of the pelvis has always been appealing to many surgeons. Transanal procedures have been performed with minimal morbidity and mortality rates. In addition, early discharge of patients and no requirement for stomas have also been contributing to its popularity among surgeons and patients.

However, the oncological outcomes of the resection of the primary tumor without proper lymphadenectomy are closely related to the risk of lymph node metastases. Therefore, recognition of risk factors for lymph node metastases (LNM) after accurate staging is crucial for patient selection. Ideally, this procedure would be reserved for patients with small primary tumors, low enough to be accessible through the anus (particularly prior to the development transanal endoscopic microsurgical techniques) and with minimal or no risk for concomitant lymph node metastases.

Risk Factors for Lymph Node Metastases

Several studies have focused on clinical and pathological risk factors for LNM in rectal cancer, particularly for patients considered for transanal local excision including pT1 and pT2 rectal cancers.

One of the most important risk factors for N+ disease is pT classification. The risk of nodal metastases progressively increases with more advanced pT stage classification. Even for the earliest tumors invading the submucosa (pT1), overall risk of lymph node metastases is around 12–13 %. Subclassification of pT1 cancers into three levels of submucosal invasion has also been correlated with the risk of lymph node metastases, with a risk of 0–3 %, 8–11 % and 11–25 % for tumors invading Sm1, Sm2 and Sm3 respectively [1, 2]. A large retrospective review of patients with pT1-2 rectal cancers reported a risk of LNM of 21 % in pT2 rectal cancer [3].

In addition to pT classification, other pathological features have also been associated with increased risk of LNM including lymphovascular invasion and tumor grade [4]. The presence of lymphovascular invasion and poor differentiation significantly increases the risk of LNM. Curiously, one study suggested that both pT1 and pT2 cancers would harbor a 100 % risk of LNM in the coexistence of poor differentiation and lymphovascular invasion [3]. Finally, distally located cancers were also found to be more likely to harbor LNM, and therefore constitute a high-risk factor [4]. Therefore, a small pT1 rectal adenocarcinoma restricted to the sm1 level, well-differentiated and with no lymphovascular invasion would be the best candidate for a local treatment with almost absent risk for lymph node metastases [5].

Local Staging

T Stage Classification

Considering specific features of the primary cancer (particularly pT status, lymphovascular invasion and tumor grade) are directly associated with the risk of LNM, primary local staging of rectal cancer is of paramount importance for the selection of appropriate candidates for transanal local excision. Diagnostic biopsies may allow proper determination of tumor grade. On the other hand, determination of lymphovascular invasion often requires excisional biopsy specimens and is therefore almost impossible to accurately assess preoperatively. Ultimately, clinical/radiological T and N classification (cT and cN) are frequently the only sources of information used for management decision of these patients.

Depth of the primary tumor may be accurately determined by the use of different radiological imaging modalities. Both endorectal ultrasound (ERUS) and high-resolution magnetic resonance (MR) have been extensively studied for this particular purpose. Both imaging

modalities provide acceptable overall accuracy for each cT classification (≥90 %) [6–8]. However, considering the risk of LNM amongst T3 and T4 rectal cancers are exceedingly high, these patients are not even considered for local excision except in extreme palliative situations. The distinction between T2 and T3 rectal cancers would therefore possibly provide a first filter for patients potentially suitable for a local procedure. A meta-analysis of accuracy rates for local staging of rectal cancer has been performed comparing different staging modalities [9]. Interestingly, ERUS was associated with higher sensitivity rates for the distinction between T2 and T3 cancers whereas specificity was nearly identical. In other words, MR may result in significantly more underestimation of T stage of these patients, potentially leading to inappropriate indication of local treatment for unsuspected T3 disease [9].

Distinguishing between cT1 and cT2 is perhaps the most relevant step in the assessment of these patients. The same meta-analysis of the results of rectal cancer staging with MR and ERUS suggests that specificity for the distinction of pT1 from pT2 was best for ERUS, even though sensitivity was similar between both modalities. Therefore, in contrast to the distinction between T2 and T3, this means that MR overestimates more frequently between T1 and T2 rectal cancer when compared to ERUS [9]. But the ideal patient for a transanal local excision is the one with a cT1 cancer, preferably restricted to sm1. This is due to the fact that the risk of LNM may also be correlated with the level of submucosal involvement. In fact, full-thickness excision allows better estimation of sm level invasion. In contrast, partial thickness endoscopic resections may not provide the entire submucosa for pathological review and therefore subdivision into thirds may be impossible. In this setting, absolute measurement of depth of tumor invasion (in specimens without entire submucosa available) may provide clinically relevant information as well. In non-pedunculated T1 cancers, invasion within the submucosa of ≤1,000 μ is associated with no risk of lymph node metastases even in the presence of lymphovascular invasion. In addition, three-dimensional ERUS in experienced hands was able to correctly identify sm level of invasion with acceptable accuracy rates [10]. In this study, patients with pT0 and pT1 sm1 were correctly distinguished from pT1 with massive invasion or pT2 with excellent accuracy rates [10].

N Stage Classification

Another very important issue in local staging during preoperative assessment of these patients is accurate lymph node classification. Unfortunately, nodal assessment (cN) is considerably less accurate than depth of invasion (cT). Overall, accuracy rates of MR and ERUS are in the range of (75–85 %) for correct nodal classification. Curiously, in the meta-analysis comparing different imaging modalities, sensitivity and specificity rates were nearly identical between ERUS and MR [9]. Still, nodal assessment may be influenced by the depth of primary tumor invasion. In one retrospective study, the accuracy of nodal staging was significantly worse for pT1 and pT2 cancers. Considering these pT1 and pT2 cancers are those potential candidates for local excision, it is rather disappointing that nodal staging was less reliable. Ultimately, the authors suggest that these limitations in early cancer nodal staging may explain frequent failures after local excision alone [11].

Defining High-Risk and Low-Risk Patients

Ultimately, surgeons should attempt to identify patients at high or low risk for development of lymph node metastases and local recurrence prior to offering local excision for rectal cancer (Table 9.1). Histological and morphologic features that define a higher risk of nodal spread in T1 tumors are poor differentiation, tumors larger than 3 cm or with more than 30 % of the bowel lumen involved, presence of lymphovascular or perineural invasion, margins less than 2 mm [3, 12–16]. pT2 tumors are also considered high risk tumors. When such features are

Table 9.1 Criteria for definition of high risk and low risk tumors

High risk	Low risk
Poor differentiation	Well and moderate differentiation
Size ≥3 cm	Size <3 cm
Circumferential involvement ≥30 % of lumen	Circumferential involvement <30 % of lumen
Presence of lymphovascular invasion	
Presence of perineural invasion	
Margins <2 mm	
pT2	

found in the preoperative assessment, local excision should be considered with caution and perhaps as indication of palliative management (due to oncological reasons or significant medical comorbidities).

However, sometimes these features are only confirmed after review of the pathological specimen following a local excision. In this case, additional treatment should be considered. One option includes completion of total mesorectal excision or salvage resection in order to provide radical lymphadenectomy. Alternatively, adjuvant radiation or chemoradiation may be used for the management of these patients [17].

Techniques of Local Excision

Preoperative Preparation

Patients are admitted at the same day or day before of the procedure after full bowel preparation. Antibiotic prophylaxis is performed at the time of anesthetic induction. The procedure is performed under general or regional anesthesia. However, in patients undergoing transanal endoscopic techniques (TEM or TAMIS) for upper lesions with higher risk of peritoneal entry, general anesthesia is preferable. Positioning of the patient is determined by primary tumor location: the lesion should preferably be located downwards. Therefore, jack-knife prone for anterior or lithotomy for posteriorly located lesions. In transanal endoscopic techniques, the lateral position should be considered in tumors located at the right or left rectal walls.

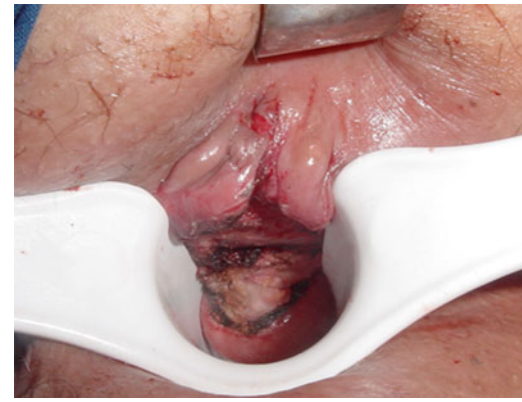

Fig. 9.1 Standard local excision: the mesorectal fat can be seen after the excision of the surgical specimen

Traditional or Standard Transanal Local Excision

An anal retractor is used to dilate the anus and obtain an adequate exposure. A lone-star retractor, may provide excellent access to the lower rectum for this purpose. Selectively, traction sutures may be placed laterally to the lesion to enhance exposure. A line of dissection with a margin of 1 cm is made with electrocautery circumferentially. The depth of resection should always reach the mesorectal fat to provide a maximal radial margin (Figs. 9.1 and 9.2). The specimen should always be fixed to a cardboard for better assessment by the pathologist (Fig. 9.3). The defect in the rectal wall is then closed transversely in a running suture, preferably with an absorbable material (PDS® or caprofyl®).

Minimally Invasive Options

Two relatively new techniques have been introduced in order to approach rectal tumors using the transanal approach with the use of rectal CO2 distention (pneumorectum), endoscopic view and minimally invasive instrumentation [18, 19]. These techniques may provide improved surgical

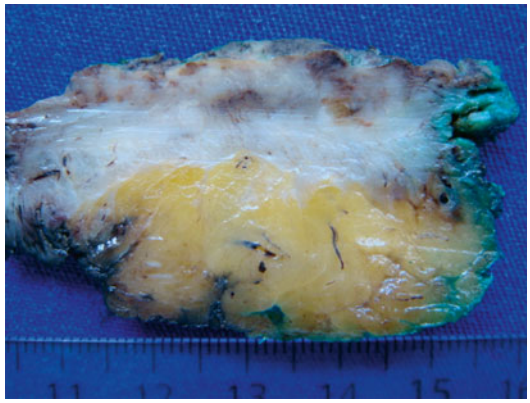

Fig. 9.2 After fixation, a significative amount of the perirectal fat can be seen providing an appropriate radial margin

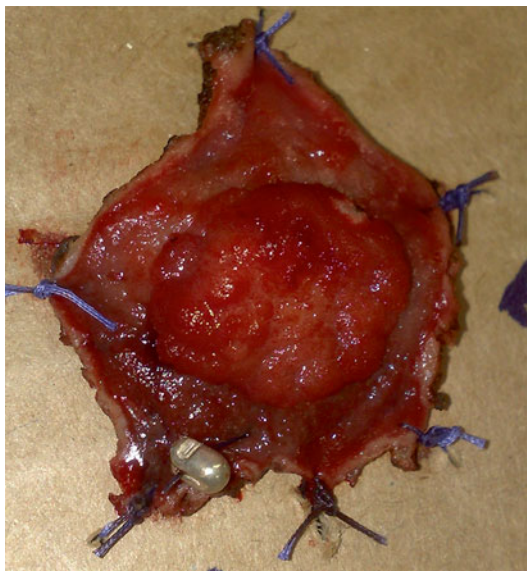

Fig. 9.3 The surgical specimen should be fixed to a surface in order to provide orientation for the pathologist

field view and access to lesions in the middle and upper rectum. Implementation of these endoscopic microsurgical approaches has resulted in significant improvements in quality of the resected specimen. In a review of 171 patients undergoing transanal endoscopic or standard local excision, margin clearance, specimen fragmentation, and local recurrence were all consistently higher among the patients operated by the traditional approach. Considering that the postoperative morbidity between the approaches is similar, the authors concluded that transanal endoscopic surgery is the procedure of choice for the local excision of rectal masses [20, 21]. Finally, this approach provides proper access to safe resection of upper rectal lesions and closure of peritoneal defects created by full-thickness excision in the anterior wall, particularly in males or post-histerectomy females.

Transanal Endoscopy Microsurgery (TEM)

The procedure is performed using a special proctoscope of 4 cm in diameter available in lengths of 12 and 20 cm. The rectum is insufflated with carbon dioxide at 10–15 mmHg. This can be achieved with the use of specific or usual laparoscopic CO2 insufflators. The optical 6-fold increase and the stability provided by the equipment, attached to the operating table, allows for an excellent view of the rectum and lesion. The proctoscope is frequently repositioned to allow best visualization of the lesion during the procedure. Once setup is complete, special endoscopic instruments are introduced through the proctoscope (usually four ports for entry) and resection is performed. In addition to the scope and two instruments manipulated by the surgeon, suction may be used through the fourth portal entry for aspiration of the smoke created by cautery (Fig. 9.4). Marking of 1 cm circumferential margins around the primary lesion prior to resection is advised to avoid disorientation. Full-thickness resection is performed using electrocautery avoiding direct manipulation of the tumor. Alternative energy sources may be used for this resection including harmonic or sealing devices. Once the specimen is removed, final check for hemostasia is performed and bleeds are carefully dealt with. In most cases, attempt to close the rectal defect is done with the use of an absorbable running suture.

The use of specific TEM equipments requires a significant investment and cost-effectiveness becomes a relevant issue. In a recent retrospective case-control study, patients undergoing TEM were compared to standard rectal resection [22]. Even though the initial investment was significantly higher for TEM, decreased costs related

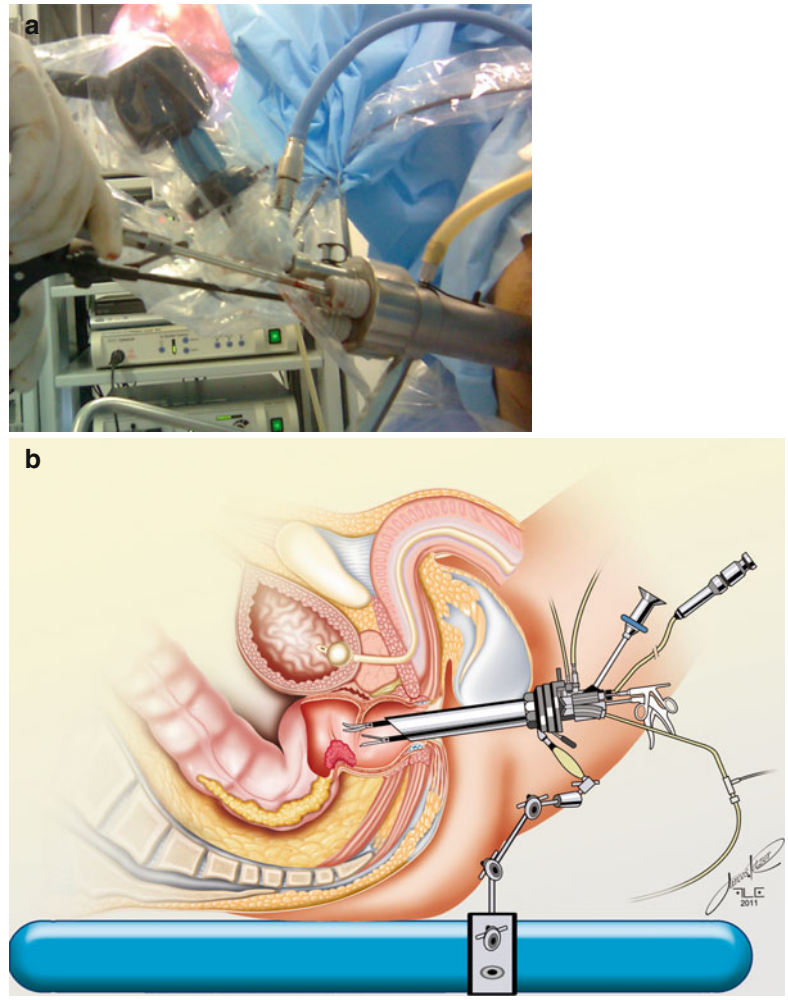

Fig. 9.4 (**a**) TEO/TEM equipment, with camera and insufflation in place. (**b**) The position of TEO/TEM equipment fixed to the surgical table and with instruments inserted (From Kosinski et al. [76])

to disposable instruments, hospital stay and stoma takedown clearly compensated differences. Ultimately, TEM resulted in a less expensive approach for the management of rectal lesions when compared to standard surgical resection despite the need for equipment purchase. In that study, the authors suggested that savings with TEM would provide compensation of the initial investment after 11–12 cases.

TAMIS (Transanal Minimally Invasive Surgery)

More recently, a variation of the previous technique has been proposed to allow transanal endoscopic microsurgery with the use of standard laparoscopic equipment [19]. This would potentially avoid the need of considerably expensive and exclusively dedicated TEM equipment. Instead, the use of simple and readily available laparoscopic equipment would allow similar efficacy with considerably lower associated costs. Also, learning curve of the procedure could be minimized by the use of routinely used as opposed to specific TEM instruments.

Several transanal ports have been suggested for this approach including disposable or reusable single-ports. After connection with the regular laparoscopic insufflator, a 5 mm laparoscopic scope is inserted to provide endorectal view. In contrast to TEM, TAMIS requires an assistant to control camera and therefore, stability of the image is lost. Once the additional instruments are inserted, the surgeon may perform the procedure very similar to the TEM technique. However,

most single ports have only 3 portal entries and therefore, smoke aspiration is not continuous. Finally, access to the lower rectum may be difficult due to significant need for instrument angulation. On the other hand, access to the upper rectum may be limited by rectal folds in some patients. Middle rectal lesions are best suited for this technique.

Transcoccygeal Excision

The posterior approach via trans sacral popularized by Kraske, was especially useful for lesions on the posterior wall within the middle or distal thirds of the rectum [23]. However, it also allows resection of lateral and anterior lesions. The advantage of this approach is that it provides exposure of the mesorectum. Therefore, perirectal nodes could potentially be removed for histopathological examination.

The patient should always be placed in jackknife prone position. The coccyx is tackled by a longitudinal incision from the perineum to the second or third sacral vertebra. Gluteal muscle insertions are released and the anococcygeal ligament is transected. Removal of the coccix is performed after complete exposure. At this point, the middle sacral artery should be ligated. The rectum is approached through the perirectal fat, and through the levator ani, separated at midline. This provides a complete mobilization of the rectum within the intraperitoneal pelvis. For posterior lesions, it is useful to use the digital rectal examination to guide the resection. This gives the orientation of the lower edge of the tumor in order to achieve 1 cm circumferential margin. For anterior lesions, posterior incision of the rectum is required, allowing resection under direct vision of the primary tumor. All the defects in the rectal wall are closed transversely in order to prevent stenosis, using running absorbable suture. Finally the levator ani are approximated at the midline and the anococcygeal ligament is reattached to the sacrum. The subcutaneous tissue and the skin are closed. Morbidity rates for this procedure are higher than for transanal excision approaches. Development of rectocutaneous fistulae ranges from 15 to 25 %, and sometimes a temporary diverting stoma is required. Other complications include urinary dysfunction, wound infection and transient fecal incontinence. In this setting, transsacral approach is being progressively less used. However, the procedure remains a viable option particularly to patients that are not amenable to a transanal approach [24].

Morbidity and Mortality

Mortality after local excision is very low, with most studies showing no mortality and others up to 2–3 % [25].

Overall morbidity has been reported to range from 9 to 45 %. Major complications are uncommon and occur in around 1.5 % of cases. Bleeding is the most common major complication, eventually requiring reintervention. Infectious complications may rarely require a diverting stoma in around 1 % of cases [26].

The single most relevant risk factor for postoperative complication is the use of neoadjuvant CRT. When preoperative CRT is delivered, TEM resection leads to a rectal wound that allows primary suturing without any technical difficulty, unless the distal margin is very close to the anal canal/verge. In this situation, even though the upper border of the wound may retain its considerable elasticity, the lower border of the wound of the anal canal is rather fixed and with little mobility. If the resection is wide enough to result in significant separation of the proximal and distal borders, significant tension will be present, a known feature to contribute for wound dehiscence. Also, the anal canal has ectodermic as opposed to endodermic nerve supply to rectum. Therefore, wound separation and mucosal discontinuity in this region may be quite painful. Finally, regardless of the level of suturing (rectal or anal canal), the borders to be sutured after a TEM resection in previously irradiated rectum will necessarily put together two previously irradiated borders. This is actually quite different from a coloanal anastomosis following neoadjuavant CRT, where the proximal colon is never included in the radiation field and therefore a NORMAL colon is sutured to an abnormal anal

canal previously treated with a significant amount of RT [27]. In fact, even after a coloanal anastomosis is constructed, the risk of dehiscence is so significant that a loop ileostomy is almost always recommended [28]. One can imagine the risk of wound dehiscence after suturing together two previously irradiated borders of rectum or anus, sometimes with significant tension depending on the level of the suture.

In fact, few studies compared the risk of wound separation and its consequences with or without previous exposure to CRT. However, retrospective studies have suggested that the risk of wound dehiscence was significantly higher when CRT was delivered preoperatively. In one of these studies, diagnosis of wound dehiscence was made after more than 1 week following TEM and healing of the dehiscence took an average of more than 8 weeks to complete. An operation that otherwise would almost never require a stoma, in this situation diversion is occasionally required [29]. In another study, even though none of the dehiscences required stomas, pain management was quite significant requiring readmission for analgesia in a significant proportion of patients [30].

Ultimately, these findings raised the issue whether any attempt to close the wound defect created by TEM should even be performed. Leaving the wound open could potentially avoid the complication of wound dehiscence and minimize its consequences. However logical this may seem, there is no good evidence to support this idea and the author's clinical experience with unclosed wounds showed no significant differences in pain control after TEM following neoadjuvant CRT for rectal cancers [30].

Outcomes

T1 Rectal Cancer – Local Excision Alone

Local excision alone was considered a valid treatment alternative for T1 rectal cancer for a long time. In the absence of prospectively randomized studies comparing full-thickness local excision to radical total mesorectal excision, most of data arises from retrospective analysis and case-series. Retrospective reviews of selected patients undergoing FTLE, oncological outcomes (local recurrence, survival and cancer-related death rates) were inferior to radical surgery for T1 disease, including higher risk for cancer-related deaths [31, 32]. Even though none of these patients were managed by transanal endoscopic techniques and there was no distinction between favorable and unfavorable tumors, the authors suggested that local excision should be restricted to patients with prohibitive medical contraindications to major surgery.

The only prospective study on local excision alone for T1 rectal cancer was performed in the United States under CALGB [33]. Between 1990 and 1995, 59 patients with T1 rectal cancer were managed by local excision alone. Ten-year local and distant recurrence rates were 8 and 5 % respectively. These encouraging results were followed by less successful outcomes in following studies. A number of studies with variable inclusion criteria, inconsistent pretreatment staging assessment and no standard pathological reporting reported on a wide range of local recurrence rates (0–30 %). The retrospective comparison of local excision to radical surgery for stage I rectal cancer consistently showed worse oncological outcomes after local excision, even though no randomization or case-matched was ever possible [31].

More recently, with significant improvements in local pretreatment staging accuracy and refinements in technical aspects of the procedure with transanal endoscopic techniques, local recurrence rates after local excision alone for selected pT1 rectal cancers remains between 10 and 20 % [34]. In addition to the considerably high local recurrence rates, salvage procedures after local recurrence offer poor oncological outcomes. A recent review of 88 patients with pT1 undergoing TEM, local recurrences were observed in 20 % of the cases [35]. Of these recurrences, only a minority had unfavorable pathological features (Sm3 invasion, lymphovascular invasion, poor differentiation). More than 80 % had advanced stage disease at the time of recurrence and even though R0 resection was possible in most cases,

3-year disease-free survival was disappointing (58 %). Alternatively, immediate salvage resection following local excision seemed to have not compromised oncological outcomes of patients with early stage rectal cancer. In a retrospective study of patients undergoing local excision followed by radical salvage resection within 30 days revealed that outcomes were similar to a matched control group of patients undergoing straight to radical surgery and comparable pathological staging [36].

Even though there is a suggestion that early or immediate salvage provides acceptable oncological outcomes for these patients, the procedure (salvage or completion TME) is not trivial. The quality of the resected mesorectum in this setting may be significantly compromised in a significant proportion of cases (moderate or poor in 36 %). Also, some features of the original procedure such as distal location of the tumor and long interval after local excision (≥7 weeks) were all associated with the risk of poor quality of the specimen.

Distant metastases, when found after FTLE for T1 tumors, usually appear synchronically with local recurrence. Although salvage surgery after local excision is feasible in most patients with T1 tumors, survival might be limited, mainly because of distant metastases [35].

Local Excision and Adjuvant Therapy

In patients that final pathology after local excision reveals high-risk features in the surgical specimen, an alternative to completion of total mesorectal excision is the use of adjuvant RT or CRT. Most studies have considered the presence of T2 tumors, close or positive resection margins, lymphovascular invasion and poor differentiation for such purposes. In the CALGB study, negative margins pT2 cancer patients were offered adjuvant 5FU-based CRT (54 Gy). In that study, 10-year local and systemic recurrence rates were 18 and 12 % respectively. Curiously, median time to recurrence for pT2 cancers was nearly 2 years, significantly shorter than for pT1 cancers (nearly 4 years) in the same study (treated by local excision alone).

The RTOG study showed slightly better results for local excision. CRT was given when local excision specimens showed unfavorable histopathological features in T1 tumors or T2 and a higher dose of CRT when margins were involved. Low risk T1 tumors were only observed without further surgery. The overall local recurrence rate was 16 % and local recurrence free-survival was 86 % for patients treated with adjuvant therapy in 5 years. These rates are similar with the ones seen for TME in the literature. There was no difference in disease free survival or overall survival between patients who received adjuvant chemoradiation and those who did not. The local recurrence rates were 1/14 (7.1 %) patients who were only followed and 2/51 (3.9 %) in those who received CRT [37].

Chakravarti et al. published a retrospective cohort of T1/T2 rectal tumors with adjuvant radiation following FTLE or FTLE alone. In the irradiation group, local control rates for high-risk T1 tumors were 100 %, while 85 % for T2 tumors. In the FTLE alone group local control rates were, respectively 89 and 33 % for T1 and T2 tumors. The addition of systemic chemotherapy with 5FU did not significantly improve local control or recurrence free survival in the irradiation group. With these results, they recommended only adjuvant CRT for high-risk tumors after local excision [38].

Neoadjuvant CRT Followed by Local Excision

Even though postoperative (adjuvant) therapy would have the benefit of offering patients treatment after confirmation of "unfavorable" pathological findings, the observation of decreased toxicity and improved local disease control in prospective randomized trials of rectal cancer in the setting of radical surgery led to the utilization of radiation and chemotherapy in the preoperative period (neoadjuvant) [39–41]. In addition, the exposure of healthy and well-oxygenated tissue, as opposed to post-operative fibrotic tissue, to radiation would theoretically improve its anti-neoplastic effects. Finally, perhaps one of

the most beneficial aspects of offering patients preoperative neoadjuvant therapy would be the effect on tumor shrinkage. The decrease in tumor size (downsizing) and shifts in tumor stage (downstaging) have been well documented after neoadjuvant therapies with radiation and chemoradiation (CRT) [42–45]. In fact, the addition of chemotherapy to radiation has been shown to significantly increase the effects on tumor size and stage when delivered preoperatively [42]. Also, this downsizing and downstaging seem to be time-dependent and therefore, at least 6, 8 or even 12 weeks may be required to obtain maximal results tumor regression [46–48].

It appeared that neoadjuvant therapy, particularly CRT, was the answers to all prayers for TEM in rectal cancer: improve local disease control, minimize toxicity, decrease tumor size, downstage cancers and allow a minimally invasive approach without all of downsides of radical total mesorectal excision (TME).

However, the expected benefits of this strategy came at a significant cost in terms of wound healing (as mentioned previously) and salvage possibilities. Also, local recurrences may still be a concern depending on baseline and post-treatment characteristics.

Local Recurrence

As mentioned earlier, local recurrence rates have historically paralleled the risk of lymph node metastases in patients treated by FTLE for rectal cancer. pT status is one of the most relevant determinants of the risk of perirectal nodal metastases both with or without chemoradiation [49–52]. In fact, studies have suggested that the risk of lymph node metastases is <5–10 % for ypT0, 10–15 % for ypT1 and nearly 20 % for ypT2 [53]. Therefore, one could expect these rates of local recurrence after treatment with CRT followed by local excision regardless of the original baseline staging.

However, radiological imaging has evolved significantly over the years and nodal staging has improved. Even though accuracy is still far from 100 %, magnetic resonance (MR) and endorectal ultrasound have been studied extensively in order to improve detection of lymph node metastases. It has been suggested that MR could safely assign patients after CRT that would be appropriate candidates for FTLE by correctly identifying ycT0-2N0 (accuracy ≥90 %) [54]. This suggests that ypT0, ypT1 and ypT2 would all be appropriate candidates for FTLE or TEM, once nodal metastases have been ruled out. In a review of patients with ycT0-2 N0 following long-course CRT and TEM, local recurrence rates were nearly 15 % [55]. In this study, most patients had ypT1/ypT2 whereas ypT0 were very few. In a recent report from a multicenter study in Italy (Phase II), 63 patients underwent CRT for cT2-3N0-1 disease at baseline [56]. Of these, 42 had ypT0 and were treated by FTLE alone with no recurrence. One patient with ypT1 and TRG2 also did not recur. However, of the 9 patients with ypT2 who refused radical TME, 2 developed local recurrences after FTLE alone (22 %). Bonnen et al., in 2004, published their results comparing 26 patients with T3 tumors submitted to neoadjuvant chemoradiation followed by local excision and 405 patients submitted to neoadjuvant CRT followed by TME. In the local excision group the pCR was 54 %. The 5-year local recurrence rate was 6 % in this group while 8 % in the TME group, and 6 % in the subgroup of complete responders in the TME group. Overall survival was 86 and 81 % in the local excision and TME groups, respectively. An update on their data [57] showed that results were maintained after a longer follow up of 63 months. They suggest that highly selected patients that respond well to CRT might be submitted to FTLE [58].

Other authors have suggested that baseline staging is also important and only cT2N0 followed by neoadjuvant CRT would be appropriate candidates for FTLE or TEM [59, 60]. In fact, the single randomized study that compared cT2N0 followed by neoadjuvant CRT and TEM or TME found in its first report advantages in early/immediate outcomes favoring TEM (less transfusion and stoma requirements, less hospital stay and less need for ICU). Local recurrence rates were similar between groups [61]. In a more recent update, local recurrence rates were still similar

between groups. However, TEM resulted in more early recurrences when compared to TME. Also, TEM was considered to be an independent risk factor for the development of recurrent disease (metastatic or local recurrence) after multivariate analysis [62]. Ultimately, local recurrence rates were all <10 % in both groups. Still, it should be noted that nearly 1/3 of the patients in each group (total of 50 patients in each group) had complete pathological response (ypT0), a known predictor of low risk for LN metastases. Also, all of the local recurrences were among patients with ypT2 residual cancers. Finally, there is still an ongoing study specifically dealing with cT2N0 rectal cancer patients managed by long-course CRT followed by FTLE (including but not necessarily TEM) [63]. One could expect that local recurrence rates will ultimately depend on the effectiveness of CRT. If CRT was highly effective, with many ypT0, local recurrences will probably be low. However, if ypT2 were frequent, one could expect higher local recurrence rates.

Tumor Fragmentation, Tumor Scatter and Local Excision After CRT

In addition to the risk of lymph node metastases inherent to ypT2 cancers despite proper staging and restaging suggesting N0 disease there are other risk factors for the development of local recurrence. Lymphatic or lymphovascular invasion has been considered a risk factor in these patients and should prompt or at least consider additional therapy in these patients as previously mentioned. However, another feature may play a role in local recurrence among these patients with residual cancer following CRT [64].

In a recent report after pathological measuring of residual cancers after proctectomy, authors identified invisible nests of tumor cells away from the residual mucosal abnormality in up to 3 cm (Fig. 9.5) [65]. This intriguing finding of tumor fragmentation after neoadjuvant CRT is now being examined in different series of patients undergoing proctectomy and TEM. These nests of tumor cells separated from the primary residual ulcer may be a result of tumor fragmentation due to irregular response to CRT. Areas of the tumor that are resistant to CRT may be surrounded by CRT-sensitive areas. CRT may lead to complete regression of the sensitive areas leaving discontinuous "nests" of tumor cells viable.

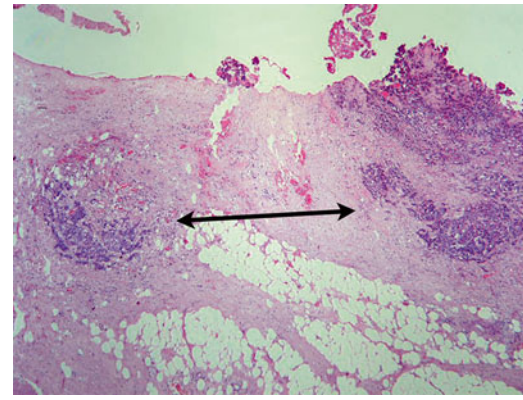

Fig. 9.5 Fragmented pattern of tumor regression showing discontinued foci of cancer cells ≥1 mm away from each other

In this setting, excision of the visible residual mucosal abnormality may not allow excision of the entire residual cancer as invisible residual cancer cells away from the ulcer may still be present [64, 66].

Ultimately, unless there is significant regression of the primary tumor ypT1 and/or ≤10 % of residual cancer cells, rectal cancers may not be suitable for local excision despite significant downsizing if tumor fragmentation is present leaving viable cancer cells away from the visible residual mucosal abnormality.

ypT0 – TEM or Watch and Wait?

Ultimately, the conclusion of this review could be that TEM would perfectly fit patients with complete pathological response after CRT due to the minimal risk of local recurrence and proper avoidance of radical surgery with its intrinsic morbidity and functional consequences. In fact, resection by TEM in these patients would merely serve as a confirmation of the excellent effects of CRT and no actual cancer cells would be removed. Postoperative complications related to wound healing would still be an issue (as

discussed previously) and even though the risk of nodal metastases is low, it seems that may reach up to 5–10 %, meaning that ultimately a radical TME is still a possibility in the case of local recurrence [64].

No immediate surgery and observation alone has been proposed for these patients with clinical and radiological evidence of a complete response to CRT (complete clinical response – cCR) [67, 68]. The absence of any residual ulceration, mass, irregularity or stenosis, in the presence of normal radiological imaging studies (including preferably MR with diffusion weighted series or PET/CT) have been considered key findings for the diagnosis of a cCR [69–71]. With this non-operative approach (at least immediately after 8–12 weeks from CRT completion), patients could avoid any of the difficulties in wound healing associated with TEM after CRT. In addition, surveillance of the rectal wall would be facilitated by the absence of a scar, granulation tissue and other fibrotic changes. Finally, in the event of a local recurrence, salvage with TME and sphincter preservation (when appropriate) would also be facilitated by no previous scarring and/or violation of the mesorectal fascia.

Ultimately, TEM may be perfect for those patients with suspicious residual cancers by clinical and radiological studies that pathology reveals complete pathological response. This may in fact represent a significant proportion of patients [72].

Perspectives

Sentinel Node

In an effort to minimize the risk leaving nodal metastases behind after local excision, the concept of sentinel node biopsy (primarily used for melanoma and breast cancer) has been applied for early rectal cancers during TEM [73]. After injection of indocyanine green solution (ICG) beneath or close the primary rectal lesion, the tumor is resected in a full-thickness fashion exposing the mesorectal fat in the vicinity of the tumor. Then, with the aid of near infra-red (NIR) optic, illumination is switched to fluorescence-guided imaging allowing for the identification and resection of previously injected ICG within local perirectal nodes. In a preliminary experience with this technique, one study has reported successful identification and resection of 1–3 nodes/patient. The idea is to allow identification of unsuspected lymph node metastases in patients undergoing transanal local excision (TEM). These patients could potentially be offered immediate conversion to total mesorectal excision, thus minimizing the risk of local recurrences [64].

In all three patients in that preliminary study (none of them having received preoperative CRT), lymph nodes were small and negative after pathological examination leading to no change in the actual management of patients [73]. Even though the technique is feasible, more studies with larger sample sizes are required to determine the sensitivity and specificity rates of this procedure before it can be definitively implemented into clinical practice. Also, identification of lymph nodes may be particularly more difficult in setting of neaodjuvant CRT due to their significant number and size reduction after treatment [74]. Ultimately, this may result in a considerable decrease in nodal harvest success rate with this approach.

Transanal Total Mesorectal Excision

Another interesting alternative for the management of rectal cancer has combined the radicality of total mesorectal excision to the minimally invasiveness of TEM. A limited number of reports describing the technical and immediate outcomes of total mesorectal excision performed transanally using the TEM platform are currently available showing promising results [75]. With this approach, it would be possible to see in the near future patients undergoing TEM for rectal cancers after CRT for sentinel node biopsy. Those with positive nodes could immediately be converted to transanal proctectomy with total mesorectal excision with no oncological compromise and still benefit from the advantages of this

minimally invasive approach. However, longer follow-up and more experience are needed prior to recommendation of this approach for the management of selected rectal cancer patients.

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Abdominosacral Resection for Rectal Cancer

10

Panagiotis A. Georgiou and Paris P. Tekkis

Abstract

Abdomino-sacral resection is an operation that is usually performed to resect recurrent rectal cancers that invade the sacrum. Occasionally it may be performed to treat advanced primary rectal cancers with threatened posterior margins or direct invasion into the sacrum. It is a procedure combined of an abdominal and perineal/sacral part aiming to resect the tumor en bloc with the adjacent structures. It carries a significant risk for mortality and morbidity. The mortality in recent years has been reported to range up to 3.5 %. This is usually secondary to a major complication. Morbidity is considered significant and ranges up to 70 %. Complete resection can be achieved up to 100 % of the operated patients but the majority of the studies report rates at the range of 55–70 %. This variation is likely due to patient selection. The overall 5-year survival following surgery ranges between 30 and 45 % with complete resection being the most important predictor for overall and disease free survival. Abdominosacral resection should be offered in carefully selected patients and carried out at tertiary centers with experience in this type of procedure for optimal results.

Keywords

Abdominosacral resection • Recurrent • Locally advanced primary rectal cancer

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Introduction

Abdominosacral resection is an operation that is usually performed to resect recurrent rectal cancers that invade the sacrum. Occasionally this is performed for advanced primary rectal cancers with threatened posterior margins or direct invasion into the sacrum (Fig. 10.1). It is a procedure

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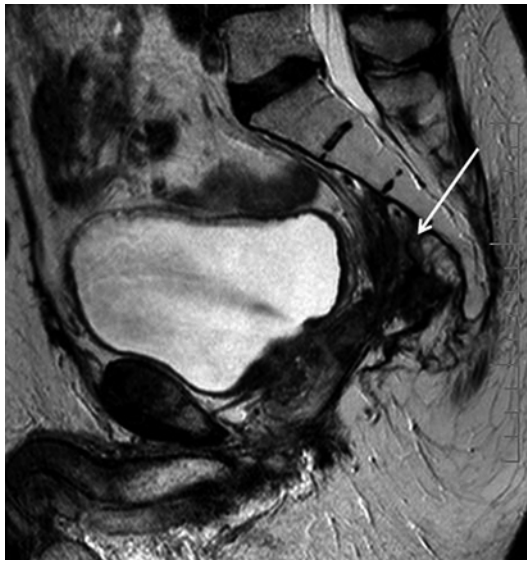

Fig. 10.1 T2 weighted MRI showing invasion of tumor posteriorly into the sacrum. The *arrow* shows tumor invasion within the posterior compartment

combined of an abdominal and perineal/sacral part aiming to resect the tumor en bloc with the adjacent structures.

Despite all the recent developments in surgery and medical therapy, up to 40 % of the patients that undergo surgery for primary rectal cancer will develop local recurrence and/or distant metastases [1–4]. Local recurrence rates have been reported as low as 2.5 % [5]. They can range up to 30 % though, with distant hepatic or lung metastases diagnosed in up to 20 and 9 % of patients respectively [4]. The majority of the recurrences will be diagnosed within the first 3 years following surgery [6]. A third of these patients will be free of distant metastases and may be eligible for a curative resection. For this group of patients, radical resection is the only option for cure, as chemotherapy and radiotherapy are unlikely to be curative and are used for palliation when used alone. Curative resection is feasible in less than a third of cases [7].

Rectal cancer surgery was initially performed during the eighteenth century with the first two reported resections resulting in the patients dying [8]. LisFranc was the first to perform a "successful" oncological resection of the rectum [9]. Perioperative morbidity was high though and was associated with poor disease free and overall survival. All operated patients that survived the operation represented with a recurrence and died.

It was the introduction of anesthesia and aseptic technique that enabled the improvement of the surgeons' performance that consequently resulted in the improvement of the perioperative outcomes. The first anatomical resection was performed by Ernest Miles [10]. He removed the draining lymph nodes while resecting the rectum, by combining the abdominal and perineal approach improving the oncological outcomes [11]. However, the functional outcomes and quality of life was adversely affected due to the presence of a colostomy and the poor sexual and urinary function.

Rectal cancer surgery was revolutionized in the late twentieth century when Professor Heald introduced the total mesorectal excision [12]. This was based on the embryologic development of the hindcut, after studies demonstrated that resection margins of 2 cm should be considered as safe. This had led him to further study the value of "holy plane" and proposed a standardized oncological rectal surgery by performing total mesorectal excision of the rectum [13].

The Japanese surgeons recommended the excision of the lateral pelvic sidewall lymph nodes to supplement the standard operation. The results from a number of studies were controversial though with a meta-analysis showing that the benefit from an extended lymphadenectomy did not seem to offer a significant oncological advantage while at the same time was shown to be associated poor sexual and urinary function [14].

The introduction of neo-adjuvant radiotherapy to the management of rectal cancer signified the reach for another important milestone. Its role was established late in the twentieth century when studies demonstrated significant reduction of recurrence rates but without any significant impact on the patients' long term survival.

The development and evolution of all the above techniques along with the acquired knowledge from the "mistakes of the past", have resulted in the progressive reduction of the local recurrence rates. However, the recurrence rates

Table 10.1 Recent Studies reporting on abdominosacral resection for locally advanced primary and recurrent rectal cancer

Author	Year	Curative intent	R0 (n)	R0 (%)	R1 (n)	R1 (%)	R2 (n)	R2 (%)	Mortality (%)	Morbidity (%)	5 years Survivawl (%)
Bosman [16]	2014	86	48	55.81	30	34.88	8	9.30	3.5	–	28
Bhangu [17]	2012	30	23	76.67	7	23.33	0	0	0	50	
Sagar [18]	2009	40	20	50	19	47.5	1	2.5	2.5	60	–
Ferenschild [19]	2009	25	19	76	4	16	2	8	0	68	30
Williams [20][a]	2008	3	3	100	0	0	0	0	0	100	–
Akasu [21]	2007	44	24	54.54	13	29.55	7	15.90	2	61	34
Melton [22]	2006	29	18	62.07	10	34.48	1	3.44	3.4	59	43
Moriya [23]	2004	57	48	84.21	9	15.79	0	0	3.5	58	42
Gonzalez [24]	2003	45	33	73.33	12	26.67	0	0	4	56	32
Yamada [25]	2002	64	51	79.69	13	20.31	0	0	1.6	56	–
Mannaerts [26]	2001	50	26	52	18	36	6	12	0	82	–
Weber [27]	2000	23	21	91.30	2[b]	8.70	0	0	0	43	–
Zacherl [28]	1999	12	12	100	0	0	0	0	0	42	–
Wanebo [29]	1999	53	45	84.91	8[b]	15.09	0	0	8	–	31
Magrini [30]	1996	16	14	87.5	2	12.5	0	0	0	50	–
Wanebo [31]	1994	47	40	85.11	7[b]	14.89	0	0	8.5	–	33

[a]This is a study reporting the feasibility of laparoscopic abdominosacral resection for locally advanced primary rectal cancer

[b]These studies did not clarify between R1 and R2

are still considered high, necessitating radical surgery to completely remove the cancer.

There is a significant variation in the patterns of recurrence and therefore the management plan should be titrated to the individual. A surgical plan can be made with the help of imaging modalities such as MRI and CT scan. The images from these modalities have been significantly improved in the recent years allowing better detection rates and identification of earlier recurrences. This has subsequently facilitated the performance of more operations for this group of patients.

Isolated anastomotic recurrences can be amenable to local resection but more extensive disease requires a more radical resection. Pelvic exenteration when the tumor invades adjacent structures, with lateral extended lymphadenectomy when there is invasion into the lateral pelvic structures. When the tumor invades the sacrum, removal of the tumor along with the sacrum is required.

The absence of accurate diagnostic tools, lack of knowledge and the anatomical/surgical challenges, have resulted in a delay in the attempts to resect recurrent rectal tumors. It was not until the mid-nineties that advanced pelvic exenterative surgery for locally advanced primary and recurrent colorectal cancer was considered as an option for cure. The first pelvic exenterative procedures were described in 1948 [15] and were associated with high mortality and morbidity rates. Numerous studies have been published since (Table 10.1) with a significant variation in the mortality and morbidity rates. This is primarily attributed to the differences in the patient selection among the studies' population. In 1981, Wanebo [32] was the first to report on the outcomes following abdominosacral resection in 11 patients with locally advanced primary (1 patient) and recurrent colorectal pelvic cancer 10 patients. All patients had neo-adjuvant radiotherapy. Plastic reconstruction surgery was performed to close the pelvic and perineal defect. The reported mortality and morbidity rates were also high.

The development of the technology and the knowledge acquired from performing these procedures had led to the improvement of the patient selection, surgical technique and medical therapy. Studies from various tertiary centers in the world

have been recently published showing an improvement of the oncological results with the mortality and morbidity rates to remain at high levels though.

The focus of this book chapter is the technique of the abdominosacral resection and this will be discussed more extensively within the book chapter.

Patterns of Recurrence

Tumor recurrence may invade any of the intrapelvic structures. With the absence of the mesorectum, the adjacent organs and structures are "unprotected" and susceptible to the tumor. The tumor may be progressing anteriorly, posteriorly, laterally or inferiorly. In some occasions it may be isolated at the anastomosis or invading the peritoneum and/or large and small bowel. Published data suggest that the posterior intrapelvic compartment that includes the presacral fascia, retrosacral space and sacrum, is the most common site of local recurrence, representing up to 56.6 % of local recurrences [29, 33–36]. Invasion within this compartment necessitates the performance of an abdominosacral resection to completely remove the tumor. In the majority of the cases tumor will be invading multiple compartments requiring multi-compartmental resection to remove the tumor *en bloc*.

The Anterior below the peritoneal reflection compartment has been shown to be the second most common site of recurrence, ranging up to 50.9 % of local recurrence [29]. This includes the genitourinary system. Invasion of the lateral compartment structures has been demonstrated to be up to 26.7 % of local recurrence [34]. Lateral compartment structures include the ureters, iliac vessels, lateral pelvic sidewall lymph nodes, fascia and bone as well as the roots of the sciatic nerve. This compartment in in continuity with the posterior compartment and often can be affected by the tumor. Tumor invasion within this compartment increases the risk of an incomplete resection. Anastomotic (central compartment) recurrence has been shown to range up to 33.9 % of local recurrences [33, 37–39]. Involvement of the perineum and perineal scar (inferior compartment) following abdominoperineal excision of rectum (APER) has been shown to be up to 14 % of all recurrences [40]. Extent of tumor within a bowel loop has been also reported at the range of 14 % [40].

Surgery for Locally Advanced Primary and Recurrent Rectal Cancer

The introduction of total mesorectal excision has significantly improved the local recurrence rates and patients survival. However, local recurrence rates are still considered to be relatively high with significant variation between centers and among surgeons [5, 41–44]. The only potential cure for this group of patients is radical surgery. This can be in the form of exenterative pelvic surgery, including total pelvic exenteration and abdominosacral resection. Patients with locally advanced primary rectal cancer requiring surgery beyond the boundaries of TME, require similar aggressive approach by performing exenterative pelvic surgery and abdominosacral resection when the tumor invades the sacrum.

Abdominosacral Resection

Abdominosacral resection of the rectum was originally performed to surgically treat primary rectal cancers [45–49]. Surgeons were fond of the technique as it provided good exposure of the rectum and tumor, facilitating its wide resection with safe surgical margins and the performance of anastomosis. This procedure was used without the disruption of the anal sphincters and their innervation. One center has suggested the use of abdominosacral resection for the surgical management of low rectal cancers, demonstrating similar oncological and functional results to the patients treated with conventional abdominoperineal excision of the rectum [50–52]. The high morbidity rates and the introduction of total mesorectal excision had led the surgeons to abandon it as treatment for

non-advanced primary rectal cancer. Wanebo [32] was the first to perform abdominosacral resection for patients with locally advanced primary and recurrence colorectal pelvic cancers. The results of operating on the first 11 patients were published in 1981, showing high rates of mortality and morbidity.

In the modern era of colorectal surgery, abdominosacral resection is used to treat locally advanced primary and recurrent rectal cancer when the cancer progresses posteriorly and breaches the retro-sacral fascia, therefore potentially threatening the posterior margins. Numerous studies (Table 10.1) have reported their results of performing abdominosacral resections in patients with locally advanced primary and/or recurrent rectal cancer. The colorectal group of Mayo clinic [30] used intraoperative radiotherapy to supplement the abdominosacral resection and reported high rates of complete resections (R0 = 87 %) associated with morbidity (50 %) and poor survival. The results of another published series of 12 patients (all with complete tumor clearance (R0)) [28] that underwent abdominosacral resection for recurrent rectal cancer showed the lowest morbidity at 42 % but 3 year survival as low as 17 %.

Results from studies that followed were more promising though. A study [26] where composite abdominosacral resection was performed in patients with locally advanced primary (n = 13) and locally recurrent rectal cancer (n = 37), demonstrated a 61 % overall local control and 41 % disease free 3 year survival. Yamada et al. [25] used the abdominosacral approach to treat patients with locally advanced primary (n = 15/22; 68.18 %) and recurrent (n = 21/42; 50 %) rectal cancer achieving overall curative resection of 79.69 and 23 % overall 5 year survival. The Memorial Sloan Kettering Cancer Group demonstrated in a series of 29 patients a 62 % complete tumor resection and 20 % 5 year survival with significant morbidity though at the range of 59 % [22]. Moriya et al. [23] reported similar complete clearance rates at 84 %. The Royal Marsden group published the results of 30 patients that underwent abdominosacral resection for locally advanced primary (8 patients) and recurrent rectal cancer (22 patients) showing an overall 66 % 3 year local recurrence free survival, concluding that the procedure is associated with a low margin-positive rate and should be considered as an acceptable treatment for this group of patients [17]. Margin-positive resection was shown to be associated with poor survival outcomes and should be avoided when possible [17]. More studies have been recently performed and reported similar results [18, 19, 21]. One recent study has investigated the feasibility of laparoscopic abdominosacral resection in three patients with locally advanced primary rectal cancer and demonstrated that it is feasible providing an acceptable cosmetic result without compromising the oncological outcome (all patients had a complete tumor resection) [20]. This study reported on only three patients.

Local Staging of Primary and Recurrent Rectal Cancer

Accurate local staging is vital for the management of this group of patients. It can provide information about the local extent of the disease and subsequently the type of surgery that is required to achieve complete removal of the tumor along with the risk of incomplete tumor resection. It also allows a detailed discussion within a multidisciplinary team to plan neoadjuvant, adjuvant and palliative therapy.

Endorectal Ultrasound

Endorectal ultrasound (EUS) has been used to diagnose recurrent disease with adequate sensitivity and specificity [53, 54]. It is a useful tool as it allows the performance of biopsies at the same time with the procedure. A meta-analysis demonstrated that EUS is very accurate in staging advanced (T4) rectal cancer with 95 % sensitivity and 98 % specificity [55]. However, it provides limited information on the extent of the disease within the adjacent structures and cannot provide adequate information to safely evaluate the tumor resectability. USS has limited field of view and

cannot be performed when there is significant stenosis caused by intra-luminal tumor or extra-luminal pressure by tumor [56]. It has limited value following APER when it can only be used transvaginally in female patients to assess tumor invasion in the anterior structures. Therefore its use in the preoperative assessment and staging of this group of patients has been gradually abandoned.

Computed Tomography (CT)

Computer tomography (CT) is the most commonly used radiological modality for detecting primary and recurrent rectal cancer. CT has been demonstrated to have a sensitivity up to 95 % in detecting local recurrence [57, 58]. However, it may often have difficulties differentiating between tissue fibrosis and local recurrence [59, 60]. It has the tendency to overstage bladder involvement [61]. Its accuracy further drops if radiotherapy had previously been applied or in cases that there was previous pelvic sepsis [62]. Its sensitivity is considered low in diagnosing tumor invasion within the anterior structures (bladder and uterus; 50 %) and loco-regional lymph nodes (33 %) [63]. One study assessed the ability of CT scan to determine the extent of the pelvic disease, demonstrating an overall accuracy of 87 % (77.5–93 %) [61]. CT scan for tumors confined in the pelvis was more accurate (89 %) than when tumors were progressing into the abdomen (80 %) [61].

Magnetic Resonance Imaging (MRI)

Magnetic Resonance Imaging has been demonstrated to be highly accurate in the pre-operative staging of locally advanced primary and recurrent colorectal intrapelvic cancer, providing significant anatomical details that enable the planning of neoadjuvant therapy and surgery [64, 65]. It is now considered the gold standard to stage patients that are considered to undergo exenterative pelvic surgery for locally advanced primary and recurrent rectal cancer. MRI has a fundamental role when surgery is considered as an option for treatment as it accurately depicts the pelvic anatomical structures and compartments relevant to surgery [64, 65]. Previous studies had shown MRI to be highly accurate in detecting colorectal tumor invasion into pelvic structures such as the prostate, seminal vesicles and the sacrum [66, 67]. One more study reported that MRI is accurate in predicting the absence of disease to non-resected organs/structures [68]. Messiou et al. [66] demonstrated that the MRI was highly accurate in diagnosing tumor invasion into individual adjacent to the rectum anatomical structures but proved to be problematic when assessing the pelvic sidewalls (sensitivity = 70 %) and the female reproductive organs (specificity = 33 %). A more recent study demonstrated that it is accurate in predicting the extent of the tumor within the pelvis and can be safely used to guide surgery for curative resection [69]. The same study showed that the MRI sensitivity was very high for all compartments but the specificity was lower for the posterior compartment. Compared to CT, MRI can more accurately differentiate recurrent cancer within a presacral scar, based on differences in signal intensity between tumor and fibrosis using T2-weighted sequences or contrast-enhanced imaging techniques [70].

Diffusion Weighted Magnetic Resonance Imaging (DW-MRI)

Diffusion-weighted MR imaging (Fig. 10.2) is a functional radiological modality that can provide indirect information about the water proton mobility within biologic tissue [71, 72], without the need of a contrast agent [73–75]. As a result, a number of studies have been performed aiming to exploit the features of diffusion-weighted imaging and try to characterize the cellular composition of different tissues. Diffusion weighted MR imaging has since found widespread application in the management of acute cerebral ischemia as it has been demonstrated to be highly accurate in its early detection [76–78].

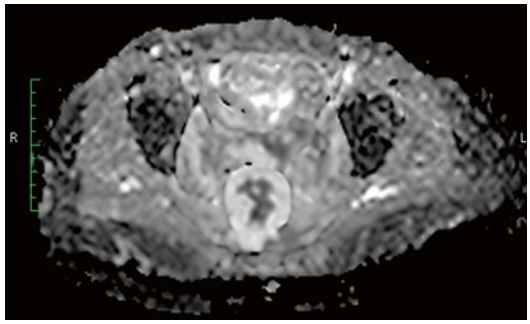

Fig. 10.2 Diffusion weighted MRI showing a cancer recurrence with mucinous component

As a consequence, there has been a rising interest about the diagnostic value of diffusion weighted MRI in oncology. Findings of recent studies suggested that the management of patients with different cancers could be benefitted from the additional information DW-MRI can provide [79–84]. In colorectal cancer, there have been a number of studies investigating the DW-MRI's efficacy in the management and prediction of oncological outcomes. In a series of 33 patients Ichikawa et al. [85] showed that DW-MRI is highly accurate in detecting colorectal cancer. Sun et al. [86] investigated its value in a series of 37 patients with locally advanced primary rectal cancer, concluding that it can be used to predict tumor response to chemoradiotherapy. Another study compared it with Positron Emission Tomography (PET) in a series of twenty five patients with colorectal cancer and reported it to be inferior in the detection of primary lesions but superior to PET in the detection of lymph nodes metastases. Lambregts et al. [87] however, demonstrated that it is not reliable to stage local lymph nodes following radiotherapy if used alone. The main benefit of adding DW-MRI in the same study was the increased number of detected lymph nodes and the improved positive predictive value for the identification of metastatic lymph nodes. Kim et al. [88] demonstrated that there is a role for DW-MRI as it can improve the diagnostic accuracy of MRI in the evaluation of the tumors' response to neoadjuvant chemoradiotherapy.

PET and PET/CT

Positron emission tomography (PET) scan is an accurate diagnostic tool and may have advantages over CT and MRI in discriminating fibrosis from cancer [89]. Exploiting the enhanced uptake of FDP-glucose by tumor cells, PET is able to detect both local recurrence and distant metastases. A meta-analysis demonstrated a PET sensitivity and specificity of 94 % for detecting local recurrences [90] with high accuracy in detecting pelvic recurrence in patients who had previously been irradiated [91]. However, limitations of PET scan include the inability to identify small volume disease and a relatively low sensitivity for detecting lymph node metastases [92]. Mucinous adenocarcinomas have poorer FDG uptake and therefore can be easily missed by PET scan [93]. In an effort to increase the confidence in diagnosing recurrence, PET with CT (PET/CT) image fusion was performed. Sapir et al. investigated the role of PET/CT in 62 patients demonstrated that PET/CT was more accurate than PEt alone for detecting local recurrence [94] but is not very helpful in evaluating anatomical tumor changes following chemoradiotherapy [95]. It might be useful in predicting pathological tumor response though [95–97].

Summary of Strengths and Weaknesses of CT, MRI and PET

CT and MRI have demonstrated high sensitivity in detecting local and distant recurrence and can provide detailed anatomical information of the affected organ and tumor extension into surrounding tissues [61, 98]. However, CT may often have difficulties determining if a suspected pelvic mass represents disease recurrence or tissue fibrosis. This becomes even more difficult if radiotherapy had previously been applied or there was previous pelvic sepsis from an anastomotic dehiscence [62].

PET scan is an accurate diagnostic tool and may have advantages over CT and MRI in differentiating scar tissue from cancer [89]. Exploiting the enhanced uptake of FDP-glucose

by tumour cells, PET is able to detect both local recurrence and distant metastases. However, limitations of PET scan include the inability in identifying small volume disease [92] and a relatively low sensitivity for detecting lymph node metastases [92]. In addition mucinous adenocarcinomas have poor FDG uptake [93] and therefore can be easily missed by PET scan.

Imaging to Exclude Distant Metastases

Accurate identification of extrapelvic disease is key for the decision to operate a patient. CT and MRI have demonstrated high sensitivity in detecting distant recurrence. Both imaging modalities can provide at the same time detailed anatomical information of the affected organ and tumor extension into surrounding tissues [61, 98]. The accuracy of CT in detecting abdominal disease has been demonstrated to be over 85 % [61] with the MRI's accuracy ranging to similar levels [64, 65].

A meta-analysis that investigated the value of US, CT, MRI and PET in detecting liver metastases, demonstrated a sensitivity of 63, 74.8, 81.1 and 97.2 % respectively and specificities of more than 93.8 %, with MRI being significantly more sensitive than CT ($p=0.05$) and equally sensitive to PET ($p=0.02$) [99]. There were no significant differences in the sensitivity between PET and CT ($p>0.05$) and neither between CT and US ($p=0.45$) [99].

Positron emission tomography (PET) has been demonstrated to be highly accurate in the detection of disseminated disease [100–103] and to have significant impact on the management of patients with suspected recurrent colorectal cancer [104, 105]. A meta-analysis reported a PET sensitivity of 91 % and specificity of 83 % for the diagnosis of distant metastases [90]. However the authors admitted that only 8/27 (29.6 %) studies were of high quality fulfilling their quality criteria at least by 80 %. Another study showed that the overall added value of PET in the management of patients with local and/or distant recurrent colorectal cancer is 8 % and suggested that PET should be used when findings remain equivocal after serial imaging review [106]. In the authors practice, all patients with locally advanced primary and recurrent rectal cancer that have potentially resectable local disease undergo a PET scan to exclude distant disease.

Selection Criteria for Surgery

Decision for surgery is made after extensive discussions at the local multidisciplinary meeting (MDM) and heavily depends on the findings of the available diagnostic modalities. Based on the radiological findings a decision will be made regarding the tumor resectability. Therefore accurate preoperative staging in extremely valuable in this group of patients as it can help to establish the extent of local disease and the presence or absence of distant metastases and therefore influence the outcome of the MDM.

Distant Recurrence

The presence of distant metastases is normally considered as a contraindication to proceed for surgery [107]. However, a number of centers have demonstrated that synchronous or staged resection of locoregional recurrence and distant metastases can have acceptable results in highly selected patients [108–110]. It is generally considered a contraindication though, due to the significant morbidity that is may be associated with this type of procedures [23, 29, 111–113].

Resectable Local Recurrence

In the absence of distant disease, surgical resection of the primary cancer or the locoregional recurrence is the only potentially curative option. Surgery for advanced primary or recurrent rectal cancer includes a range of different procedures that depend on the extent of the disease and the specific organs/structures that are

involved. Surgery has to be performed *en bloc* and is considered curative when the resection margins are free of microscopic disease (R0 resection). The presence of microscopic or macroscopic residual disease at the resection margins is defined as R1 and R2 resection respectively. It has been previously demonstrated that R1 or R2 resection can result in poorer survival [18, 114–116] and it should be consequently considered as palliative resection. A recent study showed that patients that undergo an R2 resection have similar oncological outcome with the patients that receive palliative chemotherapy [117]. Considering that this type of surgery carries considerable mortality and morbidity, identification of patients that an R0 resection can be potentially achieved is crucial and extremely difficult. Preoperative imaging with PET, CT and MRI and clinical assessment are utilized in an effort to optimize the selection of patients in whom curative resection is considered possible as well as those in whom curative resection is an unlike scenario.

Contraindications for Surgical Resection

One of the key factors that guide patient management is the patient's fitness for surgery. It is essential to assess it prior to any discussion for surgical options since the lack of fitness is often considered a contraindication when undergoing such a major procedure, due to the significant risk of death and complications. Operation is contraindicated in the presence of circumferential or extensive lateral pelvic sidewall involvement, involvement of the iliac vessels, bilateral ureteric obstruction, sciatic nerve involvement and periaortic lymph node metastases [26, 107, 108, 118, 119]. Involvement of the external iliac vessels may present with lower limp edema whereas ureteric obstruction with hydronephrosis. Tumor invasion of the sciatic nerve may present with lower limp pain and weakness. Limited tumor invasion to the lateral pelvic sidewall and invasion of the sacrum above the S2 vertebrae are considered relative contraindications since there are surgical options in both cases [23, 29, 120]. However the likelihood of a complete resection is considerably low while the perioperative risk of mortality and morbidity is higher.

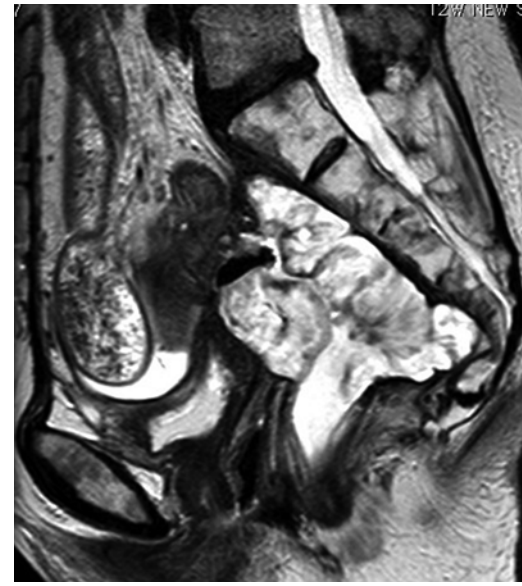

Fig. 10.3 Irresectable recurrent rectal cancer. This is mucinous adenocarcinoma invading the posterior compartment up to the level of S1

Irresectable Local Recurrence

Surgical resection and chemoradiotherapy can be used for palliation, alleviating the patients' symptoms that are related to the organs/structure that are invaded by tumor (Fig. 10.3). It has been suggested that palliative resection can have an improvement in quality of life and pain relief [121, 122]. However its use can be usually unsuitable considering the co-morbidities related with this type of surgery [123]. It is therefore important that the patients are carefully selected for palliative procedures taking into consideration possible co-morbidities and their social circumstances, as the benefits from these procedures are short term. The symptomatic relief can last up to 17 months with median symptom free interval of 4 months compared with 23 months for non-palliative procedures ($p<0.001$) [124].

The Role of a Multidisciplinary Team (MDT)

In the modern era of rectal cancer surgery, it is a common practice that the patients with primary and recurrent rectal cancer are discussed at a multidisciplinary meeting (MDM). This is usually comprised of colorectal surgeons, medical and clinical oncologists, histopathologists, radiologists and health care professionals that are involved with the management of this group of patients. .

Patient with locally advanced primary and recurrent rectal cancers are selected for surgery when they are fit to undergo general anesthesia and when there is no evidence of distant metastases. Distant metastases are generally considered a contraindication for surgery. In very few cases synchronous or staged resection may be considered. In addition contraindications that are mentioned before, are extensively discussed to avoid operating on patients that the likelihood of a complete resection is low.

Neo-adjuvant Therapy

Neo-adjuvant Radiotherapy

Patients with locally advanced primary rectal cancer will be eligible to undergo neo-adjuvant radiotherapy or chemoradiotherapy. For recurrent rectal cancer patients this option may not always be available, as the patients may have already received the full dosage of radiotherapy when they were operated for their primary cancer. Capecitabine and Bevacizumab are the commonly used chemotherapeutic agents in order to increase the tumor's sensitivity to radiation. The evidence however is limited and currently a number of studies are in progress investigating its value.

Neo-adjuvant Chemotherapy

Neo-adjuvant chemotherapy is not commonly used for locally advanced primary and recurrent rectal cancer. It is employed when reduction of the tumor size is desired in order to increase the likelihood of a successful tumor resection and reduce the risks of perioperative complications. It is still under investigation with a number of studies running to investigate its oncological benefit.

Abdominosacral Resection

Abdominosacral resection is a complex surgery that involves a big team with a special interest to this type of surgery. It can take long time to complete and can involve significant intraoperative blood loss. The team should be experienced in this type of procedure and be prepared to deal with complications during the surgery. A colorectal surgeon with a special interest in pelvic exenterative surgery is leading the team that is comprised of a spinal orthopedic surgeon, gynecologist and urologist with training in this type of surgery; and plastic surgeon. The patients are positioned in Lloyd-Davis and undergo urethral catheterization and insertion of ureteric stents by a specialist urological surgeon in the absence of tumor invasion of the bladder. Using an abdominal and perineal approach, the colorectal surgeon can mobilize the pelvic structures anteriorly and laterally, leaving the posterior structures that are involved or at thread by the tumor to be dissected last. When cystectomy is planed due to evidence of tumor invasion within the bladder, an extraperitoneal approach is used allowing an early control of the dorsal venous complex. This is followed by division of the endopelvic fascia and urethra. If a decision to perform a cystectomy is made during surgery due to tumor fixation anteriorly, the anterior compartment can be resected *en bloc* with tumor after mobilizing the pelvic sidewall. Bilateral high ligation of the internal iliac arteries can be performed in patients that undergo cystectomy. Selective ligation of the internal iliac arteries distal to the origin of the superior vesical artery may be preferred for patients that do not undergo cystectomy. The internal iliac veins are ligated during the abdominal part in high sacrectomies (at S1 or S2 level). When this is not possible, careful ligation can be achieved following division of the rectum during the perineal approach. This carries an increased risk for significant bleeding. When the abdominal

part is completed and the tumor is fully mobilized laterally and anteriorly the surgeon proceeds to the perineal part of the operation. This is performed with the patient in supine position. A combination of sharp dissection, diathermy and bipolar sealing device is used to perform an extralevator dissection of the sphincter complex. To complete the cystoprostectomy in males, the bipolar sealing device is used to the level of the previously controlled urethra. *En bloc* resection of the vagina, ovaries, pelvic sidewall, internal iliac vessels and small bowel is performed as required. *En bloc* lateral pelvic sidewall resection is performed when indicated, with procedures including extended lymphadenectomy, resection of internal iliac vessels or piriformis resection. With the patient still in supine position and the legs lowered, an ileal conduit can be fashioned by a urologist, myocutaneous tissue flaps can be harvested by a plastic surgeon and positioned temporarily within the pelvis. A colostomy is usually raised after this point and prior to the closure of the abdominal wound. Prior to the abdominal wound closure a K-Wire can be drilled through the anterior and posterior sacral plates and into the subcutaneous tissues above the tumor to mark a safe margin. The position of the K-wire can be confirmed with the use of fluoroscopic guidance.

The patient is turned into prone position to complete the operation. This is not always necessary for tumors below the level of S3. A vertical incision directly over the midline of the sacrum is performed followed by lateral dissection to mobilize the gluteus muscles laterally. The sacrotuberous ligaments, sacrospinous ligaments and the piriformis muscle are divided for sacrectomies at or proximal to the S3 level (Fig. 10.4). The sciatic nerve is identified and slinged for all high sacrectomies in order to preserve it. The dural sac is tied off and divided distal to the origin of the S2 nerve root. The sacrum is disarticulated using osteotomes, a Gigli or power saw. A periosteal lift can be performed on the anterior surface of the sacrum to the sacral segment above the osteotomy to maximize tumor clearance. For low sacrectomy (at S4/5) and if exposure is adequate, sacral division can be carried out in the supine position through the perineal incision using serial oblique osteotomies.

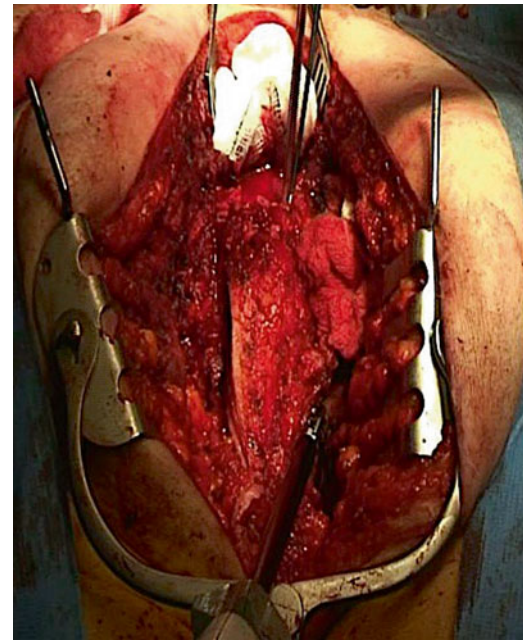

Fig. 10.4 Patient in prone during perineal dissection. Dissection of the sacrum during abdominosacral resection. Forceps point at the level of sacrectomy

Thorough haemostasis of the pelvis and perineum can be achieved suing a combination of diathermy, suture, packing and use of a topical haemostatic agent (TachoSil®; Takeda Pharmaceuticals, Zurich, Switzerland) on raw pelvic surfaces. Following resection, the specimen is reviewed to identify potential margins (Fig. 10.5) at risk and mark them for the histopathologist to review in detail. Plastic surgery is performed to reconstruct the perineal defect using a myocutaneous flap, biological mesh, omentoplasty or primary closure. CT angiography is advised to assess the patency of the inferior epigastric vessels. The size of defect will define the size of the myocutaneous flap. In order to prevent malrotation, the inferior insertion of the rectus abdominis muscle is preserved and the flap is placed in the pelvis from above to prevent any malrotation.

With the completion of surgery patients should be routinely admitted to the High dependency or critical care unit. Intravenous antibiotics are usually advised for at least 3 days. Patients should be started on total parenteral nutrition (TPN) immediately postop in anticipation of a prolonged postoperative ileus.

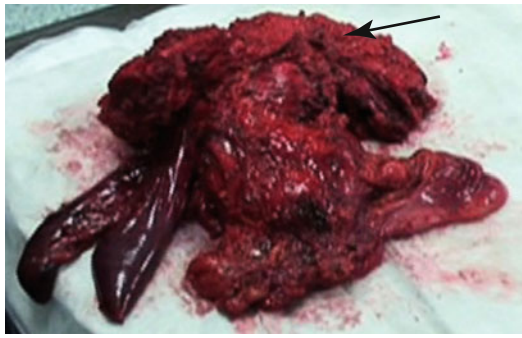

Fig. 10.5 Specimen. The specimen is macroscopically reviewed following resection for potential margins. The *arrow* shows the sacrum. Small bowel was adherent to the mass and resected *en bloc* with the specimen

Results

Abdominosacral resection surgery for locally advanced primary and recurrent rectal cancer carries significant risk of mortality and morbidity. The surgeons that look after the patients should have low threshold to escalate the care and manage complications aggressively. The mortality (Table 10.1) in the recent years has been reported to range up to 3.5 %. This is usually secondary to a major complication. Morbidity is considered significant for this type of surgery and ranges up to 70 %. A major complication can result in a prolonged hospital stay, which can last more than 30 days. The commonest complication is recurrent urinary tract infections. Systemic complications such as chest infections and deep vein thrombosis may occur. Pelvic sepsis that can result in wound dehiscence, sacral osteomyelitis or flap failure may occur. These can be managed using vacuum-assisted closure of the defect or by refashioning the flap. The pelvic sepsis may be amenable to percutaneous drainage. In high sacrectomies there is a risk for sacral nerve root injury that may result in long-term reduction in mobility.

Evidence in literature suggests that complete resection can be achieved up to 100 % of the operated patients. There is significant variation though with the majority of the studies reporting rates at the range of 55 to 70 %. This is likely to be related to patient selection. The commonest area of positive margin is the posterior and lateral pelvic sidewall. The overall 5-year survival following surgery ranges between 30 and 45 %. Complete resection is the most important predictor for overall and disease free survival, and care should be taken not to compromise it. The overall local recurrence free survival ranges at about 70 % at 3 years. This is significantly increased for R0 resections and drops for R1 resections.

Adjuvant Medical Therapy

The aim of adjuvant chemotherapy is to prevent the dissemination of the disease in high-risk patients. This is discussed at the local multidisciplinary meetings with the results of the histopathology. There are no clear guidelines for this group of patients as to which regime will benefit the patient better. A number of studies are in progress to investigate this.

Follow-Up

This group of patients is at high risk for recurrence and therefore the patients undergo an intensive follow up. In a number of centers the patients have an MRI scan of the pelvis as soon as they are clinically well. The images are used as a reference to compare with future images. This makes the interpretation of future images easier as the anatomy has been significantly altered. The majority of the recurrences are expected to be diagnosed within the first 3 years from surgery. Therefore the follow up during this period is more intense.

The follow up aims to:

- manage post operative complications
- detect recurrences, either local or distant
- detect metanchronous tumors
- facilitate the decision for further adjuvant therapies
- audit the outcomes
- assess the patients' quality of life
- reassure the patients

The process of follow-up involves clinical review, serum tumor markers, endoscopy and radiology.

Clinical Review

The follow up for this group of patients is intense and varies among different centers. Patients are usually reviewed and clinically examined every 3 months during the first 2 years following surgery. This takes place usually at tertiary centers. Several randomized studies have been performed to assess the benefits of intense follow up for primary rectal cancer, without demonstrating any statistical significance. However, these studies sample size was relatively small. A recent study [125] demonstrated more intensive follow-up for primary colorectal cancer can lead to an improved 5 year survival. These findings may be applicable to this group of patients as well.

Systemic and abdominal clinical examination takes place along with examination of the perineum and flap where applicable. Most of the patients are asymptomatic but occasionally may present with back pain due to the presence of recurrence that invades the sacral nerve. Patients may also present with symptoms and signs suggestive of dissemination of disease (i.e. anemia, cachexia).

Blood Tests: Serum Tumor Markers

Serum carcinoembryonic antigen (CEA) has been used extensively both in the USA and Europe for follow up for primary colorectal cancer for many year now with evidence suggesting that can detect recurrences up to 6 months prior to the presentation of symptoms. Evidence suggests that this test can lead to earlier diagnosis of recurrences that may subsequently be amenable to surgical management [126, 127]. This does not necessarily result to curative resection of the recurrence though and therefore second look surgery is unlikely to change survival rates on the whole. A blood test is usually taken on a 3 monthly basis for the first 2 years. This may vary among centers.

Other markers have been studied e.g. Ca19-9 (carbohydrate antigen) and TPA (tissue polypeptide); and compared to CEA but the latter seems to be the most sensitive and combinations of measured markers do not seem to change the overall sensitivity and specificity. In addition the combined use of CT and CEA does not seem to confer a significant advantage in detecting recurrences, compared to either CEA or CT alone [128].

Flexible Endoscopy/Colonoscopy

Endoscopy can only be performed through the stoma. There are no clear guidelines as to how often should be performed. A common regime for this group of patients is at 1, 2, 3 and 5 years following curative surgery. It aims to identify and describe a potential recurrence and to detect metachronous tumors. It is important to remember that most of the recurrences do not originate from the bowel lumen. Therefore endoscopic procedures are considered relatively insensitive for detecting recurrences. It may identify a recurrence indirectly by demonstrating fixation of the bowel to the adjacent structures.

Imaging

Liver Ultrasound has long been used to accurately depict liver metastatic lesions. It has high diagnostic accuracy even small lesions (e.g. 1 cm in diameter), although it is highly operator dependent. It has many supporters that even recommend its regular use as part of the follow-up process. It has been found very useful when its findings are combined with the CEA levels.

Computerized tomography (CT) has been considered an effective diagnostic tool that is employed to detect colorectal cancer recurrences. The reported diagnostic accuracy throughout the published studies has not been consistent. It has improved substantially with time though and in many centers is the diagnostic tool of choice.

Computerized tomography (CT) has its own limitation that should be taken into account. It is difficult to accurately assess the lesion's diameter and has low sensitivity in detecting lymph node recurrence. The artifacts from surgical clips make the interpretation of the images even more challenging. At the same time it is difficult to differentiating between post operative scarring and recurrence using a CT. Its current role in the modern era of rectal cancer is surgery is limited in the majority of the centers in the assessment for distant recurrences and metanchronous tumors.

Magnetic resonance imaging (MRI) is the gold standard to assess the pelvis for local recurrence. It is superior to CT in tissue characterization even in the presence of surgical artifact. It can provide detailed anatomical pictures of the recurrence with the adjacent structures. However, cost and patient factors (e.g. metal prosthesis, claustrophobia) make this investigation less usable on occasion.

One of the difficulties that MRI may have is differentiating between recurrence and scar tissue. This challenge is usually overcome by the use of serial scanning rather than just one off imaging. This can be found very useful in the presence of immediate post op MR images. Positron emission tomography (PET) may also be used in allowing differentiation of recurrence from surgical change. In most of the centers, Its use is limited for the cases that CT and MR images are equivocal.

Conclusion

Abdominosacral resection for primary and recurrent rectal cancer carries significant morbidity with acceptable mortality. It can however lead to long-term survival and should be offered to patients as an option for cure. Patient selection is crucial for this group of patients and therefore their management should be led by an MDM within tertiary center. Incomplete resection has no oncological benefit for these patient and should be avoided when possible.

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Abdominoperineal Resection

11

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Abstract

Contemporary treatment of rectal cancer incorporates multiple modalities but surgery remains the cornerstone of any strategy. Careful operative technique is vital in achieving optimal outcomes particularly with respect to local recurrence. Following the adoption of total mesorectal excision for rectal cancer, it was noted that patients with rectal cancers undergoing abdominoperineal resection (APR) faired worse compared to those undergoing anterior resection when matched for stage. Subsequent developments in surgical technique sought to address this dilemma. This chapter describes the historical context of APR, contemporary APR and its rationale, open, laparoscopic and robotic resection techniques, documents outcomes and strategies for dealing wound closure following APR.

Keywords

Rectal cancer • Abdominoperineal resection • Laparoscopic resection • Robotic resection • Complications • Outcomes

Historical Context

The earliest attempts at rectal cancer surgery were confined to palliative colostomy as described by Amussat [1]. Lisfranc published the first successful rectal tumor resection via a perineal approach in 1833 [2]. Surgery was restricted to low lying malignancies because to venture proximally led to morbidity and mortality related to breach of the peritoneum and subsequent peritonitis. While Gaussenbauer initially reported an abdominal approach to high rectal tumors this only became commonplace after the publication of Henri Hartmann's series [3, 4]. Given the prevalent operative mortality with an abdominal approach, sacral and perineal techniques persisted into the early 1900s, through the work of surgical luminaries such Lockhart-Mummery, York Mason and Bevan [3]. Although Czerny was the first to describe a radical combined abdominal and perineal approach to rectal cancers, it was the treatise

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of Sir Ernest Miles with its attendant concept of tri-directional zones of rectal cancer spread that popularized this procedure [5, 6]. The exclusively perineal approach remained commonplace as proponents such as Lockhart Mummery maintained that the morbidity and mortality associated with Miles' "radical" procedure (extralevator excision of the cancer and pelvic floor) was prohibitive. With advances in anesthesia, transfusion medicine, antibiotics and intensive care, perioperative complications decreased and the abdominoperineal resection (APR) described by Miles became the gold standard procedure after World War II [3, 5].

Indications

Advances in surgical techniques and technology have resulted in a fall in the proportion of patients with rectal cancer undergoing APR to approximately 20 % (versus restorative anterior resection) [7]. Indications for APR generally include neoplasms of the lower third of the rectum (within 5 cm of the anal verge), particularly those involving the sphincter. Motivated, informed patients with good sphincter function for whom it is technically feasible to achieve a clear one cm distal resection margin may be considered for sphincter preserving surgery. The choice of surgical procedure for low rectal cancer should however be individualized and patient factors and preferences considered. For certain patients the option of APR may be the safer or functionally preferable option with associated quality of life benefits, even when a restorative procedure is technically feasible.

The APR rate varies between surgeons, hospitals, regions and countries. Indeed the APR rate has been proposed as an indicator of overall surgical quality, although this is not a valid hypothesis due to a number of other variables [8–10].

Outcomes

Despite advances in surgery local recurrence rates of up to 40 % for rectal cancer were once commonly recorded prior to specialization [11]. Even with neoadjuvant and adjuvant chemo- and radiotherapy in the late twentieth century local recurrence rates remained at 10–15 % [12]. With the propagation of standardized surgery termed total mesorectal excision (TME) local recurrence rates of 5 % and 5 year survival of 70 % or better were increasingly reported for patients with rectal cancer amenable to anterior resection (AR) [13]. Unfortunately these results were not consistently replicated for low rectal tumors treated by APR. For rectal cancer a positive circumferential resection margin (CRM) confers a local recurrence risk and poorer prognosis [14]. Despite the introduction of TME and neoadjuvant chemoradiotherapy, circumferential margin positivity rates and local recurrence rates are higher for stage and location matched low rectal cancers following APR compared to LAR [15, 16]. In one study, 190 patients undergoing APR had a higher local failure rate (22.3 % vs 13.5 %) and a poorer 5 year survival (52.3 % vs 65.8 %) compared with 371 patients who underwent low anterior resection (LAR) during the same time period [17]. A large cohort study from Norway also reported a higher local recurrence rate (15 % vs 10 %) and a poorer 5-year survival (55 % vs 68 %) after APR than after AR [18]. Analysis of five separate European trials reported that the APR procedure was associated with an increased local recurrence rate and a decreased cancer-specific survival [19]. On the other hand, 5 year local recurrence rates of approximately 5 % have been achieved when standardized surgical techniques were employed in a meticulous fashion [20, 21]. It remains to be determined if inconsistent outcomes following APR can be explained by variation in surgical standards and approaches, or whether other factors are influential. Tumor factors (there is some evidence that tumors requiring APR are more locally advanced [22]) and location (threat to the CRM with anteriorly located tumors), anatomic considerations (possible differential lymphatic spread for low rectal cancers) and technical difficulties (surgeons following the mesorectal plane until it peters out 2 cm above the anal canal with specimen "waisting" at the pelvic floor and increased perforation rates) have been implicated in the outcome discrepancy between APR and AR [14–16].

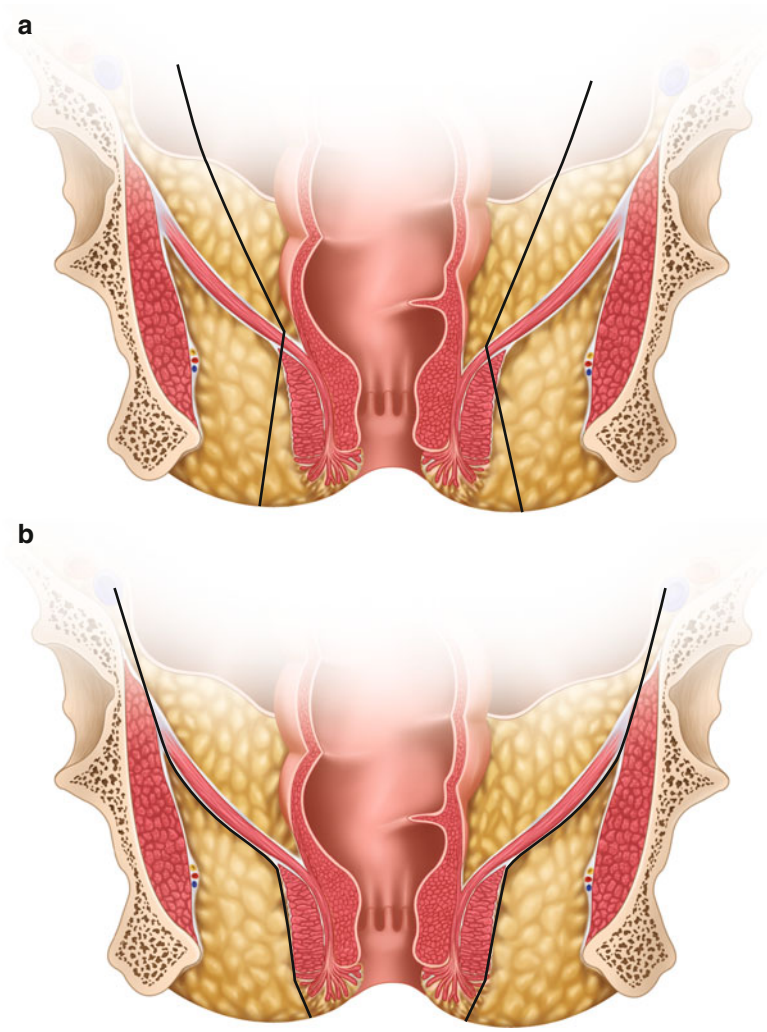

Fig. 11.1 (**a**) Plane of resection utilized when TME plane is followed to its termination. A waist is produced at the level of the puborectalis. (**b**) Plane of resection when the abdominal dissection is terminated at the level of the pelvic floor and the levators divided at the linea terminalis

Contemporary Open Abdominoperineal Resection

To address the concerns regarding the oncological safety of APR, the approach of Extra Levator Abdominoperineal Excision (ELAPE) has been relearnt in many centers. This technique follows the same principles as set out by Miles – "After reflecting the skin on either side to the requisite extent. the interval between the levatores ani (is) defined. These muscles should be divided as far outwards as their origin from "the white line" so as to include the lateral zone of spread" [6]. Specifically, the steps involved in the abdominal and perineal phases have again been standardized to avoid the anatomical deficiencies associated with following a TME plane to its termination and entering the funnel formed by the puborectalis (this leads to 'waisting') [23]. Production of an APR specimen with a "waist" at the level of the pelvic floor due to erroneously following the TME plane caudally was first described by Morson half a century ago [24] (Fig. 11.1a, b).

To achieve a 'cylindrical' specimen, the abdominal dissection is halted above the pelvic floor at the level of the sacrococcygeal joint, just below the hypogastric nerves laterally and at the lower border of the seminal vesicles or uteri cervix anteriorly. The perineal dissection is commenced via

a perianal incision of varying width according to local tumor extent, continues in the ischioanal fat outside the sphincter to the levator muscle insertions on to the pelvic side wall. In the modern iteration the coccyx is disarticulated in some cases where exposure is required (more often needed in a prone position). The levator plate is divided widely from posterior to anterior (if prone and the reverse if supine) and the specimen carefully exteriorized allowing dissection off the posterior aspect of the vagina or prostate.

Wide dissection of the pelvic floor avoids waisting of the specimen but does commonly result in perineal wound complications, even with xeno- or local tissue grafts/flaps [25]. Although general quality of life may not be impaired, perineal wound problems and pain are commonplace alongside urinary and sexual dysfunction [26].

The necessity of such an aggressively wide dissection in all comers has been questioned [27]. A comparative Swedish study comparing 79 consecutive ELAPE operations with 79 "standard APR" historical controls (performed by the same surgeons before and after a ELAPE training conference) showed no significant difference in CRM involvement, tumor perforation, or local recurrence rates between groups. However wound complications were substantially higher with a longer length of hospital stay in those undergoing ELAPE [28].This was mirrored by a study from the Mayo clinic in 2012 in which 246 patients underwent APR in the Lloyd-Davies (supine) position [29]. The local recurrence rate at 5 years was 5.5 %, not significantly different from that after AR. Furthermore, disease-free survival was the same after APE and AR. A recent systematic review demonstrated no significant difference between ELAPE and standard resections. There was no evidence that extralevator abdominoperineal excision yielded significantly lower rates of resection margin involvement or intra-operative bowel perforation compared with standard abdominoperineal excision in six independent hospital- and population-based patient series [30].

The current debate highlights a failure to communicate effectively and the importance of definitions and terminology, or rather a disabling lack of defined, standardized, internationally, and temporally acceptable terms of reference. Somewhere in the last century we left Miles behind and forgot his principles – or did we? Patients undergoing "standard" APR actually had the levators taken en bloc from the pelvic side wall thereby avoiding Morson's waist suggesting that appropriately trained, specialist surgeons already included levator excision in the AP resection of a rectal tumor (as described by Miles). Notwithstanding this, moves across Europe continue to promote 'extralevator' AP excision with formal workshops and training programs such as LOREC [31]. Hopefully such initiatives will serve to emphasize appropriately careful operative technique, standardized boundaries, and macroscopic margin targets of the current procedure.

Laparoscopic Abdominoperineal Resection (LAPR)

Laparoscopic APR (LAPR) represents a truly laparoscopic procedure with specimen extraction through the perineum. Perceived technical difficulties in the deep pelvis excluded rectal cancer patients from many of the initial laparoscopic surgery trials. It is speculated that the learning curve for laparoscopic rectal resection may be greater than 70 procedures [32]. Furthermore the oncological safety of LAPR has been questioned with a CRM positivity rate of up 16 % quoted in some studies [33]. However in these series, surgeon persistence in following the TME plane to its termination above the anorectal ring rather than the technique of laparoscopy per say appears to be the causative problem.

A number of randomized controlled trials (RCT) have now produced mature data on LAPR. Both Ng's RCT and subset analysis of the CLASICC trial showed that outcomes following laparosocpic APR were comparable to those following open resection [34, 35]. Postoperative recovery, return of bowel function and mobilization were quicker with lower analgesia requirements for patients undergoing LAPR but at the expense of longer operating time. Oncological outcomes and overall 5 year survival were equivalent [34, 35]. This is on the background

of surgeons operating early on the learning curve with an associated high conversion rate (30.4 % in the CLASICC trial). A recent meta-analysis confirmed no difference in long term or oncological outcomes between open and LAPR while LAPR was associated with fewer short term complications (OR 2.159, 95 % CI 1.426–3.269, P = 0.000) [36]. Indeed there was some suggestion that local and distant recurrence rates were actually lower with LAPR (odds ratio 2.736 and 1.994, 95 % confidence interval 1.137–6.584 and 1.062–3.742, P = 0.025 and P = 0.032, respectively) [36]. Hand assist or hybrid approaches have also been applied to APR and serve as a bridge to total LAPR, combining laparoscopic colon mobisation with the benefits of a shorter abdominal incision and manual tactile sensation for traction/counter traction [37].

APR has also been performed using various single port platforms with the device being inserted at the colostomy site [38–40]. However evidence for this technique is confined to small case series involving highly selective patient cohorts with only short term follow up. Stewart et al. involved six patients with a median BMI of 28, LN yield of 18 and negative CRM in all cases. All specimens were removed through the perineum [38].

Robotic APR (RAPR)

Robotic surgery has been applied to APR [41–43]. The erogonomics of the robotic systems may facilitate dissection of a large low neoplasm in an obese patient with a narrow pelvis thereby reducing conversion rates (Fig. 11.2) [41] and could theoretically translate into lower incidences of perioperative complication. It has been suggested that robotic APR (RAPR) may confer the benefits of laparoscopy while avoiding the prolonged learning curve associated with LAPR [42]. Straight and side docking techniques are routinely utilized (Fig. 11.3) [41, 42]. The currently available data suggest that surrogate oncological markers such as mesocolic dissection grade, lymph node number, perforation rates and margin involvement are equivalent for open, laparoscopic and robotic APR [43].

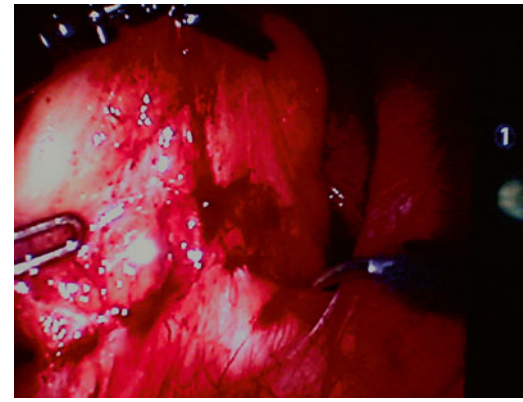

Fig. 11.2 Four articulated instruments easily accommodated in narrow pelvis of patient undergoing RALR for a large low rectal tumor (ypT3N1)

At present, the financial costs associated with the robotoc approach prohibit its wider application to APR.

Surgical Technique

Open APR

Pre-operatively all patients are sited for an end colostomy and receive stoma education. Some surgeons favor a mechanical bowel preparation (either oral laxative solution or enema) with or without oral antibiotics. Prophylactic intravenous antibiotics are administered at induction and a urinary catheter then inserted. Care must be given to appropriately pad pressure areas and potential nerve entrapment points. Neuropraxia has been reported after prolonged lithotomy [44] positioning but this was prior to widespread use of padded boots (rather than metallic stirrups) and sequential compression devices for enhanced venous blood flow and reduction of thrombotic events. After standard skin preparation, the peritoneal cavity is accessed via a lower midline infra-umibilical incision for open surgery or direct vision blunt port access for a laparoscopic approach. The sigmoid colon is mobilized beginning laterally at Todlt's line allowing medialization of the left colon to its embryonic midline position. Care is taken to protect the left ureter

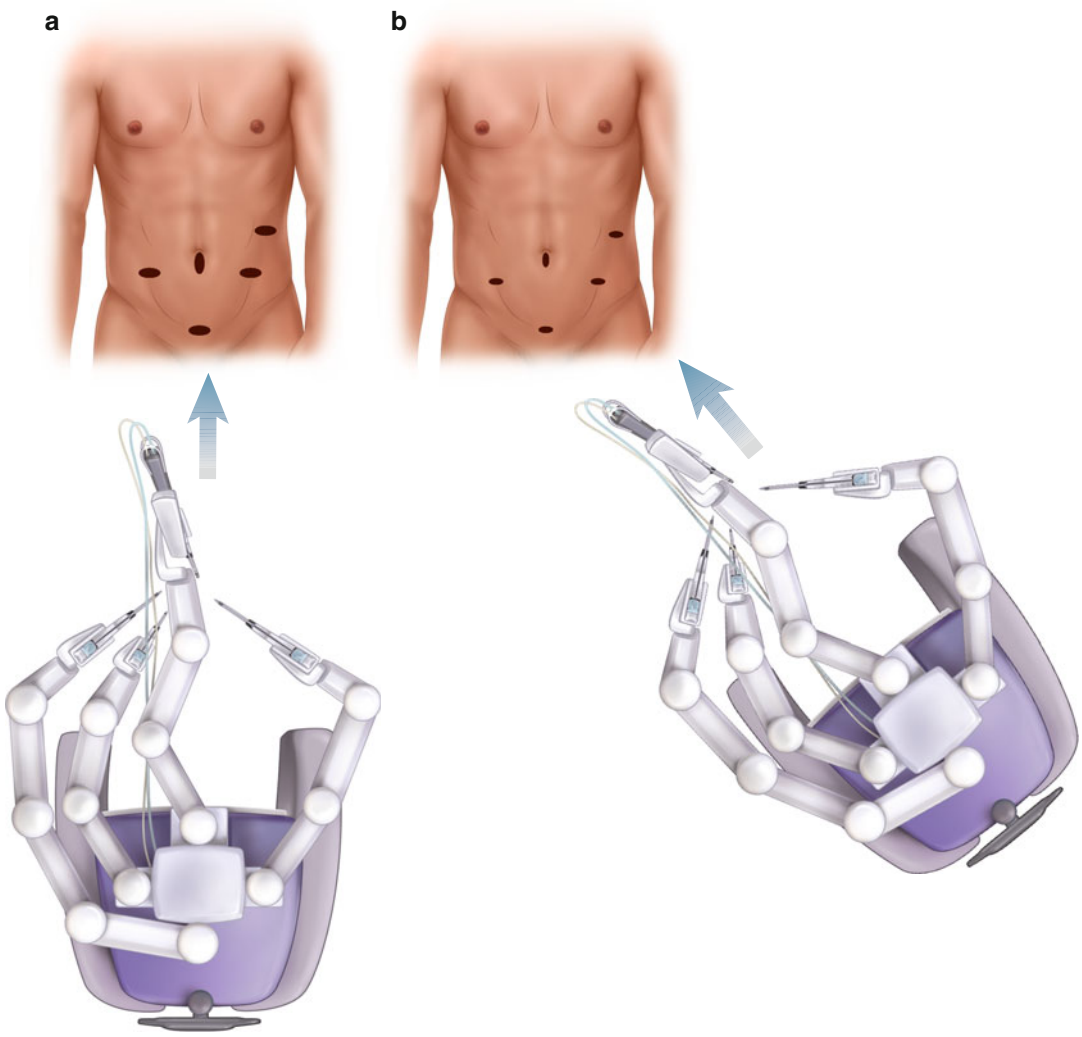

Fig. 11.3 End (**a**) and side (**b**) docking for RAPR

and gonadal vessels and maintain an intact mesocolic into mesorectal envelope by utilizing the natural fusion plane between the mesocolon and Toldt's fascia. The inferior mesenteric artery is ligated or vessel sealed within 1 cm of its origin to ensure all draining lymph nodes are harvested (while preserving the sympathetic hypogastric plexus) for histological staging. Alternatively, the 'medial to lateral' approach is used with the same steps in reverse order. There is little advantage to this and ureteric visualization is not as efficient.

Division of the mesocolon is begun proximal to the IMA and carried laterally towards the junction of the sigmoid and descending colon. The left colic artery and inferior mesenteric vein are sequentially secured as encountered. The colon is then divided after ensuring pulsatile blood flow in the marginal artery and adequate tension free length to permit end colostomy formation.

Sharp dissection is continued posteriorly, in the areolar tissue plane between the parietal pelvic wall and the visceral endopelvic fascia of the rectum, thereby ensuring an intact mesorectal envelope. The rectosacral (Waldeyer's) fascia is sharply divided and the dissection is continued

to the level of the sacrococcygeal junction. Care is taken to maintain the correct plane and avoid potentially torrential bleeding from the presacral venous plexus. Laterally the ureters are protected on the pelvic side wall and dissection is terminated just below the nervi ergentes. The lateral stalks representing condensation of the endopelvic fascia running in a posterolateral direction are divided. The peritoneal reflection is then identified and entered. The dissection is continued posterior to Denonvilliers fascia unless the tumor is anteriorly located. Recent work has demonstrated that Denonvillier's fascia is a distinct embryological entity representing a condensation of the parietal endopelvic fascia separate to the rectal mesocolic fascia. This serves to protect branches of the inferior hypogastric plexus passing to the pelvic urogenital tract. This anterior dissection is stopped at the uteri cervix in females or lower border of the seminal vesicles in males. The bowel is now divided at the junction between the sigmoid and descending colon. If the patient is to be turned prone for the perineal phase (or if the procedure a laparoscopic one), the end colostomy is fashioned at the marked site in a standard fashion.

The perineal dissection may be performed in the prone or lithotomy positions according to surgeon preference without detrimental consequences to oncological outcomes. The anal canal is ideally closed with a purse-string suture at the beginning of the operation prior to rectal mobilization to prevent spillage. An elliptical skin incision around the anal canal should be wide enough to include the sphincter and any local tumor – hence it is tailored to the tumor size, level, and extent (Fig. 11.4). The dissection is carried through the ischioanal fossa to the undersurface of the levator plate. The inferior rectal artery arising from the internal pudendal artery in Alcock's canal is encountered running from lateral to medial. It's origins from the linea terminales of the posterior obturator fascia are now circumferentially exposed. The coccyx is identified and the anococcygeal ligament is divided if necessary to facilitate coalescence of the abdominal and perineal dissections. The levator muscles are now divided laterally to join the abdominal dissection plane. The specimen is carefully exteriorized and the dissection continued anteriorly off the posterior aspect of the prostate or vagina, taking care to preserve the neurovascular bundles. This phase can be completed with the rectum in position when the specimen is too bulky to evert (Fig. 11.5). Hemostasis is secured and surgeons should be aware of an aberrant obturator artery which can cause troublesome bleeding in the small but appreciable proportion of patients who have one.

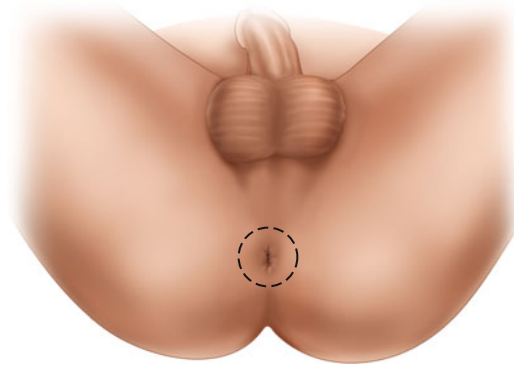

Fig. 11.4 Perineal skin incision for perineal phase of contemporary APR

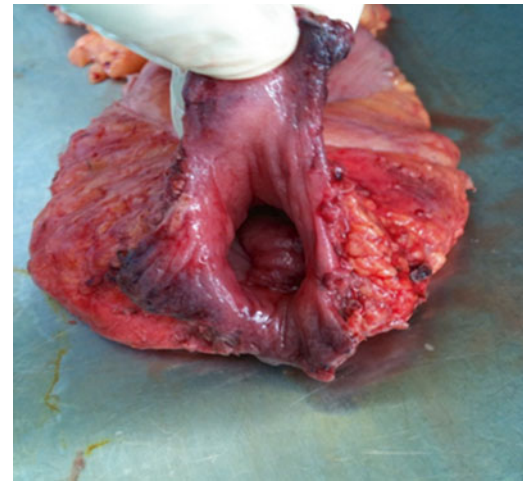

Fig. 11.5 Operative specimen for perineal phase of contemporary APR with the levators divided at their origin from the pelvic side wall. Note no evidence of Morsons waist at the level of the puborectalis

If present and mobile, the uterus can be retroflexed to facilitate pelvic closure. The authors routinely use omental pedicled flap to fill the

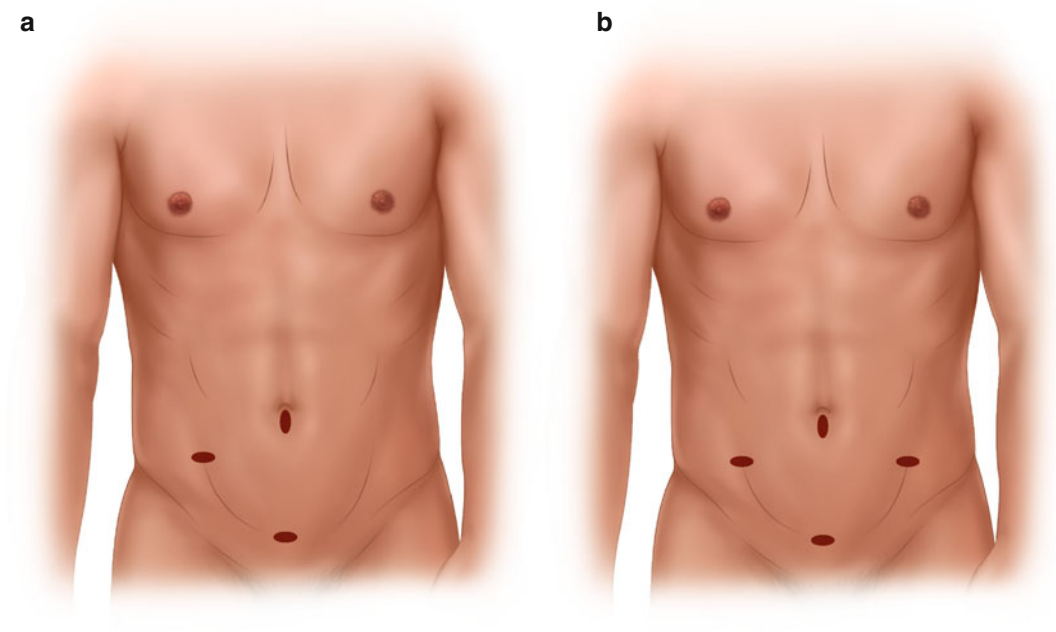

Fig. 11.6 Three-port (**a**) and four-port (**b**) configuration for LAPR

pelvic dead space and aide primary perineal wound closure [45]. This is done in layers with 2/0 polydioxanone sulfate or equivalent. The perineal skin is closed with 3/0 or 2/0 non-absorbable interrupted vertical mattress sutures (or subcuticular absorbable suture if the wound is small, clean, and non-irradiated). A closed suction pelvic drain (placed from the abdomen or perineum) is helpful in maintaining a dry perineal wound as a seroma is a common cause of wound failure without one but they are uncomfortable for patients. It is recognized that many centers routinely use a local (buttock) or distant (rectus abdominis muscle) flap, porcine/bovine dermis graft, or even their combination for closure of the perineum.

Laparoscopic APR (LAPR)

The patient is positioned as for open surgery but with an inflatable bean bag, gel mat or "mummy wrap" used to ensure the patient remains securely fixed to the operating table for steep Trendelenburg with lateral tilt for prolonged periods. Fears regarding intraocular pressure elevations have been raised but not substantiated by adverse events. The authors technique involves the surgeon and camera person on the patient's right side with an assistant on the patient's left. Camera monitors are placed at the patient's feet and left side.

The authors favor a 3 or 4 port technique (Fig. 11.6a, b) with a 5 mm camera port at or above the umbilicus. The right iliac fossa (RIF) port is a consistent operating port while the suprapubic and LIF port alternate between the surgeon and assistant. The patient is initially placed in steep Trendelenburg position and mobilization commenced lateral to medial or medial to lateral as described for open surgery. The ureter and gonadal vessels are identified and preserved. The IMA is safely sealed with an energy device unless the vessel is heavily calcified when clips or locking grips may be utilized as adjuncts or the primary tools. The lateral colonic attachments are now divided. The splenic flexure may be mobilized if there is insufficient length for a colostomy (rarely needed). At this stage the authors routinely mobilize the omentum (usually on the gastroepiploic arcade) for perineal omentoplasty later in the operation. An accessory port at the proposed stoma site is helpful in providing

counter traction (a 12 mm port is used to accommodate an endostapler for colonic division). In females it may be necessary (or helpful) to hitch up the uterus using an externally tied suture though the broad ligament. The dissection is as for open surgery and the dissection is stopped above the levator plate. At this stage the colon is divided with an endostapler and a colostomy formed at the premarked site. Again, the perineal phase may be performed in the supine position or the patient may be turned prone depending on surgeon preference.

Controversies

Patient Positioning for APR

A central tenet of recently published APR operative series is prone positioning. The prone position does afford excellent visualization, particularly during the potentially hazardous anterior mobilization of the specimen from the prostate/vagina and may facilitate nerve preservation. Prone positioning is however time consuming and can pose an anesthetic challenge. Furthermore, a number of groups have demonstrated that step wise or synchronous APR in the lithotomy or modified Lloyd-Davis position is oncologicaly safe with equivalent short and long term outcomes [46, 47]. A direct comparative study from the Cleveland Clinic involving APR performed in 81 patients in the prone position and 87 patients in the supine position showed no difference in local (equivalent at 5.7 and 12.5 % for supine and prone APR respectively) or distant recurrence (equivalent at 20 % after 7 years follow up) or overall survival (62.5 and 59.4 % 5 year survival). The patient groups were equivalent for demographic profile, use of adjuvant/neoadjuvant therapy, and tumor stage [46].

Additionally, a national multi-institutional study of standardized APR performed in the supine position demonstrated a local recurrence rate of 6.0 % at 5 years. It concluded that in patients undergoing APR by appropriately trained surgeons using a standardized approach, margin positivity was dictated by tumor stage, but not by center or surgeon [47]. In our opinion, patient position is at the surgeons discretion provided the resection is performed in a standardized manner incorporating en-bloc the pelvic floor and rectum.

Perineal Reconstruction

Short and long term perineal wound complications are common following abdominoperineal resection. Regardless of approach (open, laparoscopic, robotic, lithotomy or prone), anorectal resection produces a large fixed dead-space cavity which accumulates fluid and blood clot, promoting pelvic and perineal sepsis, abscess formation and ultimately delayed wound healing. The consequences include prolonged hospital stay, increased readmission rates, increased nursing home care requirements with resultant patient and societal financial expense [48]. Higher perineal morbidity has been described following the more radical ELAPE [26]. Primary healing rates range from 45 to 91 % depending on the study, population, concomitant use of neoadjuvant radiotherapy/chemoradiotherapy and surgical technique. Careful management of the perineal wound and pelvic cavity post APR is thus vital [48, 49]. Historically the perineum was left open and packed following APR to promote hemostasis and drainage with subsequent healing by secondary intention. Wound healing was often delayed beyond 4 months causing considerable patient discomfort [50].

Management strategies for the pelvic and perineal defects following APR have evolved to include primary perineal wound closure, closure of the peritoneum, primary closure with closed suction drainage of the pelvis drainage and pelvic wound irrigation and active closed drainage [51, 52]. Peritoneal and perineal closure was associated with fluid accumulation and subsequent infection in the dead space collection beneath the peritoneum and this technique thus fallen out of favor. The addition of irrigation to the pelvic drainage was not shown to be beneficial in an RCT from 1991 [52].

While primary perineal wound closure and closed suction is the preferred method following APR, a variety of complex, costly and

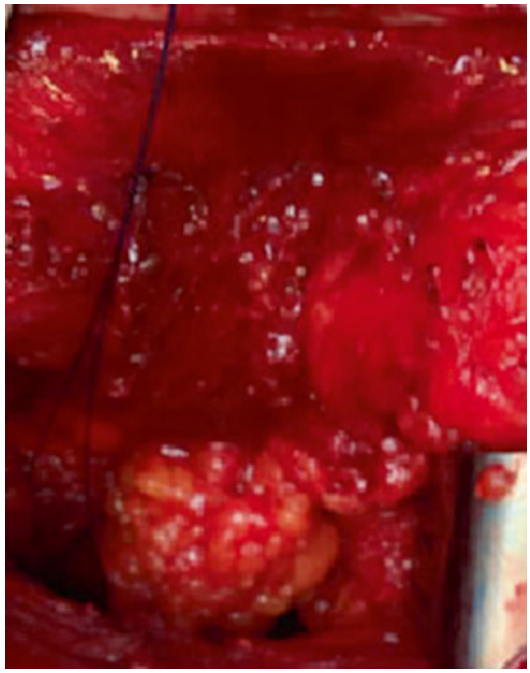

Fig. 11.7 Omentoplasty after LAPR to fill dead space in the true pelvis and aide perineal wound closure

time-consuming wound management techniques incorporating tissue transfer, such as vertical rectus abdominis (VRAM) and gracilis flap construction, have been advocated to deal with the pelvic cavity dead space and aide wound apposition [53–55]. Prophylactic biological matrix insertion has also been employed in an attempt to circumvent these difficulties [56]. Not all patients undergoing APR require such radical supplemental tissue transfer techniques. A very extensive resection for locally advanced rectal neoplasms with perianal skin involvement mandates formal myocutaneous grafting [57]. However the authors favor the use of omentum after APR. The anatomical, physiological and immunological properties coupled to availability of the omentum, especially laparoscopically, make it an excellent candidate for pedicled transfer to the pelvis [45]. Such a flap has sufficient length to reach the pelvic floor and adequate mass to fill any dead space (Fig. 11.7). A recent systematic review has shown that omental flap transfer and buttressing of the primary perineal repair following APR reduces wound infections, reoperation rates and hospital length of stay with minimal additional operative time or flap-associated morbidity [58].

For large defects or synchronous pelvic organ resection the inferiorly based rectus abdominis myocutaneous (VRAM) flap first described in 1984 provides well-vascularized tissue that can be transferred to cover significant perineal skin defects, vaginal defects, and fill the pelvic dead space created by APR. Recent studies of VRAM flap reconstruction after APR rectal cancer reported perineal wound complication rates of between 0 and 50 % [55, 56, 59]. Disadvantages include additional time and resources (frequently including a separate plastic/reconstructive team), lack of sensation to the cutaneous portion of the flap (vagina and perineum), interference with ostomy siting (especially if two stomata are required), risk of fascial dehiscence or donor site herniation (the authors routinely employ prophylactic mesh in this situation if a flap is utilized), pelvic cramps due to muscle activity, and abdominal deformation. Alternatives to VRAM include the gracilis flap (based on the major pedicle of the medial circumflex femoral artery) and glutius maximus flaps (unilateral or bilateral). Both have much to recommend them including ease of access and less deformity. The gracilis flap also has the advantage of being outside the radiation field. For recurrent rectal cancer resections a retrospective review showed that use of a gracilis flap decreased the incidence of major pelvic abscess from 46 to 12 % and significantly improved primary wound healing from 33 to 63 % [60].

Prevention of Parastomal Herniation

Parastomal herniation occurs in up to 50 % of cases after abdominoperineal resection regardless of approach [61, 62]. Fifteen percent of hernias are symptomatic. A number of strategies have been proposed to reduce the rate of herniation and the incumbent costs to patients and health care providers [61, 62]. Although not commonly performed, extraperitoneal colostomy formation may assist in reducing herniation [63]. Maturation of an extraperitoneal end colostomy laparoscopically has also been reported [64]. Use of a circular stapler to produce a defined

reinforced fascial trephine is currently under assessment [65]. Prophylactic mesh insertion at the time of stoma formation has been tested in a number of trials employing synthetic meshes or animal dermis implants in a sublay or onlay position at open and laparoscopic APR. Unfortunately outcomes to date have not been as impressive as had been expected [66–68], however concerns regarding mesh infection and complications did not come to pass. Long-term data is required to clarify the efficacy and cost effectiveness of this approach [69].

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Total Mesorectal Excision with Autonomic Nerve Preservation: "Optimized Surgery"

12

Hekmat Hakiman, Sarah Boostrom, and James Fleshman

Abstract

The superiority of total mesorectal excision (TME) for rectal cancer in reducing the incidence of local recurrence and improving long term survival compared to conventional blunt rectal dissection is well established. Impotence and other complications due to autonomic nerve injury are among the consequences of operations for treatment of rectal cancer. Sharp dissection along the parietal pelvic fascia where the parasympathetic nerves are located significantly reduces the incidence local recurrence. Autonomic nerve preservation during pelvic sidewall dissections is discussed in this chapter. Role of tumor specific TME, intraoperative nerve monitoring and importance of obtaining negative circumferential resection margin is discussed as well.

Keywords

Rectal cancer • Total mesorectal excision (TME) • Nerve sparing • Autonomic nerve preservation • Circumferential resection margin (CRM)

Introduction

The treatment for adenocarcinoma of the rectum has shifted greatly in recent decades. Today, the modern management of rectal cancer is composed of a multidisciplinary approach. Pre-operative chemotherapy and radiation for locally advanced rectal cancer have improved local recurrence and disease-free survival. Importantly, however, surgery remains the cornerstone of curative therapy. Accurate and specific pre-operative staging is of crucial importance when planning the operative portion of definitive treatment.

Historically, in the early nineteenth century, the surgical treatment of rectal cancer was mainly palliative colostomy. Well into the early twentieth century, surgeons continued to treat rectal cancer with a diverting colostomy and perineal proctectomy for symptomatic patients. This approach inherently was associated with up to an 80 % local recurrence rate and 8–20 % operative mortality [1, 2]. Subsequently, in an effort to

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improve local recurrence rates, a radical abdominoperineal resection was proposed by Miles with a mortality as high as 31 % [3]. Over the next several decades, improved understanding of lymphatic drainage of the pelvis, as well as the development of circular stapling devices for colorectal anastomoses, allowed for improvement in sphincter preservation throughout the 1970s.

Advent of Total Mesorectal Excision (TME)

In 1979 Professor Richard Heald described the "total mesorectal excision" and in 1988 the term "holy plane" was coined [4, 5] Total mesorectal excision (TME) consists of the removal of the perirectal lymphatic and adipose tissues, while maintaining the lateral and circumferential envelope of the mesorectal fat pad (Fig. 12.1). This technique gained popularity and was used as the method of choice for treatment of rectal cancer by 82 % of colorectal surgeons affiliated with colorectal surgery training programs in the late 1990s [6]. Today, this technique is universally accepted as gold standard surgical approach when performing an APR or sphincter-sparing procedure, and has replaced the conventional blunt approach to removing perirectal tissue.

TME is associated with improved local control and survival rates. The local recurrence rate following total mesenteric excision with an APR or sphincter-sparing procedure ranges from 4 to 7 % [7–9] This remains an improvement when compared to the local recurrence rates following the conventional blunt approach which ranged from 14 to 45 %, with or without postoperative radiation therapy (RT) or chemoradiotherapy [10].

Rationale for TME and Its Relationship to Anatomy of Spread of Rectal Cancer

The lymphatic and venous drainage of the rectum are cephalad and lateral (Figs. 12.2 and 12.3). The upper two thirds of the rectum drains along the pathway of the superior hemorrhoidal vein, cephalad to the inferior mesenteric nodes, and the para-aortic nodes. The lymphatic drainage of the lower third of the rectum is cephalad as well as laterally along the middle hemorrhoidal vessels to the internal iliac nodes. There are no communications between the inferior mesenteric and internal iliac lymphatics [11]. In women, lymphatic drainage above the dentate line also includes the posterior wall of the vagina and

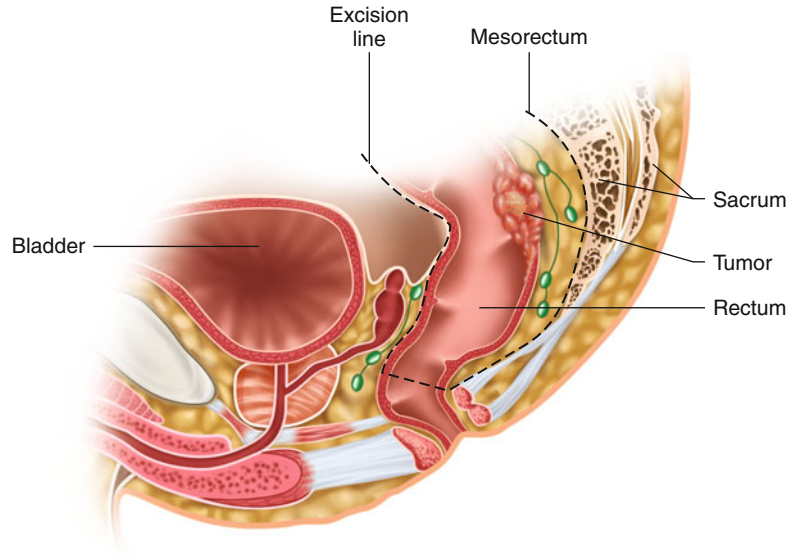

Fig. 12.1 The correct plane in total mesorectal excision

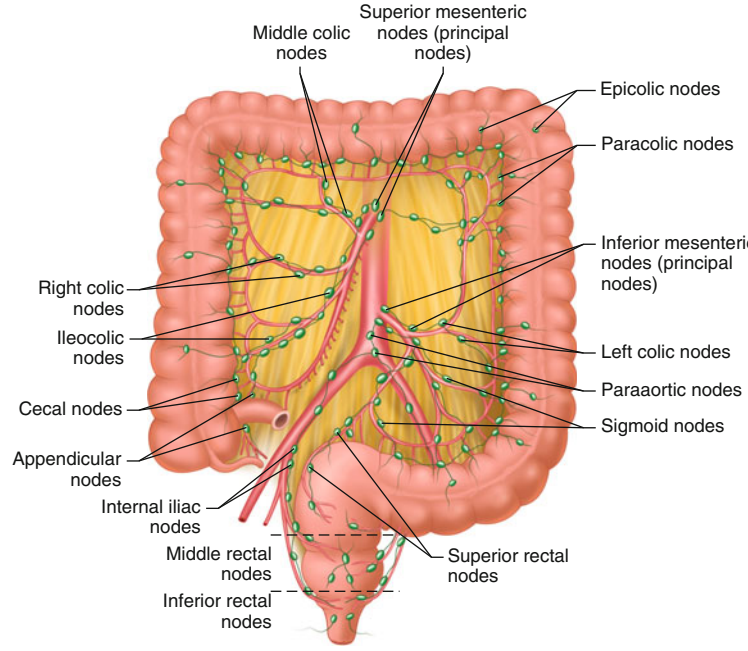

Fig. 12.2 The lymphatic drainage of the colon and rectum

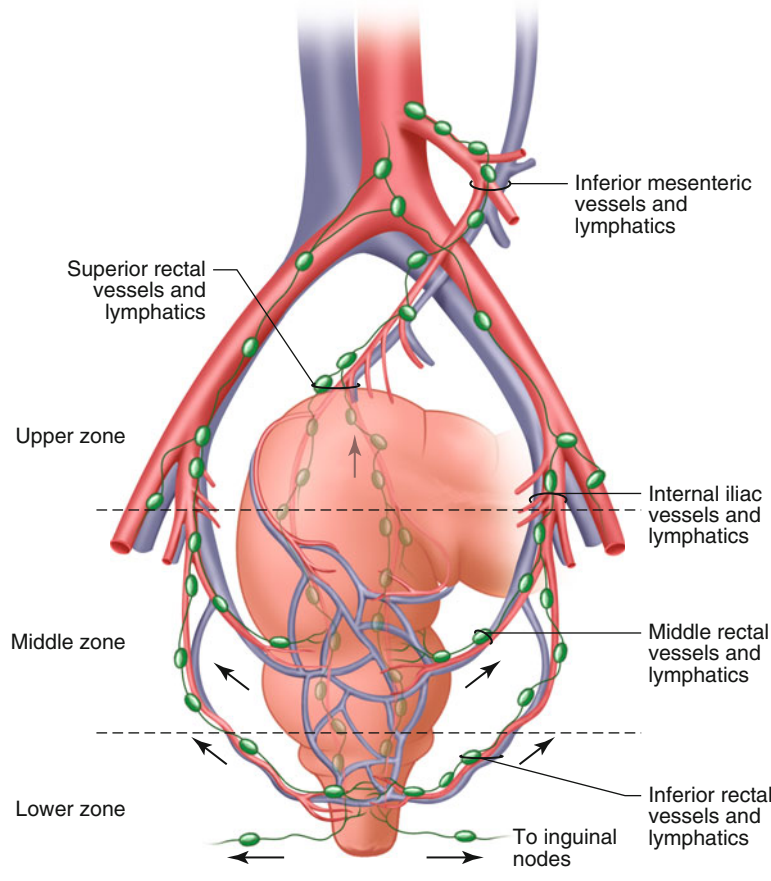

Fig. 12.3 Blood supply to the rectum and the accompanying lymphatic and venous drainage. Showing the cephalad drainage of upper rectum and lateral pathways from the middle rectum

reproductive organs. Below the dentate line, the drainage is along the inferior rectal lymphatics to the superior inguinal nodes and along the pathway of the inferior rectal artery [12].

It is believed that the improved local recurrence rates with TME is the result of improved lateral clearance and circumferential margin negativity, and removal of potential tumor deposits in the mesentery as well as a decreased risk of tumor spillage from a disrupted mesentery [13]. Improved local control appears to result in better survival [14].

Genitourinary Complications of Pelvic Dissection

TME preserves the pelvic autonomic nerves which reduces the risk of postoperative genitourinary dysfunction [10].

- Urinary dysfunction:
  - Urinary dysfunction after proctocolectomy, primarily manifested as difficulty voiding, is thought to be the result of autonomic nerve injury leading to impairments in parasympathetic innervation to the detrusor muscle and/or sympathetic innervation to the bladder neck, trigone, and urethra. Urodynamic studies reveal a significant postoperative decrease in effective bladder capacity and increases in first sensation to void and residual urinary volume compared with the preoperative evaluation [15]. Incidence of urinary dysfunction has been reported to be 30–60 %, with the greatest risk following abdominoperineal resection [16]. Urinary dysfunction persisting beyond the early (30-day) postoperative period has been reported in 12 % of patients [17].
  - Autonomic sparing procedures can be effectively performed when dissecting the pelvis. A prospective study of 20 patients undergoing a total mesorectal excision (TME) with an autonomic nerve preservation (ANP) technique and sphincter preservation found no significant difference between preoperative and postoperative mean residual volume after micturition [18].
- Sexual dysfunction:
  - Sexual dysfunction following proctocolectomy is related to the extensiveness of the dissection of the pelvic nerves and occurs in both men and women.
  - In men, damage to the sympathetic nerves during high ligation of the inferior mesenteric artery or posterior dissection at the sacral promontory can lead to retrograde ejaculation, and damage to the parasympathetic plexus (nervi erigentes) during lateral and anterior dissection can lead to erectile dysfunction.
  - The major risk factors for sexual dysfunction following proctectomy for malignant disease are advanced age, type of surgery (abdominoperineal resection versus low anterior resection), total mesorectal excision versus non-TME, and the use of preoperative radiation [19, 20]
- Female infertility
  - The majority of data regarding female infertility may be extrapolated from data specific to inflammatory bowel disease (IBD).
  - Pelvic surgery is common in patients with inflammatory bowel disease and the majority of these patients are child bearing age. The infertility rate before pelvic surgery for such women is less than 10 % which is similar to that of the general population, however, the rate of infertility following a restorative proctocolectomy is significantly increased to 26–48 % [21, 22].
  - The cause of infertility is thought to be mechanical from scarring of fallopian tubes.
  - With the recent increase in incidence of rectal cancer in younger populations, women should be counseled preoperatively regarding the risk of infertility.

Pelvic Autonomic Nerve Anatomy

Surgeons are familiar with visceral and vascular anatomy of the pelvis, however, neuroanatomy is less apparent and its importance is not appreciated.

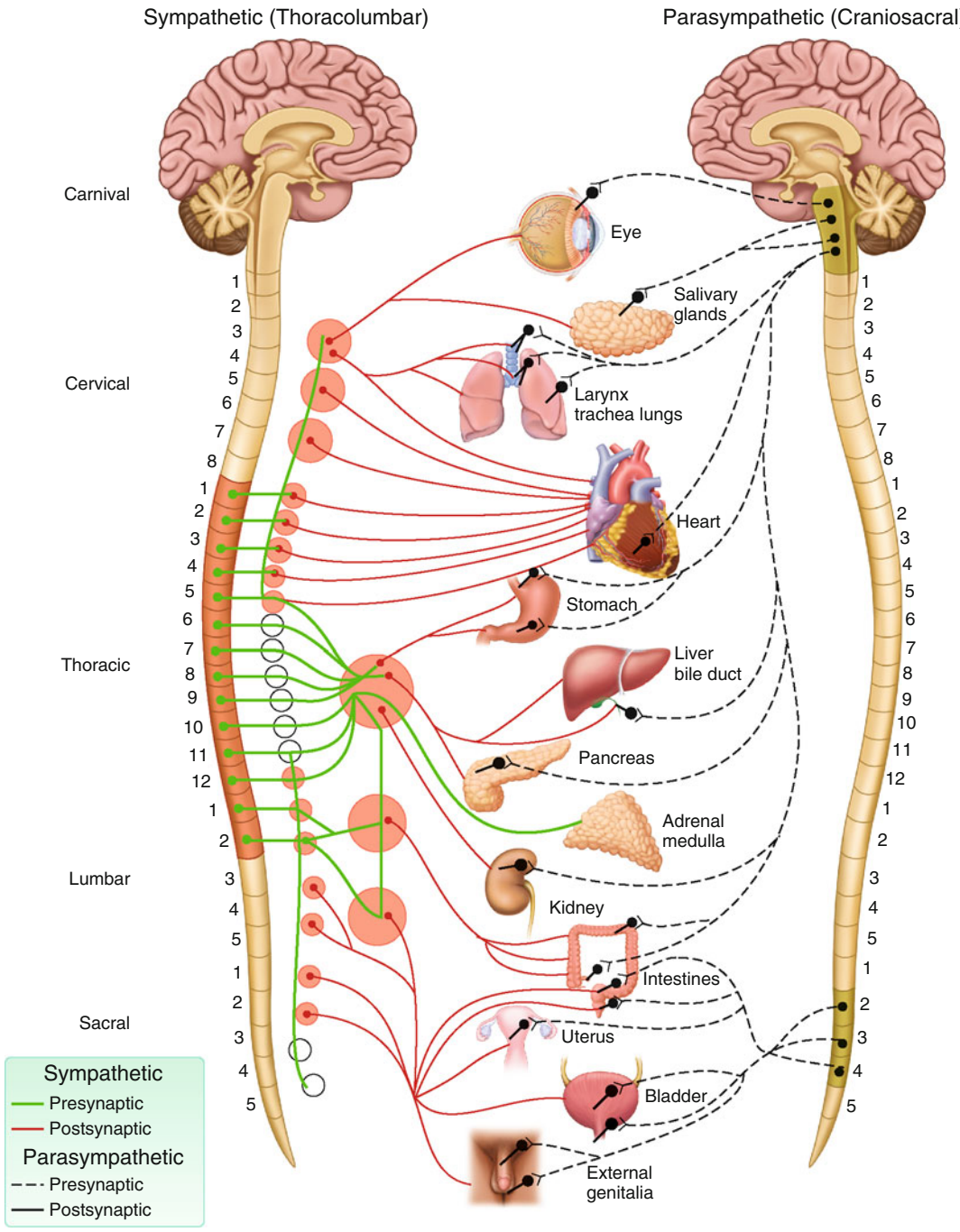

Fig. 12.4 Distribution of autonomic nervous system

The parasympathetic nervous system is referred to as the craniosacral outflow; the pelvic splanchnic nerves comprise the sacral outflow component (Fig. 12.4). They arise from the ventral rami of the S2–S4 and enter the sacral plexus. They travel with the inferior hypogastric plexus, located bilaterally on the lateral walls of the pelvis. From there, they contribute to the

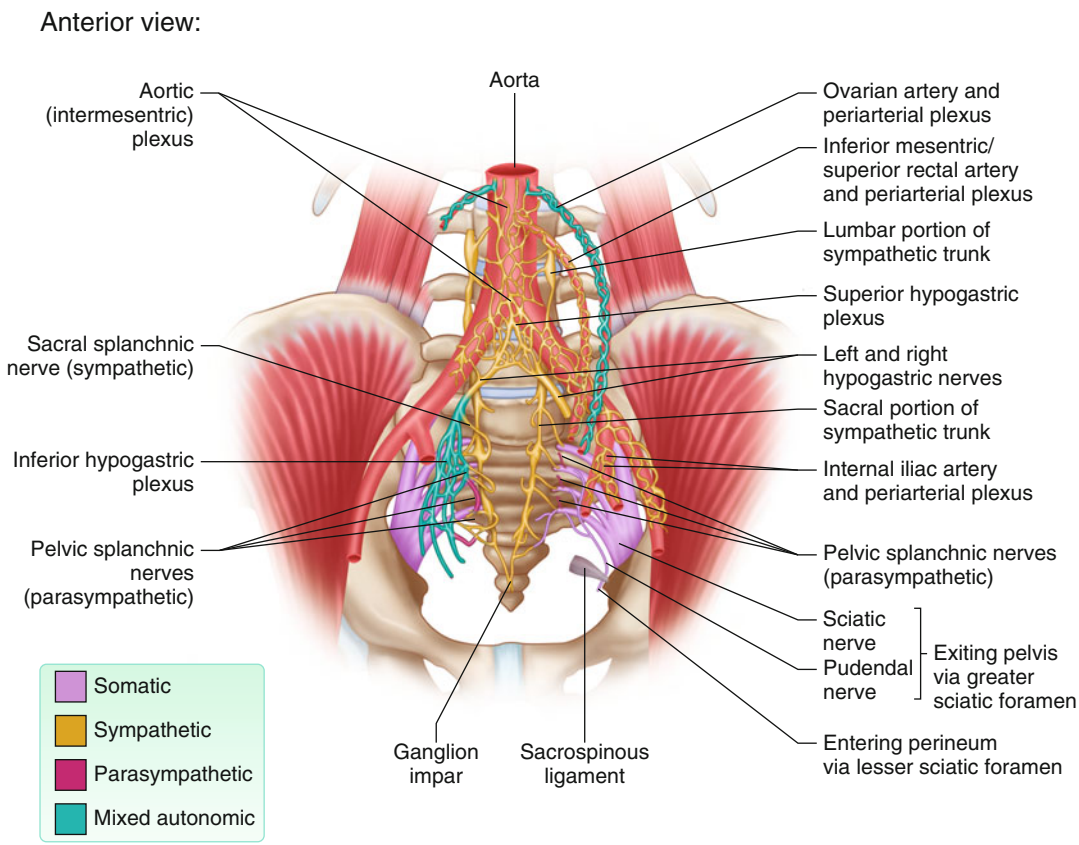

Fig. 12.5 Connections of sacral and pelvic splanchnic nerves

innervation of the pelvic and genital organs. They regulate the emptying of the urinary bladder and the rectum as well as sexual function, including erection (Fig. 12.5).

Sacral splanchnic nerves, which arise from the sympathetic trunk, provide sympathetic efferent fibers (Fig. 12.4). The superior hypogastric plexus is a ganglionic plexus that lies over the bifurcation of the aorta in the presacral space. From there, the nerves split into two hypogastric nerves that run along the internal iliac vessels. These nerves connect to the inferior hypogastric plexus on the pelvic sidewall (Fig. 12.6).

The "lateral ligament of the rectum" (LLR) has long been the subject of anatomical confusion and surgical misconception. Some surgeons believe that the lateral ligaments are artifacts produced by the obsolete process of blunt dissection during rectal mobilization [23]. Lin and colleagues performed cadaveric dissection on 32 cadavers to elucidate the anatomy of this structure [24] and report that the constant component of the lateral ligament of the rectum included the rectal branches from the pelvic plexus, whereas the middle rectal artery was not apparent in the majority of lateral ligaments. Additionally, they concluded that the LLR was located traversing between the rectum and visceral fascia, thus making it difficult to reveal the LLR if performing TME within the correct surgical plane (between visceral fascia and parietal fascia) (Fig. 12.7).

Technical Aspects of TME and ANP

The goals of a curative resection for rectal cancer include performing a wide resection of the cancer, therefore achieving histologically negative

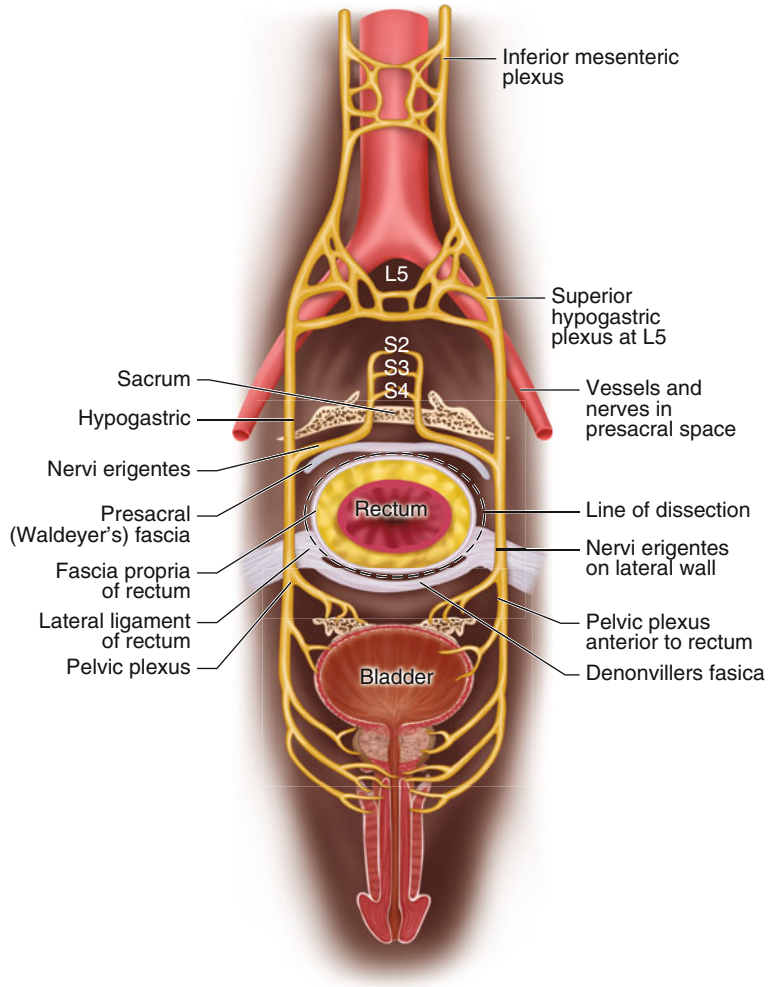

Fig. 12.6 Mesorectal plane of excision in relation to the pelvic plexus

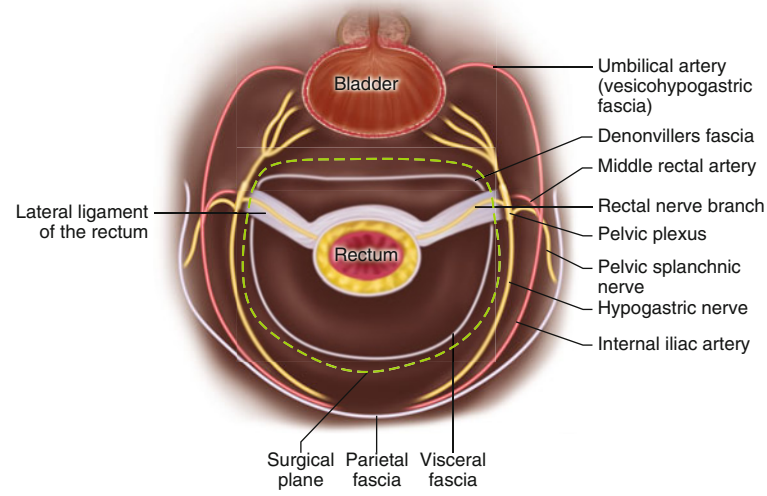

Fig. 12.7 Relationship of surgical plane with the lateral ligament

margins as well as performing a total mesorectal excision (TME) including resection of local lymph nodes.

When performing TME the following points should be kept in mind

1. Complete removal of the mesorectum, including the lateral and circumferential margins of the mesorectal envelope [10].
2. Removal of the inferior mesenteric artery (IMA) and the locoregional lymphatic system of the rectum.
3. The use of sharp, rather than blunt dissection, in the avascular plane between the parietal and visceral pelvic fascia [25]. Conventional blunt dissection violates the mesorectal circumference and potentially leads to substantial hemorrhage thus leaving residual pelvic tumor.

In regards to autonomic nerve preservation, care must be taken not to damage the pelvic plexus during lateral dissection of the lateral ligament along the pelvic sidewall. Enker [26] describes important aspects of autonomic nerve preservation technique. In addition to sharp dissection along the parietal pelvic fascia and maintaining intactness of mesorectal envelope, it is important to preserve the superior hypogastric plexus where it lies on the anterior surface of the aorta and divides into the two hypogastric nerves running along each side of the pelvis to join the inferior hypogastric plexus and the pelvic splanchnic nerves from S 2–4. For all resections, the anterior plane of dissection is immediately anterior to the fascia of Denonvilliers' in men and immediately posterior to the vagina in women. Prior to completion of the operation, the nerves should be inspected and checked for any damage.

Intraoperative Nerve Monitoring

In efforts to improve nerve sparing surgery, intraoperative electrical stimulation of pelvic autonomic nerves has been proposed in urology and gynecology [27]. Lue et al., first reported the successful use of intraoperative electrical nerve stimulation to monitor the function of cavernous nerves in 16 patients undergoing radical retropubic prostatectomy [28]. Kneiste and colleagues performed intraoperative nerve stimulation (INS) in 62 patients to confirm pelvic autonomic nerve preservation (PANP). They compared nerve stimulation to visual assessment by the surgeon and found that INS results in higher sensitivity (82 vs 46 %). In addition, the accuracy of INS in predicting PANP was higher (88 vs 83 %) and the correlation between urinary function and the findings on INS was better (kappa-value: 0.65 vs 0.40). A prospective, randomized, single-blinded, multi-center trial is underway with an expected completion date of December 2015. This study will examine the impact of continuous monitoring for preservation of urogenital function in patients with TME for rectal cancer. 188 patients will be included in two arms: TME with and without intraoperative continuous monitoring of pelvic autonomic nerves. (ClinicalTrials.gov Identifier: NCT01585727)

Laparoscopic TME

In experienced hands, mesorectal excision can be done with comparable results to open surgery [29] with the advantages of less postoperative ileus and pain, and a shorter length of hospital stay when compared to open surgery [30]. Additionally, possible benefits of minimally invasive surgery include better visualization and magnification, and lack of blunt dissection.

In terms of sexual and bladder dysfunction after laparoscopic surgery there is limited data showing its superiority. A retrospective review of patients from a previous randomized trial comparing outcomes of laparoscopic with open resection of rectal cancer found an increased risk of sexual dysfunction in those undergoing a laparoscopic compared with an open resection in men who were previously sexually active (7 of 15 versus 1 of 22 patients). There was no difference for sexual function for women. There was no difference in rates of bladder dysfunction [31]. It

should be noted that the same principles of mesorectal excision with preservation of autonomic nerves applies to the laparoscopic approach.

The technical aspects of the laparoscopic approach to nerve sparing proctectomy with mesorectal excision for rectal cancer can be found at the following link to the American Gastrointestinal and Endoscopic Surgeons (SAGES) video library: http://www.sages.org/video/laparoscopic-nerve-sparing-proctectomy-with-mesorectal-excision-for-rectal-cancer-2.

Robotic TME

Robotic rectal surgery is an emerging technology that combines the advantages of the laparoscopic approach, including reduction in postoperative pain and faster recovery, with high-quality three-dimensional vision [32]. Based upon small retrospective reviews, robotic-assisted total mesorectal excision is safe and feasible with no difference in number of harvested lymph nodes or circumferential resection margins compared with open and laparoscopic approaches [33–35]. In a case-matched analysis of patients undergoing robotic-assisted, laparoscopic-assisted, or an open approach for the resection of mid- or low rectal cancer (165 patients in each arm), no significant difference in 2-year disease-free survival was identified [36].

Lymphadenectomy and Vascular Ligation

The goal of total mesorectal excision is to harvest the complete nodal basin for staging purposes, local control, and the interruption of the metastatic process. The higher number of lymph nodes harvested, the more accurate the staging. A 12 lymph node benchmark was adopted as a quality metric by the American College of Surgeons, the National Comprehensive Cancer Network (NCCN), and the American Association of Clinical Oncology (ASCO) [37]. However, recent studies have shown that the number of harvested lymph nodes is affected by pre-operative chemoradiation [38]. It is believed that the removal of the draining lymph nodes to the level of the proximal vascular pedicle, rather than the absolute number of lymph nodes, is an important surgical principle. For colon cancer the use of a lymph node ratio (the ratio of metastatic to examined lymph nodes) has been suggested as a means of incorporating both the number of involved nodes and the total number examined into prognostic stratification [39].

The level of vascular ligation is a surrogate for resection of the nodal basin. Some authors suggest removal of the blood supply and lymphatics up to the level of the origin of the superior rectal artery, which is just caudal to the takeoff of the left colic artery (low tie) [40]. When the inferior mesenteric artery (IMA) is ligated at its origin (high tie), lymph node yield may be increased, however, no significant difference in survival has been found between the two techniques [41]. It should be noted that when nodes above the superior rectal drainage are clinically suspicious, the resection should be extended proximally to include high ligation of the IMA. In addition, high ligation of the IMA at the origin at the aorta will likely provide better mobilization for a tension-free coloanal anastomosis. On the other hand the height of vascular ligation can theoretically put nerve integrity at jeopardy at the aorta.

Extended Lateral Lymphadenectomy

Lateral lymph node dissection (LLND) includes removal of all nodal tissue along the common and internal iliac arteries. Some studies have shown improved local recurrence and survival [42]. A meta-analysis comparing LLND with conventional surgery found that LLND did not confer a significant oncological benefit, but it was associated with increased urinary and sexual dysfunction [43]. Therefore, an extended lateral lymph

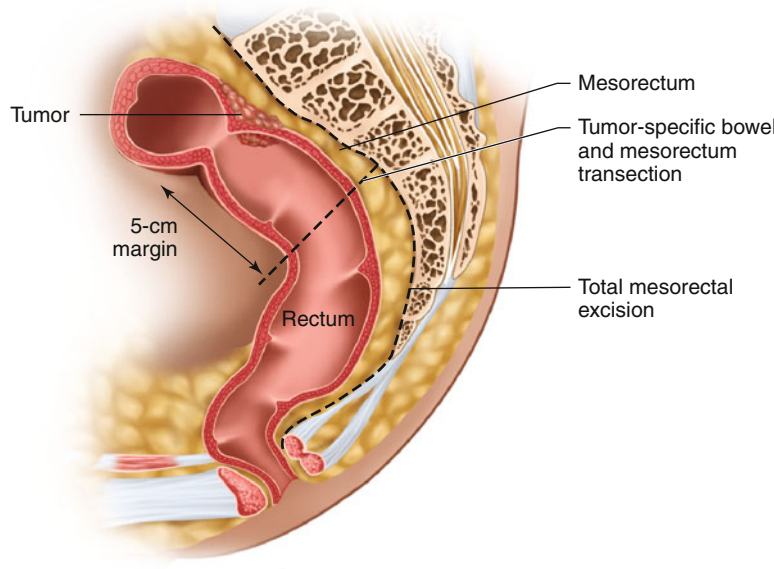

Fig. 12.8 Tumor Specific TME, TME in upper rectal cancer

node dissection is not necessary in the absence of clinically negative nodes in this region. Additionally, in a recent study from Washington University patients with enlarged lymph nodes in the lateral region on staging CT scan had no increase in local recurrence when treated with neoadjuvant chemoradiation therapy and no extended lateral lymphadenectomy [44].

Tumor Specific TME, Role of TME in Upper Rectal Cancer

The initial description of TME required a very low rectal anastomosis. The mesorectal excision would continue down to the pelvic floor and if the ischemic distal rectum was not removed it would lead to a very high leak rate. Pathological studies have suggested that distal mesorectal spread of cancer is less than 5 cm [45]. In fact, one study reported that no implants were seen beyond 1 cm of the tumor in patients who had T1 or T2 lesions [46]. Based on these results, complete removal of the entire mesorectum down to the pelvic floor is not necessary in all cases. A study from Mayo clinic included 272 patients with upper rectal cancers who underwent low anterior resection with tumor-specific mesorectal excision. This was done by performing a mesorectal excision to 5 cm below the tumor and transecting the mesorectum and rectum at a right angle at this point (Fig. 12.8). They reported local recurrence and 5-year disease free survival rates of 7 and 78 %, respectively [47]. Therefore, for proximal rectal cancers, distal mesorectal excision 5 cm below the lower border of the tumor is adequate.

Circumferential Radial Margin

Recently, there has been great emphasis on the importance of total mesorectal excision as it relates to circumferential radial margin. Quirke et al. showed that obtaining an adequate radial or CRM is critical for local control [48]. It also has

been shown that positive CRM is an independent predictor of local recurrence and decreased survival in patients who had appropriate operative treatment [49, 50]. Use of preoperative MRI and knowledge of the CRM can greatly aid in operative planning, specifically if an extra-levator approach for APR is necessary to obtain a negative CRM and reduce local recurrence [8].

Documentation Quality Analysis and Grading of TME

The operative report should communicate the preoperative evaluation, intraoperative findings, and technical details of the procedure, including extent of resection, anastomotic technique, anastomotic height, and en bloc resection of contiguously involved organs. Adverse events including tumor perforation should be clearly documented, because tumor perforation is associated with a significant increase in the risk of local recurrence and a reduction in 5-year survival [51]. Preoperative information including histological confirmation of malignancy, the estimated stage of the tumor based on preoperative imaging, the estimated level of the tumor in the rectum, and a description of preoperative treatments should be included as well [52]. Visualization of the seminal vesicles, splanchnic and lateral pelvic nerves and the lateral ligament makes the protection of autonomic nerves much easier. Clear anatomic driven dissection then becomes paramount in importance.

In recent years with mounting evidence showing the value of TME and CRM, there is a movement towards standardization of pathology reports to include the macroscopic quality of TME and microscopic CRM [53, 54]. It is recommended, therefore, that all specimens be graded for macroscopic quality of TME by trained pathologists. Descriptive reported grades include Complete (mesorectal plane), nearly complete (intra mesorectal plane), and Incomplete (visible muscularis propria). This demonstrates the importance of photo documentation (Figs. 12.9 and 12.10).

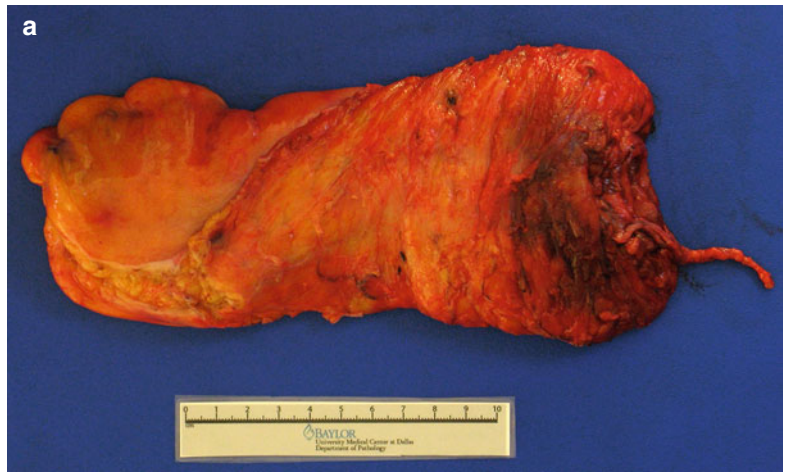

Fig. 12.9 (**a**) Photo of the posterior surface of an intact mesorectum after complete total mesorectal excision. Cross sections of complete TME, note the intact mesorectal envelope. (**b**) "Bread loafing" cross sections of a complete total mesorectal excision.

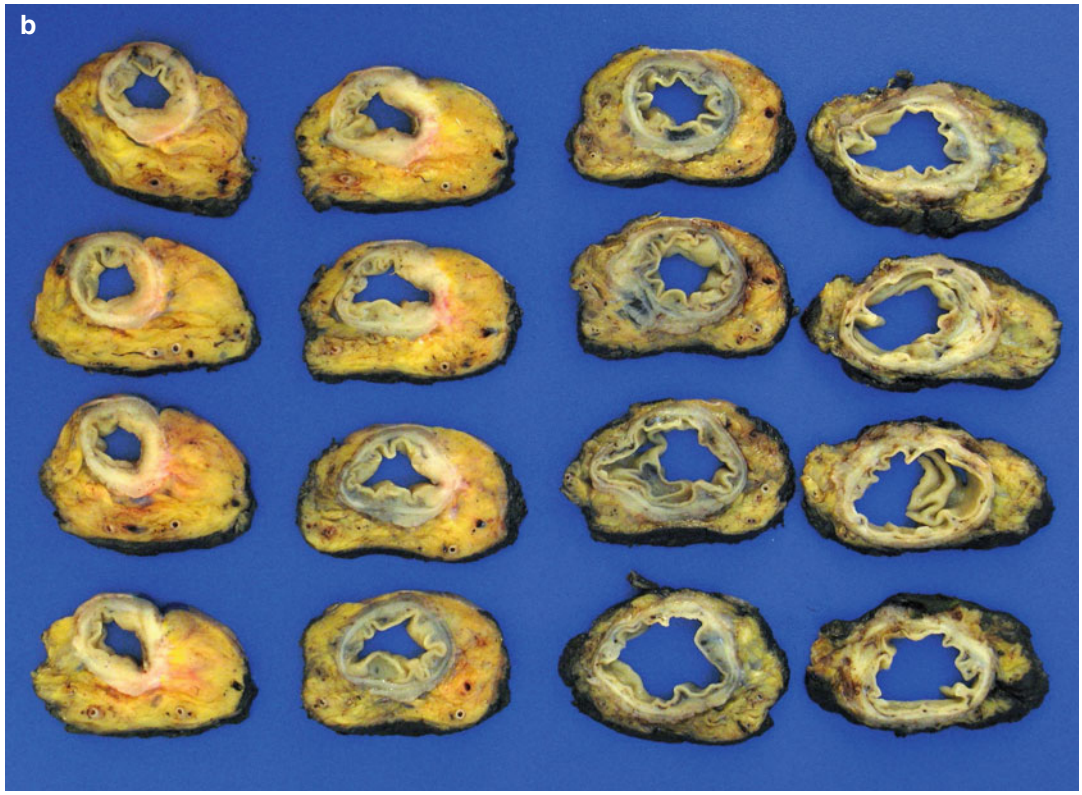

Fig. 12.9 (continued)

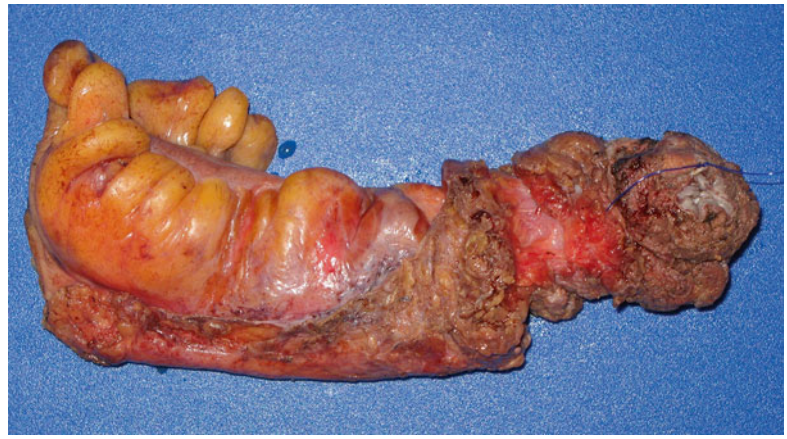

Fig. 12.10 Incomplete TME, note exposed muscularis propria

Summary

Complete surgical resection of tumor and draining lymph nodes remains the standard of care in the current treatment of rectal cancer. Local recurrence and survival is significantly improved by total mesorectal excision and obtaining negative circumferential radial margins. Attention to preservation of autonomic nerves can reduce morbidity of this operation.

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Lateral Lymph Node Dissection for Rectal Cancer

13

Shin Fujita and Kenjiro Kotake

Abstract

Lateral lymph node dissection for rectal cancer was introduced in the 1950s, but the procedure was later abandoned in the West because of high rates of associated morbidity and intraoperative bleeding. In Japan, however, lateral lymph node dissection is still the standard form of surgery for lower rectal cancer, and can be either prophylactic or therapeutic, depending on whether lateral pelvic lymph node metastasis is clinically absent or present, respectively. Because some patients with lateral lymph node metastasis can survive for more than 5 years after lateral lymph node dissection, the procedure should be attempted if technically feasible. However, the use of prophylactic lateral lymph node dissection remains controversial, even in Japan. Therefore, a randomized controlled trial (the JCOG0212 trial) to confirm the efficacy of prophylactic lateral lymph node dissection has been initiated. It is anticipated that the JCOG0212 trial will clarify the indications for prophylactic lateral lymph node dissection, and prove to be an important milestone in research on rectal cancer surgery.

Keywords

Lateral lymph node dissection • Lateral pelvic lymph node • Prophylactic dissection • Therapeutic dissection • JCOG0212 trial

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Introduction

Lateral lymph node dissection, a component of rectal cancer surgery, involves dissection of the lateral pelvic lymph nodes, which comprise the internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes. Metastasis to these nodes from lower rectal cancer occasionally occurs. Therefore, in Japan, lateral lymph

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node dissection for stage II or III lower rectal cancer is the standard operative procedure, and lateral pelvic lymph node metastasis is classified as lymph node metastasis. On the other hand, neoadjuvant chemoradiotherapy and total mesorectal excision (TME) without lateral lymph node dissection is the international standard treatment for rectal cancer, and lateral pelvic lymph node metastasis is considered to be distant metastasis in the TNM classification [1]. This article details the history, definition, rationale, procedure and future of lateral lymph node dissection for rectal cancer surgery.

History of Lateral Lymph Node Dissection

In 1895, Gerota described the upward and lateral lymphatic flow of the rectum [2] and, to our knowledge, this was the first report to document lateral rectal lymphatic flow. In 1927, Senba in Japan demonstrated the distribution of the lateral lymphatics around the internal iliac vessels and inside the obturator fossa [3]. These findings suggested that tumors in the rectum can spread upwardly and laterally by way of the upward and lateral lymphatics. In the 1950s, this new understanding of lateral lymphatic flow, and the high local failure rate after conventional rectal cancer surgery, led to Sauer and Bacon performing extensive lymphadenectomy [4] and to Sterns and Deddish performing abdominopelvic lymph node dissection [5]. However, use of these procedures did not yield the expected improvement in survival rate [5, 6], and was associated with higher rates of intraoperative bleeding and postoperative complications in comparison with conventional surgery [5]. Thereafter, reports on extended lymph node dissection including lateral lymph node dissection were rarely published except in Japan. Currently worldwide, neoadjuvant chemoradiotherapy and TME without lateral lymph node dissection are the standard treatments for rectal cancer.

Lateral lymph node dissection was introduced in Japan in the 1970s and the procedure decreased the incidence of local recurrence of rectal cancer and improved survival [7]. It then became widely accepted, and pelvic autonomic nerve-preserving lateral lymph node dissection was developed and refined from the mid-1980s [8]. Currently in Japan, lateral lymph node dissection and TME are still the standard procedure for lower rectal caner, and neoadjuvant chemoradiotherapy is not commonly used.

Definition of Lateral Pelvic Lymph Nodes

In the Japanese Classification of Colorectal Carcinoma [9], the internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes are defined as lateral pelvic lymph nodes, as indicated by the yellow circles in Fig. 13.1. The Japanese Classification employs a numbering system for lymph nodes, the internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes being numbered 263, 273, 283 and 293, respectively. The internal iliac nodes are divided into those distal and proximal to the superior vesical artery (umbilical artery), being defined as 263D and 263P, respectively. The presacral nodes (median (270) and lateral (260) nodes), sacral promontory (aortic bifurcation) nodes (280), and inguinal nodes (292) were also classified as lateral pelvic lymph nodes in the previous edition of the Japanese Classification of Colorectal Carcinoma [10]. These nodes are indicated as white circles in Fig. 13.1. Because the incidence of metastasis to these nodes from lower rectal cancer is rare [11], these nodes are no longer considered as lateral pelvic lymph nodes.

Rationale for Lateral Lymph Node Dissection

Lateral pelvic lymph node metastasis is found in about 15 % of cases of clinical stage II/III lower rectal cancer [12, 13]. Several studies from Japan have shown that the 5-year survival rate of patients with lateral pelvic lymph node metastasis is about 40 % [12–14], being comparable with that of patients with resectable liver or lung metastasis. Under the assumption that if lateral lymph node dissection not performed, local

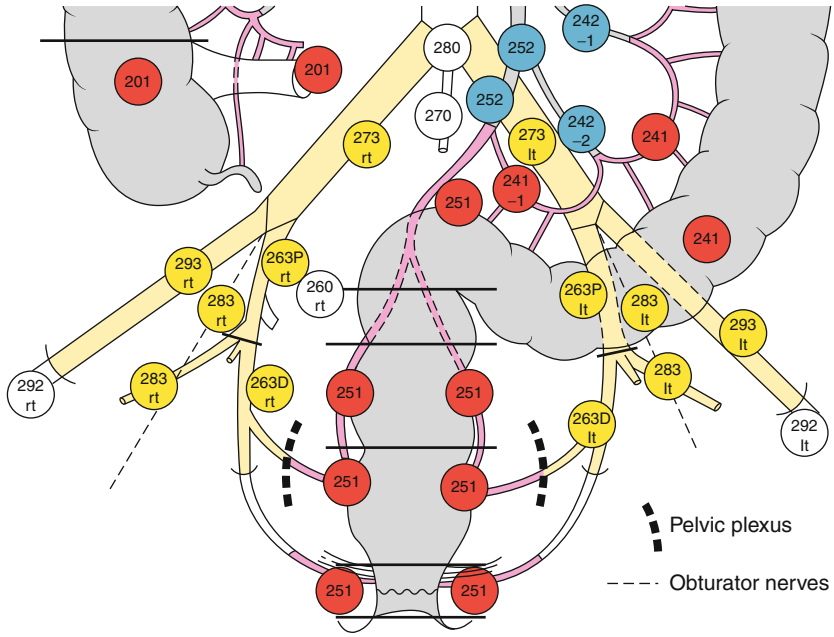

Fig. 13.1 Lateral lymph nodes (*yellow circles*) defined by the Japanese Classification of Colorectal Carcinoma. Internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes constitute the lateral pelvic lymph nodes (*white circles*). (*Red circles*) are pericolic/perirectal lymph nodes along the colon and the rectum and (*blue circles*) are intermediate lymph nodes along the major vesseles (From Japanese Society for Cancer of the Colon and Rectum [9])

recurrence would develop in the form of metastasis to these nodes and become the cause of death, the estimated improvement in the 5-year survival rate would be 6 % (0.15×0.4×100), because 15 % of patients with lower rectal cancer have lateral pelvic lymph node metastasis and 40 % of those who undergo lateral lymph node dissection will survive for more than 5 years. These figures would indicate that lateral lymph node dissection should be considered whenever lateral pelvic lymph node metastasis is suspected preoperatively. This option is known as therapeutic lateral lymph node dissection. The Guidelines 2000 for Colon and Rectal Cancer Surgery also mention that in the context of clinically suspected lateral lymph node disease, dissection should be attempted in order to remove these nodes, if it is technically feasible [15].

Figure 13.2 shows representative CT images of lateral pelvic lymph node metastasis. However, in patients without lymph node enlargement, not all lateral pelvic lymph node metastases can be demonstrated by CT or MRI, and sometimes they are only revealed after lateral lymph node dissection. Because the diagnostic accuracy of CT or MRI for lateral pelvic lymph node metastasis is imperfect [16, 17], lateral lymph node dissection is also indicated in Japan even for patients without evident enlargement of such nodes. This option is known as prophylactic lateral lymph node dissection. However, even in Japan, the indications for prophylactic lateral lymph node dissection are controversial. Therefore, on behalf of the Japan Clinical Oncology Group (JCOG), a randomized controlled trial to confirm the efficacy of prophylactic lateral lymph node dissection is currently underway (the JCOG0212 trial) [18]. Because primary analysis of the trial results is planned for 2015, no survival data are yet available. In terms of morbidity and mortality, the rates of grade 3–4 postoperative complications were similar between mesorectal excision with lateral lymph node dissection and mesorectal excision alone. At the European Cancer Congress in 2013, urinary and sexual functions after this form of surgery were also reported to be similar in these two groups [19, 20]. A previous meta-analysis of extended lateral lymph node dissection had suggested that it was associated with an increased

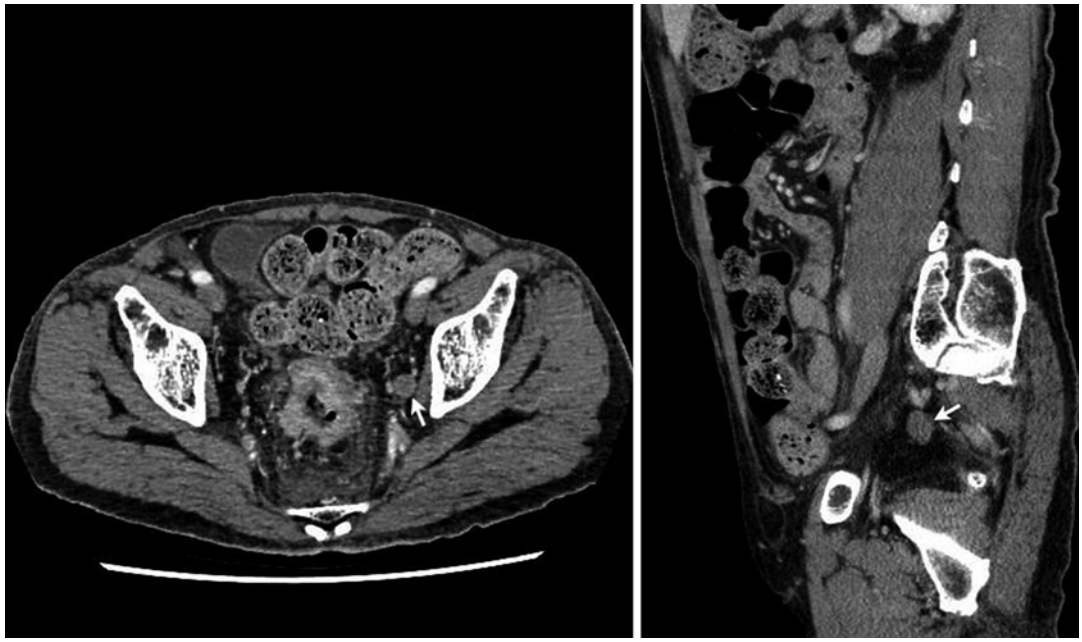

Fig. 13.2 Representative CT images (axial and sagittal sections) of lateral lymph node metastasis. Left latelaral pelvic lymph node enlargement is seen (*arrows*)

risk of urinary and sexual dysfunction, and did not confer any survival benefit [21]. This may have been due to the fact that previous retrospective studies of lateral lymph node dissection had included both autonomic nerve-preserving surgery and non-preserving surgery. In the JCOG0212 trial, however, autonomic nerve-preserving surgery was performed for all of the enrolled patients, thus accounting for the similarity of postoperative urinary and sexual functions between the groups. It is anticipated that the JCOG0212 trial will yield informative data for evaluation of prophylactic lateral lymph node dissection.

Indication Criteria for Lateral Lymph Node Dissection

The indication criteria for lateral lymph node dissection are stipulated in the 2010 Japanese Society for Cancer of the Colon and Rectum guidelines for the treatment of colorectal cancer [22]. Lateral lymph node dissection is indicated when the lower border of the tumor is located distal to the peritoneal reflection and has invaded beyond the muscularis propria (T3 or T4). This criterion is based on retrospective risk analysis of lateral pelvic lymph node metastasis [12]. The incidences of lateral pelvic lymph node metastasis in cases of clinical stage I rectal cancer and for tumors whose lower margin is located above the peritoneal reflection are very low. The lower border of the tumor is an important aspect of this criterion, because lateral lymphatic flow in the rectum exists below the peritoneal reflection. It is not appropriate to include the distance from the anal verge to the lower border of the tumor as part of the indication criteria, because the distance from the anal verge to the peritoneal reflection differs among individual patients.

Therapeutic and Prophylactic Lateral Lymph Node Dissection

As mentioned in the previous section, there are two types of procedure for lateral lymph node dissection: therapeutic and prophylactic. If a patient with rectal cancer has no clinical evidence of lateral pelvic lymph node metastasis,

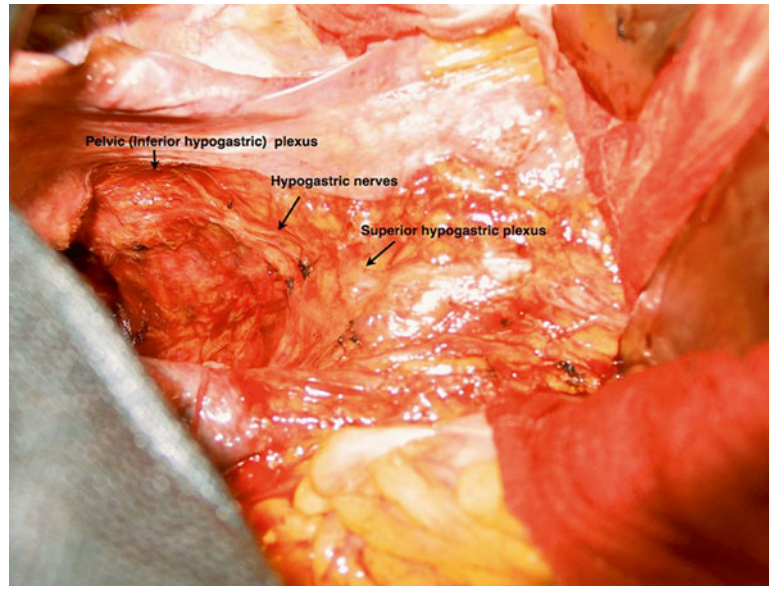

Fig. 13.3 Autonomic nerves in the pelvis. The superior hypogastric plexus, hypogastric nerve, and pelvic (inferior hypogastric) plexus can be identified

prophylactic dissection is indicated, whereas therapeutic dissection is indicated if such metastasis is present. Therapeutic and prophylactic dissection differ in their area of dissection and level of nerve preservation. In therapeutic dissection, the internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes are dissected, and the presacral and sacral promontory nodes are also dissected when metastasis is suspected. The autonomic nerves on the side where metastasis is suspected are resected. Therefore, if bilateral lymph node metastasis is suspected, the autonomic nerves are not preserved. In prophylactic dissection, the internal iliac nodes, common iliac nodes, obturator nodes and external iliac nodes are dissected, but the presacral and sacral promontory nodes are not. All of the autonomic nerves are preserved in principle.

The anatomy of the autonomic nervous system in the pelvis is an important point to consider for preservation of the autonomic nerves in rectal cancer surgery. Figure 13.3 shows the autonomic nerves after TME. Those in the pelvis include the superior hypogastric plexus, hypogastic nerve, pelvic (inferior hypogastric) plexus and pelvic splanchnic nerve. Identification of these autonomic nerves during surgery is very important for ensuring their preservation. Preservation procedures will be described in the next section.

Procedure for Prophylactic Lateral Lymph Node Dissection

In this procedure, the internal iliac nodes, common iliac nodes, obturator nodes, and external iliac nodes are dissected and the autonomic nerves are preserved. During the dissection, if any lymph nodes with metastasis are confirmed, the dissection is converted to therapeutic lymph node dissection.

Confirmation of Autonomic Nerves

After mobilization of the sigmoid colon and upper rectum, the superior hypogastric plexus can be identified at the level of the aortic bifurcation (Fig. 13.4). The fibers extending from the superior hypogastric plexus to the right and left sides of the rectum are the hypogastric nerves. These are important landmarks for ensuring that the plane of dissection stays anterior and medial to the plexus and hypogastric nerves. If this plane is maintained, these nerves and the pelvic plexus can be preserved without difficulty. Recently, an ultrasonic scalpel (Harmonic Scalpel®) or an electrothermal bipolar tissue sealing system (Ligasure®) has been commonly used for lateral lymph node dissection, especially in laparoscopic surgery.

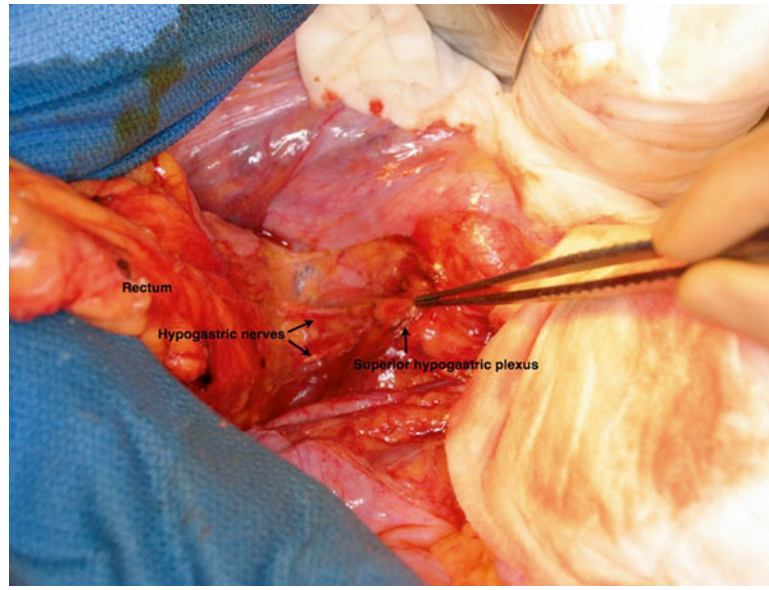

Fig. 13.4 Superior hypogastric plexus and hypogastric nerves. The superior hypogastric plexus has been picked up with forceps

Common and Proximal Internal Iliac Node Dissection

First, the ureters are exposed bilaterally, and then the ureters, the superior hypogastric plexus and the hypogastric nerves are lifted using retraction tapes to prevent accidental injury. The dissection begins along the inner side of the common and internal iliac vessels downward to the superior vesical artery while removing the fatty tissue covering the vessels. This fatty tissue includes the common and proximal internal iliac nodes. Within the layer just above the vessels, it is easy to dissect the fatty tissue and blood loss will be minimal. In prophylactic dissection, only the inner side of the common iliac vessels is dissected. After inner side resection, the fatty tissue along the outer side of the internal iliac artery is dissected. This area lies between the internal and external iliac vessels. Thereafter, dissection of the external iliac lymph nodes is performed.

External Iliac Lymph Node Dissection

The external iliac vessels are picked up using retraction tapes, and the fatty tissues only along the inner side of the vessels are dissected. After external iliac lymph node dissection, the internal obturator muscle is identified below and outside the external iliac vessels. This represents the lateral limit of lateral lymph node dissection.

Obturator Lymph Node Dissection

The obturator lymph nodes lie in the obturator fossa. At the center of the fossa, the obturator nerve runs in a cranial to caudal direction. Because the nerve is an important dissection landmark, it should be located before initiating lymph node dissection. The nerve is picked up using a retraction tape and the fatty tissues in the area are resected. The only major vessels are the obturator vessels in the fossa, and care should be taken to avoid them during the dissection to prevent bleeding. The distal limit of lateral lymph node dissection is the obturator membrane, and the dorsal limit is the piriformis muscle and sciatic nerves.

Distal Internal Iliac Node Dissection

Finally, the distal side of the internal iliac vessels is dissected, in the area between the superior vesical artery and inferior vesical artery. During the dissection, the pelvic plexus connected with

the hypogastric nerve should be located. This plexus is about 3 cm long and less than 1 mm thick. If the middle rectal artery is found, it should be ligated and cut. After the dissection, prophylactic lateral lymph node dissection is completed on the unilateral side, and resection is then performed on the other side in the same manner. Figure 13.5 shows dissected fatty tissues on the left side. The common iliac, internal iliac, and obturator lymph nodes are included among these fatty tissues.

Figures 13.6 and 13.7 are intraoperative photographs taken after prophylactic dissection, and show the preserved nerves. Figure 13.8 shows the obturator fossa after dissection, the obturator nerve and obturator vein being preserved.

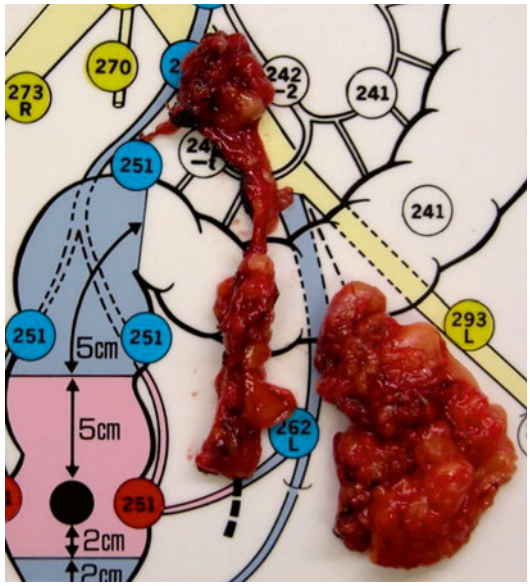

Fig. 13.5 Fatty tissues in the left pelvis removed during lateral lymph node dissection

Procedure for Therapeutic Lateral Lymph Node Dissection

If lateral lymph node metastasis is evident, the autonomic nerves should not be preserved because metastasis and direct tumor invasion are sometimes found around the nerves. If an enlarged lymph node is found during the dissection, frozen section diagnosis is important. If metastasis is negative, prophylactic lymph node dissection may be indicated. If positive, therapeutic lymph node dissection should be done.

In therapeutic dissection, unlike prophylactic dissection, the presacral nodes and sacral promontory nodes are optionally dissected. If enlargement of these nodes is detected, they should be dissected. Because the incidence of lymph node metastasis is low, routine dissection of the nodes is unnecessary.

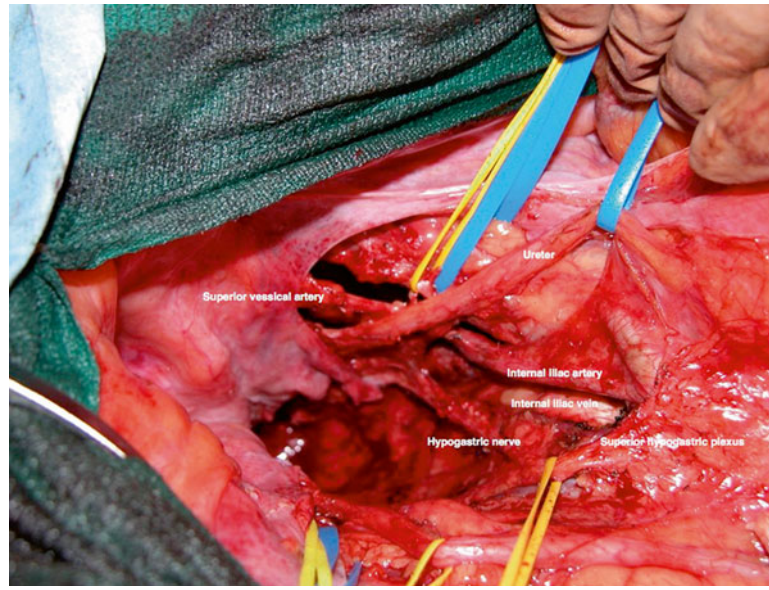

Fig. 13.6 Intraoperative photograph showing the situation after prophylactic lateral lymph node dissection. The superior hypogastric plexus and the hypogastric nerves have been preserved

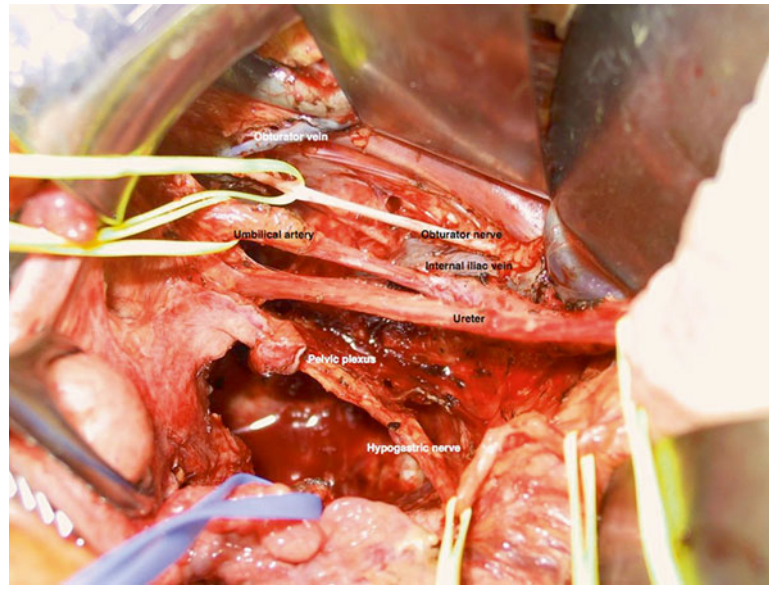

Fig. 13.7 Intraoperative photograph showing the situation after prophylactic lateral lymph node dissection. The pelvic plexus and hypogasric nerve have been preserved

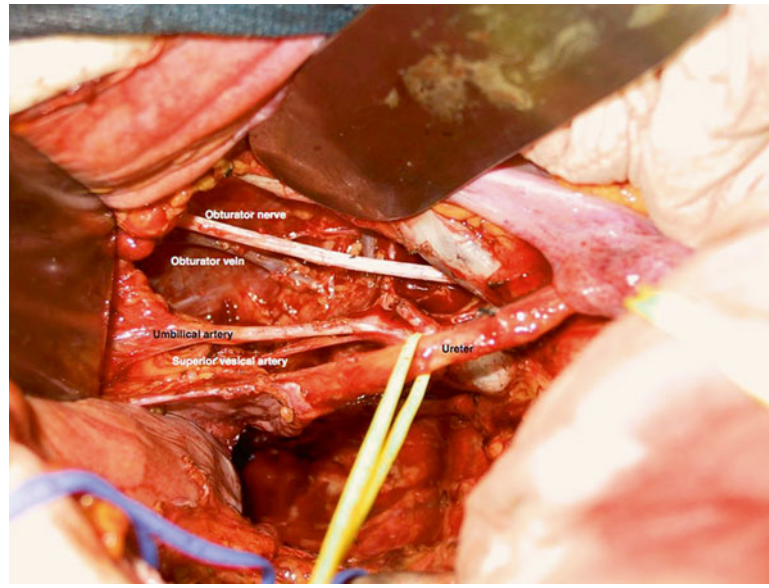

Fig. 13.8 The obturator fossa after prophylactic lateral lymph node dissection

If all the autonomic nerves are resected, the patient's quality of life is compromised because of sexual and urinary dysfunction. Therefore, partial preservation of the autonomic nerves should be performed, if indicated. For example, the autonomic nerves contralateral to any lateral pelvic lymph node metastasis should be preserved. The grade of preservation of autonomic nerves is defined in the Japanese Classification of Colorectal Carcinoma (Fig. 13.9) [9]. The degree of autonomic nerve preservation is classified into five categories. Historically, the lumbar splanchnic nerves and superior hypogastric plexus have been resected for clinical stage II/III rectal cancer in Japan. For this reason, many operations were classified as AN1 or AN0 therapeutic pelvic lymph node dissection. However, the number of such operations is decreasing as

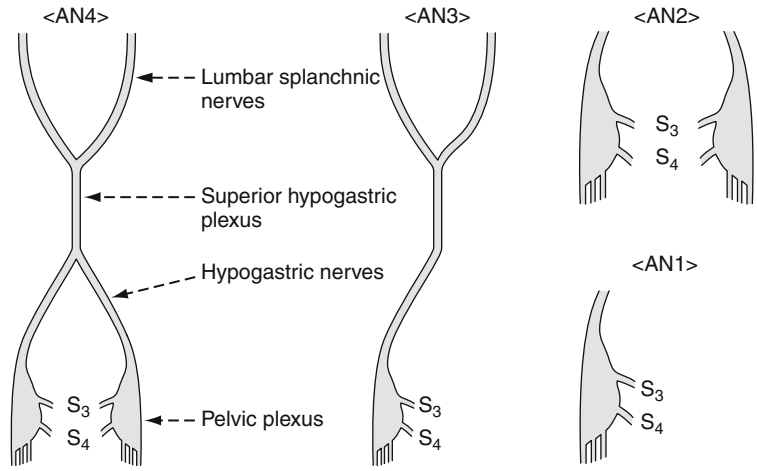

Fig. 13.9 Grade of preservation of autonomic nerves defined in the Japanese Classification of Colorectal Carcinoma (From Japanese Society for Cancer of the Colon and Rectum [9])

ANO	No autonomic nerves are preserved
AN1	Only unilateral pelvic plexus are preserved
AN2	Only bilateral pelvic plexus are preserved
AN3	All the autonomic nerves except unilateral pelvic plexus are preserved
AN4	All the autonomic nerves are preserved

efforts are made to preserve the autonomic nerves. Currently, AN3 is the main preservation pattern for therapeutic dissection.

1. Presacral and sacral promontory node dissection

   If presacral or sacral promontory lymph node metastasis is suspected, the fat tissues at these sites are removed and the superior hypogastric plexus is cut at the aortic bifurcation. If no metastasis is found in the nodes, the lymph node dissection can be omitted and the superior hypogastric plexus is preserved.
2. Common and proximal iliac node dissection

   This dissection is the same as that for prophylactic dissection. The difference is the combined resection of the autonomic nerves.
3. Resection of the autonomic nerves

   The hypogastric nerve and the pelvis plexus should be resected en-bloc with the rectum. On the distal side of the hypogastric nerve, the pelvic plexus can be identified. The pelvic plexus is resected partially or totally depending on the extent of the primary tumor, and that of the lateral pelvic lymph node metastasis. Because the plexus includes the hypogastric nerve and the pelvic splanchnic nerves from the sacral nerves S2, S3 and S4, the plexus is cut at the level of the pelvic splanchnic nerves from S2 or S3, when the plexus is preserved. If the primary tumor or lateral pelvic lymph node metastasis is extensive, the pelvic plexus should be totally resected. However, there is no consensus among Japanese surgeons with regard to the indications for partial preservation of the plexus.

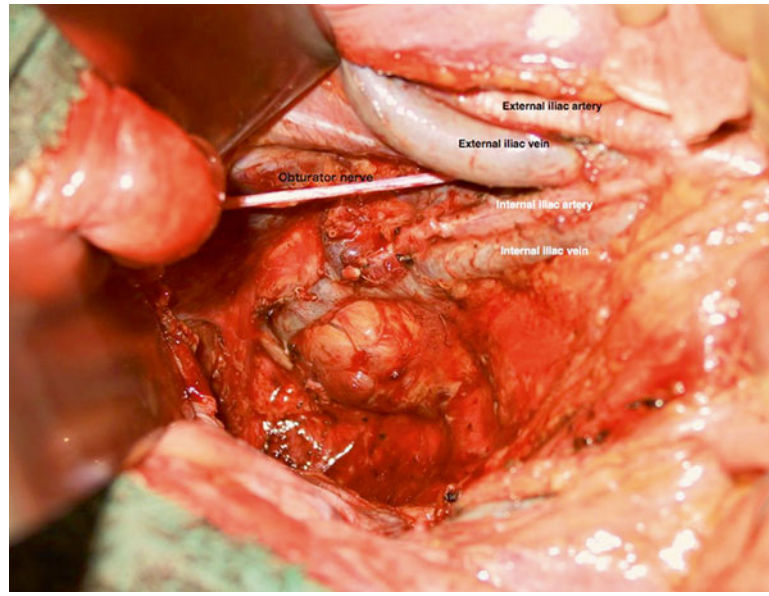

Fig. 13.10 Intraoperative photograph showing the situation after therapeutic lateral lymph node dissection. Only the obturator nerve and the internal iliac vessels have been preserved. The superior hypogastric plexus was preserved in this case

4. External iliac node dissection
5. Obturator lymph node dissection
6. Distal internal iliac node dissection

These dissections are same as those for prophylactic dissection. The difference is resection of the obturator vessels and the superior vesical artery. The vessels are ligated and cut at the distal and proximal ends in the pelvis. After resection on one side, resection is performed on the other side. If lateral pelvic lymph node metastasis is also evident on the contralateral side, therapeutic resection is also performed. If lateral pelvic lymph node metastasis is not suspected on the contralateral side, prophylactic resection is performed. Figure 13.10 shows the situation after therapeutic lateral lymph node dissection. The pelvic plexus, hypogastric nerve, pelvic splanchnic nerves, and vessels except for the obturator nerve and internal iliac vessels, are resected.

Future of Lateral Lymph Node Dissection

The results of the JCOG0212 trial will have a very important impact. If they indicate that prophylactic lateral lymph node dissection is superior to TME alone, then surgeons outside Japan will need to consider prophylactic lateral lymph node dissection as a standard operation for lower rectal cancer. A clinical trial to compare TME plus neoadjuvant chemoradiotherapy and lateral lymph node dissection will also be necessary. On the other hand, if the JCOG0212 trial demonstrates that TME alone is not inferior to prophylactic lateral lymph node dissection, then lateral lymph node dissection will not be indicated for patients without clinical evidence of lateral pelvic lymph node metastasis. However, the controversy regarding therapeutic lateral dissection for patients with clinical evidence of lateral pelvic lymph node metastasis remains.

Conclusion

More than 100 years after the first description of lateral lymphatic flow in the rectum and more than 50 years after the introduction of lateral lymph node dissection, the JCOG0212 trial marks a milestone of research on lateral lymph node dissection. This trial will clarify the indications for prophylactic lateral lymph node dissection and we anticipate that the results will mark an important step in rectal cancer surgery.

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Laparoscopic and Robotically Assisted Proctectomy

14

A. Craig Lynch

Abstract

Laparoscopic rectal surgery is technically challenging, with a clearly described learning curve. It has been shown to be feasible and safe and offers the advantages of a minimally invasive approach. Studies have demonstrated a similar mesorectal dissection with oncologically acceptable outcomes.

Current data supports robotic proctectomy as being as oncologically effective and safe as a laparoscopic approach. Advantages of a robotic approach to proctectomy include stable three-dimensional visualisation, a comfortable operating position and articulated instruments for improved dexterity.

Studies and meta-analyses to date have suggested that this results in a better quality mesorectal dissection with at least a similar oncological outcome to a laparoscopic approach with fewer conversions to open surgery and less genitourinary dysfunction. The results of currently recruiting multinational randomised studies are awaited.

Keywords

Laparoscopy • Robotic surgery • Rectal cancer • Proctectomy • Rectal surgery • Minimally invasive surgery

Laparoscopic Proctectomy

Introduction

Laparoscopic colorectal surgery has consistently been shown to be feasible and safe. It has the potential to offer many short-term advantages to patients in terms of post-operative recovery and chance of major complications. In fact in elderly patients having treatment for colonic

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cancer, randomized data would suggest that their chance of a major complication is significantly reduced [1].

Benefits seen with minimally invasive colonic surgery have been shown to translate to proctectomy, however there has been concern regarding oncologic outcomes that have limited its uptake. A minimally invasive surgical resection of a rectal cancer is a technically challenging undertaking requiring mobilization of bowel in multiple abdominal, dissection and transection of major vessels, safe specimen extraction after an appropriately-performed rectal dissection, then re-anastomosis.

The rectal resection itself requires a different technique from colon cancer. The gold standard total mesorectal excision (TME) requires precise dissection in the mesorectal plane, necessitating controlled traction and adequate vision [2].

This is technically demanding given the narrow confines of the pelvis making laparoscopic instrument manipulation difficult. The skill of the assistant are often as important as the surgeon as the procedure relies on a capable camera operator, skilled at providing appropriate counter traction during pelvic dissection.

Technique

For laparoscopic proctectomy, the patient is placed in modified low lithotomy position with legs in Allen® Yellofins® Stirrups (Allen Medical Systems, Inc.). A urinary catheter is inserted. The thighs need to be fully extended and arms tucked by the sides in order to maximize mobility of instruments during multi-quadrant dissection. The buttocks need to be over the end of the table to facilitate access for anastomotic stapling. Ensuing the patient is well fixed to the table with either a 'beanbag' or appropriate strapping is important to maintain positioning during the steep head-down maneuvers required for pelvic dissection. The beanbag needs to be wrapped over the shoulders and clear of the perineum [3].

Port placement entails a 12 mm camera port placed at the umbilicus by Hassan technique, usually a 30-degree laparoscope is required to allow adequate visualization. Two operating ports are placed under direct vision on the right side, usually lateral to the lateral border of rectus, the lowermost trocar positioned to allow adequate reach into the pelvis, but not so low as to compromise reach to the splenic flexure or access over the pelvic brim to the deep pelvis, this can be a 10 mm port if access for stapling is contemplated, otherwise both are 5 mm. A third assistant port is placed in the left lower quadrant. Sometimes if access is compromised a further suprapubic 10 mm port may be required to allow stapler access in a narrow pelvis.

The patient is initially positioned in steep Trendelenburg position, left side up, the omentum placed high over the stomach and liver and the small bowel manipulated out of the pelvis into the right upper quadrant. Initial colonic mobilization can be carried out in a medial to lateral or lateral to medial direction. Medial to lateral mobilization has the advantage of identifying major structures such as the Inferior mesenteric artery (IMA) and left ureter early in the procedure minimizing the risk of late conversion to an open procedure.

The IMA is identified, and retracted in an upward direction. The peritoneum is incised with diathermy or an energy device along the vessel's inferior border. This opens a retroperitoneal window that can be dissected and developed laterally to identify the left ureter. This is dissected posteriorly away from the colonic mesentery. The base of the IMA can then be dissected, care being taken to preserve inferior hypogastric nerves, before the vessel is divided with a vessel sealer, clips or staples. The distal divided end of the IMA can then be elevated to facilitate further development of the retrocolic plane towards the splenic flexure. The inferior mesenteric vein (IMV) is then isolated and divided at the lower border of the pancreas. Dissection can then continue along the lateral attachments of the sigmoid and left colon towards the splenic flexure. As the flexure is approached the patient is placed in a reverse-Trendelenburg position to assist with caudal retraction of the colon as the lateral attachments of the flexure are divided, the omentum mobilized free of the distal transverse colon and

the lesser sac entered. It is important that full splenic flexure mobilization is accomplished to allow adequate colonic mobilization for anastomosis.

When mobilization is completed the patient is returned to a Trendelenburg position and pelvic dissection commenced using the assistant to maintain adequate counter-traction on the rectum. Care is taken to identify and preserve left and right hypogastric nerves. The initial posterior dissection is developed through Waldeyer's fascia to the pelvic floor or as low as thought necessary for the tumour position. The right and left sides are then developed in a semicircular fashion, again using counter-traction on the mesorectum, and finally the anterior dissection is performed with steady downwards retraction on the rectum and upwards counter-traction on the base of the bladder. Denonvillier's fascia is the anterior landmark for preserving an intact mesorectum if an oncologically appropriate resection is to be performed, and dissection should continue precisely outside this fascia where, in males, the hypogastric nerves are at risk between fascia and seminal vesicles.

When the appropriate level for resection is reached, the rectum is divided at right angles with an endoscopic stapler.

It is then exteriorized through a small midline or left iliac fossa muscle splitting incision protected by a wound protector such as an Alexis® Wound retractor (Applied Medical Resources Corporation, Rancho Santa Margarita, CA).

The proximal colon is divided, the vascular pedicle identified and the proximal end of the IMA resected with the specimen to ensure adequate lymph node harvest. An anvil is then fixed in the proximal bowel end with a purse-string suture, the bowel returned to the abdominal cavity, pneumoperitoneum re-established, and stapled anastomosis performed [4].

If the patient is to have an abdomino-perineal resection (APR) the distal dissection is continued as far distal as thought appropriate, the colon divided proximally with a stapler and the proximal end exteriorized via a previously marked colostomy site and matured. The perineal dissection is then performed in the usual fashion.

Hand-Assisted Laparoscopic Proctectomy (HALS) and Single-Port Techniques

The development of hand-access ports in the 1990s has enabled surgeons to insert a hand into the abdominal cavity without consequent loss of pneumoperitoneum. This allows use of the hand as a retractor and provides enhanced tactile feedback compared to a purely laparoscopic approach. The incision required for the port is small and usually similar to that required for specimen extraction. Studies comparing a standard laparoscopic vs. hand-assisted approach have shown similar oncological outcomes [5]. Tjandra et al. demonstrated a shortening of operating time for the HALS group (169.8 vs. 188.2 min; $p < 0.0001$) [6].

Approaches to rectal dissection using a single laparoscopic port for all laparoscopic instruments have also been reported, and while feasible, with similar oncological results reported as in laparoscopic cases, it is a difficult technique with a moderate to high chance of requiring conversion to a multiport technique [7].

Outcomes

Short-term outcomes for laparoscopic and open proctectomy has been shown to be very similar. For the CLASICC trial, no difference in short-term morbidity or mortality was identified. The American College of Surgeons NSQIP study showed that laparoscopic rectal cancer surgery took longer but resulted in fewer blood transfusions, shorter hospital stay (by 2 days) and less morbidity (21 % vs. 29 %) [8].

Laparoscopic Learning Curve

Laparoscopic rectal dissection is complex with a learning curve that is thought to continue beyond 120 cases [9]. Comparisons with right-sided colonic resections have shown that, using conversion rates as an indicator, surgeon experience is an independent predictor of conversion with a learning curve approaching 50 cases [10]. The

two main patient factors resulting in increased conversions are a narrow male pelvis and increased Body Mass Index (BMI) [11].

The CLASICC trial required surgeons to have completed a minimum of 20 colorectal resections. There was concern that this was still relatively early in the surgeons' laparoscopic proctectomy learning curve and contributed to the higher than expected conversion rate to open surgery [12]. The COREAN trial, randomizing T3N0-2 patients to laparoscopic or open surgery after neoadjuvant therapy had a much lower conversion rate for the laparoscopic group (2/170, 1.2 %), influenced not only by lower BMI (24.1 kg/mÇ versus CLASICC 26 kg/mÇ), but also greater surgeon experience with the seven surgeons contributing to the trial having performed a median of 75 resections [13].

Oncological Outcome

Laparoscopic rectal surgery has been shown to be an oncologically acceptable procedure [14]. Studies have demonstrated that an oncologically appropriate TME can be performed and large case series have shown similar outcomes and survival [15].

One important component of the assessment of a procedure's oncological outcome is the quality of the resected rectal specimen. An adequate TME specimen requires an intact mesorectal fascia with a smooth surface without evidence of tearing or mesorectal defects [16]. Early results from the CLASICC trial demonstrated a slightly higher but non-significant increase in positive CRM for those having laparoscopic anterior resection. This was 16 (12 %) of 129 laparoscopic anterior resections vs. 4 (6 %) of 64 open cases, $p = 0.19$. There was no difference for those having APR (10 (20 %) of 49 laparoscopic and 7 (26 %) of 27 open, $p = 1$) [12].

The European Colon Cancer Laparoscopic or Open Resection (COLOR II) trial was designed as a randomised, international multicentre study to specifically examine the question of laparoscopic rectal cancer surgery. One Thousand one hundred and three patients with rectal cancer within 15 cm of the anal verge were randomised to either open or laparoscopic surgery [17]. Patients with T3 cancers within 2 mm of the endopelvic fascia and T4 tumours were excluded. Short-term outcomes have been published. These demonstrated the laparoscopic resections to be similar in extent with similar rates of intraoperative complications, morbidity and mortality to the open procedures. The CRM positivity rate was similar in both groups (10 %, $p = 0.850$) of note, however, was that the rate was lower for the laparoscopic group with tumours in the lower 5 cm of the rectum (15/165, 9 % for the laparoscopic group vs. 17/79 (22 %) for the open group, $p = 0.014$).

Adherence to a mesorectal excision, either complete or to 5 cm distal to the lower margin of the tumour was required, and all dissection of the mesorectum had to be completed laparoscopically to qualify as a laparoscopic case, otherwise it was classified as an open conversion. Pre-study screening of surgeons by assessment of five consecutive cases was required to be included as an operating surgeon on the study.

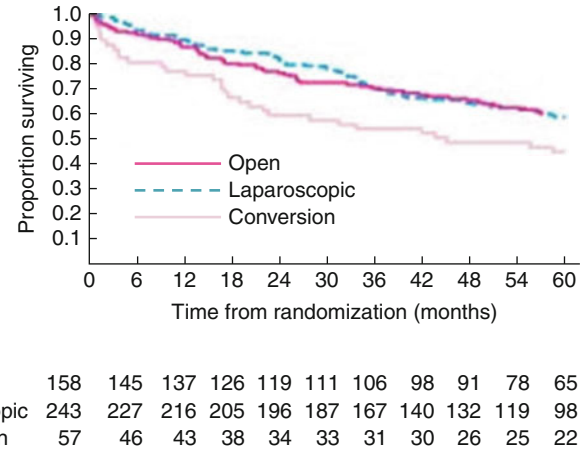
Five year follow-up of the CLASICC data however did not demonstrate a difference in survival for these patients (60.3 % for laparoscopic vs. 52.9 for open cases $p = 0.132$). There was no difference for either anterior resection or abdomino-perineal resection (APR).

Local recurrence was similarly not significantly different; 9.4 % for open versus 9.4% for laparoscopic anterior resection vs. 7.6 % for open, $p = 0.740$.

Of note those patients converted to open surgery did significantly worse, even when controlled for surgeon related factors (Fig. 14.1) The reason for this is unclear. The most common reason cited for conversion was 'advanced cancer pathology' however the cancer specific survival does not reflect this [14].

Functional Outcome

Urinary and sexual dysfunction following rectal resection for cancer has historically been



No. at risk											
Open	158	145	137	126	119	111	106	98	91	78	65
Laparoscopic	243	227	216	205	196	187	167	140	132	119	98
Conversion	57	46	43	38	34	33	31	30	26	25	22

Fig. 14.1 Five-year overall survival by actual procedure for all patients randomized by surgeons with a lower than average conversion rate (log rank test): $p = 0.013$ (Wilcoxon test) (From Jayne et al. [14])

reported as being as high as 30–40%, especially after APR. The adoption of TME dissection and autonomic nerve sparing techniques have gone some way to reducing this, however there are still risks to urinary and sexual function.

Quah et al. showed a greater deterioration in sexual activity after laparoscopic compared to open laparoscopic surgery [18].

Jayne found similar outcomes in his analysis of the CLASICC trial data [19]. Of the 247 (71.2 %) who completed questionaries 98 had a laparoscopic rectal resection and 50 an open resection. The rate of severe sexual function change in males following open rectal resection was 23 %, in keeping with previous studies. Sexual function tended to be worse after laparoscopic rectal TME, especially for erectile dysfunction. Performance of a complete TME gave a sixfold increase in the chance of postoperative sexual dysfunction compared to a partial mesorectal dissection.

A recent systematic review, seeking to synthesize expert opinion in the literature found that while there had been growing acceptance of laparoscopic colonic surgery for some time, a laparoscopic approach to rectal cancer remains controversial (Fig. 14.2) [20]. There is no doubt that laparoscopic proctectomy is a complex procedure, however in expert hands, the current evidence would suggest that long term oncologic outcomes are similar to an open approach but more randomized, long term data is needed.

Robotic- Assisted Proctectomy

Robotic-assisted proctectomy, undertaken using the da Vinci™ system (Intuitive Surgical, Sunnyvale, CA, USA) was first reported in 2003 [21]. It is apparent that there are a number of features of the robotic system that have the potential to reduce or eliminate some of the inherent problems associated with a laparoscopic approach.

The operating surgeon can be comfortably seated at the robotic console that presents a stable three-dimensional high-definition image (Fig. 14.3). Three operating and one camera arms are mounted on a patient-side cart with the instruments being inserted through ports similar to standard laparoscopic ports. The ports themselves are positioned so the 'zero-point' of the robotic instrument is centred in the patient's abdominal wall. The movements of the arm and instrument are coordinated to keep this point stationary to minimise trauma to the abdominal wall. The surgeon is in full control of the laparoscopic camera and is not reliant on an assistant to maintain position or orientation. The robotic instruments are wristed and capable of precise dexterous movements controlled by the surgeon through an intuitive console system (Fig. 14.4). Instrument movement can be scaled and tremor eliminated. The console does not provide haptic feedback that can make discrimination of tissue consistency difficult and requires care when placing traction on delicate structures or when knot-tying. Movement is possible through 7° of

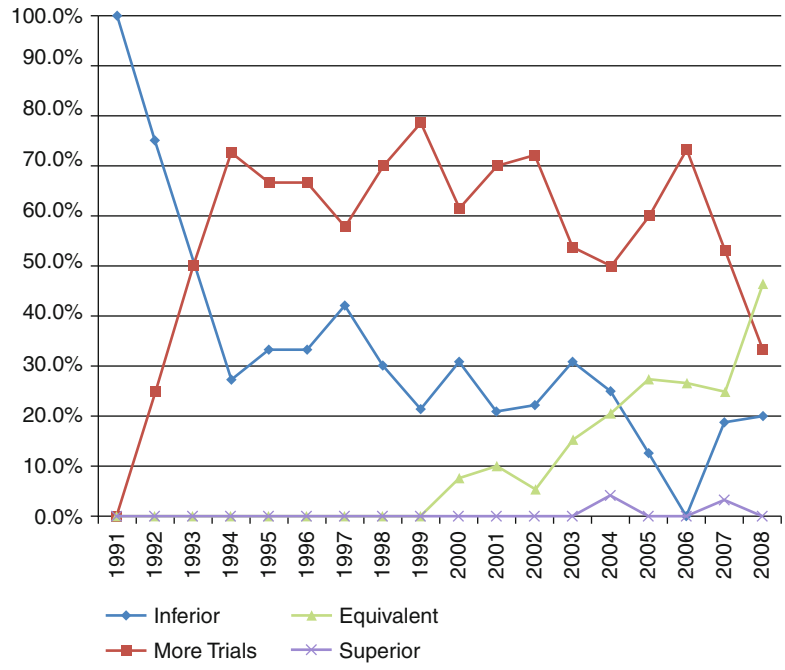


Fig. 14.2 Temporal summary of expert opinion in the literature pertaining to laparoscopic surgery for rectal cancer (From Martel et al. [20])

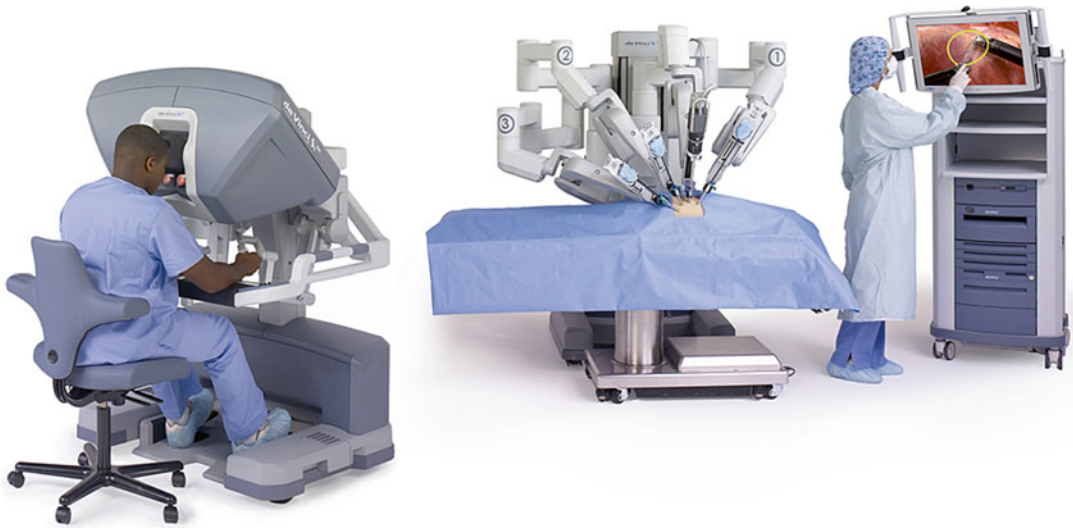


Fig. 14.3 The surgeon at the console and the patient side cart of the da Vinci Si HD Surgical System (http://www.intuitivesurgical.com) (From Freschi et al. [22])

freedom, 180° of articulation and 540° of rotation [22]. The robot itself has undergone a number of iterations, initial versions of the robot had one fewer operating arm and a more limited range of movement requiring adaption of docking techniques in order for the operating instruments to adequately reach all quadrants of the abdomen. At this point, the third generation, da Vinci Si HD is the current evolution.

Technique

Given that a proportion of the colonic mobilisation in proctectomy does not require the precise manipulative skills of the robot a number of 'hybrid' techniques have been developed where the initial component of the dissection is performed laparoscopically: usually the splenic flexure take-down, and then the cart is docked

Fig. 14.4 The daVinci master control interface used to remotely manipulate the wristed robotic instruments tip (From Freschi et al. [22])

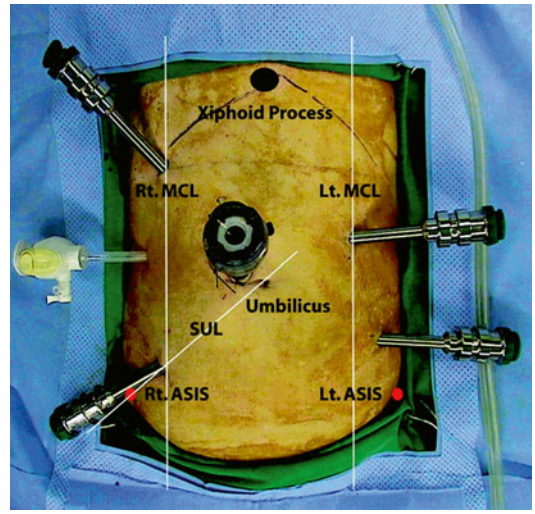


Fig. 14.5 The layout of the port placement for single-stage robotic low anterior resection. *MCL* midclavicular line, *SUL* spinoumbilical line, *ASIS* anterior superior iliac spine, *Rt.* right, *Lt.* left (From Choi et al. [23])

for IMA mobilisation and division and pelvic dissection.

Port placement is dependent of whether a hybrid or totally robotic technique is being undertaken. In either case the 12 mm camera port is usually placed just above and to the right of the umbilicus. It is important to allow adequate spacing of 8–10 cm between ports and an adequate distance from the pelvis to minimise arm clashing. Pneumoperitoneum should be established prior to placing the working ports to ensure satisfactory positioning.

Two 8 mm ports are then placed under direct vision on either side just lateral to the midclavicular line (MCL) on a line between the umbilicus and anterior superior iliac spine. For a single stage totally robotic procedure, a third 8 mm port is placed in the right upper quadrant (RUQ) in the MCL, and a fourth 8 mm port in the left upper quadrant (LUQ) just lateral to the MCL. A 5 mm assistant port is placed laterally in the right upper quadrant, and is used for added retraction, suction and irrigation [23, 24]. For a hybrid approach, the right subcostal port is omitted and the LUQ port can be brought caudally, providing an appropriate distance from the other ports is maintained (Fig. 14.5) [25].

The patient is positioned in steep Trendelenburg position, left side up and the abdomen explored laparoscopically. The small bowel is retracted out of the pelvis, and at this point the colon can be mobilised laparoscopically and the splenic flexure taken down. One disadvantage of the robot is that, once docked, the patient position cannot be changed without undocking and then redocking the robotic cart, thereby negating the helpful effect of gravity when mobilising the splenic flexure.

The robot can then be docked with the patient cart approaching and docking over the left leg (Fig. 14.6). If the inferior mesenteric vessels are to be dissected, the robotic arms are first docked with robot arm 1 in the right lower quadrant for a monopolar shears, robot arm 2 in the LUQ port for a Cadiere grasper, and robot arm 3 in the RUQ for a bipolar grasper. The mesocolon over the IMA is retracted upwards and the peritoneum opened at its base. The IMA is dissected, care being taken to protect the periaortic hypogastric nerve plexus. The IMA can be divided near its base with laparoscopic or robotic Hem-o-lok® clips (Weck Closure System, research Triangle Park, NC, USA) following clear identification of the left ureter laterally. The IMV is identified by dissecting towards the ligament of Treitz and divided at the inferior border of the pancreas. Dissection then continues under the left mesocolon towards the splenic flexure if this has not been completed laparoscopically. During

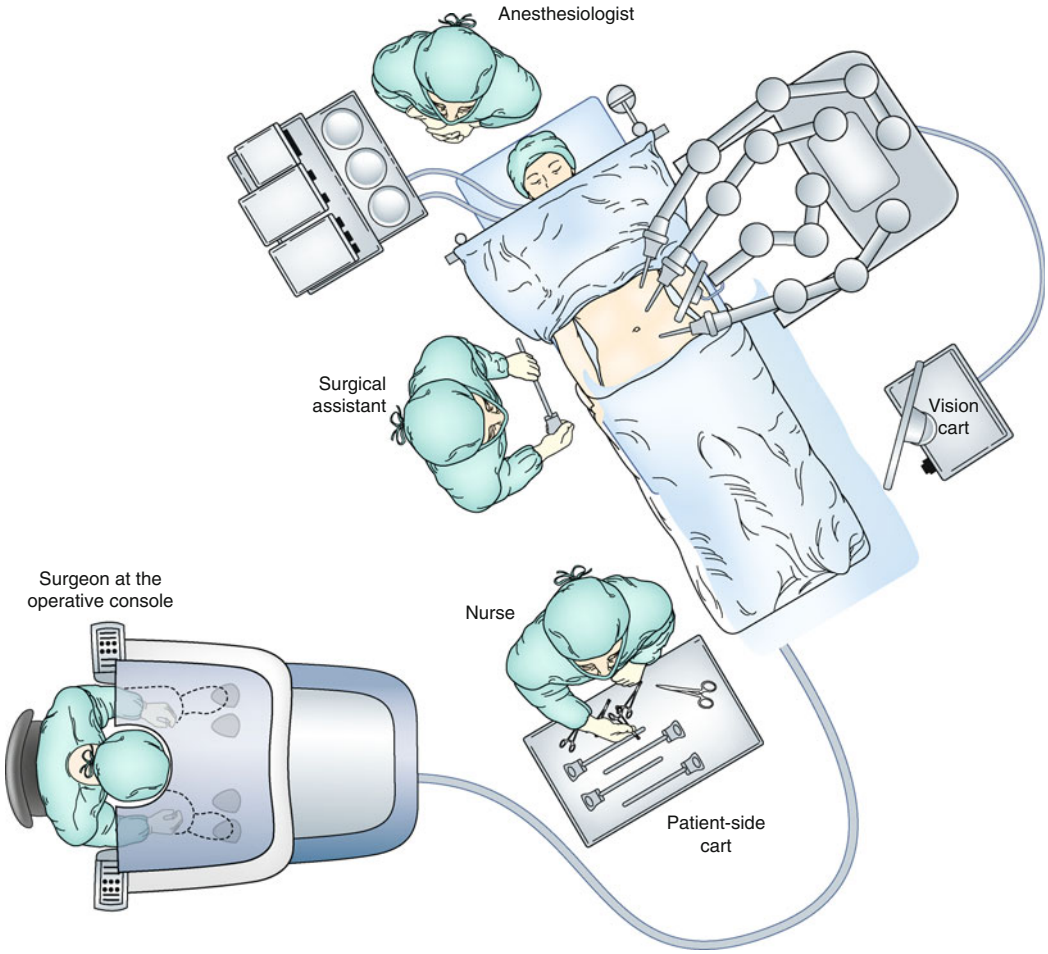


Fig. 14.6 An overhead view of the operating room configuration for robotic low anterior resection (From Choi et al. [23])

splenic flexure dissection only robot arms 1 and 3 are used to minimise external collisions.

For the pelvic dissection the robotic arms are redocked, robotic arm 2 moving to the left lower quadrant port with Cadiere forceps and robotic arm 3 to the left upper quadrant port with the bipolar forceps. The RUQ port or a further 12 mm suprapubic port can also be useful here to aid in rectal retraction.

The robotic Cadiere retracts the rectum anteriorly and the posterior mesorectal plane is dissected as far distally as possible with monopolar scissors. Lateral dissection is then performed, care being taken to preserve the inferior hypogastric nerves. Using the Cadiere to retract the vagina/prostate upwards facilitates anterior dissection, with robot arm 3 being used to provide downwards traction on the rectum (Fig. 14.7). When TME has been performed to the pelvic floor, rectal transection is performed with a laparoscopic stapler, often best accomplished with the robotic cart undocked. When the distal rectum has been divided. The robot is undocked and the rectum extracted via a small suprapubic or left iliac fossa incision with the aid of a plastic wound protector. The specimen is resected, the proximal bowel prepared, and the stapler anvil placed with the aid of a purse string suture. The bowel is returned to the abdomen and the wound either closed or wound protector

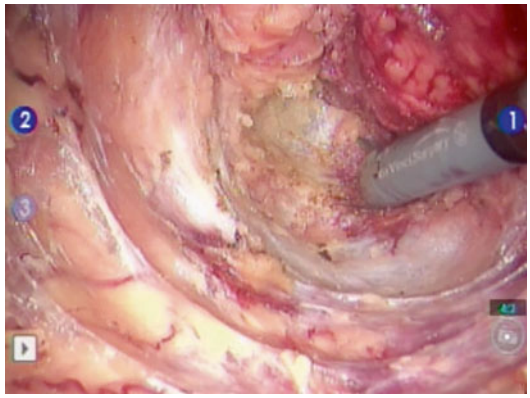


Fig. 14.7 Posterior mesorectal dissection with the Da Vinci robot

occluded with a glove placed over the top or clamped prior to re-establishing pneumoperitoneum and forming a stapled anastomosis with laparoscopic assistance.

Distal resection with the robot remains difficult. Obtaining a right-angled transection of the rectum following TME remains challenging. The options include using conventional laparoscopic stapling instruments or converting to a mini Pfannensteil incision to enable use of an open stapler. A stapler for robotic –assisted surgery is currently becoming available, however, it remains difficult to completely transect the rectum with one firing and an association between number of stapler firings and an increased incidence of anastomotic leak has been identified [26].

Another technique involves division of the rectum and placement of a purse string suture robotically to close the rectal stump and enable single-stapled anastomosis [25].

Specimen removal can be via an abdominal incision, transanally [27] or transvaginally [28].

Other novel techniques have been described to complete a robotic TME. One; robotic assisted transanal surgery for total mesorectal excision (RATS-TME) uses a commercially available GelPOINT Path Transanal Access Platform (Applied Medical, Inc., Rancho Santa Margarita CA, USA) [29]. Following the abdominal component of the procedure, the rectum is divided at the dentate line, the device is placed into the anal canal, insufflation established and the robotic arms redocked. Dissection is carried out in a cephalad direction circumferentially in the mesorectal plane to meet the dissection plane established previously from above.

Learning Curve

As well as skill in manipulating the robot instruments and camera the surgeon has to adapt to the decreased haptic feedback when performing grasping tasks. Also there is the issue of 'patient side competency.' Port placement is important to minimise arm clashing during dissection and manipulation and an appreciation of how the robotic arms move for a given input adds to ease in manipulating the bowel around the abdominal cavity.

Virtual reality trainers have been developed with the aim of enhancing learning of robot specific tasks. These have been shown to increase the rate of acquisition of new skills, and could lead to an earlier plateau in the learning curve [30], but also, when used as a warm-up, reduced errors when performing a more complex robotic task [31].

D'Annibale et al. found a decreasing trend in operating time over their first 22 cases and a statistically different operating time between cases 1–22 and cases 40–50 ($p=0.002$) [32]. Studies specifically investigating the learning curve indicate that it appears to be overcome after about 15–30 cases [33–36]. This is shorter than that seen with laparoscopic rectal surgery, and there is evidence that it is shorted by previous laparoscopic experience [37].

Perceived Benefits

Current data supports robotic proctectomy as being as oncologically effective and safe as a laparoscopic approach, but there is a lack of high quality evidence.

Meta analysis does describe a longer operating time for robotic TME, however this can vary widely across studies if a hybrid approach is used to perform part of the colonic mobilisation laparoscopically rather than a totally robotic

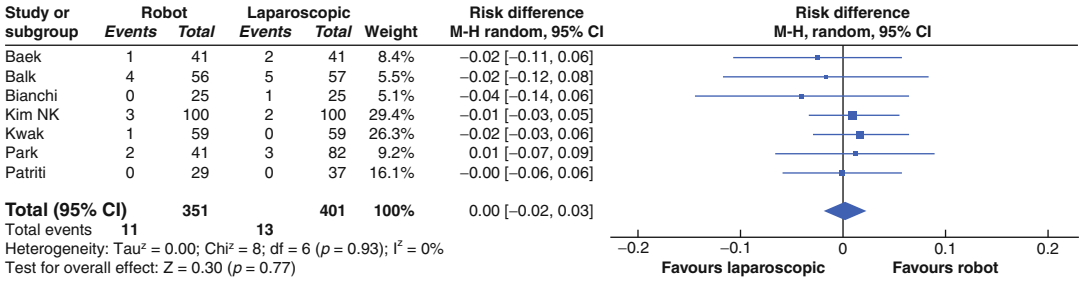


Fig. 14.8 Forest plot showing a meta-analysis of CRM status for rectal RALS vs. CLS. Risk differences are shown with 95 % CIs (From Memon et al. [44])

procedure. While all robotic procedures require some time to dock the patient-side cart, this does not appear to be a major influence on operative times, averaging less than 10 min across studies [38, 39].

Oncologic Outcomes

Only one randomized trial has been reported to date [40]. This compared 36 patients assigned to either a robotic or laparoscopic approach. No differences were observed in operative times ($p=0.477$) or in quality of mesorectal dissection ($p=0.323$). The TME specimen was graded as complete in 17 robotic cases and nearly complete in 1, compared with 13 complete specimens in the laparoscopic group and nearly complete in 3. The 2 converted cases were graded as nearly complete.

There was a non-significant difference in conversion rate (two laparoscopic, nil robotic, $p=0.486$) and a significantly shorted length of hospital stay for robotic patients (robotic-assisted, 6.9 ± 1.3 days; standard laparoscopic, 8.7 ± 1.3 days; $p<0.001$).

Quality of Dissection

One of the assumptions made of robotic proctectomy is that it allows greater operative precision, especially when performing a mesorectal dissection. Studies comparing the CRM between robotic and laparoscopic groups have found no significant difference in specimen quality (Fig. 14.8). A number of studies have examined the TME grade of RALS rectal surgery. Luca et al. graded quality of TME in 28 patients and found 22 complete, 6 nearly complete and 0 incomplete [41]. Baik et al. compared TME grade between RALS and Lap LAR and found a significantly more complete TME specimen in the RALS group ($p=0.03$) [42]. Karahasanoglu et al. found the grade of the TME specimen was complete in all 22 rectal RALS specimens [28].

D'Annibale reports a CRM of <2 mm in 6 of the laparoscopic patients and none of the robotic patients in his series of his first 50 robotic proctectomies compared with 50 laparoscopic proctectomies [32].

Kang et al., in their cohort of 165 patients, having either open, laparoscopic, or robotic surgery for low rectal cancer, found a significantly different rate of CRM involvement for open vs. robotic cases (17, 10.3 % vs. 7, 4.2 %, $p=0.034$), but no significant difference in CRM involvement between either open and laparoscopic cases (11, 6.7 %) or laparoscopic and robotic cases [43].

Other indicators of a quality oncological resection such as number of lymph nodes harvested or distal resection margin have shown no significant difference between laparoscopic and robotic approaches [44].

Surgeon Fatigue

The ergonomic position of the surgeon at the robot console has been thought to be a major advantage to performing precise surgery, especially when compared to the alternative

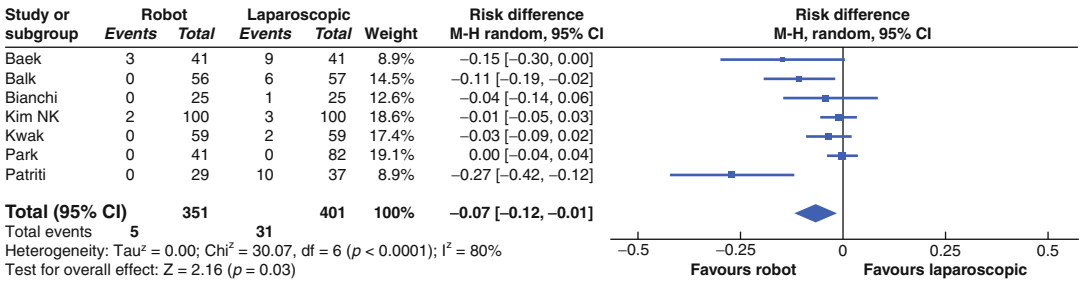


Fig. 14.9 Forest plot showing a meta-analysis of conversion rates for rectal RALS versus CLS. Risk differences are shown with 95 % CIs (From Memon et al. [44])

laparoscopic approach, standing beside the patient looking at a remote 2-dimensional monitor. In a laboratory model, robot-assisted surgery appears less physically stressful than standard laparoscopy with both the perception of effort and physical workload being less for similar mental stress [45]. One study that investigated operator and assistant fatigue by Pigazzi et al. asked surgeons to categorically self-report fatigue levels for 6 RALS and 6 CLS low anterior resections (LARs) [46]. 5/6 RALS cases and 2/6 CLS cases resulted in mild fatigue, 1/6 RALS cases and 3/6 CLS cases resulted in moderate fatigue and 1/6 CLS cases resulted in severe fatigue.

Conversion Rates

Conversion rate can be taken as a marker of procedure difficulty with a low conversion rate implying an easier operation. There is evidence that this is significantly lower for robotic proctectomy.

Pratiti et al. reported a conversion rate of 19 % in their laparoscopic group compared to none in the robotic group in spite of the majority of the robotic patients having had previous abdominal surgery and low cancers requiring complete TME [33].

In the metanalysis by Memon et al. (Fig. 14.9), a reduction in risk of conversion of 7 % (95 % CI 1–12) was found, however there appeared to be marked differences between studies, due to the small numbers in each.

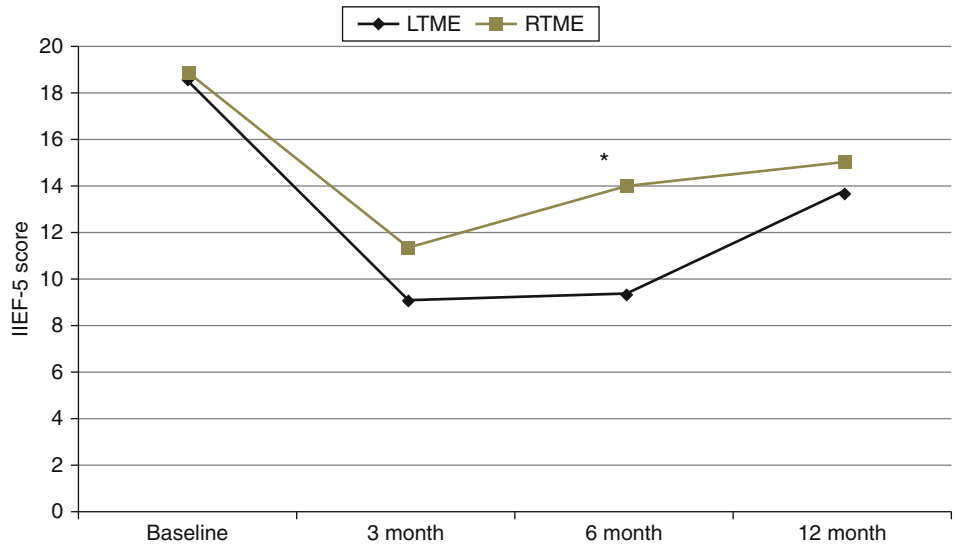
Conversion rates were again seen to be significantly lower for rectal procedures in Halabi et al.'s nationwide review of robotic-assisted colorectal surgery in the United States [47]. Although this study was unable to identify the number of cases converted from robotic to laparoscopic surgery, a robotic approach was associated with a 90 % reduction in chance of conversion to an open approach ($p < 0.001$).

There is no doubt that a laparoscopic TME dissection is a technically demanding procedure, and patient factors such as obesity, a narrow male pelvis, or a bulky tumour can require conversion to an open approach in order to get an optimal oncologic outcome for the patient. The COREAN trial group, where all surgeons involved were experienced in laparoscopic rectal surgery, were able to obtain an excellent conversion rate of 1.2 % in their laparoscopic group.

It may be that the enhanced ability to complete a difficult TME in a minimally invasive fashion may be one of the main benefits of RTME, allowing patients the enhanced recovery and shorted hospitalisation compared to an open procedure.

Genitourinary Function

Data from the CLASICC trial for laparoscopic vs. open dissection has suggested that sexual function may be worse after a laparoscopic dissection. The enhanced stereoscopic vision and improved dexterity of the robotic platform is assumed to assist preservation of autonomic nerves during mesorectal dissection. In particular the robotic platform provides stable traction and counter-traction under control of the operating



RTME	18.9 ± 4.3	11.5 ± 7.6	14.1 ± 6.1	15.1 ± 5.1
LTME	18.6 ± 5.0	9.1 ± 6.5	9.4 ± 6.6	13.7 ± 7.9
P Value	0.814	0.301	0.024	0.51

Fig. 14.10 Total IIEF-5 scores from baseline to 12 months after surgery. *Significant difference between the RTME and LTME groups (From Park et al. [49])

surgeon, and the mobile wrist allows precise use of monopolar diathermy, reducing the chance of nerve injury. There are currently no randomized trials, however Kim et al. have reported a prospective comparison of robotic vs. laparoscopic proctectomy. A similar decrease in erectile function for both groups was seen, but the robotic group experienced earlier recovery of voiding and sexual function [48].

Similar results were reported by D'Annibale et al. who found that 100 % of sexually active patients had preserved erectile function after robotic TME compared to 43 % of those following laparoscopic TME ($p = 0.045$) [32].

Park et al. have published a recent study comparing urinary and erectile function outcomes after laparoscopic and robotic TME (Fig. 14.10) [49]. There were 32 patients in each group, matched for age, tumour stage and position, procedure, with all T3, T4, or node positive disease having preoperative long-course chemoradiation. Urinary and erectile function was assessed and graded using the International Prostatic Symptom Score (IPSS) and the International Index of Erectile Function (IIEF-5) questionnaire, which comprises four questions about erectile function and one question about intercourse satisfaction, This was done before treatment and 3, 6, and 12 months post-operatively. The IPSS were elevated in both groups after surgery but demonstrated no significant difference between groups for the follow-up period. Following exclusion of patients with no preoperative sexual activity, the IIEF-5 scores for the remaining 20 patients in the robotic group were compared with the laparoscopic group. Baseline scores were similar and at 3 months, reduction in score was also similar. However, by 6 months the increase in the robotic group's score was significantly higher, returning to a similar score by 12 months.

While this does suggest some advantage to a robotic approach, presumably due to the potential

for an improved robotic dissection in the pelvis from enhanced visualization of autonomic nerves in the anterior portion of the rectal plane and on the lateral side walls. The study however, used a hybrid technique, with a conventional laparoscopic approach to mobilize the colon and dissect and ligate the IMA pedicle prior to using robotic assistance for the TME dissection. This may have placed the superior hypogastric plexus at similar risks of damage for both groups.

Cost

Aside from the significant financial outlay to purchase a robotic system, operative costs have been shown to be consistently greater for a robotic approach. Halabi's study of US data demonstrated an increased hospital charge of USD$12,965 per case [47].

There is evidence that the short-term advantages of a minimally invasive approach allow an earlier discharge and fewer resources after discharge. It has been argued that, especially among elderly patents that consideration should be given to a laparoscopic or robotic approach as the extra costs are mitigated by the reduced open conversions and subsequent inpatient and post discharge costs [50].

Barbash et al. performed a cost analysis of low anterior resection when a robot is used, factoring in savings associated with reduced complications, earlier discharge and recovery [51]. A RALS procedure increased the mean cost by $1,600 from US$16,688 for a CLS LAR. Abodeely et al. performed cost-reimbursement analysis on 4 segmental colectomies, 20 sigmoid colectomies, 5 rectopexies +/− resection, and 6 LARs/APRs performed robotically [52]. Only LAR/APR was financially beneficial to the institution with an average profit per case of US$773. For uncomplicated rectal cancer surgery cases the gain for the institution was significant and ranged from US$2,288–23,673.

The Future

Two multicentre randomised controlled trials of robotic versus laparoscopic assisted resection for rectal cancer (ROLARR [53] and ACOSOG Z605 [54]) are now recruiting; however it will be several years until data establishing the safety and efficacy of RALS proctectomy is available.

ROLARR, a multinational, prospective randomized, controlled, unblended, multinational trial has completed its accrual phase of 400 patients. It compares robotic and laparoscopic surgery for rectal cancer. The primary outcome measure is the rate of conversion to an open operation. It is also investigating differences in rate of CRM involvement, 3-year local recurrence, disease-free and overall survival, quality of life and cost-effectiveness data.

A vessel-sealing device and soon-to-arrive stapling instrument for the robotic arms will improve the ability to adequately deal with large vessels during robotic dissection.

Another technique that can be employed during a robotic procedure is the assessment of bowel perfusion by visualisation of indocyanine green fluorescence using near-infrared laparoscopy (NIR). This can allow enhanced assessment of tissue perfusion to guide bowel transection and selection of appropriate transection margins [55].

Robotic-assisted surgery for complex pelvic procedures is being reported. Patients requiring exenterative surgery for recurrent rectal cancer, endometriosis or complicated diverticular disease have the potential to benefit from this new technique; however further evidence of its efficacy is required [56].

The newest iteration of the da Vinci system, the *da Vinci® Xi™* offers improved instrument arm architecture, longer instruments, and the ability to mount the camera on any arm. These features may facilitate multi-quadrant surgery, and decrease the need for a hybrid approach or multiple dockings.

Although the Da Vinci is the only robotic platform currently being used for colorectal surgery, a number of other companies are developing instrument systems. These can broadly be described as extracorporeal or intracorporeal with instruments introduced via a NOTES approach [57]. The application of these new robotic technologies to the clinical setting is awaited with interest.

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Restorative Proctectomy and Colonic Reservoirs

15

Julie Ann M. Van Koughnett and Steven D. Wexner

Abstract

Restorative proctectomy has gained international popularity and global acceptance for the treatment of rectal cancer as an alternative to abdominal perineal resection (APR). A restorative procedure allows for the maintenance of intestinal continuity and thus the normal evacuatory pathway. Restorative proctectomy has been made feasible through the development of better surgical instruments, linear and circular staplers, and a better understanding of rectal cancer oncology. The principles of total mesorectal excision allow for proper resection of rectal cancer, respecting the mesorectal envelope and ensuring adequate circumferential (radial; lateral) and distal margins, without negating the ability to provide most patients with rectal cancer with a restorative yet also curative surgical option. When rectal cancer is treated by surgeons with expertise in rectal surgery, the rates of restorative procedures are higher, rates of permanent stoma lower, and rates of survival higher. These findings highlight the importance of extensive knowledge of the various restorative options and indications for surgeons treating rectal cancer. In the setting of distal third rectal cancers, pre-operative planning and intra-operative decision making becomes even more crucial in selecting those patients who require an APR and those who may undergo a restorative proctectomy.

Keywords

Restorative proctectomy • Rectal cancer • Total mesorectal excision • Colonic J pouch • Coloplasty

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Introduction

Restorative proctectomy has gained international popularity and global acceptance for the treatment of rectal cancer as an alternative to abdominal perineal resection (APR). A restorative procedure allows for the maintenance of

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intestinal continuity and thus the normal evacuatory pathway. Restorative proctectomy has been made feasible through the development of better surgical instruments, linear and circular staplers, and a better understanding of rectal cancer oncology. The principles of total mesorectal excision allow for proper resection of rectal cancer, respecting the mesorectal envelope and ensuring adequate circumferential (radial; lateral) and distal margins, without negating the ability to provide most patients with rectal cancer with a restorative yet also curative surgical option. When rectal cancer is treated by surgeons with expertise in rectal surgery, the rates of restorative procedures are higher, rates of permanent stoma lower, and rates of survival higher [1–4]. These findings highlight the importance of extensive knowledge of the various restorative options and indications for surgeons treating rectal cancer. In the setting of distal third rectal cancers, preoperative planning and intra-operative decision making becomes even more crucial in selecting those patients who require an APR and those who may undergo a restorative proctectomy.

Aside from the surgical assessment of whether a restorative proctectomy is feasible, it is important to note that most patients prefer to undergo a restorative procedure than a permanent stoma. When pre-operatively asked their preference of which procedure to undergo, only 5 % of patients with rectal cancer chose APR, while 30 % chose a restorative resection [5]. Sixty-five percent of patients in this study preferred to leave the decision to the surgeon [5]. Interestingly, when postoperatively re-surveyed, 46 % of patients who underwent APR would again chose that option and 69 % of patients who underwent restorative proctectomy would chose anterior resection again, perhaps suggesting that both APR and restorative proctectomy and well tolerated and better perceived after surgery than before surgery. Numerous studies have found that overall long term quality of life is, in fact, the same when APR and restorative proctectomy are compared [6–8]. While patients following a restorative proctectomy may have more pelvic pain, diarrhea, or trouble sleeping in some cases, they also have better sexual function and improved body image scores when compared to patients with a permanent colostomy [6–8]. Overall, the vast majority of patients with rectal cancer desire a restorative procedure and are happy with the functional results long term. Therefore, a restorative proctectomy should be offered whenever it can be undertaken without compromising oncologic goals.

Indications for Restorative Proctectomy

The main consideration when deciding a patient's candidacy for restorative proctectomy is the ability to achieve an acceptable distal margin. Traditionally, a 5 cm distal margin from the anal sphincters was accepted as the minimal distal margin. This margin has been thoroughly challenged in the last decade; comprehensive histological evidence has proven that a margin less than 2 cm does not negatively impact survival or local recurrence [9, 10]. In fact, a 1 cm margin has been clearly shown to offer equivalent oncologic outcomes [11–13]. Even distal margins of 5 mm or less have been shown to be safe, without adversely affecting local recurrence or survival rates [14, 15]. It has been suggested that the potential downstaging effects and reduced local recurrence rates achieved with modern neoadjuvant chemoradiotherapy in patients with mid and distal rectal cancers may be the reasons why such a short distal margin is oncologically sound [16]. Careful post-operative follow up is necessary in patients with short distal margins, as it has been shown that mucosal recurrence is associated with a close distal margin [17]. Indications for neoadjuvant chemoradiotherapy for distal tumors and the vital importance of circumferential resection margin status are discussed in other chapters.

The use of intersphincteric dissection may further expand the numbers of patients in whom intestinal continuity can be achieved [15]. Rullier and colleagues have reported on the ability to achieve good oncologic and functional outcomes with intersphincteric dissection [15, 18]. Their recently proposed classification system for low rectal tumors resulted in the ability to achieve a

restorative procedure in 79 % of 404 patients with rectal cancer less than 6 cm from the anal verge [18]. Performing partial or fully intersphincteric dissections in appropriately selected patients with juxta-anal or internal sphincter invading tumors, respectively, did not result in increased recurrence or decreased disease-free survival in their patients [18]. Fecal continence appears to be adequate in patients with partial or fully intersphincteric resections and coloanal anastomoses, though careful patient selection must take pre-operative continence and sphincter function into consideration [15, 19].

There are two patient populations often thought of as poor candidates for restorative proctectomy: elderly and obese patients. It may be incorrectly assumed by some surgeons that elderly patients have poor anorectal physiology and therefore have worse function after a restorative proctectomy. This erroneous supposition may lead some surgeons to prefer APR in the elderly population. However, chronologic age alone is not an indication for APR, even for distal rectal cancers. A case-control study of patients over 75 years of age with low rectal cancer found that the functional outcomes of a colonic J pouch anal anastomosis was good to excellent in most patients [20]. Incontinence, urgency, constipation, and laxative use (among other metrics) did not significantly differ between age groups [20]. Sphincter tone, and not age, should be considered when discussing restorative options for rectal cancer with elderly patients. Restorative proctectomy in the obese patient is similarly often feasible and is not considered a contraindication. Circumferential margin status, ability to undergo a restorative proctectomy, and long term oncologic outcomes have been shown to be similar in obese and non-obese patients [21, 22]. However, a high quality operation is undoubtedly a more technically challenging endeavor in the obese patient. Operative time and length of stay are often significantly longer for an obese patient [22]. In addition, the risk of anastomotic leak is higher after restorative proctectomy in the obese population [21]. A recent analysis of the American College of Surgeons National Surgical Quality Improvement Program (NSQIP) database found that high BMI is an independent predictor of complications in patients undergoing proctectomy [23]. Moreover, a laparoscopic proctectomy may not be feasible in an increased percentage of obese patients. The obese patient must understand these factors that may impact their outcomes during pre-operative counselling.

Technique

The critical steps of a restorative proctectomy are listed in Table 15.1. The decisions between stapled vs hand-sewn anastomosis and end-to-end anastomosis vs colonic reservoirs are discussed in detail later in this chapter. There are additional key steps in restorative proctectomy that are worth expanding upon. These critical steps begin even before the operation itself. The operating table must be capable of achieving steep Trendelenberg position during the pelvic dissection, as well and left and right tilt to facilitate dissection. The patient must be adequately padded and secured to allow for such position changes. The patient must be also positioned at the end of the operating table so that the anus is easily accessible for either a stapled or hand-sewn anastomosis. After proper secure positioning, digital rectal examination must be performed to re-familiarize the operative team with the current characteristics of the tumor including distance from dentate line, fixation, and size, all of which may have changed since the last office visit, especially following neoadjuvant chemoradiotherapy. The authors routinely employ urologist-placed bilateral ureteric stents to facilitate ureteric identification during the procedure with low associated morbidity [24]. Although bilateral stent placement requires a mean of 11 minutes it likely saves time during surgery by allowing more rapid ureteric identification [24].

Splenic flexure mobilization is routinely performed during all proctectomies. While non-randomized studies have shown that it is safe not to perform a splenic flexure mobilization in selected patients undergoing proctectomy, there are advantages to its routine use [25–27]. There are no differences in bowel perforation,

Table 15.1 Restorative proctectomy – critical operative steps

Modified lithotomy position
Digital rectal examination to assess level of tumor in relation to dentate line and fixation of tumor
Laparoscopic approach unless contraindicated
Complete mobilization of left colon
Identification of left and right ureters
Full splenic flexure mobilization
Isolation and high ligation of inferior mesenteric artery at aorta
Isolation and ligation of inferior mesenteric vein at level of duodenum
Total mesorectal excision
Critical assessment and preservation of bilateral ureters, hypogastric nerves, and nervi erigentes
Assessment of distal margin via palpation in pelvis and digital rectal examination
Digital vaginal examination to ensure adequate separation of the posterior vaginal and anterior rectal walls
Assess colon for length to perform restorative procedure
Plan specimen extraction and restorative procedure:
If adequate distal margin at 2 cm from dentate line:
Staple distal margin
Periumbilical specimen extraction
Staple proximal margin
Colonic J pouch construction if length permits
Straight circular anastomosis, coloplasty, or end-to-side anastomosis if J pouch not possible
Double stapled circular anastomosis
Air leak test with flexible sigmoidoscopy
If stapled anastomosis not possible due to distal margin less than 2 cm from dentate line:
Placement of transanal retractor and effacement of anus
Distal margin transection at or above dentate line using electrocautery
Mucosectomy or intersphincteric dissection
Transanal extraction of rectum and sigmoid colon
Transection of proximal margin
Colonic J pouch stapled construction if length permits
Hand-sewn coloanal anastomosis of J pouch or end-to-end configuration
Water test anastomosis via pelvic irrigation
Placement of pelvic drain
Construction of diverting loop ileostomy

anastomotic leak, post-operative morbidities, or oncologic outcomes if the splenic flexure is mobilized, though the average operative time is longer [25–27]. The average size of the extracted specimen is, however, longer in those patients with splenic flexure mobilization; therefore, mobilization facilitates the creation of a colonic reservoir [25]. Furthermore, it has been shown that patients who undergo splenic flexure mobilization are significantly more likely to receive a colonic reservoir than those who do not (49 % vs 22 %, p 0.039) [27]. A colonic J pouch should be routinely created as part of a coloanal anastomotic procedure whenever technically feasible. Routine ligation of the inferior mesenteric artery proximal to the left colic artery and the inferior mesenteric vein at the edge of the pancreas helps secure adequate length for a reconstruction. Moreover, routine splenic flexure mobilization and "high" ligation help ensure an optimal blood supply to a tension-free anastomosis. We evaluated 19 patients in whom a re-do low anterior resection or coloanal anastomosis was required to treat a prior colorectal anastomosis which had either leaked or strictured [28]. In 89 % of patients, a "high" ligation had not been performed and the splenic flexure had not been mobilized [28].

After a stapled anastomosis, regardless if the reconstruction is straight or a reservoir, air-leak testing should be performed. Routine intra-operative flexible sigmoidoscopy allows for the early detection of an anastomotic leak or small dehiscence as well as direct inspection of the staple line. Staple line visualization may identify bleeding or ischemic mucosa and may help reduce the risk of post-operative anastomotic complications [29]. Given that the risks of performing routine intra-operative flexible sigmoidoscopy are extremely small and the procedure does not add much operative time, routine performance is advocated to inspect the anastomosis [29, 30]. In the case of a distal hand-sewn coloanal anastomosis, flexible sigmoidoscopy is not possible to perform an air leak test. Instead, a "water leak test" is performed by using the reverse Trendelenburg position while the pelvis is filled with fluid. Additional sutures may be placed to reinforce the staple line if there is a water leak.

Hand-Sewn Versus Stapled Anastomosis

The majority of surgeons perform a stapled anastomosis whenever technically feasible. During the early days of stapled colorectal anastomoses, the results were conflicting. A randomized trial of the circular stapler in 1981 found that though the stapler carried risks of rectal tear and anastomotic defects, it allowed surgeons to "save as many as 12 % of rectums" where a pelvic anastomosis was required but a hand-sewn transanal anastomosis would have required additional rectal resection [31]. This finding is less relevant in the era of total mesorectal excision for rectal cancer. Other early studies showed that the stapled anastomosis was not associated with increased adverse outcomes, nor did it alter the risk of recurrence or survival [32–34]. However, a randomized trial of 118 patients requiring a low colorectal anastomosis concluded that the hand-sewn anastomosis should remain the standard of care [35]. In this study the early stapler did not save time, caused more complications, and was much more expensive [35]. Despite this study, work with staplers continued and results continued to improve [36, 37].

More recent studies have shown the benefits of the stapled anastomosis, leading to its widespread adoption in intestinal surgery, including restorative proctectomy. A stapled anastomosis now takes significantly less time than does a hand-sewn anastomosis; a mean of 50 min less time [38, 39]. Morbidity is similar between the techniques, although the stapled anastomosis has lower anastomotic leak and stricture rates [38, 40]. Disease-free survival, overall survival, and recurrence rates do not differ between the technique of anastomosis [39, 41]. The hand-sewn colorectal anastomosis has been shown to have equal or perhaps worse post-operative sphincter function, although there is an acknowledged bias in some of these studies where hand-sewn anastomoses are reserved for the very distal anastomoses where a stapled anastomosis would not be possible [38, 42, 43]. The most recent Cochrane review on the subject concluded that the stapled anastomosis should not be considered superior to the hand-sewn anastomosis in colorectal surgery, but found that there are few recent studies on the topic and are no longer relevant in the setting of elective surgery [44]. Operative time was not an included outcome in this review [44]. In summary, the stapled anastomosis is safe and takes less time than does a hand-sewn anastomosis. Where feasible, a stapled anastomosis should be performed, reserving the hand-sewn technique for very distal anastomoses where a restorative proctectomy would not otherwise be possible. Both techniques are very relevant and the surgeon treating distal rectal cancer must be capable of performing both of them.

For the stapled technique, a purse-string device is used to secure a continuous number 1 polypropylene suture at the proximal resection margin. Alternatively, a running number 1 polypropylene suture may be circumferentially sutured at the cut edge of the proximal resection margin of colon. Various diameter circular staplers are available. The 33 mm stapler is routinely used in the authors' practice, with the 29 mm stapler being used as an alternative for small-caliber small bowel during some ileorectal

anastomosis procedures. The distal spike of the stapler is brought out through the center of the staple line (or as close to it as possible). A Lone Star ™ rectractor is used to efface the anus if there is any difficulty passing the stapler up through the anal canal. Special attention must be given in female patients to ensure that the vagina is not entrapped in the stapled line prior to its firing. After the stapler is fired the proximal and distal anastomotic rings are inspected for complete circular integrity. These are separately labelled and sent to pathology, with the oncologic status of the anastomotic rings being of particular interest in a very distal rectal cancer and threatened distal margin. A clear correlation has been shown between the number of distal stapler cartridges used and anastomotic leak rate. For this reason, a distal purse string or a single stapler cartridge closure of the rectal stump is preferable to multiple stapler firings. For a hand-sewn anastomosis the Lone Star™ retractor is used to efface the anus. The anastomosis is oriented by placing 4 corner sutures of 2-0 Vicryl. Interrupted 2-0 Vicryl sutures are then placed circumferentially, about 3 mm apart. In both techniques, meticulous care must be taken to ensure the proximal colon is not twisted on its mesentery, the anastomosis is tension-free, and the 2 ends of bowel have good blood supply.

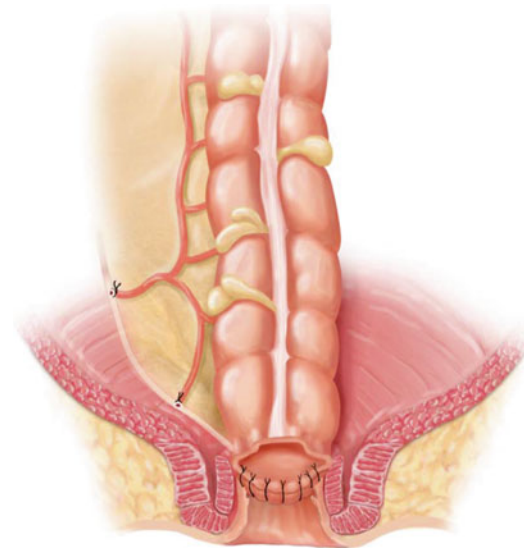

Fig. 15.1 Hand-sewn end-to-end coloanal anastomosis (With permission Wexner and Fleshman [95])

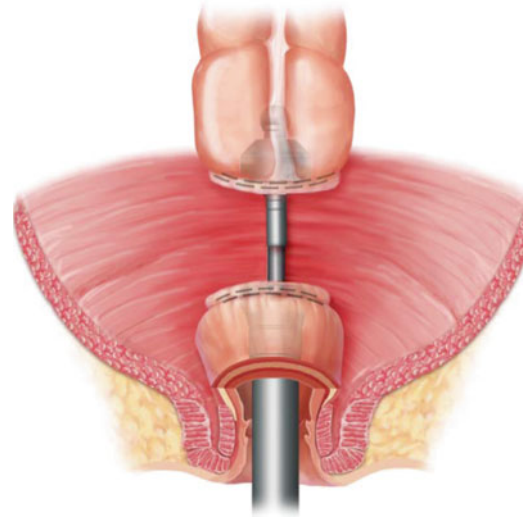

Fig. 15.2 Staple lines prepared for stapled end-to-end colorectal anastomosis (With permission Wexner and Fleshman [95])

Colonic Reservoirs

Whether stapled or hand-sewn, various configurations of the colon may be used for the colorectal or coloanal anastomosis. A straight or end-to-end anastomosis after rectal resection replaces the normally compliant rectum with a segment of sigmoid or descending colon (Figs. 15.1 and 15.2). Most patients have satisfactory bowel control and stool frequency with an end-to-end anastomosis [45]. However, there is a subset of patients who have very frequent bowel movements per day, especially in the setting of a very low anastomosis [46]. Other unsatisfactory symptoms after restorative proctectomy include incomplete evacuation, incontinence, clustering of bowel movements and urgency [47, 48]. Validated tools have been developed to quantify these symptoms, collectively known as low anterior resection syndrome (LARS) [47, 48]. Neoadjuvant radiotherapy, a coloanal anastomosis, and hand-sewn anastomosis are associated with poorer function [47]. Quality of life after restorative proctectomy is closely associated with the severity of LARS

symptoms [49]. To mitigate these symptoms, various techniques have been studied in an attempt to re-create the reservoir function of the resected rectum. These are known as colonic reservoirs and include the colonic J pouch, transverse coloplasty, and end-to-side (or "Baker") configurations.

Colonic J Pouch

The technique of creating a colonic J pouch is similar to that of an ileal J pouch, though the colonic J pouch should be much smaller. Healthy diverticular-disease-free descending colon is used for the pouch. The pouch should be assessed for adequate tension-free reach to the level of the distal rectal or anal resection margin. A 6–8 cm distance from the stapled proximal resection margin is measured and will form the efferent limb of the pouch. This limb is folded back onto the colon so that the anti-mesenteric borders are approximated. An enterotomy is then made at the apex of the pouch. A linear cutting stapler is introduced and fired along the anti-mesenteric borders to create the pouch. The staple line is irrigated and inspected for bleeding. Interrupted seromuscular sutures are placed at the level of the tip of the afferent limb for added support. For a stapled anastomosis, a purse string suture is then placed at the enterotomy and the anvil is secured. For a hand-sewn anastomosis, interrupted sutures are used to create the coloanal anastomosis. See Fig. 15.3 for an illustration of the anatomy and proper orientation of a colonic J pouch in the pelvis.

The colonic J pouch was first described for use in coloanal anastomosis after proctectomy for rectal cancer. Early series found that with the colonic J pouch, the mean number of bowel movements was 1.1 per day, maximum tolerated volume was increased on anal manometry, and significantly more patients had 1–2 bowel movements per day when compared to patients with straight coloanal anastomoses [50, 51]. Although a randomized trial comparing colonic J pouch to straight coloanal anastomosis found that the capacity of the 2 reservoirs was not significantly different a 6 months, the colonic J pouch was associated with

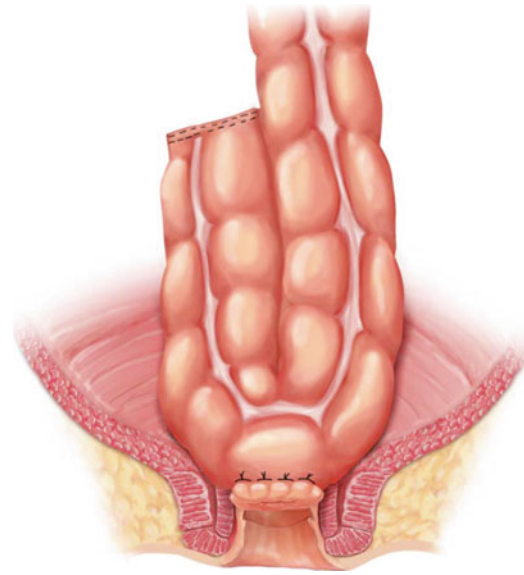

Fig. 15.3 Anterior view of a colonic J pouch in the pelvis (With permission Wexner and Fleshman [95])

better functional results, including less stool frequency and less incontinence [52]. These benefits persist up to at least 1 year post-operatively [53, 54]. One study even found better functional outcomes 5 years after colonic J pouch reconstruction [55]. These superior outcomes included decreased frequency, urgency, and nocturnal bowel movements [55]. In addition the anal pressure gradient, mean pressures, compliance, and threshold volume are all better on anal manometry testing in patients with colonic J pouches, over straight anastomoses [55, 56]. These facts may explain why the quality of life in patients with colonic J pouches is better, especially up to 1–2 years after surgery [57]. In non-randomized trials, the anastomotic leak rate is also substantially lower following colonic J pouch [53, 58]. Randomized trials, a meta-analysis, and Cochrane review have all come to the same conclusion – that colonic J pouch is superior to straight anastomosis for at least 1 year after surgery [59–61]. The Association of Coloproctology of Great Britain and Ireland state that colonic J pouch formation should be considered in their position statement on the management of colorectal cancer [62]. Given these data, the colonic J pouch should be used whenever technically feasible for low

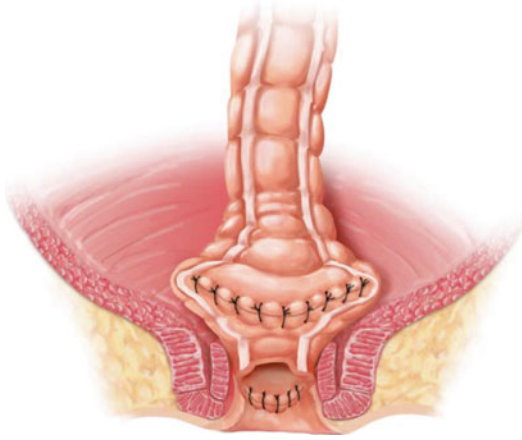

Fig. 15.4 Transverse coloplasty, shown with hand-sewn coloanal anastomosis (With permission Wexner and Fleshman [95])

colorectal and coloanal anastomoses in restorative proctectomy for rectal cancer.

Transverse Coloplasty

A coloplasty also creates a reservoir, but does not require as much redundant colon or as wide a pelvis as does a colonic J pouch. First, the colon must be assessed for length to see if a coloplasty will still allow a tension-free anastomosis in the pelvis. If so, the bowel is brought out through an incision or may also be brought out transanally if the distal resection margin is very low. Starting approximately 5 cm proximal to the proximal resection line, a 8–10 cm full thickness longitudinal colotomy is made along the antimesenteric border of the colon. Stay sutures are then used to reapproximate the colotomy transversely. Interrupted sutures are used to close the colotomy transversely, creating the colonic reservoir. A stapled or hand-sewn end-to-end anastomosis to the distal resection margin is then performed. Figure 15.4 illustrates a completed transverse coloplasty with a hand-sewn coloanal anastomosis.

Small randomized studies have compared the colonic J pouch to transverse coloplasty. When combined, the functional outcomes appear to be similar between the reservoirs [62–65]. One potential advantage of the transverse coloplasty over the colonic J pouch is that fewer patients have evacuatory difficulties or need for enemas [65, 66]. Most patients have up to 3 bowel movements per day [66]. It should be noted that one randomized trial found a trend toward more anastomotic leaks in the coloplasty group, but this was not statistically significant [65]. It is clear from many studies that both the colonic J pouch and coloplasty provide better functional results, quality of life, and superior manometry results over a straight anastomosis [67–69]. These same studies suggest that perhaps the best indication for a coloplasty is for patients in whom a colonic J pouch is not technically feasible; for example, in a narrow pelvis or a bulky mesentery [68, 69]. A study from the Cleveland Clinic found that since the technique of coloplasty was introduced, there were fewer failures in creating some form of colonic reservoir in patients requiring a coloanal anastomosis for rectal cancer [67]. Specifically, coloplasty was formed in patients in whom a colonic J pouch was not possible. However, a later multi-center randomized controlled trial which included the same institution concluded that in patients who could not have a colonic J pouch due to technical issues, coloplasty did not confer significant benefits over a straight anastomosis, perhaps because of their anatomical limits that prevented them from receiving a colonic J pouch as well [70]. Thus, the colonic J pouch should still be preferred over the coloplasty, though it is a reasonable reservoir option to consider when a pouch is not possible.

End-to-Side Anastomosis

An end-to-side, or "Baker" anastomosis, is typically secured to the distal resection line with a circular stapler, as shown in Fig. 15.5. The proximal resection margin is chosen in an area with good blood supply, free of diverticulae, and able to reach the distal resection margin without tension. There are two techniques used to introduce the anvil of the stapler. One approach is to sharply transect the specimen at the proximal margin. The anvil of the circular stapler is inserted through the open end of colon and the tip of the anvil is

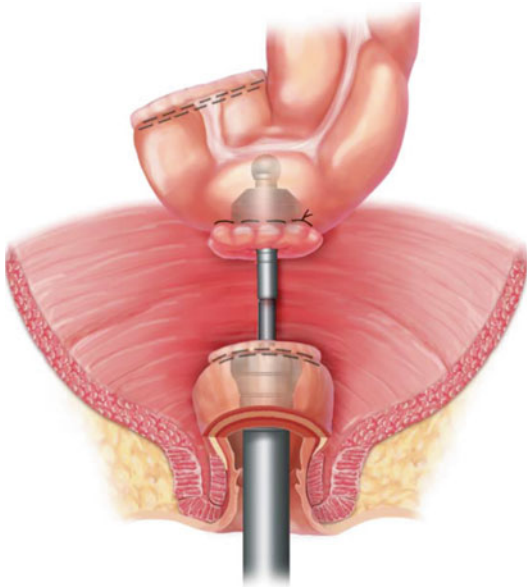

Fig. 15.5 End-to-side stapled colorectal anastomosis (With permission Wexner and Fleshman [95])

brought out through a small colotomy about 3 cm from the end of the colon on the anti-mesenteric border. The end of the colon is then closed with a linear stapler. A purse-string stitch is used to close the small colotomy around the post of the anvil. The alternative technique is to staple the transection margin of the colon. A larger, approximately 3 cm, colotomy is then made about 3 cm from the staple line on the anti-mesenteric border. A purse-string stich is placed and the anvil is inserted and secured in the same fashion as for an end-to-end anastomosis. The stapler is then fired from below under direct visualization, taking care of to keep the colon properly oriented.

The end-to-side anastomosis appears to confer many of the functional advantages of the colonic J pouch. Compared to a straight anastomosis, there are significantly fewer anastomotic leaks and similar overall anastomosis is safe, and easier and faster to create than the colonic J pouch [71, 72]. There are some subtle differences that make the colonic J pouch the preferred reconstructive option. The colonic J pouch has been shown to have better ability to evacuate in less than 15 min at 6 months post-operatively [73]. Maximal tolerable volume and volume of urgency is better in the early post-operative period in the colonic J pouch as measured by anal manomtery [74]. A 2008 Cochrane review of 4 randomized trials comparing colonic J pouch to side-to-end anastomosis did not demonstrate a functional difference between groups, but acknowledged that they were small trials and recommended larger randomized trials [62]. A more recent meta-analysis of 6 randomized trials found similar functional outcomes between the groups, but better early post-operative function in the colonic J pouch group [75]. For this reason, a colonic J pouch should be created if technically feasible. An end-to-side anastomosis is the second choice and a coloplasty is a possible third choice for reconstruction.

Colonic Rotation and Interposition

After full mobilization of the left colon and splenic flexure and high ligation of the inferior mesenteric vessels, some patients may still not have adequate colonic length to perform a restorative procedure. This problem may be attributed to prior colon resection, extent of the planned resection, or a simple variant of normal colon length. In order to achieve reconstruction in these patients, additional manoeuvers should be considered. A right colon to rectal anastomosis can be employed by fully mobilizing the right colon and rotating it into the pelvis, while maintaining ileocolic blood supply. This technique has been shown to have good results, with all patients having stoma closed, no anastomotic leak, and a mean of 3 bowel movements per day in a series of 48 patients [76]. Ileocecal rotation has also been shown to be successful after even more extensive resection of the colon [77]. After rotation of the ileocecal segment or right colon segment, the bowel may be brought through a window of the small bowel mesentery to facilitate reach into the pelvis. In addition to rotational procedures, interposition of pedicled segments of ileocecum or intervening colon have been described to allow for a reconstruction in the pelvis [78, 79]. While not commonly needed, rotational and interposition procedures are valuable tools to achieve a reconstruction after proctectomy, especially where a more extensive resection of the left colon is needed.

Fecal Diversion

A loop ileostomy should generally be created in the setting of a restorative proctectomy following neoadjuvant therapy for rectal cancer. It is created about 40 cm proximal to the ileocecal valve to facilitate subsequent closure. Meticulous care and inspection must be done to ensure proper identification of the afferent and efferent limbs during maturation. This is especially important during a laparoscopic procedure and the small intestine of each limb should be run to confirm correct orientation. The afferent limb should be everted during maturation to better facilitate pouching and minimize skin irritation. Stoma closure is often performed 12 weeks after surgery. Stoma closure should be delayed until all post-operative chemotherapy has been completed. Prior to stoma closure a water-soluble contrast enema and direct inspection of the anastomosis with sigmoidoscopy should be performed to rule out a sub-clinical anastomotic leak. Minor stricturing of the colorectal or coloanal anastomosis is usually easily dilated with the examining finger at the time of sigmoidoscopy and/or just prior to stoma closure if needed.

The need for a diverting stoma has been called into question, as stoma closure requires a second operation and hospital stay. However, numerous studies have shown that a defunctioning stoma is important after restorative proctectomy. Patients without a temporary ileostomy have significantly higher rates of anastomotic leak, peritonitis, and need for unplanned or urgent re-operations in the post-operative period [80–82]. Pooled analysis in a Cochrane review concluded that while a proximal stoma does not change post-operative or long term mortality after rectal cancer surgery, it does prevent anastomotic leaks and urgent re-operations [82]. Given that an ileostomy is safe and usually associated with only minor problems, such as dehydration, it should be recommended [82, 83]. It is vital to have enterostomal therapists and nurses who can provide education to patients on local stoma care, pouching, and most importantly fluid management and signs of dehydration. They are invaluable in reducing complications during the time a patient is diverted.

Complications and Functional Outcomes

Anastomotic leak is a risk in any intestinal surgery, but is especially significant after restorative proctectomy. A severe leak may result in the need for a permanent stoma in patients who return to the operating room and require intervention on the anastomosis. A diverting ileostomy significantly mitigates against the sequelae of a leak. Risk factors for anastomotic leak include malnutrition, smoking, obesity, and chronic disease [84]. A low anastomosis, prolonged operative time, and spill of bowel contents during the procedure are also risks that are common in restorative proctectomy for rectal cancer [84]. A quality improvement study of colorectal resections found that anastomosis less than 10 cm from the anal verge was an independent predictor of anastomotic leak [85]. Long term consequences after anastomotic leaks persist up to 3 years. At 1 year following restorative proctectomy, patients who had a post-operative leak have been shown to have more frequent bowel movements and worse bowel control [86]. At both 1 and 3 years after restorative proctectomy, these same patients also have worse mental component scores on the Short-Form 36 questionnaire [86]. A defunctioning stoma and close observation in the early post-operative period are keys to preventing, identifying, and minimizing the consequences of anastomotic leak.

As mentioned earlier, most patients have good function after restorative proctectomy and are satisfied with the decision to undergo a restorative procedure. Colonic reservoirs have been developed to obviate or at least ameliorate problems with frequency and LARS. The frequency of bowel movements continues to improve up to 5 years post-operatively in patients with a coloanal anastomosis; it is important to counsel patients with early post-operative frequency on this [87, 88]. The compliance of the neo-rectum is essential to

provide good function and minimizing sphincter and nerve trauma during the proctectomy is also important [89–91]. Incontinence after restorative proctectomy can be predicted in patients with high pre-operative fecal incontinence scores and low rectal cancers [92]. Also, patients who are incontinent 1 year after restorative proctectomy are more likely to have asymmetry of the anal sphincter during squeezing on anal manometry, suggesting that iatrogenic damage may have occurred [93]. Meticulous attention must be paid to avoid sphincter injury during dissection and anastomosis.

Difficult stool evacuation is a problem for some patients post restorative proctectomy. This complaint may be a presentation of anterior resection syndrome [47, 48]. Early colonic J pouches were more likely to have evacuatory problems, especially since the size of colonic J pouch was not standardized [94]. A study comparing 10 cm to 5 cm colonic J pouches after restorative proctectomy for rectal cancer found that the larger pouch size was associated with measured evacuatory function and reported evacuation difficulties [94]. Evacuation problems are less likely with a transverse coloplasty, although urgency, incomplete evacuation with bowel movements, and incontinence have been reported in these patients [66]. These functional problems can often be assisted with medications or enemas. They rarely require pouch revision or conversion to a permanent colostomy.

Conclusion

Most patients prefer to undergo a restorative proctectomy instead of an APR. The literature supports that shorter distal margins still provide good oncologic outcomes, thus increasing the number of patients who are candidates for restorative proctectomy. Advanced age and obesity are not contraindications to a restorative procedure. Standard precautions during laparoscopic proctectomy such as ureteric stenting and air testing with flexible sigmoidoscopy minimize complications of this complex procedure. A diverting ileostomy should be a part of the restorative proctectomy procedure to reduce the complications of anastomotic leak. Stapled distal anastomosis ideally with a single stapler firing is preferred to a hand-sewn anastomosis. Hand-sewn anastomosis should be considered in very distal tumors where stapling is not technically feasible. To reduce the risks of functional problems such as stool frequency and urgency, numerous colonic reservoirs have been studied. Colonic J pouch, transverse coloplasty, and end-to-side reservoirs have all been shown to confer superior functional results over the straight end-to-end anastomosis without increased morbidity. The colonic J pouch is the preferred best option which should be considered when adequate colonic length permits restorative proctectomy.

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Anorectal Reconstruction

16

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Abstract

Surgical treatment of low rectal malignancies may necessitate an abdominal colostomy. The dream of most patients is to avoid a permanent colostomy. To this end, total anorectal reconstruction offers a possibility for the patient to avoid a permanent colostomy while having a potentially functional quality of life. This chapter provides an overview of the indications, limitations, technique, and outcomes of anorectal reconstruction.

Keywords

Total anorectal reconstruction (TAR) • Abdominoperineal resection (APR) • Graciloplasty • Gluteoplasty • Artificial bowel sphincter • Perineal colostomy

Introduction

Total mesorectal excision is the standard technique for the surgical extirpation of rectal malignancies [1, 2], and is discussed elsewhere. The location of the malignancy with relation to the anal sphincters is the predominant determinant of a low anterior resection (LAR) or an abdominoperineal resection (APR). The desire to avoid a permanent colostomy has driven the evolution of the management of middle and low rectal cancers, with most patients undergoing sphincter-sparing procedures (coloanal, low or ultra-low colorectal anastomosis), and relegating external sphincter involvement as the only absolute indication for an APR. In select patients with good pre-operative continence, tumors that involve the internal sphincters can still undergo an inter-sphincteric resection with good oncologic and functional outcomes [3, 4]. However, tumors with distal margins involving the anal canal or within 1 cm of the sphincters require an APR. Distal tumor margin more than 2-cm from the dentate line allows a sphincter-sparing resection, whereas those between 1- and 2-cm will likely need an inter-sphincteric resection to achieve clearance. A distal resection margin of 2-cm is needed for tumors less than 5-cm from the anal verge [5] as long as a complete mesorectal excision as described by Heald [1, 6, 7] is

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undertaken. Even if the tumor location allows a sphincter-preserving resection, the presence of sphincter dysfunction as elicited by a comprehensive continence history and physical may necessitate an APR [8]. Obesity and a deep, narrow pelvis may technically prevent a low or ultra-low colorectal anastomosis, and may mandate a coloanal anastomosis via a perineal approach or an APR.

Despite the curative goal of a resection, APR with the resulting end colostomy can lead to significant psychosocial disability [9]. Extirpation of the rectum and anus leads to the loss of an adaptable reservoir, discriminatory anorectal sensory apparatus, and a complex sphincteric mechanism. The goal of total anorectal reconstruction (TAR) is to achieve a continent neo-reservoir with autologous muscle or artificial sphincter. TAR was first performed in 1930 by Chittenden [10] who after an APR, created a perineal colostomy and a neo-sphincter from a flap of gluteus maximus. Since then, the development of muscle transfer techniques, dynamization of the muscle with electrical field stimulation, sphincter augmentation, and artificial implantable sphincters have further aided in the advancement of TAR.

Re-establishment of continuity can be achieved with immediate reconstruction at the time of extirpative surgery, delayed reconstruction after an APR, or for the management of anastomotic complications after a low anterior resection.

Selection Criteria

TAR may be performed as a synchronous procedure or a delayed reconstruction after the initial APR. Well-motivated patients with T1-2 N0 tumors that have not been radiated should be eligible for synchronous TAR. For those undergoing radiation or have higher grade tumors, TAR can be offered after at least 2 years to make sure there is no local recurrence after the APR.

Obesity, advanced age, history of pelvic irradiation, and local recurrence should factor into patient selection. Frank discussion about the lack of perfect continence and need for reoperations with a possible permanent colostomy should also be discussed. Extensive pre-operative counseling may also be beneficial to screen patients unsuitable for TAR.

Principles of Total Anorectal Reconstruction

The intact continence mechanism is complex and is still not fully understood very well. Continence requires the presence of: (1) a reservoir that has the capacity to distend, store and discharge only when appropriate; (2) a sphincter complex that is closed at rest to prevent any leakage, a capability to augment the resting tone if the reservoir pressure increases, and the ability to relax and allow passage of contents; and (3) a sensory complex which can discriminate the quality and quantity of the reservoir contents. Any loss of these can result in varying degrees of incontinence. The goal of TAR is to recreate these physiologic functions. Unfortunately, anorectal excision results in the permanent loss of the sensory complex [11], and the goals of TAR involves the creation of a neo-rectal reservoir along with an autologous muscle or artificial sphincter with the goal of attaining continence or pseudo-continence.

Neo-rectal Reservoir

The main function of the rectum is to serve as a reservoir and to allow for the discrimination of distention due to accumulation in this reservoir. The colon has propulsive activity and has less capacity to store and distend. Replacement of rectum with a segment of colon can lead to significant "low anterior resection syndrome" which is characterized by urgency, frequency, stool fragmentation and clustering, incomplete evacuation, tenesmus, and even frank incontinence [12, 13]. While most of these symptoms improve after a year [14], persistent defecatory problems have been noted [15]. To decrease these symptoms, neo-rectal reservoirs were advocated, and their creations in various configurations are discussed elsewhere in this book. The improvement over

time in function of a reservoir may be due to the reduction in the propulsive activity in the colon used for the neo-rectum rather than the neo-rectum's storage [16].

The use of a pouch or a coloplasty in TAR is different, as the distal 3–4 cm of the neo-rectum will have to be surrounded by a neo-sphincter, and it is better to have the pouch of the neo-rectum lie above the neo-sphincter. Different reservoir configurations have been described with a neo-sphincter: J-pouch [17], C-shaped or lateral pouch [18, 19], triplicated ileal pouch in a patient who had undergone a proctocolectomy [20], and a coloplasty [21]. More complex reservoirs have been created, but failed to show any significant improvement in functional outcome despite the increase in morbidity [22].

Review of the literature shows that most studies focus on the neo-sphincter and little attention is assigned to the creation of the reservoir. Even studies that assess the construction of a reservoir fail to show the need for a reservoir or the configuration of a reservoir [17, 18, 22]. Some pouch configurations are associated with significant morbidity with no clear benefit. Coloplasty [23] or even a myotomy [21] just proximal to the sphincter could theoretically improve the functional outcome with minimal additional co-morbidity [24, 25], but further studies are needed to assess beneficial effects of different pouch configurations on functional outcome.

Neo-sphincter

The intact sphincter mechanism is a complex system with a basal tone at rest due to the internal sphincter complex, and a voluntary dynamic external sphincter that augments this tone to prevent any leakage of rectal contents.

Smooth Muscle Sphincter

The role of the smooth muscle internal sphincter in maintaining continence is limited, but surgical management of benign anorectal conditions with intentional or inadvertent injury to the internal sphincter have resulted in varying degrees of incontinence. TAR with creation of a neo-smooth muscle sphincter has been reported [26, 27] which was modified from a technique described by Schmidt [28]. The technique involves freeing the pericolic fat of the distal 3–4 cm of colon, dissecting the seromuscular layer from the underlying mucosa, cutting it into a spiral, long strip, and wrapping it around the bowel to create a cone-shaped muscular cuff. Twenty-two of 30 patients had satisfactory functional outcome at 6 months [27]. Several other studies have shown good outcomes after excision of the rectum and creation of a neo-smooth muscle cuff using colonic muscle [29–33]. A technically easier technique involved first denuding the mucosa and then everting the denuded colonic end prior to anastomosing the cuff to the perianal skin [34]. All these neo-smooth muscle sphincters are associated with an increase in resting intraluminal pressure at the neo-sphincter [19, 27, 33].

Despite the positive results, it is unclear if the real benefit of a free graft as a neo-smooth muscle sphincter is due to its behavior as a biological Thiersch cerclage rather than a true sphincter. Creation of a neo-smooth muscle sphincter cuff with colonic muscle is reasonable as it is easier to perform and adds minimally to the morbidity. Further studies to assess the role of this neo-sphincter in TAR are needed to assess the functional results.

Skeletal Muscle Sphincter

A variety of skeletal muscle sources have been used to create a neo-external sphincter including the gluteus maximus, adductor longus, and gracilis. Most of these were studied in the treatment of fecal incontinence, and have been adapted to TAR. Dynamization has also been used with these sources.

Gluteus Maximus

In 1902, Chetwood described the use of the gluteus maximus for the treatment of anal incontinence [35]. The use of the gluteus maximus for neo-sphincter construction after APR was first

reported by Chittenden in 1930 [10]. Though several studies have used this muscle in the treatment of fecal incontinence with varying success [36–38], its use in TAR and successful long-term outcomes have only recently been reported [39, 40]. Initial functional outcomes were poor, but improved markedly with bio-feedback and long-term functional exercises [39, 40]. Dynamic gluteoplasty has been shown to have better functional outcome in the management of fecal incontience [36, 37], but this has not been adapted for neo-sphincter reconstruction during TAR.

Unfortunately, gluteoplasty is difficult to perform, and is beset by frequent complications due to the muscular tension which leads to disruption of the ring, denervation, and eventual muscle atrophy. The procedure described by Farid seems to minimize these complications by using a fascia lata graft [41].

Adductor Longus

A single study described the creation of a neo-sphincter with the adductor longus femoris muscle during TAR [42]. Satisfactory results were obtained in 82 % of the 48 patients undergoing TAR. Unfortunately, no other studies exist using this muscle.

Gracilis

In 1952, Pickrell used the gracilis for sphincter construction for the treatment of fecal incontinence [43]. Though the gracilis neo-sphincter was incapable of maintaining prolonged muscle contraction, Simonsen used it for creation of a neo-sphincter after APR [44]. It was not until the 1990's that dynamization [45, 46] of the gracilis neo-sphincter propelled it to the procedure of choice.

Several techniques for the graciloplasty have been described. The techniques depend on whether unilateral or bilateral muscle is used, the configuration of the loop around the anus as shown in Fig. 16.1, the target of the fixation of the muscle, and timing of the dynamization with electrostimulation. Wong described an alpha loop with fixation of the tendon to the ipsilateral pubic bone [47]. Ho described fixation to the ipsilateral fascia [48]. Mander described several

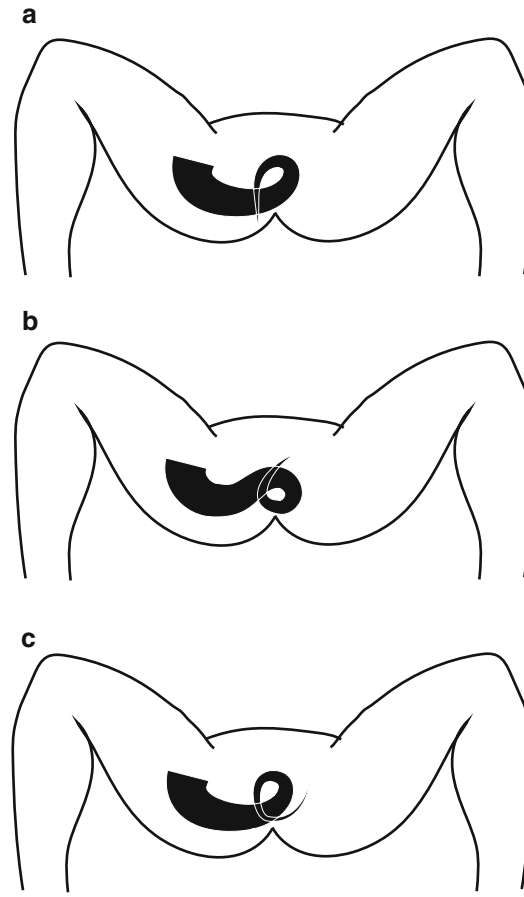

Fig. 16.1 Gracilus wrap around the colon: (**a**) alpha loop; (**b**) gamma loop; (**c**) epsilon loop

configurations: alpha loop with fixation to the ipsilateral ischial tuberosity, gamma loop with fixation to the contralateral ischial tuberosity, and epsilon loop with fixation to the contralateral ischial tuberosity [17]. Rosen described a split-sling technique with longitudinal division of the muscle and a colonic pull-through [49]. Cavina described the addition of a second gracilis in a split-sling configuration with one muscle tendon being fixed to the ischial tuberosity and the other to the pubic bone [50]. Geerdes described a double graciloplasty where the pelvic floor and sphincter complex were re-created simultaneously [22]. Some of the studies reported dynamization at the time of graciloplasty while Violi described using biofeedback before dynamization to minimize complications [51].

Graciloplasty is technically easier than gluteoplasty and achieves better functional results [52]. Dynamic graciloplasty is likely the best option for neo-sphincteroplasty during TAR and is associated with a higher success rate [46, 50]. Of the different configurations, the alpha loop is technically the easiest and most commonly used. Double graciloplasty is associated with higher morbidity and may not be ideal in TAR [53]. The largest series published by Cavina reported a 87 % success rate in 98 patients over several years [50]. However, stimulated graciloplasty still carries a high rate of complications and need for re-operation especially due to necrosis of the neo-anus, with the incidence of this complication higher after an APR than for the management of fecal incontinence [54].

Artificial Bowel Sphincter

In 1987, Christiansen and Lorentzen performed the first successful implantation of an artificial anal sphincter to treat patients with fecal incontinence [55]. A large multi-center trial noted clinical success superior to that of dynamic graciloplasty. This led to the use of the artificial bowel sphincter in TAR [56]. Encouraging results were reported by Romano et al. [57], Devesa et al. [21], and Ocares et al. [58]. However, explantation of the device can be as high as 47 % due to device-related complications [59], and long-term complications continue to increase with time [60].

Antegrade Continence Enema

The antegrade continence enema (ACE) as described by Malone et al. [61] in 1990 can be used to achieve a satisfactory pseudo-continent status with a perineal colostomy. With TAR, the most disabling symptom is constipation, and the addition of ACE can overcome this and provide better functional results in terms of both quality of continence and quality of life than retrograde enemas. Chiotasso first reported its use in conjunction with a perineal colostomy [62]. Quality of life was not significantly different between patients with an abdominal colostomy and those with an ACE and a perineal colostomy [63]. An advantage of using ACE with TAR is to render the patient pseudo-continent and to prevent disabling fecal impaction.

Outcomes

TAR attempts to restore the normal functions that have been lost: an acceptable reservoir with adequate capacity and ability to discharge, a discriminatory sensation, and a sphincter mechanism. The limitations of TAR, which in no way recreates the sensory apparatus and only partially recreates a functional reservoir and sphincter mechanism, prevent full continence in most patients.

All reports of TAR are retrospective analysis of a certain technique, with a small number of patients with relatively short follow-up. As such, only the morbidity and functional outcome can be evaluated. The impact of constipation, which is frequent after TAR, cannot be evaluated or compared between techniques. When compared with control subjects, quality of life appeared undiminished after TAR [64]. When comparing techniques, most studies fail to evaluate the role of a neo-rectum as discussed previously, and focus on the neo-sphincter.

Table 16.1 shows the outcomes of smooth muscle neo-sphincters especially when combined with ACE in TAR. As the quality of life is unchanged with ACE and a perineal colostomy [63], the addition of a neo-smooth muscle sphincter is questionable, but may act as a biological Thiersch cerclage of the colocutaneous anastomosis. The cuff has a higher-pressure zone and is able to maintain this increased pressure in most patients [31, 32], but Lasser pointed out that the lack of this tonicity did not correlate with a poor functional outcome. Early complications are related to dehiscence or necrosis of the perineal colocutaneous anastomosis, while late complications are related to mucosal prolapse and stricture of the neo-anus [31, 32]. The early complications were responsible for the conversion back to an abdominal stoma. Lack of irradiated

Table 16.1 Outcomes of neo-smooth muscle sphincters with ACE in TAR

Author	Patients (total/ evaluated)	Complications	Functional outcome
Lasser [31]	40/38	55 % 2 reconverted	87 % high satisfaction 11 % normal continence 5 % incontinence
Gamagami [32]	63/46	65 % 3 reconverted	59 % satisfactory continence 4 % incontinence
Portier [33]	18/17	33 % 0 reconverted	
Pocard [69]	12/12	Not reported	Quality of life scores equivalent to coloanal anastomosis
Hirche [65]	44/27	40 % minor, 7 % major 3 reconverted	81 % normal continence 19 % partial continence

Table 16.2 Outcomes of dynamic and adynamic graciloplasty in TAR

Author	Patients (total/ evaluated)	Dynamic	Adynamic	Complications	Functional outcome
Simonsen [44]	24/22	–	24	22 % major 65 % minor	77 % continence to solid/soft stool
Williams [46]	12	8	–		62 % continence to solid/ liquid stool
Santoro [66]	14/11	–	14	1 reconverted	73 % continence
Mander [17]	10/9	10	–	80 % complication 1 explant	100 % incontinence
Geerdes [22]	16/12	16	–	4 reconverted	31 % continence with enema
Cavina [70]	31/26	98	–	37 % complication 1 reconverted 4 explants	87 % continence to solid/ liquid stool
Rullier [53]	15/12	–	15	73 % complication 3 reconverted	78 % continence to solid stool
Rosen [49]	35	35	–	60 % complication 6 explants 5 reconverted	66 % continence to solid stool
Lirici [71]	3/3	3	–		Adequate continence
Ho [48]	17/11	17	–	40 % complication 2 battery explants	81 % continence without stimulation
Violi [51]	23/16	15	8	37 % complication	75 % continence

tissue in the pelvis may also decrease the perineal complications [33]. The higher continence noted by Hirche et al. [65] may be attributed to the perineal and neo-sphincter training, external electrostimulation of the perineal cuff, biofeedback and colonic irrigation.

Table 16.2 shows the outcomes of dynamic and adynamic graciloplasty in TAR. The overall morbidity of TAR with dynamic graciloplasty is high with frequent complications including erosion, colonic perforation, perineal sepsis, neo-sphincter necrosis, and stenosis or necrosis of the neo-anus. Device explantation in dynamic graciloplasty was also high due to erosion and infection. Despite this morbidity, dynamic graciloplasty was associated with a high continence in several studies. The continence does improve over time [48, 51].

Table 16.3 Outcomes of artificial bowel sphincter in TAR

Author	Patients	Complications	Functional outcome
Romano [57]	8	None	87 % continence Jorge-Wexner score: 3–9
Lirici [71]	3	1 skin erosion[a] 2 colon erosion[a]	Good continence of solids and gas
Devesa [21]	1	1 skin erosion[a]	Jorge-Wexner score: 6
Ocares [58]	1	1 erosion/infection[a]	

[a]Eventually explanted due to complication

Surprisingly, the continence achieved with adynamic graciloplasty was comparable to the dynamic counterparts [44, 66, 67]. Both Violi [51] and Ho [48] noted similar continence in their dynamic graciloplasty patients when the stimulator was turned off. However, patients in another series were completely incontinent without dynamization [46]. Despite these contradicting results, dynamization may not have a clear benefit, and the graciloplasty may serve as cerclage akin to the neo-smooth muscle sphincter discussed before. Interestingly, addition of ACE to TAR with a neo-reservoir and dynamic graciloplasty showed complete continence to solid and liquid stool in only 50 % of the patients [68].

Table 16.3 shows the outcomes of the artificial bowel sphincter in TAR. The largest series by Romano et al. [57] was the largest cohort with no explants of the sphincter. The rest of the reports had either skin or colonic erosion that led to the explantation of the sphincter.

Conclusion

The role of TAR and the preferred surgical approach is unclear. Patients must be extensively counseled on the lack of perfect continence, the high morbidity, and the need for re-operative surgery. The ability to understand that a colostomy may be needed in the future is essential. Foremost, the goal of curative surgery for anorectal malignancy needs to be reinforced rather than the desire for the absence of a colostomy. TAR after an APR is a challenging surgery with high morbidity. TAR at the time of an APR in select patients may be associated with lower morbidity.

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Postoperative Chemoradiation for Rectal Cancer

17

David Tan and Rob Glynne-Jones

Abstract

The management of patients with "locally advanced rectal cancer" (LARC) has evolved with a paradigm shift from postoperative to preoperative, because preoperative chemoradiation (CRT) improves local control and causes less acute and late treatment-related toxicity compared with postoperative. Hence, long-course preoperative CRT is considered a standard strategy in much of Europe and the USA.

However, the late effects on anorectal, sexual and urinary function, have prompted an increasing move to omit preoperative treatment in selected cases or early cT3N0 cancers. In addition, small early-staged low rectal cancers are increasingly being treated by local excision/transanal excisional microsurgery (TEM) in organ preservation strategies.

Consequently, the definitive surgical histopathology may reveal more advanced stages than predicted clinically, which raises the question whether such patients should be offered postoperative adjuvant pelvic radiation therapy, which also can be associated with complications (which may be more pronounced after radical surgery).

Keywords

Rectal adenocarcinoma • Neoadjuvant radiation • Postoperative chemoradiation • Radiotherapy chemotherapy • Local excision • Transanal excisional microsurgery

Introduction

In patients with locally advanced rectal cancer (LARC), not involving the mesorectal fascia (MRF), i.e., not threatening the circumferential resection margin (CRM) radical surgery with total mesorectal excision (TME) is the current standard of care. Prior to the TME era, high rates of local

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recurrence were observed after radical surgery, and 10–40 % of patients required a permanent stoma – even in tumours arising in the upper rectum. In the 1970s, non-randomised observational studies defined clinical and histopathological factors which predicted a high risk of both local and systemic recurrence in rectal cancer [1].

Three important historical studies from the USA supported the addition of 5-fluorouracil (5-FU)-based chemotherapy to radiation following surgery for the treatment of rectal cancer [2–4]. On this evidence the National Institutes of Health consensus conference endorsed the use of post-operative 5-FU based CRT for patients with stage II or III rectal cancer [5]. The integration of 5FU chemotherapy into chemoradiation schedules has traditionally been attractive as the strategy provides both a radio-sensitising agent within the pelvis, with potential systemic effects to eradicate distant micro-metastases. 5FU-based adjuvant chemotherapy has been firmly established and recommended as adjuvant treatment to prolong survival in patients following a curative resection with stage III colon cancer [6]. Hence, postoperative CRT regimens commonly involve a so called "sandwich" approach, in which 5FU-based chemotherapy is administered before and after chemoradiotherapy [3, 7].

Meta-analyses published in 2000 and 2001 further supported the benefit of the addition of radiotherapy over surgery alone [8, 9]. The Colorectal Cancer Collaborative Group published a meta-analysis in 2001 that evaluated 22 randomized trials comparing radiotherapy either before or after surgery to surgery alone. There was a trend towards an improvement in survival in the patients that received radiotherapy compared to surgery alone and support for the use of radiotherapy to reduce local recurrences from 22 to 12.5 %. With increasing confidence regarding the benefit of radiotherapy, it was being widely used by 2000. In contrast, the role of chemotherapy, while clear for colon cancer, was not as clear for rectal cancer.

Europe took a different approach. Randomised trials [10–12] showed short course preoperative pelvic radiotherapy (SCPRT) using 5×5Gy an effective treatment to reduce local recurrence in resectable and early rectal cancers. Two subsequent European trials – the Dutch TME study [13] and the CR07 trial [14] evaluated whether SCPRT simply compensated for poor surgical technique i.e. whether SCPRT still reduced local recurrence if TME was performed.

The risk of local recurrence, after a potentially curative resection, is high if microscopic tumour cells are detected within 1 mm of the CRM. So the control group recommended postoperative radiotherapy or chemoradiotherapy in the Dutch TME study and CR07 trial respectively in the event of a histopathological involved CRM. Both trials confirmed a reduction in local recurrence (LR), and demonstrated that preoperative radiotherapy is more effective than selective postoperative radiation or chemoradiation, but did not show an improvement in overall survival (OS) [13–16]. Patients with a positive CRM fared equally badly whether treated with SCPRT or postoperative CRT.

Further randomized controlled trials in both continents [17, 18] also showed reduced levels of local recurrence with less acute and late toxicity than postoperative therapy, but no improvement in disease free survival (DFS) or OS.

Hence, with the introduction of improved more accurate preoperative imaging (CT, transrectal ultrasound and MRI) to stage the patient clinically, both European and US data have served to modify the strategy of postoperative 5-FU-based chemoradiation (CRT) for patients with stage II or III rectal cancer, which has now been extrapolated to the preoperative setting.

Randomised trials have therefore established preoperative CRT as more effective than postoperative CRT [17, 18], that the RT component should be placed as early as possible if APER is performed [19, 20] and confirmed prolonged venous infusions of 5FU as the optimal concurrent chemotherapy partner [7]. However, trials have not addressed selection criteria, or the optimal radiotherapy dose or field size for CRT.

In this chapter we review the role of postoperative chemoradiation after emergency surgery, and when the histopathology suggests the staging is more advanced than predicted clinically after radical surgery or local excision. We discuss the relevant trials and make recommendations for the selection of appropriate patients for postoperative CRT.

Post-operative Chemoradiation

Historically the argument for preoperative versus postoperative chemoradiation focused on the ability to use histopathological staging rather than clinical staging and the operative findings to select appropriate patients for postoperative chemoradiation according to their risk of local recurrence. In the 1980s preoperative assessment was limited to the inexact science of digital rectal examination and the apparent tumour fixity to other structures. So surgically defined histopathology offered a better prediction of outcome, and therefore a series of randomised trials tested the respective roles of chemotherapy, radiotherapy and CRT in the post-operative adjuvant setting following surgical resection. This emphasis on postoperative CRT reflects the fact that until recently there have been no widely accepted and validated imaging methods to define locally advanced rectal cancer or unresectable disease. However, there were disadvantages in terms of enhanced acute and late toxicity from postoperative chemoradiation because of the frequent tethering of small bowel in the sacral bay by adhesions following an AP excision of the rectum (APER). The long-term toxicity of postoperative chemoradiotherapy may be more limited than we originally believed with current techniques, and with the current ability to use IMRT and specify small bowel as an organ at risk (OAR), late toxicity may be even lower.

There are many countries where postoperative chemoradiation is still performed based on histopathology for locally advanced rectal cancers and still considered as standard clinical practice. For example, the National Comprehensive Cancer Network (NCCN) guidelines recommend routine post-operative chemoradiation for initial cT1-2 N0 rectal cancers which were subsequently found to be pT3N0M0 or pT1-3,N1-2(NCCN guidelines version 3.2014) [21]. A recent Italian study reported outcomes in more than 1,000 patients treated with adjuvant 5-FU based chemoradiotherapy with patients treated from 1985 to 2005 [22]. 842 (63 %) patients were stage III and 496 (37 %) were stage II. Out of 448 recurrences observed, only 96 had local failure as a first event and only 71 of these patients died with an isolated local recurrence. Postoperative CRT may be more conventional in areas where medical resources are scarce, such that patients present late and acutely, there are long waiting-lists for radiotherapy or the MDT is not comprehensive or dysfunctional.

Selective Postoperative Chemoradiation

Selective postoperative chemoradiation on the basis of an involved CRM appears inferior to blanket SCPRT [14]. In the CR07 trial there were no details on compliance in the 53/77 patients who received selective postoperative CRT. Hence, it's not known (as it is in the German study) whether the majority of recurrences occurred in the treated or non-treated patients –i.e. whether it was an issue of compliance. In the CR07 trial doses of RT mandated were also modest (45 Gy) compared with standard postoperative CRT trials e.g. the German trial mandated 55.8 Gy postoperatively [17] and US trials used 50–54 Gy.

Despite TME surgery performed with curative intent, many patients still have a high risk of local and metastatic recurrence. As yet we lack the ability to identify rectal cancers that are never going to recur following surgery.

Finally, high quality pathological reporting is required for decisions to be made regarding additional postoperative treatment.

Randomised Trials Evaluating Post-operative CRT Versus Surgery Alone (Table 17.1)

NSABP R-01

The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial randomised 574 patients with histologically staged Dukes B and C rectal cancer following a curative resection to three groups: a control group receiving no further treatment; postoperative radiation

Table 17.1 Randomized trials evaluating postoperative (chemo)radiation versus surgery alone

Trial	No. of pts	Randomization	TME	5 year LR	5 year DFS	5 year OS	Remarks
GITSG 7175 (GITSG 1985) [2]	227	(i) Surgery alone (ii) Adj 5FU/Semustine (iii) Adj RT (40–48 Gy) (iv) Adj 5FU-RT then chemo	No	24 % 27 % 20 % 11 % (NS)	45 % 54 % 52 % 67 % (**SS**)	36 % 46 % 46 % 56 % (NS)	Long-term results demonstrated SS improved OS for combination group.
NSABP R-01 (Fisher 1988) [4]	555	(i) Surgery alone (ii) Adj MOF chemo (iii) Adj RT	No	25 % NS 16 % (**SS**)	29 %[a] 47 %[a] (**SS**) NS	37 %[a] 60 %[a] (**SS**) NS	No benefit for adjuvant MOF chemotherapy in females.
NCCTG 79-47-51 (Krook 1991) [3]	204	(i) Adj RT (ii) Adj "sandwich" 5FU-RT with 5FU/Semustine	No	25 % 13 % (**SS**)	37 % 58 % (**SS**)	46 % 53 % (**SS**)	Increased G3-4 diarrhea with CRT (4 % vs 22 %).
NSABP R-02 (Wolmark 2000) [26]	694	(i) Adj MOF chemo only[a] (ii) Adj MOF chemo + 5FU RT[a] (iii) Adj 5FU/LV chemo only (iv) Adj 5FU/LV chemo + 5FU-RT	No	CT vs CRT: 13 % vs 8 % (**SS**) MOF vs 5FU/LV: NS	CT vs CRT: NS MOF vs 5FU/LV: 47 % vs 55 % (**SS**)	CT vs CRT: NS MOF vs 5FU/LV: NS	Only males received MOF chemo due to results of NSABP R-01.
Tveit 1997 [27]	144	(i) Surgery alone (ii) Adj 5FU-RT	No	30 % 12 % (**SS**)	46 % 64 % (**SS**)	50 % 64 % (**SS**)	No serious toxicity with adj CRT.
Balslev 1986 [28]	494	(i) Surgery alone (ii) Adj RT	No	Adj RT improves 2 year LC	NS	NS	No benefit for RT in Duke's B.
MRC 1996 [29]	469	(i) Surgery alone (ii) Adj RT	No	34 % 21 % (**SS**)	45 % 48 % (NS)	46 % 52 % (NS)	Late complications rare, not worse in RT arm
ECOG 4276 (Mansour 1991) [68]	237	(i) Adj RT (ii) Adj MOF (iii) Adj RT then chemo	No data	No difference	No difference	46 % 47 % 50 % (NS)	Abstract only

TME total mesorectal excision, *LR* local recurrence, *OS* overall survival, *DFS* disease-free survival, *Adj* adjuvant, *NS* not statistically significant, *SS* statistically significant, *5FU* 5-fluorouracil, *MOF* semustine, vincristine and 5-fluorouracil, *LV* leucovorin, *RT* radiotherapy, *CT* chemotherapy, *CRT* chemoradiation

[a]In males only

therapy alone; and postoperative chemotherapy consisting of semustine, vincristine, and 5-FU (MOF) [4]. The dose of radiation was 46–47 Gy, or 51–53 Gy for those patients intended to receive a perineal boost.

Postoperative chemotherapy significantly improved DFS ($p=0.006$). with a borderline improvement in OS ($p=0.05$) from chemotherapy. Only males benefitted from chemotherapy in terms of DFS and OS, and women actually achieved worse OS (which did not reflect treatment associated deaths). Postoperative radiotherapy decreased local regional failure to 16 % versus 25 % in the control group and 21 % in the chemotherapy group ($p=0.06$ for the comparison with the control group). Radiation itself did not confer any significant benefit in terms of DFS or OS for either males or females.

GITSG 7175

The Gastrointestinal Tumor Study Group (GITSG) trial evaluated the benefit of the respective roles of radiation, chemotherapy, or combined modality therapy (chemoradiation) in the treatment of locally advanced rectal cancer [2]. After curative surgery 202 patients were randomized into four different groups: a control group receiving no further treatment; adjuvant chemotherapy only with semustine and 5-fluorouracil; adjuvant radiotherapy only at doses of 40–48 Gy, and finally a combination of chemotherapy and radiotherapy. After 80 months follow-up. significantly better DFS was observed in the combination therapy arm compared to resection alone, although there was no significant difference in OS in four groups 55 % recurred in the surgery alone control arm versus 46 % in the chemotherapy alone arm, 48 % in the radiation alone arm, and 33 % with combined CRT ($p=0.04$). The comparison between the control arm and CRT was even more significant ($p=0.009$). The long-term follow-up results of this study confirmed a significantly improved overall survival in the combination treatment group compared to surgery alone group [23].

NCCTG 79-47-51

The North Central Cancer Treatment Group (NCCTG) trial (protocol 79-47-51) evaluated a short chemotherapy regimen combined concurrently with a higher dose of radiation and the same higher-dose radiation regimen alone [3]. After curative surgery 209 patients were randomised to receive postoperative radiation therapy alone to a dose of 45 Gy plus a 5.4 Gy boost or postoperative semustine and 5-FU chemotherapy combined with the same radiation regimen. Patients randomised to CRT started treatment radiation after two cycles of chemotherapy, followed by two further cycles of chemotherapy. After a median follow-up time of over 7 years, the estimated 5-year recurrence rate in the radiation arm was 63 % compared with 42 % in the CRT arm. The CRT arm reduced overall recurrence by 34 % compared to the radiation alone arm ($P<0.003$). The addition of chemotherapy to radiation reduced both local recurrence (25 % versus 13 % $P<0.02$) and distant metastases (43 % versus 29.5 % $P<0.003$). OS was also significantly improved ($p=0.025$). CRT increased the acute toxicity in terms of nausea, vomiting, diarrhea, stomatitis, leukopenia, and thrombocytopenia. It should also be noted that a subsequent publication highlighted that there was a significant increase in severe diarrhoea (≥Grade 3) in the CRT arm (22 vs. 4 %, $p=0.001$) and this was more marked in patients who underwent a low anterior resection compared with those who had an APER ($p=0.006$) [24]. There was no significant increase in late morbidity in the CRT arm. In the light of this evidence, the National Institute of Health Consensus Conference in 1990 [25] recommended post-operative chemoradiation as the standard of care in the United States for curatively resected rectal cancer.

NSABP R-02

The NSABP R-02 trial evaluated whether adding radiation to chemotherapy was better than chemotherapy alone in terms of postoperative adjuvant therapy of Dukes B and C rectal cancers

[26]. A radiation dose of 45 Gy with a 5.4 Gy boost was used. In the light of the NSABP R-01 results, male patients were randomised to one of four postoperative treatment groups: (1) 5-FU plus leucovorin (LV), (2) 5-FU plus LV plus radiation, (3) MOF chemotherapy, and (4) MOF chemotherapy plus radiation. Female patients were randomly assigned to 5-FU plus LV or 5-FU plus LV plus radiation The chemotherapy during radiation therapy for both combined modality arms involved bolus infusions of 5-FU during the first 3 and last 3 days of radiation therapy.

The results of NSABP R-02 supported the previous results of the NSABP R-01 study, where postoperative radiation therapy resulted in decreased locoregional recurrence, but not in improved DFS or OS. In NSABP R-02 radiation therapy added to chemotherapy again reduced the cumulative incidence of locoregional recurrence as a first event (8 % versus 13 % at 5 years) compared to chemotherapy alone (HR = 0.57), but had no impact on DFS, or OS. Males treated with 5-FU plus LV compared with MOF experienced significantly better DFS (55 % versus 47 % at 5 years), but not OS (65 % compared with 62 % at 5 years).

European Studies

A randomised trial of postoperative 5FU based chemoradiation against surgery alone in Dukes B and C rectal cancer to a dose of 46 Gy demonstrated a significant improvement in local control, disease free survival and overall survival for postoperative chemoradiation [27]. Other randomised trials comparing postoperative radiotherapy with surgery alone [28, 29] showed some benefit in local control but no survival benefit. The small EORTC trial randomised only 172 patients and did not show any benefit in OS or local control from postoperative irradiation [30] following resection of locally advanced rectal carcinoma (Dukes B and C).

Many of these studies have been criticised because the design delayed the use of fully adequate systemic doses of 5FU until after the completion of the chemoradiation phase.

Randomised Trials Evaluating the Optimal Concurrent Chemotherapy Regimen (Table 17.2)

Subsequent successive studies in the postoperative setting have attempted to improve outcomes by modifying and intensifying the concurrent chemotherapy component. This strategy has been associated with only marginal success.

Intergroup/NCCTG 86-47-51 Trial

This trial reflected the fact that phase III trials comparing prolonged intravenous infusion (PVI) versus bolus 5FU suggested improved response rates in mCRC with PVI, and hence the most commonly preferred administration of 5-flurouracil was (225–300 mg/m^2 daily). To compare the bolus administration with a continuous intravenous infusion concurrently with RT, the NCCTG randomized 660 patients in two arms [7]. Both arms received concurrent radiotherapy. The first group received bolus 5FU on three consecutive days as a rapid infusion of 500 mg/m^2 while the other group received 5FU as a protracted infusion (225 mg/m^2/day). Four-year relapse free survival was 63 % in continuous infusion group while it was 53 % in the bolus arm ($P = 0.01$). Significant difference for 4-year overall survival was also observed in the same study (70 % vs 60 % in continuous infusion and bolus group respectively), ($P = 0.005$). Interestingly, no benefit was observed for local relapse in the continuous infusion group ($P = 0.110$).

Intergroup 0114

A further postoperative chemoradiation study (Intergroup 0114) compared postoperative 5FU alone versus 5FU plus low dose folinic acid, 5FU and levamisole or the combination of 5FU levamisole and low dose folinic acid in combination with radiotherapy [31]. Results showed that the novel combination regimens did not improve outcome over bolus 5FU alone.

Table 17.2 Randomized trials evaluating the optimal concurrent chemotherapy regimen

Trial	No. of pts	Randomization	TME	5 year LR	5 year DFS	5 year OS	Remarks
NCCTG 86-47-51 (O'Connell 1995) [7]	660	(i) Adj 5FU/Semustine + bolus 5FU-RT (ii) Adj 5FU/Semustine + PVI 5FU (iii) Adj 5FU alone + bolus 5FU (iv) Adj 5FU alone + PVI 5FU	No	PVI vs bolus: NS 5FU alone vs 5FU/Semustine: No SS difference	PVI vs bolus: 63 % vs 53 % (**SS**) 5FU alone vs 5FU/Semustine: No SS difference	PVI vs bolus: 70 % vs 60 % (**SS**) 5FU alone vs 5FU/Semustine: No SS difference	Higher incidence of severe diarrhea with PVI 5FU and severe leukopenia with bolus 5FU.
INT 0114 (Tepper 2002) [31]	1695	(i) Adj 5FU alone + 5FU-RT (ii) Adj 5FU/LV + 5FU-RT (iii) Adj 5FU/levamisole + 5FU-RT (iv) Adj 5FU/LV/levamisole + 5FU-RT	Some pts	No SS difference across all groups	No SS difference across all groups	No SS difference across all groups	
INT 0144 (Smalley 2006) [33]	1917	(i) "Sandwich" bolus 5FU + PVI 5FU-RT (ii) "Sandwich" PVI 5FU + PVI 5FU (iii) "Sandwich" bolus 5FU/LV + bolus 5FU/LV	No	No SS difference across all groups	No SS difference across all groups	No SS difference across all groups	

TME total mesorectal excision, *LR* local recurrence, *OS* overall survival, *DFS* disease-free survival, *Adj* adjuvant, *NS* not statistically significant, *SS* statistically significant, *5FU* 5-fluorouracil, *PVI* prolonged venous infusion, *LV* leucovorin, *RT* radiotherapy

Intergroup 0144

In addition, the Intergroup 0144 study [32] randomised 1,917 patients with pathologically staged T3-4,N0-1 rectal cancer into three arms comparing bolus and PVI of 5FU combined with 50–54 Gy of postoperative radiotherapy. With a median follow-up of 4.6 years, the overall survival was 72 % for PVI versus 67 % for bolus. However, this difference did not meet the predefined definitions of statistical significance [32]. The authors commented when discussing the risks of local recurrence – "Our patients overwhelmingly did not receive TME and had nodal evaluation inferior to current recommendations."

Greek Study

A small Greek randomised co-operative trial with 321 patients evaluated the addition of irinotecan to postoperative CRT compared to LV-bolus and 5FU with radiotherapy [33], but observed no difference between the arms in 3-year OS, DFS or and local relapse-free survival. Grade 3 and 4 toxicity were similar in both arms, but the incidence of severe leucopenia was significantly higher with irinotecan.

German Study

More recent European data [34] suggest that, based on DFS and OS, although local recurrence was similar in each group (i.e. 12 (6 %) in the capecitabine group vs 14 (7 %) in the 5-fluorouracil group), capecitabine (1,650 mg/m^2 during days 1–38) can replace a bolus regimen of 5-fluorouracil in postoperative adjuvant chemoradiotherapy regimens for patients with locally advanced rectal cancer [33]. Hence most accept that Capecitabine is equivalent to 5-FU.

Randomised Trials Comparing Preoperative and Postoperative CRT (Table 17.3)

The German CAO/ARO/AIO – 94 Trial

In the landmark German CAO/ARO/AIO – 94 trial [17] 823 patients with cT3 or cT4 stage or node positive were randomised between preoperative CRT and post-operative CRT using 5FU as a 120-h continuous infusion during the 1st and 5th weeks of radiation at a dose of 1,000 mg/m^2 of body surface. Patients were also intended to receive post-operative adjuvant chemotherapy in both arms. Acute and late toxicity were significantly reduced with the pre-operative approach – although it should be recognised that a higher radiation dose was mandated for the postoperative regimen (55.8 Gy compared to 50.4 Gy). Loco-regional failure was only 6 % in the preoperative arm versus 13 % in the post-operative arm. There was however no difference observed in the distant metastases rate, DFS or OS. Updated data with 10-year follow-up showed 17 of the 38 local recurrences in the postoperative arm was observed in the 145 patients who did not receive CRT [35].

NSABP R-03

The NSABP R-03 trial [18] randomised 267 of an initially intended 900 patients between preoperative or postoperative 5-FU-based chemoradiation. The preoperative group also received a short 6 week course of bolus 5-fluorouracil with leucovorin followed by radiation (45 Gy in 25 fractions with an additional 5.4 Gy boost). Postoperatively patients were intended to receive 24 weeks of weekly 5-FU and LV. Patients in the postoperative arm received the same chemoradiation and chemotherapy. The preoperative arm showed an advantage in 5-year DFS (64.7 % vs 53.4 %, P=0.011), but

Table 17.3 Randomised trials evaluating preoperative versus postoperative chemoradiation in resectable rectal cancer

Trial	Duration of trial	No. of pts	Randomisation	No. per arm	TME	Primary endpoint	5 year LR	5 year DM	5 year OS	5 year DFS	G3-4 toxicity
INT 0147 (No data)	5 years	53	Preop 50.4 Gy + FU/LV vs Postop 50.4 Gy + FUFA	No data	No	OS	No data (closed early)				
NSABP R03 (Roh 2010) [18]	1993–2003 10 years	267	Preop 45 Gy + FU/LV vs Postop 45 Gy + FU/LV	123 131	No	OS	11 % 11 % (NS)	Not stated	74 % 66 % (NS)	65 % 53 % (**SS**)	41 % 49 %
CAA/ARO/AIO-94 (Sauer 2004) [17]	1995–2004 9 years	823	Preop 50.4 Gy + 5FU vs Postop 50.4 Gy + 5FU	405 394	?Yes in later years	OS	6 % 13 % (**SS**)	36 % 38 % (NS)	76 % 74 % (NS)	68 % 66 % (NS)	27 % 40 %

TME total mesorectal excision, *LR* local recurrence, *DM* distant metastasis, *OS* overall survival, *DFS* disease-free survival, *NS* not statistically significant, *SS* statistically significant, *5FU* 5-fluorouracil, *LV* leucovorin

no significant difference in OS (P = 0.65). Interestingly, lower levels of acute and late treatment related toxicities were observed in the preoperative treatment arm.

Korean Trial

A small prospective trial aimed to determine the effect of different sequences of radiation and chemotherapy, after curative resection of Stage II and III rectal adenocarcinoma, on DFS and OS. A total of 308 patients were randomized to early or late postoperative radiotherapy to a dose 45 Gy in 25 fractions either starting on Day 1 of the first chemotherapy cycle in the early RT arm or on Day 1 of the third chemotherapy cycle in the late RT arm. Chemotherapy involved 8 cycles of chemotherapy, consisting of fluorouracil 375 mg/m^2/day and leucovorin 20 mg/m^2/day, at 4-week intervals. The initial results of the study were published in 2002, and suggested that early RT conferred a significant advantage in DFS compared with late RT plus chemotherapy [19]. However, after 10 years of follow-up, the trial failed to show a statistically significant advantage in DFS (71 % vs. 63 %; p = 0.162) for early RT with concurrent chemotherapy. OS was not significantly different between the two treatment groups. However, the results suggest early postoperative chemoradiation should be considered for patients requiring an abdomino-perineal resection [20].

If Preoperative CRT Is Omitted, Which Patients Should Receive Postoperative CRT?

The most important pathological and histopathological features impacting on the risk of local recurrence include: overall pathological TNM stage, T substage, R-status (R0,R1,R2), CRM status, adequacy of lymph node assessment, the number of involved lymph nodes, extracapsular extension, the presence of extranodal deposits, quality of mesorectal excision (whether within the muscularis plane), tumour differentiation, lymphovascular invasion (LVI), EMVI and perineural invasion (PNI). To some extent all of these (except PNI) can be predicted as likely by preoperative imaging, although this prediction does not account for the fallibility of the radiologist, the surgeon and the pathologist. Also there are occasionally unforeseen operative findings – with involvement of other abdominal organs or peritoneal disease. All the above need to be taken into consideration before deciding to recommend postoperative CRT (see Table 17.4), and the current variability in outcomes mean that these imaging results should always be discussed with the patient with a view to informed consent and shared decision-making.

Table 17.4 Indications in author's (RGJ) unit for postoperative chemoradiation

Sufficient and necessary	Insufficient and unnecessary
CRM ≤ 1 mm	pT1/pT2
pT4b	pT3
pN2 extracapsular	CRM >2 mm
Extranodal deposits	pT4a
pN2 if poor mesorectal quality	pN1
Sufficient	
pN2 low tumours within 4 cm of anal verge (risk of involved LPLN)	
Borderline sufficient	
pN2 if good mesorectal quality	
CRM 1–2 mm	
Circumferential obstructing tumours	

Data from Erlangen show a higher risk of local recurrence after primary surgery for patients with at least four involved regional lymph nodes [36], but it is essential to know the quality of the mesorectal excision. The number of examined lymph nodes can also be regarded as a measurement of the quality of surgery. In the EORTC 22921 trial the median number of examined lymph nodes was 8 (range 0–45) but mesorectal quality was not evaluated. In the Dutch TME study approximately 50 % had a good quality mesorectal excision, but the median number of lymph nodes retrieved was only 7 and 12 or more LN were found in only 18 % of the cases [37, 38].

Table 17.5 Grading of quality and completeness of the mesorectum in a total mesorectal excision specimen

	Mesorectum	Defects	Coning	CRM
Complete	Intact, smooth	Not deeper than 5 mm	None	Smooth, regular
Nearly complete	Moderate bulk, irregular	No visible muscularis propria	Moderate	Irregular
Incomplete	Little bulk	Down to muscularis propria	Moderate–marked	Irregular

Both the specimen as a whole (fresh) and cross-sectional slices (fixed) are examined in order to make an adequate interpretation

The Quality of the Mesorectum

Hermanek, Quirke and Nagtegaal have promoted the importance of assessing the quality of the mesorectum in the surgical specimen and recording by means of a photograph, with three grades based on the completeness of the removal of the mesorectum (Table 17.5).

A TME specimen ideally should have a smooth surface, without incisions or tearing, as an indication of successful surgery. 'Coning' is a tendency for the surgeon to cut inwards towards the central tube of the rectum during distal dissection, rather than staying outside the visceral mesorectal fascia, which gives the specimen a tapered, conical appearance. This observed feature is an indication of suboptimal surgical quality [39]. Two trials – the CLASSICC study of the Medical Research Council in the United Kingdom and the Dutch TME trial have originally defined a protocol to assess the quality of surgery. This classification has been utilised in the MERCURY study and the CRO7 study [15]. Multivariate analysis will need to be validated in future randomised studies. For this reason the quality of the mesorectum should be part of the evaluation of the need for postoperative CRT. Lymph node retrieval in rectal cancer is dependent on many factors-the tumor, the patient, the surgeon, the radiotherapist, and the pathologist, but poor quality mesorectal specimens may leave involved nodes within the patient.

The Impact of Chemotherapy on Local Recurrence

Adjuvant chemotherapy 'per se' may impact on local recurrence. In the late results of the EORTC 22921 trial, at 10 years, cumulative incidence of local relapse was 22.4 % (95 % CI 17.1–27.6) with radiotherapy alone, 11.8 % (7.8–15.8) with neoadjuvant radiotherapy and chemotherapy, 14.5 % (10.1–18.9) with radiotherapy and adjuvant chemotherapy and 11.7 % (7.7–15.6) with both adjuvant and neoadjuvant chemotherapy ($p = 0.0017$) [40]. More recent studies [41, 42] have confirmed that the addition of oxaliplatin to 5FU-based chemotherapy is more effective and improves DFS and OS in patients with Stage III colon cancer. FOLFOX is now considered an international standard as adjuvant chemotherapy for colon cancer in stage III disease or high risk stage II colon cancer after curative resection. However, 5FU based chemoradiation has not been compared against FOLFOX alone without radiotherapy.

In more recent analyses, postoperative adjuvant CRT was associated with significantly higher cause specific survival (CSS) when compared with surgery alone, but in contrast, the benefit of Neo-Adjuvant RT was not significant [43].

Local Excision/TEM

Given the morbidity of radical surgery and the emotional consequences of a permanent stoma, more conservative approaches such as local excision followed by CRT are attractive alternatives for selected cases. Traditionally, transanal operations for early rectal cancers rarely achieved complete tumour resection and high rates of local recurrence were observed. Transanal endoscopic micro-surgery (TEM) [44] offered better visualization and access, which facilitated full-thickness excisions and achieved clear surgical margins in more than 90 % of patients [45, 46]. There is now increasing interest in local excision/TEM and postoperative chemoradiation therapy

Table 17.6 Studies evaluating local excision plus post-operative RT/CRT: crude local recurrence (LR) by T stage

Author, year	No. of pts	Adjuvant treatment	Median follow-up	LR in T1 tumors	LR in T2 tumors
Willett, 1989 [69]	26	RT	5 years	10 % (1/10)	18 % (2/11)
Ota, 1992 [70]	31	RT +/– 5FU	35 months	0 % (0/16)	7 % (1/15)
Valentini, 1996 [71]	21	RT	4½ years	11 % (1/9)	17 % (2/12)
Wagman, 1999 [51]	39	RT +/– 5FU	41 months	0 % (0/6)	24 % (6/25)
Steele, 1999 [53]	51	5FU-RT	4 years	Not tested	14 % (7/51) (5-year rate)
Greenberg, 2008 [54]			7.1 years		18 % (10-year rate)

(CRT) as an organ -sparing approach for selected small early staged low rectal cancers – particularly in the elderly and frail.

The current rationale for local excision of cancers in the low rectum derives from a report from St Marks Hospital [47]. The stumbling block for accepting that local excision is equally effective to radical surgery in fit patients is finding selection criteria that identify patients unlikely to recur. A multitude of factors such as size, ulceration, imaged depth of penetration, detection of regional lymph node involvement and pathological grade have been reasonably successful at categorising patients as high or low risk. For example, in a single institution experience, the likelihood of microscopic regional nodal involvement was shown to be rare in T1 tumours but increased to 10–30 % in T2 tumours, and was as high as 60 % in T3 tumours [48]. Hence current data suggest that this approach should be limited to patients with either T1 tumours with no(?) adverse pathologic factors or favourable T2 tumours. Transmural (T3) tumours have a much higher (approaching 25 %) local recurrence rate [49].

One of the first to document postoperative adjuvant chemoradiation following local excision [50] reported a DFS of 88 % with a median follow up of 27 months for the 17 patients. A subsequent retrospective study suggested post operative RT/CRT was of benefit with 5-year local control after local excision increasing from 33 to 85 %, but several late local failures beyond 5 years following irradiation were observed [45]. In a later study of 39 patients treated with local excision followed by postoperative radiation therapy +/– 5-FU-based chemotherapy, crude local failure increased with increasing T stage: 0 % T1, 24 % T2, and 25 % T3. Actuarial local failure at 5 years was 31 % for T2 disease [51]. In another small retrospective study, after a median follow-up of 3 years, all 12 patients who received local excision and radiotherapy remained disease free, whereas a 50 % recurrence rate was observed in patients who refused adjuvant radiotherapy [52].

In the non-randomised prospective CALGB trial 51 patients with T2 cancers received CRT after local excision, and 7/51 experienced isolated local recurrence [53]; In the updated results with more than 7 years median follow-up, the local control rates appeared less impressive [54]. NCCN guidelines appear to recommend abdominal surgery for these patients, but many might still choose to decline radical surgery. Usually patients are obliged after informed discussion to choose between anterior resection/APER or postoperative adjuvant CRT.

The results of local excision and postoperative RT/CRT are limited to a few small studies (Table 17.6), but there have been no randomised controlled trials, which randomise a local treatment e.g. local excision and (chemo)radiation versus AP excision of the rectum. In general, the strategy of using post-operative chemoradiation to compensate for inadequate surgery has historically been associated with limited success. However, experience in post-operative (chemo) radiation has been gained for low lying T2 and T3 rectal cancers in groups of patients considered inoperable either because of their poor general condition relating to age or frailty, performance status or severe other co-morbidity and also in those patients who, despite informed explanations, have adamantly refused to undergo an AP excision of the rectum.

Radiotherapy Target Delineation/ Planning

The major challenge in radiotherapy planning remains to achieve the best chance of cure with the least probability of late morbidity. The probable site of subclinical disease needs to be encompassed with adequate doses, while simultaneously ensuring that the surrounding normal tissues are spared as far as possible. The major organs at risk in the pelvis include the small bowel, anal sphincter and bladder. Clinical target volumes (CTV) for small early pT1 and pT2 cancers after local excision (if radiotherapy is required) may not be the same as the preoperative CTV in more locally advanced cT3 and cT4 tumours.

Despite recent advances in imaging (allowing visualisation of structures such as the mesorectal fascia) and more meticulous radiation treatment delivery, total dose and field size remains controversial, reflecting different conventions, skills, and day-to-day practices. Inter-trial comparisons suggest that local control rates are not improved with larger field sizes or higher radiotherapy doses i.e. 50.4 Gy in 1.8 Gy fractions. There is a trend towards reduced overall and bowel toxicity with smaller field sizes i.e. superior border below sacral promontory, and a lower dose of 45 Gy in 1.8 Gy fractions. In addition, the trials with the lowest rates of overall and bowel toxicity (ACCORD-12/0405 PRODIGE 2, STAR-01 and NSABP R-04) also utilized daily continuous concurrent chemotherapy regimens and, in the case of STAR-01, 3D conformal radiotherapy techniques [55].

The Roels delineation guidelines were developed for CTV delineation in the preoperative setting [56], and identified five predominant areas of risk for local recurrence and potential lymph node involvement. Advice is also given regarding coverage of primary tumour, radiologically involved lymph nodes, mesorectum, perirectal nodes, external iliac nodes, internal iliac nodes and presacral nodes. In contrast, the RTOG guidelines are a one-size-fits-all consensus of experts [57].

Target Delineation Following Radical Surgery

Following radical curative surgery there is clearly no GTV. Hence a CTV is delineated with expansion for PTV. We are not aware of recommended field sizes for postoperative CRT. It seems sensible to examine the planning CT scan for evidence that mesorectal tissue is still present as this is associated with local recurrence and should be delineated as part of the CTV, since some local recurrences historically reflected inadequate mesorectal resection [58]. In a Danish study, inadvertent residual mesorectal tissue was commonly observed on postoperative MRI (54 (40 %) of 136 patients), particularly after partial mesorectal excision [59].

Target Delineation Following Local Excision

In the case of post operative CRT after local excision, the whole mesorectum will be in situ. Early cT1and cT2 rectal tumours and the extent of lymph node dissection have been discussed [60]. For cT1 cancers only 1 % were pN2 and only 3/198 patients had lymph node metastases beyond the pararectal mesorectum. In contrast, for cT2 tumours 58/194 (30 %) had N1 and 14 (7 %) had N2 nodal disease, but only 8/194 (4 %) had lymph node metastases beyond the pararectal mesorectum. Descriptions of mapping of sites of lymph nodes within the mesorectum in more advanced stages are sparse and performed on few patients [61]. We therefore usually treat the whole mesorectum 5 cm in the cephalad direction superior to the excison site of the primary tumour, and 3 cm distal following local excision.

Complications of Postoperative CRT After Radical Surgery

The actuarial risk of chronic small bowel toxicity is reported to vary between 7 and 42 % at 5 years [24, 62]. In historical series, the larger the volume

of small bowel (SB) irradiated, the higher the risk of acute and late toxicity [62–66]. More recent trials with more modern radiotherapy techniques and the use of capecitabine [67] have shown a more favorable toxicity profile and compliance than those of the German or NASBP R-03 trial.

It is clear therefore that the potential for using IMRT to reduce the amount of small bowel within the CTV superiorly and anteriorly in small tumours and using concurrent capecitabine may reduce the risks of late bowel toxicity.

Conclusion

There is increasing controversy regarding the role of pre and postoperative CRT combined with radical surgery – particularly in the case of pT3N0 patients. There is little evidence from SEER data that postoperative adjuvant CRT is of benefit in curatively resected rectal cancer with pT3N0 histology. If the decision to omit preoperative radiotherapy is flawed by inaccurate clinical staging, postoperative CRT may be required to salvage a high risk of local recurrence. Postoperative CRT can be associated with complications (often more pronounced after radical surgery). We recommend necessary, sufficient, borderline sufficient and insufficient indications for the use of postoperative chemoradiation. However, this selection can only be rationally performed if there is evidence of the quality of the mesorectum in the TME specimen, and there are sufficient nodes resected (although there is an association between these two factors). We recommend the radiation component should be placed as early as possible.

Compliance to postoperative CRT is often poor –particularly after APER because of healing problems, and morbidity is significant. Hence treatment should be individualized, and patients treated selectively and with caution, according to the predicted risk of local versus metastatic disease, and the potential for late morbidity.

Postoperative Chemoradiation Learning Points

- Local recurrence after radical surgery for rectal cancer can cause devastating symptoms
- Most postoperative adjuvant trials were performed in patients with clinically staged pT3-4 N0 or N+(or ultrasound based)
  - Most trials evaluating postoperative chemoradiation were performed in the pre-TME era, which might limit their application in modern practice.
  - Outcomes with adjuvant chemotherapy alone in rectal cancer have been of more limited benefit than colon cancer (Cochrane review)
  - Post-op RT alone may modestly improve local control, but has no impact on distant metastases, disease-free survival, or overall survival and RT alone is therefore considered obsolete.
  - Prospective randomized trials showed that combined CRT with 5-FU improved local control, distant control, as well as survival in two randomized trials
  - Postoperative chemoradiation is associated with morbidity, which characteristically has a late onset and is often permanent.
  - RT plus continued infusion of 5-FU improves survival over bolus 5-FU. Other concurrent drugs have so far not shown additional benefit
  - For postop T3-4 or N+: Adjuvant chemotherapy (5-FU/LV), followed by continuous infusion 5-FU+RT, then additional 5-FU/LV, or alternatively, initial continuous infusion 5-FU+RT followed by adjuvant chemotherapy, has been recommended in NCCN guidelines

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18 Patient Surveillance After Curative-Intent Treatment for Rectal Carcinoma

Frank E. Johnson, Anna M. Priddy, and David Y. Johnson

Abstract

This chapter briefly describes the history of patient surveillance after curative-intent primary treatment for rectal carcinoma. It spans prehistoric times to the present. Notable scientific advances and notable innovators are mentioned.

Keywords

Anesthesia • Second-look procedure • Randomized trials • Computer • Surveillance

Cancer is known to have afflicted prehistoric humans. Skeletal remains with features characteristic of osteogenic sarcoma (and perhaps myeloma and bony metastases from soft tissue cancers) have been discovered. These lesions were quite uncommon, presumably because life expectancy was short and because most cancers occur in old people. The earliest known remaining written document dealing with human illness is the Edwin Smith Papyrus, dating from pharaonic times (2500–3000 BC) and discovered in Egypt. The author is believed to be Imhotep, a high official in the kingdom whose expertise extended to architecture, law, and other disciplines. In this document, cancer was recognized as an illness with no effective treatment. Understanding human disease progressed over the centuries from that time, with contributions from many disciplines.

Claudius Galenius, also known as Galen (born in modern-day Turkey in 129, died 216) conceptualized disease as a manifestation of imbalances among four body humors, an exercise in observation and intuition but without testable hypotheses. His concept led to treatments (such as bloodletting) for various illnesses that we now consider to have been useless or harmful. His influence, incredibly, extended 18 centuries to the twentieth century. Sir William Osler (born in Canada in 1849, died 1919), arguably the world's

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most renowned internal medicine expert of his time, advocated bloodletting as a legitimate form of therapy in the early twentieth century [1]. It persists in many areas of the world. Because the Galenic concepts were eventually shown to be incorrect, surveillance based on his system would have been unworkable.

What we now call the scientific method evolved gradually at the end of the Dark Ages (fifth – fifteenth centuries). Dominant figures were Albert the Great, a Catholic saint (born in present-day Germany in 1193, died 1280), his student Saint Thomas Aquinas (born in present-day Italy in 1225, died 1274) and Sir Francis Bacon (born in England in 1561, died 1626). Bacon's magnum opus was Instauratio Magna. This concept characterized the beginning of the Renaissance, the humanist development of western civilization that signaled the end of medieval times and the beginning of the modern era, transforming science, literature, music, politics, and all other facets of human life. It arose in many centers of higher learning throughout the world, but primarily in Europe. This empirical method featured development of a hypothesis, testing of the hypothesis, critical evaluation of the test results, revision of the hypothesis, repeated testing, and eventual derivation of an evidence-based conclusion. It resulted in an explosion of knowledge that continues to the present. Its relevance to rectal carcinoma is clear.

Andreas Vesalius (born in modern-day Belgium in 1514, died 1564) is credited with beginning the rational description of human anatomy, based on the dissection of human bodies. Innumerable others have added detail to the corpus of knowledge of anatomy of all living organisms, with tools unimaginable to Vesalius. Without our current understanding of human anatomy, the relevance of pelvic lymph nodes would be lacking, the concept of anatomic layers of the rectum would be unknown, and the techniques we now use to resect and/or irradiate rectal carcinoma would be unavailable. Modern concepts of surveillance after curative-intent treatment for rectal cancer rely heavily on his work.

Antonie van Leeuwenhoek (born in 1632 in modern-day Holland, died 1723) was an apprentice in a fabric shop with an interest in lenses. He developed a technique for making high quality spherical glass lenses and used them when he built his microscopes. His invention revealed micro-organisms (such as bacteria), cells of multicellular organisms (such as sperm), and intracellular structures (such as nuclei). As with gross anatomy, which had been revolutionized by direct experimentation, the light microscope was followed by other imaging systems, ranging from electron microscopy to monoclonal antibody-based tissue stains. Without the knowledge and concepts that resulted from these tools, modern concepts of rectal cancer surveillance would be similarly unknowable. The long list of other transformative advances from the Renaissance to the present should be evident to most readers of this book.

William Harvey (born in England in 1578, died 1657), a physician, was the first to correctly describe the circulation of blood. His magnum opus (De motu cordis et sanguinis in animalibus) was – and remains – essential to the science of surgery and physiology. John Hunter (born in Scotland in 1728, died 1793), a physician-scientist, discovered the nature of the lymphatic system. His work further rationalized medical and surgical practice and appeared just before major surgical procedures were feasible. His work provided an explanation of lymphatic metastases.

Another advance which presaged the concept of surveillance was that of effective general anesthesia. The history of mind-altering substances undoubtedly begins with ethanol, used by most, if not all, centers of prehistoric civilization. Unfortunately, ethanol proved not to be an effective anesthetic agent. Many physicians and scientists, as well as non-expert thrill seekers, discovered effective anesthetic agents, beginning in the late seventeenth century. Often the discovery was fortuitous, apparently, and pursued only as a form of entertainment. American, European, Chinese and Japanese centers were important in understanding the doses that were safe to use, the side effects, and so forth. Opium and its derivatives, nitrous oxide gas, and diethyl ether were in common use by the mid-eighteenth century. Sir

Humphry Davy (born in England in 1778, died 1829) discovered the medical use of nitrous oxide. He, James Watt, Samuel Taylor Coleridge, and others used nitrous oxide for its pleasurable effects but Davy did not consider it as an anesthetic. Crawford W. Long (born in America in 1815, died 1878), a Georgia physician educated at the University of Pennsylvania, used diethyl ether for recreational purposes, as did other students. He noted that those who inhaled its vapor often stumbled, fell, and otherwise injured themselves, but only noticed pain after the effect of the ether had worn off. He performed many operations using NO_2 and is considered the discoverer of anesthesia. William T.G. Morton (born in America in 1819, died 1868) was a Harvard-educated dentist who first publicly demonstrated that diethyl ether was an effective anesthetic agent. He used it during operations on ~2,000 soldiers in the American Civil War. This development enabled the conduct of major surgery world-wide.

Rectal carcinoma was known to be common in the eighteenth century. It was not possible to cure this disease with radical surgery until effective anesthesia (typically diethyl ether applied by a gauze sponge placed over the face, enabling its vapors to be inhaled) became available in the mid-eighteenth century. The first attempts at curative-intent surgery were often unsuccessful, for obvious reasons. Anesthesia was rudimentary. Muscle relaxants were unknown. No monitoring devices except physical examination were available. Even blood pressure was measured by simple palpation of accessible arteries. Measurement of serum electrolytes, blood counts, and so on, was unavailable. The realization that germs cause disease was unknown and sterile technique was therefore not undertaken. Blood transfusions were unavailable. Patients were not given intravenous fluids. The surgeon had to devise the operation without guidance from prior experience and evidence. We can scarcely imagine now how any patient survived rectal cancer surgery at that time.

In spite of everything, those with rectal cancer sought surgeons who might cure them. They realized that their fate without radical surgery would be agonizing and they took their chances. When rectal cancer surgery was successful, some who had been cured of the index cancer died of a new colonic cancer. Metastases which had not been detected intra-operatively by the surgeon often killed the patient a few months or years after the index operation. Still, armed with the knowledge that rectal cancer was otherwise incurable, the courageous surgeons (and their even more courageous patients) relied on the knowledge accumulated since the beginning of the Renaissance and succeeded in eradicating the cancer surprisingly often. We can speculate that the physicians and surgeons of the time wondered whether it might be worthwhile to try to reoperate and resect recurrent rectal cancer or a new primary colon cancer arising in the colostomy (thus marking the beginning of the concept of surveillance) but it appears that no surveillance measures were ever recorded.

In the nineteenth century, Charles Babbage (born in England in 1791, died 1871), the Lucasian Professor of mathematics at Cambridge University, addressed the problem of mathematical calculations, which were numerous, tedious, and done by humans at that time. Mistakes were rare but devastating. He drew a detailed plan of a mechanical device to perform mathematical calculations of all sorts. This device was never constructed because of its complexity but modern engineers believe that it would have worked perfectly. He is generally credited with the invention of the computer. Modern applications of the computer are innumerable. Surveillance after primary treatment of rectal cancer as we know it would be impossible without computers.

Great progress in microbiology was made in the late nineteenth century. Robert Koch (born in Germany in 1843, died 1910), a chemist and a founder of the discipline of microbiology, identified the organisms responsible for several diseases (cholera, anthrax, tuberculosis). He strengthened the concept that microorganisms can cause disease and enunciated the famous Koch's Postulates, four simple rules by which causality of an infectious disease could be clearly established. He was a major force in public health and improved the instruments and techniques relevant to a microbi-

ology laboratory. For his work, he was awarded the Nobel Prize in Medicine in 1905. Louis Pasteur (born in France in 1822, died 1895) was another giant in the fields of chemistry and microbiology. He demonstrated that microorganisms cause disease (and are responsible for fermentation of beer). He showed that vaccination was dramatically effective in preventing various infectious diseases. He proposed that keeping microorganisms from entering the body would prevent infection, thus abruptly changing surgical practice. The improvements in public health led to an increase in the human lifespan, which has continued to the present. Since rectal carcinoma largely affects old people, the numbers of survivors of rectal cancer who might benefit from surveillance has grown as well.

Detection of disease was markedly improved by the discovery of x-rays by Wilhelm Konrad Röntgen (born in Germany in 1845, died 1923). In the case of rectal carcinoma, this enabled lung and bone metastases to be detected easily. Development of the barium enema test and other radiological studies utilizing various contrast agents proved very useful and safe, although primitive dosimetry and tissue tolerance limits led to serious (even fatal) radiation-related adverse events. What we now know as surveillance then expanded its scope and encompassed not only detection of recurrent cancer but also the detection of treatment-related events, neither of which could be usually treated successfully in the early twentieth century. Subsequently, unrelenting research and clinical insights markedly improved the accuracy of diagnostic radiological studies and decreased the incidence of symptomatic radiation-related injuries.

In the early twentieth century, progress was also made on other fronts. The British surgeon John Percy Lockhart-Mummery (born in England in 1875, died 1957) and his colleague, the British pathologist Cuthbert E. Dukes (born in England in 1890, died 1977), working at St. Mark's Hospital in London, established a method of excising rectal cancer that met simple criteria: it was anatomically reasonable, it was fast, and it removed all evident cancer. If all evident cancer could be extirpated, some patients were cured. Those with unresectable cancer could be advised about their prognosis so they could make plans for their future. A colostomy was sometimes created as well for those with abysmal prognoses. The technique of rectal cancer surgery initially described by Lockhart-Mummery and Dukes improved incrementally until the concept of total mesorectal excision (TME) was introduced by R.J. (Bill) Heald (in 1982) and is now widely practiced [2, 3].

Dukes and Lockhart-Mummery were also responsible for another innovation, the Dukes staging classification [4]. It was based on postoperative pathological examination of the resected tissue. It was simple and had great prognostic power. The concept of staging subsequently blossomed throughout the world, with the development of staging systems of various descriptions for most types of cancer. By the late twentieth century, the American Joint Committee on Cancer (AJCC) staging system and the European International Union for Cancer Control (UICC) staging system, with input from Japanese and other less well known systems, were merged into a single entity, with successive editions incorporating advancements in knowledge and deleting or modifying components, as evidence suggested. The stage of rectal carcinoma affects the various strategies for surveillance proposed by various expert groups.

During the late nineteenth century, another source of improved medical care was the founding of professional societies. These were inaugurated in wealthy nations, particularly in Europe, America, Canada, and Japan in the nineteenth century. Even many middle-income and low-income countries now have public health entities, modeled on the American Public Health Association (founded in 1872), societies such as the American Medical Association (founded in 1847) and the American College of Surgeons (founded in 1913). The Royal College of Surgeons (initially The Company of Barber-Surgeons), was established in 1540 as a trade guild, then split by an Act of Parliament into two entities (surgeons and barbers) in 1745. Both were granted Royal Charters in 1800. The surgeon entity was renamed The Royal College of

Surgeons in London. It was granted a new Royal Charter in 1843 and acquired its current name: The Royal College of Surgeons of England. The Royal College also played a major role in improving professional standards, fostering research, and adapting to the National Health Service. Most nations have experienced similar evolutions in health care systems. The American Proctologic Society, founded in 1899 and later named the American Society of Colorectal Surgeons (ASCRS), was able to focus on quality improvement at many levels [5]. ASCRS members proposed and instituted quality standards, held regular meetings, and collaborated with similar organizations throughout the world.

Among the topics to emerge from the productive ferment was the question of what to do when a rectal carcinoma patient has received curative-intent surgery and later develops metastases. Enter Owen H. Wangensteen M.D., Ph.D., chairman of the surgery department at the University of Minnesota. His remarkably bold concept was called "second-look" surgery. This entailed reopening the abdomen or chest, searching for metastases, and resecting all of them, if technically feasible. This process was vigorously pursued, with re-explorations and re-resections carried out up to six times, in some cases. Some patients died of complications of surgery and many were found to have unresectable recurrences after one or more attempts, but some were rendered free of disease for the remainder of their lives. This provided a strong rationale for surveillance after initial resection of various cancers, including rectal carcinoma, based on the premise that early detection of local recurrence and metastases would improve cure rates. The limited surveillance modalities available in Wangensteen's time (chest radiographs, radionuclide scans, and endoscopy chief among them) were followed by ever more powerful (and accurate) tools. This strategy eventually was abandoned [6]. However, the concept of surveillance (and possible cure) of patients with recurrent rectal cancer was firmly established by this bold clinical experiment.

This proliferation of surveillance modalities eventually led to cost containment efforts, which persist to the present. The problem of costs of medical care was of particular interest in the nations with national health systems. The first was instituted in the USSR in 1937. They are nearly universal in modern industrial nations. The economic burden of cancer survivorship in the United States and in other countries is quite high [7]. Cost containment for surveillance after cancer treatment has been difficult to achieve. Many analyses of the state of medical care have been offered. A full edition of *JAMA* featuring this topic (*JAMA* 310:1877–1998; 2014) was recently published. Patients and their relatives demand state-of-the-art surveillance for their loved one; those who pay for this use various methods of reining in costs. The development of mathematical techniques to study societal problems provided a practical tool--the randomized clinical trial--to address this conundrum.

The emergence of surveillance as a component of medical practice clearly follows a pattern. A new concept (e.g., the scientific method) is followed by discoveries of fundamental features of a natural process which, in turn, results in practical applications. In the early 1990s, our research group decided to address a practical problem in clinical care related to the treatment of cancers of all sorts: how should one follow a patient after curative-intent primary therapy? We searched the relevant literature but found very little empirical data pertaining to this topic. We then decided to try an alternate approach: how do clinical experts follow their own patients? For colorectal cancer, we chose to determine how members of the American Society of Colorectal Surgeons (ASCRS) followed their own patients after curative-intent initial therapy. For this, we developed a survey [8]. We asked ASCRS surgeons who commonly performed surgery for colon carcinoma what surveillance modalities they used. We consulted the existing literature to decide which modalities to offer on the survey. We sent the survey instruments by surface mail to the members of ASCRS, along with a stamped, self-addressed return envelope and a cover letter explaining the reason for the survey and the way we wanted to the recipient to respond to the survey. We were surprised by the results. There was

Table 18.1 Summary of intense vs. less intense randomized trials for colorectal cancer surveillance

Study, year	Surveillance intensity	Number of patients randomized	Median observation time (months)	Overall recurrence rate (%)	Number of second bowel cancers	Radical reoperation rate (%)	5-year survival rate (%)
Ohlsson (1995)	Less	54	82	33	NR	17	67
	More	53		32		29	75
Makela (1995)	Less	54	>60	39	NR	14	54
	More	52		42		23	59
Schoemaker (1998)	Less	158	>60	NR	5	NR	70
	More	167			3		76
Kjeldsen (1997)	Less	307	>60	26	3	NR	68
	More	290		26	7		70
Pietra (1998)	Less	103	>60	19	1	10	58
	More	104		25[a]	0	65	73[b]
Secco (2002)	Less	145	>60	53	NR	16	48
	More	192		57		31	63

Adapted from Figueredo et al. [14]. http://www.biomedcentral.com/content/pdf/1471-2407-3-26.pdf
[a] $p < 0.05$
[b] $p < 0.05$

apparently no consensus. We then sent this survey to the members of the Society of Surgical Oncology and got similar results [9]. We also attempted to find explanations for the dramatic variation in surveillance intensity after curative-intent rectal cancer surgery we had documented. For example, we found that there was an effect of initial TNM stage, but not enough to explain the overall variation [10]. Our group has subsequently conducted similar surveys (now web-based) focusing on various other solid tumors. In each case, there was no consensus. At about the same time, a number of clinical trials were conducted to determine the optimal surveillance strategy for patients with colorectal cancer after curative-intent primary treatment. As of 2003, researchers at Cancer Care Ontario (CCO) identified six randomized clinical trials comparing more intensive vs. less intensive strategies for rectal cancer patients after curative-intent primary treatment [11]. All had serious flaws, as shown in Table 18.1.

In 2013, Johnson et al.[12] summarized the then-current recommendations of the following institutions:

- The National Comprehensive Cancer Network (Table 18.2).
- The American Society of Clinical Oncology (Table 18.3).
- The European Society for Medical Oncology (Table 18.4).
- The National Institute for Clinical Excellence (NICE) of the United Kingdom (Table 18.5).
- Cancer Care Ontario (Table 18.6).
- The American Society of Colon and Rectal Surgeons (Table 18.7).
- The Society for Surgery of the Alimentary Tract (Table 18.8).
- The Fox Chase Cancer Center (Table 18.9).
- The University of Sydney (Table 18.10).
- The National Kyushu Cancer Center (Table 18.11).
- McMaster University, Canada (Tables 18.12 and 18.13).

The evidence base of all the cited trials (and thus all the recommendations of the professional societies, governmental entities, and other professional guideline creators) has been rather weak, particularly with respect to the numbers of subjects. In 2000, Professor John N. Primrose and many collaborators in the U.K. launched another trial (FACS: Follow-up After Colorectal Surgery), one with adequate sample size, clear definitions of goals and methods, long follow-up, excellent statistical support, and funding from the U.K. government. It was published in 2014 [13]. The objective of the trial was to assess the effect of scheduled measurement of

Table 18.2 Rectal cancer; obtained from NCCN (www.nccn.org) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit	2–4	2–4	2	2	2	0
Serum CEA level[b]	2–4	2–4	2	2	2	0
Chest/abdominal/pelvic CT[c]	1	1	1	0–1	0–1	0
Colonoscopy[d, e]	1	0–1	0–1	0	0–1	0–1
Proctoscopy[f, g]	2	2	2	2	2	0
PET-CT scan is not routinely recommended.						

NCCN guidelines were accessed on 1/28/12. There were minor quantitative and qualitative changes compared to the guidelines accessed on 4/10/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]For T2 or greater lesions

[c]If patient is a potential candidate for resection of isolated metastasis

[d]For patients at high risk for recurrence (e.g., lymphatic or venous invasion by tumor, or poorly differentiated tumors)

[e]Colonoscopy in 1 year except if no preoperative colonoscopy due to obstructing lesion, colonoscopy in 3–6 months. If advanced adenoma (villous polyp, polyp >1 cm, or high grade dysplasia), repeat in 1 year. If no advanced adenoma, repeat in 3 years, then every 5 years

[f]For patients status post low anterior resection of the rectum

[g]Patients with rectal cancer should also undergo limited endoscopic evaluation of the rectal anastomosis to identify local recurrence. Optimal timing for surveillance in not known. No specific data clearly support rigid versus flexible proctoscopy. The utility of routine endoscopic ultrasound for early surveillance is not defined

Table 18.3 Colorectal cancer; obtained from ASCO (www.asco.org) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit	2–4	2–4	2	2	2	0[b]
Serum CEA level[c, d]	4	4	4	0	0	0
Chest/abdomen CT[e]	1	1	1	0	0	0
Colonoscopy[f, g]	1	0	1	0	1	0-1
Flexible proctosigmoidoscopy[h]	2	2	2	2	2	0
Routine blood tests (i.e., CBC, LFTs), fecal occult blood testing, yearly chest x-rays are not recommended.						
Use of molecular or cellular markers should not influence the surveillance strategy.						

ASCO guidelines were accessed on 1/28/12. There were no significant changes compared to the guidelines accessed on 10/31/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]Physician visit after 5 years at the discretion of the physician

[c]For patients with stage II or III disease if the patient is a candidate for surgery or systemic therapy

[d]Since fluorouracil-based therapy may falsely elevate CEA values, waiting until adjuvant treatment is finished to initiate surveillance is advised

[e]For patients who are at a higher risk or recurrence, and who could be candidates for curative-intent surgery. A pelvic CT scan should be considered for rectal cancer surveillance, especially for patients who have not been treated with radiotherapy

[f]All patients with colon and rectal cancer should have a colonoscopy for pre- and perioperative documentation of a cancer- and polyp-free colon. If normal at 3 years, once every 5 years thereafter

[g]For colorectal cancer patients with high-risk genetic syndromes, the physician should consider the guideline published by the American Gastroenterology Association

[h]For rectal cancer patients who have not received pelvic radiation

Table 18.4 Rectal cancer; obtained from ESMO (www.esmo.org) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit	2	2	0	0	1	0–1
Rectosigmoidoscopy	2	2	0	0	0	0
Colonoscopy[b]	1	0	0	0	1	0–1
Imaging of liver, lungs	1	0	1	0	0	0

The value of regular clinical, laboratory and radiological examinations are not known.

ESMO guidelines were accessed on 1/28/12. There were minor quantitative and qualitative changes compared to the guidelines accessed on 10/31/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]A completion colonoscopy, if not done at the time of diagnostic work-up (e.g. if obstruction was present), should be performed within the first year. History and colonoscopy with resection of colonic polyps every 5 years

Table 18.5 Colorectal cancer; obtained from NICE (www.nice.org.uk) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit[b, c]	≥2	≥2	≥2	0	1	0
Serum CEA level	≥2	≥2	≥2	0	0	0
CT scan of chest, abdomen, pelvis[d]	≤1	≤1	≤1	0	0	0
Colonoscopy[e]	1	0	0	0	1	0

Start reinvestigation if there is any clinical, radiological, or biochemical suspicion of recurrent disease.

Stop regular follow-up when the patient and healthcare professional have discussed and agreed that the likely benefits no longer outweigh the risks of further tests or when the patient cannot tolerate further treatments.

NICE guidelines were accessed on 1/28/12. There were major quantitative and qualitative changes compared to the guidelines accessed on 10/31/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]Start follow-up at a clinic visit 4–6 weeks after potentially curative treatment

[c]CEA, CT, and colonoscopy were the only quantitative recommendations given. We inferred that office visit would be recommended as frequently as these

[d]A minimum of two CTs of the chest, abdomen, and pelvis in the first 3 years

[e]Surveillance colonoscopy at 1 year after initial treatment. If this investigation is normal, consider further colonoscopic follow-up after 5 years, and thereafter as determined by cancer networks. The timing of surveillance for patients with subsequent adenomas should be determined by the risk status of the adenoma

carcinoembryonic acid (CEA) and computed tomography (CT) as followup to detect recurrent colorectal cancer with curative intent. This was a randomized clinical trial in 39 National Health Service hospitals in the United Kingdom. There were 102 eligible participants recruited between January 2003 and August 2009 who had undergone curative surgery for primary colorectal cancer, including adjuvant treatment when indicated with no evidence of residual disease on investigation. In addition to followup colonoscopy, the patients underwent one of four followup regimens: minimal followup, with one CT scan at 12–18 month, CEA testing every 3 months for 2 years, then every 6 months for 3 years and a single CT scan at 12–18 months, CT scan every 6 months for 2 years, then annually for 3 years, or combined CEA testing and CT scan as above. The primary endpoint was enhanced detection of metastatic disease potentially curable with surgery. After a mean of 4.4 years, the more intensive screening strategies increased the percentage of patients detected with potentially curative recurrence by 4.4–5.7 %, compared with minimal followup. In the opinion of the authors of this chapter, this trial has proved to be the best one ever conducted on the topic of rectal cancer surveillance

Table 18.6 Colorectal cancer; obtained from CCO (www.cancercare.on.ca) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit[b]	1–2	1–2	1–2	1	1	1
Serum CEA level	1–2	1–2	1–2	1	1	1
Chest x-ray	1–2	1–2	1–2	1	1	1
Liver ultrasound	1–2	1–2	1–2	1	1	1
Colonoscopy[c]	1	0–1	1	0–1	1	0–1

When recurrences of disease are detected, patients should be assessed by a multi-disciplinary oncology team including surgical, radiation, and medical oncologists to determine the best treatment options.

Patients should be encouraged to participate in clinical trials investigating screening tests added on to their clinical assessment.

CCO guidelines were accessed on 1/28/12. There were major quantitative and qualitative changes compared to the guidelines accessed on 10/31/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]For patients at high risk of recurrence (stages IIb and III). In patients at high risk of relapse but who have co-morbidities that may interfere with prescribed tests or potential treatment for recurrence, or who are unwilling to undergo prescribed tests or potential treatment for recurrence, clinical assessments yearly or for suggestive symptoms of relapse. For patients at lower risk of recurrence (stages I and Ia) or those with co-morbidities impairing future surgery, only visits yearly or when symptoms occur are recommended

[c]Colonoscopy postoperatively if not yet done. If polyps present, excise as they are potential precursors of colorectal cancer; repeat colonoscopy yearly as long as polyps are found. If there are no polyps, repeat colonoscopy in 3–5 years. All patients should have a colonoscopy before or within 6 months of initial surgery, repeated yearly if villous or tubular adenomas >1 cm are found; otherwise, repeat every 3–5 years

Table 18.7 Colon and rectal cancer; obtained from ASCRS (www.fascrs.org) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit[b]	3	3	0	0	0	0
Serum CEA level	3	3	0	0	0	0
Colonoscopy[c]	1	0	0	1	0	0–1

Periodic anastomotic evaluation is recommended for patients who have undergone resection/anastomosis or local excision of rectal cancer.

There is insufficient data to recommend for or against chest x-ray as part of routine colorectal cancer follow-up.

Serum hemoglobin, hemoccult II, and liver function tests (hepatic enzymes tests) should not be routine components of a follow-up program.

Routine use of hepatic imaging studies in the follow-up of colorectal cancer should not be performed.

ASCRS guidelines were accessed on 1/28/12. These are new quantitative guidelines compared to the qualitative guidelines accessed on 12/13/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]Data concerning proper timing of office visits, CEA, and CXR is insufficient to recommend one particular schedule of follow-up over another; however, office visits and CEA evaluations should be performed at a minimum of three times per year for the first 2 years of follow-up

[c]Complete visualization of the colon should be performed if practical in all patients being considered for colon or rectal cancer resection; posttreatment colonoscopy should be performed at 3-year intervals

and should now be considered the gold standard. The results have been presented at many sites.

The FACS Trial will undoubtedly not remain the gold standard for the indefinite future, of course, as more sensitive, less costly, and/or more specific surveillance methods are developed and/or effective salvage regimens for recurrence become available. Another large randomized trial (Gruppo Italiano Lavoro per la Diagnosi Anticipata), based in Europe, is now mature and the results are expected to be published soon.

Table 18.8 Cancer of colon or rectum; obtained from SSAT (www.ssat.com) on 1/28/12 [12]

	Years posttreatment[a]					
	1	2	3	4	5	>5
Office visit[b]	2–4	2–4	2–4	1	0	0–1
Serum CEA level	2–4	2–4	2–4	0	0	0
Colonoscopy[c]	1	0	0	1	0	0–1

Based on clinical indications, radiographic imaging such as chest x-ray, ultrasound, CT and/or MRI scan may also be indicated to evaluate for regional recurrence or metastatic disease.

Whole body FDG-PET scanning is a new modality that may be useful in selected circumstances for identifying metastatic disease.

Patients with recurrent colon or rectal cancer who do not have evidence of distant disease may be candidates for surgical resection with or without adjuvant radiation therapy.

Localized hepatic or pulmonary metastases detected during surveillance should be evaluated for possible resection. If one or a few lesions can be completely resected, survival is significantly prolonged.

SSAT guidelines were accessed on 1/28/12. These are new quantitative guidelines compared to the qualitative guidelines accessed on 12/18/07

[a]The numbers in the table indicate the number of times the modality is recommended during the indicated year post-treatment

[b]Serum CEA level and colonoscopy were the only quantitative recommendations given. We inferred that office visit would be recommended as frequently as these

[c]Colonoscopy 1 year after surgery and then every 3 years

Table 18.9 Surveillance for colorectal cancer patients after curative-intent treatment at the Fox Chase Cancer Center [12]

	Year				
Modality	1	2	3	4	5
Office visit	4	4	2–3	2–3	2–3
Serum CEA level	4	4	2–3	2–3	2–3
Colonoscopy	1	[a]	[a]	[a]	[a]
CT scan abdomen/pelvis	1	1	1	[a]	[a]

After 5 years of surveillance, a patient who is clinically well is discharged to the primary care physician

The number in each cell indicates the number of times a particular modality is recommended during a particular posttreatment year

CEA carcinoembryonic antigen

[a]Dictated by findings at a previous colonoscopy and serum CEA level

Table 18.10 Surveillance for patients with colorectal cancer after curative-intent primary therapy at the Royal Prince Alfred Hospital, Sydney [12]

	Years posttreatment				
Modality	1	2	3	4	5
Office visit	2–4	2–4	1–2	1–2	1–2
DRE and sigmoidoscopy[a]	2–4	2–4	1–2	1–2	1–2
Serum CEA level	2–4	2–4	1–2	1–2	1–2
Colonoscopy	1[b]	0	1	0	0
CT scan abdomen/pelvis	1	0	0	0	0
EAUS[c]	2	2	2	2	2

The number is each cell includes indicates the number of times a particular modality is recommended during a particular posttreatment year

DRE digital rectal examination, *EAUS* endoanal ultrasonography

[a]Digital Rectal Examination and sigmoidoscopy for patients after anterior resection

[b]Early postoperative colonoscopy is indicated if the proximal part of the colon was not examined preoperatively

[c]For patients after local excision of rectal cancer

Table 18.11 Surveillance for patients with stages I, II and III rectal cancer after curative-intent treatment, National Kyushu Cancer Center, Japan [12]

	Year posttreatment[a]				
	1	2	3	4	5
Office visit Digital rectal examination	4	4	4	2	2
Serum CEA and CA19-9 levels	2	2	2	0	0
Chest-/abdomen-/pelvis-computed tomography	4	4	4	2[+]	2[b]
Colonoscopy[c]	1	1	1	0	0

For chest imaging, chest CT is more desirable, although chest X-ray is permitted instead
For abdominal imaging, abdominal CT is more desirable, although abdominal ultrasonography is permitted instead
The number is each cell includes indicates the number of times a particular modality is recommended during a particular posttreatment year
CEA carcinoembryonic antigen
[a]Surveillance for only 5 years is recommended. Thereafter, the patient is returned to the primary care doctor
[b]For patients with stage I or stage II disease, chest/abdomen/pelvis CT can be once a year in years 4 and 5
[c]The recommended frequency of colonoscopy after 5 years is not determined

Table 18.12 Current recommendations for stage I disease

	Time after primary treatment				
Category	Year 1	Year 2	Year 3	Year 4	Year 5
Clinic visits	2	2	2	1	1
Blood tests (CEA, liver)	2	2	2	1	1
Chest X-ray	1	1	1	1	1
CT abdomen and pelvis	1	1	1	–	–
Colonoscopy[a]	1	–	–	–	–

Adapted from guidelines I and II
[a]3–5 years later if first scope is normal

Table 18.13 Current recommendations for stage II and III disease [12]

	Time after primary treatment				
Category	Year 1	Year 2	Year 3	Year 4	Year 5
Clinic visits	2	2	2	1	1
Blood tests (CEA, liver)	2	2	2	1	1
Chest X-ray	1	1	1	1	1
CT or MRI abdomen and pelvis[a]	1	1	1	1	1
US abdomen[b]	1	1	1	–	–
Colonoscopy[c]	1	–	–	–	–

Adapted from guidelines I and II
[a]Recommended end of the year
[b]Recommended mid-year
[c]3–5 years later if first scope is normal

Patterns of recurrence may be different in rectal cancer than colon cancer. Followup after rectal cancer surgery should emphasize the detection of loco-regional recurrence in the pelvis and pulmonary metastases as compared to recurrence after colon cancer surgery, where detection of liver metsastases is important. Furthermore, since there are procedures such as local excision, abdominoperineal resection and restorative proctosigmoidectomy, surveillance should be tailored to the original procedure performed.

The purpose of surveillance after potentially curative therapy for colorectal cancer is early identification of those patients who might potentially be cured by surgical intervention. Colonoscopic surveillance is utilized to screen for second primary cancers and polyps. Early diagnosis of an asymptomatic recurrence may

result in resection of recurrent disease for cure. Some meta-analyses support a modest survival benefit. It appears that scientific progress will lead to major changes in prevention, detection, and treatment of rectal carcinoma, with corresponding changes in surveillance after curative-intent primary treatment.

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Surgical Approach to Locally Recurrent Disease

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Leandro Feo, Michael Polcino, and Julio Garcia-Aguilar

Abstract

Over the past two decades, major advances in surgery, chemoradiotherapy, and postoperative care have contributed to dramatic improvements in recovery and survival for patients with rectal cancer. Most significantly, from the surgical point of view, has been the adoption of total mesorectal excision (TME) as the standard of care. Nevertheless, some patients will recur. Locally recurrent rectal cancer is a difficult condition to manage, and long-term survival is unlikely without additional treatment. Surgery is the only potential cure. Ideally, this will involve a multidisciplinary team of specialists including medical and radiation oncologists, colorectal surgical oncologists, urologic surgeons, gynecologic surgeons, plastic and reconstructive surgeons, orthopedic surgeons, vascular surgeons, and possibly neurologic surgeons. However, surgical treatment of recurrent rectal cancer should be undertaken only in carefully selected patients who are fit enough for the extensive, potentially morbid procedures necessary, whose tumors are amenable to resection with negative margins, and who have been counseled regarding the impact of re-resection on postoperative function and quality of life.

Keywords

Rectal cancer • Total mesorectal excision • Recurrent rectal cancer • FOLFOX chemotherapy • Intra-operative radiotherapy

Introduction

Over the last 20 years, major improvements in treatment have made locoregional control of rectal cancer possible. Most significantly, from the surgical point of view, has been the introduction and practice of total mesorectal excision (TME). As stated by Heald, TME entails "an optimal dissec-

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tion plane around the cancer which must clear all forms of extension and circumscribe predictably uninvolved tissues" [1]. Optimal TME mandates sharp dissection (rather than the traditionally blunt dissection); precise removal of the mesorectum includes the cylindrical mesentery and associated nodal tissue in its entirety, as an en bloc "package" contained within the sheets of the endopelvic fascia. Heald and the Basingstoke group reported a local failure rate as low as 5 % with an intact TME [2]. These excellent results have been attributed to improved lateral clearance, more thorough removal of potential tumor deposits in the mesentery, and decreased risk of tumor spillage from a disrupted mesentery. Adopted as the surgical "golden standard", the widespread use of TME has lowered rates of recurrence and improved survival dramatically, compared to historical levels. Advances in technology and postoperative care have also contributed to better patient recovery and survival.

While surgery is fundamental to the treatment of most rectal cancers, chemotherapy and radiotherapy have also played significant roles. The goal of systemic chemotherapy is to reduce the risk of distant recurrence. The goal of pelvic radiation is to improve local control. Many tumors respond to radiation by downsizing, becoming amenable to less extensive resection than would otherwise be necessary. For these reasons, neoadjuvant chemoradiation is widely accepted as part of the standard of care in locally advanced (T3/T4 and/or N1) primary rectal cancer. The combination of chemotherapy, radiotherapy, and surgery is known as multimodality or trimodality treatment. While there are considerable benefits to this intensive approach, there are also drawbacks. Treatment-associated morbidity is higher in patients who receive radiation, regardless of whether it is given preoperatively or postoperatively. Nevertheless, the increasingly sophisticated use of preoperative chemoradiation followed by TME has demonstrated a 10-year overall survival of 58 % and recurrence-free survival of 62 % [3].

Despite these measures, some patients will recur. Relapse may be systemic, local, or both. However, 25–50 % of patients with recurrent rectal cancer show no signs of systemic disease. Following treatment of the primary lesion, recurrent systemic disease often appears as metastatic deposits in the liver or lungs. The surgical field is the third most common site [4]; this area, including the site of the primary tumor, regional and retroperitoneal lymph nodes, and the anastomosis, drain tracts, and surgical scars, is where rectal cancer recurs locally.

Locally recurrent rectal cancer is a very difficult condition to manage, and is associated with considerable morbidity and mortality. In the absence of metastasis, however, re-resection of local recurrence can be curative [5]. The overall goals of surgical treatment are complete tumor eradication, preservation of function, and avoidance of complications. Achieving these goals may be technically challenging. In a previously irradiated surgical field the anatomical planes are disrupted, making the area generally hostile to evaluation and intervention. In order to obtain negative surgical margins, a multi-organ en bloc resection is often necessary. The involvement of a multidisciplinary team—including experienced oncologic specialists from the fields of urology, gynecology, orthopedics, plastic and reconstructive surgery, and vascular surgery—will help the colorectal surgeon plan operative treatment. Even so, postoperative morbidity is common, ranging widely (15–70 % or greater) depending on the complexity of the procedure [6]. Consequently (unlike the comparatively straightforward resection of small, isolated metastases in the liver or lung) a curative-intent surgical approach to locally recurrent disease has not been universally accepted as a treatment option. However, while some tumors may show some response to chemotherapy or radiation alone, very few patients with surgically untreated local recurrence survive more than 2 years. Surgery remains the only potentially curative treatment in this setting, and the one that is most likely to provide substantial pain control and improved quality of life.

Risk Factors

Risk factors for locoregional recurrence may be broadly categorized as anatomic, pathologic and surgical.

Anatomic

The location of the surgical field within the narrow pelvic cavity, and the dual lymphatic drainage—cephalad along the inferior mesenteric vessels and laterally toward the internal iliac vessels—increase the chances of local tumor spread. The more distally a tumor is situated within the rectum, the greater the chance that it will recur locally [7, 8]. As the stage of a primary rectal cancer increases, so does the risk of recurrence. A properly resected stage I rectal cancer rarely recurs locally. However, the risk increases in stage II and III rectal cancers, even when adjuvant chemotherapy and radiation are added to the treatment regimen. Yiu et al. reviewed the University of Minnesota experience with T4 rectal cancers. Pelvic wall involvement was associated with decreased survival as compared to visceral involvement [9].

Pathologic

Lymphovascular and perineural invasion, poor differentiation, mucinous and signet ring cell histology, perforating or obstructing tumors, and large tumor size are associated with increased risk. Molecular markers such as mutant p53 gene expression, CD133 and CD44, as well as decreased expression of Bcl-2 [5, 6] indicate a greater possibility of tumor recurrence. Similar to the pathogenesis of distant metastatic disease, these features are intimately associated with the biology of the tumor.

Surgical

Surgically, achieving adequate negative circumferential and distal margins plays a key role [1, 10]. Technically poor or incomplete resection with positive margins greatly increases the risk. When surgical margins are compromised, the rate of local recurrence may be as high as 78 % [2, 10]. In a study of 52 patients undergoing rectal resection, Quirke et al. found that 12 of 14 patients with positive radial margins developed recurrence [10, 11]. Furthermore, surgeon and hospital volume are associated with improved outcomes. Etzioni et al. recently reviewed the SEER database and found that patients treated by board-certified colorectal surgeons in high volume centers and/or NCI designated cancer centers had better overall survival [12].

It is important to emphasize that these three factors: narrow pelvis, a large tumor with aggressive biology, and a poor initial operation, may act together to create the "perfect storm".

Diagnosis

In 70 % of cases, recurrent rectal cancer presents within 2 years after the primary surgery; 85 % present within 3 years. However, some cases are diagnosed many years after the initial operation [6, 13, 14]. Surveillance regimens aim to identify recurrences before they become symptomatic and while they are still potentially resectable [13, 15]. Meta-analyses of six prospective randomized trials suggest that rigorous surveillance may provide a survival advantage, but there is lack of consensus on frequency of clinic visits and types of diagnostic tests. The current National Comprehensive Cancer Network (NCCN) guidelines recommend follow-up with carcinoembryonic antigen (CEA) testing every 3–6 months for 2 years, then every 6 months for a total of 5 years; annual computed tomography (CT) scan of the abdomen and pelvis for 5 years; and physical examination at scheduled clinic visits. Despite these recommendations, a recent population-based cohort study of 57 patients concluded that 70 % of patients were diagnosed between scheduled exams [15].

Symptoms of local recurrence may vary, and the majority of patients are diagnosed when they present symptomatically [16]. The most common symptoms are refractory pelvic pain (which is a predictor of poor long-term survival) [17], bowel obstruction, rectal or vaginal bleeding, and urinary problems. A common manifestation in patients who have had abdominoperineal resection (APR) is a non-healing perineal wound. Whenever symptoms suggestive of

recurrence arise, a detailed history and complete physical examination must be done. This includes digital rectal exam in patients who have undergone sphincter-preserving surgery, and pelvic exam in females. If recurrent tumor is identified, endoscopy and imaging studies will help assess extent of disease and surgical risk; a complete colonoscopy should be performed if possible. Intraluminal recurrences are easily diagnosed with endoscopy and biopsy. Cystoscopy is required for patients who present with urogenital symptoms, as these strongly indicate tumoral invasion of the ureters and bladder [18].

CEA is routinely measured during follow-up surveillance after primary rectal cancer resection. Elevation of this tumor marker is frequently the first sign of recurrence [19]; however, elevated CEA is present in only about 50 % of patients. Patients with elevated CEA should undergo further work-up, including imaging studies.

Imaging Studies

CT is the primary imaging modality used in follow-up, and it is especially helpful in depicting metastases in the lungs and liver and evaluating regional adenopathy [20]. Most patients undergo CT scanning of the chest, abdomen and pelvis. Hocht et al. developed a CT-based 3-dimensional data collection system to evaluate the pattern of recurrence of rectal cancer, with special emphasis on lateral tumor extension. They found that most recurrences were located in the posterior aspect of the bony pelvis, and less than 5 % of these recurrences involved the pelvic sidewall. The sacrum and coccyx were involved in 30 % of patients (Fig. 19.1) [21]. However, in patients who have already had surgery or radiation therapy, the fat planes between the tumor and adjacent organs may be obliterated, and CT will not adequately distinguish scar tissue from tumor.

Magnetic resonance imaging (MRI) is more effective than CT in detecting and staging local

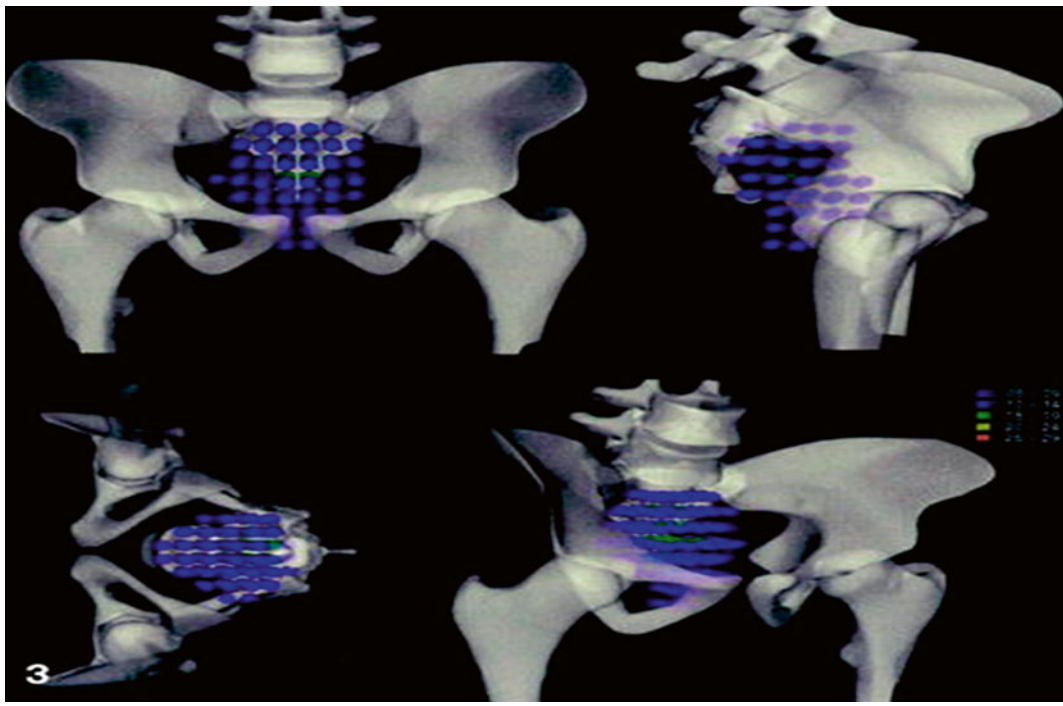

Fig. 19.1 CT 3-dimensional system to evaluate pattern of recurrence (With kind permission from Springer Science + Business Media: Höcht et al. [21], p. 110)

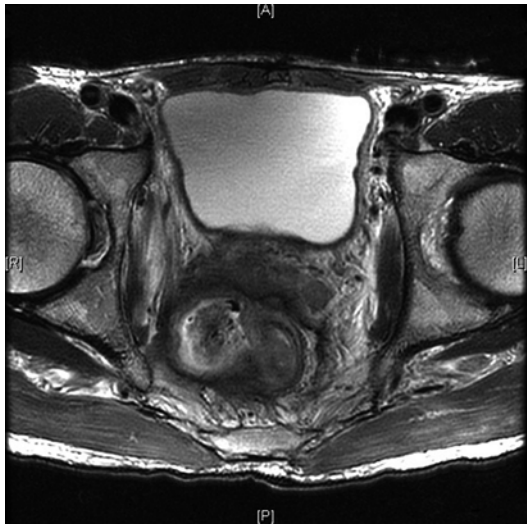

Fig. 19.2 Advanced pelvic recurrence with invasion of seminal vesicles, lateral sidewall, obturator internus muscle

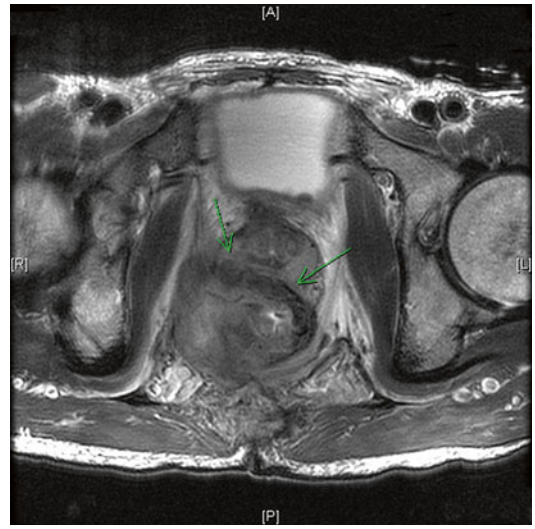

Fig. 19.3 Rectal recurrence with arrows invasion of pelvic sidewall and prostate

recurrence [22]. An MRI should be done to ascertain the extent of pelvic sidewall involvement, sacral involvement, and involvement of the major pelvic nerves, all very important elements to take into account during the surgical planning. Diffusion-weighted MR imaging (DW-MRI) is a promising technique for detecting small-volume tumor, and preliminary data indicates that it accurately delineates pelvic recurrence (Figs. 19.2 and 19.3) [22].

Endorectal ultrasound is another imaging modality that can be performed at the bedside and can be helpful in diagnosing recurrent disease in certain circumstances. It is most beneficial when the disease recurs after a local excision. However, the utility of ERUS is limited after a TME because it provides little information regarding the extent of the disease and cannot assess tumor resectability [23].

On many occasions, it is difficult to identify local recurrences using conventional imaging modalities, due to an inability to distinguish between surgical changes, tumor recurrence, or benign lesions. Under these circumstances, positron emission tomography (PET)/CT plays a key role in diagnosing rectal cancer recurrence. This imaging modality entails use of the glucose analog fluorodeoxyglucose (FDG), a marker of the enhanced glucolytic activity characteristic of cancer cells, as well as the anatomical resolution of the CT scan. FDG-PET CT offers the opportunity to localize small lesions by detecting small increases in the metabolic activity in areas or organs that, on conventional imaging, appear to be negative. Such findings lead to modification of therapeutic interventions. On the other hand, if the results of conventional imaging are equivocal, PET/CT may be useful for confirming or excluding metastatic disease, and investigating an otherwise inexplicable elevation of CEA. A recent meta-analysis comparing FDG-PET, FDG-PET/CT, CT, and MRI in the detection of recurrent colorectal cancer in patients with high suspicion of recurrent disease, based on symptoms or elevated CEA, suggested that FDG-PET and FDG-PET/CT performed more accurately than CT scan alone. PET/CT also demonstrated greater accuracy than MRI in identification of lymph node recurrence in a lesion levels analysis [22]. In another meta-analysis, FDG-PET without CT scan showed an overall sensitivity of 97 % and a specificity of 76 %. These findings led to changes in the management of 29–40 % of patients initially diagnosed with tumor recurrence. This

Table 19.1 Proposed classification systems for locally recurrent rectal cancer

Authors/Institution	Classification	Description
Wanebo et al. [29]	TR1 or TR2	Intraluminal local recurrence at the primary resection site following local excision or at the anastomosis site
	TR3	Anastomotic recurrence with full thickness penetration beyond the bowel wall and into the perirectal fat
	TR4	Invasion into adjacent organs, including the vagina, uterus, prostate, bladder and seminal vesicles, or into presacral tissues with tethering but not fixation
	TR5	Invasion into bony ligamentous pelvis, including the sacrum, low pelvis, side walls or sacrotuberous/ischial ligaments
Mayo Clinic [25]	F0–F3	Degree of fixation both in terms of site (anterior, sacral, right or left, and number of points of fixation)
Memorial Sloan Kettering [26]	Anterior	Anastomotic, mesorectal or perirectal soft tissue, or perineum following abdominoperineal excision of rectum
	Posterior	Genitourinary tract, including the bladder, vagina, uterus, seminal vesicles and prostate.
	Lateral	Sacrum and presacral fascia
	Axial	Soft tissue of the pelvic sidewall and lateral bony pelvis.
Yamada [27]	Localized	Adjacent organs or connective tissue
	Sacral	Invades S3, S4, S5, Coccyx and periosteum
	Lateral	Invades sciatic nerve, greater sciatic foramen, side wall and upper sacrum S1.

imaging modality also proved to be cost-effective [24]. However, despite the advantages of FDG-PET, its accuracy depends on tumor size and FDG uptake. Lesions measuring less than 1 cm in diameter are more difficult to detect with PET scanning, as are mucinous tumors (which have poor FDG uptake). Finally, FDG-PET cannot be used to detect or evaluate local recurrence if there is residual inflammation of the tumor bed secondary to chronic leaks.

Regardless of the imaging studies used to help diagnose a local recurrence, histologic confirmation is imperative. In the setting of an extraluminal recurrence the biopsy can be done percutaneously, under radiological (CT) guidance; in the setting of intraluminal or anastomotic recurrence, biopsy can be obtained endoscopically.

Delineating the precise location of a local recurrence is important when assessing the feasibility of surgical resection. While there is no standardized approach to categorizing recurrence by location, several groups have proposed classification systems (Table 19.1). Yamada and colleagues described three different patterns of invasion: localized (recurrence into adjacent organs or connective tissue), sacral, and lateral (sidewall invasion). In this study the 5-year survival was 38 % for localized tumors, 10 % for sacral tumors, and 0 % for laterally invasive tumors [28]. A group at Memorial Sloan Kettering Cancer Center has described a nomenclature based on anatomical location of tumor within the pelvis, defining recurrence as either axial (anastomotic, mesorectal or perirectal soft tissue, or perineum); anterior (involving the genitourinary tract); or posterior (involving the sacrum and presacral fascia, and the lateral bony pelvis) [27]. The Mayo Clinic bases its classification system on degree of fixation, while also considering factors such as sites of fixation and invasion (Fig. 19.4) [26]. Wanebo and colleagues have proposed a system utilizing the TNM model: TR1–TR5, in parallel to TNM staging [25]. All of these classification systems have advantages and drawbacks, but their heterogeneity makes it difficult to compare outcomes and methodology.

Treatment Approach

When rectal cancer recurs in the pelvis, several important issues should be discussed and reviewed before proceeding with surgery. It is best if these decisions are discussed in a multidisciplinary setting, since treatment of the patient with pelvic recurrence will often involve

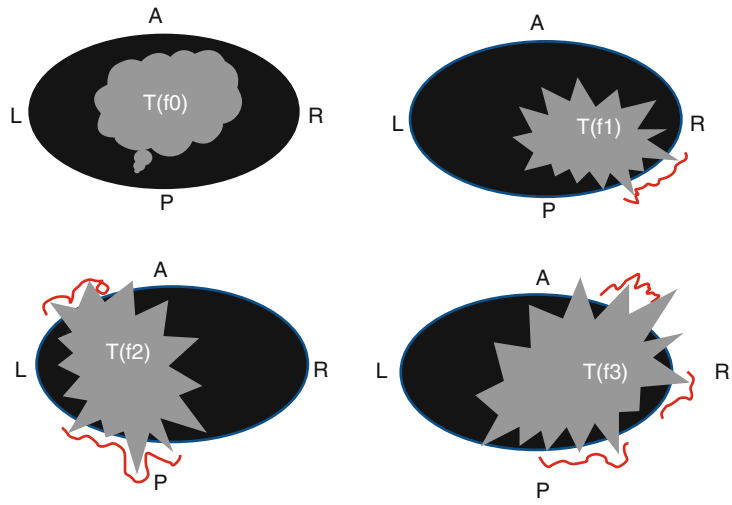

Fig. 19.4 Mayo Clinic classification of pelvic recurrence 1996. *f0* no fixation, *f1* fixation in one area (*red line*), *f2* fixation in two areas, *f3* fixation in three areas (From Ferenschild et al. [30])

colorectal surgical oncologists, radiation oncologists, medical oncologists, and other specialists. The questions that must be answered are as follows: (1) Is there any evidence of distant metastases? If the answer is yes, surgery for the rectal recurrence will not be curative. (2) Is the recurrence resectable? (3) Has the patient received chemotherapy and radiation prior to recurring? If the answer is yes, will the patient benefit from additional therapy before proceeding to surgery? Furthermore, if the patient has already received radiation, has he or she received the maximum allowable dose? (4) If the tumor is not resectable, will the patient benefit from palliative surgery?

Preoperative Treatment

The goal of preoperative treatment is to downsize the recurrent tumor, increasing the possibility of re-resection with negative margins. Therefore, the initial evaluation is an assessment of tumor resectability. In patients with a resectable tumor who did not receive neoadjuvant chemoradiation during treatment of their primary tumor, preoperative combined modality therapy should be delivered in order to increase the possibility of achieving negative surgical margins [29]. Patients who have had a full dose of external beam radiotherapy in the past are generally not candidates for additional radiation. If the patient has received less than 50.4 Gy, however, a modified dose is sometimes given. Some centers advocate additional radiation doses of up to 30.6 Gy, with or without sensitizing chemotherapy, in patients previously treated with 50.4 Gy [29]. Some locally recurrent colorectal cancers do respond to chemotherapy, and aggressive chemotherapy without radiation may be a treatment option for some. The literature on this topic is sparse, and currently there is no definitive consensus regarding chemotherapy for locally recurrent rectal cancer. Hu et al. found that combining FOLFOX with radiotherapy provided better survival than radiotherapy alone in patients with locally recurrent rectal cancer [31]. Following preoperative chemotherapy and/or radiotherapy, re-staging should be done to exclude interim development of distant metastasis and ascertain the extent of the local recurrence. Clinical work-up should also evaluate the recurrent tumor's degree of fixation. For patients with unresectable disease, palliative treatment aimed at alleviating symptoms and improving quality of life should be discussed.

Surgical Considerations

Radical surgery that achieves negative margins is the only potentially curative option for patients with local recurrence. Without surgical intervention, locally recurrent rectal cancer carries a dismal prognosis: median survival is typically

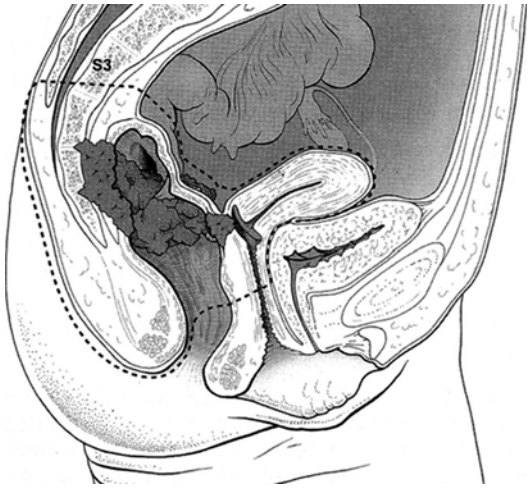

Fig. 19.5 Circumferential margins and planes of dissection. *dotted lines* represent circumferential resection margins/planes of resection, *S3* indicates level

6–7 months [32]. Surgical planning involves determining what type of surgery will be performed, based on the anatomic feasibility of achieving an R0 resection, estimation of acceptable risk for short- and long-term complications, impact on quality of life, and mortality risk (Fig. 19.5). Rigorous preoperative assessment of the patient's fitness for undergoing such a major operation is crucial [33]. A patient who is generally healthy (ASA I–III, no evidence of metastatic disease) may be considered for potentially curative resection. Patients with poor status (ASA IV-V) are not candidates for the extensive surgery that is normally required. Proper evaluation and risk assessment should include identification of any findings that would contraindicate re-resection. When assessing a locoregional recurrence, the first step is to exclude peritoneal disease. This is often missed during preoperative imaging and evaluation. Patients with peritoneal carcinomatosis are considered to have metastatic disease. These patients require a different treatment approach, which may include cytoreductive surgery, intraperitoneal chemotherapy, or palliative surgery, such as a colostomy, if the tumor cannot be adequately cyto-reduced.

The presence of metastatic disease (except in the case of isolated resectable metastases), sciatic pain, bone or nerve involvement by tumor, and hydronephrosis generally preclude resection. Lower limb edema, secondary to lymphatic or venous obstruction of the external iliacs, is an ominous sign of extensive disease and is considered an absolute contraindication to surgery. Encasement of the common or external iliac vessels, bilateral ureteral obstruction, or circumferential involvement of the pelvic wall by tumor, indicate a low probability of obtaining negative margins. Unilateral involvement of the internal iliac vessels may be compatible with an R0 resection in selected cases. Tumors involving the iliac vessels and ureters may also invade bony structures, such as the sacrum. Sacral invasion above the S1–S2 juncture almost invariably requires that the patient undergo internal fixation, secondary to sacroiliac instability. Some centers consider that sacral invasion above S2 contraindicates surgery. Prognostic factors should be taken into consideration. Patients who are deemed physically fit enough to withstand the rigors of the planned surgery must also be evaluated psychologically, and counseled regarding the potential impact of an extensive radical re-resection on their postoperative function and quality of life.

In up to 50 % of cases, recurrence is confined to the pelvis and theoretically amenable to cure [34, 35]. Unfortunately, due to the daunting complexity and morbidity associated with these procedures, many patients who may be resectable at the time of diagnosis are not offered surgery as an option. Consequently, they are often referred to a tertiary care center for surgical evaluation much later, when the recurrent tumor has progressed and is, in fact, unresectable.

At our institution we offer resection of locally recurrent rectal cancer in patients in whom resection with negative margins can be achieved. Total pelvic exenteration—with or without sacrectomy—can be performed in carefully selected patients. While this extensive procedure can afford prolonged survival in properly selected patients, it is an extensive operation entailing considerable morbidity.

During resection for a rectal recurrence, nonstandard planes of dissection must be utilized; this is due to the recurrence and the previous

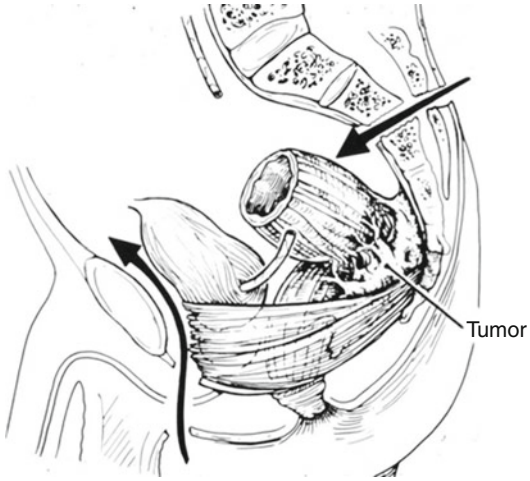

Fig. 19.6 Pelvic exenteration: abdominal phase [56]

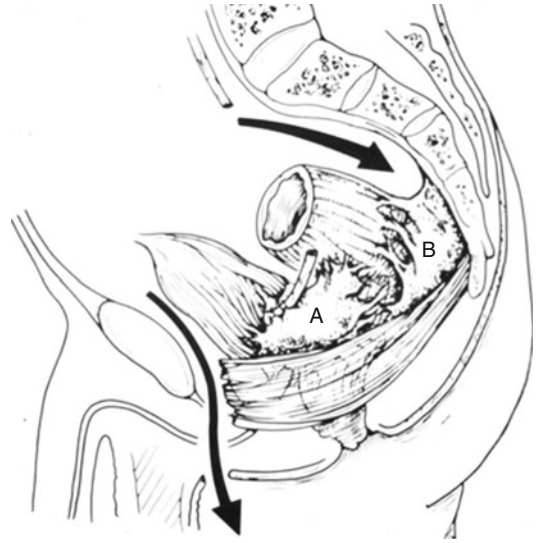

Fig. 19.7 Pelvic exenteration: perineal phase. *A* anterior plane of dissection; *B* posterior plane of dissection [56]

dissection along standard anatomical surgical planes [36]. It is difficult to distinguish between scar tissue and recurrent tumor, and the planes that were opened during the initial surgery may now be affected by tumor. Therefore, the surgeon should be prepared to perform a wide resection through uninvolved planes. Pelvic structures such as ureters and blood vessels may be displaced due to previous surgery, cancer recurrence, or scar tissue. Ureters are often located more medially in patients who have had previous surgery [37]. The plane of dissection should be lateral to the endopelvic fascia, so as to ensure that all previously dissected planes are included within the specimen, and any remaining fascia propria should be included within the surgical specimen [36]. This may involve resection of neighboring anatomic structures and organs (Fig. 19.4) [13, 38]. The majority of patients require an en bloc resection of adjacent anatomy such as the abdominal wall, bladder, pancreas, and duodenum; and the uterus and ovaries in female patients [38]. Finally, the pelvic dissection should be lateral to the levators [25].

Surgery and Location of Recurrence

Centrally located pelvic recurrences are often treated with either a low anterior resection (LAR) or APR. Anterior recurrences attached to the genitalia or the urologic organs usually require a complete pelvic exenteration (Figs. 19.6 and 19.7) [39]. Posterior recurrences adjacent to the sacrum can be treated with a partial sacrectomy, preferably below the level of S3 [25]. Lateral recurrences involving the pelvic sidewall and sciatic notch are difficult to resect with negative margins. As a general rule, a recurrent tumor is rarely resectable if the fat plane medial to the obturator internus is obliterated. Invasion of the sacrum (above the level of S2) and invasion of the pelvic sidewall nearly always preclude surgery (Figs. 19.8 and 19.9).

In anterior recurrences the urinary system is often involved, requiring resection of the ureters and possibly the bladder, as well as the prostate and/or seminal vesicles in male patients [18, 41]. Some cases require extensive perineal resection and reconstruction with tissue flaps [42], usually a rectus abdominus or a gluteal advancement flap. Posterior recurrences may involve the sacrum and require sacral resection, with control of the dural sac and sacral nerves. Ideally, treatment of patients with locally recurrent rectal cancer will involve a multidisciplinary team of specialists including medical and radiation oncologists, colorectal surgical oncologists,

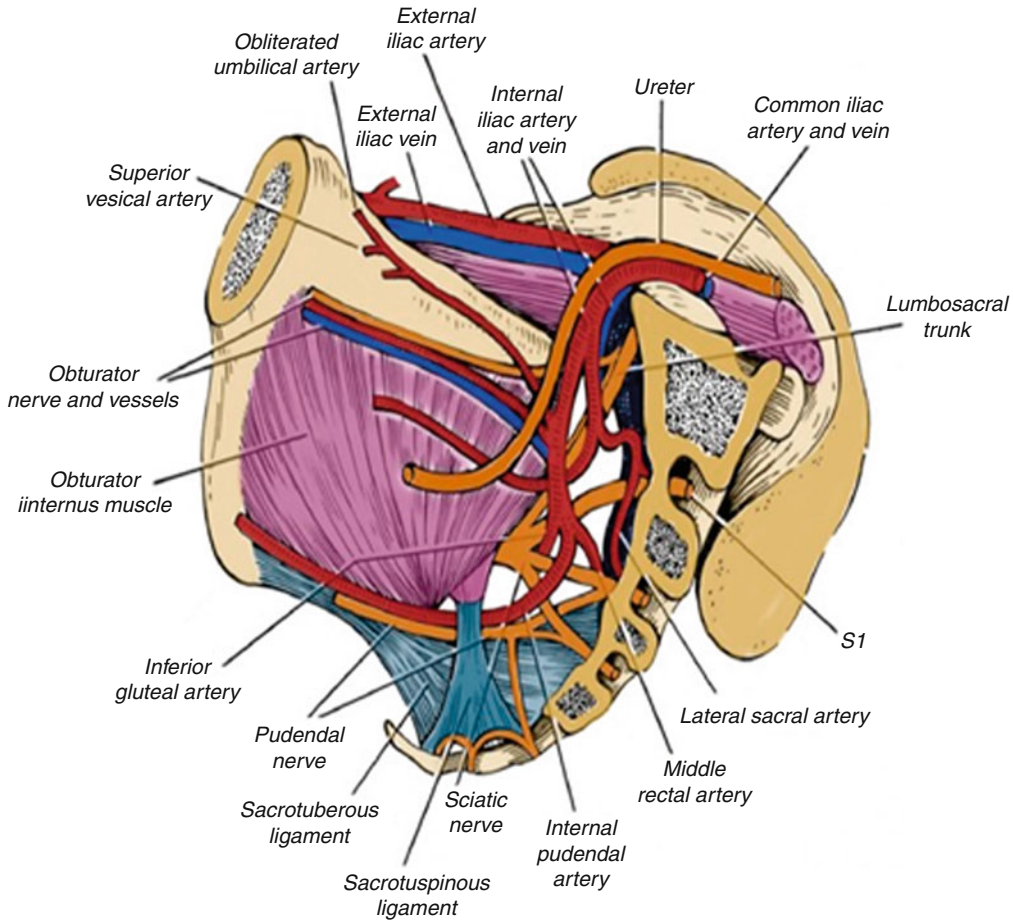

Fig. 19.8 Vascular nerves and muscle planes during lateral dissection (Modified from Austin and Solomon [40])

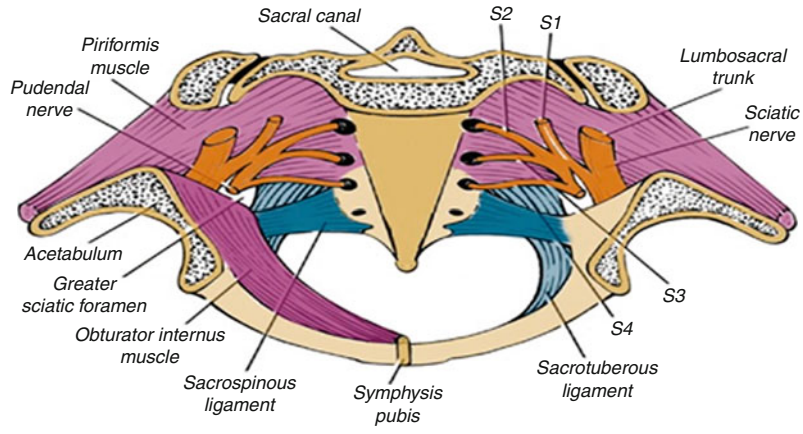

Fig. 19.9 Pelvic view and structures involved with posterior and lateral recurrence (Modified from Austin and Solomon [40])

urologic surgeons, plastic and reconstructive surgeons, orthopedic surgeons, vascular surgeons, and possibly neurologic surgeons. Operations for locally recurrent rectal cancer are generally lengthy, with extensive blood loss and large fluid shifts. A thorough and complete preoperative evaluation by the anesthesia team is paramount (Figs. 19.10, 19.11, and 19.12).

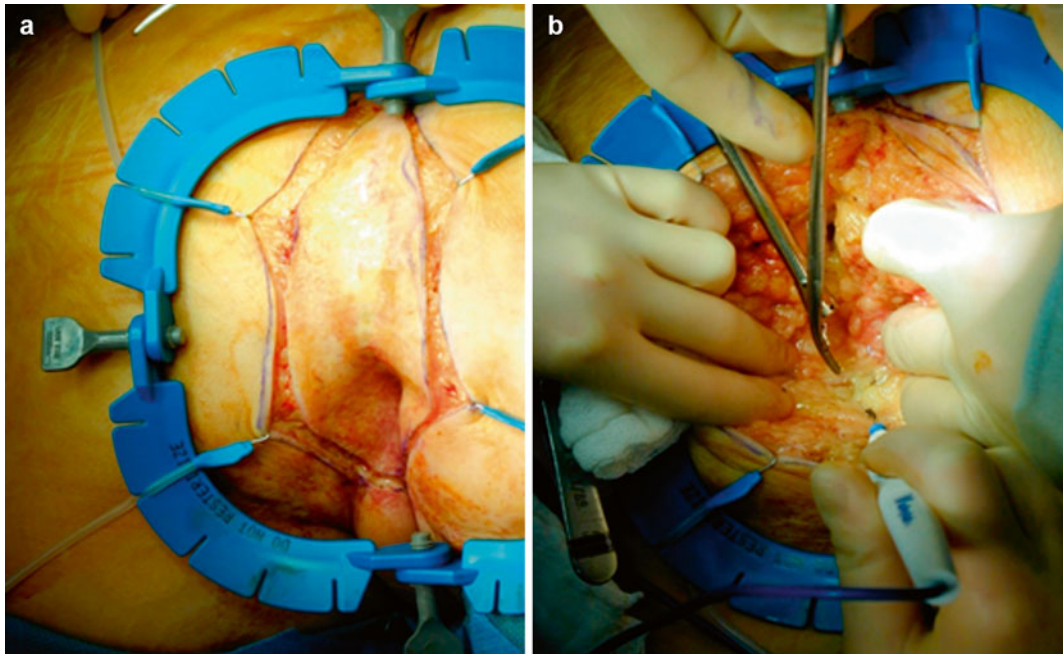

Fig. 19.10 (**a**) Perineal dissection – incision; (**b**) Dissection ischiorectal fat

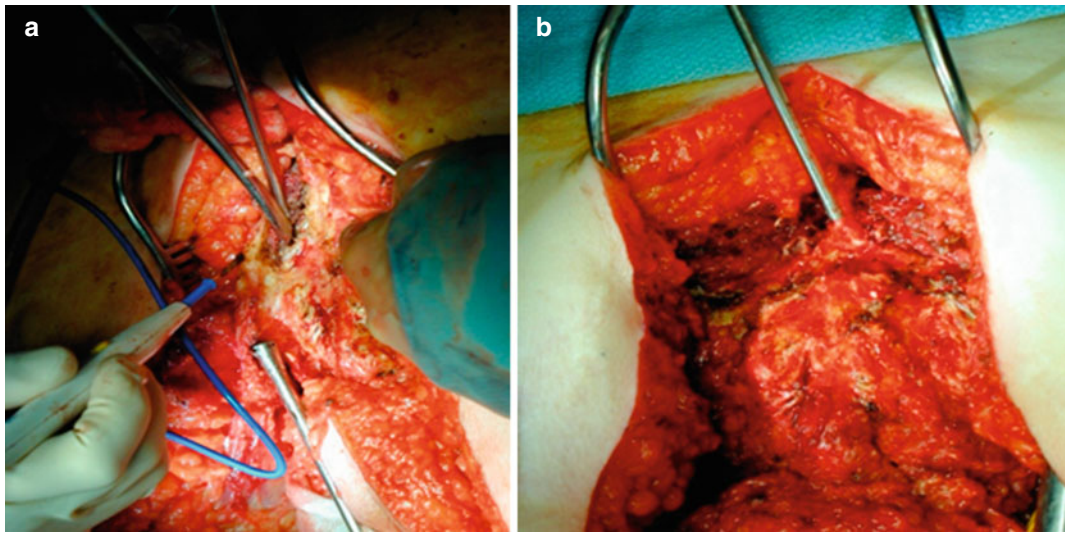

Fig. 19.11 (**a**) Periosteal elevation; (**b**) The levators are divided and the dissection is continued posteriorly, dividing the sacrospinous and sacrotuberous ligaments. The gluteus muscles are detached from the periosteum of the sacrum

Intraoperative Radiation

Despite exhaustive planning and strict selection criteria, an R0 resection with microscopic margins cannot be achieved in all cases. Patients with recurrent rectal cancer, who have often received a maximum dose of external beam radiation during treatment of the primary tumor, are not candidates for additional external beam radiotherapy. However, they may be considered for intraoperative radiation treatment (IORT). IORT has the advantage of directing deeply penetrating

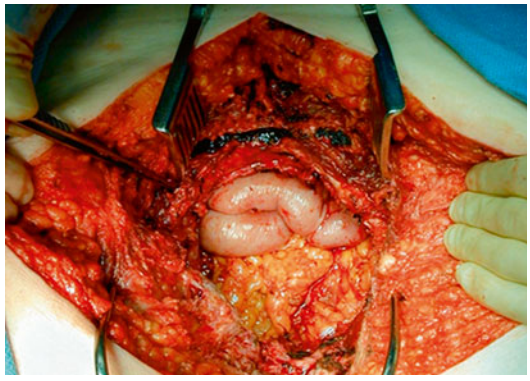

Fig. 19.12 Sacral view, perineal defect; division of the piriformis muscles in the upper limit of the ischiorectal fossa

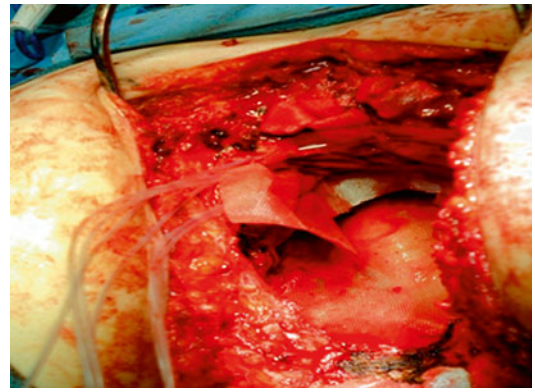

Fig. 19.14 Brachytherapy

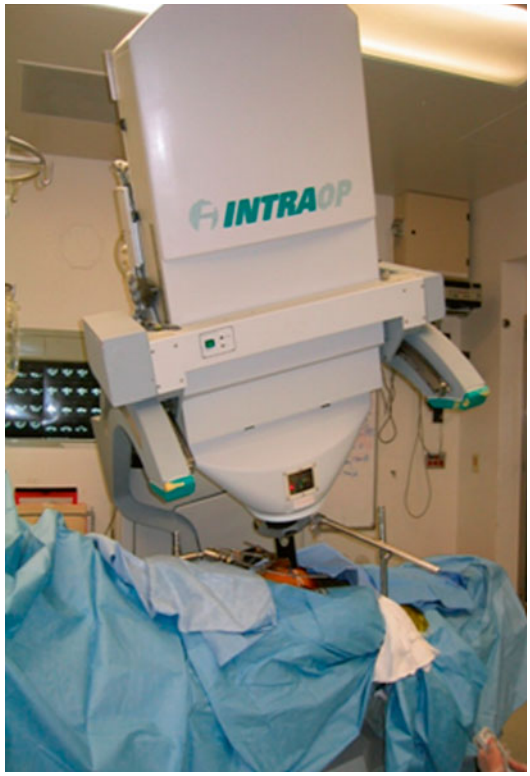

Fig. 19.13 Intraoperative radiotherapy (IORT)

radiation to a specific area of residual tumor, sparing adjacent structures and organs. Radiation by electron beam IORT [43] or by high-dose-rate intraoperative brachytherapy can be delivered to the site of tumor immediately after resection [44] (Fig. 19.13). A drawback is that it may be technically difficult to aim the radiating beam at certain areas of the pelvis. Furthermore, the dedicated linear accelerator required for IORT is too expensive for most medical centers to purchase and maintain.

Interstitial brachytherapy, on the other hand, may represent a less costly alternative for some, because the radiation can be given in the postoperative setting. Afterloading brachytherapy catheters can be attached intraoperatively to areas with compromised surgical margins. The catheters are flexible, and the width and length of each implant can be adapted to the contours of a specific anatomical site (Fig. 19.14). These catheters may migrate, however, causing the patient discomfort and pain [45].

The literature describing IORT is difficult to interpret, as it is limited to a relatively small number of patients treated at specialized centers. Hahnloser et al. reported 3- and 5-year survival of 42.4 and 20.8 %, respectively, in patients with residual disease; 3- and 5-year survival for patients with no residual disease was 43.3 and 27 %, respectively [43]. Five-year survival was 36 % for patients with negative surgical margins, but only 11 % for those with positive margins [46]. The potential morbidity resulting from IORT includes delayed healing, infection, or fistulae. The ureters and peripheral pelvic nerves are most sensitive [46]. Ureteral damage

secondary to radiation may be alleviated by stents. Unfortunately, there is no treatment for nerve damage.

Reconstruction

At the completion of either an APR or pelvic exenteration, there is often a sizable defect in the perineum which cannot be primarily closed. Our plastic surgery colleagues have developed various rotation flaps to reconstruct the perineum. The goal of reconstruction is to fill the dead space and create adequate skin coverage with non-irradiated tissue [47]. In our institution, the flap most commonly created by our plastic surgeons is the vertical rectus abdominus myocutaneous flap. The flap is based on the deep inferior epigastric vessels. The advantage of this flap is that it provides a large skin island with underlying muscle. However, it necessitates a laparotomy incision, and there is decreased abdominal wall strength and increased risk of ventral wall hernias. Thigh flaps, conversely, do not require a laparotomy incision and provide abundant skin and muscle [47]. However, thigh scars can be quite large. The gluteal flap (unilateral or bilateral) is another excellent option. These are based on the inferior gluteal artery perforator and are generally raised in a V-Y fashion [47]. They are technically simple to create, and the blood supply is reproducible. However, the patient must be treated in the prone position; postoperatively, the patient cannot sit for several weeks, so as to minimize the risk of necrosis.

Patient Outcomes

Memorial Sloan Kettering reviewed their experience with surgical salvage for recurrent rectal cancer, following initial radical resection of a primary rectal cancer, in patients treated from 1986 to 1995 [48]. Resection was possible in 103 of 131 patients. Overall 5-year survival was 24 % among all 131 patients. Of the 71 patients who had an R0 resection, 5-year survival was 35 %. Patients with an R1 resection had 5-year survival of 23 %, and patients with an R2 resection had 5-year survival of 9 %. Table 19.2 compares various studies reporting on surgery for locally recurrent rectal cancer.

Tepper et al. reported the results of the Intergroup 0114 study, which examined various adjuvant chemotherapy regimens following resection of stage II and III rectal cancers [16]. Seven hundred and fifteen patients (42 %) developed recurrence, at a median follow-up of 8.9 years. During long-term follow-up of 500 of these 715 patients, 123 developed local recurrence. Forty-five patients (37 %) underwent resection for recurrent tumor. Five-year survival in patients who had surgery was 20 %, compared to 10 % in those who did not. Five-year survival for patients undergoing liver and lung resections

Table 19.2 Survival after surgical salvage of recurrent rectal cancer

Study	Resections (n)	R0 resections	Survival
Salo 1999 [48]	103	71 (68.9 %)	35 % (R0 5-year survival)
Tepper 2003 [16]	45	Unknown	20 % (5-year survival resected group) 10 % (5-year survival unresected group)
Kruschewski 2012 [49]	39	18 (46 %)	35 % (R0 5-year survival)[a]
Bhangu 2012 [50]	70	45 (64 %)	69 % (R0 3-year survival) 56 % (R1 3-year survival) 20 % (R2 3-year survival)
Alberda 2014 [51]	93	54 (58 %)	28 % (5-year survival no nRTx) 43 % (5-year survival nRTx)[b]

[a]Combined colon and rectal cancer recurrence
[b]*nRTx* neoadjuvant radiotherapy

for metastatic disease was 31 and 33 %, respectively.

Kruschewski et al. reported on a series of 82 patients who had undergone R0 resection for a primary colon or rectal cancer [49]. Fifty-six (68 %) had surgery for rectal cancer. Re-resection with R0 margins was achieved though multi-organ or pelvic exenteration in 9 patients with recurrent rectal cancer. In concurrence with previous studies, R0 resection was associated with significantly longer survival than R1 or R2 resections: overall survival for the entire cohort was 106.1 months after R0 resection, 72.5 months after R1 resection, and 37.9 months after R2 resection; overall survival for patients with inoperable recurrence was 42.2 months. Despite the improved survival associated with R0 resections, these procedures carried a high risk of morbidity: the re-laparotomy rate for the entire cohort was 13 %, and total morbidity was 77 %. Complications such as wound infection, abscess, obstruction, ureteral or bladder injury, sepsis, renal or heart failure, thrombosis, and pneumonia were common.

Bhangu et al. reviewed the experience of the Royal Marsden Hospital, reporting on 127 patients with recurrent rectal cancer treated at that institution between 2007 and 2011 [52]. The 1-, 3-, 5- and 10-year local recurrence rates were 22, 72, 85, and 96 %, respectively. Of the patients who proceeded to surgery, 64 % had an R0 resection, 20 % an R1 resection, and 16 % an R2 resection. The 3-year survival rates for R0, R1, and R2 resections were 69, 56, and 20 %, respectively. There was no statistical difference in survival between patients undergoing an R2 resection and those who were managed palliatively or non-operatively. In another study, Bhangu and colleagues performed a systematic review of the literature, focusing on resection margins in locally recurrent rectal cancer [50]. In concordance with previous studies, R0 resections were associated with improved survival; resections resulting in positive margins were associated with an increased rate of recurrence and worse survival. Specifically, median survival for R0 resection was 28–92 months; for R1 resection, 12–50 months; for R2 resection, 6–17 months.

Alberda et al. analyzed and compared outcomes in patients with resectable locally recurrent rectal cancer after TME, with and without previous neoadjuvant radiotherapy (RT) [51]. One hundred and thirty-nine patients had surgery, with 93 patients undergoing curative surgeries. The median survival in patients who received neoadjuvant RT was 42 months, compared to 38 months in patients who did not receive neoadjuvant RT.

The outcomes of posterior pelvic exenteration with sacral resection for posterior recurrence are not very different from the outcomes of resection for tumor located in other areas of the pelvis. Patients with R0 resection have longer survival than those with R1 or R2 resections. Median survival for patients with R0 resection ranges from 31 to 45 months [53–55]. Nevertheless, these challenging procedures are associated with a high morbidity rate and increased use of transfusion, and the risk of pelvic abscess and perineal wound breakdown is high.

Conclusion

Long-term survival for patients with locally recurrent rectal cancer is unlikely without additional treatment. Chemotherapy and external beam radiation may be considered for patients with local recurrence who did not receive chemoradiotherapy for their primary tumor. While chemotherapy and radiation are associated with some improvement in the setting of recurrent rectal cancer, they do not offer the best chance for long-term survival. Surgery is the only potentially curative treatment, but it should be undertaken only in carefully selected patients who are fit enough for the extensive and potentially morbid procedures required, who have tumors amenable to resection with negative margins, and who have been counseled regarding the impact of re-resection on their postoperative function and quality of life. The addition of IORT may be advantageous. However, obtaining negative surgical margins has the greatest impact on survival.

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Metastatic Rectal Cancer

20

Thorvardur R. Halfdanarson and Joleen M. Hubbard

Abstract

Colorectal cancer is a common malignancy and up to 20 % of patients have metastases at diagnosis and up to 50 % of those with localized disease will suffer a recurrence. The problem of metastatic colorectal cancer is therefore substantial. Most patients with metastatic colorectal cancer are treated with palliative intent where the treatment is aimed at prolonging survival and maintaining the quality of life of patients for as long as possible. There have been major advances in the management of metastatic colorectal cancer in the last decade with the advent of multiple new agents for systemic therapy, both cytotoxic drugs and biological agents such as VEGF and EGFR inhibitors. As a result, the overall survival of patients with metastatic colorectal cancer has improved markedly. Furthermore, biomarkers are assuming a larger role in the management of and allow for more tailored management of individual patients.

Keywords

Colorectal cancer • Metastases • Chemotherapy • Biological therapy • 5-fluorouracil • Capecitabine • Oxaliplatin • Irinotecan • Bevacizumab • Aflibercept • Cetuximab • Panitumumab • RAS mutations

Introduction

Colorectal cancer is the third most common malignancy in humans and a leading cause of cancer deaths. In 2014, 96,830 new cases of colon cancer and 40,000 new cases of rectal cancer were expected to be diagnosed in the US. During the same period, 50,310 deaths were expected [1]. Up to 20 % of patients have distant metastases at the time of diagnosis and close to 50 % of patients with localized disease will suffer

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a recurrence, usually in the form of metastases [2]. Metastatic colorectal cancer is therefore a major clinical problem and there is a great need for better treatment options. Once at advanced stage, rectal cancer and colon cancer are treated the same.

In select cases, metastatic lesions, usually in the liver or lungs, can be surgically removed or ablated with a substantial chance of long-term survival. This is best determined by a multidisciplinary evaluation including specialists in surgery, radiology, and medical oncology. For the majority of patients with metastatic colorectal cancer who are not surgical candidates for procedures with curative intent, survival can be markedly prolonged with chemotherapy.

There has been a steady evolution of therapy for metastatic colorectal cancer with the advent of new drugs in the two last decades. Prior to the year 2000, the options for therapy of metastatic colorectal cancer were very limited with 5-fluorouracil being the mainstay of therapy, usually given with leucovorin. Since 2000, multiple new drugs, both cytotoxic as well as more targeted drugs, have been found to be valuable and have subsequently been approved for use. These drugs include irinotecan, oxaliplatin, capecitabine, bevacizumab, aflibercept, cetuximab, panitumumab and regorafenib. The addition of these cytotoxic and biologic agents into the treatment strategy for metastatic colorectal cancer has improved median overall survival from 11.5 months (with 5-fluorouracil/leucovorin alone) to nearly 30 months [3].

General Principles and Goals of Therapy

The goals of therapy vary among individual patients. Select patients receive chemotherapy as part of a multimodality curative treatment strategy. Most with metastatic disease fall under the category of palliative therapy, where the disease is incurable, and balancing treatment efficacy with toxicity becomes critical. The goals of therapy can broadly be defined in the following way but there is a considerable overlap among these groups of patients:

1. Conversion therapy: This applies to patients with metastatic disease where there is a reasonable chance of surgically removing or ablating all sites of known disease. Patients with large and unresectable but relatively few liver metastases fall under this category. By using effective systemic therapy with a high response rate, many patients can successfully undergo a liver resection. A high radiographic response rate is critical in this patient population and regimens with substantial toxicity are often very appropriate.
2. Adjunctive therapy: Patients with upfront resectable liver metastases do benefit from either perioperative or postoperative chemotherapy. The additional benefit provided by chemotherapy is small.
3. Symptomatic therapy: Patients suffering from severe symptoms secondary to tumor bulk, may benefit from upfront aggressive systemic therapy. Such therapy has the potential to quickly relieve symptoms. In some situations, it is reasonable to start with aggressive initial chemotherapy and then decrease the intensity of the chemotherapy once the symptoms are under better control.
4. Therapy given to prolong survival: Most patients fall under this category where curative therapy is not an option but the goal is to prolong survival as much as possible without causing much decrease in the quality of life of the patients. In this group, it becomes critical to balance the efficacy of the therapy against the toxicity. Objective tumor response is not nearly as important in this group as patients can derive substantial survival benefit without showing a major radiographic response.
5. Best Supportive Care: Some patients are too frail to receive any systemic therapy and best supportive care may be the only appropriate option. Other patients may choose not to receive chemotherapy for their metastatic colorectal cancer and it is therefore helpful to be aware of the prognosis of patients who receive no therapy. Without systemic therapy, the average survival of patients is 5–6 months [4, 5].

Systemic Therapy for Metastatic Colorectal Cancer

With the advent of newer treatment agents, it has become clear that the survival is longest among those patients who receive all of the available active agents [6, 7]. Therefore, every attempt should be made to offer all the approved drugs to all eligible patients. Recent trials have consistently shown that median overall survival in patients receiving active therapy exceeds 2 years, indicating a very substantial survival benefit of therapy. The 5-year survival is now reaching 10 % compared to 1 % before the advent of more effective therapy [8]. Moreover, there is also a benefit in terms of quality of life where treated patients not only survive longer but also suffer fewer symptoms and have superior quality of life.

We recommend starting chemotherapy as soon as possible after the diagnosis of metastatic disease, even if patients are asymptomatic. There is a dearth of literature on the optimal timing of initiating chemotherapy and the risks of waiting with initiating therapy. Patients with asymptomatic metastases, especially liver and peritoneal metastases, may quickly become symptomatic from organ dysfunction such as hyperbilirubinemia and small bowel obstruction and therefore ineligible for treatment with some of the active agents available. We therefore prefer instituting therapy early as that gives the patients the best chances of getting exposed to all of the available agents.

Symptomatic patients undergoing chemotherapy should be offered an early referral to a palliative medicine specialist. There is evidence that focused palliative therapy delivered along with conventional chemotherapy in patients with lung cancer may result in improved survival. Early institution of palliative therapy remains to be studied in a population of patients with mCRC but until such data becomes available, an early referral for palliative therapy is recommended, especially for symptomatic patients.

Many patients succumb to their disease without being offered all the available and active drugs [9]. While the survival of patients has improved in recent years, the benefits seen in clinical trials may not be generalizable to all patients with metastatic colorectal cancer. Patients enrolled in clinical trials are in generally younger, more fit, and have less comorbidities than the general mCRC population, all factors that may independently improve survival [10, 11]. The impact of systemic therapy on the physical function and quality of life needs to be carefully considered for the individual patient.

Short Overview of the Available Agents for Systemic Therapy

There are seven drugs approved for the treatment of mCRC in the US as of 2014. These drugs have different indications and not all have single-agent activity. 5-fluorouracil, capecitabine, oxaliplatin and irinotecan are conventional cytotoxic agents but biologic agents including monoclonal antibodies and kinase inhibitors are assuming a larger role in therapy.

- 5-Fluorouracil (5-FU) has been the mainstay of therapy for CRC, both in advanced and early stages. It is an antimetabolite that interferes with DNA synthesis, primarily by inactivating thymidilate synthase. 5-FU is also incorporated into RNA which further induces cell injury. 5-FU is active as monotherapy but more frequently given in a combination with other agents. There are several different and effective methods for delivery of 5-FU and it is usually given with leucovorin which enhances its activity. 5-FU given as a prolonged infusion, usually over 46–48 h every 2 weeks, is as effective as 5-FU given as a bolus and less likely to result in hematologic toxicity. Many chemotherapy regimens use a combination of 5-FU bolus and prolonged infusion (such as FOLFOX6) but other regimens like FOLFOX7 omit the bolus entirely given the increased incidence of neutropenia with bolus 5-FU therapy. Omitting the bolus does not seem to limit the efficacy of the treatment, at least not in patients undergoing palliative therapy where the efficacy and toxicity of the treatment needs to be carefully balanced.
- Capecitabine is an oral prodrug of 5-FU which is readily absorbed by the intestinal

tract and converted to 5-FU in three enzymatic steps after absorption. Capecitabine is usually given twice daily over 2 weeks with a 1-week break. Capecitabine is active as monotherapy and has been shown to be non-inferior to infusional 5-FU, both as a single agent [12, 13] and in combinations and is increasingly being used in combination with other drugs such as oxaliplatin [14–18]. Capecitabine has a somewhat different toxicity profile than 5-FU. It is less likely to cause mucosal damage and bone marrow suppression (neutropenia and thrombocytopenia) but more likely to cause skin rash, usually of the hands and feet and hyperbilirubinemia [12, 13]. Capecitabine is contraindicated in patients with severe renal insufficiency and has several important interactions with other drugs, most notably warfarin.

- Irinotecan is an intravenous cytotoxic agent that inhibits topoisomerase I resulting in DNA damage. Inhibition of topoisomerase I disrupts DNA integrity and interferes with DNA replication, transcription and repair. Irinotecan is converted to an active metabolite, SN-38, which is responsible for cytotoxic action of the drug. SN-38 is detoxified by a drug-metabolizing UDP-glucuronyl transferase 1A1 (UGT 1A1). Certain genetic polymorphisms (including the UGT1A1*28 allele) can result in excessive toxicity of irinotecan. Patients homozygous for the UGT1A1*28 allele have a higher incidence of GI toxicity and neutropenia from irinotecan [19]. About 10 % of the North American population is homozygous for UGT1A1*28 and genetic testing is available and may identify patients at risk of having excessive toxicities [20]. Irinotecan has substantial activity when given alone [21, 22] but is more commonly given in a combination with 5-FU and targeted agents. The main toxicity is gastrointestinal with abdominal cramping and diarrhea. The diarrhea can be very severe and lead to hypovolemia and electrolyte imbalances. Given the GI toxicity, irinotecan is usually not used in combination with capecitabine.
- Oxaliplatin is a platinum derivative, which exerts its cytotoxic effect by binding to purine DNA bases and disrupting the normal function of cellular DNA. Oxaliplatin has little single-agent activity against colorectal cancer and is always given in a combination with other agents. Oxaliplatin is neurotoxic and a common cause of sensory polyneuropathy and acute neurosensory symptoms, especially cold-induced dysesthesia. The sensory neuropathy secondary to oxaliplatin use is dose-dependent and cumulative and can be irreversible. Oxaliplatin-induced neuropathy is major cause of morbidity in patients treated for colorectal cancer. Planned discontinuation of oxaliplatin after a set number of treatments with re-introduction at progression seems to decrease the incidence and severity of the neuropathy.
- Bevacizumab is a recombinant humanized monoclonal antibody that binds to and neutralizes vascular endothelial growth factor (VEGF) and prevents its binding to the VEGF receptor [23, 24]. The mechanism of action of bevacizumab is complex and not fully understood. Bevacizumab inhibits tumor angiogenesis, growth, and metastasis in numerous tumor models. It also reduces intratumoral interstitial pressure and potentially promotes the delivery of cytotoxic drugs. Bevacizumab has very limited activity as monotherapy for colorectal cancer but has been shown to modestly improve overall survival and progression free survival when added to conventional chemotherapy effective. Bevacizumab is generally very well tolerated but it has several unique adverse effects [25]. Bevacizumab has been associated with delayed wound healing and bowel perforation and should be withheld at least 6–8 weeks prior to elective surgery and for 6–8 weeks postoperatively [26]. Bevacizumab increases the risk of arterial thromboembolic events and hypertension and is likely best avoided in patients of high risk of cardiovascular complications such as a

recent history of a coronary event or a stroke [27, 28].

- Aflibercept is a recombinant decoy receptor fusion protein that blocks angiogenesis by binding to VEGF (a VEGF trap) and placental growth factor (PlGF) [29, 30]. Aflibercept is currently approved in a combination with FOLFIRI after patients have progressed on oxaliplatin-based therapy based on the results of a large randomized trial [31]. As with bevacizumab, aflibercept is associated with bowel perforation, delayed wound healing and arterial thromboembolic events. The role of aflibercept in the management of metastatic colorectal cancer remains to be further characterized as similar results can be achieved by continuing bevacizumab beyond first progression.
- Regorafenib is a multiple target kinase inhibitor that inhibits VEGF receptors among other targets [32]. The anti-tumor effects of regorafenib are largely secondary to its antiangiogenic effects. Regorafenib is currently approved in the USA for therapy of metastatic colorectal cancer previously treated with cytotoxic chemotherapy and biologics (last-line therapy) based on a large randomized trial comparing it to best supportive care [33]. The benefits of regorafenib are modest and the toxicities can be severe, including hand-foot skin reaction, diarrhea, fatigue, and hypertension. Regorafenib is currently being studied in combinations with other agents as more upfront therapy but its use is currently restricted to patients where all other approved treatments have failed.
- Cetuximab and panitumumab are monoclonal antibodies against the epidermal growth factor receptor (EGFR) and are currently approved as both monotherapy and in combination with other agents for metastatic colorectal cancer [34]. Both of these drugs bind to the EGFR, thus leading to inhibition of its downstream signaling affecting cell survival and proliferation. Patients whose tumors harbor a RAS mutation do not derive benefit from treatment with EGFR monoclonal antibodies [35–37]. The main toxicity of cetuximab and panitumumab is dermatologic as both drugs frequently cause skin rash that can be severe and very detrimental to the patient's quality of life.

Predictive and Prognostic Molecular Markers

Certain biomarkers are predictive of survival of patients with advanced colorectal cancer and some do predict response to therapy. Fifty to 60 % of patients harbor KRAS and NRAS tumor mutations and these patients do not benefit from therapy with EGFR monoclonal antibodies and testing tumor tissue for these mutations is now mandatory. The American Society of Clinical Oncology (ASCO) issued guidelines in 2009 on KRAS testing that recommend against using cetuximab or panitumumab in patients with KRAS mutations of exon 2 [38]. Since the publication of these guidelines, it has become known that KRAS mutations outside of exon 2 and NRAS mutations also predict a lack of response to EGFR directed therapy [35, 39]. This has led to the concept of all-RAS testing which is currently recommended. The conventionally used exon 2 KRAS mutation analysis will not identify the additional 15–20 % of patients with non-exon 2 KRAS mutations and NRAS mutations who will derive no benefit from anti-EGFR therapy. BRAF mutations are seen in 5–10 % of patients with colorectal cancer and have been consistently shown to predict worse survival [40, 41]. While BRAF mutations may be a strong predictor of overall survival, the role in predicting responses to therapy is less clear. BRAF mutation analysis is therefore not currently recommended to guide treatment decisions. There are no biomarkers available that reliably predict response in patients receiving cytotoxic agents or VEGF inhibitors. Multiple other molecular markers are being explored but RAS mutation testing is currently the only one routinely used to help selecting therapy for patients with advanced colorectal cancer.

Initial Therapy

Multiple options exist for initial therapy of mCRC and the treatment has to be individualized for each patient. Previous models of colon cancer therapy frequently included different "lines of therapy". For example, the initial therapy was considered first-line and when the patient was found to have progressive disease, second-line therapy was offered. For those patients who still had a reasonably good performance at the time of progression on second-line therapy, third line therapy was often offered. This model has now been abandoned in favor of a "continuum of care" model [42]. The continuum model incorporates several concepts that reflect the current practice in the management of advanced colorectal cancer based on recent trials. Patients are increasingly being offered maintenance therapy following an induction phase with more aggressive chemotherapy and some patients opt for treatment breaks followed by reintroduction of the same therapy, either after a set time interval or upon progression (see section "Treatment interruptions and maintenance therapy" below). Patients may change therapy for other reasons than progressive disease, sometimes for reasons related to adverse effects of therapy but later in the course of their disease return to that same therapy. The lines of therapy are therefore becoming increasingly blurred.

The most common chemotherapy initially recommended is a cytotoxic doublet containing a fluoropyrimidine such as 5-FU or capecitabine with either oxaliplatin or irinotecan given with a biologic agent, either a bevacizumab or an EFGR inhibiting monoclonal antibody (Table 20.1). Infusional 5-FU is more effective and better tolerated than the older regiments of bolus 5-FU [43]. The addition of irinotecan or oxaliplatin to 5-FU and leucovorin improves both survival and response rates [44–48]. Commonly used initial cytotoxic regimens include FOLFOX, CAPOX and FOLFIRI (Table 20.2). Combination chemotherapy is preferred over sequential single-agent therapy although the latter may be used in select patients, such as the elderly and infirm, after careful counseling. Sequential single-agent therapy has been compared with combination therapy in at least two large clinical trials [53, 54]. While there was not a statistical difference in the overall survival among the groups, the survival was relatively short by modern standards. Furthermore, the use of sequential therapy does not harness the synergistic effect of the different cytotoxic agents. More importantly, patients receiving single-agent sequential therapy were not likely to be offered all the available effective agents upon progression. This is an especially important concern as studies have shown a relationship between the number of agents received and time on therapy and overall survival [42].

FOLFOX and FOLFIRI can both be considered very appropriate front-line treatments. There are several versions of FOLFOX in use and perhaps the most commonly used one is modified FOLFOX 6 (mFOLFOX6) which consists of 5-FU given as a bolus on day 1 along with leucovorin and oxaliplatin followed by a 46-h continuous infusion of 5-FU with an ambulatory pump. Modified FOLFOX7 (mFOLFOX7) does not contain a 5-FU bolus on day 1 but is otherwise similar. mFOLFOX7 appears to be less likely to cause neutropenia than FOLFOX regimens containing a 5-FU bolus and may therefore be a very suitable regimen for patients with advanced disease receiving palliative chemotherapy.

There is no difference in outcome in terms of survival or response rate between FOLFOX and FOLFIRI assuming patients have access to the other regimen upon progression [49, 50]. The selection of the chemotherapy backbone depends on several factors:

- Prior adjuvant therapy: Patients who have a recurrence of a previously resected early-stage colorectal cancer, and received oxaliplatin in the preceding 12 months, should be considered for irinotecan-based therapy, with the intent of reintroducing oxaliplatin at a later time point in the course of the disease.
- Comorbidities: Comorbidities may dictate the selection of initial therapy. For example, a patient with underlying neuropathy, such as diabetic neuropathy, may be better served with irinotecan-based regimen (FOLFIRI) instead of oxaliplatin-based regimen (FOLFOX)

Table 20.1 Key clinical trials of initial (first-line) chemotherapy in patients with metastatic colorectal cancer

Author	Year	Number of patients	Therapy	RR (%)	p-value	PFS (mos)	p-value	OS (mos)	p-value
5-FU and leucovorin vs. capecitabine									
de Gramont [43]	1997	216	Bolus 5-FU/LV	14	0.0004	5.5	0.0012	14.2	0.067
		217	Bolus + infusional 5-FU/LV	33		6.9		15.5	
Hoff [13]	2001	303	Bolus 5-FU/LV	16	0.005	4.7	0.72	13.3	0.974
		302	Capecitabine	25		4.3		12.5	
Van Cutsem [12]	2001	301	Bolus 5-FU/LV	16		4.7	0.65	12.1	0.33
		301	Capecitabine	19		5.2		13.2	
Irinotecan-containing regimens									
Saltz [44]	2000	231	IFL	39	<0.001	7.0	0.004	14.8	0.04
		226	Bolus 5-FU/LV	21		4.3		12.6	
		226	Irinotecan	18		4.0		12.0	
Douillard [45]	2000	188	5FU/LV	31	<0.001	4.4	<0.001	14.1	0.031
		199	Irinotecan + 5-FU/LV	49		6.7		17.4	
Köhne [46]	2005	216	Infusional 5-FU/FA	62	<0.001	8.5	<0.001	20.1	0.278
		214	Irinotecan + infusional 5-FU/FA	34		6.4		16.9	
Oxaliplatin-containing regimens									
de Gramont [47]	2000	210	Bolus + infusional 5-FU/LV	22	0.0001	6.2	0.0003	14.7	0.12
		210	Bolus + infusional 5-FU/LV + oxaliplatin	51		9.0		16.2	
Goldberg [48]	2004	264	IFL	31	0.002[a]	6.9	0.0014[a]	15	0.0001[a]
		267	FOLFOX	45		8.7		19.5	
		264	IROX	35	0.03[a]	6.5		17.4	
Porschen [15]	2007	233	FUFOX	54	0.7	8	0.117	18.8	0.26
		241	CAPOX	48		7.1		16.8	
Cassidy [16]	2008	1,017	FOLFOX	37	NS	8.5	NS	19.8	NS
		1,017	CAPOX	37		8		19.6	
Ducreux [17]	2011	150	FOLFOX	46	NS	9.3	NS	18.9	NS
		156	CAPOX	42		8.9		20.1	
Díaz-Rubio [18]	2007	174	FUOX	46	0.539	9.5	0.153	20.8	0.145
		174	CAPOX	37		8.9		18.1	

(continued)

Table 20.1 (continued)

Author	Year	Number of patients	Therapy	RR (%)	p-value	PFS (mos)	p-value	OS (mos)	p-value
Tournigand [49]	2004	109	FOLFIRI → FOLFOX	56	0.26	14.2	0.64	21.5	0.99
		111	FOLFOX → FOLFIRI	54		10.9		20.6	
Colucci [50]	2005	164	FOLFIRI → FOLFOX	31	0.6	7	0.64	14	0.28
		172	FOLFOX → FOLFIRI	34		7		15	
Three drug combinations (5-FU, oxaliplatin and irinotecan)									
Falcone [51]	2007	122	FOLFIRI	41	0.0002	6.9	0.0006	16.7	0.032
		122	FOLFOXIRI	66		9.8		22.6	
Souglakos [52]	2006	146	FOLFIRI	37	0.168	6.9	0.17	19.5	0.17
		137	FOLFOXIRI	43		8.4		21.5	

Note that there is a substantial variation in the dose and toxicity profile among the regimens listed in the table. Please consult the original reports for details
CAPOX: capecitabine and oxaliplatin, *FA*: folinic acid, *FOLFOX/FUFOX*: 5-FU, leucovorin and oxaliplatin, *FOLFOXIRI*: 5-FU, oxaliplatin and irinotecan, *FUOX*: 5-FU and oxaliplatin, *IFL*: irinotecan, 5-FU and leucovorin, *IROX*: Irinotecan and oxaliplatin, *LV*: leucovorin, *Mos*: months, *NS*: not significant, *OS*: overall survival, *PFS*: progression-free survival, *RR*: radiographic response rate
[a]Compared to FOLFOX

Table 20.2 Commonly used chemotherapy regimens

Regimen	5-FU bolus	5-FU infusion	Leucovorin	Capecitabine	Oxaliplatin	Irinotecan	Cycle length (days)
Modified de Gramont	400 mg/m^2	2,400 mg/m^2 over 46 h	400 mg/m^2	None	None	None	14
mFOLFOX6	400 mg/m^2	2,400 mg/m^2 over 46 h	400 mg/m^2	None	85 mg/m^2	None	14
mFOLFOX7	None	2,400–3,000 mg/m^2 over 46 h	200 mg/m^2	None	85 mg/m^2	None	14
CAPOX	None	None	None	850–1,000 mg/m^2 for 14 days	130 mg/m^2	None	21
FOLFIRI	400 mg/m^2	2,400 mg/m^2 over 46 h	400 mg/m^2	None	None	180 mg/m^2	14
FOLFOXIRI	None	2,400–3,200 mg/m^2 over 46 h	200 mg/m^2	None	85 mg/m^2	165 mg/m^2	14

Bevacizumab, cetuximab and panitumumab can be added to either FOLFIRI or FOLFOX (the addition of cetuximab to FOLFOX is still under investigation). Bevacizumab can be added to CAPOX. Aflibercept can be added to FOLFIRI but the combination is only approved as second-line therapy after progression on FOLFOX with or without bevacizumab

mFOLFOX: modified FOLFOX

Table 20.3 Eastern Cooperative Oncology Group (WHO/Zubrod) performance status

Performance status	Description
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all self-care but unable to carry out any work activities. Up and about more than 50 % of waking hours
3	Capable of only limited self-care, confined to bed or chair more than 50 % of waking hours
4	Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair
5	Dead

Table 20.4 Karnofsky performance status

Performance status	Description
100	Normal. No complaints. No evidence of disease
90	Able to carry on normal activity. Minor signs or symptoms of disease
80	Normal activity with effort. Some signs or symptoms of disease
70	Care of self. Unable to carry on normal activity or to do active work
60	Requires occasional assistance, but is able to care for most of needs
50	Requires considerable assistance and frequent medical care
40	Disabled. Requires special care and assistance
30	Severely disabled. Hospitalization is indicated although death not imminent
20	Hospitalization necessary, very sick, active supportive treatment necessary
10	Moribund. Fatal processes progressing rapidly
0	Dead

as initial therapy given its neurotoxicity. Similarly, patients with ileostomy may have difficulties tolerating therapy with irinotecan and capecitabine given the risk of diarrhea. Irinotecan should also be used with great care in patients with liver dysfunction. Oxaliplatin is safe to use even in significant renal and hepatic insufficiency.

- Performance status: Patients should undergo a thorough evaluation, including assessment of performance status and comorbidities by a medical oncologist prior to commencing therapy. Performance status is relatively easy to assess and the two most common used tools are the Eastern Cooperative Oncology Group (ECOG) performance scale and the Karnofsky performance score (Tables 20.3 and 20.4) [55, 56]. Patients with impaired performance score may not be candidates for intensive multiagent systemic therapy but can still derive significant benefit, both in terms of survival improvement and quality of life with fluoropyrimidine monotherapy. (See the section on the elderly and those with impaired performance below)

Capecitabine can be safely substituted for 5-FU in oxaliplatin-based regimens in the management of metastatic colorectal cancer [14–17]. The optimal dose of capecitabine is not well defined and there appear to be substantial regional differences in tolerance to capecitabine, likely based on different pharmacogenomics variations in different populations as well as life-style and dietary patterns. Capecitabine has been found to be effective when used in a combination with irinotecan (CAPIRI) [57], but we do not recommend this as a routine option for first line therapy given the risk of complications, especially gastrointestinal toxicity.

Triple cytotoxic drug regimens such as FOLFOXIRI have been evaluated in patients with metastatic colorectal cancer and have been shown to be safe and effective as initial chemotherapy but whether such an aggressive approach improves overall survival remains to be seen [52, 58, 59]. The overall survival of patients in the

triple-drug arms does not appear to be superior when compared to recent studies comparing sequential cytotoxic doublet therapy with biologics, especially when maintenance therapy is used. Furthermore, toxicity favors doublet therapy over triple-drug therapy.

The Role of Biologic Drugs

Most newly diagnosed patients treated in the US will receive initial therapy that incorporates biologics, most commonly bevacizumab. Biologic therapy directed against VEGF and EGFR has been extensively studied and found to provide additional benefit when given in conjunction with cytotoxic agents (Table 20.5).

Bevacizumab has been shown to have relatively modest benefits in terms of improving overall survival and progression showing a prolongation in overall survival of 2–3 months over cytotoxic therapy alone but consistently seen across multiple trials [60–65, 71]. Bevacizumab has no clinically meaningful efficacy when used alone. Bevacizumab is very well tolerated and is extensively used in upfront chemotherapy as well as in the maintenance phase of the treatment. The most important adverse effects of bevacizumab therapy are arterial thromboembolic events, hemorrhage, bowel perforation and impaired wound healing [26, 28, 71]. Continuing bevacizumab beyond progression of the first cytotoxic regimen is beneficial. In those circumstances, the chemotherapy backbone regimen is changed but the bevacizumab continued as adjunctive therapy. This concept has been explored in a randomized trial where continuing bevacizumab beyond first progression was found to prolong both overall survival and progression-free survival [72]. The results of observational studies provide further support of using bevacizumab beyond first progression [73–75].

Cetuximab and panitumumab, both monoclonal antibodies directed against EGFR, are effective both as monotherapy and in combinations with cytotoxic agents [3, 36, 66–68, 76–78]. The beneficial effects of the available EGFR targeting drugs are limited to patients with cancers that have no RAS mutations (RAS wild-type). The optimal chemotherapy backbone for regimens including EGFR inhibitors is not known. Two trials limited to KRAS wild-type patients did not show additional benefit of cetuximab when added to oxaliplatin-containing regimens [66, 67]. A smaller study reported improved progression-free survival but not overall survival when cetuximab was added to FOLFOX [68]. The benefits of adding cetuximab to oxaliplatin-based chemotherapy are therefore uncertain. The additional benefits of cetuximab when given with cytotoxic chemotherapy are modest. For example, cetuximab when added to FOLFIRI, significantly prolonged overall survival (23.5 vs. 20.0 month) and progression-free survival (9.9 vs. 8.4 months) compared to FOLFIRI alone in patients with KRAS wild-type tumors [78]. The benefit of adding EGFR directed drugs to chemotherapy is also supported by the findings of meta-analyses of completed clinical trials [79, 80]. Similar results were reported when panitumumab was combined with FOLFOX and the benefits were limited to patients with RAS wild type tumors (all-RAS wild-type) with evidence of harm from panitumumab in patients with RAS mutated tumors [35, 69].

The optimal biologic agent to be used in upfront therapy in patients with all-RAS wild-type tumors is unknown. The benefits of bevacizumab and the EGFR inhibitors appear to be of a similar magnitude. Two recent studies suggested superiority of an EGFR inhibitor over bevacizumab in the first line therapy when given in a combination with either FOLFOX or FOLFIRI in KRAS wild-type patients but a third large randomized phase 3 trial did not show a difference among the two biologic agents [3, 70, 81]. What is remarkable in these last three trials is the fact that median survival is now reported to be around 30–40 months in the population of patients with RAS wild-type tumors. At this point in time, FOLFOX or FOLFIRI with either bevacizumab or an EGFR-inhibiting monoclonal antibody (cetuximab or panitumumab), are reasonable initial choices in patients with all-RAS wild-type tumors. For patients with RAS mutated tumors, either FOLFOX or FOLFIRI with bevacizumab

Table 20.5 Key trials of biologic agents in combination with cytotoxic chemotherapy as first line therapy in patients with metastatic colorectal cancer

Author	Year	Number of patients	Therapy	RR (%)	p-value	PFS (mos)	p-value	OS (mos)	p-value
Addition of bevacizumab to chemotherapy									
Hurwitz [60]	2004	411	IFL	35	0.004	6.2	<0.001	15.6	<0.001
AVF2107		402	IFL + bevacizumab	45		10.6		20.3	
Saltz [61]	2008	701	FOLFOX/CAPOX	38	0.99	8	0.0023	19.9	0.77
NO16966		699	FOLFOX/CAPOX + bevacizumab	38		9.4		21.3	
Fuchs [62]	2007	137	FOLFIRI	47	NR	7.6	NR	23.1	NR
BICC-C		57	FOLFIRI + bev	58		11.2		28	
		141	mIFL	43	NR	5.9	NR	17.6	NR
		60	mIFL – bev	53		8.3		19.2	
Kabbinavar [63]	2005	241	5-FU/LV	34	0.019	5.6	<0.0001	17.9	0.008
		249	5-FU/LV + bev	25		8.8		14.6	
Tebbutt [64]	2010	156	Capecitabine	43		5.7		18.9	
MAX		157	Capecitabine + bev	56		8.5	0.01[c]	18.9	0.314[c]
		158	CBM	67	0.006[b]	8.4		16.4	
Cunningham [65]	2013	140	Capecitabine	10	0.04	5.1	<0.0001	16.8	0.18
AVEX		140	Capecitabine + bev	19		9.1		20.7	
Addition of cetuximab to chemotherapy (KRAS wild-type)									
Van Cutsem [36]	2009	172	FOLFIRI	43		8.7	0.02	24.9	NS
CRYSTAL		176	FOLFIRI + cetux	59		9.9		21.0	
Maughan [66]	2011	815	FOLFOX/CAPOX	57	0.049	8.6	0.6	17.9	0.67
MRC COIN		815	FOLFOX/CAPOX + cetux	64		8.6		17.0	
Tveit [67]	2012	97	FLOX	47	0.89	8.7	0.66	22.0	0.48
NORDIC VII		97	FLOX + cetux	46		7.9		20.1	
Bokemeyer [68]	2011	97	FOLFOX	34	0.0027	7.2	0.0064	18.5	0.39
OPUS		82	FOLFOX + cetux	57		8.3		22.8	
Venook [3]	2014	559	FOLFOX/FOLFIRI[a] + bev	NR		10.4	0.55	29.0	0.34
CALGB/SWOG 80405		578	FOLFOX/FOLFIRI[a] + cetux	NR		10.8		29.0	

Addition of panitumumab to chemotherapy (KRAS wild-type)									
Douillard [35, 69]	2014	331	FOLFOX	57	0.02	8.6	0.01	19.7	0.17
PRIME		325	FOLFOX + Pmab	48		10.0		23.9	
All RAS wt		259	FOLFOX			7.9	0.004	20.2	0.009
		253	FOLFOX + Pmab			10.1		25.8	
Schwartzberg [70]	2014	142	FOLFOX + bev	54		10.1	0.353	24.3	0.009
PEAK		143	FOLFOX + Pmab	58		10.9		34.2	
All RAS wt			FOLFOX + bev	61		9.5	0.029	28.9	0.058
			FOLFOX + Pmab	64		13		41.3	

Bev bevacizumab, *Cetux* cetuximab, *CBM* capecitabine, bevacizumab and mitomycin C, *NR* not reported, *NS* not significant, *Pmab* panitumumab
[a]FOLFOX or FOLFIRI per treating physician's choice
[b]CBM vs. capecitabine
[c]Capecitabine vs. capecitabine + bevacizumab

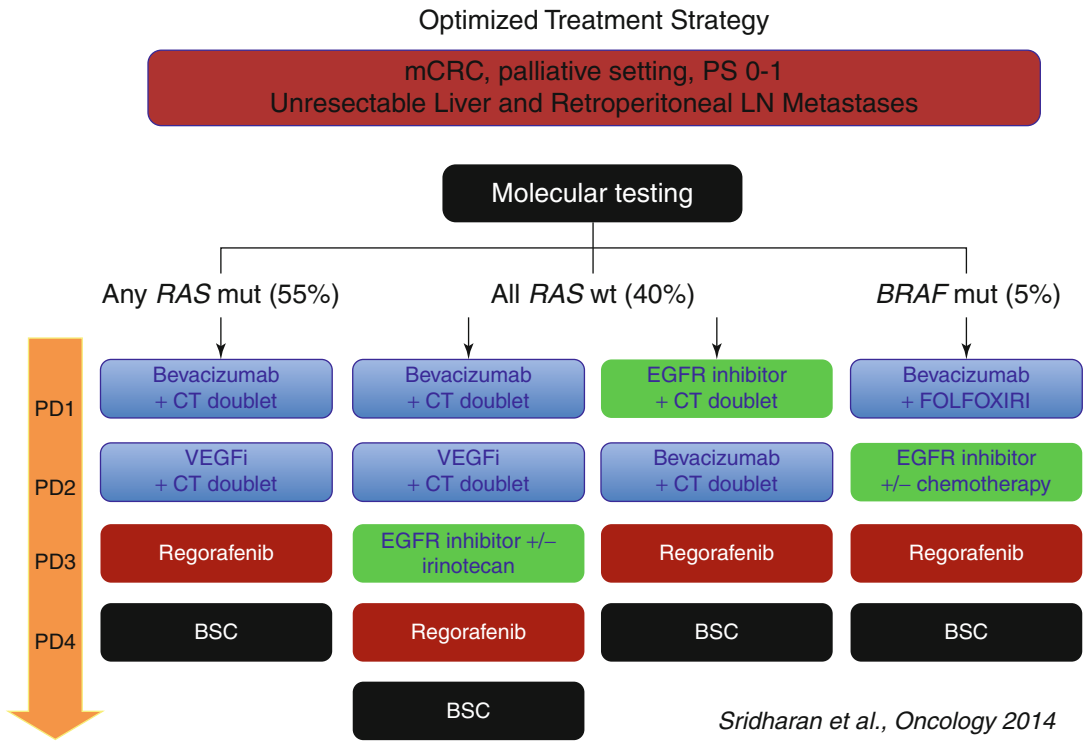

Fig. 20.1 Management strategies in patients with metastatic colorectal cancer. Abbreviations: *BSC*: best supportive care, *CT*: chemotherapy, *EGFR*: epidermal growth factor receptor, *FOLFOXIRI*: folinic acid (leucovorin), 5-fluorouracil, oxaliplatin and irinotecan, *mCRC*: metastatic colorectal cancer, *mut*: mutated, *PD*: progressive disease, *VEGF*: vascular endothelial growth factor, *VEGF inhibitor*: bevacizumab or aflibercept, *wt*: wild-type (From Sridharan et al. [82]. Copyrighted 2014. UBM Medica. 111938:814BN)

unless contraindicated, is appropriate as first-line therapy.

At the time of progression, it is reasonable to change the chemotherapy backbone and those receiving first-line FOLFOX (or CAPOX) should be offered FOLFIRI (or single-agent irinotecan) and vice versa. The patients with RAS mutated tumors should remain on bevacizumab or be switched to aflibercept, upon progression on first-line cytotoxic therapy, as VEGF inhibition beyond first line of cytotoxic therapy is beneficial. Patients with RAS wild-type tumors who began therapy with bevacizumab and either FOLFOX or FOLFIRI and then progress, should be offered EGFR-directed therapy as second-line along with cytotoxic therapy. Continuing bevacizumab or switching to aflibercept and using EGFR-directed therapy in third-line is also an option (Fig. 20.1).

Cetuximab has activity when given as a single agent in patients who are intolerant of cytotoxic chemotherapy. Cetuximab was compared to best supportive care in patients who had either progressed on available therapy or had contraindications to such therapy and was found to be superior to best supportive care with a median overall survival of 6.1 versus 4.6 months [76]. The benefit was limited to patients with tumors that were KRAS wild-type where the median overall survival in treated patients was 9.5 months vs. 4.8 months in patients receiving best supportive care [77]. Patients with KRAS mutated tumors derived no benefit from cetuximab monotherapy in this trial. Not only was there a survival benefit of cetuximab monotherapy in patients with KRAS wild-type tumors, but treated patients also reported substantial benefits in terms of quality of life [83]. Panitumumab has also been

shown to prolong progression-free and overall survival and as seen with cetuximab, the benefits are limited to patients with KRAS wild-type tumors [84–86]. Cetuximab and panitumumab seem to have similar efficacy when used as monotherapy in chemotherapy-refractory metastatic colorectal cancer [87]. With more patients receiving cetuximab earlier on in the course of their treatment, the role of single-agent EGFR directed therapy is likely to have less of a role in the management of metastatic colorectal cancer but it still remains an option for patients with less than optimal performance status and for those who wish to avoid cytotoxic chemotherapy.

Patients who have experienced cancer progression on all available regimens and still have preserved performance status may be offered regorafenib monotherapy. Regorafenib was compared to best supportive care in a randomized phase III trial and resulted in a modest improvement in median overall survival (6.4 versus 5 months) [33].

Patients should be encouraged to participate in clinical trials of new therapeutic agents at all stages of their illness and especially after exhausting all available treatment options provided their performance is still good.

Treatment Interruptions and Maintenance Therapy

Patients with metastatic colorectal cancer who are interested in maximizing their survival should expect to be on continuous therapy until they have exhausted all the available treatment options. Older regimens such as 5-FU with leucovorin are well tolerated with negligible cumulative toxicities. Oxaliplatin, when incorporated in treatment regimens, has cumulative and dose-dependent sensory neuropathy which can be extremely debilitating and a major detriment to the quality of life of patients. Debilitating neuropathy is seen in 10–15 % of patients who have received a cumulative dose of oxaliplatin of 800 mg/m^2 or more. Limiting oxaliplatin exposure can therefore decrease the risk of neuropathy and is commonly employed. A reasonable approach is to discontinue the oxaliplatin after 4 months of therapy (typically eight treatments of FOLFOX or six treatments of CAPOX) and continue with some form of maintenance therapy. This approach has been tested in several trials [88–91]. Planned discontinuation of oxaliplatin does not seem to result in impaired survival but may allow patients to stay on therapy for longer and with less toxicity and potentially improve overall survival. Complete chemotherapy breaks may have adverse effect on survival compared to maintenance therapy [89] and such breaks are generally discouraged. The optimal maintenance therapy remains unknown but recent studies have suggested that a combination of fluoropyrimidines (either capecitabine or 5-FU with leucovorin) may be both effective and well tolerated [92, 93].

Treatment of Elderly Patients and Patients with Impaired Performance Status

The median age of patients diagnosed with colorectal cancer of all stages in the US is 68 years, and 35 % are 75 years or older [2]. With an aging population in the Western hemisphere, colorectal cancer in the elderly is likely to become even a larger problem. Therapy of older adults with advanced cancer is challenging for multiple reasons, especially given the higher prevalence of comorbidities, polypharmacy, and impaired performance status in many of these patients [94–96]. Chronological age is a poor predictor of physical function and reserve and is therefore of limited use when selecting therapy for patients. Elderly patients should ideally undergo a thorough assessment of physical and cognitive function prior to commencing therapy. As a rule, fit elderly patients with minimal comorbidities, derive the same benefit of therapy as their younger counterparts [97–101]. Toxicities may be slightly increased among the elderly, especially neuropathy resulting from the use of oxaliplatin. Elderly patients, especially those at risk of falling, may therefore not be good candidates for oxaliplatin given the risk of neuropathy.

Fit older patients should generally be offered the same therapy as younger patients after a thorough counseling on the benefits and risks of therapy. Biological agents seem to be as safe and effective in older patients as long as there are no contraindications [102–105]. Elderly patients felt to be an excessive risk of side effects from either oxaliplatin or irinotecan can be offered monotherapy with fluoropyrimidines such as 5-FU with leucovorin or capecitabine, or in a combination with either bevacizumab or an EGFR inhibitor provided there are no contraindications to biologic therapy. Capecitabine seems to be as effective as 5FU in the elderly and can safely be given in conjunction with either bevacizumab or cetuximab [65, 106, 107]. Capecitabine should be used with caution as elderly patients frequently have impaired renal function and increasing the risk of adverse effects. Furthermore, compliance to oral therapy needs to be monitored carefully and very clear instructions given to avoid medication errors, especially in elderly patients taking multiple oral medications simultaneously [108].

The treatment of patients with poor performance (ECOG Performance Score of 2 or higher) follows similar principles as the treatment of elderly patients. Patients with PS of 2 that is felt to be secondary to the cancer itself, should be counseled on chemotherapy and offered treatment, as they may experience significant benefit in terms of quality of life and many patients will have an improvement in the performance as the cancer responds to therapy. Patients with performance score of 2 seem to derive significant benefit from therapy although the toxicity is increased and overall survival is shorter that in patients of better performance status [109]. Patients unable to tolerate irinotecan or oxaliplatin should be considered for fluoropyridine monotherapy with the addition of a biological agent if there are no contraindications. The patients should be monitored carefully for toxicity and dose-reductions used as needed to ameliorate adverse effects. Cetuximab and panitumumab monotherapy can be considered in the elderly and patients with impaired performance status.

Chemotherapy and Liver Resections

Liver metastases are a substantial clinical problem in patients with metastatic colorectal cancer. The liver is the most common site for distant metastases and liver metastases are a substantial cause of morbidity and mortality in patients. Resection and/or ablation of liver metastases can provide long-term disease control and even cure [110–112] and chemotherapy has a role in the management of metastases limited to the liver [113].

Patients with colorectal cancer liver metastases may be broadly grouped into 4 categories:

1. Patients who have readily resectable metastases.
2. Patients who have either unresectable or borderline resectable metastases but could potentially be resected after successful cytoreductive chemotherapy (conversion therapy).
3. Patients who have extensive metastases, which will likely never be resectable.
4. Patients with liver metastases and comorbidities that prevent hepatic resection.

The term “conversion therapy” is used where the intent of the treatment is to render unresectable disease resectable with preoperative chemotherapy. The term perioperative or neoadjuvant chemotherapy should be reserved to the treatment administered to patients with liver metastases that are resectable. Thus, the intent of conversion therapy is clearly different from the intent of neoadjuvant therapy although both treatments are given with the intent of improving long-term outcomes [113].

The resectability of liver metastases should be determined by a surgeon with experience in liver resections, and preferentially in a multidisciplinary setting. Patients with a limited number of unresectable liver metastases may benefit from neo-adjuvant chemotherapy. Such therapy may render the metastases resectable but the risk of the treatment has to be weighed carefully against the benefits. Oxaliplatin can result in sinusoidal obstruction within the liver but it is unclear if such liver abnormalities increase postoperative complications and affect the outcome of surgery [114, 115]. Irinotecan is associated with hepatic

steatosis and steatohepatitis and prolonged irinotecan-based chemotherapy prior to liver resection, may increase the risk of complications and even mortality [116, 117]. The risk of complications may increase with an increasing duration of the pre-operative chemotherapy, and there may be limited benefits in terms of further tumor regression beyond 4–6 months of therapy [118]. Patients should also be given adequate time to recover from chemotherapy prior to liver resection. Liver resections within 4 weeks from completing chemotherapy are associated with a higher rate of complications [119].

The effect of cytotoxic chemotherapy on overall survival in patients with resectable liver metastases is still under debate. A pooled analysis of two trials evaluating adjuvant 5-fluorouracil after liver resection showed a marginal benefit from adjuvant chemotherapy with a non-significant improvement in both median DFS and OS [120]. A large European trial randomized patients to either upfront liver resection versus perioperative chemotherapy with FOLFOX for six cycles before and six cycles after resection [121]. There was an increase in 3-year progression-free survival (PFS) from 28.1 to 35.4 months with perioperative FOLFOX at the cost of an increase in reversible postoperative complications (16 % vs. 25 %; $p=0.04$) but not increase in peri- or postoperative mortality. With long-term follow-up of this trial, median overall survival was 61.3 months (95 % CI 51.0–83.4) in the FOLFOX arm versus 54.3 months (41.9–79.4) in the surgery alone arm [122]. This increase in overall survival was not statistically significant, however this may be due in part lower than planned enrollment in the trial. Therefore, many oncologists utilize perioperative FOLFOX in patients with resectable liver metastases. The addition of irinotecan to 5-FU and leucovorin does not appear to improve outcome when compared to 5-FU and leucovorin alone as adjuvant therapy after surgery for resectable liver metastases [123].

The role of biologic agents in conjunction with chemotherapy in the management of patients with resectable liver metastases remains to be determined. Bevacizumab likely provides little additional benefit with a risk of postoperative complications and is not routinely recommended. Cetuximab when given with chemotherapy may actually be harmful when given as perioperative therapy in patients with resectable liver metastases [124].

Patients with initially unresectable liver metastases present a different problem. Under those circumstances, more aggressive upfront therapy may be warranted and there may be a role for biologic agents given with cytotoxic therapy. Several prospective and retrospective studies have been performed and the results in terms of conversion rate (i.e. conversion from unresectable to resectable liver metastases) and complete resection vary widely. Between 10 and 35 % of patients with initially unresectable liver metastases will be able to undergo surgery after neoadjuvant chemotherapy with a 5-year survival approaching 30 % [113, 125]. This is a substantially improved survival over chemotherapy alone for unresected stage IV disease. Complete pathological responses are uncommon, even when there has been a complete radiographic response so resection is still recommended, even though the metastases may no longer be perceptible [126, 127]. Complete pathological response to neoadjuvant chemotherapy, when achieved, does predict a better outcome following liver resection [128, 129].

Chemotherapy regimens containing three cytotoxic drugs (FOLFOXIRI) may be more effective in converting unresectable liver metastases to resectable ones when compared to two-drug regimens [51, 130, 131]. While objective response rates may be higher with a three-drug regimen, not all studies have confirm a higher complete resection rate [59]. Therefore, the role of three-drug regimens as conversion therapy for unresectable liver metastases remains unclear. The addition of cetuximab to chemotherapy in patients liver metastases and cancer with KRAS mutations has been shown to result in high radiographic response rates and possibly increased resectability in an uncontrolled phase II study and a small randomized trial [132, 133]. These findings need to be confirmed in larger randomized trial. FOLFOX, FOLFIRI and FOLFOXIRI

are all reasonable regimens for patients who are being considered for conversion therapy. For patients whose tumors are all-RAS wild-type, FOLFIRI with cetuximab or FOLFOX or FOLFIRI with panitumumab can be considered. Bevacizumab can also improve response rates, and can be used in patients with RAS mutated and unmutated colorectal cancer [61]. If bevacizumab is used preoperatively, it should be discontinued a minimum of 6–8 weeks prior to surgery to avoid postoperative wound healing complications.

Evaluation of Patients While on Therapy

Patients with metastatic colorectal cancer undergoing systemic therapy should be evaluated at regular intervals. A clinic visit prior to each treatment, typically every 2–3 weeks is considered good practice. A laboratory evaluation at every visit is recommended and should include a complete blood count, chemistries including renal and liver function and measurements of the carcinoembryonic antigen (CEA) in those patients who have an elevated level at diagnosis. Imaging studies should be done every 2–3 months or even more frequently if clinically indicated based on changes in symptoms. Computerized tomography (CT) or magnetic resonance imaging (MRI) imaging is preferred and routine use of positron emission tomography (PET/CT) is discouraged unless the disease cannot be reliably measured with CT or MRI.

Conclusion

Metastatic colorectal cancer is a common problem and a major cause of death and morbidity among cancer patients in general. Substantial advances have been made in the management of colorectal cancer patients and the survival of patients has markedly improved in the last two decades. There are now multiple options for systemic therapy that include both conventional cytotoxic agents and newer biologic agents. Biomarkers, especially RAS mutation analyses, are increasingly being used to guide treatment decisions. Combination chemotherapy that includes a biological agent, either a VEGF or EGFR inhibitor, should be considered for most patients with adequate performance score. Systemic therapy should be thought of as a continuum of care rather than distinct "lines of therapy". More aggressive therapy with preplanned phases of less intensive maintenance phases appears to minimize adverse events and prolong the time patients remain on therapy and therefore maximize survival and maintain quality of life. Patients with metastatic colorectal cancer interested in systemic therapy should expect to remain on continuous therapy long-term as the exposure to all available therapeutic agents with no or limited therapy-free holidays seems to result in the best prolongation of survival. Judiciously used treatment breaks can be used if patients wish to be off therapy for some time, or if toxicities become problematic. Elderly patients and those with impaired performance status can be successfully treated with a meaningful prolongation of survival and preservation of quality of life. Less intense regimens and single-agent treatments may be considered in that population. Patients should be encouraged to participate in clinical trials whenever possible.

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Locally Advanced Disease

21

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Abstract

Surgical resection is the mainstay of treatment for rectal cancers. For the vast majority of patients with rectal cancers the tumor is located within the mesorectal fascia and is resected with total mesorectal excision (TME) with excellent clinical outcomes. A small percentage of patients have tumors that extend beyond the mesorectal compartment with invasion into the fascia propria or beyond into surrounding structures or with local lymph node involvement (stage II or III). These patients with locally advanced rectal cancer are difficult to treat with surgery alone due to an increased risk in local disease recurrence. In recent years, new technologies and advances in treatment protocols have resulted in a multidisciplinary approach that has yielded improved clinical and oncological outcomes.

Keywords

Colorectal cancer • Locally advanced rectal cancer • Surgery • Total mesorectal excision • Neoadjuvant chemoradiation

Introduction

Surgical resection is the mainstay of treatment for rectal cancers. For the vast majority of patients with rectal cancers the tumor is located within the mesorectal fascia and is resected with total mesorectal excision (TME) with excellent clinical outcomes. A small percentage of patients have tumors that extend beyond the mesorectal compartment with invasion into the fascia propria or beyond into surrounding structures or with local lymph node involvement (stage II or III). These patients with locally advanced rectal cancer are

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difficult to treat with surgery alone due to an increased risk in local disease recurrence. In recent years, new technologies and advances in treatment protocols have resulted in a multidisciplinary approach that has yielded improved clinical and oncological outcomes.

Initial Evaluation

When planning treatment for all rectal cancers, thorough evaluation and accurate clinical staging are vital as the optimal therapy is drastically different for varying stages of disease. As with all rectal cancers, initial evaluation for locally advanced rectal cancer begins with a thorough history and physical. Digital rectal exam (DRE) should be performed in addition to rigid proctosigmoidoscopy to determine the distance of the lesion to the anal verge. These exams can also reveal information about the tumor, including fixation to surrounding structures, tumor bulk, general location and circumferential involvement. It is not possible to determine detailed information regarding tumor extent or staging through physical exam alone and further imaging is required. All patients with rectal cancer should have a complete colonoscopy to evaluate for synchronous cancers (up to 3 % incidence) and polyps (up to 30 % incidence) [1–4].

Staging

Clinical staging of rectal cancers is performed according to the American Joint Committee on Cancer (AJCC) TMN system (Tables 21.1 and 21.2) [5]. Locally advanced rectal cancers are generally considered to be stage II or III. Available imaging modalities for staging include CT scan, endorectal ultrasound (EUS), and high resolution MRI with specific rectal protocols. A CT scan of the chest, abdomen and pelvis should be routinely obtained to evaluate for distant metastasis,

Table 21.1 Colorectal cancer AJCC staging definitions

Primary tumor (T)	TX	Primary tumor cannot be assessed
	T0	No evidence of primary tumor
	Tis	Carcinoma in situ: intraepithelial or invasion of lamina propria
	T1	Tumor invades submucosa
	T2	Tumor invades muscularis propria
	T3	Tumor invades through the muscularis propria into pericolorectal tissues
	T4a	Tumor penetrates into the surface of the visceral peritoneum
	T4b	Tumor directly invades or is adherent to other organs or structures
Regional lymph nodes (N)	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis in 1–3 regional lymph nodes
	N1a	Metastasis in 1 regional lymph node
	N1b	Metastasis in 2–3 regional lymph nodes
	N1c	Tumor deposit(s) in the submucosa, mesentery, or nonperitonealized or perirectal tissues without regional nodal metastasis
	N2	Metastasis in 4 or more regional lymph nodes
	N2a	Metastasis in 4–6 regional lymph nodes
	N2b	Metastasis in 7 or more regional lymph nodes
Distant metastasis (M)	M0	No distant metastasis
	M1	Distant metastasis
	M1a	Metastasis confined to one organ or site
	M1b	Metastasis in more than one organ/site or the peritoneum

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Table 21.2 Colorectal Cancer AJCC Anatomic Staging Groups

Stage	T	N	M
0	Tis	N0	M0
I	T1	N0	M0
	T2	N0	M0
IIA	T3	N0	M0
IIB	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1-T2	N1/N1c	M0
	T1	N2a	M0
IIIB	T3-T4a	N1/N1c	M0
	T2-T3	N2b	M0
	T4b	N1-N2	M0
IIIC	T4a	N2a	M0
	T3-T4a	N2b	M0
	T4b	N1-N2	M0
IVA	Any T	Any N	M1a
IVB	Any T	Any N	M1b

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most commonly found in the liver and lungs. CT imaging may also reveal involvement of adjacent organs, however it is not considered the ideal imaging modality for locoregional staging. EUS has historically been the most accurate modality for T staging, with accuracy ranging from 85 to 95 %, compared to 52–74 % for CT and 71–91 % for MRI [6]. The efficacy of EUS is limited, however, by inability to maneuver past stenotic or bulky lesions. Nodal staging remains difficult and on recent meta-analysis, none of the imaging modalities were superior to the others, with sensitivities and specificities of 55 and 74 % for CT, 67 and 78 % for EUS, and 66 and 76 % for MRI [7]. Recent advances in MRI techniques have improved its utility in rectal cancer staging. Specifically, MRI is the best modality to evaluate the circumferential margin (CRM), defined as the distance from the tumor to the mesorectal fascia, which is important for surgical planning [8, 9]. Because of this, MRI is becoming the staging modality of choice in centers that are trained in the specific protocols for rectal cancers as standard pelvic MRI will not provide the same information [10]. Following staging, it is recommended that the patient's case be discussed in a multidisciplinary format with input from pathologists, radiologists, and surgical, medical and radiation oncologists to determine the best recommended course of treatment.

Neoadjuvant Therapy

The management of stage I and IV rectal cancers will not be discussed in this chapter. The preferred treatment for stage II and III rectal cancers has changed drastically over the past several years. Reduction in local recurrence rates and disease-free survival was shown with the use of postoperative radiation therapy in conjunction with 5-Fluorouracil (5-FU) in two prospective randomized trials, prompting the National Cancer Institute to issue a consensus statement in 1990 recommending the use of adjuvant therapy for stage II and III tumors [11]. In recent years however, is has been demonstrated that neoadjuvant chemoradiation is preferred as it has greater efficacy, lower toxicity, and improved oncologic outcomes than adjuvant therapy [12]. Potential benefits of preoperative radiation when compared to postoperative include decreased risk of irradiation of the small bowel, no anastomotic radiation, improved compliance, lower toxicity, and better tumor oxygenation leading to increased radiosensitivity. There is strong evidence to support the use of both short-course (5 Gy daily for 5 days without chemotherapy) and long-course (45–50.4 Gy total given at 1.8–2 Gy per fraction over 5–6 weeks administered with 5-FU chemotherapy) radiotherapy.

The Swedish Rectal Cancer Trial, originally published in 1997, first demonstrated the benefit of preoperative radiation [13]. This study showed that patients who received short-course radiotherapy (SCRT) followed by surgery had reduced local recurrence (11 %) and prolonged 5-year overall survival (58 %) than those who had surgery alone (27 and 48 %, respectively). Radiation was, however, associated with increased gastrointestinal complications and led to more readmissions in the 6-month postoperative period [14].

Despite this, the long-term benefits of preoperative radiation where still seen after a median follow-up of 13 months, with improved overall survival (38 % vs. 30 %) and decreased local recurrence (9 % vs. 26 %) [15]. The Dutch TME trial, published in 2003, demonstrated the benefit of SCRT when combined with TME [16]. Though local recurrence was significantly lower (2.4 % vs. 8.2 %) in patients who received SCRT before TME compared to those who underwent TME alone, there was no difference in overall survival. There was no long-term survival improvement from SCRT, but analysis showed improved recurrence rates for patients with mid and low rectal tumors, but not tumors in the upper rectum [17].

In 2004, the German Rectal Cancer Study Group published the results of their investigation into the efficacy of neoadjuvant versus adjuvant long-course chemoradiotherapy (LCCRT) in combination with TME [18]. Results showed that when given preoperatively, LCCRT decreased local recurrence to 6 % versus 13 % postoperative. While there was no significant difference in disease-free survival or overall survival, neoadjuvant therapy resulted in less acute and long-term toxicity, as well as an improved rate of sphincter preservation. One striking benefit of LCCRT, seen in this study, is significant tumor downgrading (pathologic staging is lower than initial clinical staging). Additional studies have shown that up to 20 % of patients will have complete pathologic response to treatment, with no viable tumor cells remaining in the resection specimen [19, 20]. In a study comparing preoperative SCRT to LCCRT there was no difference in local recurrence, disease free survival or overall survival [21, 22]. However, LCCRT was associated with decreased positive CRM rate as well as a higher percentage of patients with complete pathologic response when compared to SCRT.

Based on these studies, both neoadjuvant SCRT and LCCRT are recommended in combination with TME for locally advanced tumors [12]. LCCRT has the advantage of potential tumor downsizing and/or regression which may allow for less radical resection. Risks of increased surgical morbidity, GI complications and sexual dysfunction have been associated with preoperative radiotherapy [23]. SCRT tends to be the preferred treatment in Northern Europe and Scandinavia, while LCCRT remains the treatment of choice in North America and some European countries. The role of newer neoadjuvant chemotherapeutic agents, selective radiation, and neoadjuvant chemotherapy in addition to SCRT are all currently being investigated. Optimal timing of surgery following neoadjuvant therapy is debated, but generally occurs 1–2 weeks after SCRT, and 6–8 weeks following LCCRT [12, 24]. Several recent studies have investigated an increased interval following LCCRT, with the thought that additional tumor downsizing and increased rates of complete pathologic response (no residual tumor) may be possible. Meta-analysis demonstrated a 6 % increase in complete pathologic response when a longer interval (greater than 8 weeks) was used, with comparable oncologic outcomes, though these results have not been proven prospectively [25].

As imaging technology improves the ability to accurately define tumor characteristics preoperatively, some have advocated a more limited use of neoadjuvant therapy. The MRI and Rectal Cancer European Equivalence (MERCURY) study showed satisfactory oncologic outcomes in patients with "good prognosis" stage I, II and III rectal tumors treated with surgery alone [26]. "Good prognosis" tumors were predicted to have negative circumferential margins, and were identified as tumors >1 mm to the mesorectal fascia, with no evidence of extramural venous invasion, spread less than 5 mm from the bowel wall (T stage T2, T3a and T3b), and no encroachment into the intersphincteric plane. For patients ultimately treated with surgery alone, the local recurrence rate was 3.3 %, with 5-year overall and disease-free survival rates of 68.2 and 84.7 % respectively. Acceptable oncologic outcomes were still demonstrated at 5 year follow-up, with the conclusion that neoadjuvant therapy may not be needed in these selected patients with low likelihood of margin involvement seen on preoperative high resolution MRI [27].

Adjuvant Therapy

Currently, there is no definite evidence of a survival or oncologic benefit to the use of adjuvant chemotherapy. In the European Organization for Research and Treatment of Cancer (EORTC) 22921 trial, the addition of 5-FU-based adjuvant chemotherapy to preoperative chemoradiation showed no difference in local recurrence [28]. Subgroup analysis suggested an improved overall and disease free survival in patients with pathologically downstaged tumors, however, additional long-term results showed no actual benefit [29, 30]. Compliance to adjuvant therapy is often low, and many patients are unable to tolerate the regimens following surgery. Investigations into the use of newer chemotherapy agents are ongoing. The addition of oxaliplatin to 5-FU-based chemotherapy regimens (FOLFOX) for colon cancers has been shown to improve recurrence rates and disease free survival [31]. Whether this benefit extends to the use of FOLFOX in rectal cancer is currently under investigation. Despite the lack of evidence, adjuvant chemotherapy is currently recommended for all patients with locally advanced rectal cancer [12, 32]. This recommendation also includes patients with tumors that were clinically under-staged and did not undergo the recommended neoadjuvant therapy as described above.

Surgical Management

Total Mesorectal Excision and Circumferential Margins

Complete surgical resection (R0 resection) is the cornerstone of curative therapy for rectal cancer and is the goal of all operative intervention. Historically, treatment consisted of complete rectal resection using blunt dissection of the rectal fascia. However, this was associated with local recurrence rates up to 30 % [33]. This blunt dissection failed to obtain clear circumferential resection margins (CRM), which has since been shown to be an independent predictor of local recurrence and survival [9, 34].

The promotion of the concept of total mesorectal resection (TME) in 1982 drastically changed the techniques of rectal resection [35]. By utilizing sharp dissection of the avascular plane between the visceral and parietal endopelvic fascial layers, the entire mesorectum, including rectal lymphatic drainage, may be excised en bloc with the rectum itself. This paradigm shift in surgical approach drastically improved outcomes, with local recurrence rates dropping from 30 % to as low as 5 % and 5-year survival increasing from 50 % to nearly 75 % [36]. Mesorectal excision has been proven to be safe, with decreased morbidity and increased preservation of the pelvic autonomic nerves. TME, as part of a low anterior resection or abdominoperineal resection, is the operation of choice for tumors of the middle and lower rectum [12]. For tumors of the upper rectum, a complete TME may not be necessary. However, pathologic examinations have identified tumor cells in the mesorectum up to 4 cm distal to the primary tumor [37, 38]. As such, current recommendations are for a tumor-specific mesorectal resection for tumors of the upper rectum, extending no less than 5 cm distal to the lower tumor margin [12].

The level of optimal vascular ligation has been debated. Ligation at the level of superior rectal artery origin (“low tie”) has been shown to provide an appropriate proximal lymphatic resection [39]. A higher ligation including the inferior mesenteric artery (“high tie”) may increase lymph node yield, though there is no difference in survival when compared to a lower ligation [40]. Additionally, high ligation of the inferior mesenteric artery allows for improved mobilization to create a tension-free anastomosis without increased risk of anastomotic leak [41]. As such, although official recommendations indicate that a low tie is acceptable in the absence of clinically suspicious nodes above that level, many surgeons prefer and recommend a high tie in all patients [12].

Distal Resection Margins

Distal intramural spread is uncommon and rarely extends more than 1 cm [42, 43]. In light of this, a distal resection margin of 2 cm (down from an original minimum of 5 cm) is currently recommended [12]. For low lying tumors located at or below the mesorectal margin where a 2 cm margin would necessitate abdominoperineal resection, a 1 cm margin has been shown to be acceptable and may allow for increased rates of sphincter preservation through ultra-low anterior resection [44]. Meta-analysis has shown that early tumors, downstaging following neoadjuvant therapy, low serum CEA levels and good or moderately differentiated tumors are most suitable for distal resection margin <2 cm [45].

Sphincter Preservation

Sphincter preservation is an important part of rectal cancer surgery and should be considered when adequate margins are feasible. While abdominoperineal resection (APR) remains the treatment of choice when safe distal margins cannot be obtained, there is debate surrounding the possibility of increasing sphincter preservation in these patients. Some argue that neoadjuvant therapy may allow for tumor downsizing, which could permit low anterior resection in patients initially felt to require APR. There is no conclusive data regarding this subject. Despite some researchers, such as the German Rectal Cancer Study Group, demonstrating a statistically significant increase in the number of sphincter-sparing operations in patients who received neoaduvant therapy, others have shown no clear benefit [18, 23, 46]. There is currently no consensus or official recommendations regarding sphincter preservation, and additional studies are required. Patients with very low tumors, poor preoperative function, involvement of the levators and sphincter complex, and incontinence are best served with APR [47].

When sphincters can be preserved, the formation of a colonic reservoir should be considered to decrease the incidence of urgency, clustering, increased bowel frequency, and incontinence. Colonic J-pouch has been demonstrated to be superior to a straight coloanal anastomosis, with reduced urgency and bowel frequency [48, 49]. Defunctioning stoma, with loop ileostomy preferred, is recommended for all patients to reduce anastomotic leak and reoperation rates [50].

Locally Invasive Tumors

Multivisceral Resection

Surgical resection may be more extensive for patients with T4 tumors that invade into surrounding pelvic structures or with N1 tumors that have nodal involvement. To achieve an R0 resection, all involved structures should be resected en bloc along with the rectum and mesorectum [12]. This most often involves the bladder, prostate, vagina, uterus, ovaries, and ureters and a multidisciplinary surgical team is advised when available. Partial resection of the involved organ may be feasible, however, complete resection is often required as part of a multivisceral resection. Resection of all direct adhesions to the tumor is also recommended, as it is impossible to assure no residual microscopic disease in these structures, especially following radiation to the area. For more extensive disease, and in patients with prostate and/or bladder involvement, a total pelvic exenteration is often indicated for optimal resection and reconstruction. Five-year survival and local recurrence rates are comparable to those of non-locally invasive tumors [51]. Lateral lymph node dissection should be performed in patients with clinically suspicious nodes. While Japanese studies have shown lateral lymphadenectomy in patients without apparent clinical involvement improved locoregional control, no oncologic benefit was found on meta-analysis when compared to conventional surgery [52, 53].

Intraoperative Radiotherapy

Tumor fixation to the bony and muscular structures of the lateral and posterior pelvis presents

a difficult situation due to the difficulty in removing these structures to achieve R0 resection. Additionally, some tumors may have very narrow or involved margins that make complete resection challenging. Intraoperative radiotherapy (IORT), first developed in the 1960s in Japan, has been used as an adjunct to improve local control in these situations where there is expected microscopic or gross involvement [54, 55]. This technique allows for the delivery of focused radiation specifically to at-risk areas under direct visualization and with minimal exposure of surrounding structures. IORT is delivered using intraoperative electron beam radiotherapy (IOERT) or high-dose-rate brachytherapy (HDR-IORT), with no significant differences in outcomes between the methods [56, 57]. There have been no randomized trials investigating IORT, however, several series have demonstrated it to be safe with improvement in local control and overall survival [51, 55, 58–60]. These series have been relatively small, and some other studies have not been able to demonstrate significant survival benefits [58, 61–63]. Because of this IORT has not been adapted into current standards of care, however, it may be utilized as an adjuvant when available for difficult tumors that may otherwise be deemed unresectable due to margin involvement.

Minimally Invasive Surgery

As laparoscopic approaches have become more common in colorectal surgery, the efficacy of laparoscopic TME has been studied. The Medical Research Council Conventional versus Laparoscopic Assisted Surgery in Colorectal Cancer (MRC CLASSIC) trial, the first to investigate the issue, showed a non-significant increase in the rate of positive CRM in the laparoscopic group [64]. Despite this, the finding was not associated with a significant difference in 5-year local recurrence rates [65]. Several other studies have since demonstrated no difference in the rate of positive CRM or in the rate of complete mesorectal resection between open and laparoscopic approaches [66, 67]. Similarly, no difference in disease-free or overall survival has been demonstrated between laparoscopic and open groups [66, 68, 69]. Collectively, the current evidence indicates that use of laparoscopic TME results in equivalent oncologic outcomes as compared to open surgery, and is currently considered an acceptable option for surgical resection [12, 70]. As with all laparoscopic operations, there is a significant learning curve to the technique and it is recommended that surgeons planning to perform laparoscopic TME should have adequate experience and technical expertise prior to offering the option to patients [12].

"Wait and See" Techniques

Up to 20 % of rectal cancer patients may experience complete pathological response to neoadjuvant therapy, with no viable tumor cells identified in the surgical specimen [71]. Current recommendations are for these patients to still undergo standard radical resection as described above [12]. However, some advocate that for these patients, where the tumor has been fully sterilized by neoadjuvant therapy, additional radical resection is unnecessary. Initial results from Brazil, where a "wait and see" policy was used for patients with complete pathologic response, were favorable with overall and disease-free survival 5-year survival rates of 93 and 85 % respectively in their small study population [72, 73]. Despite these findings, systemic review of this type of non-operative management for rectal cancer concluded that the results from the highly selected cases included in the Brazilian studies could not be extrapolated to include all rectal cancer patients [71]. A major limitation to this approach remains the inability of current imaging modalities to reliably predict true complete pathologic response [74, 75]. A policy of "wait and see" remains experimental and requires additional study including randomized trial before any recommendation for widespread use may be made.

Conclusion

- All patients should receive a full history and physical, digital rectal exam, rigid proctosigmoidoscopy, colonoscopy, CT scan of the chest/abdomen/pelvis, as well as EUS and/or MRI with specific rectal cancer protocols as part of work-up and staging
- All patients with stage II or III rectal cancer should receive multimodal neoadjuvant therapy utilizing 5-FU based chemotherapy in combination with either short course or long course radiation.
- Surgical resection should be performed 1–2 weeks following short course radiotherapy, or 6–8 weeks following long course chemoradiotherapy therapy regardless of apparent downgrading or complete pathologic response.
- Total mesorectal excision, as part of low anterior resection or abdominoperineal resection, should be performed for tumors of the lower and middle rectum, with distal margins of at least 2 cm, or 1 cm if located at the mesorectal margin.
- Tumors in the upper rectum should undergo tumor-specific mesorectal resection to at least 5 cm below the distal margin of the tumor.
- Surrounding pelvic organs with direct tumor invasion as well as any direct adhesions to the tumor should be resected en bloc with the TME specimen.
- Intraoperative radiotherapy, though still controversial and not widely available, may be used in cases of narrow or microscopically incompletely resected tumors to reduce the rate of local recurrence.
- Sphincter preservation should be attempted if appropriate margins are feasible; diverting stoma and colonic j-pouch are recommended following surgical resection to reduce anastomotic leak rates and side effects resulting from the loss of colonic reservoir.
- Current evidence supports laparoscopic TME as an acceptable approach with no difference in rates of positive CRM or distal margins when performed by experienced surgeons.
- Current standard of care is for all patients to be offered adjuvant chemotherapy using 5-FU based chemotherapy despite a lack of evidence that its use improves outcomes.

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Less Common Rectal Tumors

22

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Abstract

While the majority of malignant rectal neoplasms are adenocarcinomas, and the majority of anal malignancies are squamous cell carcinomas, other less frequent histologic subtypes are encountered in the rectum and anus. They include carcinoid tumors, rectal lymphoma, anorectal melanoma, neuroendocrine carcinoma (NEC) of the rectum, vascular lesions, squamous cell carcinoma of the rectum and its variants, rectal sarcomatous lesions, including gastrointestinal stromal tumor (GIST) of the rectum, leiomyosarcoma and Kaposi's sarcoma. These less common histiotypes will undoubtedly be encountered in clinical practice and deserve mention. Due to their rarity, these tumors frequently pose a challenge with diagnosis, staging, pathology, management, and follow-up. In this chapter we will discuss tumor biology, natural history and treatment options for these rare tumors and offer a data-driven, evidence-based approach to guide their management.

Keywords

Rectal carcinoid tumor • Rectal lymphoma • Anorectal melanoma • Neuroendocrine carcinoma • Diffuse cavernous hemangioma • Squamous cell carcinoma of the rectum • Adenosquamous carcinoma • Gastrointestinal stromal tumor • Sarcoma • Leiomyosarcoma • Kaposi's sarcoma

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Introduction

While the majority of malignant rectal neoplasms are adenocarcinomas, and anal malignancies are squamous cell carcinomas, this chapter focuses on other more infrequent histologic subtypes of the rectum and anus. These histiotypes include carcinoid tumors, rectal lymphoma, anorectal melanoma, neuroendocrine carcinoma (NEC) of the rectum, vascular lesions, squamous cell carcinoma of the rectum and its variants, rectal sarcomatous lesions, including gastrointestional stromal tumor (GIST) of the rectum. Due to their rarity, these tumors, when encountered in clinical practice, often present difficulties with diagnosis, staging, management, pathology and follow-up. In this chapter we will discuss tumor biology, natural history and treatment options for these rare tumors. Often times these lesions can be controversial or present diagnostic and therapeutic dilemmas due to their infrequency and physician unfamiliarity; this chapter offers a data-driven, evidence-based approach to guide the management of these tumors.

Carcinoid Tumors of the Rectum

In 1907 Oberndorfer first used the term "Karzinoid" to describe small "cancer-like" neoplasms thought to have a more benign clinical course [1]. Carcinoids are considered part of a heterogeneous group of neuroendocrine tumors arising from Kulchitsky's or enterochromaffin cells in the crypts of Lieberkuhn. Enterochromaffin cells are part of the amine precursor uptake and decarboxylation (APUD) system and are capable of synthesizing and secreting over 40 different biogenic amines and peptide hormones, including many neurotransmitters [2].

The gastrointestinal (GI) tract is the site of 70 % of carcinoids; the most common location for carcinoid tumors is the ileum, containing 28 % of all lesions [3]. The rectum is the third most common site of carcinoid tumors, comprising 12.6 % of all carcinoids [4], while the colon is the location of 7.8 % of carcinoids [3]. Evidence suggests that the incidence of rectal carcinoid may be increasing, perhaps due to the more frequent use of endoscopy for diagnosis and screening purposes [3, 5–7]. Carcinoid tumors comprise only a small percentage, approximately 0.1–1 %, of all rectal cancers [8–10].

The term "carcinoid" is somewhat controversial in that it historically has been used to describe neuroendocrine tumors that were capable of exhibiting diverse clinical behavior (see section "Neuroendocrine carcinoma (NEC) of the rectum"). While most carcinoid tumors have an indolent course, are slow growing, and have minimal potential for distant spread, they are malignant and can metastasize. Although outcomes for those with localized disease are excellent, 10–20 % of rectal carcinoids will metastasize with associated poor survival outcomes [3, 5, 10–13]. Traditionally, carcinoids have been classified by embryologic site of origin (i.e. foregut, midgut and hindgut-derived tumors), which emphasized clinical and anatomic distinctions rather than histologic and immunohistochemical differences between each category. In 2010 the World Health Organization (WHO) updated their classification system, categorizing all GI neuroendocrine tumors ("NETs"), including carcinoids, based on both gastrointestinal location of origin and histopathologic characteristics. These NETs were separated by histologic grade, into three groups on the basis of cell differentiation, mitotic count, or proliferation as determined by the Ki-67 index [14]. Carcinoids are considered the more benign, well-differentiated grade 1 tumors amongst the GI NETs. The American Joint Committee on Cancer (AJCC) also published a tumor, node, metastasis (TNM) classification system for GI NETs to standardize staging [15]. Improved classification and staging of these tumors will hopefully aid in directing future therapeutic management.

Clinical Presentation and Diagnosis

Most patients with carcinoid of the colon and rectum are diagnosed in their fifth or sixth decade of life [5, 9–12, 16]. Studies suggest a slight male preponderance and higher rates of

population-corrected black versus white and Asian versus non-Asian ratios for rectal carcinoids [3, 5]. Most rectal carcinoids are asymptomatic and approximately half are diagnosed incidentally during endoscopic evaluation for adenocarcinoma or other unrelated anorectal diseases [10, 17]. Although symptoms such as hematochezia, rectal pain, or change in bowel habits due to other concomitant conditions are common, symptoms directly attributable to the tumor itself are rare. If the carcinoid tumor itself is symptomatic, the lesion is likely to be advanced [8, 9, 17–19]. Rectal carcinoid tumors are usually located in the mid-rectum, 5–10 cm from the anal verge [20], and appear as small, firm, yellow, submucosal nodules [21]. Occasionally they may grossly appear as pedunculated, sessile or ulcerated lesions [22]. Development of an additional metachronous or synchronous primary malignancy may be present in up to 55 % of patients which necessitates a thorough physical examination and endoscopic evaluation of the entire colon and rectum [5, 8, 23, 24]. Endoscopic Ultrasound (EUS) has become a useful tool in the diagnosis and staging of rectal tumors, including carcinoids, assessing features such as tumor size, depth of invasion, and lymph node involvement [19, 25]. EUS guides treatment management and helps determine the feasibility of endoscopic removal versus transanal excision or radical surgery.

Histologically, carcinoids are composed of small uniform cells arranged in a variety of patterns, described as nests, cords, trabeculae, rosettes, or tubules of cells that infiltrate surrounding mucosa and submucosa [26, 27]. Overall, 80 % of intestinal carcinoids, demonstrate the ability to take up silver stains (argyrophilic) and many are able to reduce silver stains (argentaffinic) [5]. Only 50–60 % of rectal carcinoids, however, possess argyrophilic properties, and few are argentaffinic [5, 11, 26], Immunohistochemical analysis aids in the histologic diagnosis of carcinoid tumors. Non-specific markers of NE differentiation, such as neuron specific enolase and chromogranin, are seen in the majority of rectal carcinoids [5, 11, 28]. Immunohistochemistry also demonstrates the many hormonal products synthesized by rectal carcinoids such as pancreatic polypeptide, carcinoembryonic antigen, prostate specific antigen, serotonin, glucagon and somatostatin [5, 11, 29]. Individual lesions often produce more than one hormone or peptide; additionally, carcinoid metastases may not synthesize the same product as the primary tumor [5, 11, 29]. Although identification of these products is helpful in confirming the histologic diagnosis of carcinoid, no association between any biochemical product and tumor behavior has been demonstrated.

"Carcinoid syndrome" is a group of symptoms comprised of diarrhea, flushing, telangiectasia, dyspnea or wheezing, and hemodynamic instability caused by systemic release of neuroendocrine products such as serotonin by carcinoid hepatic metastases [30]. Long-term sequelae include carcinoid cardiac disease or right-sided valvular heart disease. Carcinoid syndrome is confirmed by the presence of elevated urinary levels of 5-hydroxyindole-acetic acid (5-HIAA), a break-down product of serotonin, in conjunction with classic symptoms. However, patients with rectal carcinoids, including those with hepatic metastasis, rarely display carcinoid syndrome or produce elevations of urinary 5-HIAA for reasons that have yet to be elucidated [4, 5, 12].

Treatment and Prognosis

Due to the heterogeneity of rectal carcinoids and their behavioral variability, management guidelines remain controversial. Tumor size correlates with the risk of metastases and has therefore been used to guide treatment. Historically, tumors are classified as <10 mm, 10–19 mm, and ≥20 mm (Table 22.1). Risk factors for carcinoid metastases include tumors greater than 10 mm, ulceration, depth of invasion, patient age greater than 60 years, and muscularis, perineural, or lymphovascular invasion [11–13, 17, 31–33]. Tumor characteristics associated with survival outcomes were tumor size, muscular invasion, and the presence of metastases [34, 35]. Although 5-year survival outcomes for those with localized disease is

high at 86 %, outcomes significantly worsen for those with nodal disease and again for those with distant metastases. Five-year survival rates of 32 % are observed with metastatic carcinoid tumors of the rectum [3].

The majority of diagnosed rectal carcinoids (65–80 %) will be less than 1 cm in diameter, which carries a 3–5 % risk of metastasis [5, 10, 33]. Both local transanal excision and endoscopic resection has demonstrated to be safe and curative for the vast majority of patients with these small carcinoids that lack adverse features – tumors less than 10 mm, without invasion of the muscularis propria and without ulceration, or less than 10 mm with adequate endoscopic surveillance [19, 36]. Rectal carcinoids ranging from 1 to 1.9 cm in diameter are associated with a 10–30 % chance of metastases [5]. Transanal excision is commonly performed for intermediate-sized rectal lesions, confined to the submucosa, without histologic risk factors [16, 37]. Most authorities recommend that patients with tumors of 1–1.9 cm in size, with invasion of the muscularis propria or other adverse features, and no evidence of metastatic disease, should undergo low anterior resection (LAR) or abdominoperineal resection (APR) with mesorectal excision [11, 17]. Lesions ≥2 cm have a 75 % chance of metastasizing [37], a median survival of 7 months [8], and a 10-year mortality of 60 %. Most studies support the use of APR or LAR with mesorectal excision for treatment of these larger tumors both for cure and for palliation [4, 16, 36, 37]. Aggressive surgical intervention, however, has never been shown to improve survival compared with local excision in tumors >2 cm. Adjuvant chemotherapy and radiotherapy has occasionally been used for large carcinoids, without clear evidence of benefit [17]. Our algorithm for the treatment of rectal carcinoids based on size is depicted in Fig. 22.1.

Table 22.1 Metastatic potential of rectal carcinoids

Diameter (cm)	Metastatic potential (%)
<1.0	3–5
1.0–1.9	10–30
≥2.0	>75

Adapted from Koura et al. [12], Grossmann et al. [219]

The most frequent sites of rectal carcinoid metastasis are lymph nodes and liver, with less common sites including brain, bone, peritoneum and lung [5, 8, 9]. Various combinations of chemotherapeutic agents have been used for metastatic rectal carcinoids, with little improvement in survival outcomes [8]. Lastly, neuroendocrine tumors can recur many years after surgical resection. The vast majority of carcinoids are Stage I tumors, or submucosal tumors less than 2 cm in size, and have an extremely low risk of recurrence. Therefore, there is no clear indication to perform long-term endoscopic or radiographic surveillance. Routine annual radiographic surveillance

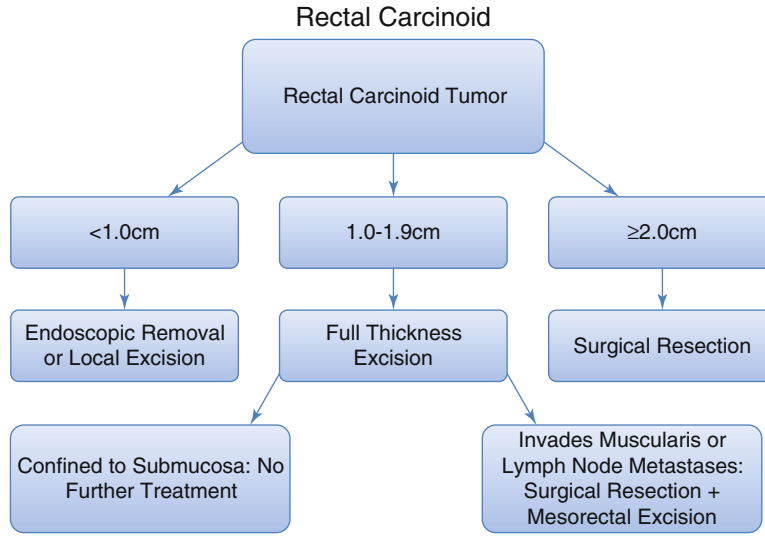

Fig. 22.1 Suggested algorithm for management of rectal carcinoid based upon tumor size

with CT or MRI should be considered for Stage II (invading muscularis) or III (regional lymph node involvement) NETs because of their high risk of systemic metastases, even years after treatment [16].

Lymphoma of the Rectum

Primary Lymphoma of the Rectum

The large intestine is the site of 6–12 % of all gastrointestinal lymphomas [38–40]. Rectal lymphoma can represent a primary rectal malignancy or metastases from a nodal origin, known as secondary rectal lymphoma. The vast majority of rectal lymphomas are sequelae of systemic lymphoma. Primary rectal lymphoma is exceedingly rare, representing only 0.2–0.4 % of all primary colorectal malignant neoplasms [39, 41–43]. Almost all primary colorectal lymphomas are non-Hodgkin, B cell lymphomas [42, 44]. Very few cases of Hodgkin lymphoma have been reported in the literature and these are often associated with HIV or EBV-infection, inflammatory bowel disease or immunocompromised hosts [45–47].

Differentiation of primary from secondary colorectal lymphoma is necessary because both the survival outcomes and the therapeutic management of the two are distinct. In 1961 Dawson et al. introduced criteria to diagnosis primary gastrointestinal lymphoma [48]. In order to classify a GI malignancy as a primary lymphoma several criteria must be met. These include: no palpable peripheral lymphadenopathy, no mediastinal lymphadenopathy, normal white blood cell count on peripheral blood smear, only mesenteric lymph nodes adjacent to the tumor are involved at laparotomy, and no malignant lymphomatous disease of the liver and spleen. One detriment of this classification system is the difficulty distinguishing between secondary lymphoma and those with primary GI lymphoma who present with widely metastatic disease. There is no standardized classification or staging system for GI lymphoma and lymphoma staging systems, designed for traditional nodal-based lymphoma, fail to provide adequate prognostic treatment guidance for primary GI lesions. Several staging systems exist for GI lymphoma including the Ann Arbor staging with Musshoff modification [49], the international prognostic index (IPI) [50], the Paris staging system [51] and the WHO classification system [52]. The Ann Arbor staging system, originally designed for Hodgkin's lymphoma, and its Musshoff modification, adopted for extranodal disease in 1977, is a very elementary system. The International Non-Hodgkin's Lymphoma Prognostic Factors Project developed of the International Prognostic Index (IPI) for patients with a diffuse large B-cell lymphoma (DLBCL) that consisted of Ann Arbor stage, patient characteristics and simple laboratory measurements. The Paris staging system has increasingly gained significance due to its ability to distinguish primary from distant lymphoma manifestations depending on involved organ. Recently there has been greater advocacy for use of the WHO system, which characterizes lymphomas on the basis of morphology, immunophenotype, molecular genetics, and clinical features [53–55]. This system has allowed clinicians to better predict the clinical behavior of the lymphoma as well as modify management to achieve greater therapeutic success.

Clinical Presentation and Diagnosis

Primary rectal lymphomas are most often diagnosed in males in their fifth through seventh decade of life [56, 57]. Presenting symptoms, similar to other rectal neoplasms, include abdominal pain, weight loss, palpable abdominal mass or, most commonly, lower gastrointestinal bleeding [42, 58, 59]. Obstruction and perforation however are rare in patients with colorectal lymphoma [60]. Distal rectal lesions may be appreciated on physical examination; however, higher more proximal lesions require contrast enema or colonoscopy for identification. There are no unique radiologic or colonoscopic features to differentiate primary rectal lymphoma reliably from more common rectal tumors. Endoscopic appearance of colorectal lymphomas are variable and have been described as fungating, ulcerative, infiltrative, ulcerofungating, and ulceroinfiltrative types, with fungating and ulcerofungating types being more common [61]. CT scan and

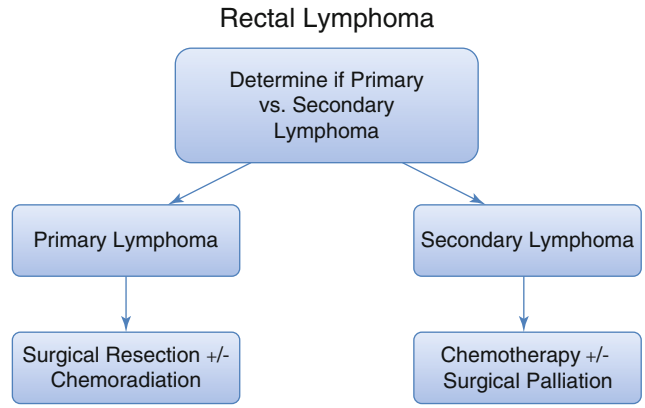

Fig. 22.2 Suggested algorithm for management of primary and secondary rectal lymphoma

double-contrast barium enema demonstrate both focal and diffuse lesions [62]. Histologic patterns are variable and multiple biopsies with immunohistochemistry and molecular studies are often necessary for definitive diagnosis [57, 63].

Primary rectal lymphoma has been associated with a number of conditions, including longstanding ulcerative colitis [40, 64, 65], pelvic irradiation [66], HIV and EBV infections [67, 68], as well as solid organ transplantation [69]. A number of investigators have recently described primary rectal lymphomas arising in homosexual men [70–72]. While no definitive causal relationship has been identified, all of these conditions are known to cause immune system alterations, which may explain their association with primary rectal lymphoma.

Treatment and Prognosis

Given the rarity of primary colorectal lymphoma, studies concerning management are limited to small, retrospective observational studies. Treatment remains variable, however, historically it has been managed with surgical resection with or without the addition of chemotherapy. Depending on the stage of the lesion, surgical resection is performed both with curative intent and to prevent further complications such as hemorrhage, perforation or obstruction [42, 73, 74]. Surgical resection for primary rectal lymphoma includes LAR, APR, or transanal excision depending on the tumor location and extent of invasion. The role of radical surgery in the management of indolent rectal lymphoma is somewhat controversial due to the associated morbidity of rectal resection with a complication rate around 20 % [60, 75, 76]. Chemotherapy which includes cyclophosphamide, vincristine, doxorubicin and prednisolone (CHOP) is given to improve survival; using this regimen, disease-free survival rates of 35–45 % at 4 years have been realized in patients with aggressive lymphoma [77]. The addition of rituximab to standard CHOP-based therapy has also been showed to further improve survival outcomes [78]. Primary radiotherapy for unresectable lesions, high-risk surgical candidates, and patients who are unwilling to undergo surgery, have also been described, with some success [79–81]. Most authors advocate adjuvant radiotherapy or chemoradiation [43, 56, 75, 79].

Most authors advocate for adjuvant chemotherapy in addition to surgical resection. Avilés et al. demonstrated 10-year survival outcomes of 83 % in 53 patients with primary colonic lymphoma treated with complete surgical resection followed by chemotherapy. However, this is likely to be related to the very select population of Stage IE tumors, which were studied [75]. Overall 5-year survival for primary colorectal lymphoma is 30–60 % [56, 73, 79, 82–84]. As expected there is better survival for patients presenting with localized disease (50 % 5-year survival) compared with those presenting with regional lymph node metastasis (24 % 5-year survival) [79]. The histologic grade of the of primary lymphoma in addition to stage may also impact prognosis [43]. A management outline of rectal lymphoma is depicted in Fig. 22.2.

Secondary Lymphoma of the Rectum

Secondary lymphoma of the rectum is defined as regional lymph node metastasis to the rectum. In patients with metastatic lymphoma of nodal origin, 5–46 % will have some degree of GI tract involvement [38, 79]. Presenting symptoms of metastatic lymphoma to the rectum are hematochezia and weight loss [56]. Primary therapy for metastatic lymphoma remains chemotherapy. Surgical intervention is generally of little benefit for the treatment of secondary rectal lymphoma unless it is for complications of these lesions such as intussusception, perforation, obstruction or uncontrollable hemorrhage. Lastly, prognosis is poor with overall 5-year survival of only 15 % [56].

Anorectal Melanoma

Anorectal melanoma (ARM), a type of mucosal melanoma, is an aggressive disease with a bleak prognosis. Although melanocytes do not normally occur in the rectal mucosa, malignant melanomas have been found to arise from areas of normal-appearing melanocytes, suggesting that certain individuals may have melanocytes present in the mucosa of the rectum [85, 86]. ARM is a rare tumor of the rectum, accounting for between 1 and 2 % of lower gastrointestinal malignancies and less than 2 % of all melanomas [87–89]. The incidence of ARM is thought to be increasing for reasons that are unclear [90–92]. After the head and neck and female genital tract, the anorectum is the third most common mucosal site of melanoma involvement [90].

Clinical Presentation and Diagnosis

ARM is commonly diagnosed in the sixth and seventh decades of life [93–96]. Anal bleeding is the most common symptom in those diagnosed with ARM [93, 94, 96]. The mean duration of symptoms before presentation is 5–6 months [93, 94, 96]. Multiple factors are thought to contribute to a delay in diagnosis of ARM. Frequently these lesions can be amelanotic in up to 20–25 % of cases; additionally, they are often confused with benign diseases such as hemorrhoids due to similar presenting symptomatology [88, 91, 94, 95, 97]. Two thirds of lesions are found in the anal canal or anal verge and approximately a third of cases are found in the distal rectum [92, 93]. While anal melanoma may vary slightly from rectal melanoma in initial presentation or recurrence patterns, recent data suggests there is no difference in survival outcomes by melanoma location within the anorectum [98].

Treatment and Prognosis

Despite multiple therapeutic approaches including surgical resection, radiation, and systemic therapy alone or in combination, prognosis and survival remain dismal for ARM [95, 98, 99]. More radical surgical resection has not been shown to alter survival outcomes. Even when patients are appropriately pathologically staged after rectal resection there is no survival difference between patients who undergo APR or wide local excision (WLE). There is a higher morbidity associated with APR; however, WLE may be associated with a higher rate of local recurrence [89, 95, 97, 100, 101]. There may be some role for radiation as palliative therapy in locally advanced, recurrent, or metastatic disease, but this too has not improved prognosis.

Commonly, the disease is advanced at initial presentation with regional nodal spread in up to 20 % of patients and systemic metastases in up to 40 % [87, 88, 90–93, 96]. Five-year overall survival is estimated at 20–22 % with a disease-free survival of 16–17 % [87–90, 92, 93, 100, 102]. Recurrence is often systemic and fatal. A predictor of poor outcome is thought to be the presence of perineural invasion in the primary tumor; however, unlike cutaneous melanoma, lymph node status has not shown an impact on survival [95, 100, 103].

Due to the uniformly poor prognosis of ARM, efforts combining surgical resection with effective systemic therapy will be required for the successful management of this disease. Recently

survival outcomes have improved in the treatment of cutaneous metastatic melanoma through advances in both immunotherapy and targeted therapy. Ipilimumab, a monoclonal antibody targeting cytotoxic T-lymphocyte antigen 4 (CTLA-4), was the first agent to improve overall survival in patients with metastatic melanoma in a phase III, randomized, control trial [104, 105]. Additionally, vemurafenib, an inhibitor of mutant BRAF, has increased both progression-free and overall survival in a phase III trial in patients with melanoma containing the V600E BRAF mutation [106]. Lastly, various inhibitors of KIT, such as imatinib mesylate, sunitinib, nilotinib and dasatinib, have also demonstrated survival benefit in a subset of patients with metastatic melanoma harboring mutant KIT [107]. BRAF and KIT mutation rates vary in mucosal melanomas according to anatomic site [108, 109]. Thus, it can be hypothesized that those ARM which are more immunogenic may represent better targets for drugs such as ipilimumab which exert its effect through immune system modulation, while those which possess KIT or BRAF mutations may demonstrate a therapeutic response to targeted inhibitors, such as imatinib and vemurafenib. While no current study has specifically examined ARM treatment with these new drugs, new trials utilizing these agents, including ipilimumab, BRAF- and KIT-inhibitors, for the treatment of all mucosal melanomas, are underway.

Neuroendocrine Carcinoma (NEC) of the Rectum

Neuroendocrine tumors (NETs) of the rectum are rare, comprising 0.2–0.4 % of colorectal malignancies [110–112]. Neuroendocrine neoplasms have been described in multiple organ systems, including respiratory, genitourinary and endocrine organs in addition to the gastrointestinal tract. The most common location of NETs in the large bowel is the rectum, followed by the cecum and sigmoid [111–115]. These lesions possess an endocrine function in that they are able to synthesize and secrete a multiple amines and hormones, including several neurotransmitters. Through advancements in both immunohistochemistry and microscopy GI neuroendocrine tumors were further categorized by degree differentiation [110, 114, 116, 117] and it is now known that many different rectal neoplasms (including carcinoids, certain anaplastic tumors, and small cell tumors) display neuroendocrine features [110]. Thus, GI neuroendocrine tumors incorporates a spectrum of well to poorly differentiated tumors of various sizes. The term "carcinoid" has been used to describe a subgroup of smaller, indolent, well-differentiated GI NETs while neuroendocrine "carcinoma" represented the poorly differentiated, more aggressive lesions in this group. This naming taxonomy still lacked clinical significance, however, because even small, low-grade carcinoids may metastasize (see section on "Carcinoid tumors of the rectum").

Table 22.2 The WHO 2010 Gastrointestinal Neuroendocrine Tumor (NET) grading classification

	Morphology	Mitotic count	Ki67 index (%)
Grade 1	Low grade	<2/10 HPF	≤2
Grade 2	Intermediate grade	2–20/10 HPF	3–20
Grade 3	High grade	>20/10 HPF	>20

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Recently, there has been improvement in both classification and prognostic value of these tumors, beginning with development of the 2010 WHO guidelines which grades NETs based upon degree of differentiation as determined by immunohistochemical features of mitoses and Ki-67 index (see Table 22.2) [118, 119]. Carcinoids are considered to be low or intermediate grade NETs of the colon and rectum (Grade 1 or 2), or well-differentiated lesions. Grade 3 or poorly differentiated lesions are considered neuroendocrine carcinomas of small cell type, and less frequently large cell carcinoma. This has since further been elaborated upon by the American Joint Cancer Committee (AJCC) and the European Neuroendocrine Tumor Society (ENETs) who have developed a Tumor, Nodal, Metastasis staging system (TNM) in accordance with the WHO classification [16, 120, 121]. Validation studies confirmed that TNM staging systems accurately

stratify colorectal NETs in a prognostically significant way [122, 123]. Additionally, the WHO grading guidelines, based on the Ki67 proliferative index, demonstrated statistically significant different survival outcomes between all grades on multivariate analysis further confirming the value of this classification system [124]. Thus, this separation of colorectal NETs into prognostically relevant subgroups by the TNM staging and WHO grading systems may aid in more streamlined, standardized treatment of these lesions in the future.

High-grade tumors or neuroendocrine carcinomas (NECs) contain abundant necrosis, either confluent or punctate within nests of tumor cells where as low-grade neuroendocrine neoplasms (e.g., carcinoid) generally possess some degree of typical native organ architectural patterns [125]. Up to half of colorectal NETs may contain non-neuroendocrine elements such as squamous or adenocarcinoma components [112, 114, 115, 117]. The pathogenesis of these tumors is not clear. One hypothesis is that pluripotent stem cells within the colonic epithelium exist and undergo malignant transformation leading to NE differentiation. Conversely, another hypothesis is that some adenocarcinomas, during malignant transformation, may develop NE characteristics. Additionally, there are genetic similarities between colorectal adenocarcinomas and highly aggressive NECs which are not shared by the more benign, well-differentiated carcinoid tumors. This suggests that there may not be a common origin between these subtypes of neuroendocrine tumors despite ultrastructural and immunohistochemical similarities. Loss of heterozygosity for the APC (adenomatous polyposis coli), DCC (deleted in colorectal carcinoma), or p53 genes, which are seen in adenocarcinomas are common for NECs, but are not associated with well-differentiated carcinoid lesions [125]. The exact reasons behind this remain unclear.

Clinical Presentation and Diagnosis

Most patients diagnosed with NETs of rectum are in their 50s–60s [5, 9–12, 16]. There is a slight male predominance and higher rates of rectal NETs among black and Asian populations [3, 5]. The incidence of colonic and rectal NETs may be increasing, perhaps due to the more frequent use of endoscopy for diagnosis and screening purposes [3, 5–7]. Most patients with rectal NETs are asymptomatic and are diagnosed incidentally in patients undergoing screening or endoscopic testing for unrelated reasons [10, 17].

Abdominal imaging (CT or MRI) combined with lower endoscopy provides significant information to aid in the staging and diagnosis of colorectal NETs. Endoscopic Ultrasound (EUS) has also played a key role in staging and treatment of rectal NETs; by providing data on size, depth of invasion, and lymph node involvement EUS helps determines the feasibility of conservative (endoscopic or transanal excision) management or the necessity of radical surgery (LAR or APR) [19, 25]. Electron microscopy and immunohistochemistry, are often required however for definitive diagnosis. Immunohistochemistry provides information on NE differentiation and bioactive amines. Rectal NE carcinomas, like rectal carcinoids, seem relatively incapable of producing carcinoid syndrome (even with liver metastases). Lastly, when small cell NEC of the rectum is diagnosed on rectal biopsy, which is histologically identical to small cell carcinoma of the lung, a search to rule out a pulmonary primary tumor must be performed.

Treatment and Prognosis

High-grade colorectal NETs, unlike low or intermediate grade carcinoids, are extremely aggressive tumors with poor prognosis. This tumor is associated with a 58 % 6-month survival rate, and a 6 % 5-year survival rate in some series [16, 110]. All rectal NETs, including well-differentiated tumors, have an overall 5-year survival of 88.3 %, with localized disease having a rate of 90.8 %, regional disease at 48.9 % and those with distant metastases 32.2 % [3]. This finding reflects that most of rectal carcinoid tumors (82 %) are localized at diagnosis, with a median size of only 0.6 cm [123]. Colon NECs proximal to the

rectum are more aggressive on average, with a 5-year survival of only 62 % across all stages [3]. These tumors have a high propensity for nodal and distant metastasis. As high as 65–80 % of patients will have nodal or distant metastasis at presentation [110, 126, 127]. Tumor grade, tumor size, depth of invasion, lymphovascular invasion, elevated mitotic rate and lymph node involvement significantly predict malignant behavior in localized rectal NETs [128]. According to one analysis of the literature, metastases were observed in 2 % of patients with rectal NETs measuring less than 1.0 cm, 10–15 % of tumors measuring 1.0–2.0 cm, and 60–80 % in patients with tumors measuring greater than 2.0 cm [129]. Patients appear to have a marginally better prognosis if they present without metastatic disease, have an adenocarcinoma component within their tumor, or respond to chemotherapy. Surgery, particularly in the presence of metastatic disease, may not offer a survival benefit for the majority of patients [127].

There is no standardized management of rectal NETs; as with carcinoids, treatment has been guided by tumor size. Because of their low risk of metastatic spread, localized disease or tumors that are small (<1 cm) and confined to the mucosa or submucosa (T1) can be managed with endoscopic resection or transanal excision. In lesions of 1–1.9 cm, transanal endoscopic microsurgery (TEMs) should be considered, which allows for deeper, full-thickness excision [130]. Larger tumors and those with adverse features should undergo APR or LAR. Palliative resection in advanced disease may be offered particularly where debulking may improve symptoms or relieve obstruction.

There are no good treatment outcomes for patients with metastatic colorectal NETs [16]. Metastatic hindgut NETs are incurable and optimal management requires a multidisciplinary approach with chemotherapy [131]. Palliative chemotherapy with or without radiation therapy has been used for adjuvant therapy and for treatment of metastatic disease without a clear survival benefit. For those few hindgut patients with functional tumors, somatostatin analogs are effective in the management of carcinoid syndrome and may delay disease progression. Liver-directed therapy and surgical debulking can improve the quality of life for some patients.

Due to the high rates of recurrence in colonic and rectal NETs, they require surveillance for recurrence even after successful complete resection at surgery except where the risk of recurrence is very low i.e. pT1a lesions <1 cm. There is little common consensus as to the best surveillance modality, interval period or length of surveillance but the European Neuroendocrine Tumour Society (ENETS) has published guidelines based upon tumor size [120]. Lesions <1 cm that are well differentiated (G1) with no invasion of the muscularis or lymphovascular invasion require no follow-up if resection is complete. Lesions that are between 1 and 2 cm or are higher grade should undergo annual follow-up with endoscopy, EUS and MRI. Lesions that are >2 cm: one endoscopy, CT or MRI scan, and serum marker within the first year. For high grade (G3) tumors: surveillance endoscopy, CT scan and serum marker every 4–6 months in the first year, and thereafter at least annually. ENETS recommends follow-up for at least 10 years [120], while NANETS guidelines recommend surveillance for up to 7 years [16].

Vascular Lesions

Vascular lesions occur throughout the GI tract and frequently present in a delayed fashion after repeated episodes of bleeding and unwarranted procedures. The nomenclature of vascular lesions has been tainted by confusion and misnomers, but two main categories of vascular lesions have emerged: hemangiomas and vascular malformations [132]. Hemangiomas are usually absent at birth but appear at 6–8 weeks of life. Their course is marked by rapid proliferation followed by spontaneous involution. They have a high endothelial cell turnover. Vascular malformations, however, are usually present at birth, have normal endothelial cell turnover and grow in proportion with the person [133]. Vascular malformations are further classified according to their dominant abnormality into arteriovenous, venous,

lymphatic, lymphatic-venous, and capillary malformations. The term hemangioma is often erroneously used to describe vascular malformations in the GI tract. The commonly used term "cavernous hemangioma" will here be replaced by the more correct term "cavernous malformation" or "diffuse cavernous malformation." Hemangiomas do occur in the GI tract but far more infrequently than vascular malformations. Intestinal vascular malformations are classified into capillary, cavernous (localized or diffuse infiltrating), mixed, and hemangiomatosis. Of rectosigmoid malformations, 80 % are of the cavernous type. The localized type of cavernous malformations is frequently polypoid and symptomatic while the diffuse type can be multiple and has been reported up to 30 cm in length. Some types can be circumferential and invade surrounding structures.

Diffuse Cavernous Malformation

Diffuse cavernous malformation (previously diffuse cavernous hemangioma) of the rectum is a rare condition albeit an important differential diagnosis in rectal bleeding. Approximately 130 cases have been described in the literature [133]. The first case was described in 1839 by Buie and Nesselrod in their paper "Erectile tumor of the anus." Diffuse cavernous malformations comprise approximately 20 % of intestinal angiomas [134]. They can be found anywhere in the GI tract but occur most commonly in the rectosigmoid area, or in 50–70 % of cases [135].

Pathology

The malformation can be limited to a small area or be diffuse and infiltrate adjacent structures such as the bladder or uterus. The diffuse cavernous malformations are of variable sizes, sometimes up to 20–30 cm in length and are occasionally found in multiple locations [134]. These lesions do not have malignant potential and might be better classified as hamartomatous rather than neoplastic lesions. Malignant degeneration is exceedingly rare. The diffuse infiltrating cavernous hemangioma may replace the bowel wall from serosa to mucosa. Histologically, these malformations are composed of multiple dilated tortuous vessels within a stroma containing abundant smooth muscle and fibrous connective tissue [136]. Diffuse cavernous malformations are associated with Klippel-Trénauny syndrome [137] and Kasabach-Meritt syndrome [138].

Clinical Presentation and Diagnosis

The disease is characterized by recurrent, moderate-to-massive, and sometimes fatal, gastrointestinal bleeding. Blood transfusions are frequently required. The first episode usually occurs in childhood or infancy [139]. The mean age at diagnosis was 6.5 years in Londono-Schimmer's series of 15 patients [140]. A delay of several years from initial presentation to diagnosis is not uncommon and up to 80 % of patients have undergone at least one unwarranted surgical intervention in an attempt to correct their condition, most often a hemorrhoidectomy [139, 141, 142]. The bleeding is usually painless and often intensifies with each successive episode [135]. Approximately 17–25 % of patients present with obstructive symptoms from voluminous growth into the bowel lumen, intussusception, or occasionally, volvulus. Rarely, a rectal cavernous malformation may cause tenesmus, urgency and incomplete evacuation [134]. Although the diagnosis is frequently delayed, it can be suspected from a family history or personal history of mucocutaneous lesions, anemia, frank bleeding or signs of obstruction. The lesion may be palpable on rectal exam and other vascular lesions of the mucous membranes or skin may be seen.

This vascular neoplasm is usually diagnosed by one of several different modalities. Endoscopy is diagnostic and frequently shows nodular masses which are soft and compressible and deep blue, purple or dull red in color [143]. Biopsies are generally contraindicated due to the risk of severe bleeding. Phleboliths are normally not seen on abdominal x-ray in younger individuals but are seen in 50 % of plain x-rays in patients with diffuse cavernous malformations [144]. Phleboliths in unusual areas in the pelvis in a person with history of rectal bleeding and constipation should prompt suspicion of diffuse cavernous

malformation. Barium enema can show irregularity, nodularity and obstruction. CT is an excellent diagnostic modality that reveals both the extent of malformation and possible invasion into adjacent structures. CT findings include marked transmural thickening of the bowel and mesentery, heterogeneous enhancement, bowel narrowing, nodular indentations of the rectosigmoid wall, and anterior displacement of the rectum [145]. Angiogram shows the lesion well and can localize active bleeding but is invasive and has been replaced by more modern imaging modalities such as CT or MRI. MRI has excellent soft tissue discrimination, has the ability to show blood flow without the use of intravenous contrast, and does not use ionizing radiation [145]. Phleboliths, however, are poorly detected on MRI [145]. Ultrasound is also a useful imaging modality but is user dependent.

Treatment and Prognosis

The treatment of diffuse cavernous malformations is surgical. Fatal bleeding in untreated patients was reported as high as 45 % in a small series [145]. Treatments such as embolization, radiotherapy and sclerotherapy have thus far been unsuccessful. Sphincter-saving resection with coloanal anastomosis with radical removal of the abnormal tissue is the procedure of choice in these usually young patients with benign disease [146, 147]. Abdominoperineal resection with a permanent end colostomy was used with relatively low morbidity and mortality in the early patients [148]. This soon fell out of favor for sphincter-preserving resections, now the procedures of choice. Colonic pull-through procedures have been performed with some success, like the Soave procedure [140, 149], and a modified Soave procedure [150]. Small polypoid cavernous malformations usually are limited to the submucosa and have been safely removed with endoscopic cautery snare polypectomy [151]. However, the safety of this intervention is unclear and massive hemorrhage could ensue. The following criteria for endoscopic polypectomy have been proposed: size $\leq$2.5 cm, pedunculated or sub-pedunculated polyp, and depth of lesion limited to the submucosa [143].

Lymphangioma

Rectal lymphangiomas are exceedingly rare with only a few reported cases to date [152]. These lesions consist of abnormal dilatation and mass-like proliferation of lymphatic channels. They have been incidentally detected during colonoscopy, but when symptomatic, present with pelvic pain and rectal bleeding [153, 154]. On colonoscopy, they frequently appear pedunculated or as cystic submucosal nodules with a smooth, translucent surface that is easily compressible. Lymphangiomas less than 20 mm in size can be removed by snare polypectomy but larger, sessile, and infiltrating lesions may require surgical resection [155].

Hemangiopericytoma

Hemangiopericytoma is a rare tumor first described in 1942 by Stout and Murray [156]. It is comprised of profuse proliferation of capillaries surrounded by sheets of rounded, sometimes elongated pericytes [157]. They can become quite large and cause compressive symptoms, obstruction, intussusception and gastrointestinal bleeding [158]. These tumors are variable in their behavior and occur in all age groups without a gender predilection. While some tumors remain localized for decades, some are malignant, with approximately a third developing aggressive invasion or metastases, more commonly in older patients [159, 160].

Metastases can be detected years after removal of the original tumor. Out of 106 cases reported in 1976, 26 were in the retroperitoneum and pelvis [161]. Seven cases of colorectal hemangiopericytoma were reported in 1959 [162]. Their size ranged from 3.5 to 26 cm in greatest dimension. Local recurrence and distal metastases were common.

Treatment consists of complete surgical excision. Due to the rarity of the tumor and unpredictable biological behavior, there remains controversy about their management. Neoadjuvant chemotherapy and adjuvant radiation may have a role in larger and unresectable tumors [163–165].

Squamous Cell and Adenosquamous Carcinoma of the Rectum

Squamous Cell Carcinoma of the Rectum

Squamous cell carcinoma of the colon and rectum is extremely rare with approximately 70 cases reported in the literature [166], comprising approximately 0.1 % of all colorectal neoplasms [167]. The rectum harbors nearly half of these tumors. Williams et al., in 1979 set forth criteria for the diagnosis of primary colorectal squamous cell carcinoma: (1) The lesion may not be a secondary metastasis from another primary lesion. (2) There should be no squamous-lined fistula track, where squamous carcinoma is known to originate. (3) A rectal squamous cell carcinoma should not be an extension from an anal squamous cell primary [168].

The rectum normally does not contain squamous cells, but several theories have been proposed to explain the development of squamous cell carcinoma in this location: (1) Proliferation of pluripotent stem cells, which exist in the mucosal crypts following mucosal injury. (2) Squamous metaplasia resulting form chronic irritation [169], although squamous metaplasia is rarely seen; similarly squamous cell carcinoma is rarely seen. (3) Persistent embryonal nests of committed or uncommitted ectodermal cells remaining in an ectopic site after embryogenesis. This could explain the lower rectal squamous carcinomas, but is unlikely to explain colonic tumors. (4) Squamous differentiation arising in an adenoma. Rare adenomas have been found to have squamous differentiation, which could indicate the parallel adenoma-carcinoma sequence of squamous cells [168, 170]. Squamous carcinomas have clinicopathological features in common with adenocarcinomas; the age and sex distribution of affected patients are similar for adenocarcinoma and squamous cell carcinoma; the anatomic distribution of adenomatous and squamous tumors is similar within the large bowel, although the number of squamous cell tumors is too low to allow for a meaningful statistical correlation. No association has been found between HPV subtypes 6, 11, 16 and 18 and squamous or adenosquamous carcinoma [171]. Immunohistochemical staining of keratin suggests a pluripotent endodermal stem cell origin for both squamous call carcinoma and adenocarcinoma of the rectum [172].

Clinical Presentation and Diagnosis

Squamous cell carcinoma of the rectum usually presents in the fifth decade of life (range 33–93) and more often in women than in men [172]. Symptoms at presentation are similar as with adenocarcinoma, such as abdominal pain, hematochezia, diarrhea, constipation, anorexia and weight loss. Lafreniere et al. reported positive lymph nodes in 57 % of patients at diagnosis [173]. Distant metastases at diagnosis were found in 21 % of patients to either lungs, liver, vertebrae, omentum mesentery, peritoneum or adrenal glands [173]. Concomitant conditions such as ulcerative colitis, colonic duplication, schistosomiasis, amoebiasis, ovarian cancer, endometrial cancer, ovarian teratoma, prostate cancer, and a chronic colocutaneous fistula have all been reported but a causative relationship is uncertain [167, 170]. A tenth of patients were found to have antecedent, synchronous or metachronous adenocarcinoma [167]. Although no definitive conclusion can be drawn from this due the rarity of the disease, it suggests that clinicians should maintain a heightened awareness for the risk of other neoplasms.

Diagnosis is obtained with physical exam and endoscopic examination with biopsies. Tumor and nodal staging can be further achieved by endorectal ultrasound. The presence of distant metastatic disease is evaluated by X-ray or CT of the chest, and abdominopelvic CT.

Treatment and Prognosis

The optimal treatment for these rare tumors is not clearly defined but has been primarily surgical in the form of segmental resection or abdominoperinal resection. Primary palliative chemotherapy was reported in one patient with some response [174]. The pendulum seems to be swinging towards non-surgical management with the first-line treatment being combination chemoradiation

therapy as described by Nigro and is now the standard of care for squamous cell anal cancer [175, 176]. Case reports and case series suggest that rectal squamous cell carcinoma responds well to initial chemoradiation therapy, with surgery reserved for salvage treatment of non-responders, partial responders or for recurrence [173, 177–179]. The need for subsequent surgery is unclear, but a sphincter-preserving surgery should be feasible in most cases [172].

Possibly due to the rarity of colorectal squamous cell carcinoma, initial data suggested a poor prognosis with 30 % 5-year survival [180]. When examining a larger number of cases, the prognosis seems to be similar stage-for-stage to node-negative colorectal adenocarcinoma (stages I and II). The prognosis is worse, however, when nodal disease occurs in SCC than for adenocarcinoma of a similar stage [166]. Features that predict a poor prognosis include right-sided colon lesions, ulcerated or annular cancers, node-positive disease, grade 3 or 4 cancer, and stage IV disease [166].

Adenosquamous Carcinoma of the Rectum

Adenosquamous carcinoma is an extremely rare malignancy with an incidence of 0.025–0.1 % of all colorectal cancers [181]. As its name implies, it has both glandular and squamous histologic components, both of which are malignant and can metastasize. The mean age at diagnosis of adenosquamous cell carcinoma is in the sixth and seventh decades with an equal gender distribution [167, 182]. Although Cagir et al. found the rectum and distal colon to be affected most often [181], others have found adenosquamous carcinoma more frequently in the right colon [166, 182].

The cause of adenosquamous lesions is unknown, but the theories for histogenesis mirror the ones for squamous colorectal cancer. There may be an association with ulcerative colitis [183], polyposis, schistosomiasis, ovarian adenocarcinoma and endometrial adenocarcinoma [184]. The squamous component seems to metastasize more frequently and is more aggressive than the glandular component [184].

Adenosquamous carcinoma seems to be more aggressive than adenocarcinoma and have a worse prognosis stage for stage. Cagir et al. also found that 85 % of their patients presented with regional or metastatic disease [181].

The primary treatment modality for these tumors is surgery. Adjuvant chemotherapy is frequently used but the benefit is unknown in this uncommon disease [185]. The Nigro regime has also been used as an adjunct after surgery [181].

In a recent population based study using the California SEER database, Masoomi et al. identified 99 cases of adenosquamous carcinoma [182]. They found that adenosquamous tumors present with more advanced disease and more poorly differentiated tumors. The 5-year survival was worse compared to adenocarcinoma with an increased overall mortality. They concluded hat adenosquamous tumors should be considered a poor prognostic factor in patients with colorectal cancer. The overall 5-year survival is 30 % or less [182] and the mean survival is 12 months [181].

Sarcomas of the Rectum

Leiomyosarcoma of the Rectum

Sarcomatous tumors of the colon and rectum are rare and include tumors such as fibrosarcoma, angiosarcoma, leiomyosarcoma and GIST. Before the discovery that most leiomyosarcomas are in fact gastrointestinal stomal tumors, 95 % of colorectal sarcomas were attributed to leiomyosarcomas. Their earlier described incidence of 0.07–0.1 % of all rectal malignant tumors is in fact much lower [186]. They are most common in the lower third of the rectum [186, 187]. They remain difficult to diagnose and are very aggressive with a poor prognosis.

While GISTs arise from interstitial cells of Cajal and express KIT, leiomyosarcomas have a distinct lineage from smooth muscle cells and do not express KIT. Our previously held notions on leiomyosarcoma need to be redrafted with newer studies using modern diagnostic criteria, based

on findings from true leiomyosarcomas rather than findings from GISTs.

Pathology

Leiomyoma and leiomyosarcoma are found throughout the GI tract with 7 % of them in the rectum [186]. Leiomyosarcomas are usually larger than leiomyomas; they are soft to rubbery firm, and frequently very vascular [188]. They arise from smooth muscle in the muscularis mucosa, round or longitudinal muscle of the bowel wall, or from the vascular smooth muscle [188]. Malignant degeneration of benign leiomyoma has been described, although the exact pathogenesis is not known [188, 189].

Histologically, leiomyosarcomas appear as well-differentiated smooth muscle cells, composed of elongated cells growing in fascicles with at least focal pleomorphism and high mitotic activity [190]. Microscopic differentiation between leiomyoma and leiomyosarcoma can be very difficult [188]. Immunohistochemically, they are positive for actin and desmin and negative for KIT and CD34, differentiating them from GIST tumors [190]. Based on the number of mitoses per 10 consecutive high-power fields, the tumor is classified into high-grade (10≥/10 HPFs) or low-grade tumor (<10 mitoses/10 HPFs) [191].

Spread is local, with direct invasion, or bloodborne, most often to lungs and liver, but also to peritoneum, brain and spine. Metastases to lung and liver is the most common cause of death [186]. Although it is generally said that leimyosarcoma does not spread to lymph nodes [191], there are case reports of lymph node involvement, mainly with very poorly differentiated tumors [188].

Clinical Presentation and Diagnosis

The tumor occurs more frequently in males, while benign leiomyomas tend to occur more frequently in females [188]. The tumor is most often diagnosed in the fifth and sixth decades. Presenting symptoms include bleeding, constipation, rectal pain, sense of fullness and diarrhea [186]. Most tumors appear as submucosal masses that mainly grow into the lumen but also can grow away from it [186]. The tumor may protrude into the lumen or partially occupy the circumference of the rectum. Approximately 50 % of the tumors are ulcerated [188]. Khalifa et al. carefully reviewed 136 cases of rectal leiomyosarcoma [186]. The majority of tumors were in the lower rectum, and 89 % of them were palpable by rectal exam. The tumor size ranged from 1 cm to 15×10×20 cm but tumors up to 30 cm have been identified [192]. Diagnosis is made by endoscopy and biopsy, although biopsies can be difficult to obtain [188].

Treatment and Prognosis

The mainstay of treatment is surgical. Any clear recommendation regarding the choice of treatment is difficult for this rare malignancy, but a few trends have emerged from several case reports and retrospective series [186, 187, 193]. It is important to recognize the selection bias when comparing the different surgical approaches as patients are selected for surgery based on size and state of their primary tumor. Local excision has been followed by high local recurrence rates up to 60–67 %, necessitating a more aggressive surgical approach [186, 194] The local recurrence rate after abdominoperineal resection is much lower, 20–24 %, but this has not translated into a difference in long-term survival when comparing the two general surgical modes [186, 187, 192, 194]. The disease-free survival at 5 years was 32 % after wide local excision and 52 % after radical resection but overall survival was identical [187].

Randleman Jr et al. concluded that anorectal lesions smaller than 2.5 cm in diameter and confined to the bowel wall could be treated with wide local excision and patients with larger, nonconfined lesions might do better with a more radical resection [193].

Adjuvant radiotherapy was used early on but was soon believed to be of little benefit [188, 195]. No benefit of either radiation treatment or chemotherapy has been shown [193].

The overall prognosis for patients with rectal leiomyosarcoma is poor with a 5-year survival of 40 % [196] and median survival of 33 months [192]. A young age at diagnosis (under 50 years)

and a high histologic tumor grade have been found to be poor prognostic factors, stressing the need to identify adjuvant treatments for these patients [187, 192, 194]. Recurrence has been noted 15–17 years after treatment, underlining the need for long-term follow-up [192].

Rectal Gastrointestinal Stromal Tumor

Gastrointestinal stromal tumors (GISTs) have been recognized as the most common mesenchymal tumors of the GI tract. Prior to the advent of immunohistochemical diagnostics, most GI stromal tumors were identified as leiomyosarcoma. GISTs occur in 1.1–2 persons per 100,000 [197]. The rectum is the third most common site for GIST, accounting for 4–5 % of all GIST tumors [190, 198]. The tumor occurs more commonly in males and usually between the fifth and seventh decades of life [190].

The tumors originate from the interstitial cells of Cajal and are characterized by over-expression of KIT protein (CD117), which is a transmembrane receptor tyrosine kinase (TK) [199]. This overproduction results from gain-of-function mutations in the KIT proto-oncogene resulting in tumor proliferation or inhibition of apoptosis [200]. In rare cases, the mutation is not in the KIT proto-oncogene, but in the platelet-derived growth factor receptor-alfa (PDGFRA) gene. A high degree of sequence homology between KIT and PDGFRA explains the inhibitory ability of imatinib on both. All but a minority of GISTs express KIT. KIT is also expressed by other tumors, such as melanoma, Ewing's sarcoma, angiosarcoma, mastocytoma, and seminoma.

Most GISTs are sporadic, but families with germline KIT or PDGFRA mutations have been identified. There is an association between hereditary syndromes such as von Recklinghausen's disease and Carney's triad (gastric GIST, paraganglioma, and pulmonary chondroma) [201]. The National Institute of Health risk stratifies GISTs into four risk groups based on their mitotic rate and size; high-risk, intermediate risk, low risk, and very low risk (see Table 22.3) [200].

Table 22.3 NIH consensus criteria for GIST risk groups

	Tumor size	Mitotic rate
Very low risk	<2 cm	<5/50 HPF
Low risk	2–5 cm	<5/50 HPF
Intermediate risk	<5 cm	6–10/50 HPF
	5–10 cm	<5/50 HPF
High risk	>5 cm	>5/50 HPF
	>10 cm	Any mitotic rate
	Any	>10/50 HPF

With kind permission from Springer Science+Business Media: Hassan et al. [200]

Pathology

On histology, GISTs are characterized by spindle cell type, epitheloid type, or rarely mixed type. GISTs usually have scant stroma. KIT-negative GISTs have been identified, although most are KIT-positive; 7–9 % of rectal GISTs are KIT-negative [200]. These tumors are still thought to be responsive to tyrosine kinase inhibitors. Staining for KIT protein should be a diagnostic aid for GIST. Absent KIT protein does not exclude GIST; mutational analysis of KIT or PDGFR genes can then be considered [202].

Clinical Presentation and Diagnosis

Approximately half of rectal GISTs are asymptomatic and discovered incidentally during work-up for unrelated symptoms [200]. Symptomatic patients present with anal bleeding and perianal pain, most commonly, but also with difficult defecation, pressure, diarrhea and dysuria [203]. Most rectal GISTs show extraluminal tumor growth with a "tip of the iceberg" view on endoscopy, which necessitates pre-operative cross-sectional imaging [204]. Rectal GISTs are significantly smaller than intestinal and gastric GISTs [205]. Most rectal GISTs occur in the lower rectum [206]. Non-gastric GISTs are more likely to show malignant behavior than gastric GISTs [197].

Treatment and Prognosis

The main treatment for localized GISTs is surgical resection, and the goal of surgery complete resection with an intact pseudocapsule. Small rectal GISTs that are amenable to local excision

can by removed in this manner if a negative microscopic margin is obtained [200]. Local recurrence rates are high and occurs in approximately 50–80 % of patients after curative resection [207, 208]. Recurrence after surgical resection is more likely in the presence of high-risk features, mainly ≥5 mitoses/50 high-power fields, tumor size ≥10 cm and location in the small bowel [208]. GIST does not metastasize through lymphatics. Distant metastases are uncommon from anorectal GIST, and if they occur, tend to be to sites that are less commonly affected by metastatic GIST, including lungs, bone, adrenal glands, and other rare sites [207]. Most anorectal GISTs are high risk (86 %), usually on account of their high mitotic rate rather than large size [207].

The 5-year disease-specific survival after local resection only is around 55 % with a median survival of 66 months [209]. GISTs respond poorly to conventional cytotoxic chemotherapy and to radiotherapy, but the advent of the tyrosine kinase inhibitor imatinib mesylate has revolutionized the treatment of GIST. The first-line treatment of metastatic GIST is imatinib, with a 2-year survival of approximately 70 % and median survival of 58 months, depending on the mutation status [208]. Imatinib is given by mouth, usually 400 mg daily [210]. Side effects are rare and include dermatitis, abdominal pain, and diarrhea.

In general, small GISTs located within 5 cm from the anal verge can be resected trans-anally. Lesions in the mid-rectum can be resected through a trans-sacral approach, and anterior rectal wall lesions through a transvaginal approach. There is no need for lymph node clearance or TME. Large, advanced lesions in the lower rectum or recurrent tumors, or tumors resist resistant to TKI in this location, are removed with an APR. Laparoscopic sphincter-sparing surgery appears safe and feasible [211].

Pre-operative tyrosine kinase inhibitor can downsize the tumor or make an unresectable tumor resectable, render the surgery more conservative, easier, safer, preserve tissue and function, with higher likelihood of negative margins [198, 212]. It may prevent rupture of a tumor in the confined pelvic space. Adjuvant imatinib improves recurrence-free survival [210].

Table 22.4 Risk stratification of primary rectal GIST by mitotic index and size

Tumor parameters		Risk for progressive disease (%)
Mitotic rate	Size	
≤5/50 HPF	≤2 cm	None (0 %)
	>2, ≥5 cm	Low (8.5 %)
	>5, ≤10 cm	Insufficient data
	>10 cm	High (57 %)
>5/50 HPF	≤2 cm	High (54 %)
	>2, ≥5 cm	High (52 %)
	>5, ≤10 cm	Insufficient data
	>10 cm	High (71 %)

The data is based on long-term follow-up of 111 rectal GISTs. From Miettinen and Lasota [220], Copyright 2006, with permission from Elsevier

The most important prognostic factors for GIST are tumor size, mitotic rate and location of primary tumor (see Table 22.4) [208, 209]. The completeness of resection and tumor rupture also affect outcomes. Microscopic margins do not seem to negatively impact survival. Other prognostic factors are cellular proliferation index estimated by Ki67 immunohistochemistry, diffuse mucosal invasion, which is seen in aggressive GISTs only, aneuploidy, which is a marker of malignancy, and telomerase expression [201].

The risk of disease relapse persists for years after resection of primary disease highlighting the need for extended surveillance with imaging [200]. Patients with positive KIT should be enrolled in a clinical study.

Kaposi's Sarcoma of the Rectum

Moritz Kaposi initially described Kaposi's sarcoma in 1872 [213]. Kaposi's sarcoma initially had three epidemiologic forms: the classic form, which occurs mainly in elderly men of Mediterranean and Eastern European descent; the endemic form which is mainly seen in equatorial Africa, an aggressive and often fatal form; and the post-transplant or iatrogenic form which occurs with immunosuppression. The fourth form is named epidemic or AIDS-related Kaposi's sarcoma. Human herpesvirus 8 (HHV-8) was

identified in 1994 from Kaposi's sarcoma skin lesions [214], and has since been found in over 95 % of Kaposi's sarcoma lesions, regardless of their source or clinical subtype [215]. HHV-8 is the primary and necessary factor in the development of Kaposi's sarcoma in the usually immunosuppressed host.

Clinical Presentation and Diagnosis

Kaposi's sarcoma most frequently involves the skin, but more frequently involves the GI tract in homosexual males with AIDS, or in over 50 % of cases [216]. The average age at presentation of anorectal Kaposi's sarcoma in a series of eight patients was 34 years [217]. When the bowel is involved, it usually precedes skin involvement. The oral cavity and buccal mucosa is frequently involved and lesions should be sought on exam. Bowel involvement is generally asymptomatic but rectal involvement is frequently accompanied by proctalgia, bleeding and diarrhea [217]. The symptoms, however, are frequently caused by other anorectal infections or colitis, rather than the sarcomatous lesion per se [217]. Isolated anorectal involvement is less common than disseminated Kaposi's sarcoma involving the GI tract, skin and/or lymph nodes. Rare cases of colorectal Kaposi's sarcoma were initially diagnosed as ulcerative colitis [218].

Pathology

Kaposi's sarcoma predominantly involves the submucosa with late involvement of the mucosa and sometimes deeper layers of the bowel wall. Lesions are seen as red nodules, plaques or macules on endoscopy. Biopsies must include submucosa for correct diagnosis [218]. Histologically, Kaposi's sarcoma is characterized by vascular clefts and spindle cells, the presumed tumor cells [213].

Treatment and Prognosis

Treatment of Kaposi's sarcoma of the rectum consists most importantly of correction of the immunodeficiency, by reducing or halting immunosuppressive medications or, in the case of HIV/AIDS, use of highly active antiretroviral treatment (HAART). HAART has been shown to prevent, halt and shrink the growth of Kaposi's sarcoma [215]. Progression of Kaposi's sarcoma seems to be further delayed by foscarnet, which is used for cytomegalovirus infection. The response of Kaposi's sarcoma to HAART is unpredictable, therefore, specific local and systemic therapy is frequently used as well. Kaposi's sarcoma, especially the classic form, is responsive to radiation therapy but the response of the epidemic, AIDS-related form is less durable [215].

Cytotoxic drugs, mainly liposomal anthracyclines, paclitaxel, vinca alkaloids, and bleomycin, are used in widespread mucocutaneous disease, lymphedema and visceral disease. Response is generally lower in the epidemic form compared to the classic form. Liposomal doxorubicin is by many physicians considered a first-line treatment for patients with advanced Kaposi's sarcoma. Interferon-alpha has shown promising results. Experimental therapies, including inhibitors of angiogenesis such as inhibitor of VEGF (vascular endothelial growth factor), thalidomide, and retinoids have activity against Kaposi's sarcoma [215].

Death is usually not attributed to Kaposi's sarcoma, but to other AIDS-related disease or complications. Surgery is often sufficient for patients with single cutaneous lesions but is usually not indicated other than for a diagnostic biopsy in anorectal Kaposi's sarcoma [217].

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Quality of Life in Rectal Cancer Patients

23

Therese Juul, Henriette Vind Thaysen, and Tina Yen-Ting Chen

Abstract

As more and more patients are surviving rectal cancer, owing to advances in treatment, survivorship issues are now at the forefront of clinical practice and research. The patient's well-being or quality of life (QoL) is inevitably affected by rectal cancer and its treatment, usually in a variety of ways. The exact impact depends on the aspect of life concerned, tumor characteristics, the treatment involved, the measurement method and timing, as well as the patient. This chapter presents a collection of current knowledge regarding QoL in rectal cancer patients, including the conceptual definition of QoL, QoL measurement and interpretation, QoL following standard and complex rectal cancer surgery, QoL after neoadjuvant therapy, and QoL with or without a permanent colostomy. Better understanding of QoL in rectal cancer not only facilitates enhanced patient information, communication and shared decision-making throughout the patient journey, but also underpins initiatives towards preventing and managing adverse effects to ensure that both the length and quality of the patient's life are optimized.

Keywords

Rectal cancer • Rectal neoplasms • Quality of life • Health-related quality of life • Patient-reported outcomes • Survivorship • Adverse effects • Functional outcomes

Introduction

Over the past few decades, advances in the treatment of rectal cancer (RC) have resulted in substantially improved survival and local control. Unfortunately, while oncological outcomes have improved, a large proportion of the growing survivor population experiences adverse effects

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of RC and its treatment, impairing their quality of life (QoL). Consequently, QoL studies are now recognized as critical in describing patient-reported outcomes, highlighting the impact of RC and its treatment on the patient's well-being. Better understanding of QoL in RC not only facilitates enhanced patient information regarding relevant problems throughout the patient journey, but also underpins initiatives towards preventing and managing these problems to ensure that both the length and quality of the patient's life are optimized.

Conceptual Definition of Quality of Life

QoL represents the general well-being of individuals or groups of people. It is a broad concept that can take on various meanings [1], and essentially encompasses all aspects of life. In light of the breadth of the concept, the term "health-related quality of life" (HRQoL) was introduced, narrowing the focus to aspects of life that are directly affected by changes in health. Even though all aspects of life could contribute to or be influenced by health (especially in chronic illness) [2], some aspects of life, such as political and cultural, are usually distant from health concerns, and are less amenable to medical intervention [3]. HRQoL has been defined inconsistently, and has often been used interchangeably with "health status" or "functional status" [4]. Of the various definitions of HRQoL, the most pragmatic, comprehensive and rigorous is one proposed by The United States Centers for Disease Control and Prevention, which is commonly adopted:

"An individual's or group's perceived physical and mental health over time" [5].

With the notion of HRQoL being widely accepted, "QoL" and "HRQoL" are now virtually synonymous in healthcare. For the purpose of consistency, only "QoL" will be used henceforth in this chapter, with the term assuming the definition of HRQoL.

The essence of QoL lies in its subjectivity and multidimensionality [6]. A patient's view of his or her QoL may be quite different from the view of the clinician or those close to the patient, but since QoL is an individual's or group's own perception, the patient's subjective judgment of QoL should be the gold-standard.

Although QoL has been defined differently, there is a high level of consensus that it is a multidimensional construct. Several QoL models have been presented, providing the fundamental framework to its conceptualization and guiding its measurement [7]. A model originally formulated by Wilson and Cleary [8], and subsequently revised by Ferrans et al. [9], stands out from the others for describing the causal relationships between the full spectrum of outcome endpoints, from conventional clinical to patient-reported variables. Moreover, most elements of this model clearly correspond to common focuses and scopes of QoL evaluation. We have adapted this model to further delineate the readily identifiable determinants and dimensions of QoL (Fig. 23.1). The model serves to give an overall conceptual outline, and is by no means exhaustive.

The way the model works is that as you move down the diagram, the focus shifts from the biochemical level to the person as a whole, through to how the person operates as part of the society [8], thereby promoting a holistic and patient-centered approach to outcome assessment. A dimension positioned higher in the diagram underlies the lower dimensions.

As illustrated in Fig. 23.1, characteristics of the individual and the environment can interact with and alter all dimensions of QoL [9]. These characteristics include intrapersonal, interpersonal, institutional, community and public policy factors [9]. Biological function involves basic pathophysiological processes occurring at the molecular, cellular or whole organ levels [9]. Not only can biological function manifest in symptoms, it can also have direct or indirect effects on the other subsequent dimensions of QoL [9]. Symptoms are a person's somatic sensations. The person's experience and interpretation of symptoms are major determinants of functional status, general health perceptions and overall QoL [9]. Functional status refers to a

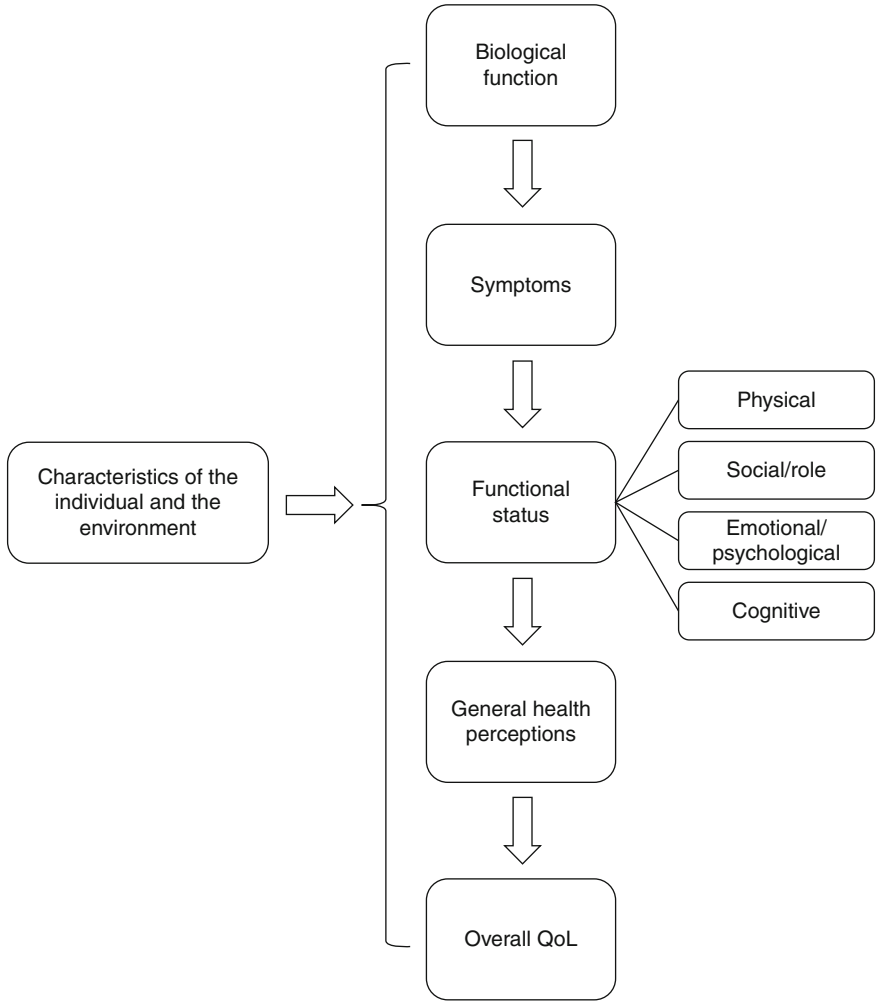

Fig. 23.1 Conceptual model of QoL (Adapted from the model first devised by Wilson and Cleary [8], and later revised by Ferrans et al. [9])

person's ability to perform tasks. It is generally conceived that physical, social/role, emotional/psychological and cognitive functioning are the most pertinent areas of functional status for evaluating QoL [10]. General health perceptions integrate the earlier dimensions, but are more than a mere summary of them. When forming an ultimate judgment or rating of their health, people take all elements that are applicable to their personal context into account (not just those that have been identified in the model), including the relative weighting or importance of each [9]. Overall QoL is based on all of the earlier components, but also incorporates happiness and satisfaction with life, which are very much shaped by the person's values, preferences and circumstances [9].

Quality of Life Measurement

As explained earlier, QoL is an individual's or group's perceived health [5], and the patient's subjective judgment should be the gold-standard. The measurement of QoL thus involves asking patients to rate their own impression of QoL. Such a questionnaire is termed a "QoL instrument". Numerous instruments have been developed to date, aimed at

assessing different QoL dimensions. There are instruments that concentrate on one dimension, with some instruments focusing on symptoms, some focusing on an area of functional status and so on. However, given that QoL is a multidimensional construct, instruments that only explore one dimension of QoL cannot be conceptually considered true or comprehensive QoL instruments. For example, the Low Anterior Resection Syndrome Score (LARS score) is a five-item scoring system for assessing bowel function after sphincter-preserving rectal cancer treatment [11]. Its scoring is designed to reflect the impact of bowel dysfunction symptoms on overall QoL, but because its scope is limited to bowel dysfunction symptoms, the LARS score does not conceptually qualify as a QoL instrument.

QoL instruments are often classified as generic or disease-specific. Generic QoL instruments are designed for evaluating the combined effects of all health problems that the patient endures, whereas disease-specific instruments are designed for examining the effects of one particular condition or a similar group of conditions. Therefore, disease-specific instruments are more relevant and sensitive to the condition of interest, but generic instruments are more sensitive to comorbidities, and enable comparison of QoL between different condition groups. Depending on the purpose and context of QoL measurement, one type of instrument may be more suitable than the other.

Some of the most commonly used QoL instruments in RC are summarized in Table 23.1. All of these instruments are multidimensional, patient self-administered, and have been validated according to robust psychometric criteria.

QoL instruments allow standardized quantification of QoL that can readily support treatment decision-making, evaluation and follow-up, in both clinical research and routine practice contexts. Apart from established QoL instruments, qualitative methods are also used to assess QoL at times, and could elicit information that is not captured quantitatively. However, qualitative methods are more difficult to standardize, and the interpretation and application of such results are more complex and laborious. Qualitative methods are hence not as practical and sustainable as quantitative QoL instruments in measuring QoL.

Response Shift Phenomenon

Most clinicians have probably encountered patients who state that they appreciate life even more after surviving a cancer diagnosis. In general, patients who experience life-threatening diseases often change their internal benchmark and reconceptualize "good QoL" over the disease trajectory to accommodate their illnesses [30, 31]. Furthermore, during the course of RC, many patients adapt to their new situation, and learn how to cope with pain, fatigue, bowel-, urinary- and sexual dysfunction and so forth. Consequently, reports of QoL improving in RC patients over time to a level even superior to baseline, and reports of RC patients having better QoL scores than a comparable group of the general population, are not uncommon. On the contrary, some patients may find a relatively stable situation (by objective standards) increasingly distressing, especially if an expected improvement does not occur. Thus, the patient's rating of QoL may change over time even though no objective change has been observed. This phenomenon is referred to as "response shift". Response shift should be taken into consideration in longitudinal studies with a follow-up period of several years, and when comparing QoL of RC patients with the general population [32].

Interpretation of Quality of Life Results

Changes in QoL scores over time and differences in QoL scores between groups can be difficult to interpret. What does, say, an 11-point difference between two groups, or a 7-point improvement in a patient or a group actually mean? Do these numbers indicate a trivial, small, moderate or large difference or improvement? Due to the fact that a statistically significant difference does not necessarily imply that the difference is also of any clinical importance, it is crucial to define what size difference (the minimum difference) is considered clinically relevant. In clinical trials, this should be done a priori.

Table 23.1 Commonly administered QoL instruments in rectal cancer

Instrument	Type/ specificity	Items	Domains/(sub)scales/dimensions	Scoring	Comments
RAND-36/short-form 36 (SF-36)[12–15] A shorter form, consisting of a subset of questions, is also available (SF-12)[16, 17] Latest version: version 2 (SF-36v2)	Generic	36	Physical functioning Role-physical Bodily pain General health Vitality Social functioning Role-emotional Mental health Health change over past year (reviewed separately from the above domains)	3, 5 and 6-point Likert scale; item score 1–6. Domain score = sum of item scores transformed into 0–100; norm-based scoring (scored in relation to the general population) is also possible (mean 50, standard deviation 10); 2 standardized summary scores can be calculated (physical component summary and mental health component summary). No single total score. Higher score = better QoL. Health change over past year is a single item that is analyzed when it is of interest.	Most extensively used QoL instrument worldwide. Can facilitate comparison of QoL with the general population in a wide range of countries. Can facilitate comparison of QoL with a wide range of other disease populations. More sensitive to comorbidities, but less relevant and sensitive to rectal cancer than cancer- and colorectal cancer-specific instruments. Interpretation of multiple domains may be complicated.
EuroQol-5D (EQ-5D) [18–20] Latest version: EQ-5D-5 L	Generic	6	Mobility Self-care Usual activities Pain/discomfort Anxiety/depression Self-rated health (reviewed separately from the above dimensions)	5-point Likert scale; item number 1 (no problems) to 5 (extreme problems). Only 1 item per dimension, and dimension level is the 1-digit item number selected; the digits for the 5 dimensions can be combined to form a 5-digit number profiling the person's health state (the numerals 1–5 have no arithmetic properties and is not a score but a description of the person's health). Self-rated health is recorded on a 20 cm, vertical visual analogue scale with the top endpoint labeled "the best health you can imagine" and the bottom endpoint labeled "the worse health you can imagine", corresponding to the score range 0–100; higher score = better health.	Very succinct, and is thus quick and easy to administer. Can facilitate comparison of QoL with the general population. Can facilitate comparison of QoL with other disease populations. Can facilitate calculation of quality-adjusted life years (QALYs) for economic appraisal of interventions. More sensitive to comorbidities, but less relevant and sensitive to rectal cancer than cancer- and colorectal cancer-specific instruments. Lack of arithmetic properties of dimension level may render interpretation and comparison difficult.

(continued)

Table 23.1 (continued)

Instrument	Type/ specificity	Items	Domains/(sub)scales/dimensions	Scoring	Comments
European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core (EORTC QLQ-C30) [21, 22] Latest version: version 3.0	Cancer-specific	30	Global health status/QoL **Functional scales**: Physical functioning Role functioning Emotional functioning Cognitive functioning Social functioning **Symptom scales**: Fatigue Nausea and vomiting Pain Dyspnea Insomnia Appetite loss Constipation Diarrhea Financial difficulties	4 and 7-point Likert scale; item score 1–7. Scale score = mean of item scores transformed into 0–100. No single total score. Higher score on functional/global health scale = better QoL; higher score on symptom scale = worse QoL.	Extensively used QoL instrument in cancer. Can facilitate comparison of QoL with the general population. Can facilitate comparison of QoL with other cancer populations. Less relevant and sensitive to rectal cancer than colorectal cancer-specific instruments. Because the instrument targets cancer, conceptually, it should not be sensitive to non-cancer comorbidities. Interpretation of numerous scales is complicated.

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal Module (EORTC QLQ-CR38/CR29) [23, 24] Latest version: EORTC QLQ-CR29 (CR38 is the older version)	Colorectal cancer-specific	29 (on its own) or 59 (with EORTC QLQ-C30) for those with a stoma 28 (on its own) or 58 (with EORTC QLQ-C30) for those without a stoma	EORTC QLQ-C30 scales plus **Functional scales**: Body image Anxiety Weight Sexual interest (men) Sexual interest (women) **Symptom scales**: Urinary frequency Blood and mucus in stool Stool frequency[a] Urinary incontinence Dysuria Abdominal pain Buttock pain Bloating Dry mouth Hair loss Taste Flatulence[a] Fecal incontinence[a] Sore skin[a] Embarrassment[a] Stoma care problems Impotence Dyspareunia [a]Scale is scored separately for stoma and non-stoma patients	4-point Likert scale; 1 (not at all) to 4 (very much). Scales scored in the same fashion as EORTC QLQ-C30.	More relevant and sensitive to rectal cancer than generic and cancer-specific instruments. Should always be used with EORTC QLQ-C30 (stipulated by its authors), and as a result may be somewhat lengthy and time-consuming to complete. Because the instrument targets colorectal cancer, conceptually, it (this refers to EORTC QLQ-CR29 alone, and not EORTC QLQ-C30) should not be sensitive to comorbidities or facilitate comparison of QoL with non-colorectal cancer populations. Interpretation of numerous scales is complicated.
Functional Assessment of Cancer Therapy – General (FACT-G) [25, 26] Latest version: version 4	Cancer-specific	27	Physical well-being Social/family well-being Emotional well-being Functional well-being	5-point Likert scale; item score 0 (not at all) to 4 (very much). Subscale score = sum of item scores transformed into 0–24 for emotional well-being and 0–28 for all other subscales. Single total score (0–108) = sum of all 4 subscale scores. Norm-based scoring is also possible. Higher score = better QoL.	Extensively used QoL instrument in cancer. Can facilitate comparison of QoL with the general population. Can facilitate comparison of QoL with other cancer populations. The single total score is easy for interpretation and comparison. Less relevant and sensitive to rectal cancer than colorectal cancer-specific instruments. Because the instrument targets cancer, conceptually, it should not be sensitive to non-cancer comorbidities.

(continued)

Table 23.1 (continued)

Instrument	Type/ specificity	Items	Domains/(sub)scales/dimensions	Scoring	Comments
Functional Assessment of Cancer Therapy – Colorectal (FACT-C) [27, 28] Latest version: version 4	Colorectal cancer-specific	9 (on its own) or 36 (with FACT-G)	FACT-G subscales plus an additional colorectal cancer subscale	Response scale and item scores are the same as FACT-G. Subscales scored in the same fashion as FACT-G, with the additional colorectal cancer subscale score transformed into 0–28 (the 2 ostomy items in the subscale are not currently scored). FACT-C Trial Outcome Index (0–84) = sum of physical well-being, functional well-being and colorectal cancer subscales scores. FACT-C total score (0–136) = sum of all 5 subscale scores.	More relevant and sensitive to rectal cancer than generic and cancer-specific instruments. The single Trial Outcome Index and total score are easy for interpretation and comparison. Should always be used with FACT-G (stipulated by its authors). Because the instrument targets colorectal cancer, conceptually, it (this refers to FACT-C alone, and not FACT-G) should not be sensitive to comorbidities or facilitate comparison of QoL with non-colorectal cancer populations. The ostomy items are not scored and hence difficult to interpret.
Rotterdam Symptom Checklist (RSCL) [29]	Cancer-specific	39	Physical symptom distress level Psychological distress level Activity level impairment Overall valuation of life	4 and 7-point Likert scale; item score 1–7. Subscale score = sum of item scores transformed into 0–100. No single total score. Higher score = worse QoL, except for the activity scale, where higher score = better QoL.	Can facilitate comparison of QoL with other cancer populations. Less relevant and sensitive to rectal cancer than colorectal cancer-specific instruments. Because the instrument targets cancer, conceptually, it should not be sensitive to non-cancer comorbidities. Not as commonly used as some other cancer-specific instruments like EORTC QLQ-C30 and FACT-G. Consequently, although it can facilitate comparison of QoL with the general population, the reference values are not as well established.

Some investigators have examined and dealt with this issue by measuring the patient's perceived extent of change using a "subjective significance questionnaire", and ascertaining the corresponding difference in EORTC QLQ-C30 scores [33]. Guidelines have been published accordingly in order to support the interpretation of EORTC QLQ-C30 results [34]. Nonetheless, for many QoL instruments, no consensus has been reached regarding this issue, and a clinically relevant difference has not been determined yet. Therefore, no specific guidelines are presented here. Instead, clinicians and researchers working with a specific QoL instrument are encouraged to search the literature for the most up to date evidence within this field in order to base their sample size calculation, analysis and interpretation of results on the most recent knowledge.

Population-based normative or reference values can be useful when interpreting QoL results. These values represent the QoL level of the general population. Thus, reference values assist in the interpretation of QoL data in clinical cancer trials by providing estimates of the QoL level one would expect for a group of patients, had they not been sick. Furthermore, reference values can offer further information regarding the distribution of scores for each scale, and thereby facilitate sample size calculations. Given that it is well documented that QoL is influenced by age and gender, reference values should be age- and gender stratified [35]. In studies where QoL is compared between patients grouped by gender or age, reference values can help to clarify whether differences observed are related to the disease or simply reflect unspecific differences normally found in the general population.

Reference values have been published for a number of QoL instruments (please see the "Comments" column in Table 23.1).

Quality of Life After Rectal Cancer Surgery

During the past decades, numerous studies have shown that essentially all QoL dimensions are affected during the first year after surgery compared with general population norms, with the greatest differences observed at the time of discharge from hospital. Six months postoperatively, global QoL and pain approximate norm reference, but patients still fare worse in physical-, role- and social functioning, as well as being more affected by symptoms and problems like fatigue, dyspnea, insomnia, constipation, diarrhea and financial difficulties [36–38]. However, in general, descriptive cross-sectional and longitudinal studies among RC survivors have concluded that long-term overall QoL after treatment is good [36, 39, 40].

Nevertheless, a few problems persist to be common and bothersome for many years after the initial treatment for RC, affecting several dimensions of QoL. Bowel-, urinary- and sexual dysfunction are issues that continue to trouble RC patients for some years after the initial treatment [41]. Therefore, these issues are described in further detail below.

Factors known to influence the prevalence and severity of bowel-, urinary- and sexual dysfunction are age, gender, tumor level and stage, type of surgery and neoadjuvant therapy [42–49].

Bowel Dysfunction

Recent studies have reported that 50–90 % of RC patients undergoing the sphincter-preserving surgical procedure low anterior resection (LAR) suffer from at least some degree of bowel dysfunction postoperatively [50, 51]. Many patients suffer from a range of bowel dysfunction symptoms including fecal incontinence, urgency, frequent bowel movements and clustering, which are collectively referred to as (low) anterior resection syndrome (LARS or ARS) [11, 52]. The risk of bowel dysfunction mainly depends on tumor level and height of anastomosis [53].

In a recent study of LARS using the aforementioned LARS score, the authors found that out of 183 patients who underwent sphincter-preserving resection, 29 % had "no LARS", 25 % "minor LARS" and 46 % "major LARS" at 12 months after surgery [54]. They also found that the syndrome had a considerable impact on the patient's

everyday life, and was associated with impairment in several QoL dimensions. Studies have shown that bowel dysfunction undermines mental health, social- and physical functioning, and that fecal incontinence is associated with poorer levels of lifestyle, coping, depression and embarrassment [41, 55, 56]. In a cross-sectional study of 81 RC patients with no stoma, bowel dysfunction was shown to be negatively associated with global QoL, physical-, role- and social functioning [57]. In two recent studies, one being a follow-up study of 260 non-stoma patients and the other a cross-sectional study of 796 non-stoma patients, global QoL, fatigue, insomnia, physical-, role-, emotional- and social functioning were shown to be strongly associated with LARS [54, 58]. Moreover, the latest follow-up of patients in the famous Dutch total mesorectal excision (TME) trial using the LARS score revealed that 46 % of the surviving cohort experienced "major LARS" even more than 14 years after treatment, which was also associated with poorer QoL in a number of dimensions [59].

Even though LARS is undoubtedly highly prevalent, it has previously been poorly defined and hence inconsistently measured and reported. Consequently, prevalence estimates of LARS vary significantly between studies. Novel tools that have been rigorously developed and validated for international use, like the LARS score [11, 60] and the Memorial Sloan-Kettering Cancer Center (MSKCC) Bowel Function Instrument [61], enable standardized assessment of LARS across centers and borders, and will hopefully facilitate valid comparisons of results and meta-analysis on the subject in the future.

Patients with a permanent stoma after RC surgery also suffer from problems related to bowel and/or stoma dysfunction. Stoma formation through the rectus muscle is complicated by parastomal herniation in up to 50 % of cases, and this is a distressing problem that reduces the QoL of stoma patients [62, 63]. Leakage of stools, need for frequent bag-changing, stoma care-related problems, sore skin, odor and noise from the stoma, embarrassment and travel challenges are issues commonly reported by patients, affecting several dimensions of QoL [38, 64–66].

Urinary Dysfunction

Urinary dysfunction is common after RC treatment and consists of urinary urgency and incontinence, increased frequency of urination, incomplete bladder emptying and urinary retention [41, 45]. Urinary dysfunction has been demonstrated to be associated with worse social functioning and more pain [41].

In the Dutch TME trial, urinary dysfunction was investigated in 785 patients 5 years after surgery. Long-term incontinence was reported by 38 % of patients, of whom 72 % had a normal preoperative function. Long-term difficulty in bladder emptying was reported by 31 % of patients, of whom 65 % had a normal preoperative function. The authors concluded that urinary dysfunction after RC treatment is mainly caused by autonomic nerve damage during surgery, and found that preoperative radiotherapy was not associated with urinary dysfunction [45, 46], which is similar to the conclusion of a recent systematic review and meta-analysis on the topic [67].

Sexual Dysfunction

Sexuality is a key part of adult QoL. Even though sexual activity declines with age, and the median age of RC patients is around 70 years, the majority of RC patients are sexually active prior to the treatment of their disease [68]. Sexual problems after surgery for RC are common. They are multifactorial, inadequately discussed, and often untreated. Nevertheless, the impact of RC treatment on sexual function is poorly investigated, and the majority of existing studies are limited by low response rates, especially among women, indicating that the issue is still taboo [40, 67].

Specific sexual problems in women are dyspareunia, reduced libido, arousal, lubrication and orgasm. Whereas in men, these are impotence, decreased libido, orgasm and ejaculation [56, 57]. The reported rates of sexual dysfunction vary significantly, ranging from 23 to 69 % in men, and from 19 to 62 % in women [69]. In a study involving 180 patients undergoing

curative RC surgery, 29 % of women and 45 % of men reported that "surgery made their sex lives worse" [70].

An unusually high response rate (>75 %) was obtained in the Dutch TME trial. Only patients who were sexually active before RC treatment (79 % of male patients and 52 % of female patients) were evaluated ($n=757$). Results showed that general sexual dysfunction, erectile dysfunction and ejaculation problems were reported by 76, 80 and 72 % of male patients, respectively. In female patients, increase in general sexual dysfunction, dyspareunia and vaginal dryness were reported by 62, 59 and 57 %, respectively. Two years after treatment, 29 % of men and 18 % of women were no longer sexually active [68].

Another study of 457 RC patients revealed that male RC survivors had more problems with erectile function (54 %) than males in the general population (27 %). Furthermore, 68 % of male RC survivors reported ejaculation problems. Lubrication problems and dyspareunia were more common in female RC survivors (35 and 30 %, respectively) than females in the general population (5 and 0 %, respectively). Male RC survivors scored lower on the EORTC QLQ-CR38 sexual functioning scale compared with the general population. However, scores on the QLQ-CR38 sexual enjoyment scale were similar between the two groups. Female RC survivors reported worse sexual functioning as well as less sexual enjoyment than the general population. For both genders, the differences in sexual functioning and/or sexual enjoyment identified were clinically meaningful [43].

Sexual dysfunction is significantly more severe in men, and men feel more distressed by it than women. Sexual function has been shown to be impaired in all age groups, but younger patients have a more severe impairment of sexuality, which leads to profound emotional symptoms. Strain due to impaired sexuality is significantly higher for patients aged ≤69 years compared with older patients [48, 71].

Although many studies have documented that a large proportion of RC patients experience sexual dysfunction after their treatment, it is still not entirely clear how to define the presence of sexual dysfunction, sexual problems and sexual disorders, and thus estimates vary across studies. Furthermore, studies within this taboo field are compromised by low response rates, especially among women. Hopefully, the increasing attention on these very important matters will lead to more high-quality research in the future.

Quality of Life with or Without a Permanent Colostomy

The presence of a permanent stoma has historically been viewed as a factor that reduces QoL. Therefore, it is thought that preservation of bowel continuity would be superior to the formation of a permanent stoma whenever the oncological outcome is deemed equivalent [51]. With the introduction of stapling devices and improved surgical techniques, permanent colostomy rates have decreased, and anastomoses are now performed at very low levels.

As discussed earlier, it is evident that a large proportion of non-stoma patients suffer from severe bowel dysfunction, which affects their QoL substantially [54, 58]. In addition, stoma care has improved considerably during the past decades, both with respect to available products and to the information and guidance provided by specialist nurses. When taking all of these factors into account, the superiority of sphincter preservation does not appear as definite as once believed. Thus, many studies have investigated the QoL of RC patients after LAR versus abdominoperineal resection (APR).

A Dutch study published in 2014 examined the physical and mental consequences of a stoma among 1019 RC survivors 1–10 years after diagnosis. They found that stoma patients reported statistically significant lower global health status/QoL, physical-, role- and social functioning, but fewer problems with constipation and diarrhea compared with those without a stoma. All differences were of small clinical relevance [72].

In a Cochrane review updated in 2012, the authors concluded that there is no clear difference in global QoL with or without a permanent stoma

[73]. The results of 35 studies, all non-randomized and representing 5,127 participants, were analyzed in the review. In 14 out of the 35 studies, the authors found that patients undergoing APR/Hartmann's operation did not demonstrate worse QoL than patients undergoing LAR. The remaining studies identified some differences, but these were not consistently in favor of non-stoma patients. Amongst the included studies, there was a clear tendency towards stoma patients reporting significantly more sexual problems, but less diarrhoea and constipation compared with non-stoma patients. Therefore, no firm conclusion was drawn, but the authors stated that "the included studies challenge the assumption that anterior resection patients fare better" [73].

Similarly, in a meta-analysis of 1,443 patients from 11 studies, no difference in global QoL was found. Nevertheless, stoma patients showed superior future perspective, cognitive- and emotional functioning scores than non-stoma patients, while non-stoma patients tended to score more positively on vitality, sexual- and physical function [74].

Therefore, the question of whether LAR or APR is superior with regards to QoL cannot be answered unequivocally, since different dimensions of QoL are affected, and it is not conceptually or philosophically sound to directly compare different dimensions (for example, which is worse: impaired cognitive or physical function?). Rather than searching for a simple yes or no answer to the question, emphasis should be placed on describing the different dimensions of QoL affected with and without a permanent stoma. This will lead to more comprehensive preoperative information for patients, which would be of particular interest to those for whom either a LAR or an APR is a feasible and reasonable option. The everyday life of one patient is different from another, and hence patients may have different preferences. Consequently, no single procedure fits all. Thorough information about how QoL is affected differently with and without a stoma is essential in facilitating joint decision-making between the clinician and the patient regarding what the best solution is for the individual patient.

Therefore, the formation of a stoma should not always be deemed a failure of surgical treatment, and high APR rates do not necessarily reflect suboptimal surgical quality, especially given that APR rates do not correlate well with other indicators of rectal surgery quality at the hospital level [75]. Instead, relevant measures of QoL, with particular attention to bowel-, sexual- and urinary problems, should be used in combination with other established indicators such as mortality and recurrence rates, for the evaluation of surgical quality.

Impact of Laparoscopic Surgery on Quality of Life

As QoL has become a standard endpoint in the evaluation of relatively new or emerging treatments, there has been an increasing interest in how QoL compares after laparoscopic versus open RC surgery. Nevertheless, the evidence is scarce and conflicting. Some studies exploring short-term QoL outcome have found differences in favor of laparoscopic surgery, reporting better body image, less pain and superior global QoL as early as 1 week after the operation [76]. At 3 months, laparoscopically operated patients seem to experience less sleep disturbance, fatigue, physical and gastrointestinal symptoms [77]. Better scores in general health, physical- and social functioning have also been found at 1 year [78, 79]. However, a recent randomized multicenter trial could not confirm these results, as the study did not find any differences in QoL at 4 weeks, 6 and 12 months after surgery [64].

In terms of urinary- and sexual function, there is no evidence that laparoscopic surgery causes less harm to urinary function than open surgery. The results for male sexual function are contradictory [80, 81]. Data concerning female sexual function are very limited due to low response rates in most of the studies [81].

Robotic-assisted laparoscopic operations have recently been introduced in the surgical treatment of RC. So far, a few non-randomized studies have indicated that robotic surgery is associated with an earlier recovery of normal voiding

and sexual function compared with conventional laparoscopic surgery [82–84]. A currently running randomized trial (the ROLARR study) will further clarify and provide more definitive evidence regarding whether robotic surgery leads to superior QoL than laparoscopic surgery [85].

The Impact of Neoadjuvant Therapy on Quality of Life

A large proportion of patients undergo neoadjuvant therapy in addition to surgery, and its effects on QoL have been investigated recently in several studies.

In a follow-up study of QoL after RC surgery with or without preoperative radiotherapy, the authors analyzed data from 990 patients and concluded that short-term preoperative radiotherapy leads to more sexual dysfunction, slower recovery of bowel function, and impaired daily activity postoperatively. However, these effects do not have a serious impact on QoL [42].

The Dutch TME trial group has published studies focusing on the three major areas of post-treatment dysfunction, namely urinary-, bowel- and sexual dysfunction. Patients were randomized to TME surgery with or without preoperative short-course radiotherapy, and the authors concluded that preoperative radiotherapy adversely affects bowel- and sexual function [44, 68], but not urinary function [46].

In 2013, a systematic review and meta-analysis of the effect of preoperative radio(chemo)therapy on long-term functional outcome in RC patients operated with TME technique was published. Study designs, evaluation parameters and clinical characteristics of the patients varied considerably among the identified studies. Therefore, comparison of these studies was limited, and only a few studies were eligible for the purpose of meta-analysis. The authors found that the quality of studies on long-term functional outcome was low. However, the meta-analysis showed that preoperative radio(chemo)therapy negatively affects anorectal function after TME, while no statistically significant effect of preoperative radio(chemo) therapy on erectile function was found. The effect of preoperative radio(chemo)therapy on urinary continence showed no statistical significant difference either [67].

A Cochrane review published in 2013 included five trials in the meta-analysis. The focus of the review was on traditional "hard" outcomes, like recurrence rates, survival, pathological response, morbidity and so on, but the authors also stated that the very limited data available from the included studies precluded a meta-analysis of QoL-related parameters. Thus, they concluded that "the effects of preoperative chemo/radiotherapy on functional outcome and quality of life are incompletely understood and should be addressed in future trials" [86].

Quality of Life After Complex Rectal Surgery for Primary Advanced Rectal Cancer and Locally Recurrent Rectal Cancer

Advances in RC surgical techniques have made it possible to perform complex, exenterative resections beyond the TME planes in patients with primary advanced or locally recurrent RC. Such surgery may include bladder reconstruction, sacrectomy and perineal reconstruction. Due to the complex and extensive nature of the treatment, postoperative morbidity is high (15–68 %) [87], and the impact on QoL would be even greater than standard surgery, as normal anatomy and bodily function are more disrupted. However, only a few studies have been published on how such complex surgery affects QoL, with various methodological issues including retrospective design, small sample size and a high amount of missing data. The studies have mainly examined patients who are disease-free after being treated with potentially curative resection [88].

Overall, QoL seems to be worst (lowest level of functioning and highest degree of symptoms) preoperatively and improves after surgery [89]. Results from two studies evaluating QoL in the first 2 years after surgery showed that improvement mostly occured during the first year [89, 90]. One year after surgery, QoL of patients treated with exenterative surgery was comparable

to that of patients treated with standard surgery for primary non-advanced RC. On the other hand, lower levels of physical- and emotional role functioning were found compared with the general population, indicating that these patients, despite improving from preoperative levels, continue to experience limitations in their physical and psychological health.

Longer-term QoL after complex surgery for RC has only been studied in cross-sectional settings and inconsistent results have been reported [91, 92]. One study found that the QoL in this group of patients was poorer in terms of global QoL, body image, fatigue, pain, defecation problems, role-, physical-, and social functioning than in patients treated with standard surgery for primary non-advanced RC [92]. In contrast, another study found that QoL was similar between the two groups [91]. In a study exploring QoL using qualitative interviews, patients treated with complex surgery described a negative impact on daily activity. The interviews also revealed that while patients had a highly focused desire to seek wellness and cure, there was some misunderstanding of the therapeutic options and treatment morbidity [93].

Patients treated for local recurrence seem to have worse QoL in relation to future perspective, body image, physical- and social functioning, as well as a higher degree of pain compared with patients treated for non-advanced and primary advanced RC. However, a comparison between these patients categorized as three discrete groups (as opposed to lumping primary advanced and locally recurrent RC into one group) has only been conducted in one study [38].

There is little information regarding sexual activity, enjoyment and problems following complex surgery due to very low response rates in most of the studies. Nonetheless, based on the available literature, it appears that sexual functioning is worse after surgery compared with the patient's preoperative activity [38, 94]. In a study of sexual function after vaginal reconstruction with a vertical rectus abdominis myocutaneous flap, half of the women were sexually active before surgery. Although the desire for sexual contact was unchanged after surgery, only 14 % reported sexual activity [94]. In a cross-sectional study, male patients treated for local recurrence reported more problems with erectile function and feeling less masculine than patients treated for non-advanced and primary advanced RC [38]. Despite a high prevalence of sexual dysfunction, few patients reported the use of aids, suggesting that patients may have insufficient awareness of the management of sexual dysfunction [38].

Even though the evidence regarding QoL after complex, exenterative surgery for RC is scarce, it is clear that various dimensions of QoL are impaired for variable periods of time. As outlined in the Beyond TME consensus statement [95], more knowledge of QoL in this area is needed to examine whether subgroups of patients are more affected by the treatment than others. Future efforts should be directed towards prospective data collection and must include patients undergoing both curative and non-curative surgery.

Conclusion

The impact of RC and its treatment on QoL is diverse. The exact effects depend on several factors, including the dimension of QoL concerned, tumor characteristics, the treatment involved, the measurement method and timing, and of course, the patient him or herself. Even in similar circumstances, the values, standards, expectations, adaptation and coping abilities, as well as the resultant perception of one patient differ from another, and could also differ over time within the same patient. Consequently, generalizations and comparisons of QoL, both cross-sectional and longitudinal, need to be interpreted with caution. Despite that there is no "average" or "typical" individual patient in reality, the evidence on overall QoL trends in RC presented in this chapter can hopefully enhance the clinician's understanding of the topic, and further strengthen patient information, communication and shared decision-making. There does appear to be a measurable correlation between QoL and some objective markers of oncological status [96–101], but more research is needed to better guide the clinician in weighing, substituting and

combining QoL with other clinical measures in choosing the most appropriate management for the patient and assessing outcomes. Finally, more work is also required in further developing and consolidating the prevention and management of QoL issues, in order to optimize both the length and quality of the patient's life.

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Palliative Options in Patients with Stage 4 Rectal Cancer

24

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Abstract

Twenty to 30% of patients with rectal cancer will present with unresectable disease. Although chemotherapy is the primary treatment modality for patients with asymptomatic unresectable rectal cancer, half of all these patients may require a palliative procedure at some point due to obstruction, perforation, bleeding and/or pain. The surgeon is critical to the multidisciplinary team and will provide guidance as to the appropriate treatment strategy. Thus, it is imperative that a surgeon who commonly treats these patients to have knowledge of all treatment modalities available. The aim of this chapter is enhance the reader's knowlege of palliative strategies for patients with stage 4 rectal cancer.

Keywords

Rectal cancer • Unresectable rectal cancer • Palliative resection • Stage 4 rectal cancer • Bowel obstruction • Bowel perforation • Rectal stent • Self-expanding metallic stents (SEMS) • Endoscopic laser therapy • Nd:YAG

Introduction

Despite recent declines in the incidence of newly-diagnosed rectal cancer, 20–30 % of patients will present with unresectable disease [1]. Additionally, half of all rectal cancer patients may require a palliative procedure due to advanced disease or recurrence at some point during their disease process [2, 3]. Furthermore, while chemotherapy is the standard of care in those with stage 4 rectal cancer with no symptoms [4, 5], operative or endoscopic intervention is often indicated in those who develop

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obstruction, perforation, bleeding and/or pain [1, 6]. Therefore it is in the best interest of a surgeon who commonly treats these patients to be familiar with the approaches to care in these complex patients who are often in the last months of their lives.

The primary goal of palliative treatment is to improve symptoms from both the primary tumor and its sequelae, and although adhering to routine oncologic principles is preferred, it may not be feasible. Palliative interventions are intended to improve the patient's quality of life with little impact on survival [7]. Success is achieved by alleviating symptoms without the development of new symptoms or hastening death. Palliative therapies include resection or diversion of fecal stream, endoscopic-based interventions, or adjuvant therapies such as chemotherapy and radiation therapy [3, 8].

Sites of both the primary tumor and metastasis are highly variable making individualized care of patients with unresectable rectal cancer essential. Moreover, a multidisciplinary approach is recommended to determine optimal timing of procedures, chemotherapy and/or radiation therapy [9]. The surgeon is a vital member of this multidisciplinary team. It is the surgeon who will provide information on the operative and nonoperative approaches to the problems facing the patient. With this insight the patient can choose their best option by carefully balancing the risk/benefit ratio with personal preferences [3]. The goal of this chapter is to enhance the reader's armamentarium for the management of patients with stage 4 rectal cancer. Unfortunately, there is a paucity of prospective randomized controlled trials evaluating the optimal treatment for symptomatic patients with stage 4 disease. Thus, the majority of recommendations are based on expert opinion from single institution studies.

Evaluation

Appropriate staging of rectal cancer is critical prior to proceeding with management as optimal treatment is dependent on nodal status and the presence or absence of distant disease. Colonoscopy should be performed to evaluate the entire colon and rectum for synchronous lesions or other pathology. Rigid proctoscopy is performed to localize the lesion and to confirm its location in the rectum and its relationship to the three rectal folds [10, 11]. A complete history and physical examination with assessment of performance status and tumor-related symptoms should be evaluated. A digital rectal exam performed by an experienced surgeon is critical to assess the relationship between the tumor and critical pelvic structures such as the anorectal ring, the prostate or vagina, and the coccyx or sacrum. Appropriate laboratory studies including a complete blood count (CBC), liver function tests (LFT), and carcinoembryonic antigen (CEA) are obtained. Computed tomography (CT) of the chest, abdomen and pelvis with oral and intravenous contrast must be obtained to evaluate for presence of metastasis. This is used in conjunction with endoscopic ultrasound (EUS) or magnetic resonance imaging (MRI) of the pelvis, which determines tumor depth and/or invasion to adjacent structures and lymph node involvement [2, 12].

EUS and MRI have been found to be very similar in their ability to stage rectal cancers. A meta-analysis of 90 studies evaluating EUS, CT and MRI in staging rectal cancer demonstrate similar sensitivity of 94 % for EUS and MRI for muscularis invasion but significant differences in sensitivities with 86 and 69 % respectively ($P=0.02$). Nodal staging demonstrates equally low sensitivity and specificity for EUS and MRI with 67 and 78 %, and 66 and 76 % respectively. Although the authors conclude that EUS is more accurate for rectal cancer staging, this technology is limited by tumors located 8–10 cm from the anal verge, stenotic tumors, and the modality being operator-dependent [13]. MRI has been found to be superior to EUS in evaluating circumferential resection margin [14–16], and both MRI and CT are required to evaluate more centrally-located lymph nodes (iliac, mesenteric or retroperitoneal) [13]. Thus, EUS is utilized in the vast majority of rectal cancers for local staging with MRI used as an important adjunct [12].

The role of fluorodeoxyglucose-positron emission tomography (FDG-PET) is somewhat

Table 24.1 Contraindications to surgical intervention

Contraindications to R0 Resection
Tumors involving the sciatic nerve
Tumors encasing the common and/or external iliac arteries
Tumors obstructing the bilateral ureters
Tumors causing extensive fixation to the lateral pelvic side wall
Multiple peritoneal metastasis
Metastasis involving the vital structures
Poor performance status

controversial. There is very little to no role for this imaging modality in the workup of primary rectal cancer. However, it can be helpful in evaluating equivocal findings on CT or in patients unable to undergo intravenous contrasted studies [2, 12].

Resectability of a primary tumor is defined by complete resection of all disease with negative margins, the so-called R0 resection [17]. The most current National Comprehensive Cancer Network (NCCN) guidelines do not advise resection unless an R0 resection is intended [18, 19]. Contraindications to surgical intervention with curative intent include both anatomic and patient characteristics. Tumors involving the sciatic nerve, encasing the common and/or external iliac arteries, obstructing the bilateral ureters, and/or causing extensive fixation to the lateral pelvic side wall are not suitable for R0 resection. Multiple peritoneal metastasis and/or metastasis involving vital structures, and/or poor performance status are also contraindications to resection with curative intent [3, 20] (Table 24.1).

In those patients who are unable to undergo a R0 resection, close monitoring for symptoms that could be palliated by surgical, endoscopic-based, and/or multimodal adjuvant therapies should be performed [4]. Symptomatic patients with stage 4 rectal most commonly present with obstruction or change in bowel habits (20–40 %), bleeding (25–44 %), or pain (6–20 %) [21–23]. Again, it should be stressed that due to the variability in both patients and their tumors, treatment should be individualized and a multidisciplinary team approach is strongly advised.

Operative Intervention

In general, embarking on an operative intervention in a patient with stage 4 rectal cancer in an elective setting is meaningful only if the operative risk is low and the patient has a reasonable life expectancy (at least 2–6 months) [7, 21, 24–29]. In an emergent setting however, the question to be answered is what intervention to offer as an operation may be the only therapy to improve short-term survival [21, 30]. Potentially life-threatening complications include obstruction, perforation and bleeding. The American Society of Colon and Rectal Surgeons (ASCRS) identifies three goals of treatment in the emergent setting: (1) prevent the immediate negative impact of complication such as sepsis and death, (2) achieve tumor control, and (3) allow for the initiation of adjuvant or systemic therapy [4]. Interventions should be individualized based on presenting symptom or symptoms, and available imaging and therapeutic modalities.

Obstruction

Malignant bowel obstructions occur in 10–28 % of rectal cancer patients, and 30–40 % of these resolve with conservative measures such as nasogastric tube (NGT) decompression and bowel rest [7, 21, 23]. These conservative measures are widely-available, inexpensive, and stabilize the patient with low risk of bleeding and perforation from the intervention [31]. However, in patients with persistent or recurrent obstructive symptoms, a more aggressive therapy should be offered. While all operative approaches are palliative in this setting by definition, they can be broadly categorized into venting procedures and resectional procedures.

Venting procedures include gastrostomy tube placement and stoma placement to proximally divert the fecal stream. Venting gastrostomy tube placement, either placed endoscopically or surgically, for bowel decompression allows for discontinuation of an NGT, and potential discharge from the hospital to home or hospice [32, 33]. These should be considered in those patients who

have maximized their chemotherapy options, are in the most terminal stages of their disease, or in those who are medically frail from malnutrition and/or other comorbidities. Gastrostomy tube placement is associated with high success rates between 86 and 100 % [34], and immediate improvement in patient symptoms [35]. However, a recent retrospective review demonstrates high major procedural-associated complications (10.2 %), with the majority (59.3 %) of patients being maintained NPO despite percutaneous endoscopic gastrostomy (PEG) placement [36]. Additionally, it should be stressed that in those who undergo PEG tube placement, survival is not significantly improved with median survival of only 66–147 days [34].

A proximal fecal diversion is a great option for those patients who are both fit and willing to undergo an operative procedure. In these patients, the site of obstruction and extent of proximal distension often determines the best surgical option. Diverting fecal stream with a diverting stoma may be the only feasible option in obstructed patients with significant comorbidities or uncertainty of life expectancy, considerable tumor burden or carcinomatosis, or underlying fecal incontinence [1, 37, 38]. In patients with acute malignant obstruction, diverting stoma is the preferred surgical option as it has been demonstrated that patients who undergo emergent primary resection demonstrate worse overall survival when compared to those who underwent elective surgery [39].

While these diverting stomas can be palliative in the sense that they relieve the obstruction, it should always be considered that the stoma itself may have significant adverse effects on the patient's quality of life with leakage, prolapse or retraction causing limitations in quality of life [40]. One-third of patients develop complications from their stoma including the aforementioned complications as well as skin irritation, pain or partial necrosis [7, 41, 42] not to mention the short-term complications of the procedure itself such as wound infection or ileus [43]. If the decision is made to divert the fecal stream in an obstructed patient a sigmoid or transverse loop colostomy is typically fashioned [1, 44]. Despite placement of diverting stoma, many patients may continue to have pelvic pain due to tumor invasion and/or persistent rectal drainage or bleeding [1]. All of these symptoms worsen the patient's quality of life.

For these quality of life reasons, resection of the affected segment or a subtotal colectomy with or without reanastomosis (Hartmann procedure) should be considered in those patients presenting with obstruction who are able to tolerate lengthier procedures and who have resectable primary tumors. Historically, obstructions were managed with a three-stage approach in which a diverting colostomy was created during the first operation followed by resection and then reanastomosis during the second and third operations respectively [45]. This was due to patients being very ill with severe dehydration and malnourishment. Additionally, bowel mucosa is friable and patients often do not undergo adequate bowel preparation making reanastomosis undesirable. However, it was found that two-stage procedures were equally effective and associated with shorter hospital stays, and soon a two-stage approach consisting of a Hartmann procedure followed by reanastomosis was adopted. Some centers have now adopted a one-stage approach consisting of a subtotal colectomy with ileocolic anastomosis with equal mortality rates as a two-stage procedure [45].

A low anterior resection (LAR), an abdominoperineal resection (APR), or even pelvic exenteration may be indicated in those with advanced disease and significant symptoms such as severe tenesmus, incontinence, constipation or diarrhea, or intractable pain due to local invasion into nerves [7]. These procedures are less than ideal due to unnecessary risk in terminally ill patients but may be suitable for some patients with longer life expectancies. Tumor size and location in addition to patient factors such as body habitus and comorbidities dictate which procedure is most suitable. In a patient with poor anal function or in a patient who has undergone pelvic irradiation, a Hartmann procedure may be the preferred approach [3]. However, if the tumor involves the sphincter complex, an APR may be the procedure of choice [44]. Additional indications for extensive resection include colovaginal or colovesical fistulae, or tumors that have perforated and

are the source of pelvic sepsis [1, 20]. In general, a Hartmann procedure or LAR is preferred over APR for palliation due to decreased perineal wound complications and decreased pain [46].

A laparoscopic approach to diversion or resection may be used as it is associated with a shorter recovery including a faster return of bowel function and shorter hospital stay, and thus a shorter interval to initiating chemotherapy [3]. Additionally, a laparoscopic approach is associated with less pain and fewer postoperative complications making this approach in patients with limited life expectancy appealing [1, 7, 47]. However, a dilated colon may make performing a laparoscopic procedure technically very challenging and not worth the operative risk [1, 3]. Ultimately, the choice in operative approach should dictated by surgeon experience and comfort level.

Perforation

Bowel perforation is a life-threatening complication occurring in 2–9 % of colorectal cancer patients [48, 49]. The patient with stage 4 rectal cancer and bowel perforation is frequently ill and the challenge in this setting is primarily due to the patient's condition and the emergent nature. Perforation most often occurs near or at the site of the tumor, and occurs as a result of tumor necrosis or adjacent inflammation. Perforation occurring proximal to the site of the tumor is most commonly due to distal obstruction and proximal bowel dilation resulting in local ischemia and transmural necrosis [50].

Prior to pursuing an operative intervention patients and their families should be counseled and expectations of the operation should be managed. It is important in these situations that patients truly understand the implications of undergoing a surgical procedure including both the risks and benefits as well as potential outcomes [51]. The surgical procedure performed will be dependent on the site of perforation and whether intraabdominal sepsis is present. If the perforation occurs proximal to an obstructing tumor, resection of both the affected bowel segment and an oncologic resection should be performed. A perforation at the site of the tumor that is contained should be managed with resection of the involved structures en bloc. Free perforation with peritonitis requires resection of the involved segment and fecal diversion with a stoma [4]. A primary anastomosis may successfully be achieved in the emergency setting but is contraindicated in patients with fecal peritonitis. A staged procedure should be performed in this patient population, especially when in a patient who is requiring vasopressor support or who has major co-morbidities [52]. The goal in performing a staged procedure is to prevent anastomotic dehiscence as this is associated with worse overall survival and need for re-operation [53].

A recent study of 1,004 patients with bowel obstruction in the setting of stage 4 colon cancer was recently undertaken using the Surveillance, Epidemiology and End Results (SEER) – Medicare database. The authors found that median survival after obstruction was less than 3 months with 12.7 % of patients admitted to the hospital dying while inpatient. Moreover, the authors found that the overall ratio of days in the hospital to days out of the hospital did not differ between surgical and nonsurgical therapies (1:5), and surgical intervention was not associated with improved survival [26]. Furthermore, it is clear that patients with bowel perforation in the setting of colorectal cancer demonstrate high morbidity and mortality rates of 43–60 % and 5–40 %, respectively [54–57]. This is thought to be due to a result of both the underlying malignancy and preoperative state of the patient as well as the developing or ongoing sepsis [54]. Given these findings, it is critical that patients have a clear understanding of the risks and benefits of surgical intervention.

Bleeding

Bleeding due to the primary tumor occurs less frequently than obstruction. Patients typically present with chronic blood loss which does not require surgical intervention. However, in patients who present with acute massive blood loss, patients should be aggressively resuscitated and closely monitored in an intensive care setting

if unstable [58, 59]. Indications for surgery include persistent hemodynamic instability despite at least six units of blood products, failure of endoscopic techniques to halt bleeding, recurrent bleeding after initial stabilization or accompanied by shock or bleeding requiring greater than three units of blood products per day [60].

Small tumors that cause persistent bleeding and/or symptomatic anemia may be amenable to transanal excision (TAE) or transanal endoscopic microsurgery (TEM) [1, 61, 62]. Transanal procedures have been found to be safe procedures with low morbidity when compared to radical surgery [63–65]. These procedures offer a minimally invasive debulking while minimizing the complications associated with radical surgery, and should be offered to unfit or unwilling patients to more radical procedures [62]. The main limitation to a transanal approach is large obstructing tumors that are unable to be bypassed with a shorter rigid scope [66].

Palliative Resection

Traditionally, palliative resection was, and continues to be performed to prevent obstruction, bleeding and pain in asymptomatic or minimally symptomatic patients. However, it is not currently recommended that patients with asymptomatic tumors undergo routine resection, and systemic chemotherapy should be the primary treatment modality [4, 12]. Despite this, there continues to be a number of proponents for palliative resection in asymptomatic patients with more than two-thirds of patients who present with stage 4 colorectal cancer undergoing resection of the primary tumor according to a study based on the Surveillance, Epidemiology, and End Results (SEER) database [67]. Proposed advantages to palliative resection include improvement in quality of life, prevention of complications of the primary tumor such as obstruction, bleeding or pain as well as improvement in survival rates [8, 68]. Additionally, performing a palliative resection potentially avoids an emergent resection as it has been demonstrated that resection in an elective setting demonstrates a decrease in mortality when compared to resections in an emergent setting [44, 69–71].

Regardless of any proposed benefit, the resection of primary tumors on asymptomatic patients is not without potential risks. Morbidity rates from resections have been demonstrated to be as high as 23–48 % [72], and resections may actually worsen quality of life [30, 73] and lead to poorer survival rates [74]. Additionally, it has been argued that many patients will die from progression of systemic disease rather than the development of a primary tumor complication, and these patients need not undergo an invasive procedure [72, 73, 75]. In fact, a retrospective study by Patel et al. demonstrated that only 4.3 % of patients treated with neoadjuvant chemotherapy progress to complete obstruction and subsequent perforation [43]. In another study of patients undergoing chemotherapy for synchronous colorectal metastasis, only 7 % of patients required intervention for obstruction, perforation or bleeding [76]. Of most concern is that palliative resection delays the initiation of chemotherapy [67, 77]. It is clear that chemotherapy improves both quality of life and survival in patients with unresectable rectal cancer [78, 79]. Thus, interruption or postponement of this therapy to perform resection in an asymptomatic patient is currently not advised.

Despite the risks of resection, a number of retrospective studies have been performed evaluating palliative resection of the primary tumor. Cirocchi et al. recently performed a study for the Cochrane Collaboration evaluating survival in patients undergoing resection of an asymptomatic primary tumor versus chemotherapy. The authors evaluated seven retrospective studies summarized in Table 24.2 [80–86], and found no differences in overall survival and no significant reduction in risk of complication in the resection group [87]. In contrast, Stillwell et al. performed a meta-analysis of eight retrospective studies and found a significant survival benefit in patients undergoing resection of the primary tumor ($p < 0.001$), and a 7.3 times higher complication rate from the primary tumor in those treated with chemotherapy alone [88]. Recently,

Table 24.2 Palliative resection of primary tumor in patients with unresectable colorectal cancer

Study	Study period	Study design	Primary site	Metastatic sites	Resection (n)		Morbidity (%)	Overall survival (months)	Mean follow-up (months)	Conclusion
					Post resection chemotherapy (n, %)	Nonresection (n)				
Scoggins et al. [80]	1985–1997	Retrospective, single institution	Colon and rectum	Liver, lung, omentum, peritoneum	66 0 (0 %)	23	30.3 % Resection 8.7 % Nonresection	14.5 Resection 16.6 Nonresection (P = .59)	N/A	No survival advantage to resection
Tebbutt et al. [81]	1990–2000	Retrospective, single institution	Colon and rectum	Peritonal/ omental and non-peritoneal/ omental	280 0 (0 %)	82	19.3 % Resection 23.2 % Nonresection	14 Resection 8.2 Nonresection (P = .08)	30 Resection 19 Nonresection	Incidence of complications in nonresection group is acceptably low
Ruo et al. [82]	1996–1999	Retrospective, single institution	Colon and rectum	Liver, extrahepatic	127 0 (0 %)	103	20.5 % Resection 29 % Nonresection	16 Resection 9 Nonresection (P < 0.001)	N/A	Significant survival benefit in resected patients
Michel et al. [83]	1996–1999	Retrospective, single institution	Colon and rectum	Liver, lung	31 30 (97 %)	23	N/A Resection 21.7 % Nonresection	21 Resection 14 Nonresection (P = .718)	N/A	Non-surgical management is rational alternative
Benoist et al. [84]	1997–2002	Retrospective, single institution, case control	Colon and rectum	Liver, extrahepatic	32	27	19 % Resection 14.8 % Nonresection	23 Resection 22 Nonresection (P = .753)	24	Nonresection is option of choice
Galizia et al. [85]	1995–2005	Retrospective, single institution	Colon and rectum	Liver	42 42 (100 %)	23	21 % Resection 30.4 % Nonresection	15.2 Resection 12.3 Nonresection (P = .003)	21 (5–61)	Benefit to resection
Seo et al. [86]	2001–2008	Retrospective, single institution	Colon and rectum	Liver, lung, peritoneum, distant node, bone, brain	144 144 (100 %)	83	20.2 % Resection 20.5 % Nonresection	22 Resection 14 Nonresection (P = .013)	49 (7–89)	First-line chemotherapy is safe without increased risk of intestinal complications

the National Surgical Adjuvant Breast and Bowel Project C-10 (NSABP C-10) published the results of their prospective trial evaluating the safety of Bevacizumab to systemic chemotherapy with infusional fluorouracil, leucovorin, and oxaliplatin (mFOLFOX6) as the initial treatment for stage 4 colon cancer. The authors found that 87 % of patients did not develop symptoms from the primary tumor over a median follow-up of 20.7 months. They concluded that asymptomatic patients should undergo initial systemic therapy as the rate of serious adverse events from the primary tumor is acceptably low and the majority of patients would avoid unnecessary surgery [89].

It has been widely acknowledged that the survival benefit seen in patients who have undergone palliative resection may be due to selection bias [4]. These patients tend to actually be symptomatic and physiologically fitter [30]. Moreover, the studies have all been retrospective reviews evaluating outdated chemotherapy regimens [4]. To address these issues, several prospective studies are currently underway. Although these are studies primarily addressing metastatic colon cancer, guidelines regarding management of late stage rectal cancer may be developed as a result. The University College Hospital in London, England has completed a phase III trial evaluating overall survival in patients with metastatic colorectal cancer receiving chemotherapy with and without surgery. Results have not yet been published [90]. The Dutch Colorectal Cancer Group (DCCG) is currently accruing patients with synchronous unresectable metastatic colorectal cancer to a randomized phase III trial investigating overall survival in patients undergoing resection of the primary tumor followed by systemic therapy compared to patients receiving systemic therapy alone [91]. Additionally, the SYNCHRONOUS trial is a multicenter, randomized controlled trial in Germany evaluating the safety and efficacy of resection of the primary tumor in patients with metastatic colon cancer prior to initiating systemic therapy. Primary endpoint is overall survival with secondary endpoints determining time-to-development of tumor-related complications and intervention required [92].

Endoscopic Interventions

Most patients do not require emergent surgery and obtaining radiographic data becomes important in determining optimal treatment [93]. In addition to localizing the issue, determining the presence of carcinomatosis or ascites is essential as the presence of either is associated with unsuccessful surgery [94]. Nonoperative intervention is the preferred route in those patients with carcinomatosis or ascites, those who demonstrate poor performance status, or those with an unacceptably high operative risk.

Endoscopic-based therapies are an attractive alternative to operative intervention as they are less invasive and can be performed on an outpatient basis without general anesthesia. Endoscopic interventions are able to relieve obstructions, bleeding and/or pain rapidly and effectively. These are important considerations when electing to intervene on patients with limited life expectancy.

Rectal Stents for Obstruction

An alternative to surgical intervention in those presenting with obstruction may be endoscopic stenting to allow patency of the bowel lumen. Given the high morbidity and mortality associated with emergent surgery for colorectal obstruction, self-expandable stents (SEMS) were initially used to convert an emergent surgery to an elective surgery [95]. Placement would allow for rapid decompression and the ability to stabilize the patient with minimal sedation and less cost [96]. This evolved to utilizing SEMS for bridging to definitive surgery or for palliative therapy [97–99].

A SEMS procedure entails placement of a metallic stent across the tumor with the aid of endoscopy, fluoroscopy, or both [100] (Figs. 24.1 and 24.2). Over the course of 24–72 h, the stent expands and becomes incorporated into the tumor by pressure necrosis [96]. Technical success and clinical rates have been demonstrated to be as high as 98.7 and 95.9 % respectively, and 93 and 91 % respectively in the palliative setting [92]. Following stent placement, patients are able to be

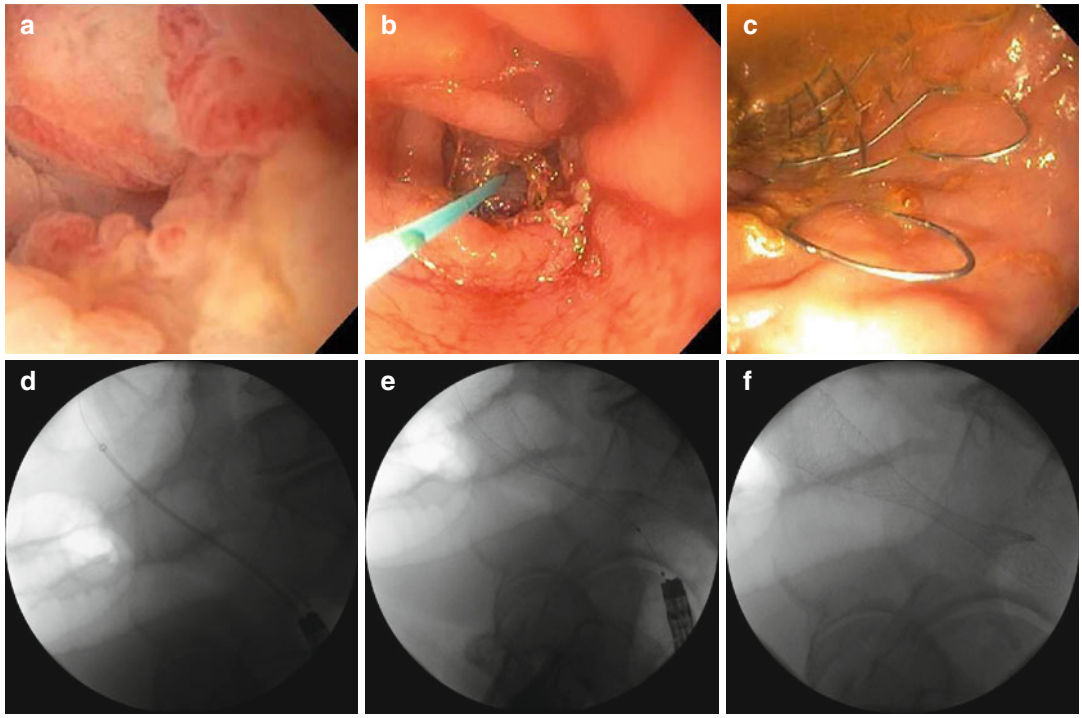

Fig. 24.1 (**a**) Malignant stricture. (**b**) Guidewire through stricture. (**c**) Stent deployment. (**d**) Guidewire through stricture. (**e**) Stent deployment. (**f**) Final stent placement. Placement of a self-expanding metallic stent in an obstructing colon cancer with the aid of endoscopy and fluoroscopy

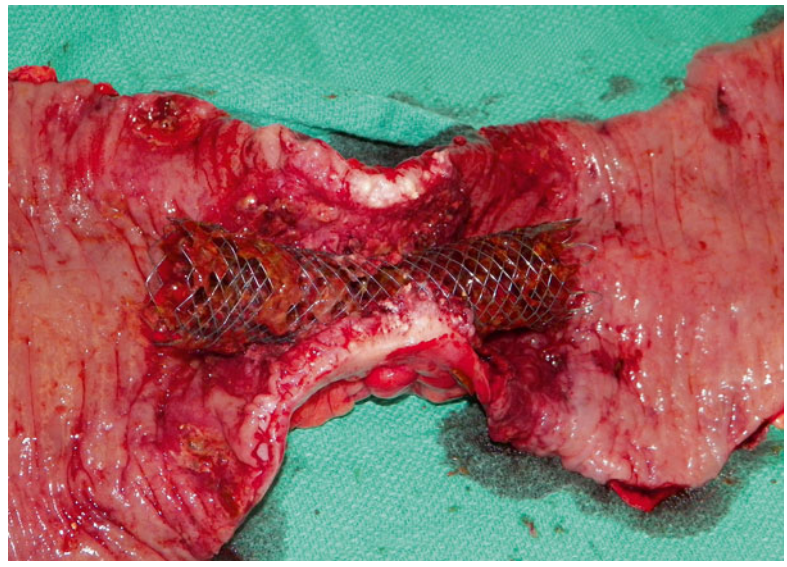

Fig. 24.2 In situ stent of obstructing colon cancer

resuscitated and optimized for any potential subsequent surgical procedure without the need for diverting stoma placement [96, 101–103]. Retrospective studies have demonstrated that stent placement is associated with increased rates of primary anastomosis during subsequent operations and shorter hospital stays [92, 103, 104]. Additional advantages to SEMS include the use of covered stents for colovaginal or colovesical fistulae as well as patients having the ability to

undergo chemoradiation with the stent in place [96, 105, 106].

Contraindications to the use of colon and rectal stents include perforation and certain characteristics of the tumor that could increase risk of perforation including a long segment of tumor or significant angulation of the colon or rectum [107]. Tumors must be able to be traversed with a guidewire in order for successful stent placement. Additionally, tumors cannot be located within 5 cm of the anal verge to allow for placement of overlapping stents and to prevent the development of pain, tenesmus and incontinence after placement [108]. SEMS is also not indicated in patients with obstruction due to external compression such as metastasis [94].

Although the overall mortality rate of SEMS is low at 1 % [92], complications of SEMS do exist including perforation, migration, reobstruction and bleeding. Perforation rates have been reported to occur in 3.8 % of patients [109]. Although the exact mechanism is unclear, it has been proposed that early perforation is due to balloon predilation, rapid expansion of the balloon or the stent, or guidewire manipulation [109]. Late perforation, occurring less frequently, may be due to friable tissue and poor vascularity particularly in previously irradiated tissue. Additionally, certain chemotherapeutic agents have been associated with an increased risk of perforation [89]. Migration, although typically less serious than perforation, occurs at a rate of 10 % [110]. This is likely due to the tortuosity of bowel and its lack of fixation to adjacent structures and organs in addition to active peristalsis [31, 111, 112]. Tumor shrinkage following chemoradiation, balloon dilation or poorly-sized stents have also been proposed to cause stent migration [110]. Covered stents have been found to have increased rates of migration due to a decrease in tumor ingrowth when compared to the more commonly used uncovered stents [113]. Bleeding occurs in approximately 5 % of patients who have undergone stent placement [109].

A number of retrospective reviews from single institutions have reported primarily positive outcomes. The first randomized trial comparing colostomy to SEMS demonstrated 57 % long-term patency until death [114]. Fiori et al. published another small series of 22 patients with similar morbidity and mortality between colostomy and SEMS groups [115]. A multicenter RCT from the Netherlands was closed prematurely due unacceptably high perforation rate in the SEMS group [116]. A Cochrane Review of five randomized trials evaluating colorectal stents and emergent surgery in malignant colon obstructions, including two of the three previously mentioned, concluded that SEMS has no advantage over emergent surgery. Emergent surgery demonstrates higher clinical success with no differences in overall complication or 30-day mortality rates between the two groups. However, SEMS is safe in this setting with acceptable rates of complications, and the advantage of shorter length of hospital stay [117]. Table 24.3 summarizes several of the studies evaluated in this review [114–116, 118, 119]. Thus, although SEMS has not been demonstrated to be superior to traditional surgical approaches to malignant bowel obstructions, it may be useful in select patients.

Laser Therapy for Obstruction and Bleeding

Endoscopic laser therapy is useful for the treatment of both obstruction and bleeding due to intrinsic lesions of the bowel. Advantages of endoscopic laser therapy are the ability to treat tumors under direct visualization and being widely available [31].

The Neodymium: Yttrium-Aluminum-Garnet (Nd:YAG) is the most commonly used laser and has been found to be safe and effective with success rates as high as 85–95 % [66]. Relief of obstruction is immediate and may be repeated if necessary. Application is fairly simple and can be performed in an outpatient setting without general anesthesia [66, 120]. The Nd:YAG laser works by causing coagulative necrosis or vaporization through optic fibers and is not absorbed by water or blood [3, 120]. The depth of penetration is approximately 4 mm and more controlled than electrocoagulation [120]. Overall,

Table 24.3 Randomized prospective trials evaluating self-expanding metallic stents (SEMS) compared with surgical intervention

Study	Study period	Site of obstruction	Stent (n)	Surgery (n)	Hospital stay (days)	Morbidity	Primary outcome	Conclusions
Fiori et al. [115]	2001–2003	8 Sigmoid 14 Rectum	11	11 transverse colostomy	2.6 Stent 8.1 Surgery (P<0.0001)	0 % Stent 9.1 % Surgery (P=NS)	Mean time for GI tract canalization: 1 day Stent 3.1 days Surgery (P<0.0001)	SEMS is an effective alternative to surgery
Xinopoulos et al. [114]	1998–2002	12 Sigmoid 18 Rectosigmoid	15 14 stent	15 stoma	28 Stent 60 Surgery (P=N/A)	60 % Stent 13.33 % Surgery (P=N/A)	Efficacy and safety	SEMS is a palliative alternative to colostomy with better quality of life
van Hooft et al. [116]	2004–2006	5 Descending colon 16 Rectosigmoid	11 10 stent 1 did not develop imminent obstruction and was not stented	10 6 resection with primary anastomosis 1 moved to stent arm due to myocardial infarction	12 Stent 11 Surgery (P=.46)	72 % Stent 10 % Surgery (P<0001)	Survival in good health outside of the hospital	Unexpected high rate of perforation (6 of 11) in the stent arm caused early closure of trial
Cheung et al. [118]	2002–2005	48 Left-sided colon	24	24 11 Hartmann 11 resection with primary anastomosis	13.5 Stent 14 Surgery (P=.7)	8 % Stent 50 % Surgery (P=N/A)	Success of 1-stage operation: 67 % Stent 38 % Surgery (P=.04)	SEMS is a safe and effective bridge to surgery
van Hooft et al. [119]	2007–2009	98 Left-sided colon	47	51 12 resection with primary anastomosis	N/A	53 % Stent 45 % Surgery (P=.43)	Global health status: 63 Stent 61.4 Surgery (P=.36)	Stenting has no clinical advantage to emergency surgery

complication rates have been reported to be between 2 and 15 % and primarily due to bleeding and perforation [76, 121]. Palliation is maintained in approximately half of patients surviving 6 months. In patients with circumferential tumors or in patients with pain, Nd:YAG is not useful in palliation [120].

Endoscopic argon plasma coagulation (APC) utilizes ionized argon gas to deliver electrical current and provide both fulgaration and hemostasis [116]. It has been demonstrated in a retrospective trial of 272 patients with obstruction to have an immediate success rate of 85 % and low major complication rate of 2 % [122]. APC causes a more superficial ablation (2–3 mm) thus poses less of a risk of perforation compared to the Nd:YAG laser. However, APC is less effective at relieving obstruction.

With growing interest in utilizing radiofrequency ablation (RFA) for solid tumor destruction including liver and prostate malignancies, investigators have evaluated the use of RFA for colorectal cancers. Vavra et al. performed RFA on 12 patients with rectosigmoid tumors found to be unresectable to evaluate feasibility and safety. In their preliminary study, the authors demonstrate no treatment-related morbidity or mortality [123]. Based on this, more studies will likely be performed to assess the use of RFA in colon and rectal cancers.

Chemotherapy

Advances in chemotherapy have allowed a 30 % response rate of 5-fluorouracil (5-FU)-based therapy [124, 125], in addition to improved survival and quality of life with symptom relief in as little as 1–2 weeks [76, 79, 126]. The median survival of those with metastatic colon and rectal cancer is approaching 24–34 months with newer chemotherapy regimens [2, 127] compared to 6–9 months in untreated patients [7]. Additionally, chemotherapy has the potential of converting unresectable disease to resectable disease [2]. Fifty to 60 % of patients are downstaged with neoadjuvant therapy with 20 % of patients demonstrating a complete pathologic response [128–132].

It is recommended that patients with unresectable disease undergoing chemotherapy should be reevaluated for resection every 2 months [12]. Reevaluation should include evaluation of the patient's general condition, side effects as well as the impact of quality of life of chemotherapy, and physical examination. A CEA level and CT of involved regions should be obtained [2].

In patients with stage 4 rectal cancer, chemotherapy should focus on palliation rather than cure [33, 93]. In patients considered never resectable and having symptoms, treatment goal should be to rapidly reduce the tumor in order to relieve symptoms. Asymptomatic never resectable patients should not undergo intensive treatment as the goal of therapy is to prevent tumor progression with low toxicity [37, 98]. Ultimate treatment selection should be based on both tumor and patient characteristics that is beyond the scope of this chapter [37, 98]. The reader is advised to review Chaps. 17 and 20, for a more comprehensive analysis of chemotherapy regimens.

Radiation

As previously stated, systemic therapy has been demonstrated to improve both survival and quality of life in patients with stage 4 rectal cancer. However, there is a subset of patients who do not respond appropriately and require local therapy for relief of pelvic pain, tenesmus, obstruction or bleeding. No formal guidelines exist for the delivery of radiotherapy for palliation in rectal cancer. Additionally, radiotherapy is likely underused due to concern for toxicity. However, a recent systematic review by Cameron et al. evaluated 27 studies of palliative radiotherapy in symptomatic patients with rectal and rectosigmoid cancers. The authors concluded that radiotherapy is effective with a pooled overall response rate of 75 % in 1,084 patients with acceptable toxicity [133]. Currently, the authors are conducting a study to determine the optimal fractionation schedule for palliation in patients with incurable prostate and rectal cancer [134]. Please refer to Chap. 17, for additional information on radiation therapy in patients with rectal cancer.

Conclusion

A significant number of patients diagnosed with rectal cancer will be or become ineligible for curative therapy. Although chemotherapy is currently the standard of care in asymptomatic patients with stage 4 rectal cancer, a number of patients have or will develop symptoms of their primary tumor. Palliative surgical interventions are oftentimes critical to improving the remainder of a patient's life. Thus, the surgeon plays a vital role in the multidisciplinary team in determining optimal timing of an operative intervention, and having knowledge of the various therapies is essential.

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Rectal Cancer Treatment in the Elderly

25

Ricardo G. Orsini, Siri Rostoft, and Harm J.T. Rutten

Abstract

Elderly rectal cancer patients are a heterogeneous group of patients ranging from the very fit to the frail patients who are at high risk of treatment complications. Most elderly have comorbidities which adversely affects outcome. In addition treatment related complications have more impact on outcome in elderly patients. Therefore a different approach compared to younger patients is needed. Only after a meticulous assessment of the physiological status and adequate counselling of the patient an individual treatment plan can be determined. Shared decision making is essential in the treatment of rectal cancer in the elderly.

Keywords

Rectal cancer • Colorectal cancer • Elderly patients • Geriatric assessment • Colorectal resection • Neo-adjuvant treatment • Anastomotic leakage • Transanal endoscopic microsurgery • Self-expending metal stenting

Introduction

In the Western population, with increasing life expectancy, there will be more and more patients affected by rectal cancer. Most of these patients are treated according to (inter)national guidelines or driven by expert meetings. But in the heterogeneous group called "elderly", ranging from very fit to very frail patients there is no consensus about the optimal therapy and multimodality therapy is less often used in this group. Overall, the elderly with rectal cancer are at risk for receiving under treatment. This chapter will give some guidance in assessing

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the physiological fitness of the elderly and determination of the he optimal treatment for the individual patient.

Frailty and Performance of the Elderly

In elderly patients the physiological age can be a poor reflection of the chronological age. According to Balducci there are two chronological landmarks [1]. The lower boundary of senescence is the age of 70, because between 70 and 75 years the incidence of age related changes increases sharply and 85 years may be considered as a red flag indicating a risk of frailty. Frailty is defined as "an elderly patient who is at heightened vulnerability to adverse health status change (such as hospitalization, mortality, nursing home admission) because of a multisystem reduction in reserve capacity", but it is still widely discussed how to identify frailty in an individual patient [2, 3]. In elderly with rectal cancer, identifying frailty is important because frailty is a predictor for post-operative complications, and frail patients have a shorter life-expectancy than non-frail patients [4, 5]. Figure 25.1 is an illustration on how the physiological reserve declines due to ageing and frailty.

In the period between the two previously mentioned landmarks, assessing the condition and vulnerability of the individual elderly can be very difficult. The most evidenced base process to detect and grade frailty for severity is a comprehensive geriatric assessment (CGA) [6]. A CGA has been shown to detect frailty in geriatric oncology patients [7–9]. In a large prospective Norwegian study the CGA was used to predict post-operative complications and mortality in electively operated colorectal cancer patients >70 years [5]. Severe comorbidity was predictive of severe complications, whereas instrumental activities of daily living dependency (IADL) and depression were predictive of any complication [10]. Impaired nutrition and comorbidity predicted early mortality. The CGA evaluates several domains including

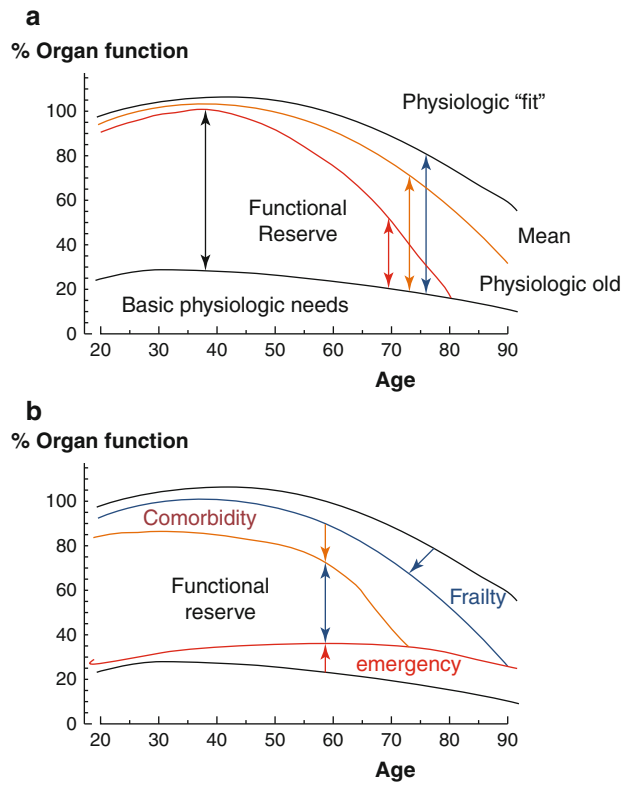

Fig. 25.1 Physiological function and functional reserve. (**a**) The natural decline of organ function (physiological function), basic physiologic needs and functional reserve. (**b**) The influence of co-morbidity on organ function and an emergency on basic physiologic needs. Frail patients have lower physiological function resulting in a small the functional reserve. In case of an emergency (such as surgery) a minor complication may deplete the functional reserve and increases the risk of worse outcome and mortality

functional status, mobility/risk of falls, cognition, depression, comorbidity, polypharmacy, social situation and geriatric syndromes. It has been suggested to categorize patients into three groups according to CGA results: fit patients, vulnerable patients and frail patients [11].

Other functional assessment-scores include the Barthel index and oncological performance status scales such as The Karnofsky performance status scale (KPS) and the Eastern Cooperative Oncology Group performance status (ECOG PS). The Barthel index is useful for assessing the functional ability of an elderly person at time of diagnosis. The KPS is validated in patients with cancer but is poorly validated in elderly patients as it does not include many areas of impaired functioning seen in the elderly [12]. Furthermore, multiple studies have shown that for older cancer patients a CGA obtains additional information to the performance status and chronological age and has been proven feasible [9, 13, 14].

Although a CGA may be used to detect frailty, it is time consuming and a resource intensive process. Particularly during a pre-operative outpatient visit, when the treatment options are discussed, normally not much time is left for assessing whether the patient is fit for (multimodality) treatment, and a CGA is too time consuming. Easier classifications such as the American Society of Anesthesiology classification (ASA) gives an estimation of a patient's anaesthetic risk, but high ASA-scores have not been proven to be predictive for post-operative morbidity and mortality [5, 15]. A test easily done during a pre-treatment visit is the timed-up-and-go test (TUG). It is a straightforward and quick test where the patient is observed and timed while he rises from an arm chair, walks 3 m, turns, walks back and sits down again. Based on multiple studies the TUG is considered normal if a patients requires $\leq$20 s to complete the test [16]. In a multicenter cohort study containing onco-geriatric patients, twice as many patients were identified as at risk for post-operative complications using TUG compared to using ASA-classification [17].

The Acute Physiology and Chronic Health Evaluation II (APACHE II) score is a surgical assessment scale and includes 12 physiological measurement including clinical and laboratory parameters [18]. Although the APACHE II has a good prognostic capacity, it does not consider the nutritional status of the patient, which is particularly important in elderly patients. The test is relevant in the immediate post-operative period for both younger and elderly patients, but pre-operatively it provides little information about the suitability of elderly patient to undergo cancer treatment [12]. Another surgical assessment scale in predicting morbidity and post-operative mortality in general surgery and patients with colorectal cancer, is the physiological and operative severity score for enumeration of mortality and morbidity (POSSUM) which contains 12 physiological and six operative variables [19]. Unlike APACHE II, it contains information about cardiac arrhythmias and ECG findings. The intra operative score factors include information about the type and timing (emergency or elective) of the surgical procedure and if there is per-operative contamination. Both surgical assessment scales provide some information about pre-operative frailty, but focuses particularly on the post-operative period. They are useful in the pre-operative selection of elderly patients and prediction of morbidity and mortality, but they cannot be used as an exclusion for cancer treatment [12].

Another way to assess the patient is the use of comorbidity scores, because comorbidity may predict a patient' physiological status and reaction to therapy. The adult comorbidity evaluation-27 (ACE-27), cumulative illness rating scale for geriatrics (CIRS-G) and the Charlson comorbidity index have been developed and validated in elderly patients with cancer. The CIRS-G is more time consuming than the Charlson comorbidity index, but both are considered as reliable tools to assess comorbidity [12, 13].

The International Society of Geriatric Oncology (SIOG) brought together a surgical risk assessment tool composed of geriatric assessment tools in order to obtain a comprehensive picture of the onco-geriatric patient [15]. These tests were brought together in the PACE (Preoperative Assessment of Cancer in the

Elderly). Included in the pace are; the Mini-mental state examination, Activities of daily living (ADL), Instrumental activities of daily living (IADL), Geriatric depression scale, Brief fatigue inventory (BFI), ECOG PS, ASA score and Satariano's index of comorbidities. The PACE was validated in a prospective study where a 20-min interview was administered within 2 weeks prior to planned surgery. In total 460 patients with a mean age of 76.9 years were included. The authors found that the likelihood of having a postoperative complication is increased by 50 % when patients have a dependent IADL, abnormal ECOG PS or a moderate to severe BFI measured prior to surgery. Disability measured by a dependent ADL was found to best predict an extended hospital stay, but dependent IADL and abnormal ECOG PS were also significantly associated with prolonged hospital stay. Overall they recommend that PACE is used routinely in surgical practice and that it may be a valuable tool in the decision process concerning whether the elderly is a candidate for surgical intervention [15].

In summary, there is still a lack of one easily applicable and validated assessment tool that offers a quick estimation of the patient's physiological fitness and is acceptable for surgeons, oncologists and geriatricians. Simple measures of objective performance status such as TUG are promising [20]. Multiple studies have showed that the CGA seems to be the best assessment scale to help clinicians make difficult decisions in elderly patients [12, 21]. Identifying functional limitations, for example, highlights the need to offer exercise and resistance training to the patient prior to surgery. There is increasing evidence that this might decrease the rate of post-operative complications and improve survival [22, 23]. In addition, an assessment of cognitive function is also important when consulting with an older patient before any treatment is given. The number of patients with cognitive dysfunction increases with increasing age, and it is mandatory for the treating surgeon to realize whether the patient is capable of consenting to the treatment plan.

Do We Need to Work-Up the Elderly Differently?

In the elderly it is important to bring in the life expectancy in the decision-making process. In the elderly there are huge differences in life expectancies comparing the fittest quartile of persons to the ones in the lowest quartile. For example, for women who reached the age of 80, the fittest quartile has a life expectancy of at least 13 years, while the sickest quartile has a life expectancy less than 4.6 years [24]. For males who reached the age of 80 the fittest quartile has a life expectancy of at least 10 years and the lowest quartile less than 3.3 years. In the decision making process, it is important to estimate whether the patient belongs to the fittest quartile, the median, or the sickest quartile. Life expectancy estimates can be used to determine if an elderly is likely to benefit from treatment. Patients who belong to the fittest quartile are likely to benefit from the best oncological treatment, whereas in those patients who belong to the lowest quartile oncological outcome becomes less important. In those patients quality of life is more important and a less invasive approach can be desirable.

Overall increasing age and rectal cancer is associated with an increased likelihood of under treatment with local excision rather than radical surgery and multimodality therapy. This was confirmed in a small American population based study, where age also had a significant impact on whether patients received surgery alone or had surgery and chemo radiotherapy. Elderly who did receive the multimodality treatment had significantly better survival compared to elderly receiving suboptimal treatment [25].

Another population based study among rectal cancer patients using the SEER registry also found a decreased use of any cancer treatment, an increased use of local excision and a decreased use of radical surgery [26]. They also reported lower disease stages and decreasing survival rates as age increased. An explanation for the lower disease state and survival could be due to surgical under treatment, as accurate staging is not possible with local excision.

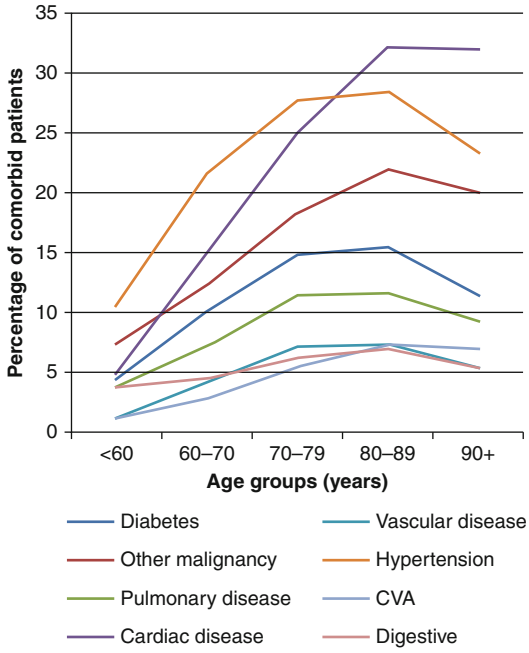

Fig. 25.2 Prevalence of comorbidity in CRC patients. The figure presents the prevalence and distribution of specific comorbid diseases for different age groups (From Van Leersum et al. [27])

An important aspect of rectal cancer treatment in the elderly is the fact that most of these patients are affected by comorbidities. Figure 25.2 shows the patterns of different comorbid diseases in Dutch CRC patients according to age. In this population based sample 30 % of patients <60 years suffered from comorbidities compared to 71 % of the patients aged >80 years [27]. In addition, a rising prevalence of comorbidities in all age groups was found during the study period. Regardless of age, having comorbidity is associated with adverse outcome after colorectal surgery [28, 29].

European data showed improved colorectal cancer care in the elderly, with increasing in the proportion of patients resected for cure, a decrease in post-operative mortality and improvement in stage of diagnosis [30]. A Norwegian cancer registry-based study has also shown that the survival in rectal cancer patients older than 75 years have improved significantly from early (1994–1996) to late (2001–2003) time periods after implementing national management strategies [31]. Knowing that the survival gap between young and elderly is closing, we are doing better.

To lower the risk of under treatment further all elderly patients have to be adequately staged. It starts with optimal workup prior to any treatment given in the case of non-obstructive rectal cancer [32]. For primary diagnosis and screening the endoscopy and full biopsy is the modality of choice. For further workup the diagnostic modality of choice is the Magnetic Resonance Imaging (MRI), given that it provides detailed images of the dissection planes, pelvic and mesorectal fascia [33]. The mercury study group reported a good correlation with extra-mural spread and the MRI has been shown to predict a positive circumferential margin (CRM) [34]. With the use of Computed Tomography (CT) liver or pulmonary metastasis and enlarged intra-abdominal lymph nodes can be identified. The resolution of the CT is insufficient for accurate assessment of the dissection planes and CRM involvement. Endoscopic rectal ultrasound is sensitive enough to stage the depth of submucosal involvement, but cannot evaluate the mesorectal fascia as reliably as MRI [34, 35].

In case of obstructive rectal cancer or emergency surgery, surgeons have to be aware that it is better to place a deviating stoma and perform the resection in a more elective setting after adequate staging and neo-adjuvant treatment.

After accurate staging all elderly patients need to be discussed in a multi disciplinary team (MDT) meeting [36, 37]. Recent studies have demonstrated a significant improvement in oncological outcome due to MDT meetings, resulting in decreased recurrence rates and increased survival [38, 39]. The factors influenced by MDT meetings and contributing to this improved oncological outcome include an increased number of patients undergoing an MRI in pre-operative staging, who received neo-adjuvant treatment, who underwent surgery for metastatic disease and who receive adjuvant therapy [38–41].

Furthermore it can be advocated to involve a geriatrician in these MDT meetings because of the difficulty to assess the physiological fitness of

the older patient [37]. We believe that discussing such a patient in a MDT meeting will make it easier to assess whether the patient it fit for surgery and from which neo-adjuvant treatment the patient will benefit the most. In case of irresectable or metastatic cancer or if the patient is considered too frail for surgery, the MDT can discuss which palliative treatment suits the patients most properly.

Neo-adjuvant Treatment

Elderly patients are underrepresented in clinical trials. Only 20–25 % of the patients enrolled in clinical trials are 70 years and older [42, 43]. Large observational studies have also shown that aggressive treatment and the use of (neo)adjuvant treatment largely depends on the chronological age of the patient [21, 44–47]. Remarkably, this was already reported in the early 90s [48–50] but it seems that there has not been many changes. Even though fit older patients have been shown to tolerate cancer treatment and have additional survival benefit from (neo-)adjuvant therapies [32, 51, 52].

Dutch population based data and data from the Dutch TME trial showed that elderly have better biological tumour response to neo-adjuvant radiotherapy than younger patients [53]. Not only did the local recurrence rate decrease with neoadjuvant short course radiotherapy, but improvement was also seen in the distant metastatic rate and the cancer specific survival rate. In contrast, radiotherapy in younger patients only improves local control. Although the oncological response is better due to neo-adjuvant treatment, the overall survival rate has not improved. Elderly suffer from more complications compared to younger patients and the impact of complications is more severe. The increased mortality rate was not associated with neo-adjuvant treatment but directly attributable to surgery but this could also be due to power defect. Another population based study found a doubling of post-operative complications (especially deep infections and wound problems) in patients aged ≥75 years who were treated with pre-operative radiotherapy compared with elderly not treated with radiotherapy [54]. However, radiotherapy did not influence the 30-day mortality rate and decreased the local recurrence rate.

A review by Martijn et al. including 9 RCT's and 10 population based samples, concluded that the best possible treatment should be given to all patients irrespective of age [55]. This means the use of short course radiotherapy in case of primary resectable cancer and the use of long course chemo radiotherapy in case of locally advanced rectal cancer. With regard to toxicity they found no differences between young and older rectal cancer patients when modern radiotherapy techniques with small tissue volumes are used. Exceptions should only be if the patients' condition makes the patient unable to fulfil the combination of treatment. Another pooled analysis of 9 randomised controlled trials also showed that acute and late side effects of radiation therapy had the same toxicity in the elderly as the young [56]. Other recent studies are less positive. A small study showed a high rate of treatment deviation in patients aged ≥75 years. In their sample of 36 patients only 4 (17 %) did not deviate from the original treatment plan despite the ECOG performance scale of 0 or 1 [57].

In the French ACCORD12/PRODIGE 2 trial patients were randomly assigned to 45 Gy/25 fractions radiotherapy with concurrent Capecitabine or 50 Gy/25 fractions radiotherapy and Capecitabine and Oxaliplatin [58]. In a recent exploratory analysis the tolerance to treatment was investigated for elderly patients (aged ≥70 years) [59]. Less elderly patients completed the radiotherapy treatment compared to patients <70 years (4.2 % vs. 1.4 % $p=0.03$). No differences were observed in the chemotherapy administration. In elderly patients there was a higher incidence of grade 3–4 toxicity (25.6 % vs. 15.8 % $p=0.01$), and fewer patients underwent surgery (95.8 % vs. 99 % $p=0.008$).

Recent results from the Swedish Rectal Cancer Registry showed promising results regarding short course radiotherapy without direct curative surgery, but surgery was planned more than 4 weeks after completion of the radiotherapy [60]. Tumour stage, lymph node positivity and circumferential involvement were significantly downstaged. Pathologic complete response occurred in 8 % of the patients and 11 % had a higher TNM

stage at pathological classification. Of all patients, 38 % had post-operative complications, what is in line with larger samples. This study shows feasibility of short-course radiotherapy with a longer waiting period, particularly for older patients and patients with comorbidity, although younger patients could also fare well with this treatment regimen. To further investigate the effect on survival the Stockholm III trial is conducted [61]. In this study patients are randomised in three groups; short-course radiotherapy with direct or delayed (4–8 weeks) surgery or long course radiotherapy with delayed surgery. This trial will give insight in the feasibility of this regimen and impact on local control and survival. Interim analyses showed that compliance was acceptable and severe acute toxicity was low. Immediate surgery after radiotherapy had a tendency to more complications, but only if the surgery was delayed beyond 10 days after completion of the radiotherapy [61].

The main factors associated with a higher toxicity of chemotherapy are functional status impairment, dependency in ADL, depressive symptoms and polypharmacy [62]. In elderly patients where there is doubt about the physiological fitness the administration of Capecitabine has been recommended [62–64]. However in the FOCUS 2 study where only frail patients were included, it was associated with higher rates of grade 3–4 toxicity compared to infusional 5-FU/LV administration (37 % vs. 27 %) [65]. A review focussing on first line treatment strategies in elderly with metastatic CRC concluded that a combination therapy consists of Capecitabine and Oxaliplatin or Irinotecan [64] should be considered in older patients with adequate performance and functional status with reasonable life expectancy. The decision for Oxaliplatin or Irinotecan should be based on comorbidity, the drug specific toxicity and patients´ wishes. For frail elderly, single agent of Capecitabine could be considered.

Surgery and Its Morbidity

Surgery is considered reasonably safe, also for most elderly patients, and surgery should not be denied on the basis of age alone [66, 67]. Whereas after elective surgery mortality rates will increase only minimally with age, in emergency surgery cases the mortality rates are higher. Emergency surgery is too burdensome in elderly, probably due to the limited functional reserve of many elderly [1] and all efforts should be made to avoid emergency surgery [32, 36]. A study from the United Kingdom [68] analysed 36,767 non elective colorectal resections and divided patients in three age groups: 70–75 years, 76–80 years and >80 years. Almost half of the patients received surgery for a malignancy and 21 % for diverticulosis. The 30 day mortality rates were 17, 23 and 31 %, respectively, for the three age groups. Furthermore, 1-year mortality was more than 50 % in the oldest age group. In their population of non-elective cases, 1 in 4 cases aged 70 or older dies within 30-days of surgery indicating that non-elective surgery in elderly patients must be avoided.

A Dutch study with non-elective colon resections found that in elderly patients with two or more additional risk factors, a non-elective resection should be considered a high-risk procedure with a mortality risk of up to 41 % [69]. Another population based study [29] found that emergency surgery in rectal cancer patients was associated with a higher risk of post-operative complications and increased mortality rates. Preoperative pulmonary, cardiovascular or neurological comorbidity was also associated with post-operative morbidity and mortality.

A review, which included 28 of the 60 eligible studies investigated differences between young and elderly CRC patients analysing a total 34,194 patients [70]. Post-operative mortality in the 65–74 year age group was about 1.8 times higher compared to patients aged <65 years. For patients 75–84 this was 3.2 times higher and 6.2 times higher in patients aged 85+ years. These series include a mix of patients who underwent curative, palliative, emergency and elective surgery. Elderly patients were more often affected by respiratory complications when age increased. Patients aged 65–74 years were twice as likely to have respiratory complications compared to those <65 years, for older patients this rate rose up to 3 times as likely compared to those <65 years. No differences were seen according to

age and the prevalence of anastomotic leakage (overall incidence rate 4.4 %). This could be due to using different definitions of this complication or the different methods of follow-up to detect this complication. Older patients were more likely to receive emergency surgery or no surgery. An increased frequency of comorbid conditions in the elderly was seen, however in elderly patients undergoing surgery there was no evidence for increased morbidity in patients aged 85 and over, indicating the possibly careful selection of patients fit enough for surgery. Survival rates were reduced in elderly patients but in cancer specific survival age-related differences were much less clear. Furthermore a large proportion of the elderly patients in this study survived for 2 of more years from surgery, irrespective of their age. This indicates the role of selection bias in the elderly.

Devon et al. [71] investigated differences in CRC surgery outcomes between patients aged 50–74 years and patients aged 75 years and older. There were no differences in emergency surgery or palliative surgery between both groups. Elderly had more post-operative complications, especially cardiopulmonary compared to the younger age group. In hospital mortality rates were also higher in the elderly population (4.2 % vs. 1.0 %). The 5-year overall survival rate was better in younger patients, but no differences were seen in the colorectal cancer specific survival rates at 5 years. The adjusted colorectal cancer hazard ratio was also not significant different for patients aged 75 years and older compared to younger patients. Noteworthy, elderly patients in this study had lower disease stage at presentation compared to younger patients, indicating that elderly are less likely offered surgery for advanced cases.

Advanced age is not a contra-indication for laparoscopic surgery in elderly patients and can be considered as safe [72]. In a study among 535 patients with CRC, including 201 (37.6 %) patients aged 70 years or older patients were randomly assigned to receive open surgery or laparoscopic surgery [73]. The elderly had higher ASA score compared to younger patients. In the elderly the laparoscopic procedure had significant lower morbidity rate (20.2 % vs. 37.5 %, $p=0.001$) and decreased hospital stay (9.5 vs. 13.1 $p=0.0001$) compared to elderly receiving open surgery. Interestingly, in the younger age group these differences were less pronounced. Other studies supports these findings where decreased morbidity, decreased hospital stay and earlier return of bowel function are seen after laparoscopic surgery compared to open surgery in elderly patients [74–76].

Surgery and Its Mortality

The 30-day mortality highly underestimates the risk of dying in the first year [77, 78]. In a study among 2131 patients who were operated with curative intent for stage I-III CRC the 30-day mortality rate was 4.9 %, but rose to 12.4 % in the first post-operative year [79]. For rectal cancer patients risk factors for excess mortality in the first post-operative year were age ≥75 years (RR 7.0 p=0,009), Charlson score of >1 (RR 5.2 $p=0.01$) and post-operative surgical complications (RR 5.9 $p=0.02$). Patients aged ≥75 years with rectal cancer had a 1-year mortality rate of 15.6 % compared to 6.8 % for patients aged 65–74 and 2.3 % for patients <65 years. Another study showed doubling of the 30-day mortality rate already within 90 days post-surgery [78].

In Fig. 25.3, unpublished data of the Dutch Surgical Colorectal Audit (DSCA) of 44,202 patients demonstrate the relation between increasing age, comorbidity, emergency surgery and complications on 30 day mortality of colorectal cancer patients.

Results from the Dutch TME study combined with population based data showed that the 6-months post-operative mortality rate was significantly increased in patients ≥75 years compared with patients <75 years (Fig. 25.4) [80]. A large Danish population based study with CRC patients found also increased mortality rates in elderly patients [81]. Patients aged 76–80 years had survival rates of 91 and 75 %, patients aged 81–85 years had rates of 86 and 70 % at 30-day and 6 months, respectively, compared to 94 and 81 % in patients aged 61–75 years. Regarding 5-year relative survival rates, only minor differences were seen between the three age groups.

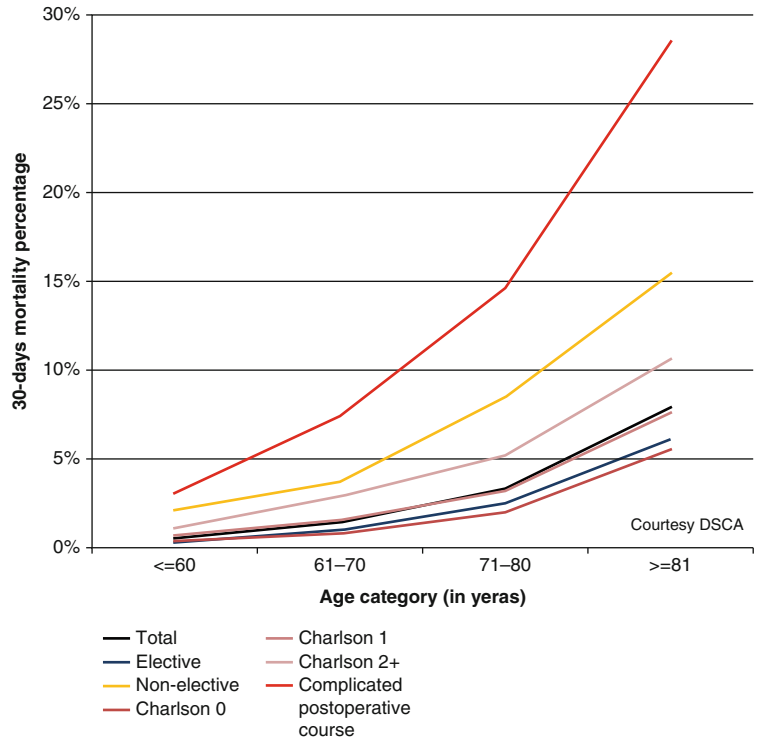

Fig. 25.3 Unpublished data of the DSCA demonstrating 30-days mortality in 44,202 registered colorectal cancer patients in relation to comorbidity, emergency operation and complicated postoperative course

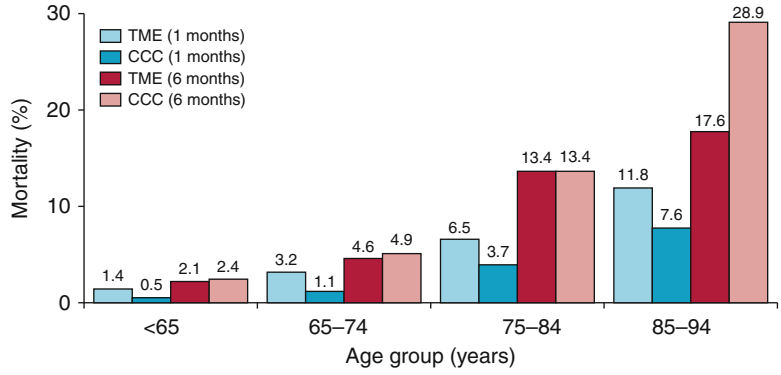

Fig. 25.4 Postoperative mortality. The figure presents the 1- and 6-month mortality per age group in the Dutch TME study and the population-based Comprehensive Cancer Centre (CCC) databases (Reprinted from Rutten et al. [80], Copyright 2008, with permission from Elsevier)

A French population based study showed that lowering the 30-day mortality rate from 18 to 8 % led to a relative improvement of 27.5 % in 5-year survival [82]. Other Dutch and Danish data also showed that the main difference in survival between young and elderly is due to the first post-operative year [77, 81]. Those elderly CRC patients who survive the first post-operative year have the same cancer related survival as younger patients. These findings emphasize the importance of post-operative care and after correction for post-operative mortality, survival in the elderly is not worse than in younger patients.

Anastomosis or Permanent Stoma?

Data from the Dutch TME study have shown that elderly patients are liable to more complications compared to younger patients [80]. In addition the consequences these are more severe. In their study anastomotic leakage occurred at similar rate but the ensuing mortality rate in younger

patients was 8.2 % compared to 57 % in elderly patients. Other complications including abscesses, sepsis, pulmonary and cardiac complications were associated with an increased risk of dying within 6 months post-surgery in elderly patients.

A recent study using data from the Dutch Colorectal Audit including only colon resections also found that increasing age and anastomotic leakage is associated with increased mortality [83]. Patients aged 65–80 had an OR of 3.15 and patients aged >80 years an OR 5.16 for mortality after anastomotic leakage compared to younger patients.

These studies highlight the necessity to prevent major complications such as an anastomotic leakage in the elderly. To minimize the consequences of an anastomotic leakage a diverting stoma is placed. Interestingly, in the TME study up to 20 % of the elderly patients did not have their stoma's reversed and in another study only half of the elderly patients had their stoma reversed at 18 months [84].

In order to minimize post-operative morbidity and mortality due to anastomotic leakage in those patients at risk for complications, a permanent end colostomy may be considered. In the decision making process the assumed benefits of avoidance of a stoma have to be weighted against the potential life threatening complications of anastomotic leakage and the morbidity of stoma reversal. When patients are confronted with the choice between a permanent colostomy and restoration of bowel continuity, most will choose bowel continuity. We believe that a permanent stoma is feasible for elderly patients with a low situated rectal carcinoma, also in relation with health related quality of life (HRQL). In a population based sample with only low situated rectal cancer patients we found comparable HRQL between elderly patients with a permanent stoma and those with no stoma [85]. In addition, in comparison with a normative population, no large differences were seen. These findings are supported by other studies where no relevant impact on HRQL of a permanent stoma was found [86, 87].

The low anterior resection syndrome (LARS), a complex of functional symptoms occurring after a low anterior resection, is frequently seen after a low anterior resection. In a large Danish study [88], using the LARS score [89], severe LARS was observed in 41 % of all patients. The LARS increases morbidity, influences HRQL and results in poor functional outcome. Particularly in the elderly, the benefits of an anastomosis over a permanent stoma have to be weighed against the risks of anastomotic leakage or the morbidity of LARS.

Post-operative Care

Surgery creates a similar stress response to a trauma including a hormonal, immunological, neurological and haematological response [90]. These responses are essential for recovery [91]. If these responses are not managed correctly peri-operatively, it is associated with poor outcome. For example, abnormalities of fluid and electrolyte balance may adversely affect organ function and surgical outcome and is associated with increased mortality and morbidity including cardio-respiratory complications, increased infections and wound healing complications [92–95]. Furthermore, a positive fluid balance in elective colonic resections results in a delay in return of gastro-intestinal function and a prolonged hospital stay [96]. Particularly elderly are pre-disposed to significant fluid and electrolyte abnormalities. Age-related pathophysiological changes, poor physiological reserves and/or polypharmacy make it difficult to manage an optimal physiological state and a zero fluid balance. Particularly in the first post-operative hours elderly and particularly frail patients should be monitored in the intensive care unit were vasopressin and inotropic agent can be given in order to maintain adequately organ tissue perfusion. Furthermore, post-operative care has to focus on complications, and aggressive assessment and treatment of these complications are needed. Particularly in the case of anastomotic

leakage early and aggressive management may result in lower overall mortality [97].

Elderly and the Role of Local Excision

Minimally invasive approaches such as the transanal endoscopic microsurgery (TEM) has been shown to have lower morbidity and compared to anterior resection [98]. TEM is also considered as a safe technique in high risk patients and is well tolerated [99, 100]. For T1N0 tumours, TEM has almost equal local recurrence rates as TME surgery [101]. However, multiple studies have shown that TEM carries a higher risk of local recurrence particularly in T2-T3 N0 tumours [102, 103].

A more recent development in neoadjuvant treatment is chemoradiotherapy. Promising results were found when patients with cT2-T3 tumours were treated with neoadjuvant chemoradiotherapy followed by TEM [104, 105]. In a study 70 T2N0 patients were treated with long course neoadjuvant CRT followed by a TEM or a laparoscopic anterior resection 6–8 weeks after the end of the CRT. In this study, similar local recurrence, distant metastasis and survival rates were found [104]. In a study with cT2-cT3 patients after CRT downstaging was associated with low local recurrence rates and in patients with complete remission (ypT0) zero local recurrence was seen [105]. In patients with ypT1 local recurrence rates of 0–6 % were seen and for ypT2 6–20 % local recurrence rates were observed. Another study containing 35 patients with pT2 tumours treated with TEM after long course radiotherapy found only one local recurrence in the follow-up period [106]. The probability of surviving 8 years after treatment in this study was 83 %.

However, in frail patients who are unfit for surgery the addition of chemotherapy to radiotherapy might be associated with increased morbidity. As mentioned earlier, elderly respond well to neo-adjuvant radiotherapy, so maybe there is a role in frail elderly for neo-adjuvant radiotherapy followed by a longer waiting period and complementary TEM surgery.

The Wait and See Approach

In some patients, there is a role for the wait and see approach after clinical complete response (cCR) after initial neo-adjuvant treatment. Habr-Gama included 71 patients with mainly cT3 tumours who had a cCR after chemoradiotherapy and found only two patients with local recurrence after a follow-up of 57 months [107]. Of these two patients, one underwent a successful salvage operation. Three other patients developed distant metastasis during follow-up. In another study by Habr-Gama a local failure rate of 4.2 %, a 5-year overall survival rate of 96 % and a disease free survival rate of 72 % were reported [108].

In the most recent Habr-Gama study, patients with cT2-4 N0-2 M0 who had cCR 8 weeks after RCT (long course radiotherapy and 5-FU) were enrolled in a strict follow-up program with no immediate surgery [109]. In their population 49 % had cCR at initial assessment. Local recurrence developed in total in 31 % of the patients in who salvage therapy was possible in ≥90 % of these patients in both early and late recurrences. Of these 28 local recurrences, 17 were found within 12 months and 11 after 12 months. In total 17 patients (19 %) with cCR experienced unresectable (local or systemic) disease during follow-up.

A Dutch study is the only other study who also reported low recurrence and disease free survival rates [110]. In total 21 patients were included in the wait and see policy group. The follow-up consisted of MRI, CT and colonoscopy. In this study only one patient had a local recurrence and received successful salvage surgery after a median follow-up of 25 months. The 2-year overall survival and 2-year disease free survival rates reported in this study were 100 and 89 %, respectively. Other studies have reported less promising results with local recurrence rates ranging from 23 to 83 % [111].

The differences between reported local recurrence rates can be due to heterogeneity of the patient population, different interpretation of cCR on MRI or study design. Furthermore, most studies regarding this topic are Habr-Gama

series. Glynne-jones and Huges concluded that at present evidence for the wait and see approach is insufficient, but the data has to be translated to the individual patient in the context of overall life expectancy [111]. In addition, patients should be included in the decision making process in which evidence and tailored information is shared aimed to support those patients considering a wait and see approach.

In clinical trials, after pre-operative chemoradiotherapy a pCR is achieved in up to 25 % of the patients [112]. Furthermore, results from studies mentioned earlier are promising, but only in a minority of the patients and after careful patient selection surgery can be avoided. Future challenges lies in ways to achieve more pCR without increasing toxicity. A future treatment modality could be a more intensified radiotherapy treatment. Normally external beam radiotherapy is delivered with a total of 45–50.4 Gy divided over multiple fractions. Delivery of doses higher than 50 Gy is difficult without increasing morbidity due to the tolerance of normal tissue. The challenge is to increase the radiotherapy dose without increasing without increasing the morbidity. A possible and future modality could be endocavitary radiotherapy or a combination with external beam radiotherapy. Endocavitary or contact radiotherapy for the treatment of rectal cancer was first introduced in France by Lamarque and Gross in 1946 and was later popularised by Papillon in the period 1950–1990 [113]. In this period Papillon reported a 5-year survival rate of 75 % after treating 300 patients with the "Papillon technique". More recent studies from the UK and France have shown feasibility for contact radiotherapy in selected cases and frail elderly patients [114, 115]. Another endocavitary approach is brachytherapy and has also shown promising results combined with contact radiotherapy or external beam radiotherapy with our without chemotherapy [116]. Gerard concluded that endocavitary irradiation can be safely combined with external beam radiotherapy but radiotherapy without surgery should be restricted to highly selected patients such as frail patients or those refusing surgery [117].

Surgery with neo-adjuvant treatment remains the standard of care for rectal cancer. In highly selected cases there is a role for a more conservative approach with radio- or chemo-radiotherapy without surgery. More studies and technical developments in this field are needed to guide the oncologists and surgeons in the selection of patients benefiting from non-operative management.

Stenting

In selected cases with obstructive rectal cancer with poor prognosis a self-expending metal stenting (SEMS) can be a good alternative to surgery but this should always be discussed in a MDT [118, 119]. In a non-randomised prospective study a SEMS was successfully placed in 38/40 patients, with a re-intervention rate of 19 % [120]. Compared with the complication rate of 32 % in those patients treated with surgery a SEMS can be considered as a good alternative to surgery. In a German study, 79 % of the patients found relief by a SEMS and 20 of the 37 patients died with a SEMS in place and required no surgical intervention [121]. SEMS are associated with less risk, shorter hospital stay and less morbidity and mortality than surgical resection [122]. The most devastating complication is a perforation that occurs in approximately 5 % of the patients and surgical treatment in those cases is a high risk intervention [123].

The EURECCA experts concluded that in case of palliative treatment of rectal cancer with a very poor prognosis (expected less than 3 months), due to pulmonary or liver metastases, self-expending metal stenting (SEMS) could be considered, as adjuvant to radiotherapy [124]. In the curative treatment of rectal cancer, stent placement is inferior to emergency surgery in case of an acute obstruction and is associated with increased morbidity [125, 126].

Tailored Approach, Quality of Life and Shared Decision

In the last decade, rectal cancer treatment has evolved from a surgery alone treatment to a multimodality and multidisciplinary treatment. Using international guidelines and guidelines from consensus meetings, we now know which treatment

strategy is needed to achieve optimal oncological outcomes. In some cases, a very intensive treatment and extended resections are necessary in order to achieve the best oncological outcome. We have unpublished data that elderly have comparable HRQL after extended resections compared with elderly after non-extended resections in an series with particularly locally advanced cases. Other studies support the finding that elderly have comparable HRQL after treatment compared to younger patients [127, 128]. But it is known that some HRQL levels do not reach baseline levels even after 2-years post-surgery, which suggests that elderly will suffer a more permanent impaired physical function than younger counterparts [128]. In the end it seems that elderly and particularly fit elderly have a good HRQL after treatment.

Different from treating young patients is the fact that elderly can have other expectations of life making oncological outcome less important. In the young this may also be the case, but probably less commonly. This highlights the importance of shared decisions with a tailored approach in order to serve the patient´ expectations of life and wishes. In shared decision-making, doctors and patients actively discuss and decide on therapeutic interventions, in order to reach a common goal instead of clinician driven goal based oncological outcome [129]. This is extremely important in elderly patients in whom expectations of HRQL and for example a stoma play a more important role in the decision process than oncological outcome. Shared decision making is the cornerstone for adequate treatment in the elderly.

Centralization and Auditing

We have tried to give some guidance in the treatment of rectal cancer. Nevertheless, rectal cancer treatment is complex and requires experiences in all fields of cancer care. In locally advanced cases multivisceral resections are often required and an experienced surgeon for these cases is necessary. Centralization of these advanced cases will likely lead to more experience among varying disciplines at expert centers, positively influencing oncological outcomes due to improved rates of radical resections [130] and lowered morbidity and mortality rates secondary to improved post-operative care [129, 131]. Also for elderly in whom there is doubt about the appropriate treatment given or in elderly with advanced cases referral to an expert center can mean a difference in outcome. In expert centers there is normally a high awareness for treatment and post-operative complications, therefore complications may be easier identified with more experience in the "know-how" to treat them.

We believe that centralization is mandatory in advanced rectal cancer cases, but this may also be the case in elderly rectal cancer patients. Why not centralise these patients? It can be advocated that the frail elderly do not benefit from centralisation if the travel distance is too far and travelling is too burdensome. But in these cases a consult with an expert center may be sufficient.

Because of the under representation of elderly patients in clinical trials it is difficult to extrapolate the results from trials to the older patients. It can be expected that randomised controlled trials involving elderly continue to be exceptional in future rectal cancer trials and studies. Why not use data from auditing and registries? The Dutch Colorectal audit is one of the most recent nationwide audits on rectal cancer and has already shown an increased use of MRI, MDT meetings and pathologists reporting CRM involvement [132]. In addition, less post-operative complications were seen and more radical resections were performed. With the use of auditing and registries, it may be possible to identify elderly patients at risk for under- or overtreatment, and from which therapeutic approach they benefit the most. This may lower the risk of doing more harm than good.

When using international or expert meeting guidelines, registries or auditing there is no need to create a scale between countries or clinicians but it should be used as sharing expertise in an effort to make sure that every patient, including elderly are treated with the best cancer care.

Conclusion

The incidence of older patients with rectal cancer is rising. Therefore, elderly and frail patients with rectal cancer will be more commonly part of the daily practice. The most

important aspect in treatment of elderly is the risk of under treatment. Clinicians have to be aware that older patients need proper staging with endoscopy, MRI and CT prior to any decision making or treatment given. When patients present with obstructive rectal cancer in an emergency setting, surgery has to focus on limiting complications, and therefore creation of a diverting stoma is the treatment of choice. After this procedure a full diagnostic work-up is still necessary followed by a MDT meeting. Prior to an MDT meeting it is useful to assess the physiological fitness of the patients primarily to know if the patients it fit enough for multi-modality treatment. Regardless of age, in the case of a fit elderly, we believe that treatment should be given according to international set guidelines and is the same as for younger patients. In cases where the clinician is in doubt about the condition of the elderly patient, a CGA may be useful and the geriatrician has to be involved in the treatment decision progress. Also in the elderly, the most important prognostic factor for survival is achieving a radical resection. In advanced cases, neo-adjuvant treatment is needed in order to achieve the best oncological outcome. Awareness of post-operative complications is especially important in elderly patients in whom complications results in higher post-operative mortality. We believe that it is mandatory to observe elderly patients an ICU post-operatively if their ASA score is >2. In these patients, early complications and disruption of the normal physiology may be appropriately handled with the use of vasopressin or inotropic agents in order to maintain a well-balanced fluid balance. Furthermore in elderly patients it can be considered to create a permanent colostomy in order to lower the ensuing mortality rate after an anastomotic leakage. In selected cases there is a role for the "wait and see" approach. For frail patients and elderly patients with non-resectable rectal cancer, treatment should focus on improving and prolonging a good quality of life. In such cases, a single agent chemotherapy or stenting could be the treatment of choice.

In the end, the crux of rectal cancer treatment in the elderly lies in shared decision making. Particularly the older patient knows clearly what he wants regarding HRQL and life expectancy.

Key Points

1. Age is an independent prognostic factor. However, a certain chronological age for an individual patient is not necessarily the most relevant factor. Instead the age-related physiologic changes in individual patients should be known prior to decision making.
2. Co-morbidity is a prognostic variable which should be analysed carefully and optimised before commencement of any treatment.
3. Acute surgery should preferably be avoided or if necessary as minimised as possible
4. Elderly colorectal cancer patients represents a very heterogeneous group ranging from the very fit who are untitled to full oncological treatment to the very frail who are at high risk of treatment complications. Elderly require individualised treatment which can only be decided after a meticulous assessment of the functional status
5. Existing guidelines may be evidence based, but cannot be validated for elderly in general and certainly not for the compromised elderly
6. If an elderly is considered physiological fit for treatment, neo-adjuvant treatment with radical resection is the treatment of choice.
7. Counseling the elderly patient should be from the perspective of the patient, which may be quite different for expectations from a younger patient.
8. In elderly colorectal cancer patients shared decision making is the cornerstone for adequate treatment.

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Costs of Rectal Cancer Patient Management

26

Katherine S. Virgo

Abstract

Approximately 13.7 million Americans with a history of cancer were alive on January 1, 2012 [1]. By 2020, it is estimated that this number will rise to 18.1 million cancer survivors. The associated national medical costs in 2010 dollars are estimated at $157.77 billion [2]. These figures do not include the psychosocial costs associated with living with cancer. Such patients may suffer prolonged and often intense pain, as well as living with the constant threat of disability, recurrence, and death. Despite the substantial resources devoted to cancer care, there is still comparatively little patient level information available regarding the costs of care, though such analyses are much more common now than they were 15 years ago. Common cancers are generally the focus of most cost analyses due to constraints of available datasets. Though colorectal cancer is usually included in these cost analyses, rarely are rectal cancer patient management costs examined separately. This chapter analyzes the costs of rectal cancer patient management focusing primarily on initial treatment costs and costs incurred during the 5 year period after treatment.

Keywords

Rectal cancer • Cost • Charge • Surgery • Treatment • Continuing care • Survivorship

Introduction

Approximately 13.7 million Americans with a history of cancer were alive on January 1, 2012 [1]. By 2020, it is estimated that this number will rise to 18.1 million cancer survivors. The associated national medical costs in 2010 dollars are estimated at $157.77 billion [2]. These

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figures do not include the psychosocial costs associated with living with cancer. Such patients may suffer prolonged and often intense pain, as well as living with the constant threat of disability, recurrence, and death. Despite the substantial resources devoted to cancer care, there is still comparatively little patient level information available regarding the costs of care, though such analyses are much more common now than they were 15 years ago. Such information can provide valuable information on patterns and intensity of care as they change over time. These data are also crucial in comparisons of alternative therapies which are comparable in terms of patient outcomes. Common cancers are generally the focus of most cost analyses due to constraints of available datasets. Though colorectal cancer is usually included in these cost analyses, rarely are rectal cancer patient management costs examined separately.

A substantial number of patients are diagnosed with rectal cancer each year. Approximately 40,000 new cases of rectal cancer were predicted in the U.S. for 2014 [3]. The majority are treated with curative intent and enter follow-up programs. Although rectal cancer can occur early in life, rectal cancer disproportionately affects those 65 and over. The age adjusted incidence rate is 52.3 per 100,000 population compared to 6.8 per 100,000 population for those under 65 years of age [4]. The number of persons dying of colorectal cancer each year in the U.S. is 50,310 (Similar data no longer reported separately for rectal cancer) [3]. The 5-year relative survival rate for persons diagnosed with rectal cancer is 66.5 % [4]. If rectal cancer is detected while still localized, the 5-year relative survival rate is 87.9 %. These rates fall dramatically if the tumor is more widespread at diagnosis to 69.8 % if regional lymph nodes are involved and 13.4 % if distant metastases are present [4].

The options available to rectal cancer patients for treatment of the initial primary lesion are essentially surgical and can impose great financial burden, particularly if the patient lacks sufficient insurance coverage. Alternatively, palliative therapy is also costly. The primary treatment modality for most patients is radical surgical resection. Neoadjuvant and adjuvant radiation and chemotherapy are often used to improve the results attained with this surgical approach. Though a substantial portion of the direct medical costs to the patient for treatment of rectal cancer may be covered by insurance (private, Medicare, Medicaid), many of the hidden costs are often not covered and can be substantial, such as the costs of prescription and nonprescription medicines, transportation, child care, homemaker services, orphan drugs, and lost wages [5]. Data from the nationally representative 2011 MEPS Experiences with Cancer Survivorship Supplement measuring the financial impact of cancer show that 11.9 % of cancer survivors were unable to cover their share of the costs of medical care and 7.1 % had to borrow money or go into debt [6].

This chapter analyzes the costs of rectal cancer patient management focusing primarily on initial treatment costs and costs incurred during the 5 year period after treatment. Few studies follow patients beyond 5 years and even fewer separately provide cost data for all three phases of disease progression, as defined by Baker (initial, continuing, and terminal) [7]. Screening costs and costs related to diagnosis of the initial primary are not analyzed here. Similarly only those studies which report rectal cancer costs separately from colon cancer costs are included.

Methods

Literature Review

A PubMed search of the literature for the past 15 years (1999–2014) was performed to identify citations measuring the cost of rectal cancer patient management. This chapter updates an earlier work analyzing the period 1984–1998 [8]. Keywords used in the search included rectal neoplasms, costs, charges, fees, economics, resection, treatment, and therapy. Articles were eliminated if they examined costs for patients with non-invasive tumors only, if they examined

costs of procedures approved only for use in clinical trials, if they lacked average (per-patient) cost or charge data, or if only nationwide or statewide totals were provided and insufficient data were available to calculate costs or charges on a per-patient level. Also eliminated were many studies which were described as cost-effectiveness, cost-benefit, cost-utility, or cost-minimization analyses, but were mere statements that patient care can be expensive and lacked objective data or formal analyses to substantiate such statements. Studies pertaining to robotic surgery were excluded from the current analysis, as the topic was deemed deserving of a separate paper.

Cost Analyses

All data were identified as either costs or charges. In those instances where it was unclear whether costs or charges were the basis of the analysis, charges were assumed since complete cost data are generally difficult to obtain. Costs are generally defined as resources expended by the manufacturer of the output to produce a given unit of output. These resources typically include such items as personnel, supplies, capital equipment, and overhead. Charges are defined as the price paid by the purchasers of the output to the producer of the output. Charges are generally derived from a facility's cost of producing the unit of output plus some percentage profit. In the case of health services, purchasers are patients or third party payers such as insurance companies.

An exception to the assumption of charges in the presence of ambiguity was made for studies conducted in countries with national health insurance. One might presume that a national health insurance system would not bill itself for more than the cost of a given service and, therefore, it could be assumed that the data reported in such studies referred to costs. However, private hospitals operate within many of these countries. Therefore, unless the article specifically stated that the data were derived from the national health insurance system, the data were interpreted as charges.

The year associated with the cost or charge data was then identified for each article. For those articles which did not provide this information, the year preceding publication of the article was assumed if the publication date was in the first 6 months of the year. The current year was assumed if the publication data was in the last 6 months of the year. For example, if the publication date was March 2000, 1999 data were assumed; if the publication data was November 2000, 2000 data were assumed. The importance of identifying the year associated with the data was twofold. First, for articles authored by individuals from outside the U.S., such data are needed to permit selection of an appropriate exchange rate for conversion of the cost or charge data to a common currency (U.S. dollars). This is necessary to facilitate the use of all studies which meet the inclusion criteria in the analyses. For the eight articles presenting cost or charge data in other than U.S. dollars, the exchange rate for the midpoint of the year was used for conversion [9]. The applicable U.S. dollar exchange rates for the British pound were 0.62 for 2011, 0.54 for 2006, and 0.65 for 2002. The applicable U.S. dollar exchange rates for the remaining currencies were 1.78 for the 2002 Australian dollar, 37.44 for the 1998 Belgian franc, 1.01 for the 2000 Euro, and 105.19 for the 2008 Japanese yen.

The second reason for identifying the year associated with the data was to permit establishment of a baseline from which cost or charge estimates could be inflated to a common year. All costs or charges were inflated to 2014 U.S. dollars using the medical care component of the Consumer Price Index [10]. Since 1960 this component has never been negative. The medical care component increased 3.5 % in 1999, 4.1 % in 2000, 4.6 % in 2001, 4.7 % in 2002, 4.0 % in 2003, 4.4 % in 2004, 4.2 % in 2005, 4.0 % in 2006, 4.4 % for 2007, 3.7 % for 2008, 3.2 % for 2009, 3.4 % for 2010, 3.0 % for 2011, 3.6 % for 2012, and 2.5 % for 2013. A 10-year (2004–2013) average increase in the medical care component of 3.6 % was used as an estimated increase for 2014.

Discounting to factor in the time value of money was not conducted by this author for

studies which did not report already doing so as it was not possible without data for each year of costs. Such data were generally not provided in the published articles. The time value of money is the principle that $1 today is worth more than $1 in the future because current dollars can be invested and, by earning interest, yield more dollars in the future. Discounting is generally used in a cost-benefit or a cost-effectiveness analysis to determine the present value of a stream of funds to be received in the future or costs to be incurred in the future [11].

For studies measuring costs, it was generally assumed, unless otherwise stated, that all direct medical costs were included and all indirect costs were excluded. Direct medical costs are defined as expenses to a facility or health care system (rather than to the patient) related solely to the conduct of a specific activity. Direct costs represent resources expended to provide such services as inpatient services, outpatient services, nursing home services, and hospice services. Components of direct costs include the costs of medical personnel, supplies, and equipment. Indirect costs are defined as costs which cannot be identified with a single activity, service, or product. Such costs are shared by all services based on some unit of service indicator (e.g., heating, light, air conditioning, security).

For studies measuring charges, it was generally assumed, unless otherwise stated, that total medical charges were included and all indirect and psychosocial costs were excluded. Total medical charges are defined for the purposes of this study as expenditures borne by the patient or third party payer for inpatient services, outpatient services, nursing home services, and hospice services. Components of total medical charges include hospital charges, physician fees (inpatient and outpatient), nursing home charges, hospice charges, and prescription drug charges. Indirect costs refer to the costs associated with time lost from work and reduced productivity while on the job due to morbidity and mortality. Psychosocial costs refer to deteriorations in quality of life such as economic dependence and social isolation [11].

Results

Of the over 200 articles identified by the Pub Med literature search and additional hand searching of reference lists, 17 articles were identified which analyzed rectal cancer patient management costs or charges and were not focused solely on robotic surgery (Table 26.1). Only one article contained cost data for all three phases of disease progression [12]. Most of the remaining articles provided data for only the initial phase or the initial phase plus a portion of the continuing care phase of disease progression. The three other studies which did follow patients until death did not separately report costs by phase [13–15]. One study focused exclusively on advanced rectal cancer patients, though not nationwide in scope, did include data from five countries [15]. The 17 identified articles measuring costs have been categorized and will be discussed under the following six specific topic areas with the more general articles discussed first followed by the procedure-specific articles: (1) lifetime and treatment-phase specific costs [12]; (2) advanced cancer care costs [15]; (3) surgery (total mesorectal excision (TME), anterior resection (AR), or abdominoperineal resection (APR)) with or without preoperative radiotherapy [13, 14, 16]; (4) transanal endoscopic microsurgery (TEM) [17–19]; (5) stomas and anastomotic leakage [20, 21]; and (6) open versus laparoscopic surgery [22–28].

Lifetime and Treatment-Phase Specific Costs

The article by Lang et al. [12] is a particularly well written article that fills a void in the recent rectal cancer literature. While lifetime treatment costs for colorectal cancer patients were reported as early as 1989 by Baker et al. and more recently by Etzioni [29] among others, it was not until the early to mid-1990s [30, 31] that attempts were made to separately measure such costs for rectal cancer patients. Data from these pre-2000 articles, though still referenced, are severely out of date. It is important to separately report costs for patients diagnosed with rectal cancer as costs are

Table 26.1 Rectal cancer treatment cost literature 1999–2013

	Time definition	Perspective	No of patients	Costs/charges included	Cost/charges as reported in original study[a]	Costs/charges in 2014 U.S. $
Lifetime and treatment-phase specific costs						
Lang et al. [12]	**Initial**: Up to 1 year after diagnosis and before the last year of life. Patients were only included if lived at least 13 months after diagnosis **Continuing**: Period between first and last year of life if lived at least 25 months **Terminal**: Final year of life or period from diagnosis to death if lived less than 13 months	Medicare and private insurance payments (cost to 3rd party payers) as well as patient co-pays and deductibles (cost to the patient) in 2006 U.S. $; Future costs discounted at 3 % per year	15,582	Charges as a proxy for direct costs of inpatient hospital (including prescription drugs and chemotherapy) and skilled nursing facility stays, outpatient hospital services (including chemotherapy), physician and laboratory services, home health, and hospice care	Initial: $32,683 Continuing: $5,254 Terminal: $14,878 Excess lifetime costs: $26,544	$42,784 $6,878 $19,476 $34,748
Advanced cancer care costs						
Neymark and Adriaenssen [15]	Date of diagnosis to death or last known visit Median follow-up was 530 days	Cost to the national health insurance system in Italy, England, France, Germany, and Belgium in 1998 Belgian francs, using unit prices from Belgium for all five countries	200	Direct costs of hospital stays, outpatient visits, home health visits, physician and laboratory services, radiological examinations, and chemotherapy	Stage III: 881,778 BF $28,552 Stage IV: 716,564 BF $19,139	$51,892 $34,784

(continued)

Table 26.1 (continued)

	Time definition	Perspective	No of patients	Costs/charges included	Cost/charges as reported in original study[a]	Costs/charges in 2014 U.S. $
Surgery with or without PRT						
van den Brink et al [13]	Date of random assignment to TME with or without preoperative radiotherapy until recurrence or death (median follow-up = 38 months; range = 13–68 months)	Cost to society calculated using Markov modelling in 2002 U.S. $, discounted at 3 % per year	1,861	Direct costs of primary treatment, continuing care, and recurrence treatment including inpatient and outpatient services, nursing home care, diagnostic procedures, chemotherapy, and radiotherapy. Travel and out-of-pocket costs are included as are indirect costs associated with lost productivity, informal care and time	PRT + TME: $115,000 TME: $105,200 Cost per QALY: $25,100	 $177,130 $162,036 $38,661
van den Brink et al. [16]	12 month period after total mesorectal excision	Cost to the patient and costs to the Dutch National Health Authority in 2012 €	179	Direct medical costs of inpatient and outpatient services, home health services, medications, and stoma care products	**Provider-reported cost**: 3,730 € or $3,486 **Patient-reported cost**: 3,300 € or $3,084	 $3,702 $3,275
Dahlberg et al. [14]	Date of random assignment to AP/APR with or without PRT until death or 8 years	Cost to society (primarily the national health insurance system) in Sweden in 2001 U.S. $, discounted at 3 % per year	27 PRT + AP; 21 PRT + APR; 18 AR only; 30 APR only	Direct costs of inpatient and outpatient services as well as care for complications and recurrence. Hotel and travel expenses for PRT were also included. Indirect costs, such as lost productivity, were excluded	PRT + AP/APR: $35,268 AP/APR: $30,080 Cost per LY gained: $3,654	 $56,875 $48,509 $5,893
TEM						
Maslekar et al. [17]	Date of TEM or AR to date of hospital discharge	Cost to the national health insurance system in the UK in 2006 £	124 cases; 52 controls	Direct costs of inpatient surgery, intensive care unit and inpatient bed days, and cost of disposable items. Staff, diagnostic testing, and medication costs were excluded because assumed equivalent between the two groups. Estimated equipment costs of £40,000 were also excluded	AR without ileostomy: £4,135; $7,643 AR with ileostomy: £6,323; $11,688 TEM: £ 567; $1,048 11.5 procedures to recover capital costs	 $10,005 $15,300 $1,372

Farmer et al. [18]	Date of hospital admission for TEM or AR to a median follow-up of 33 months (range 20–48 months)	Cost to the national health insurance system in Australia in 2002 Australian $. Unclear if any costs are borne by the patient	36 benign; 14 malignant	Direct costs of inpatient bed days and disposable equipment, and physician (medical) fees. Equipment costs not provided or included	TEM: Aust $2,400 U.S.$1,348 AR: Aust $7,900 U.S. $4,438	 $2,076 $6,836
Hompes et al. [19]	Date of hospital admission for glove TEM to a median follow-up of 5.7 months (range: 2.7–9.4 months)	Cost to the national health insurance system in the U.K. assumed in £. No detail provided. Assume 2011 £	8 benign; 6 malignant	Direct cost of port only included. Costs of complications or conversion to traditional TEM are not included.	TEM with reusable trocars: £31; $50 TEM with disposable ports: £82.50; $132	 $55 $145
Stomas and AL						
Kang et al. [20]	Date of hospital admission for AR to hospital discharge	Charges primarily to third party payers using 2006–2009 data in $. Unclear how much of the cost was born by the patient. 2009 $ assumed	72,055	Total charges associated with the AR admission. Anastomotic breakdown after discharge excluded from analysis.	AR without AL:$51,413 AR with AL: $93,110	$60,238 $109,093
Koperna [21]	Date of LAR through less than 1 year of follow-up. Median follow-up not provided	Cost to the hospital provider in 2000 €	19 LAR with stoma; 48 LAR without stoma or AL; 3 LAR no stoma, with AL	Direct costs per bed day of inpatient and ICU care were comprised of cost of laboratory services, diagnostic imaging, endoscopy, supplies, medications, operating room costs, and costs of devices used during surgery. Indirect costs of lost productivity were not included	**LAR no stoma or AL**: €8,400; $7,850 **LAR with AL**: €13,985; $13,070 **LAR no stoma and AL**: €42,250; $39,486	$13,242 $22,047 $66,606

(continued)

Table 26.1 (continued)

	Time definition	Perspective	No of patients	Costs/charges included	Cost/charges as reported in original study[a]	Costs/charges in 2014 U.S. $
Open versus laparoscopic surgery						
Franks et al. [22]	Date of surgery until 3 months after surgery	Cost to the national health insurance system in the UK in £ using data from a variety of years. 2002 £ assumed	222 LAP; 112 Open	Direct costs per day of inpatient care, ICU care, operating room costs including staff time and supplies, chemotherapy and radiotherapy costs, and complication costs including related readmission costs. Indirect costs associated with lost productivity were also included	**Direct** LAP: £7,148; $10,963 Open: £6,596; $10,117 **Indirect** LAP: £1,112; $1,706 Open: £1,224; $1,827 **Total** LAP: £8,260; $12,669 Open: £7,820; $11,994	 $16,886 $15,583 $2,628 $2,814 $19,514 $18,474
Braga et al. [23] (incorporates all patients in Braga et al. 2005 article) [24]	Date of surgery until a median of 54.2 months after surgery	Cost to the hospital in $. 2006 $ assumed.	83 LAP; 85 Open	Direct costs of surgery (including per hour operating room costs and surgical instruments), routine surgical care per day, complications (including medical, laboratory, technical, and diagnostic services, surgical and therapeutic interventions, prolonged length of stay, associated outpatient visits	Excess costs for LAP compared to Open: OR: $1,748 Surgical care: –$648 Complications: –$749 Total: $351	 $2,288 –$848 –$980 $460

Park et al. [25]	Day of admission until date of discharge	Cost to the national health insurance system in Korea and cost to the patient in $ as components of total charges. The early learning phase was May 2003-July 2004 and the post-learning phase was August 2004–January 2006. Though unclear, costs are assumed to be inflated to at least 2005 levels and reported in U.S. dollars	116 LAP; 81 Open	Direct costs of operating room (including equipment, labor and disposable and reusable supplies) as well as anesthesia, laboratory, radiology, nursing, medications, and admission services. Hospital profit and specialist fees also included. Chemotherapy and radiotherapy costs were excluded as well as indirect costs	Learning phase total charges LAP: $8,088 Open: $6,192 Post-learning phase total charges LAP: $7,983 Open: $7,045	 $11,011 $8,430 $10,868 $9,591
Leung et al. [26]	Date of surgery until date of discharge	Cost to the hospital in US $. 2003 $ assumed	203 LAP; 200 Open	Direct costs for hospital inpatient services and disposables, and per hour operating room costs based on “market rates”	LAP: $9,297 Open: $7,148	$13,769 $10,586
Son et al. [27]	Date of surgery until 3 months after surgery	Cost to the national health insurance system and cost to the patient in 2009 $ based on billed charges	130 LAP; 125 Open	Charges as a proxy for the cost of hospitalization for surgery and readmission for complications (including operation, anesthesia, nursing, laboratory, medications, radiologic tests, disposables). Specialist fees and indirect costs were excluded	Total charges LAP: $7,467 Open: $5.667 Patient co-payment: LAP: $1,602 Open: $899	 $8,749 $6,640 $1,877 $1,053

(continued)

Table 26.1 (continued)

	Time definition	Perspective	No of patients	Costs/charges included	Cost/charges as reported in original study[a]	Costs/charges in 2014 U.S. $
Fujii et al. [28]	Rectal transection procedure, from start to finish	Cost in Japanese yen. 2008 yen assumed	107 stapling; 28 Y-hood	Direct cost of the automatic stapling unit and Y-hood	Stapling (2–4 times): 92,505 yen	
					$3,486	$4,215
					Y-hood: 53,107 yen	
					$3,084	$3,729

AL anastomotic leak, *APR* abdominoperineal resection, *AR* anterior resection, *LAP* laparoscopic surgery, *LAR* low anterior resection, *PRT* postoperative radiotherapy, *TEM* transanal microscopic endosurgery, *TME* total mesorectal excision

[a]For studies reporting costs/charges in currencies other than U.S., the foreign currency has been converted to U.S dollars based on conversion rate at the time of the study

generally higher for these patients when compared to patients diagnosed with colon cancer as this chapter will demonstrate.

Using the linked Surveillance Epidemiology and End Results (SEER) Medicare database, Lang et al. [12] calculate excess lifetime health care costs separately for patients with colon (N = 41,256) and rectal cancer (N = 15,582) overall (and combined), by stage, age at diagnosis, and stage within age at diagnosis. As outlined in Table 26.1, services included in these cost calculations are inpatient hospital (including prescription drugs and chemotherapy) and skilled nursing facility stays, outpatient hospital services (including chemotherapy), physician and laboratory services, home health, and hospice care. Charges were used as a proxy for costs. Future costs over time were discounted at 3 %. Excess costs were defined as the difference in costs between rectal cancer patients and matched controls. Excess lifetime healthcare costs in 2006 U.S. dollars ranged from −$18,770 for patients with TNM stage IV disease to $49,020 for those with TNM stage II disease. The excess costs for stage IV were negative because the controls outlived those with rectal cancer. In comparison to patients diagnosed with colon cancer, patients with rectal cancer had higher excess costs for TNM stages I, II, and III, but significantly lower excess costs for TNM stage 0 and IV. By age, excess costs were highest ($36,790) for patients ages 66–74 at diagnosis and were lowest for those 85 years of age and older ($12,960). In comparison to patients with colon cancer, patients with rectal cancer had similar excess costs at ages 66–74 and significantly lower costs at both ages 75–84 and 85 and older.

Lang et al. [12] also report total costs (not excess costs) for patients with rectal cancer by phase of disease progression (initial $32,683, continuing care $5,254, and terminal $14,878) as well as by stage and age within phase. Initial care was defined as the period up to 1 year after diagnosis and before the last year of life. Patients were only included in the initial care period if they lived at least 13 months after diagnosis. Continuing care was defined as the period between the first and last year of life if the patient lived at least 25 months. Terminal care was defined as the final year of life or the period from diagnosis to death if the patient lived less than 13 months. Similar cost data are provided for patients with colon cancer and all patients combined. Differences between colon and rectal cancer costs appear to be highest in the continuing care phase overall and by both stage and age. I strongly urge readers of this chapter to seek out this article as a reference.

Advanced Cancer Care Costs

Neymark and Adriaenssen [15] measured variation in resource utilization and costs associated with ten hospitals across five countries (Italy, England, France, Germany, and Belgium). Unit costs from Belgium for 1998 were applied to resource utilization for all countries in the study due to lack of unit cost data at a similar level of detail for countries other than Belgium. Costs to the national health care systems of the respective countries included those associated with hospital stays, outpatient visits, home health visits, physician and laboratory services, radiological examinations, and chemotherapy. Twenty patients from each of the ten facilities with a new diagnosis of TNM stage III or IV colon or rectal cancer participated in the study. Unfortunately, reported costs were unstable due to the small number of patients per facility. During a median follow-up of 530 days, total costs for patients diagnosed with TNM stages III and IV rectal cancer were $23,552 and $19,139 in 1998 U.S. dollars.

Surgery (TME, AP, APR) with or Without Preoperative Radiotherapy

Two studies evaluate the costs of surgery with and without preoperative radiotherapy. One is a cost-effectiveness study [14] and the other is a cost-utility study [13]. Dahlberg et al. [14] reported data on a sample of 98 cases from a single Swedish health care region participating in the much larger Swedish Rectal Cancer Trial. Patients were followed from AP or APR with or

without 1 week of high-dose fractionated (5×5 Gy) preoperative radiotherapy for 8 years or until death. Costs to society, primarily the national health insurance system in Sweden, included those associated with inpatient and outpatient services as well as care for complications and recurrence. Hotel and travel expenses for preoperative radiotherapy were also included. The additional cost for patients who underwent preoperative radiotherapy was $5,188 with a discounted additional life years gained of 1.42 compared to those not undergoing preoperative radiotherapy. The cost per life year gained was estimated at $3,654 (CI: $908–$7,292). No other study at this point in time had yet shown a significant survival benefit for preoperative radiotherapy. Thus, the authors used sensitivity analysis to examine the effect of a much smaller survival benefit of 10 months rather than the 21 month pre-discounting figure. Under this assumption, the cost per life year gained would vary from $1,897 to $15,238. Small sample size may account for the larger survival benefit (21 months) identified. The lack of adjustment for quality of life losses may also have an impact, as pointed out by van den Brink [13].

Van den Brink [13] took a slightly different approach conducting a cost-utility analysis based on patient data, but using computer simulation with literature-based assumptions to predict outcomes, such as recurrence, and associated costs. Specifically, transition state Markov modelling was conducted of TME with and without short-term (5×5 Gy) preoperative radiotherapy. Data on 1861 patients with resectable rectal cancer were obtained from 84 hospitals in the Netherlands, 23 hospitals in other European countries, and 1 Canadian hospital. Costs to society included those associated with primary treatment, continuing care, and treatment of recurrence including inpatient and outpatient services, nursing home care, diagnostic procedures, chemotherapy, and radiotherapy. Travel and out-of-pocket costs were included as well as indirect costs associated with lost productivity, informal care and time. After a median follow-up of 38 months after random assignment to a treatment group, the total costs in 2002 U.S. dollars for preoperative radiotherapy and TME were $115,000 ($66,300 in health care costs and $48,700 in non-health care costs) compared to $105,200 ($56,800 and $48,400, respectively) for TME alone. Clearly, the primary difference was in health care costs ($9,500) rather than non-health care costs ($300). Based on the total difference in costs of $9,800 and the difference in lifelong QALYs of 0.39, the costs per QALY was $25,100 which is considered acceptable, as it is less than the $50,000 threshold commonly used. However, the cost per life year gained in this study was considerably higher than that identified by Dahlberg et al. [14]. This study [13] is notable as it is one of the few studies reviewed in this chapter that included indirect costs. These added costs clearly contributed to the difference in costs per year life gained compared to the Dahlberg et al. [14] study.

A third study assessed whether patients or providers were better sources of data on health care utilization and costs [16]. This study of 179 patients across 49 hospitals combines data from the cost-utility analysis reported above with data collected from weekly patient cost and utilization diaries and health care utilization data collected from secretaries of surgical departments, pharmacies, and suppliers of stoma care products for the 1 year period after the patient's TME surgery. Costs to the Dutch National Health Authority and to the patient included those associated with inpatient and outpatient services, home health services, medications, and stoma care products. For the 12 month period after TME, divided into three intervals (discharge to 3 months, 3–6 months, and 6–12 months) convergent validity was high between providers and patients for outpatient visits and inpatient admissions. Though small sample size limits the generalizability of the results, a significant difference was detected for medications ($p < .001$) and borderline significance was detected for stoma care products ($p < .01$), with providers consistently reporting higher utilization and, therefore, costs. The authors recommended greater reliance on providers in future studies for medication and stoma care utilization reporting. The total costs in 2012 U.S. dollars were $3,486 as reported by providers

and $3,084 as reported by patients. This study serves as a valuable resource to researchers designing studies where cost is of importance and limited funds are available for data gathering.

TEM

Two studies evaluated the costs of TEM versus AR as a method of treatment for select rectal cancers [17, 18]. The larger (N = 176) of the two studies [17] focused solely on costs from the date of the surgery to the date of hospital discharge. Though inpatient and intensive care unit bed day costs as well as costs of inpatient surgery and disposable items were included, equipment costs were not directly factored in. Labor, diagnostic testing and medication costs were excluded as the authors assumed such costs would be equivalent between patients undergoing AR with or without ileostomy and those undergoing TEM. The complication rate was 8 % for the TEM group and 29.5 % in the AR group. It is unclear whether complications after discharge were included in these rates, as costs of complications after discharge were not included. The majority of patients in this study had well- to moderately-differentiated pT1 disease or were elderly or at high risk with pT2 disease. No TEM procedures required conversion to open. Total costs to the national health insurance system in the UK associated with TEM were $1,048 in 2006 U.S. dollars. For AR with and without ileostomy, the costs were $11,688 and $7,643, respectively. The authors estimated that it would take 9–10 months, given current caseload (no number provided), to recoup the $73,937 TEM purchase price. The assumption by the authors that labor, diagnostic testing, and medication costs would be equivalent and, therefore, could be excluded from analysis seems an unfortunate decision given the difference in complication rates. Thus, the difference in costs between TEM and AR as calculated by the authors should be considered conservative and are likely higher in favor of TEM.

The Farmer et al. study [18] was a very small study primarily focused on patients with benign lesions and patients who had already had an open procedure but with positive margins, but did include 14 patients with malignant rectal lesions, 12 of whom underwent TEM for cure. Patients were followed for a median of 33 months (range 20–48 months). The perspective of the cost analysis was unclear, but appears to be cost to the national health insurance system in Australia. The analysis included only inpatient bed day costs, physician fees and the cost of disposables. Though equipment costs were neither provided nor included in the analysis, the statement is made that the savings per case easily covered the equipment cost. It is not clear at what point in time equipment costs were covered as the study reports on the first 50 cases conducted at the facility. The cost in 2002 U.S. dollars of TEM compared with that for AR was $1,348 and $4,438, respectively. Inflating the 2002 U.S. dollar figures reported here to 2006 levels using the medical care component of the U.S. Consumer Price Index [10] as a proxy to permit comparison with Maskelar et al. [17], suggests higher total costs for TEM and lower costs for AR (either with or without ileostomy) than reported in the earlier study.

An even smaller (N = 14) study [19] evaluates the use of a glove port in TEM compared to traditional TEM. Only six patients had malignant rectal cancer (3 pT1, 1 pT2, and 2 pT3), only four of whom were believed to have had malignant rectal cancer preoperatively. Median follow-up from date of hospital admission was 5.7 months (range 2.7–9.4 months). Only the cost of the port itself was included. The costs of conversion to traditional TEM, which was necessary for two patients, were not addressed. There was no statement that "intent to treat" was the method used to categorize patients. Thus, it is assumed that those who converted to traditional TEM were classified as traditional TEM. The cost of treating the two patients with postoperative complications (fever treated with oral antibiotics and bleeding requiring transfusion of 2 units) was also not factored in. Nevertheless, the cost to the national health insurance system in the UK in 2011 U.S. dollars for TEM with reusable trocars was $50 and for TEM with disposable ports was $132. The very

small sample size and exclusion of complication-related costs limits the generalizability of this study.

Stomas and Anastomotic Leakage

Two studies addressed the topic of anastomotic leakage, a complication occurring in 5–20 % of patients after rectal cancer surgery. A very large (N = 72,055) study [20] uses charge data from the Nationwide Inpatient Sample (NIS) for 2006–2009 as a proxy to estimate the cost of anastomotic leakage after AR for rectal cancer. Charges included all those associated with the AR admission, which would include the treatment cost for complications arising from surgery. Anastomotic breakdown after discharge was excluded from analysis. Patients with inflammatory bowel disease were excluded from the analysis as were emergency room admissions. Raw numbers were weighted to reflect national averages. Approximately 94 % of patients underwent open procedures for which the incidence of anastomotic leak was higher (16.06 % versus 14.04 %). Overall, the leak rate was 13.68 %. Multivariate analysis revealed that weight loss and malnutrition, fluid and electrolyte disorders, male gender, and stoma placement were associated with a higher risk of anastomotic leak. Important variables, such as cancer stage, tumor location, history of abdominal surgery or radiotherapy, were not available in the NIS file and, therefore, not factored into the analysis. Smoking was also excluded from analysis as it was infrequently coded. Charges in 2009 dollars associated with AR without anastomotic leak were $51,413 (C.I. $28,430–$59,558), compared to $93,110 (C.I. $39,149–$109,701) when anastomotic leak was present. It is unclear what portion of the charges was borne by patients as opposed to third party payers. It is assumed that third party payor covered the majority of the costs.

The second study [21] was a very small study (N = 70) designed to assess the costs of stomas and anastomotic leak. Patients from a single facility were followed from the date of low anterior resection (LAR) for less than 1 year (exact follow-up duration not reported). The location of the tumor among patients who had no stoma was primarily the proximal third (45.1 %) and middle third (35.3 %) of the rectum. For those patients with stomas, 73.7 % were for tumors located in the distal third of the rectum. Assessed costs per bed day of inpatient and ICU care included the costs of laboratory services, diagnostic imaging, endoscopy, supplies, medications, operating room costs, and the costs of devices used during surgery. The indirect costs of lost productivity were excluded. Total costs to the hospital provider in 2000 U.S. dollars for LAR with no stoma or anastomotic leak were $7,850. For LAR with stoma but without anastomotic leak, costs totaled $13,070. Costs were significantly higher for LAR with anastomotic leak, $39,486. Though a small study, the intended purpose was to raise awareness around the need to establish a benchmark for LAR with respect to stomas and anastomotic leak. The authors suggested that a benchmark of 10 % or less would hold costs down to $11,215 per patient treated.

Open Versus Laparoscopic Surgery

Five articles compared the costs of laparoscopic and open surgery for rectal cancer. All found laparoscopic surgery to be more expensive than open surgery, primarily due to longer operation time and higher equipment costs, not factoring in the specialized surgical skills required. With the exception of Braga et al. [23], all calculated short-term costs, either during the surgical admission alone or within 3 months of surgery. Franks et al. [22] reported on the costs of a subset of 334 patients diagnosed with rectal cancer and 348 diagnosed with colon cancer who participated in the Conventional vs. Laparoscopic Surgery in Colorectal Cancer (CLASICC) trial. This is one of the few studies that provided separate data on the indirect costs of lost productivity. Included in the direct costs were inpatient and ICU bed day costs, operating room costs, including staff time and supplies, chemotherapy and radiotherapy costs, and complication costs including related readmission costs. Patients were randomized to

the two treatment arms and followed until 3 months after surgery. Total costs to the national health insurance system in the UK in 2002 U.S. dollars for laparoscopic versus open surgery for rectal cancer were $12,669 and $11,994, respectively. Direct costs alone for rectal cancer were $10,963 for laparoscopic surgery and $10,117 for open surgery. Indirect costs were $1,706 and $1,877, respectively. Rectal cancer costs were consistently higher than colon cancer costs in all three categories (total, direct, and indirect) for both procedures, Total costs for laparoscopic versus open surgery for colon cancer were $8,569 and $8,441, respectively.

Two papers by Braga et al. [23, 24] were identified in the literature search, but the 2007 version included all rectal cancer cases that were included in the 2005 version and had a longer median follow-up period of 54.2 months after surgery. This study differs from the others on this topic in that only excess costs for laparoscopic surgery, in comparison to open surgery, were reported, rather than also reporting separately the costs for both laparoscopic and open surgery. As a result, it was somewhat difficult to compare the results of this study to those of others in the group. The sample size (N = 168) was about half that of the Franks et al. [22] study with respect to patients treated for rectal cancer. However, the study is similar to that of Franks et al. [22] in that patients were randomized to the two treatment arms. Total costs to the hospital included those associated with surgery (including per hour operating room costs and surgical instruments) and routine daily surgical care, as well as costs due to complications (including medical, laboratory, technical, and diagnostic services, surgical and therapeutic interventions, prolonged length of stay associated with complications, and related outpatient visits). The net excess costs to the hospital in 2006 U.S. dollars for laparoscopic surgery as opposed to open surgery were $351. Excess costs for laparoscopic surgery by category were $1,748 for operating room costs, −$648 for surgical care, and −$749 for complications. Negative values for a particular cost category indicated that laparoscopic surgery was less expensive then open surgery.

The analysis of Son et al. [27] takes a different perspective than the previous two, focusing on costs to both the Korean national health insurance system and to the patient based on billed charges. The sample size (N = 255) was somewhat larger than Braga et al. [23] but smaller than Franks et al. [22] In addition, the study was more narrowly focused on surgery for cT3N0–2 mid or low rectal cancer after preoperative fluoropyrimidine-based chemoradiotherapy (50 × 4 Gy). Patients were a subsample from the Korean National Cancer Center, one of the facilities participating in the larger COREAN trial [32]. Patients were randomized after preoperative chemoradiotherapy to the two surgical treatment arms and followed for 3 months after surgery. Total charges included those associated with hospitalization for surgery (including inpatient bed day costs) and readmission for complications (including operation, anesthesia, nursing, laboratory, medications, radiologic tests, and disposables). Specialist fees and indirect costs were excluded. Total charges in 2009 U.S. dollars were $7,467 for laparoscopic surgery and $5,667 for open surgery. Patient co-payments were $1,602 for laparoscopic and $899 for open surgery. It is assumed that patient co-payments were included in the total reported charges. Thus, costs to the Korean national health insurance system would be $5,865 and $4,767, respectively. Overall operation costs and, specifically consumables, were significantly more costly for laparoscopic surgery, as was anesthesia, while medical therapy and nursing were more expensive for open surgery.

The next two studies [25, 26] compared costs between laparoscopic and open surgery only for those patients diagnosed with rectosigmoid cancer (N = 403). Costs were not separately reported for cancers of the sigmoid colon versus rectum. Leung et al. [26] focused solely on costs associated with the surgery as accrued during the initial admission. Total costs to the hospital included those for hospital inpatient services and disposables as well as per hour operating room costs based on "market rates." In 2003 U.S. dollars, the total costs of laparoscopic surgery were $9,297 versus $7,148 for open surgery. Twenty patients

in the laparoscopic surgery group and 15 patients in the open surgery group were found to have local invasion intraoperatively. The total costs of the operation for this subgroup were $9,729 and $9,850, respectively. Total costs as identified in this study are difficult to compare with those reported by the studies discussed thus far due to the limited definition of the patient population and time period for which costs were assessed.

Park et al. [25] reported on the results of one surgeon at one hospital in Korea who performed both laparoscopic and open surgery for rectal cancer. The intent was to examine the impact of the learning curve on costs for laparoscopic surgery. As the surgeon was observed over time, once the operation time plateaued for laparoscopic surgery, all such surgeries performed thereafter were deemed post-learning curve phase. Over the same time interval, no change was observed in open surgery operation times. Total charges, as a proxy for costs, primarily to the national health insurance system for the 197 patients in the study included costs associated with the operating room (equipment, labor, and disposable and reusable supplies) anesthesia, laboratory, radiology, nursing, medications, and admission services. Hospital profit and specialist fees, for which the patient is billed, were also included. Chemotherapy and radiotherapy costs as well as indirect costs were excluded. The study spanned May 2003–January 2006 with the learning phase ending at July 31, 2004. During the learning phase, total costs in U.S. dollars were $8,088 for laparoscopic surgery and $6,192 for open surgery. In the post-learning phase, total costs in U.S. dollars were $7,983 and $7,045, respectively. The portion of these costs borne by the patient was $5,310 and $3,425 in the learning period and $4,899 and $3,781 in the post-learning period, respectively. It is unclear whether there was an increase in unit costs over time already factored into the total costs reported by the authors. It is also possible that costs for the learning period truly reflect costs for the 2003–2004 period and those for the post-learning phase reflect costs in the 2004–2006 period. Assuming the latter to be the case, the difference in costs reported by the study should be considered conservative. It was assumed for purposes of the current analysis, that costs were reported in at least 2005 U.S. dollars. It is unclear whether the data were collected prospectively or retrospectively. This distinction is particularly important to interpreting the results of this study, because the surgeon who was observed is one of the authors of the study.

Fujii et al. [28], the final study in this section on laparoscopic surgery, examined the use of clamp forceps and a Y-shaped vinyl hood for rectal transection as a method of avoiding anastomotic leakage and potentially minimizing costs associated with multiple stapling. Total costs included those associated with the various automatic stapling unit devices and the Y-hood. This was a small study of 135 patients; 28 underwent the Y-hood procedure, primarily using the Contour Curved Cutter device, and the remainder underwent the standard procedure involving multiple stapling, primarily using the EndoGIA97 device. The rate of anastomotic leakage was higher (11.2 %) in the multiple-stapling group compared to the Y-hood group (7.1 %). Based on the limited components included in the cost comparison, total costs in 2008 U.S. dollars were $879 for the multiple-stapling method and $505 for the Y-Hood group method. The generalizability of the study is questionable given the very small sample size and limited scope of the cost analysis.

Conclusion

As demonstrated by the preceding discussion, the major difficulty in understanding the cost literature in the rectal cancer field is directly related to the varying inclusion and exclusion criteria as well as differences between health care systems with respect to how health care services are reimbursed. Another major problem is the lack of information for many studies regarding the cost analysis methodology. Greater detail is generally provided for the clinical details of these studies, but little to no detail is provided on whether cost or charge data were utilized, what year's currency the results were presented in, whether discounting was used and the reasoning, and the

perspective of the analysis. Economists have often called for standardization in the details provided in cost studies [33, 34]. In reviews of the literature to identify whether any studies would meet various proposed criteria, few pass the test [35].

Assumptions are a recurring problem in cost analyses in general. Researchers often "assume away" indirect costs or labor, for example, because of the assumed difficulty in calculating associated costs. Often made in haste before consulting either the literature or an economist, such assumptions often negate the true value of the work. As is frequently said, "the devil is in the details." The advantage of tools such as Markov modelling, as used by van den Brink et al. [13], is the ability to test the impact of various assumptions on outcomes and costs in sensitivity analysis.

As a result of the lack of standardization, cost and charge estimates vary widely. It is hoped that this review of the cost literature at least points out some of the shortcomings and allows the reader to examine such studies more carefully. Limitations of the various studies have been highlighted as have major contributions of selected studies. Future research on costs among patients diagnosed with rectal cancer should take a much broader approach and address costs, not only during the initial surgical admission, but throughout the survivorship continuum. Potential topics for study include examining the financial burden of rectal cancer and the potential for significant medical debt and even bankruptcy among rectal cancer survivors, analyzing insurance trajectories over time and whether rectal cancer survivors are foregoing care due to cost, delving into employment patterns and whether rectal cancer survivors are locked into a particular job because of the insurance coverage associated with the job, and examining utilization and costs of prescription drugs throughout the lifespan of rectal cancer survivors. Research is also need to further the work of Landrum et al. [36] which analyzed whether living in a *Dartmouth Atlas* identified high health care spending area was associated with receiving recommended adjuvant chemotherapy and radiation therapy for stage II and III rectal cancer. This work could clearly be expanded to examine compliance with the current guidelines of the American Society of Colon and Rectal Surgeons or National Comprehensive Cancer Network.

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Quality Assurance in Rectal Cancer Management

27

Anne J. Breugom, Petra G. Boelens, and Cornelis J.H. van de Velde

Abstract

Rectal cancer management has evolved over the past decades. Major improvements in locoregional recurrence rates and survival were made by the introduction of total mesorectal excision (TME). The use of preoperative (chemo)radiation and the possibility of more accurate staging with MRI scanning resulted in further improvements in rectal cancer outcomes.

To further optimise and improve the quality of rectal cancer care, quality assurance in rectal cancer treatment is of great importance. Auditing is an effective instrument to monitor the quality of care and to improve outcome. Other tools to improve the quality of rectal cancer care are for example guideline formation, multidisciplinary team management, and care pathways.

Keywords

Quality assurance • Audit • Multidisciplinarity • Guidelines • Quality indicators • Cancer registry

Introduction

Each year over 200,000 patients in Europe die of colorectal cancer [1]. It is one of the most commonly diagnosed cancers and its incidence is still increasing. About one third of all colorectal tumours develop in the rectum. Rectal cancer management significantly evolved over the past decades. Major improvements in locoregional recurrence rates and survival were made by the introduction of total mesorectal excision (TME) [2–4]. Moreover, the possibility of accurate preoperative staging with MRI scanning [5–8], as well as the use of preoperative (chemo)radiation resulted in further improvements in rectal cancer management [9, 10]. Although preoperative (chemo)radiation demonstrated a reduction in 5-year locoregional recurrence rates, no survival benefit was shown [10]. Besides, there is currently no evidence to administer adjuvant chemotherapy as standard treatment for rectal cancer patients.

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With the use of combined treatment modalities, rectal cancer management has become increasingly complex. To further optimise and improve the quality of rectal cancer care, measuring and monitoring rectal cancer treatment are of utmost importance.

What Is Quality Assurance?

Quality assurance can be defined as all those planned and systematic activities required realising minimal standards of high quality cancer care. Quality assurance programmes aim to optimise quality of care by determining standards and assuring that these standards are met [11]. Quality assurance is important for adequate medical decision making and is not a new concept in healthcare. During the Crimean war, Florence Nightingale (1820–1910) assessed and improved quality of nursing care by routinely measuring health outcomes with death as endpoint. About 50 years later, Ernest Amory Codman (1869–1940), a surgeon at Boston Massachusetts General Hospital, developed the 'End Result' idea. He defined this as: 'The common sense notion that every hospital should follow every patient it treats, long enough to determine whether or not the treatment has been successful, and then to inquire, "If not, why not" with a view to preventing similar failures in the future' [12]. Although it sounds very sensible to do so, Codman did not receive any support on his 'End Result' idea and finally, he was ostracised. Quality assurance implementation has endeavoured many obstacles; medical professionals were concerned that their performance would be regarded as unsatisfactory or misinterpreted by media as malpractice. Nowadays, the importance of structural quality assurance in cancer management is increasingly recognised. However, transparency about patient outcomes is still scarce in several disciplines involved with cancer care.

Current insights show that the combination of implementing surgical techniques, registering outcome and feedback on performance, all improve clinical outcome of rectal cancer surgery [13–16]. For example, in non-metastasised rectal cancer management, surgery is the main curative treatment modality. Before the introduction of TME surgery [2, 3], unacceptable high rates of pelvic recurrence and distant relapse resulted in poor survival. National rectal cancer audits were able to improve local recurrence rates and survival [13–15].

However, in an evolving medical landscape of integrated multidisciplinary care, it can be quite difficult to assess the quality of 'tailor-made' or 'personalised' cancer care. Next to this challenge, inevitably there will be an ongoing debate on how to measure quality, what standards ensure good quality, and how this is influenced by case mix, doctors and patient preferences.

Tools for Quality Improvement

Quality improvement in rectal cancer care can be achieved by a number of methods; randomised trials, clinical evidence based guidelines, meetings and workshops, registry and auditing outcome/performance, multidisciplinary teams (MDTs), integrated care pathways, and performing patient satisfaction questionnaires (Table 27.1). This chapter will focus on most of these aspects.

Cancer Registries

Since the mid-twentieth century, cancer registries have supplied population-based, comparative survival statistics. The first population-based registry in Denmark that started in 1943 was collected data (1) as a basis for an individual follow-up of patients, (2) for reliable morbidity statistics with a view to an accurate estimate of therapeutic results, and (3) for accurate evaluation of variations in incidence of malignant neoplasms. Other countries followed this initiative by setting up cancer registries.

In 1989, EUROCARE (EUROpean CAncer REgistry-based study on survival and CARE of cancer patients) was funded, based on collaboration

Table 27.1 Tools to improve cancer care

Tools to improve cancer care	Strengths	Weaknesses
Randomised trials	Proof of treatment effects	Selection bias, high costs, time-consuming, confounding factors
Evidence based guidelines/ consensus	Create awareness, focus on key treatments	Rapidly outdated
Meetings and workshops	Create awareness, focus on key treatments	Dependent on speakers/teachers for quality of information transfer
Registry and audit patient characteristics and treatment outcome	Reflect performance and show where improvement can be made	Time-consuming, trouble specifying quality
MDT before and after treatment	Echo of guidelines, reflect on decisions, multidisciplinary communication	Influence of workload/time pressure, dominant persons in a group, team morale
Integrated care pathways	Improve the speed of diagnosis and improve patient communication	Costs to realise the pathway, might not reach individual patient wishes
Patient satisfaction surveys	Reflect on performance	Compliance

between the Istituto Nazionale Tumori (Milan, Italy), the Istituto Superiore di Sanità (Rome, Italy) and population-based cancer registries from 12 European countries, with incidence and survival data available. EUROCARE is a cancer epidemiology research project on survival of European cancer patients [17]. The aims of the EUROCARE project are (1) to describe cancer patient survival in Europe, (2) to disclose whether there are any differences between populations, and if so, how large they are, how they evolve and how reliable the survival estimates [18]. This project was the first to compare cancer survival rates between populations. In the EUROCARE-4 study, colorectal cancer patients diagnosed between 2000 and 2002 demonstrated a mean 5-year relative survival of 56.2 %. However, there was large variation in survival among European countries. Especially North and Central Europe showed best survival rates, while survival rates in the Czech Republic and Poland were substantial lower (45.2 % and 46.0 % respectively) than average [19]. In the most recent EUROCARE-5 analysis, 5-year relative survival increased for rectal cancer with a similar variation between European regions [20].

Comparing survival of patients diagnosed with cancer between different populations is difficult to interpret, as more prolonged survival may depend on later death or earlier diagnosis (adding "lead time"). In order to be able to compare survival rates between different registries, standardised information on disease stage at diagnosis, on diagnostic procedures used for staging, and on treatment decisions are necessary. These items are usually not available from population-based cancer registries.

European Audits

Auditing is an effective instrument to monitor the quality of care and to improve outcome, and can be defined as systematic and independent check-up of outcome data of patients undergoing certain procedures followed by feedback on performance (Fig. 27.1). This way, health care professionals get continuous feedback, own practices will be compared with selected quality standards. The identified gaps provide opportunity for continuous quality improvement. To achieve this, health care providers need to specify clinical endpoints that define high quality care most appropriate. Measuring these endpoints can be challenging in practice. For example, we do know that patients with less than ten nodes found have worse outcomes in general, and we know that more lymph nodes are found if more are requested by (inter-) national recommendations [21].

Since 1993, several European countries initiated a surgical audit. Most audits were initiated

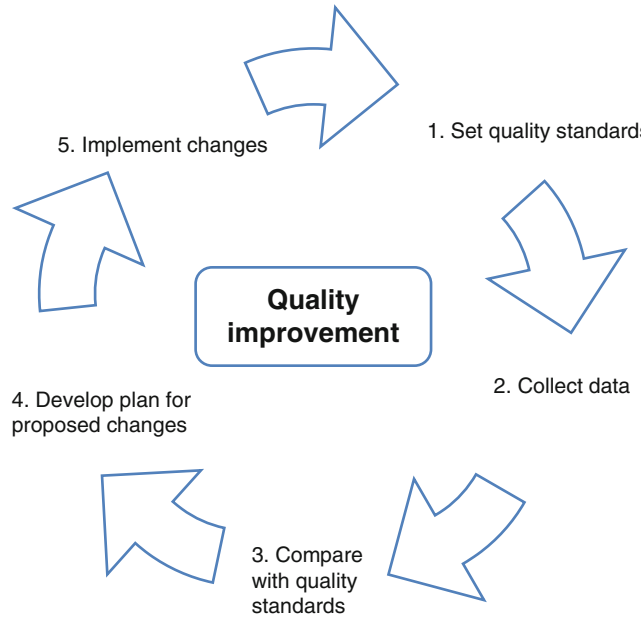

Fig. 27.1 Audit cycle (From Breugom et al. [11], by permission of Oxford University Press)

for rectal cancer, because of poor outcomes and variation in outcomes between hospitals and individual surgeons. Later, most rectal cancer audits expanded with registry of colon cancer outcomes. Currently, there are eight surgical (colo)rectal audits in Europe (Table 27.2). The Norwegian Rectal Cancer Project started in 1993, and is the first initiated audit. Outstanding results were achieved after 4 years: the share of applied TME surgery increased from 78 to 92 % and the local recurrence rate dropped from 28 to 7 % [13]. Moreover, auditing appeared to be cost effective. Currently, the audit is called the Norwegian Colorectal Cancer Project. The Swedish Rectal Cancer Registry (now: the Swedish Colorectal Cancer Registry), an audit for rectal cancer patients, also demonstrated remarkable results [22]. More than 97 % of the patients with invasive rectal cancer were recorded. According to the Swedish healthcare system, pathologists and surgeons are obliged to report cancer diagnoses to the Swedish Cancer Registry. Between January 1995 and December 2003, 13,343 patients treated for rectal cancer were registered. Postoperative mortality declined under 2.5 % and the 5-year local recurrence rate was 9.5 % [22].

Furthermore, rectal cancer survival improved from 36.1 % in the period 1960–1964 to 57.6 % in the period 1995–1999 in Sweden [23]. It is noteworthy that survival of rectal cancer patients even exceeded colon cancer survival, whereas considerable improvements were made by implementation of adjuvant therapy for colon cancer patients during that period, while this did not have an effect on rectal cancer patients. This demonstrates the benefits of structural surgical training and feedback. After the excellent results of the Norwegian Rectal Cancer Project, several other countries have initiated audits on (colo)rectal cancer (Table 27.2).

Although all national audits showed remarkable results, variation in outcomes between and within European countries still exists. To reduce variation within Europe, the EURECCA project has been initiated. EURECCA is the acronym of European Registry of Cancer Care (or in short European Cancer Audit) and is initiated to form a European platform for sharing data of registries and audits to learn from each other, as well as to form a core dataset in Europe. EURECCA Colorectal aims to improve colorectal cancer care in Europe by harmonising and standardising cancer management. Furthermore, subgroups of patients, such as older patients are often excluded from trials. With large population-based studies, evidence can also be obtained for these

Table 27.2 National audits

Country	National/ regional date of launch	Name	Website
Norway	National 1993	Norwegian Rectal Cancer Project	www.kreftregisteret.no/
Denmark	National 1994	Danish Colorectal Cancer Group (DCCG) database	http://www.regionh.dk/kliniskedatabaser/menu/Nationale+databaser/Dansk+Kolorektal+Cancer+Database.htm
Sweden	National 1995	The Swedish Colorectal Cancer Registry	–
Italy	1999	STORM	http://www.storm.edu/
Germany, Poland, Lithuania, Naples	2000	International quality assurance in colorectal carcinoma	–
UK	2001	National Bowel Cancer Audit Programme	http://www.hqip.org.uk/national-bowel-cancer-audit-programme-nbocap/
Spain	2006	The Spanish TME project	–
Netherlands	2009	Dutch Surgical Colorectal Audit	http://dsca.clinicalaudit.nl/

subgroups. Moreover, for certain topics, as for example omission of surgery in rectal cancer patients with a complete remission after neoadjuvant chemoradiation, it is not possible to set up a trial. By developing a uniform worldwide database of all these patients, we will get insight in the value of the 'watch and wait' approach after a complete remission.

Quality Indicators

Safety, effectiveness, patient-centeredness, timeliness, efficiency, and equity, are the six quality concepts that are nowadays implemented in health care organisations. To improve the quality of care, measurement plays an important role and can be done by using quality indicators. This way, potential problems that might need attention can be identified. Quality indicators are defined as 'measurable characteristics of care that reflect the quality of care' and serve as standards by which *structures*, *processes*, or *outcomes* of care can be measured. Structural indicators include information on the hospital organisation, while process indicators describe medical care, and outcome indicators focus on outcomes as for example mortality and morbidity. Process indicators have the advantage that data are mostly present in existing databases and that the influence of case-mix is limited. However, outcome indicators are clearer in their relation with quality of care, but are affected by case-mix factors (for example gender, age, ASA classification, Charlson comorbidity index, and previous operations) for which one needs to adjust. Without adjusting for case-mix, hospitals with the sickest patients can incorrectly be stated as the worst hospitals.

Quality indicators are preferably based on scientific evidence, but when limited or weak evidence exists, they need to be developed based on consensus within expert panels (for example by using the 'Delphi' method). Quality indicators that are based on scientific evidence have *content validity* and indicators that are based on consensus have *face validity*. Defining measurable characteristics can be a challenge, just as developing a 'perfect' quality indicator. However, a good quality indicator must at least have been tested for feasibility, reliability, acceptability, validity, and sensitivity to detect changes.

More specific for rectal cancer, examples for process indicators could be:

- The amount of patients discussed within multidisciplinary team meetings
- The amount of patients with adequate tumour staging by MRI of the pelvis before resection
- The amount of patients of which the circumferential resection margin (CRM) of the resection specimen was described in the pathology report [24].

Traditional outcome quality indicators for rectal cancer care were for example survival and recurrences. Nowadays, endpoints as quality of life or functional outcome might be more important for patients than surviving rectal cancer with many invalidating complaints, such as diarrhoea, urinary incontinence, and sexual dysfunction. This shows the importance of assessing and reassessing every quality indicator at a regular basis to evaluate if it still is the most appropriate indicator to represent quality.

Guideline Formation

Another essential component in order to improve the quality of cancer care is guideline formation. Guidelines are needed as a basis for health-care professionals in treating rectal cancer patients. However, since science rapidly evolves, it must be taken into account that guidelines are not always completely up-to-date.

Recommendations in guidelines must be based on highest available evidence. Randomised trials are needed to test hypotheses under experimental conditions, while large cohort studies are necessary to translate the use of a certain treatment on population level. If no evidence is available, agreement on recommendations can be based on expert opinion. An expert panel needs to consist of representatives of all disciplines involved in rectal cancer care. Moreover, especially in international guidelines, the representatives within the expert panel must be equally distributed between the different countries.

To avoid potential bias, the methodology to achieve consensus by voting on statements is of utmost importance. One of the methods that can be used is the 'Delphi' method, followed by discussion within the consensus group and further voting rounds. After a consensus meeting, the level of evidence (I-IV) on which the final statement is based must be provided, as well as the level of recommendation (A-D), the level of agreement, and the percentage of disagreement.

In December 2012, the latest multidisciplinary consensus meeting for colorectal cancer, using the 'Delphi' method, was held [25]. Besides the actual listing of topics and their rating, experts who attended the consensus meeting wrote reviews to discuss the main points of recommendations [21, 25–28].

Multidisciplinary Team

Multidisciplinary team management will enhance cancer care in many ways. It is the reflection of adherence to guidelines and the rebuttal of non-adherence to guidelines. Moreover, it gives interaction between the disciplines with field specific expertise. The increasing complexity of cancer management and the many specialties involved in the treatment encompass the danger that potentially sub-optimal care could be given. In an ideal situation all patients would receive optimal treatment from an expert specialist team, coordinated by one case officer.

Multidisciplinary Team

- Radiation oncologist
- Medical oncologist
- Gastroenterologist
- Surgeon
- Pathologist
- Radiologist
- Nurse specialist

Multidisciplinary care has become an integral part of cancer care in many western countries. Multidisciplinary team (MDT) meetings were organised to warrant that care delivery is consistent with the best available evidence from all different disciplines. The presence of different specialists means a consideration of the full range of therapeutic modalities available for each patient. All new patients with cancer should be presented in a MDT meeting. Patient characteristics, staging and proposed treatment need to be discussed. All restaged patients should be discussed again, as well as all operated patients.

Ideal MDT Moments

- Preoperative
- Postoperative
- After neoadjuvant or upfront treatment: effect of treatment; clinical restaging
- After adjuvant treatment
- After 6 months of palliative treatment

There is clear evidence that MDT meetings result in a change in patient management. In Denmark, an improved postoperative mortality was found after implementation of colorectal MDT's [21]. However, evidence on improved patient outcomes after MDT meetings is still limited [29–32]. This could be caused by poor study designs that have been used and the fact that the findings are often confounded by changes over time, including improved treatments, and technology and service changes.

Although multidisciplinary care is incorporated as standard care in many countries, access to such care still varies among countries and hospitals. The significance of good communication is evident, and is expected to become even more vital as cancer is resolved into a greater number of biomarker-determined disease subtypes. As an example, both the European CanCer Organisation (ECCO) and the European Society of Surgical Oncology (ESSO) have incorporated multidisciplinary cancer care in their mission.

It is recommended that every patient should be discussed in several MDT sessions. MDTs should adhere to the latest guidelines and consensus documents. The use of decision trees can be helpful in the treatment process (Fig. 27.2). Decisions outside guidelines and consensus papers should be carefully discussed within MDT meetings as well as with the patient and has to be described in the patient file or dossier.

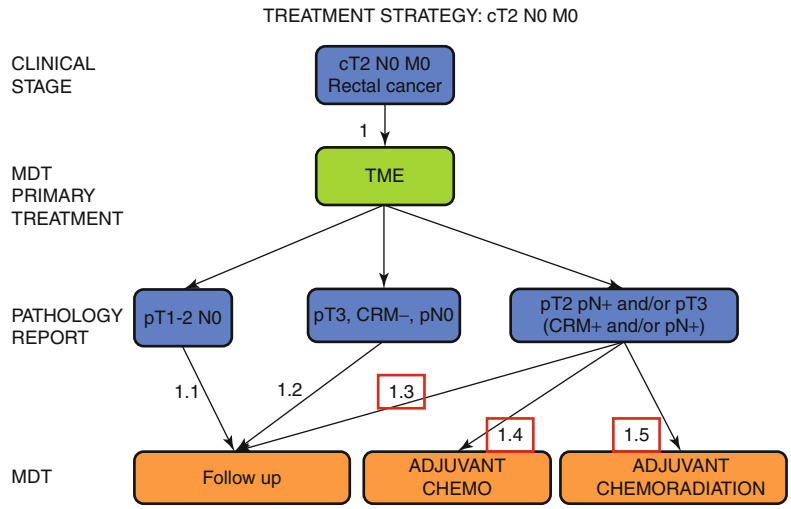

Fig. 27.2 Example of a decision tree (Reprinted from van de Velde et al. [25], Copyright 2014, with permission from Elsevier)

Care Pathways

Care pathways (CPs) are structured multidisciplinary management plans that aim to promote organised and efficient care of patients with a specific clinical diagnosis based on best available evidence and guidelines. The most described pathway of the past decade is the ERAS, Enhanced Recovery After Surgery [33, 34]. Care pathways aim to translate national guidelines into local protocols and their use into daily practice. Besides, CPs are a tool to improve systematic collection of clinical data for audit. However, the exact value of CPs to realise an improvement for the patient is still not fully discovered.

There are several suggested advantages and disadvantages of care pathways. The first advantage is the speed up of the diagnostic process. Faster diagnosing allows a quick start of treatment, as well as a reduced period of uncertainty. Moreover, increased coherence is also an advantage. Improved consistency of care between physicians provides a better overview for the patient, lowers the risk of contradictory opinions, increases the opportunity for patient empowerment, and reduces the risk of mistakes. The last advantage is cost reduction. Avoiding overlap of work (e.g. re-obtaining information from the patient, repetition of the same blood tests and re-entering personal information) is in favour of physicians, patients, and others involved in healthcare. Moreover, reducing hospital stay and the amount of outpatient visits lead to reduction of costs. In summary, with the use of CPs, professionals are likely to provide better care for the patient.

Disadvantages are that protocols might leave less room for personal preferences of both the physicians and the patient. If comorbidity is an issue, the pathways might not be appropriate. Professionals become specialists in one direction and a reduction of diversity might encourage routine approaches without a more personal approach.

Volume-Outcome Measures

Avoidable surgical deaths were suggested to be related to poor experience with surgical procedures involved [35]. In the absence of better information or criteria that describe surgical quality, task forces aiming to increase surgical safety and surgical quality have incorporated the ‘volume norm’. High risk elective procedures in high volume centres would reduce the risk of operative avoidable death [36].

Inverse relationship between volumes of surgical procedures per hospital with surgical outcome is at present available of many surgical cancer treatments. Hospitals are divided in high

and low volume depending on the procedure. There is an effect of the surgeon and procedural volume on postoperative mortality and long-term survival.

Ever since the manuscript of Birkmeyer et al. has been published [35], a large number of studies on the effect of hospital volume on outcomes after gastrectomy have been published. Many other cancer surgery types are being centralised at this moment, such as pancreatic cancer surgery, hepatic surgery, breast cancer surgery, and colon and rectal cancer surgery.

Meanwhile, using hospital volume as the sole basis for referral to improve outcome is criticised. Low volume hospitals can have excellent outcomes, and vice versa. There have been studies performed on the surgeon's volume, but these studies have found contradictory results. It has been suggested that centralisation in combination with auditing is more effective compared with centralisation alone. A Cochrane review by Archampong et al. 2012 demonstrated a volume-outcome relationship in colorectal cancer surgery [37] with a stronger relationship on surgeon level than on hospital level. This review shows country differences in outcomes. Therefore, on a national level, registration systems should be established and centralisation of services is required. All included studies in this review were observational by design and thus overall quality of the evidence was low. Moreover, definitions of caseload and colorectal specialists differed between the studies. Still, this is the best available method to investigate volume-outcome relationships given ethical considerations [37].

Checklists

In aviation and other high risk industries, it is common practice to use checklists. Nowadays, checklists are endorsed in medical practice as well. Many countries mandate preoperative "time-outs" to minimise the risk of accidental mistakes, such as operating on the mistaken site or the wrong patient and "sign-outs" to realise a debriefing of the procedure and postoperative strategies still to be performed. Among quality measures for patients undergoing surgery, surgical checklists have been proven effective and highly suggestive to reduce complications [38]. Implementing surgical checklists have shown to reduce postoperative complications in several randomised trials [39, 40] and are therefore rendered obligated routine practice in the Netherlands for example.

Patient Involvement in Decision Making

Traditional outcome measures such as cancer-specific survival, overall survival and disease-free survival are still of great value, but might fail to explain more patient-centred endpoints such as quality of life and functional outcomes after cancer treatment. Diarrhoea after formation of a low rectal anastomosis or a perineal hernia after abdomino-perineal resection can fully obscure the quality of life with invalidating complaints.

We need to focus more on involving patients in the discussion about their treatment. With 'shared decision making' (SDM), clinicians and patients decide together on treatment strategies while using the best available evidence. This sounds sensible but not all physicians are/were trained to unravel or explicate patient's preferences in the same session that diagnosis and treatment are discussed or even the operation is already scheduled [41]. It was assumed that physicians do not always choose according to the patient's preferences but according to 'substitute preferences' [42]. In a study of 150 patients with prostate cancer facing radiation therapy, physicians were asked to judge which patient would choose which dosage when given the possibility of choosing between two radiation dosages. Patients were provided with a decision aid (DA), clearly showing all profits and risks of each dosage scheme. Physicians proposed the preference that the patient would choose and patient preferences were compared. Physicians undervalued patient's decision making preferences and that patients would choose the less harmful treatment [42]. Therefore, it might not just be the patient that needs advising but the physician that needs

to be updated in 'information flow' to and from the patient.

To illustrate the following situation, in rectal cancer management neoadjuvant chemoradiation can result in a complete remission, and the logical question is whether it is safe to avoid extensive rectal resection for the benefit of organ sparing. Evidently, the oncological safety and proof of this approach is not yet there to fully follow the retrospective observations of single series [43, 44]. Adopting a non-operative strategy in patients who achieve complete tumour regression avoids the risks of surgical morbidity and mortality. The complete response rate is about 11–38 %. However, it remains unclear how a safe follow-up is established and how a complete response is specified. In a UK questionnaire, 69 % of surgeons declared that they would never discuss non-operative treatment in patients with rectal cancer who were fit for curative surgery, but 30 % was open minded to consider omitting surgery for those who responded in a cCR after CRT [45].

A recent Cochrane meta-analysis concluded that using decision aids including all treatment options with the percentage of success and failure of the treatment, improve the knowledge of the patients about the intervention options of his/her disease and reduce decisional conflict [46].

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Remedial Surgery Following Failed Colorectal or Coloanal Anastomosis

28

Gilles Manceau and Mehdi Karoui

Abstract

Low colorectal (CRA) and coloanal (CAA) anastomosis are associated with early complications such as anastomotic leakage and late complications including chronic anastomotic stricture, leakage and fistula. In these situations, redo surgery with the aim to perform a new CRA or CAA may represent the last surgical option to avoid a permanent stoma. However, these procedures are challenging and technical with potentially high intraoperative and postoperative morbidity. One of the biggest challenges is to bring down a sufficient length of healthy colon in a scarred pelvis to perform a well-vascularized and tension-free anastomosis. The aim of the chapter is to provide abdominal surgeons a general overview of the means to overcome these intraoperative problems and to review the available literature on this particular subject.

Keywords

Redo surgery • Colorectal anastomosis • Coloanal anastomosis • Deloyers procedure • Retroileal • Soave procedure

Introduction

Low colorectal (CRA) and coloanal (CAA) anastomosis can be considered as high risk surgical procedures with a significant percentage of anastomotic-related complications. In the early postoperative period, the most feared of them is anastomotic dehiscence, which occurs in 10–15 % of patients despite fecal diversion with a loop ileostomy or colostomy [1]. Breakdown of the suture line can manifest itself in many ways, from no symptom thus detected incidentally on a routine computed tomography scan or

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water-soluble contrast enema, to abdominal catastrophe with generalized peritonitis requiring urgent reintervention, dismantling of the anastomosis, low Hartmann's procedure and end colostomy [2].

CRA and CAA are also associated with late anastomotic complications including chronic anastomotic stricture observed in up to 30 % of patients [3], chronic leakage with pelvic abscess (1–5 %) [4, 5] and recto-vaginal or recto-urethral fistulae. These complications lead to abdominal pain, recurrent abscesses, fecal incontinence, disabling constipation and negatively impact on the patient's quality of life. Late complications are all the more serious that they are very difficult to treat and result in nearly 20 % of patients to a permanent stoma (non-reversal of diverting stoma or secondary stoma formation that will be left in place) [6–8].

When surgeons have to deal with a patient with a chronic CRA or CAA related complication, management needs to be progressive and the first step should be as conservative as possible including: transanal dilatation, various endoscopic maneuvers (hydrostatic balloon dilatation, microwave coagulation, electrocauterization, argon plasma coagulation), use of a circular stapler and repair by sphincteroplasty [9, 10] in case of chronic anastomotic stricture; fibrin glue injection, mucosal advancement flap, use of a transrectal endo-vacuum and sinus unroofing with marsupialization [11–13] for patients with anastomotic leakage and chronic related pelvic sepsis; and transanal approach with flap formation (rectal or vaginal), Martius' bulbocavernosus-fat flap, gracilis interposition [14, 15] in case of low recto-vaginal or recto-urethral fistula.

At the end, after failure of one or several of these treatments, redo surgery with the aim of create a new CRA or CAA may represent the solution of last resort. However, these procedures are highly challenging with many technical difficulties. The aim of the chapter is to give abdominal surgeons a general overview of the means to overcome these intraoperative problems and to review the literature on this particular subject.

Technical Issues When Considering Redo Surgery for Failed CRA or CAA

After an extended left colectomy, the remaining colon can be unable to reach the rectal stump without undue tension. Before considering completion of colectomy, one should ensure that the whole of the left colon including the splenic flexure has been fully mobilized, with division of the root of the left transverse mesocolon, section of the inferior mesenteric vein at the inferior border of the pancreas, division of the left colic pedicle and division of the coloepiploic attachments. Despite these usual surgical manoeuvres, if the residual transverse colon is of inadequate length to reach the rectum or anus in a tension-free fashion with colonic lowering posterior to the mesentery, three additional procedures have been described to allow restoration of large bowel continuity. The objective of these procedures is to avoid unnecessary total colectomy with ileorectal anastomosis which has been reported to be associated with poor functional results [16].

Procedure 1: The Retroileal Transmesenteric Colorectal Anastomosis

The first technique to take down a well-vascularized colon into the pelvis is the transmesenteric lowering of the colon (Fig. 28.1). Typically, it requires a complete division of the root of the transverse mesocolon along the pancreas up to the hepatic flexure with division, if present, of the main trunk of the middle colic artery. The remnant colon is also free from its omental attachments and then brought through an avascular window of the mesentery, usually in the terminal part of the ileum, on the right of the superior mesenteric artery. This operative technique requires keeping a certain length of transverse colon to perform the pelvic anastomosis. Thus, the right colic artery needs to be preserved for adequate blood supply.

This procedure was first described in 1961 by André Toupet [17, 18]. At the beginning, the aim of this transmesenteric passage was to perform a

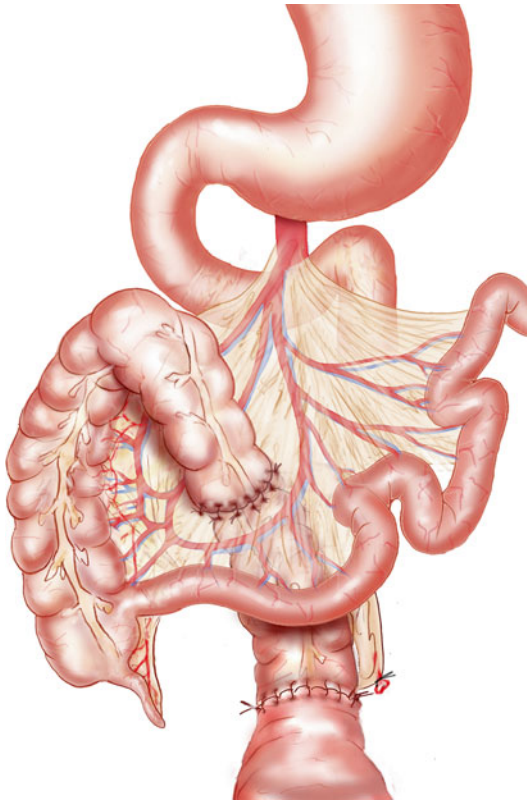

Fig. 28.1 Colorectal anastomosis with transmesenteric passage of the transverse colon and closure of the peritoneal defect

tension-free anastomosis between the transverse colon and the sigmoid colon following a left segmental colectomy, with passing the colon on the left of the superior mesenteric artery. The transmesenteric route of the transverse colon was then taken up in 1976, with an opening of the meso created in the right mesocolon, between the right colic artery and the ileocolic artery [19].

In the literature, studies reporting this retro-ileal tunnel are few. In 1978, Turnbull gave the results of 11 patients [20]. There were six patients with complicated, extensive diverticulitis, four patients with colon cancer located to the splenic flexure and one patient with radiation stricture of the descending colon. They all had a resection of the left colon and the distal part of the transverse colon. Postoperative mortality was nil. Early postoperative morbidity was 18 %, with one postoperative ileus managed nonoperatively and one wound infection. Functional outcome was considered good by the authors but not detailed. Hogan and Joyce described a case report of redo surgery using this retro-ileal anastomosis for chronic anastomotic leakage after previous segmental left colectomy [21]. Recently, Sileri and colleagues reported their experience of 10 patients, with two of them operated on by laparoscopy [22]. Indications were the following: two left colon cancers, two left colon cancers with associated diverticular disease, two iterative resections for metachronous left colorectal cancer, two synchronous colon cancers and two patients with extensive diverticular disease. Functional outcome assessment revealed that only two patients routinely used loperamide-based medication. There was no complication related to the surgical procedure, especially the occurrence of small bowel obstruction. Indeed, this point is of importance, as this technique is associated with a theoretical risk of internal hernia through the mesenteric window, and the lowered transverse colon needs to be fixed all around the ileal mesenteric defect with interrupted sutures. Conversely, a too narrow peritoneal opening could lead to colonic obstruction or create an obstacle to venous return.

Procedure 2: The Deloyers Procedure

Another technique is Deloyers procedure. It comprises an isoperistaltic anastomosis between the transverse or right colon and the rectum or anus, after full mobilization and reversal of the residual colon around the axis formed by the ileocolic pedicle (Fig. 28.2). This technique requires also a section of the mesenteric root up to the duodenojejunal flexure. Once the origin of the right colic artery and the middle colic artery are identified, both pedicles are transected and the devascularized colon is resected. The remaining colon (usually including the cecum, the ascending colon up to the hepatic flexure) is then returned in a counterclockwise direction. This craniocaudal trigonometric rotation maintains the cecum in the right iliac fossa, with its anterior surface facing the retroperitoneum, or places it in the right

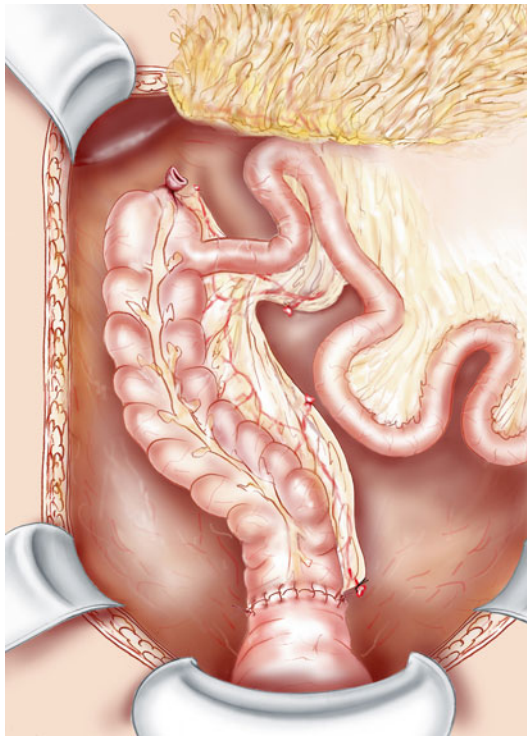

Fig. 28.2 Isoperistaltic colorectal anastomosis after Deloyers procedure with reversal of the colon. The small intestine is repositioned and should not come under the right mesocolon with incarceration

hypochondrium, depending on the length of the remaining colon and the level of the anastomosis.

This procedure was first presented by Lucien Deloyers in November 1963 at the meeting of the Surgical Society of Lyon [23]. This Belgian surgeon (1901–1982) detailed this transposition of a colonic segment on a series of 11 patients, aged 17–44 years and operated on between 1956 and 1962. The indications were four ulcerative colitis, three megacolons, three dolichocolons with chronic constipation and one colonic polyposis sparing the right colon. An associated proctectomy was necessary in four of them. There was no postoperative death and according to the author, the postoperative course was uneventful with no need for reintervention. During follow-up, the number of stools per day ranged from one to three.

In the initial description of the technique, the cecum was placed under the liver, in place of the hepatic flexure, with ascending colon occupying the right paracolic gutter and fixed to the parietal peritoneum with interrupted sutures. At control barium enema, the cecum came back most of the time in the right iliac fossa, without this change of position has modified functional outcome.

Since this first publication and during 50 years, only four studies, involving a total of 32 patients, have been published on this procedure [24–27]. All these reports were focused on specific indications such as Hirschsprung's disease and severe chronic constipation. Prevot reported a series of 7 patients with one postoperative death and good functional outcome in 83 % of cases [24]. The study of Costalat and colleagues included 18 consecutive patients with colonic inertia [25]. In their series of five Duhamel procedures for Hirschsprung's disease operated on by laparoscopy, Bonnard and colleagues used this surgical maneuver for an infant of 5 months whose disease reached the left half of the transverse colon [26]. Tang and colleagues analyzed the postoperative course of 12 children with a diagnosis of intestinal neuronal dysplasia who underwent extended laparoscopic colectomy with Deloyers procedure and transanal endorectal pull-trough procedure, with two anastomotic leakage (17 %) [27]. Finally, a small retrospective study including three patients gave results of this right colonic transposition technique, with two synchronous colorectal tumors and one unifocal stricturing Crohn's disease affecting the entire left colon and distal transverse colon [28].

We reported a series of 48 consecutive patients operated on over a period of 12 years [29]. The Deloyers procedure was used as a salvage technique for low CRA or CAA. The main indications were Hartmann reversal, failed previous colorectal anastomosis with anastomotic leakage and chronic pelvic sepsis or chronic stenosis, extensive diverticular disease, left colon cancer, ischemic colitis requiring extended left hemicolectomy and iterative colectomy for colon cancer. In total, 32 patients (66 %) had a previous left colectomy or rectal resection. There was one postoperative death from nonsurgical cause. Thirty-seven patients (77 %) had uneventful postoperative course and no anastomotic leakage

occurred. Only one patient required a new diverting stoma because of poor functional results at the end of follow-up. For those whose functional outcome could be evaluated, the median number of bowel movements per 24 h was 3 (range, 1–7) and 82 % had fewer than 4 bowel movements.

All patients were operated on by laparotomy. Although laparoscopic approach is theoretically feasible, it should be noted that this surgery is demanding, as evidence by the median operative time of 415 min in our series. This technique of reconstruction is rarely indicated (3.7 % of all CRA and CAA performed in our institution). However, it always allowed to take down a colonic segment with good blood supply and of sufficient length to perform a tension-free anastomosis in the pelvis or even at the level of the anal margin for 10 patients (21 %). By analogy, in the study of Rombeau and colleagues [20], the transmesenteric lowering of the colon was necessary in 11 of 302 patients operated on for resection of the descending colon at the Cleveland Clinic from 1966 to 1976, which represents 4 % of all CRA in 10 years. Based on these figures, it can be estimated that digestive surgeons need additional tricks to further lengthen the colon in about 5 % of cases.

Before division of the right colic vessels, we recommend to perform a clamping test with a vascular clamp for a few minutes to determine adequacy of blood supply with the ileocolic artery and the marginal artery of Drummond. In our series, an additional colonic resection was necessary for seven patients (15 %) due to the occurrence of ischemia in the terminal part of the remaining colon. Similarly, because appendicectomy would be technically difficult after this procedure, we systematically remove the appendix at the time of surgery.

In 2013, Dumont and colleagues reported a retrospective study of 39 patients operated on for an extended left colectomy with restoration of bowel continuity after either right colonic transposition or complete intestinal derotation with creation of a complete mesenterium [30]. However, the right colonic transposition described in this study was not a typical Deloyers procedure, as the remnant colon was rotated anteriorly at 180° in the sagittal plane, placing the mesocolon of the lowered colon in front of the terminal ileal loop. This could cause small bowel obstruction by compression or, in the event of a postoperative ileus, could place the CRA or CAA under tension [31]. The main surgical indication for an extended left colectomy was intraperitoneal disease (82 % of patients). There was no postoperative death. Postoperative morbidity was 28 %, including three anastomotic leakages requiring reintervention (7.7 %), with no difference between the two groups.

One of the criticisms to this procedure is the risk of vascular kinking of the ileocolic pedicle due to the 180° rotation of the colon. However, we systematically divide the entire mesenteric root, so that the torsion of the pedicle is distributed over a large length. In the study by Dumont and colleagues, this maneuver was not performed and one patient required a total colectomy with an ileorectal anastomosis due to intraoperative ischemia [31].

Procedure 3: Subtotal Colectomy with Cecorectal End-to-End Anastomosis

When the right colon cannot be preserved, the last alternative is subtotal colectomy with antiperistaltic end-to-end cecorectal anastomosis. It allows preservation of the terminal part of the ileum, the ileocecal valve and the cecum, with no visceral rotation or vascular torsion. The entire remaining colon should be completely mobilized. Colonic resection leaves in place only the cecum and the proximal part of the ascending colon vascularized by the terminal branch of the superior mesenteric artery with the ileocolic artery. After systematic appendectomy, the cecum is brought into the pelvis and a cecoproctostomy is then fashioned by anastomosing the base of the cecum to the rectum [32]. In case of mechanical anastomosis, the colonic section line can be used as the entrance for the circular stapler, after introducing the anvil in the rectal stump [33].

Studies that reported results of this technique are few and focused mainly on the surgical

treatment of chronic constipation with colonic inertia resistant to medical treatment (after failure of dietary measures and long-term laxative treatment) and confirmed objectively with a colonic transit time study [34–39]. There should not be any sign of terminal constipation on defecography and manometry, and no cause of colorectal obstruction on colonoscopy. Four of these studies were retrospective non-comparative monocentric studies of small effective, with a total of 74 patients [32, 34–36]. The short-term results were judged to be good in all the studies, with no postoperative morbidity or mortality. Three publications came from the same surgical team, with probable duplicate results from the same cohort [32, 34, 35]. A comparative retrospective study of 37 patients evaluated subtotal colectomy with restoration of intestinal continuity using this technique or by ileorectal anastomosis [37]. Overall rate of postoperative morbidity was similar between both procedures (11.8 % after cecorectal anastomosis vs. 10 % after ileorectal anastomosis). However, after a median follow-up of 4 years, functional results were significantly improved for patients with cecorectal anastomosis in terms of mean number of bowel movements per day (2.4 ± 0.9 vs. 3.4 ± 0.8; $p = 0.0014$), anal incontinence evaluated with the Wexner score (4.3 ± 1.8 vs. 5.8 ± 1.9; $p = 0.0223$) and quality of life evaluated with the gastrointestinal quality of life index (GIQLI) (119.8 ± 7.5 vs. 111.1 ± 12.0; $p = 0.0455$). Finally, a retrospective study of 79 patients compared subtotal colectomy with cecorectal anastomosis or ileosigmoid anastomosis [38]. At 12 months postoperatively, the number of bowel movements per week was in favor cecorectal anastomosis (10.2 ± 5.4 vs. 15.5 ± 3.8; $p < 0.05$). However 26.8 % of patients after cecorectal anastomosis had persistent constipation and routinely used laxatives, versus 6.7 % after ileosigmoid anastomosis ($p < 0.05$). Similarly, the use of enemas was significantly higher after cecorectal anastomosis (11.8 % vs. 2.2 %; $p < 0.05$). Overall, the percentage of patient satisfaction was significantly higher after subtotal colectomy with ileosigmoid anastomosis (93.3 % vs. 73.5 %; $p < 0.05$).

Descent of the Colon Through the Pelvis: The Soave Procedure

Pelvic dissection during salvage surgery for anastomotic complication, and particularly in septic ones, can be of great difficulty and hazardous due to inflammatory phenomenon and fibrous tissues. It can be particularly dangerous for all neighboring structures (pelvic nerves, presacral veins, ureters, vagina). One possible solution to allow the colon to reach the anal canal in a scarred pelvis is Soave procedure. This transrectal coloanal sleeve anastomosis has been originally described by Soave in 1964 for the treatment of Hirschprung's disease [40]. As reported by Parks, this procedure can be used in case of rectovaginal fistula [41], and also in case of rectourinary fistula [42] or when the pelvis seems completely "frozen" and a perirectal plan of cleavage is not visualized [43].

The pelvic dissection is performed down to the fistula or stenosis located at mid or low rectum. After transection of the rectum and submucosal infiltration with saline-adrenaline solution, the mucosa is excised from the residual rectal stump along the plane of the submucosa and the dissection is continued downwards as far as possible. The patient placed is then placed in the lithotomy and Trendelenburg position to complete the mucosectomy from the dentate line *via* a perineal approach. After excision of the mucous coat, the colon is then delivered through this rectal muscle tube and a handsewn straight CAA is performed (Fig. 28.3). In case of fistula, the site of the fistula is thus covered by healthy tissues with the colon lowered to the perineum. To facilitate the delivery in case of narrow and fibrotic pelvis, a laparoscopic wound retractor can be placed through the pelvic hole. It allows the colon to slide more easily without excess traction and helps prevent injury of the mesocolon [44]. The residual rectal muscular sleeve must allow the passage of at least three fingers. If this is not the case, the denuded rectum is transected vertically on the posterior wall to increase its diameter.

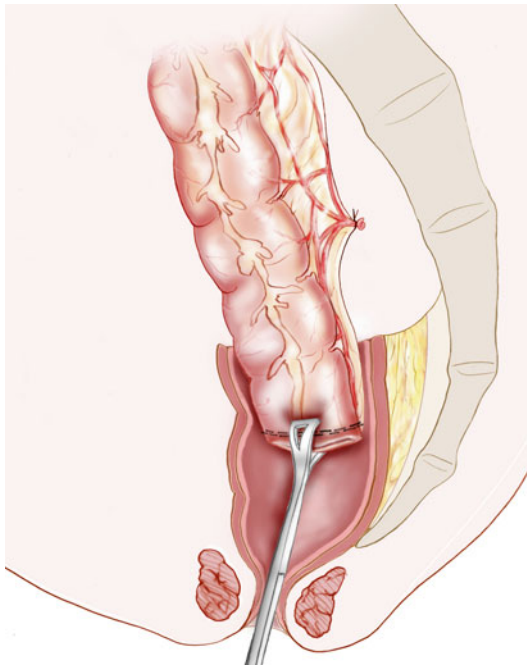

Fig. 28.3 Soave or Parks procedure. A Babcock clamp is introduced through the anal canal to grasp the colon and to gently pull it down in this muscular tunnel. In case of rectovaginal or rectourethral fistula, the lowered colon can be rotated so the mesocolon is placed in front of the defect

Literature Review of Studies Dealing with Redo Surgery for Failed Colorectal or Coloanal Anastomosis

To date, only three surgical teams have reported their experience of redo surgery for failed CRA or CAA, with four retrospective studies and a total of 176 patients (Table 28.1) [3, 45–47]. The first study of Saint-Antoine hospital specially focused on intractable anastomotic stricture [3]. This anastomotic-related complication was also the main indication for redo surgery in the other studies [45, 47].

Although demanding with prolonged operative time, redo CRA or CAA was technically feasible in almost all cases. However, it should be emphasized that these procedures were performed by highly experienced surgeons in colorectal surgery, as reflected by the large number of patients referred to these centers after the initial surgery. Redo surgery must be performed by means of a midline laparotomy with the patients placed in the Lloyd-Davis position to facilitate exposure and access to the pelvis and perineum. In the series of Lefevre and colleagues, six patients (18 %) were operated on by laparoscopy, with a conversion rate of 50 %. The main intraoperative complication was bladder injury, especially in case of low Hartmann's procedure, when the bladder falls back against the sacrum and strongly adheres to it. Intraoperatively, the percentage of failure with inability to dissect the pelvis and to perform a redo anastomosis was 6 % in the study by Lefevre and colleagues and 4.5 % in the study by Pitel and colleagues [46]. It was nil in our experience [47]. Additionally, by including long-term postoperative morbidity, the rate of success of redo surgery with a functionnal anastomosis and no stoma reached more than 70 %. Lefevre and colleagues performed an univariate analysis to identify risk factors that may predict failure of redo surgery: male gender ($p=0.0351$), CAA during the first procedure ($p=0.0031$) and creation of a hand-sewn CAA during redo surgery ($p=0.0385$) are the three identified factors. This emphasizes the difficulties of performing a deep dissection in a narrow and fibrotic pelvis.

The number of patients requiring an associated procedure to obtain a tension-free anastomosis with a shorter route for the colon to reach the pelvis was high including 31 Deloyers procedures and 21 Toupet procedures (30 % of all patients). This underlines that surgeons who take care of patients with such anastomotic complications should not ignore these surgical maneuvers. Similarly, the use of the Soave procedure was judged preferable and safer in 53 patients (30 %) for the dissection of the rectal stump to spare neighbouring structures.

Redo surgery needs to be considered after a significant lapse of time and in selected patients, after ensuring that less invasive techniques have failed. In case of previous surgery for rectal cancer, care must be taken to exclude local pelvic recurrence, especially as it has been reported that

Table 28.1 Literature review of published series on redo surgery for failed colorectal or coloanal anastomosis

	Schlegel and colleagues [3]	Lefevre and colleagues [45]	Pitel and colleagues [46]	Genser and colleagues [47]
Study period	1992–1996	1999–2008	2000–2010	1998–2011
Total number of patients	27	33	66	50
Initial disease, n (%)				
Colorectal cancer	13 (48)	19 (58)	52 (79)	29 (58)
Diverticular disease	7 (26)	11 (33)	3 (5)	19 (38)
Inflammatory bowel disease	0	2 (6)	0	0
Others	7 (26)	1 (3)	11 (17)	2 (4)
Indications for Redo Surgery, n (%)				
Chronic pelvic sepsis	0	5 (15)	21 (32)	14 (28)
Anastomotic stricture intractable by endoscopy	27	17 (52)	10 (15)	20 (40)
Hartmann's reversal	0	6 (18)	13 (20)	8 (16)
Rectovaginal fistula	0	0	22 (33)	3 (6)
Anastomotic cancer recurrence	0	5 (15)	0	5 (10)
Procedures before Redo Surgery, n (%)				
New anastomosis attempted before RS	NM	6 (18)	6 (9)	2 (5)
At least more than one laparotomy after the first surgery	NM	18 (54)	59 (90)	25 (50)
Redo surgery (%)				
Number of patients with a stoma at the time of RS	15 (59)	13 (39.4)	NM	21 (42)
Age at RS (years)	51[a]	56.8[a]	59.8[b]	61.9[a]
Delay initial surgery – RS (months)	15.1[b]	41[a]	9.9[a]/8.4[b,c]	14[b]
Operative time (min)	NM	279[a]	NM	422[a]/435[b]
Immediate failure of RS, n	0	2(6)	3 (4.5)	0
New CRA, n	7 (26)	19 (58)	0	26 (52)
New CAA, n	20 (74)	12 (36)	66 (100)	24 (48)
Associated techniques to perform anastomosis :				
Deloyers procedure	0	4	5	22
Delayed CAA	0	2	2	2
Soave procedure	19	2	27	5
Transmesenteric passage of the colon	0	1	20	0
Defunctioning stoma	24 (89)	29 (93)	66 (100)	37 (74)
Immediate postoperative outcome (%)				
Mortality	0	0	0	0
Morbidity:	5 (18.5)	18 (55)	21 (32)	13 (26)
Anastomotic leakage or isolated pelvic abscess	1	10 (30)	5 (8)	0
Ileus	0	4 (12)	0	2 (4)
Length of hospital stay (days)	NM	16.5[a]	14.1[a]/13[b]	15[a]/13[b]
Rehospitalization, n	NM	5 (15)	6 (9)	1 (2)
Reintervention, n	NM	7 (21)	10 (15)	1 (2)
Long-term outcome (%)				
Follow-up (months)	28.7[a]	28.7[a]	47.9[a]/35.7[b]	60[a]/36[b]
Morbidity:				
Stenosis	0	1(3)	0	2 (4)
Chronic fistula	0	1(3)	3 (5)	0
Functional anastomosis at end of follow-up, n	27 (100)	23 (70)	52 (80)	44 (88)

Table 28.1 (continued)

	Schlegel and colleagues [3]	Lefevre and colleagues [45]	Pitel and colleagues [46]	Genser and colleagues [47]
Functionnal results:				
Constipation rate	8 (30)	2 (9)	NM	2 (5)
Incontinence rate	3 (11)	4 (17)	NM	7 (16)
Number of bowel movements per day	NM	3.2[a]	NM	2.9[a]/2[b]

NM not mentioned, *RS* redo surgery, *CRA* colorectal anastomosis, *CAA* coloanal anastomosis
[a]Mean
[b]Median
[c]Time between diagnosis of the anastomotic pathology and redo surgery

anastomotic leakage after rectal cancer surgery significantly increases the risk of local relapse [48]. In the series reported by Pitel and colleagues in which the mean delay was less than 10 months, two patients subsequently developed local recurrence. Thus, it seems that an interval of nearly 1 year between the initial procedure and redo surgery should be respected, after control of local sepsis, correction of any malnutrition and careful imaging evaluation. This waiting period also allows the reduction of intra-abdominal adhesions from previous surgeries.

Pelvic anatomy in the reoperative surgery setting can be substantially modified. Apart from certain structures that can serve as landmarks to reach the perineum (i.e. aortic bifurcation and common iliac arteries, sacrum, vagina and prostate), others may be widely displaced. This is particularly the case of the ureters, which are sagittalized compared with their normal path. In the series by Pitel and colleagues [46], nearly 30 % of the patients had preoperative ureteric stenting to help identifying their abdominal and pelvic course during dissection, to prevent injury and to facilitate repair in case of injury. Abdominal surgeons should not hesitate to call on other specialist surgeons like urologists to optimize the course of surgery.

Although for functional reasons the use of a colonic J-pouch is the standard for low CRA or CAA, 28 patients (56 %) in our experience [47] and 52 patients (79 %) in the series of Pitel and colleagues [46] had restoration of bowel continuity with a straight end-to-end anastomosis. The choice of a direct CAA can be explained by the narrow passage for the lowered colon that does not ensure enough space for the pouch, the length of the remaining colon and the fear of staple-line disruption, especially in case of urinary or vaginal fistula with apposition of suture lines. In these situations, an interposition omental flap should be associated, pediculized on the left or right gastroepiploic artery. Moreover, among all patients with a straight end-to-end anastomosis, four of them had a delayed CAA, also known as the Turnbull–Cutait abdominoperineal pull-through procedure [49, 50]. In this situation, a direct CAA is usually fashioned on the fifth postoperative day. The major benefit of this procedure is that it theorically avoids the need for a prophylactic covering stoma because of the adhesions occurring in the interval between the colon and the anal canal. However, in case of redo CRA or CAA, nearly all patients already have a diverting stoma at the time of surgery. A delayed CAA can be used in selected patients with chronic pelvic inflammation or sepsis due to ongoing sepsis [49].

Conclusion

For patients with anastomotic failure after colorectal resection, permanent stoma is not a fatality. Except in cases of rectal cancer recurrence, management of patients must be gradual. Redo CRA or CAA is a demanding procedure with potentially high intraoperative and postoperative morbidity. It must be performed by surgical teams with high expertise in colorectal surgery as it often requires particular procedures to ensure sufficient length of vascularized bowel to be pooled down into the pelvis.

As redo CRA or CAA is first and foremost a functional procedure to avoid a permanent

stoma, the patient's wishes and desire should be the main elements to take into account for the final decision.

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Complications of Rectal Cancer Surgery

29

Elizabeth R. Raskin and Robert D. Madoff

Abstract

Complications are inherent to rectal cancer surgery. Anatomic challenges of the pelvis, preoperative radiation therapy, and advanced disease contribute to the increased incidence of postoperative complications. Prolonged hospitalization and/or readmission are commonly required and adversely contribute to the overall cost of surgical care. In addition, health-related quality of life has been shown to be significantly impacted by major complications and prolonged hospitalization. Postoperative complications can lead to a delay in adjuvant chemotherapy administration and have been associated with decreased disease-free and overall survival.

Keywords

Complications • Anastomotic • Urinary • Sexual • Dysfunction • Injury • Infection

Introduction

Complications are inherent to rectal cancer surgery. Anatomic challenges of the pelvis, preoperative radiation therapy, and advanced disease contribute to the increased incidence of postoperative complications. Prolonged hospitalization and/or readmission are commonly required and adversely contribute to the overall cost of surgical care [1]. In addition, health-related quality of life has been shown to be significantly impacted by major complications and prolonged hospitalization [2]. Postoperative complications can lead to a delay in adjuvant chemotherapy administration and have been associated with decreased disease-free and overall survival [3].

Small Bowel Obstruction

Small bowel obstruction (SBO) is one of the most common postoperative complications after proctectomy with an incidence ranging from 2 to 12 % [4–8]. Symptoms include nausea, vomiting, abdominal pain, and distention. Postoperative adhesions, abdominal wall hernias, and defects in

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the pelvic floor serve as the largest contributors to SBO [4, 9, 10]. While SBO occurs in about 10 % of patients who undergo curative resection for rectal cancer, abdominoperineal resection is associated with a higher incidence of SBO compared to sphincter-preserving surgery [9, 11]. A protective loop ileostomy has also been associated with an increased risk of SBO as a result of twisting of the loop, adhesive kinking, and edema at the level of the fascia [11, 12].

Typically, SBO can be differentiated from ileus with radiologic studies (e.g. CT scan or small bowel follow through) by demonstrating proximal distended small bowel with distal decompressed bowel. The vast majority of early SBO can be treated expectantly with nasogastric tube decompression, bowel rest and fluid resuscitation without subsequent risk of bowel ischemia [10]. Operative indications in the early postoperative period include evidence of laparoscopic port site herniation, internal hernia, radiologic evidence of compromised bowel, and prolonged obstruction. Although late SBO is most frequently caused by adhesions, recurrent pelvic disease should be ruled out.

Ureteral Injury

Iatrogenic ureteral injuries are reported in 0.2–7 % of rectal cancer resections [13].

The proximity of the ureters to the plane of dissection can pose a technical challenge, especially in the narrow male pelvis and in a previously irradiated field. Bulky and locally invasive tumors can distort the normal path of the ureter and the surrounding anatomy.

Injuries to the ureter typically occur in three specific locations: at the takeoff of the inferior mesenteric artery, at the pelvic brim, and at the level of the lateral rectal attachments.

Distal third ureteral injuries occur most commonly (91 %), followed by the middle third (7 %), and the proximal third (2 %) [14].

Conflicting data exist regarding the protective effect of prophylactic ureteral stent placement. While they can provide tactile identification of the ureters and assist in recognition of ureteral injuries, ureteral stents do not prevent iatrogenic injury. Ureteral trauma resulting in transient hematuria and anuria due to luminal edema has been reported with stent placement [15, 16].

Lighted stents have been used successfully without significant morbidity in laparoscopic colorectal resections [15]. Prophylactic ureteral stent placement should be considered in the patient with extensive disease, an irradiated pelvis, and a previously operated pelvis.

Early recognition of a ureteral injury is critical to salvaging urinary and renal function and minimizing morbidity. The diagnosis of iatrogenic ureteral injury can be made with the injection of methylene blue intravenously or retrograde through ureteral stents. An on-table intravenous pyelogram may also be performed.

Bladder Injury

Bladder dysfunction is a well-recognized complication of pelvic surgery. Reports range from 2 to 50 % of rectal cancer resections [17]. Postoperative urinary retention (PUR) is defined as the inability to effectively void with a full bladder.

Changchien and colleagues looked at the incidence of PUR in 2,355 colorectal cancer resections and found PUR to be 1.7 % for colon cancer and 9.1 % in patients with rectal cancer ($p < 0.0001$) [18]. Several studies have suggested a correlation between tumor height from the anal verge and the risk of injury to the bladder's innervation, with the highest risk of PUR occurring after abdominoperineal resection [19]. Transient or permanent injury to the superior hypogastric plexus at the sacral promontory level or of the nervi erigentes at the pelvic side wall level can occur during the pelvic dissection [19, 20]. Many authors have reported male sex as a risk factor for postoperative urinary retention after rectal resection, while others have found no difference between the sexes.

Iatrogenic injury of the bladder has been reported in approximately 4.5 % of colorectal procedures [14]. Urinary catheter decompression is recommended at the outset of all operations as

traumatic lacerations and punctures have been reported with routine intraabdominal entry and laparoscopic trocar placement. Risk factors for traumatic bladder injury include prior radiation, previous pelvic procedures, and chronic pelvic inflammation and infection.

Early recognition and repair of injuries are paramount to proper restitution of bladder function and avoidance of such complications as colovesical, enterovesical, and vesicocutaneous fistula.

Unrecognized bladder injuries typically present in the early postoperative period. Symptoms and findings may include incisional drainage, oliguria, increased surgical drain volume, and vaginal drainage. Proximal diversion with percutaneous nephrostomy tubes may be needed if the bladder defect is large or fails to heal with bladder decompression.

Urethral Injury

Urethral injuries are relatively rare during rectal resection. The most common urethral injury occurs during traumatic bladder catheter placement. Direct urethral injury can also occur during the distal rectal dissection or perineal portion of an abdominoperineal resection, especially in the setting of prior irradiation. All recognized urethral injuries should be repaired at the time of surgery. Absorbable suture such as 5–0 chromic or Vicryl should be used. A catheter should be left in place for at least 2 weeks before performing a retrograde urethrogram.

Significant urethral injuries (greater than 25 % circumference) may require a more complex repair (i.e. dartos interposition muscle flap or gracilis flap) by a urologist to ensure adequate coverage and blood supply. Rectourethral and urethroperineal fistulae have been reported after inadequately repaired or unrecognized urethral injuries. Symptoms may include pneumaturia, fecaluria, pelvic sepsis, or urine draining through the rectum or from the perineal wound. A cystourethrogram can be done to demonstrate a fistula. Most small (<2 cm) fistulae in a non-radiated pelvis will heal with fecal diversion. If a persistent fistula is noted after 3–6 months, operative management is warranted. Transanal, transsphincteric (York-Mason), transabdominal, and transperineal approaches have been described. Vanni et al. reported on 74 patients (35 non-radiated, 39 irradiated) who underwent an anterior perineal repair with muscle interposition flap [21]. After a mean follow up of 20 months, 100 % closure was demonstrated with the non-radiated group and 84 % closure with the irradiated group. Fecal diversion was only performed in the irradiated group (31 %). The highest rates of healing and bowel restitution after the transperineal approach including gracilis flap interposition.

Urinary and Sexual Dysfunction

Historically, urinary and sexual dysfunction were commonly accepted complications of rectal cancer surgery. Reports of up to 35 and 60 % of patients experienced postoperative bladder and sexual dysfunction, respectively, prior to the introduction of the total mesorectal excision (TME) technique in 1982 [22]. TME dramatically decreased the frequency of urogenital dysfunction by advocating circumferential mobilization and dissection of the rectum along the parietal pelvic fascia, with careful identification and avoidance of the pelvic autonomic nerve pathways [23]. While influenced by patient age, preoperative function, stage of disease, and prior radiation therapy, postoperative urogenital dysfunction is precipitated by intraoperative nerve injury. Health-related quality of life is adversely affected by pelvic nerve injury with patients experiencing decreased physical and social function, sexual activity, and body image [24].

Normal bladder and sexual function are coordinated by the sympathetic input from the superior hypogastric plexus and hypogastric nerves and parasympathetic input from the pelvic splanchnic nerves and nervi erigentes. The superior hypogastric plexus and the origin of the hypogastric nerves reside just inferior to the origin of the inferior mesenteric artery (IMA) and are vulnerable to injury during a high ligation of the IMA. The hypogastric nerves can also be

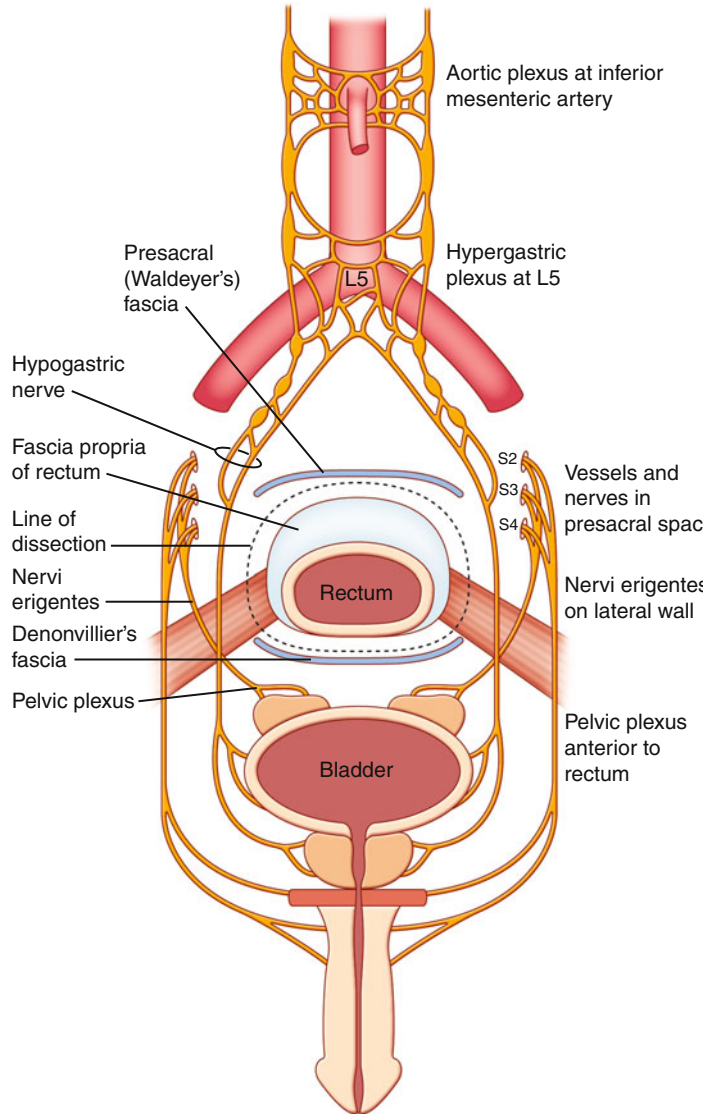

Fig. 29.1 Deep pelvic dissection anatomy

injured during the dissection of the upper rectum from the sacral promontory. Damage to these fibers may result in decreased bladder compliance and bladder neck incompetence. Ejaculatory difficulties, such as retrograde ejaculation, and impaired vaginal lubrication may be experienced by men and women, respectively.

The proximal pelvic splanchnic nerves are at risk for injury during the lateral dissection of the rectum. The more distal nervi erigentes are particularly vulnerable during the anterior dissection if Denonvillier's fascia is separated from either the prostate and seminal vesicles or the posterior aspect of the vagina. The nervi erigentes travel in an anterolateral fashion, residing just anterior to Denonvillier's fascia at the lateral border of the seminal vesicles in a man and the cardinal ligaments in a woman (Fig. 29.1). Injury to the parasympathetic nerves may manifest as erectile dysfunction in men while women may experience the inability to achieve arousal and/or orgasm. Hypocontractility or acontractility of the bladder may be experienced by both sexes, resulting in postoperative urinary retention (PUR). Opinions are divided regarding whether Denonvilliers' fascia lies anterior or posterior to

the anatomic fascia propria plane [23, 25]. Lindsey et al. argue that a radical "extra-anatomic anterior dissection in the extramesorectal dissection plane" is warranted to address anterior tumors, despite the potential risks for nerve injury [23, 25].

Bleeding

Hemorrhage can occur suddenly when the presacral fascia is breached and pelvic veins are injured. Manual pressure or suture ligation can curtail most presacral venous bleeding. Hemoclips, packing, electrocautery, and topical agents such as absorbable gelatin sponges (Gelfoam), microfibrillar collagen (Avitene), and oxidized regenerated cellulose (Surgicel) can be used for hemostatic purposes for mild presacral bleeding. Conversely, injury to the basivertebral veins can cause massive, life-threatening bleeding if not recognized early and appropriately managed. Hemorrhage from these veins cannot be controlled with suture ligature, cautery, or topical hemostatic agents. The basivertebral veins are bridging veins between the internal vertebral venous system which lies deep to the sacrum and the anterior external venous plexus which resides on the anterior surface of the sacrum between S3 and S5. These veins are most commonly injured when blunt dissection is used for the posterior dissection. If the site of bleeding can be identified, pressure from a single finger should be able to adequately temporize the bleeding while resources are mobilized. A titanium thumbtack advanced through the bleeding point into the sacrum can be effective in controlling massive bleeding. Other authors have advocated "welding" a strip of skeletal muscle into the sacral venous orifice using high current electrocautery. Any attempts at definitively stopping this type of bleeding should be done when the patient is adequately stabilized and appropriate blood products are available for resuscitation. When bleeding is uncontrollable, the pelvis should be packed for 24–48 h with subsequent return to the operating room to complete the procedure.

Surgical Site Infection

Estimated to occur in up to 30 % of resections. surgical site infection (SSI) is the greatest contributor to surgical morbidity after rectal cancer surgery. Risk factors for SSI include immunosuppression, malnutrition, diabetes mellitus, prior irradiation, fecal contamination during surgery, extensive surgery, length of hospitalization prior to surgery, age >60, and ASA class >2 [1, 26–29]. SSI is divided into superficial incisional, deep incisional, and organ/space infections.

Superficial incisional infection is characterized by localized swelling, erythema, warmth and purulent drainage and is initially treated by opening the wound, followed by routine dressing changes. Antibiotics should be initiated if cellulitis persists despite wound decompression. Deep incisional infection involves the rectus muscle and/or the fascia and may result in fascial dehiscence. Treatment includes IV antibiotics, wound exploration with debridement of infected tissues, and repair of fascial dehiscence.

Necrotizing fasciitis (NF) is a rare, but potentially fatal deep incisional infection caused by toxin-producing, virulent bacteria such as group A hemolytic Streptococcus and Staphylococcus aureus [30]. Characterized by rapid and extensive soft tissue and fascial necrosis, unrecognized NF can swiftly lead to widespread organ failure and death. After the initial innoculation, an opportunistic polymicrobial infection of aerobic Gram negative and anaerobic organisms ensues in this hypoxic environment. Early diagnosis accompanied by aggressive multi-disciplinary intervention is essential. Presenting symptoms of NF include a disproportionate amount of pain and tenderness around a wound with minimal skin changes, quickly followed by fever, erythema, crepitus, skin mottling, blistering and sloughing. Resuscitation including broad-spectrum antibiotics (e.g. Penicillin G, Clindamycin, and Gentamicin), followed by aggressive operative debridement of all necrotic and infected tissues is mandatory for preventing death from septic shock.

Typically presenting within the first postoperative week, most organ/space infections are precipitated by intraoperative fecal contamination,

unrecognized enterotomies, or anastomotic leaks. Clinical symptoms such as fever, leukocytosis, abdominal and/or pelvic pain should prompt the ordering of a CT scan of the abdomen and pelvis to investigate for intraabdominal or intrapelvic abscess. Rectal contrast can help identify a potential fistulous connection from the anastomosis to a nearby collection. First-line treatment should consist of broad spectrum antibiotics and percutaneous drainage of abscesses greater than 2 cm. Reimaging, including administration of contrast through the drain, should be performed after several days of bulb suction drainage to check for persistence of fluid. Recalcitrant pelvic sepsis may warranted operative management, including proximal fecal diversion.

Perineal wound infection, a form of deep incisional infection, occurs in up to 50 % of abdominoperineal resections. The circumferential excision of the distal rectum and anal canal through the pelvic floor results in a poorly perfused dead space that is susceptible to bacterial overgrowth. When a wide resection through the pelvic floor is performed (either due to a bulky or locally invasive tumor or to surgeon preference for an extralevator perineal resection (ELAPE)), there may be very little levator muscle available to close the perineal defect. Ischiorectal fat is left for reapproximation, creating a closure with a notoriously poor blood supply. A closed space infection may ensue that can present with perineal pain, foul-smelling drainage, and wound dehiscence. The incision should be opened and locally explored for fluid collections. Broad-spectrum antibiotics with gram negative and anaerobic coverage should be instituted. Wound care consisting of either gauze packing or negative pressure therapy (VAC) can help expedite healing by secondary intention. Interestingly, wound dehiscence, after APR, regardless of infection, has been associated with decreased survival [31].

Clostridium Difficile

Clostridium difficile-associated colitis is caused by toxins secreted by the eponymous Gram positive anaerobe and is associated with symptoms ranging from mild, watery diarrhea to fulminant colitis. Reports of *C. difficile* colitis after colorectal resection range from 1.3 to 21 % with a greater predilection in the patient with immune system dysfunction, fecal stasis, long-term antibiotic use, and chemotherapy administration [32–34]. First-line treatment includes stopping antibiotics and initiating either metronidazole or vancomycin. Surgical intervention may be necessary if the patient does not respond to treatment or clinical course worsens. The mortality rate for patients who progress to fulminant colitis or toxic megacolon is 35–80 % [32].

Thromboembolism

Venous thromboembolism (VTE) frequently occurs in the setting of malignancy and represents a spectrum of diseases including deep vein thrombosis (DVT) and pulmonary embolus (PE). Specific to rectal cancer treatment, risk factors for VTE include tumor factor activation, intravascular inflammation resulting from chemotherapy and radiation therapy, extensive abdominal and pelvic surgery, and prolonged immobilization. Prophylactic anticoagulation should be initiated prior to surgery and continued for at least 7–10 days. High-risk patients should extend the prophylaxis for a total of 4 weeks. Weight-based low-weight molecular heparin (LWMH) is recommended for extended prophylaxis.

Deep vein thrombosis is typically heralded by unilateral extremity swelling, warmth, and erythema. A palpable cord may be appreciated. Although lower extremity DVTs occur more frequently, upper extremity DVTs may also be seen, especially in the setting of an indwelling central venous catheter. Duplex venous ultrasonography is the recommended diagnostic modality. Initial treatment includes subcutaneous LMWH, IV unfractionated heparin (UFH), monitored subcutaneous UFH, or subcutaneous fondaparinux. Acute DVT should be treated for at least 5 days and until the INR is $\geq$2.0 for 24 h. A vitamin K antagonist (VKA) (e.g. warfarin) should be initiated with LMWH, UFH, or fondaparinux on the first treatment day. VKA should be adjusted to

maintain a target INR of 2.5 for 3–6 months. An inferior vena cava (IVC) filter can be placed in patients who are high-risk for bleeding, but anticoagulation should subsequently be initiated if the bleeding risk resolves.

Pulmonary embolus is a dreaded complication that occurs when a DVT propagates through the venous system into the pulmonary vessels. Symptoms may include dyspnea, tachnypnea and pleuritic chest pain. Acute cardiopulmonary collapse may ensue. Treatment includes hemodynamic stabilizatiion, systemic thrombolytic therapy, and subsequent anticoagulation for 3–6 months. Routine IVC filter placement is not recommended.

Indefinite anticoagulation is advised for both DVT and PE in patients with a thrombotic diathesis and with metastatic malignancy.

Anastomotic Issues

Anastomotic complications can be devastating after restorative rectal cancer surgery. Bleeding, leak, and stricture are the most commonly encountered complications after low anterior resection.

Anastomotic Bleeding

Minor bleeding or oozing from the anastomotic staple line is common and can be easily managed with manual pressure, interrupted suture ligation of a discrete portion of the anastomosis, or circumferential suture reinforcement of the entire staple line. Cautery can be used sparingly for hemostasis, but caution should be exercised to prevent a thermal burn that could then lead to a delayed anastomotic disruption.

Postoperative bleeding typically presents as the passage of bloody stools or clots after restitution of bowel function. Conservative management, including assessment of vital signs, serial hemoglobins, and fluid resuscitation, should be initially employed. Transfusion of packed red cells may be needed if the blood loss is substantial. Coagulopathies should be corrected with blood products, factors, and/or vitamin K.

Persistent bleeding and massive hematochezia, despite conservative efforts, are rare, but warrant more aggressive management. After proper resuscitation, proctoscopy should be performed. Care must be taken not to disrupt the fresh anastomosis while adequately investigating the nature of the bleed and suctioning out intraluminal contents. Proctoscopy with lavage and evacuation of the clot may suffice to curtail the persistent oozing. A 1:100,000 saline solution with epinephrine can be instilled into the rectum and left for 5–10 min prior to reevaluation. Oversewing of the low colorectal anastomosis can also be performed. For the more proximal anastomosis, flexible endoscopic evaluation may be warranted in which hemoclips can be deployed and epinephrine can be injected into the bleeding site.

Anastomotic Leak

Anastomotic leak (AL) is one of the most dreaded complications of rectal cancer surgery. Subdivided into clinically recognized (clinical leak) and unrecognized (subclinical leak) anastomotic disruptions, AL can present either early in the postoperative period or in a delayed fashion (>30 days after surgery). The incidence of clinical leak ranges from 2 to 36 % with an associated mortality rate between 6 and 22 % [27, 35–37] AL is associated with decreased health-related quality of life (HRQL), especially when poor functional results, anastomotic stricture, or diverting ostomy are involved [35, 37] Signs and symptoms of AL include fever, sepsis, and peritonitis in a patient with radiologic evidence of free extravasation of intraluminal contrast, a contained perianastomotic fluid collection, or a presacral fluid collection. Succus draining to the skin, vagina, or urethra may also be a harbinger of an AL complicated by fistula.

Patient factors, such as male sex, poor nutritional status, compromised immune system, history of prior pelvic radiation, and comorbidities such as morbid obesity and diabetes mellitus, have been associated with an increased risk for AL [35, 37, 38].

There appears to be inverse relationship between AL and the location of the tumor, as distal lesions notoriously present greater surgical difficulty. Vignali et al. reported a 7.7 % AL rate with low anastomoses (<7 cm from the anal verge), while only a 1 % AL rate with high anastomoses (>7 cm from the anal verge) [39]. Resection of distal tumors may also lead to the truncation of oncologically safe distal margins when sphincter preservation is attempted. Cong and colleagues found in a multivariate analysis that AL was 6.18 times greater in patients with distal margins <1 cm compared to those with distal margins ≥1 cm ($p = 0.009$) [40].

Interestingly, AL rates surged after the introduction of the TME technique. These early studies reported clinical leak rates ranging from 16 to 23 % [27, 41–43]. It had been suggested that TME endangered the blood supply of the rectal stump, however increased experience with TME, including laparoscopic TME, has resulted in comparable AL rates to non-TME procedures [38, 44–51].

While AL is not prevented by fecal diversion, the severity of the clinical presentation of AL has been lessened by the presence of a proximal loop ileostomy [11, 52].

While a CT scan of the abdomen and pelvis may demonstrate free intraabdominal air and fluid, a gastrografin enema can be more useful in delineating the location and magnitude of a suspected AL. Luckily, the large majority of contained AL will heal with conservative management including systemic antibiotics and bowel rest. Ultrasound or CT-guided drain placement is recommended for walled-off fluid collections ≥2 cm.

Clearly, surgical intervention is warranted for the patient with free extravasation of contrast on CT scan, as well as, the unstable patient with clinical symptoms of intraabdominal sepsis. Fluid resuscitation and broad-spectrum antibiotic administration should be initiated early, followed by surgical exploration with liberal irrigation of any purulent and/or feculent ascites. Anastomotic integrity determines whether a primary repair can be attempted with or without proximal diversion. A takedown of the colorectal anastomosis with diverting end colostomy and closure of the rectal stump is recommended with a significant dehiscence, in the setting of substantial pelvic contamination, or in the unstable, septic patient. Pelvic drainage can be considered after primary repair of an anastomotic defect or when the rectal stump cannot be adequately closed.

Several technical principles should be adhered to in order to minimize AL. First, adequate blood supply to the two anastomotic stumps should be verified. Second, suturing or stapling of the anastomosis should be meticulously performed. This should be followed by a "leak test" in the operating room which involves insufflating the rectum with occlusion of the proximal bowel lumen, while submerging the anastomosis under saline or water. In addition, the integrity of the anastomotic rings should be carefully inspected. Lastly, a tension-free anastomosis should be created, which may warrant the release of the splenic flexure. High ligation of the inferior mesenteric artery and vein can provide additional laxity of the proximal bowel.

Anastomotic Stricture

Stricture is typically the long-term result of anastomotic ischemia, dehiscence, or leak. Disruption of more than 25 % of the luminal circumference will often result in excessive fibrosis of the anastomotic line. Stenosis can also be seen in the diverted patient as the anastomosis does not experience auto-dilatation from the passage of stool. Symptoms of stricture depend on the location of the anastomosis, the degree of stricture, and the consistency of stool. Patients may experience diarrhea, constipation, urgency, soiling, and tenesmus. As tumor recurrence can be heralded by such pronounced changes in bowel habits, endoscopic evaluation is important to differentiate between benign and malignant stricture. Benign strictures can be initially treated with stool softeners and enemas. Digital dilatation can be performed for low anastomoses while higher anastomoses (>7 cm) may require dilatation with Hegar's dilators or balloon dilatation with a flexible endoscope. Refractory strictures may require either transanal incision of fibrotic scar or revisional surgery.

Incisional and Parastomal Hernia

The incidence of incisional and parastomal hernia after colorectal surgery is estimated to be up to 30 and 60 %, respectively [53–55]. Surgical site infection and morbid obesity are the two largest contributors to hernia formation [29, 54, 55]. Murray found patients who developed a SSI were more than 1.9 times as likely to develop an incisional hernia compared to those who did not have a SSI [29]. Schreinemacher [54] and DeRaet [56] reported significantly higher rates of incisional and parastomal hernias in patients with BMIs ≥30 and with waist circumferences in excess of 100 cm (Fig. 29.2). Other risk factors include low albumin levels, diabetes mellitus, chronic immunosuppression, male gender, anemia, and old age [55, 56]. Persistent coughing, abdominal distention, retching/vomiting, and development of excessive intraabdominal ascites in the postoperative period can contribute to tension on the fascial closure and should be minimized, if possible.

While multiple sources have reported decreased incisional hernia rates with laparoscopic resection for colorectal cancer compared to open surgery [57], increased hernia rates have been reported with laparoscopy at the specimen extraction site (especially with midline extraction) [58–61]. The data remain inconclusive regarding the potential protective effect of laparoscopy in regards to hernia formation [57, 62].

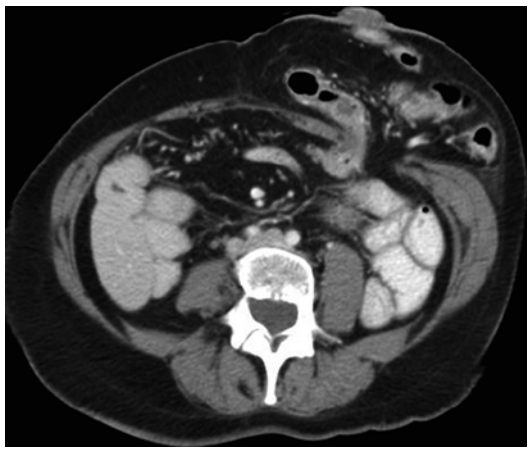

Fig. 29.2 Parastomal hernia (colostomy)

Perineal Hernia

Perineal hernia is a rare complication that can result after infection or poor healing of the perineal wound. Small bowel can bulge inferiorly, leading to skin breakdown and even evisceration. Symptoms range from pressure, pain, or fullness in the perineum to obstructive symptoms. Intraoperative attempts to prevent this complication include pelvic drain placement, closure of the pelvic parietal peritoneum, myocutaneous flap construction (gracilis, rectus abdominus, inferior gluteal), posterior rotation of the uterus, and placement of biologic mesh to bridge the pelvic hollow. Repair may also include flap construction or biologic mesh placement, necessitating both an anterior and posterior approach.

Ostomy Issues

Ostomy creation is fraught with potential complications including ischemia, stenosis, retraction, prolapse, parastomal hernia, peristomal skin erosion, and pouching difficulties.

Ischemia arises when the arterial blood supply is compromised by aggressive ligation of the adjacent mesentery, inappropriate division of vascular arcades, or by excessive tension on the mesentery. Superficial ischemia results in congestion and sloughing of the mucosa, but rarely requires surgical intervention. Full-thickness necrosis above the fascia may lead to stenosis and retraction of the stoma below the skin. Dilatation or local revisional surgery should be performed if evacuation difficulties arise. Recalcitrant stenosis or deep stomal retraction may necessitate a laparotomy to adequately mobilize the preceding bowel and revise the stoma. Urgent reoperation is warranted for necrosis that extends below the fascia, in order to stanch perforation.

Retraction may also occur with inadequate mobilization of the bowel limbs, resulting in excessive tension on the stoma (Fig. 29.3). Revision may be needed if pouching difficulties or peristomal skin breakdown ensues.

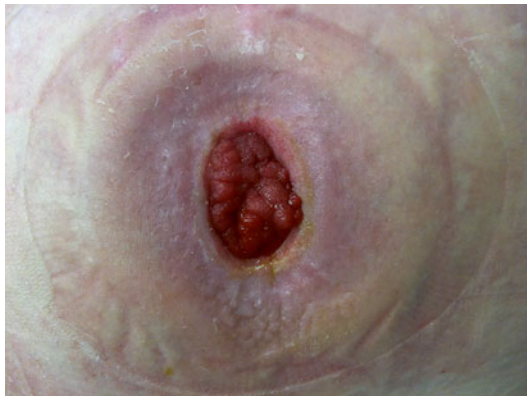

Fig. 29.3 Retracted stoma

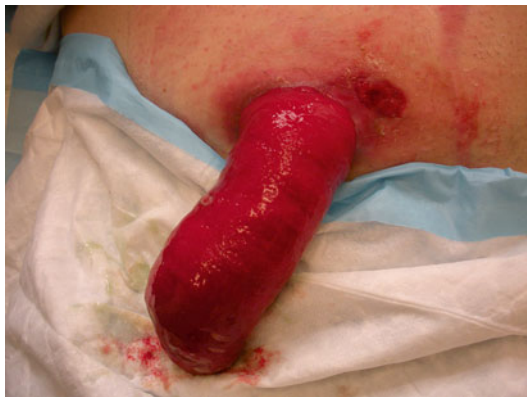

Fig. 29.4 Prolapsed ileostomy

Prolapse occurs when redundant proximal bowel invaginates through the distal portion of the stoma (Fig. 29.4). Rates ranging from 2 to 42 % have been reported, with the greatest incidence occurring in loop ostomies [63, 64]. Conservative measures such as manual reduction should be initially exercised to prevent incarceration, obstruction, and possible strangulation. Treatment may include local revision, conversion from a loop to an end ostomy, or stoma reversal, if possible.

Bowel Dysfunction

Bowel dysfunction is frequently encountered after sphincter-preserving surgery. Anterior resection syndrome (ARS), a constellation of symptoms including fecal urgency, incontinence, clustering, increased bowel movements, and emptying difficulties, has been reported in up to 60–90 % of patients who undergo low and ultralow anterior resection [65–67]. Loss of reservoir function, decreased rectal compliance as a result of neoadjuvant radiation, and injury to the anal sphincter complex and/or pelvic nerves contribute to ARS. Patients should be carefully counseled prior to surgery about the likelihood of experiencing one or more of these symptoms, as quality of life has been shown to be significantly impacted by ARS. Treatment initially includes modification of bowel movements with either bulking agents or antidiarrheal medications. Patients with significant fecal retention or emptying difficulties may benefit from enemas. Anastomotic stricture should be considered in patients with refractory obstipation. In addition to medications, biofeedback can be an adjunct to improving fecal frequency, urgency, constipation, and incontinence [67].

Conclusion

Intraoperative, early postoperative, and late postoperative complications are well-recognized in rectal cancer surgery. The anatomic challenges of the pelvis coupled with advanced tumors and neoadjuvant therapy pose an elevated risk of iatrogenic injury. Difficult pelvic dissection is associated with pelvic nerve injury which may manifest as urinary, sexual, and/or defecatory dysfunction. Sequelae of anastomotic complications might warrant further surgical intervention such as revisional surgery or diversion. Prophylactic therapies such as preoperative antibiotics and anticoagulation are encouraged to minimize such complications as surgical site infection and thromboembolism. A frank discussion with the rectal cancer patient regarding surgical risks and potential complications is highly advised.

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