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Editor

Rectal Cancer

Modern Approaches to Treatment

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Contents

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Rectal Anatomy: Clinical Perspective

1

Slawomir Marecik, John Park, and Leela M. Prasad

Introduction

This chapter will discuss the anatomy of the rectum and pelvis as it relates to the diagnosis and surgical management of rectal cancer.

Over the last 30 years, a significant amount of progress has been made to more fully understand rectal and pelvic anatomy. Professor Bill Heald stressed the importance of proper anatomical technique during rectal dissection based on embryological development and led efforts for its ultimate widespread utilization [1]. Subsequently, the advent of minimally invasive techniques in the last decade of the twentieth century made it possible to appreciate the pelvis from a different perspective. Laparoscopy now provided a magnified view and allowed for surgical procedures to be recorded for further analysis and widespread teaching. As a result, it became easier to understand the nuances of rectal surgery.

Advances in technology including robotic surgery have further advanced our ability to visualize surgical pelvic anatomy. Several factors have played an important role in this advancement, including improved ability to "freeze" and appreciate the operating field, as well as improved precision of dissection and more hemostatic techniques [2]. At the same time, new methods of processing and handling the cadaveric material allowed for more effective study of pelvic anatomy in the lab [3, 4].

Finally, the last 15 years have seen the role of magnetic resonance imaging (MRI) rapidly evolve. Today, it is one of the main diagnostic tools in rectal cancer [5]. With improved resolution and quality of images obtained, MRI technology has improved our understanding of both pelvic anatomy, as well as rectal cancer overall [6, 7]. In fact, MRI has helped to validate previous observational anatomical studies in reproducible and objective ways.

Rectum

Anatomically, the rectum is the last segment of the large intestine that occupies the posterior pelvis along the concavity of the sacral bone. This organ can be 12–18 cm long, with the proximal end located at or just below the level of the sacral promontory and the distal end at the junction with the anal canal (Figs. 1.1, 1.2, and 1.3). The length of the rectum can vary and is dependent on its distention, body habitus, and amount of mesorectal fixation. It is an organ with an increased ability for accommodation and ability to change its size. The rectum differs from the colon as it

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contains a complete outside layer of longitudinal muscle within its wall. This feature results in the lack of haustra and taenia strips. The wall of the rectum consists of several layers, which can be fully appreciated during endorectal sonography. These are mucosa with muscularis mucosae, submucosa, muscularis propria, and surrounding mesorectal fat (Fig. 1.4). The rectum lacks the free-floating appendices epiploicae. Because the transition between the colon and the rectum is not abrupt, another distinct segment, the rectosigmoid, can be appreciated. This 4–8 cm segment is usually the narrowest part of the large intestine, when not counting the appendix.

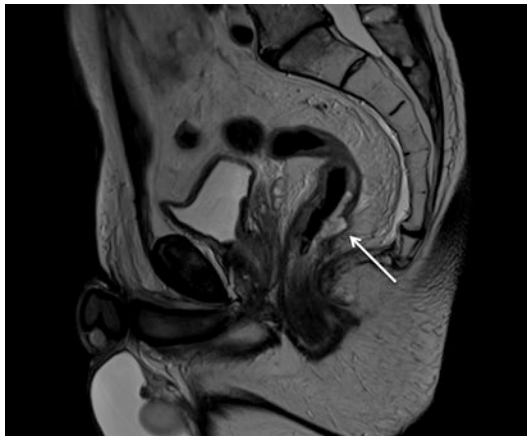

Fig. 1.1 MRI of pelvis (sagittal, T2 sequence), male, ulcerated tumor in the posterior, lower rectum (*arrow*)

Endoscopically, the rectum is wider than the rest of the left colon. The rectum's most distal part, the ampulla, is the widest, allowing for safe retroflexion of the flexible endoscope. In linear measurements, this part, when distended, is at least two to three times wider than the width at the anorectal junction. Additionally, the change in size between these two segments takes place in a very short distance, an important fact to consider during bowel stapling. The high accommodation properties of the rectum result in increased thickness of the non-stretched rectal wall. On average, three internal folds can protrude into the lumen of the rectum (valves of Houston) when the bowel is moderately distended; however, anatomical variations exist [8] (Fig. 1.3). These folds involve approximately 25–75% of the circumference and

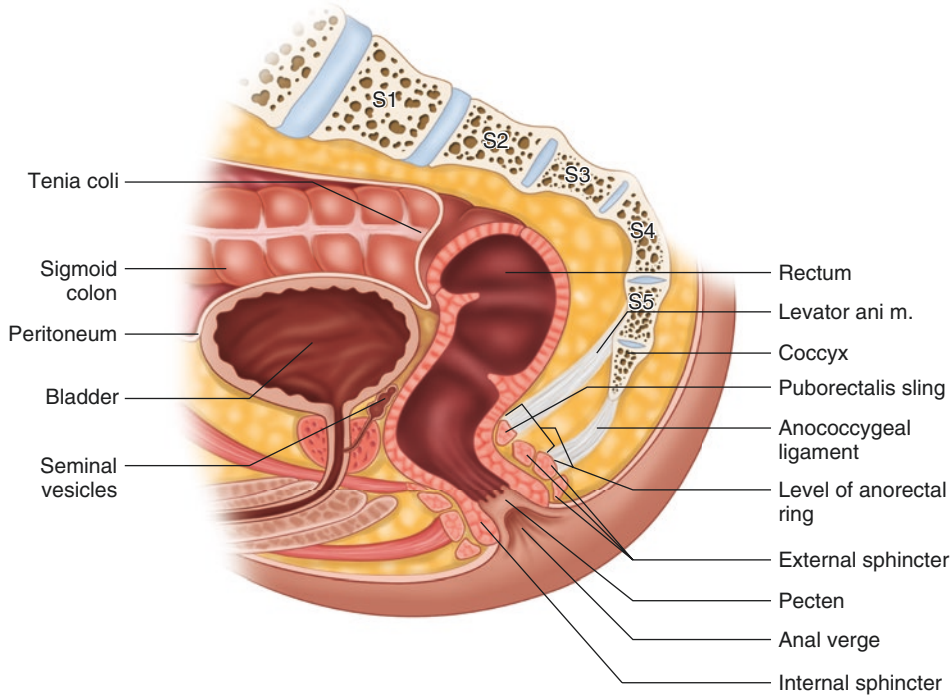

Fig. 1.2 Rectal anatomy, lateral view

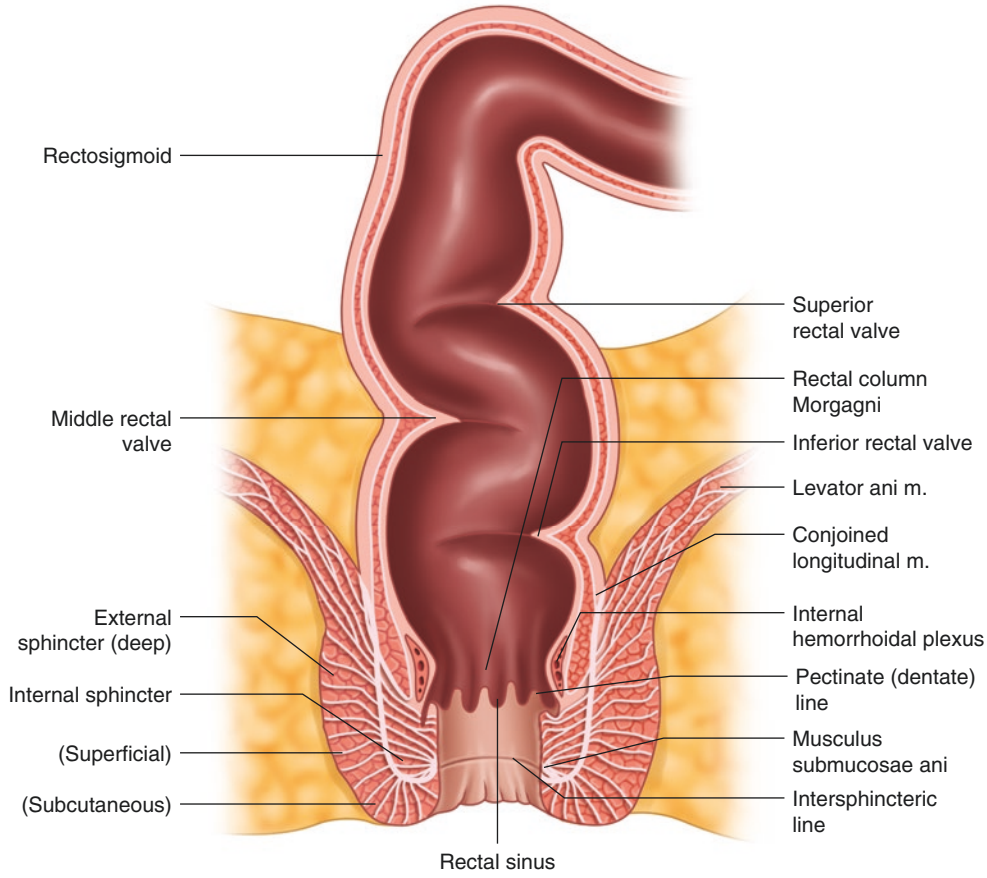

Fig. 1.3 Rectal anatomy, AP view

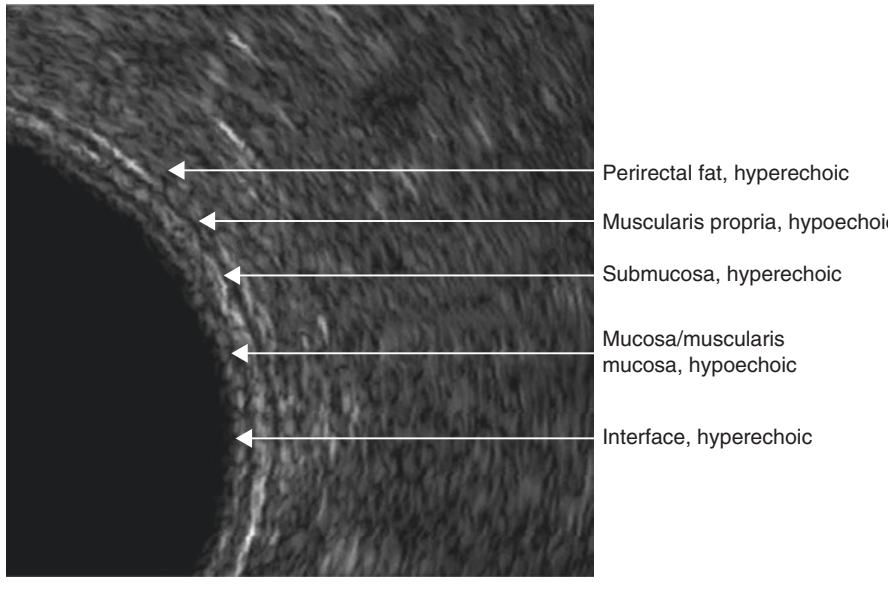

Fig. 1.4 Endorectal ultrasound, layers of the rectal wall and the mesorectum

are the result of increased muscular fiber concentration in the circular layer of the bowel wall. The lowest valve is located approximately 3–5 cm above the anorectal junction. The second valve (Kohlrausch's plica) is on the opposite side and often corresponds with the level of the anterior peritoneal reflection in an individual of average weight and height. The third valve is located on the left side. Together, all three valves create several mild curvatures that need to be negotiated during endoscopic exam or transanal insertion of the stapler. Inadvertent incorporation of the folded valve into the staple line during transanal stapling may result in anastomotic leak.

Still more important curves to consider, however, are those seen on lateral projection, including a 90-degree (anorectal) angle between the ampulla and the anal canal, and a gentler anterior curve along the concavity of the sacrum. The sharp anorectal angle forms the "posterior rectal shelf" and contributes to fecal continence. It can be easily appreciated upon digital exam (Fig. 1.2). Unfortunately, it can also make it difficult to properly evaluate the posterior cancers of the very distal rectum during transanal sonography. In this case, it is difficult to orient the ultrasound beam perpendicularly to the posterior wall of the most distal rectum. Both angles may need to be negotiated safely during transanal stapler insertion.

Mesorectum

In the majority of individuals, the circumference of the rectal tube, excluding significant portion of the anterior aspect, is surrounded by adipose tissue called mesorectum (Fig. 1.5). Initially, the term mesorectum was considered a misnomer [9]. Today, it is accepted as a proper term describing a package of adipose tissue surrounding the rectal tube in a distinct fascial layer (fascia propria of the rectum or FPR). The mesorectum contains vessels, lymphatics, and lymph nodes as well as minor nerve fibers. In obese individuals, the lower half of the rectum is often completely surrounded by the mesorectum due to abundant anterior fat deposits.

The significance of the mesorectum is mainly related to the lymph nodes, which are frequently

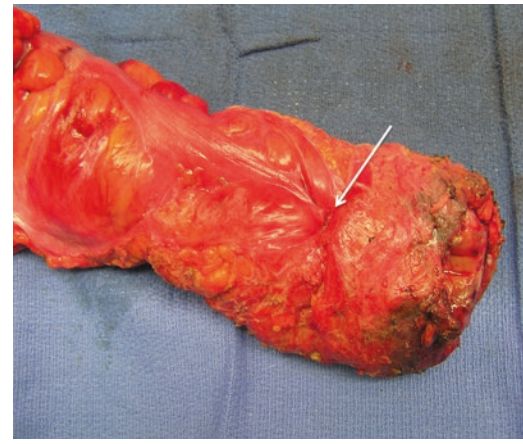

Fig. 1.5 Rectum after total mesorectal excision (peritoneal reflection marked with *arrow*)

the site of locoregional tumor spread and should be resected en bloc along with the involved segment of the rectal tube [1]. Clinically, the average number of lymph nodes within the entire mesorectal specimen can vary anywhere between 5 and 20 (up to 40 in some anatomical studies) and can be reduced after preoperative radiation therapy [10–13]. In its distal part, the mesorectum tapers out and frequently disappears in thin individuals (Fig. 1.6). This allows the rectal tube to be in direct apposition to the convexity of the pubococcygeus and iliococcygeus (levator ani) muscles and the concavity (groove) of the anococcygeal raphe (Fig. 1.7).

Fascial Layers of the Pelvis

Fascia Propria of the Rectum

The fascia propria of the rectum (FPR) is also referred to as mesorectal fascia, investing fascia, or visceral pelvic fascia. It creates a thin envelope surrounding the mesorectum and the anterior part of the bowel not covered by the mesorectum, thus forming a distinct anatomical package. This package can be surgically dissected out in toto during total mesorectal excision. Moving cephalad, the mesorectal fascia is an equivalent of the mesocolic fascia that covers the left colon. It fuses with the endopelvic fascia and the presacral fascia.

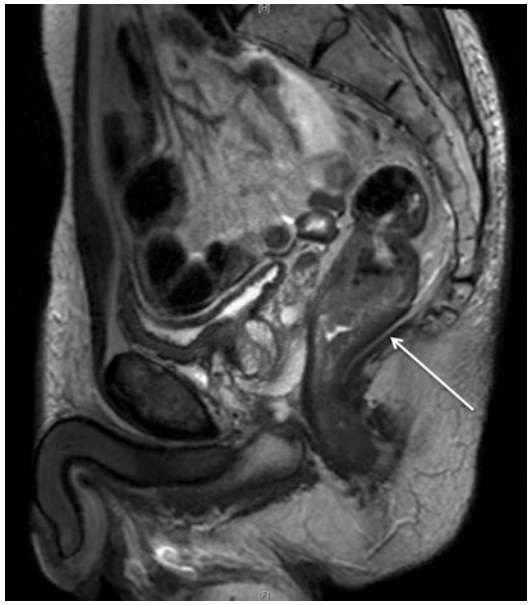

Fig. 1.6 MRI, T2 sequence, thin male; thinned out (absent) mesorectum in the lower aspect of the posterior rectum

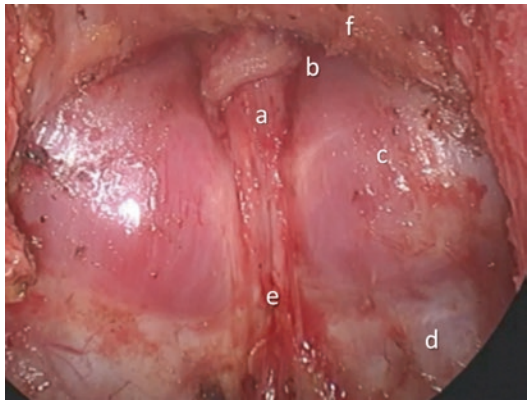

Fig. 1.7 Posterior pelvis after total mesorectal excision: *a* rectal stump, *b* pubococcygeus muscle, *c* dome of the iliococcygeus muscles, *d* coccygeus muscle, *e* anococcygeal raphe, *f* anterior pelvic structures covered by an intact Denonvilliers' fascia

Endopelvic Fascia

The endopelvic fascia is a distinct fascial layer that covers the floor and sidewalls of the entire pelvis. In obese individuals, a certain amount of adipose tissue can be found underneath the endopelvic fascia or even in between its particular layers (Fig. 1.8). On the other hand, in a thin patient, it can be translucent (Fig. 1.9). In the lateral aspects of the pelvis, the endopelvic fascia extends to the sides, covering the origin of the levator ani muscles at the tendinous arch along the internal obturator muscle.

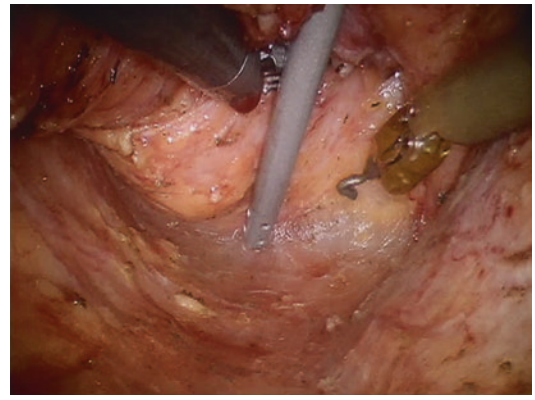

Fig. 1.8 Endopelvic fascia in a patient with visceral obesity, presacral segment, upper half of total mesorectal excision

Presacral Fascia

The presacral fascia lines the posterior aspect of the cylindrical mesorectal compartment in front of the sacrum. In the posterior midline, it covers the promontory as a continuation of the abdominal Toldt's fascia into the pelvis (Fig. 1.8). Descending deeper into the pelvis, this fascia lines the midline portion of the sacrum, spreading anteriorly and laterally in the arcuate fashion in order to cover the medial portion of the piriformis muscles, the sacral foramina containing sacral nerves roots, and the midline and posterior portion of the levators.

Denonvilliers' Fascia

In the anterior aspect of the extraperitoneal rectum, extending slightly above the peritoneal reflection, there is a distinct layer of fibroelastic tissue called the Denonvilliers' fascia. It is a trapezoidal sheet separating the mesorectal compartment from

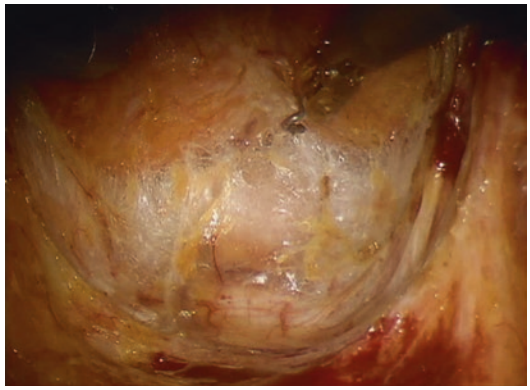

Fig. 1.9 Endopelvic fascia in a thin patient, presacral segment, upper half of total mesorectal excision. Visible presacral structures: veins, arteries, sympathetic ganglia

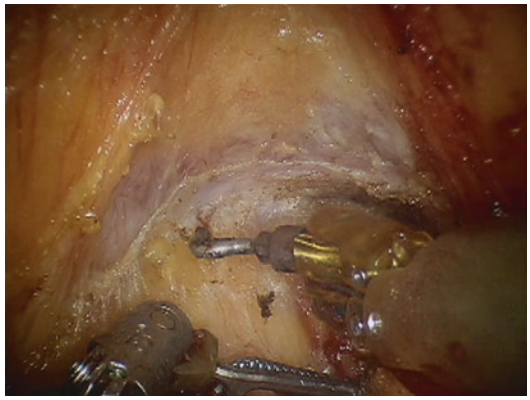

Fig. 1.10 Denonvilliers' fascia, male patient, level of seminal vesicles (*visible cut edge*)

the anterior pelvic structures (Fig. 1.10). In men, Denonvilliers' fascia stretches in a concave fashion between both pelvic sidewalls as a cover of the anterior pelvic compartment, which includes the bladder, seminal vesicles, vasa deferentia, ureters, prostate, and both neurovascular (genitourinary) bundles. In women, Denonvilliers' fascia stretches in a concave fashion from both pelvic sidewalls covering the posterior wall of the vagina as well as the genitourinary neurovascular bundles.

During anterior rectal mobilization, the dissection can be carried out on either side of Denonvilliers' fascia as indicated by the tumor. It is important to note, however, that in men, this exposes the fine neurovascular plexus of the seminal vesicles and

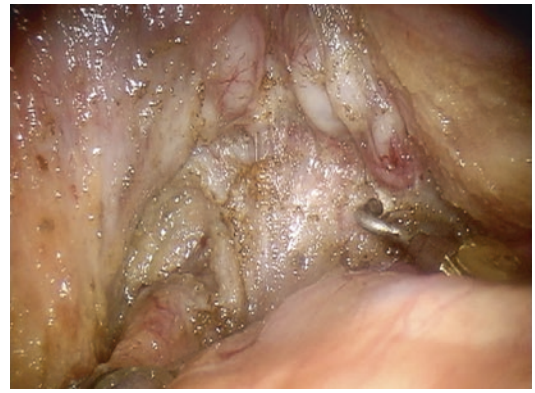

Fig. 1.11 Denonvilliers' fascia cut and deflected posteriorly, exposing the seminal vesicles

prostate, while in women, it exposes the sinusoidal vessels of the vaginal wall. In addition, seminal vesicles and associated neurovascular structures can be exposed and at risk for injury (Fig. 1.11).

Waldeyer's Fascia

There is some controversy with regard to Waldeyer's fascia in rectal anatomy texts [14–17]. While this fascia, also known as rectosacral fascia, has been an anatomical and cadaveric observation, it has limited impact on rectal cancer surgery, as long as the principles of total mesorectal excisions are followed. Many textbooks depict Waldeyer's fascia as an anteroinferior extension of the presacral fascia, separated from the latter at the S4 level and running toward the rectal tube [14, 15, 17]. Others have depicted it as a layer penetrating the mesorectum [16, 18] or a layer running closer to the levator muscles that requires sharp division in order to provide full posterior rectal mobilization [15].

Parietal Fascia (Fascia of the Lateral Compartment)

The parietal fascia (PF) separates the mesorectal compartment from the lateral pelvic compartment and transitions into Denonvilliers' fascia anteriorly.

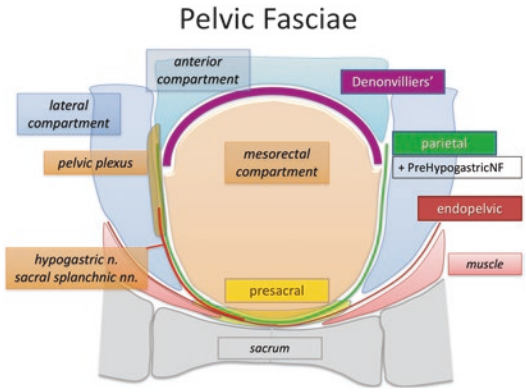

Fig. 1.12 Parietal fascia of the mesorectal compartment (*blue*) originating from the endopelvic presacral fascia separates the mesorectal compartment (MC) from the lateral compartments (L) and transitions into Denonvilliers' fascia (DF) in the region of the lateral tethered surface (LTS)

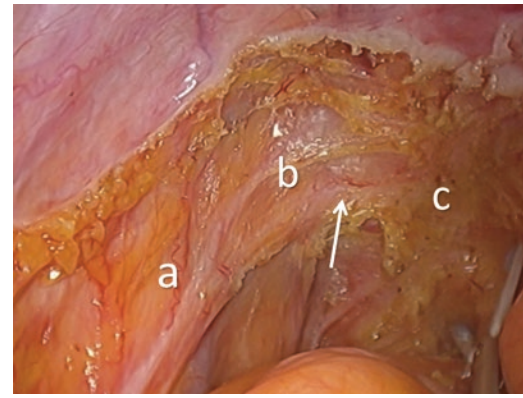

Fig. 1.13 Lateral tethered surface (LTS) on the left side, the point of insertion (*arrow*) of nerve fibers from the pelvic plexus (*b*) to the mesorectum (*c*); left hypogastric nerve (*a*)

The PF is closely related to the hypogastric nerve and the pelvic plexus, putting these structures at risk during dissection. At the mid-rectal level, it can also be adhered to the mesorectal fascia, a result of small nerve endings (nervi recti) entering the mesorectum from the pelvic plexus. When medial retraction is applied to the mesorectum, a tethering can be observed [19] (Figs. 1.12 and 1.13). This has been described in the literature as the "lateral ligament" [20]. We prefer the term "lateral tethered surface" (LTS). The tethering is caused by the small nerve structures, fatty and connective tissue, and small blood vessels crossing from the lateral to mesorectal compartment [21].

Peritoneal Coverage

The upper portion of the rectum is invested by peritoneum anteriorly and laterally, while the middle part only anteriorly. Finally, the lower rectum is completely extraperitoneal below the peritoneal reflection. Thus, in an average-sized individual, the peritoneal reflection corresponds to the level of the second valve of Houston. This translates to the level at about 6–8 cm from the anal verge in women and 7–10 cm in men. Patient habitus such as height, obesity, and pelvic musculature can affect these distances.

Anatomical Relations

The anatomic relations of the rectum should be carefully considered during surgical resection, particularly with locally advanced tumors which extend beyond the mesorectal fascial plane. Posteriorly, these structures include the sacrum, coccyx, piriformis, and levator ani muscles, as well as the sacral nerve roots. Anteriorly, the bladder or uterus and vagina in women and seminal vesicles, neurovascular bundles, and the prostate or urethra in men may be at risk. Potentially involved lateral structures may include the hypogastric nerve trunks, the ureter, or the lateral structures such as the internal iliac vessels or associated nodal compartments.

Anus

The anus is the terminal portion of the alimentary tract. It consists of the anal canal and the anal margin. In the clinical sense (surgical and also functional), the anal canal extends from the anorectal junction, at the superior border of the levator hiatus, to the anal verge (Fig. 1.3). The anal verge is the point of contact of the examiner's thumb made to the anoderm during digital rectal exam using the index finger. The average length

of the anal canal in women is 2.5–3.5 cm, and in men it is 3–4 cm. This length is dependent on the muscle tension and is shorter under general anesthesia and deep sedation.

The anal margin is a circular, doughnut-shaped area located outside the anal verge within a 3–3.5 cm radius. The anal canal is a functional unit created by the sphincter muscle complex which can dilate to accommodate stool evacuation. It is located anteriorly and inferiorly from the coccyx, anterior to the deep postanal space and next to the ischioanal space. In women, it is posterior to the distal vagina, while in men it is posterior to the membranous portion of the urethra, the origin of bulbospongiosus (often described as bulbocavernosus) muscles, and Cooper's glands.

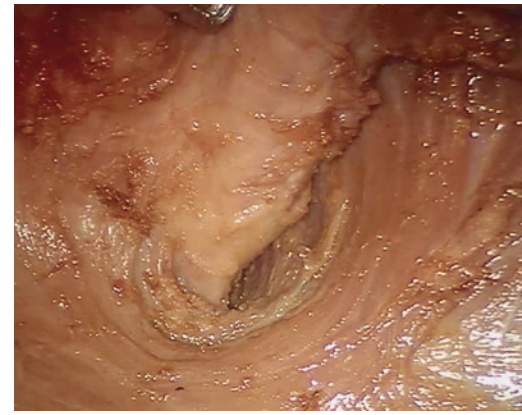

Fig. 1.14 Avascular intersphincteric plane; longitudinal conjoined tendon covering the internal sphincter; view from the pelvic side (courtesy of Prof. Amjad Parvaiz)

Sphincter Complex

The sphincter muscle complex is comprised of two muscular tubes (Fig. 1.2). The external tube (external sphincter) is longer and thicker and derived from striated (skeletal) muscle. The internal tube (internal sphincter) is significantly thinner and slightly shorter and comprised of smooth muscle. The difference in length between the two sphincter tubes creates the intersphincteric groove which is an easily palpated important landmark.

The external anal sphincter is a 3–4 cm long elliptically shaped structure. It works as one functional unit comprised of four subunits, including the most cephalad puborectalis sling and three ring-like layers: deep, superficial, and subcutaneous [22]. The puborectalis muscle is a U-shaped muscular band originating from the pubis and linking the levators plate to the rest of the external sphincter. This muscle is responsible for creation of the anorectal angle and, in large measure, for overall fecal continence. The external sphincter complex, through its superficial unit, is fixed to the coccyx by the anococcygeal ligament located below the levators plate. It is also fixed anteriorly to the perineal body where it merges with the transverse perineal muscles.

The internal sphincter muscle is a 2.5–3.5 cm long tubular structure located inside the longer tube of the external sphincter muscle. It is made by concentric smooth muscles lamellae. Overall, the thickness of the internal sphincter tube is approximately 2–4 mm. At the anorectal junction, the internal sphincter transitions into the inner circular muscle layer of the rectal wall. An outer longitudinal layer of the rectal wall, together with some fibers of the levator muscles, creates a very thin muscular layer called the conjoined longitudinal muscle (CLM) [23]. The CLM runs within the intersphincteric space thus separating both the internal and external sphincter tubes. This observation is strictly anatomical and does not have any specific clinical implications for rectal cancer surgery. However, for the surgeon performing intersphincteric dissection, it is more practical to associate the conjoined longitudinal muscle with the internal sphincter. The intersphincteric space is a potential space of surgical dissection and does not contain any relevant vasculature (Fig. 1.14).

Lining of the Anal Canal

The anal canal lining consists of rectal-type mucosa in the upper half and cutaneous coverage in the lower half. The demarcation line between

these embryologically different types of epithelium is called the dentate line (pectinate line), a sawtooth line located in the middle of the anal canal. Above the dentate line, an interposed transitional zone exists (6–12 mm segment) containing the columnar, transitional, and squamous epithelia [24]. The upper half of the anal canal contains 6–12 longitudinal mucosal folds (columns of Morgagni), which also extend below the dentate line as the anodermal folds. These folds are the result of the constricting effect of the sphincter complex on the lining of the anal canal. The columns of Morgagni are connected at their bases by the anal valves covering the outlets of the anal crypts.

The lining of the upper half of the anal canal is purple due to abundant underlying internal hemorrhoidal plexus. The lining of the lower half of the anal canal, called the anoderm, is pale pink, smooth and shiny, and devoid of true skin structures like hair, sweat, or sebaceous glands. At the level of the anal verge, the skin acquires pigmentation and hair follicles, as well as typical dermal structures, including the apocrine glands. Proximal to the dentate line, the bowel is derived from the endoderm and is supplied by the autonomic (sympathetic and parasympathetic) nerves, while distal to the dentate line, the epithelium has somatic innervation.

Pelvic Floor

The pelvic floor, also known as the pelvic diaphragm, is a sheet-like muscular structure created by a complex of muscle units. The purpose of the pelvic floor is to support the pelvic viscera and allow for secure passage for the alimentary and genitourinary tracts. While the levator ani muscle complex makes up the main "bulk" of the pelvic floor, complete coverage of the pelvic outlet involves three additional areas. The symmetrical greater sciatic foramina in the posterolateral pelvis are covered by two piriformis muscles. The midline defect in the anterior pelvis is covered by the deep transverse perineal muscle supported by a thickened portion of the endopelvic fascia on its cephalad surface called the urogenital membrane (also known as hiatal ligament) (Fig. 1.15).

Internal Obturator Muscle

Proper understanding of the levator ani muscles involves discussion about the internal obturator muscle. The lateral attachments of the levator ani muscles are directly associated with this structure. The internal obturator muscle is attached to the inner surface of the superior and inferior ileopubic rami as well as to the obturator membrane spread over the obturator foramen (Figs. 1.15 and 1.16). From here, the muscle runs in the posterior direction, lining the entire lateral portion of the true pelvis and exiting it via the lesser obturator foramen (Fig. 1.17). The fascial coverage of this muscle creates an insertion place for the levator ani muscles (tendinous arch) . The tendinous arch runs dorsally as a straight line from the pubic symphysis, parallel to the superior ileo-pubic ramus, reaching the ischial spine. The insertion of the levator ani muscles, together with the lower aspect of the internal obturator muscle, can be appreciated from underneath the pelvic floor during the perineal phase of the abdominoperineal resection. It is also an important landmark during wide transection of the levators. In fact, in individuals with well-developed pelvic musculature, the bulky internal obturator muscle may be one of the structures narrowing the pelvic space, thereby adding difficulty during pelvic dissection (Fig. 1.17).

Levator Ani Muscles

The levator ani muscle complex is a widely spanning sheet-like muscular structure covering the majority of the pelvic outlet. It is approximately 2–4 mm thick. The four structural subunits of the levator ani muscle are identified and named after their origin and final insertion. These include the puborectalis, pubococcygeus, iliococcygeus, and coccygeus (Fig. 1.15).

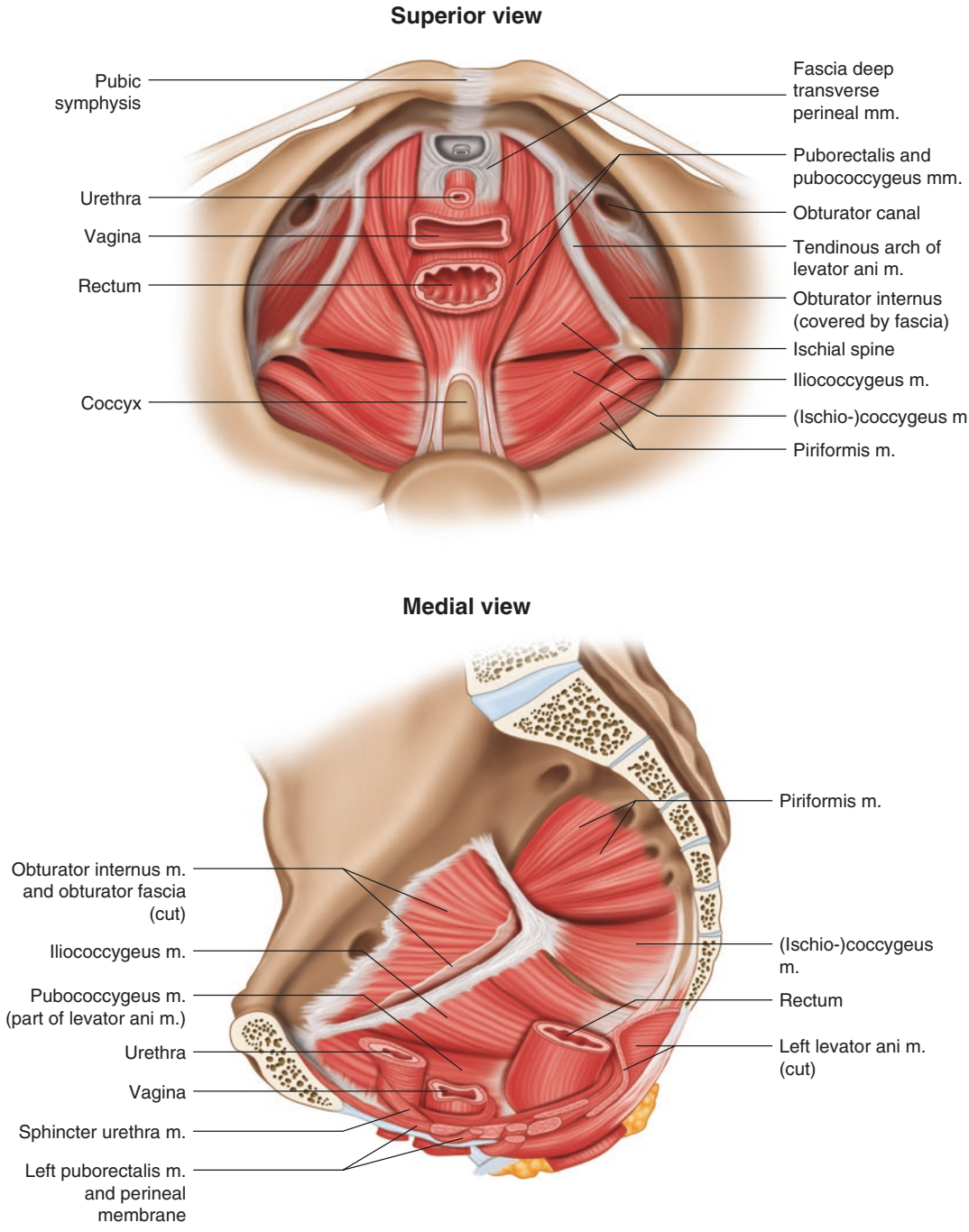

Fig. 1.15 Muscles of the pelvic floor

Puborectalis Muscle

The puborectalis muscle has a band-like structure that forms the middle portion of the levator ani. It originates from the posterior pubis and slings around the anorectal junction. This muscle is responsible for creating the anorectal angle, exerting a compression effect on the anorectal junction and contributing to fecal continence. Controversy exists over the association of the puborectalis

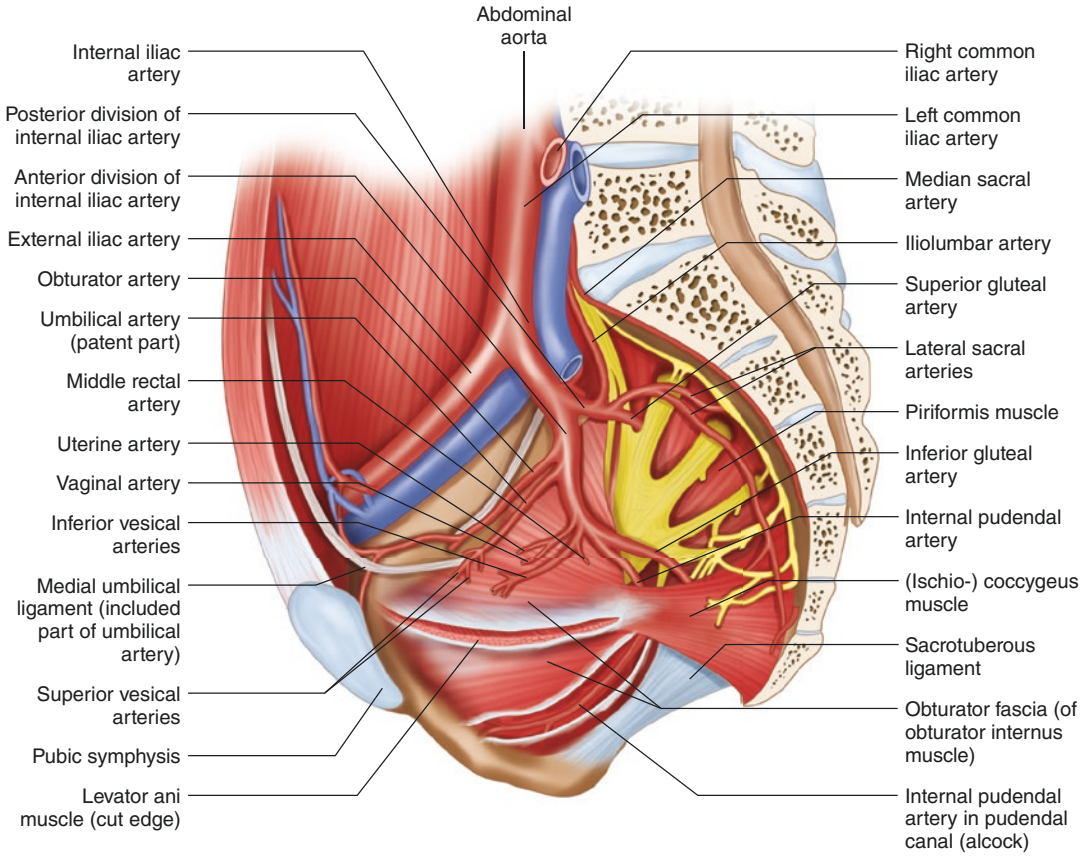

Fig. 1.16 Relation of pelvic arteries to pelvic floor muscles and the sacral plexus

muscle with either the levator ani complex or the external sphincter complex [25–28]. As a result, from the clinical perspective, it is acceptable to consider the puborectalis muscle as an anatomical and functional link between the levator and sphincter muscle complexes.

Pubococcygeus Muscle

The pubococcygeus originates from the anterior half of the internal obturator fascia along the tendinous arch. It then runs dorsally, medially, and downward toward the lower sacrum. In the midline, the fibers intertwine with the fibers from the opposite site to create anterior part of the anococcygeal raphe. More anterior, some of the fibers do not come together, and it is here, joining the puborectalis muscle, that they create an open space in the anterior pelvic floor, called the levator hiatus. The posterior aspect of the levator hiatus accommodates the anorectal junction (rectal hiatus), and the anterior aspect is reserved for the urogenital structures (urogenital hiatus). A thickening of the endopelvic fascia creates the urogenital membrane (hiatal ligament), thereby fixing the urogenital structures to the levator muscle complex. During standard dissection, the rectal surgeon will see only a small medial portion of the pubococcygeus muscle since most of it is covered by the anterior pelvic structures.

Iliococcygeus Muscle

The iliococcygeus muscle is the largest part of the levator ani muscle that is visible during the rectal dissection. It is a paired, symmetrical muscle and has a sheet-like structure that undergoes

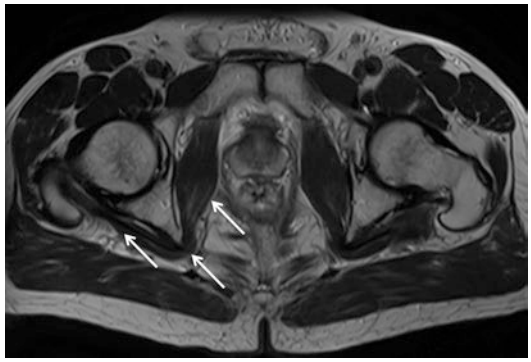

Fig. 1.17 Internal obturator muscle (*arrows*), MRI, T2 sequence in a muscular male, contributing to narrowing of the mesorectal compartment

significant deformation into dome-like surfaces. The anterior portion of the muscle originates from the posterior part of the internal obturator fascia. The posterior origin of the iliococcygeus muscle is located at the ischial spine. Bilateral iliococcygeus muscles are joined in the midline groove of the anococcygeal raphe, which extends posteriorly to the coccyx and lower sacrum (Figs. 1.7). In most individuals, the lateral origins of the muscles are covered by the contents of the lateral pelvic compartments. Additionally, the more muscular the individual is, the steeper the domes of the iliococcygeus muscles are. The dome effect is also indirectly related to obesity because the increased amount of adipose tissue within the ischioanal fossa exerts a mass effect from underneath the muscle, which contributes to significant bulging of the posterior levator ani muscles (Figs. 1.7 and 1.18).

Coccygeus Muscle

The coccygeus muscle, also known as the ischiococcygeus, is a short, sheet-like structure covering the sacrospinous ligament (Figs. 1.7 and 1.15). It is located just below the inferior border of the piriformis muscle and is considered to be rudimentary in humans [29]. The coccygeus muscle creates the most posterior part of the levator ani muscle, and some of the fibers of this muscle are able to reach the lower sacrum, upper coccyx, and the anococcygeal raphe. Additionally, these fibers crisscross with the fibers of the vestigial sacrococcygeal muscle. This crisscross can create a tiered posterior attachment of the levator ani muscle to the sacrum, which should be taken into account during abdominoperineal resection when the posterior levators are being transected.

Other Muscles of Pelvic Floor

Rectococcygeus Muscle

The rectococcygeus muscle is a small, paired muscle located at the posterior aspect of the levator hiatus. It is associated with the most anterior portion of the anococcygeal raphe and frequently has a V-like shape, "hugging" the posterior aspect of the very distal rectal tube (Fig. 1.19). It is located just above the posterior sling of the puborectalis muscle where it "guards" the entrance to the posterior intersphincteric space. In colloquial surgical language, it is frequently referred to as the "last band" to cut during open posterior mesorectal excision.

Piriformis Muscle

The piriformis muscle is a paired muscle originating from the lateral aspect of the sacral bone between the S2 and S4 segments (Fig 1.15). Contrary to other pelvic floor muscles, it originates medially and runs laterally (and inferiorly) where it exits the pelvis through the greater sciatic foramen, finally attaching to the greater trochanter. From the standpoint of the pelvic floor, the important function of this muscle is its coverage of the symmetrical posterolateral space (greater sciatic foramen) that is not covered by the levator ani complex. For this reason, it should also be considered as the muscle of the pelvic floor (Figs. 1.15 and 1.20). A bulky piriformis muscle may contribute to narrowing of the mesorectal compartment. The medial origin of the muscle is directly related to the sacral foramina and the sacral nerve roots. The sacral nerve plexus rests on the anterior surface of the piriformis muscle

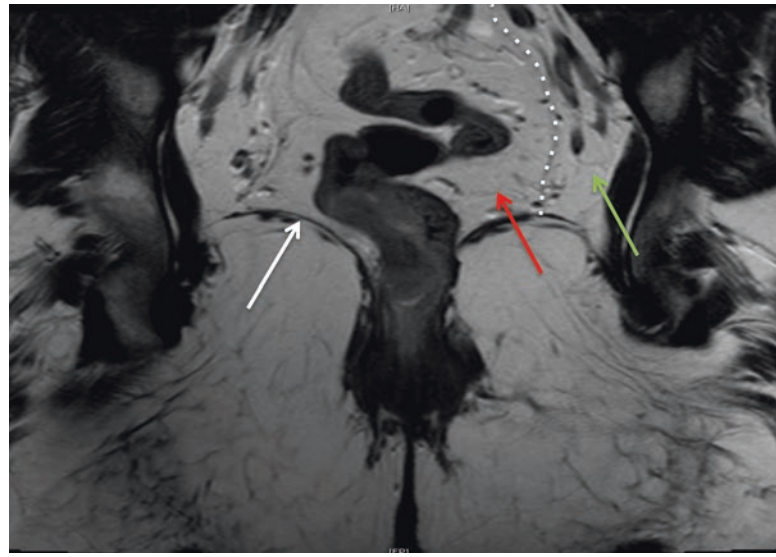

Fig. 1.18 Bulging of posterior levator ani muscles (domes of iliococcygeus muscles marked with *white arrow*), mesorectal compartment (*red arrow*), lateral compartment (*green arrow*), parietal fascia (*dotted line*) MRI, T2 sequence, coronal view

(Fig. 1.16). The piriformis fascia covers the surface of the muscle and is in direct contact with the endopelvic (presacral) fascia.

Deep Transverse Perineal Muscle

The deep transverse perineal muscle is a sheet-like structure between the inferior pubic rami. It is located anterior to the sphincter muscle complex and directly underneath the hiatal ligament, covering the urogenital hiatus of the levator ani. It also contains an anterior opening surrounded by the circular urethral sphincter as well as the vaginal opening in women (Fig. 1.21).

Superficial Transverse Perineal Muscle

The superficial transverse perineal muscle is a narrow band-like, paired muscular structure that is spread between the ischial tuberosity across the center of the perineum (Fig. 1.21). Both muscles join in the center, in front of the sphincter muscle complex, and contribute to the creation of the perineal body. The muscles are in direct contact with the deep transverse perineal muscle located directly above them.

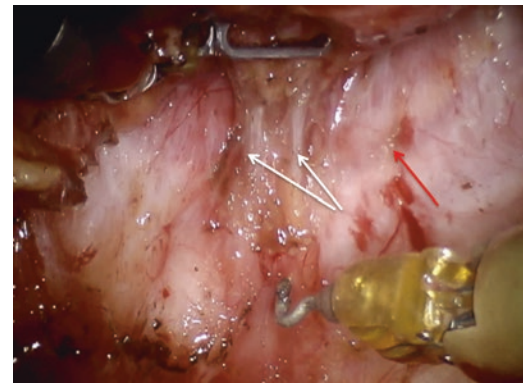

Fig. 1.19 Rectococcygeus muscle (*white arrow*), right iliococcygeus muscle (*red arrow*)

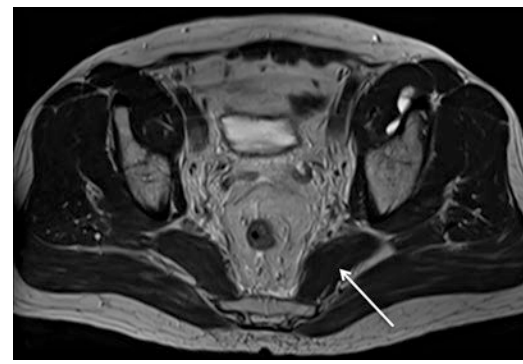

Fig. 1.20 Piriformis muscle, MRI, T2 sequence

Other Structures Associated with Pelvic Floor

Sacrospinous and Sacrotuberous Ligaments

The sacrospinous ligament (SSL) is a triangular-shaped ligament attached to the lower sacrum and the ischial spine (Fig. 1.22). At its base on the sacral bone, the sacrospinous ligament is closely related to the sacrotuberous ligament, which spans from the lower sacrum to the ischial tuberosity. Both of these ligaments should be divided during sacral amputations. The pudendal nerve and the internal pudendal vessels pass behind the SSL, wrapping around it medially and inferiorly to enter Alcock's canal.

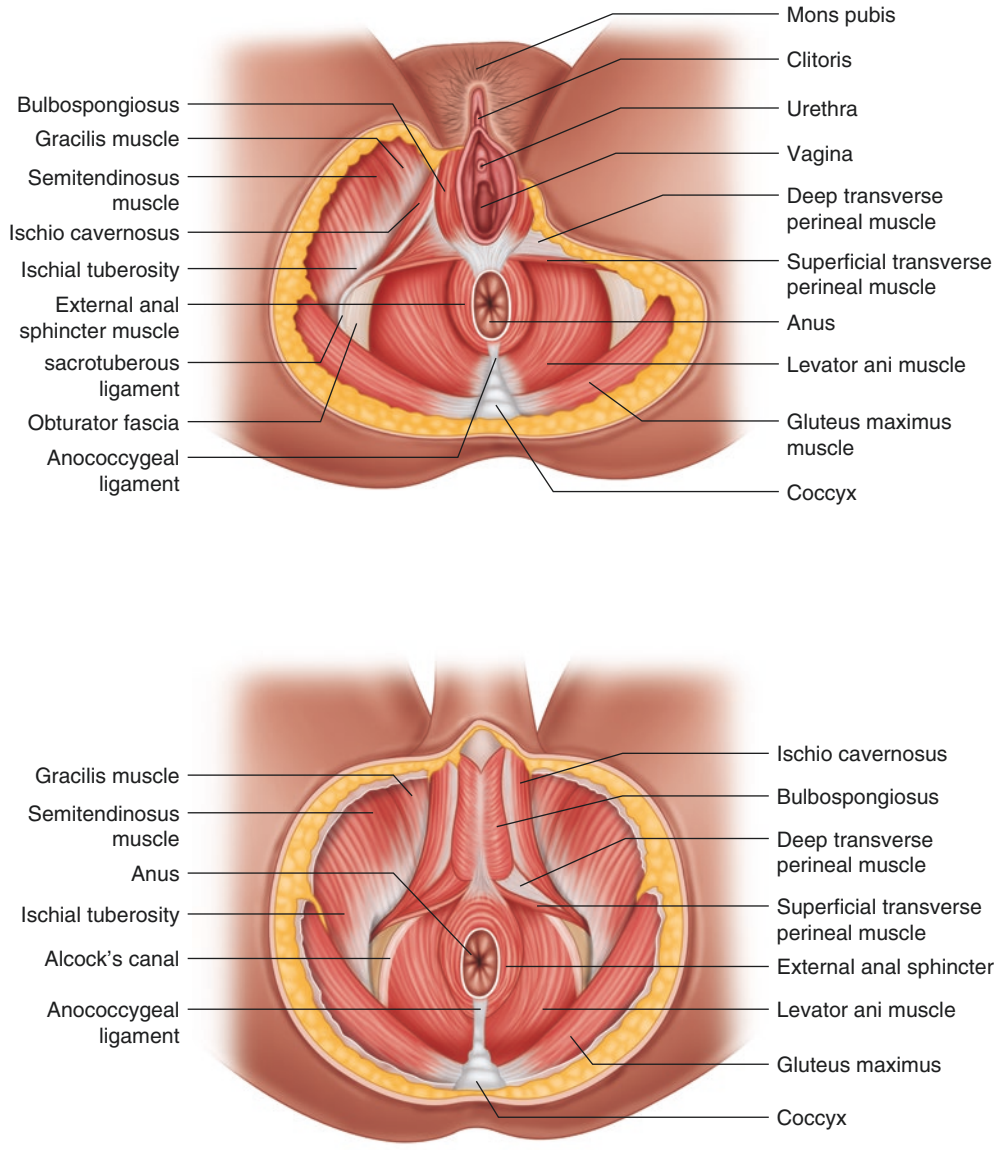

Fig. 1.21 Muscles of perineum

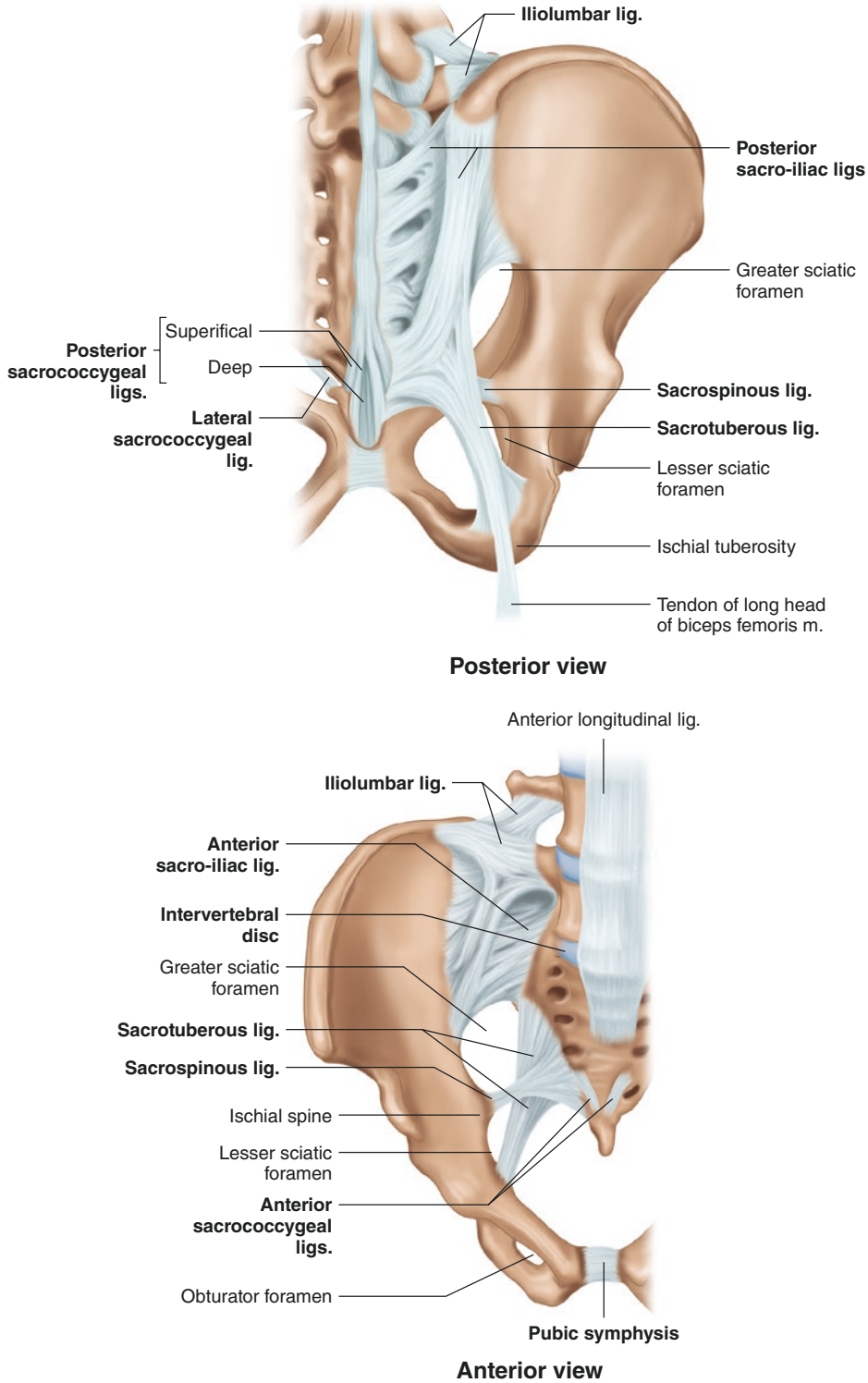

Fig. 1.22 Sacrospinous and sacrotuberous ligaments

Alcock's Canal

Alcock's canal, also known as the pudendal canal, is a tunnel-like fascial structure containing the internal pudendal vessels and the pudendal nerve. It originates at the inferior sciatic foramen just below the ischial spine and the sacrospinous ligament. Alcock's canal runs anteriorly along the inferior border of the internal obturator muscle and the inferior ileo-pubic ramus and then pierces the urogenital membrane to supply the genitals (Fig. 1.21).

Arterial Blood Supply

The inferior mesenteric artery provides the blood supply to the left colon and the rectum (Fig. 1.23). The rectum and the anus are also supplied by the internal iliac system or hypogastric vessels (Fig. 1.24). The rectum, in contrast to the colon, is almost never subject to significant ischemia, unless due to iatrogenic reasons. Because the left colon is often used as a substitute of the resected rectum, knowledge of the left colon vascular anatomy is critical to maintain sufficient blood supply in the segment used for reconstruction.

Inferior Mesenteric Artery

The inferior mesenteric artery (IMA) originates from the abdominal aorta [30]. In most cases, the IMA is located 3–4 cm below the third portion of the duodenum (Fig. 1.25). In obese patients, the IMA is surrounded by the adipose tissue of the mesocolon. Occasionally, some adhesions are encountered between the mesentery of the small bowel and the mesocolon, thus obscuring access to the vessel root. The fibers of the (pre)aortic nerve plexus condensate below the inferior mesenteric artery and can adhere to it (Fig. 1.27). The main trunk of the IMA gives the left colic artery, while the main vessel continues along the left side of the aorta toward the promontory. The left colic artery gives away its first ascending branch that runs cephalad in the direction of the splenic flexure in close proximity to the inferior mesen-

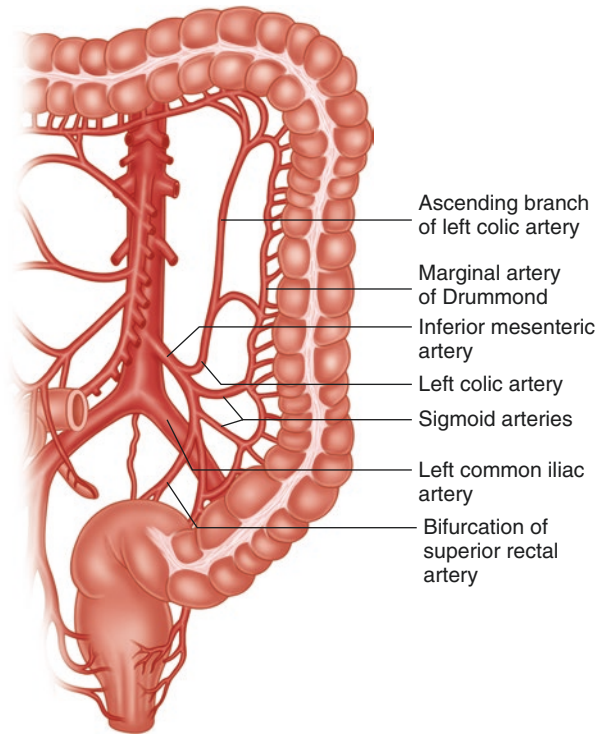

Fig. 1.23 Arterial blood supply to the left colon

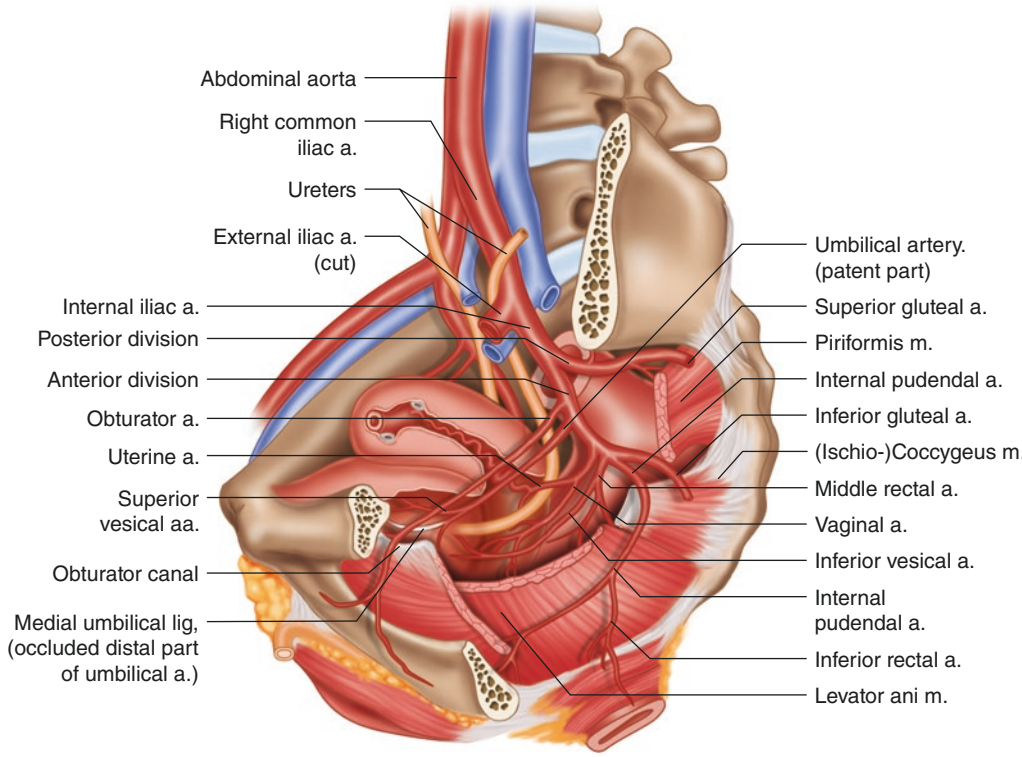

Fig. 1.24 Arterial blood supply to the pelvis

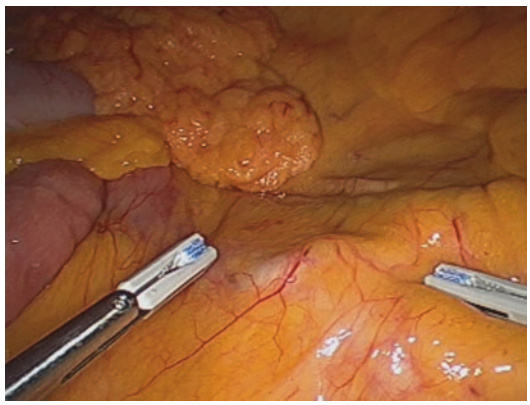

Fig. 1.25 Origin of the inferior mesenteric artery several centimeters below the third portion of duodenum

teric vein, usually within 1 or 2 cm although this anatomy is quite variable. The rest of the left colic artery continues to supply the left colon and also communicates with the sigmoid branches.

Marginal Artery

The marginal artery of Drummond is a conduit system of collateral arterial networks along the mesenteric border of the entire colon. This system connects the superior and inferior mesenteric arteries, which is of particular importance during rectal and sigmoid resections when the inferior mesenteric artery is divided. The marginal artery of Drummond provides the main blood supply to the segment of the left colon used for reconstruction (Fig. 1.23).

Superior Rectal Artery

The superior rectal artery (SRA) is a continuation of the IMA. The SRA runs in the base of the rectosigmoid mesentery and comes closer to the bowel due to the shortening of the mesocolon at

the rectosigmoid junction. Here, it gives away the rectosigmoid branch followed by the upper rectal branches which split into the left and right terminal branches running downward in the posterolateral aspects of the mesorectum. In the lower half of the mesorectum, they communicate with the branches from the middle rectal vessels and via the intramural network with the inferior rectal arteries [31].

Middle Rectal Arteries

The middle rectal artery (MRA) is a branch of the internal iliac artery. The MRA participates in the intensive collateral network with the SRA and the inferior rectal arteries.

Inferior Rectal Arteries

The inferior rectal artery (IRA) is the main vessel supplying the blood flow to the anal canal and the sphincter muscle complex. It is a branch of the internal pudendal artery arising in the proximal (posterior) portion of Alcock's canal. After leaving Alcock's canal, the IRA traverses the fat of the ischioanal fossa from the posterolateral direction. It subsequently splits into the smaller branches supplying the sphincter muscle complex. There is no extramural communication between the IRA and MRA. Rather, a very efficient intramural collateral network exists between these two vessels.

Internal Iliac Arteries

The internal iliac artery (IIA), traditionally known as the hypogastric artery, is the main artery supplying the pelvis. The IIA supplies the walls and viscera of the pelvis, the buttocks, and the genitourinary organs, as well as the medial compartment of the thigh. The IIA originates next to the promontorium and descends toward the greater sciatic foramen. The posterior trunk is short and gives off the iliolumbar artery, the lateral sacral artery, and the superior gluteal artery. During dissection in this lateral compartment, a "trifurcation" of vessels may be encountered and can lead to bleeding if not adequately identified and controlled. The anterior trunk runs through the lateral pelvic compartment and gives off the obturator artery, umbilical and superior vesical vessels, uterine artery (in women), inferior vesical artery, middle rectal artery, inferior gluteal artery, and the terminal branch, the internal pudendal artery. A loose fascial plane can be found spread between the IIA and its branches extending toward the bladder (Fig. 1.24).

Internal Pudendal Arteries

The internal pudendal artery (IPA) is the terminal branch of the anterior trunk of the internal iliac artery. It originates at the level of the inferior border of the piriformis muscle and crosses the pelvic floor to enter the pudendal canal (Alcock's canal) after wrapping behind the sacrospinous ligament. In the posterior (proximal) aspect of the pudendal canal, it gives away the inferior rectal artery (IRA) and continues anteriorly to supply the genitals (Figs. 1.21 and 1.24).

Middle Sacral Artery

The middle sacral artery originates in the posterior aspect of the aortic bifurcation, and it descends in the midline on the surface of the sacrum.

Venous Drainage

The veins of the left colon and the anorectum generally follow the corresponding arteries. The main exception involves the cephalad part of the inferior mesenteric vessels. The venous drainage of the left colon is directed into the liver via the inferior mesenteric vein (IMV) to the portal system. The rectum is drained through both the portal and the caval systems.

Rectal Veins (Superior, Middle, Inferior)

The superior rectal vein drains the rectum and upper anal canal and is one of the main tributaries of the IMV. The middle rectal veins drain the lower rectum and the upper anal canal and return the blood to the internal iliac veins. The inferior rectal veins drain the lower anal canal via the internal pudendal veins into the internal iliac veins.

Inferior Mesenteric Vein

The IMV is created by the confluence of the superior rectal vein and the left colic vein. Initially, it runs in the base of the left mesocolon lateral from the inferior mesenteric artery. After crossing the left colic artery, it then runs cephalad as the most medial vascular structure accompanied by the ascending branch of the left colic artery. Of note, there is no corresponding artery to this segment of the IMV. At approximately 2–3 cm below the pancreatic border, it receives its last branch from the splenic flexure (Fig. 1.26). It then passes laterally from the ligament of Treitz and behind the body of the pancreas to enter the splenic vein. In order to obtain full mobilization of the left colon for reconstruction following rectal resection, the IMV should be ligated below the inferior pancreatic border and cephalad to its splenic flexure branch.

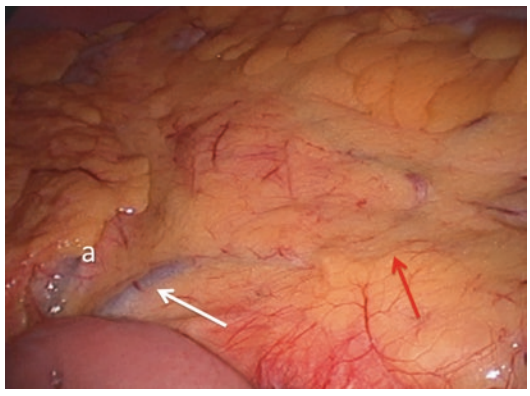

Fig. 1.26 Base of the inferior mesenteric vein (*white arrow*), right below the pancreas (*a*); the splenic flexure tributary is marked with the *red arrow*

The IMV can almost always be seen at the base of the descending mesocolon, even in obese individuals. This is in contrast to the IMA, which is frequently obscured at its origin by the adipose tissue. It is not uncommon, however, for adhesions between the small bowel mesentery, the transverse, and the left mesocolon to obscure access.

Internal Iliac Veins

The internal iliac vein with its tributaries is a paired vessel, accompanying its namesake artery. It joins the external iliac vein to form the common iliac vein just above the sacroiliac joint.

Presacral Venous Plexus

The middle (median) sacral vein, two lateral sacral veins, and the intercommunicating veins comprise the presacral venous plexus. It is an avalvular system communicating with the internal vertebral venous system of the sacrum through the basivertebral vessels emerging from the sacral foramina [32]. These veins are easily avulsed during improper dissection. The hydrostatic pressure of the basivertebral vein system can achieve 20 cm H_2O [32] and can cause life-threatening, difficult to control hemorrhage. The lateral sacral veins run in close relation to the sacral foramina, on the surface of the sacral nerve roots and the sacral origin of the piriformis muscle.

Lymphatic Drainage

The mesorectum is the most important site of the lymph node metastasis from rectal cancer. Although rare, it is possible to develop distant metastasis without locoregional metastasis within the mesorectum or the lateral pelvic compartment. The lymphatic drainage of the anorectum follows the corresponding arteries, with the exception of the vessels of the lower anal canal.

Thus, the upper two thirds of the rectum drains into the local lymph nodes along the superior rectal vessels, and from there, it is transported to the lymph nodes along the inferior mesenteric artery and subsequently to the para-aortic lymph nodes. Lymph drainage from the lower third of the rectum and proximal anal canal travels cephalad along the superior rectal vessels and laterally to the internal iliac and obturator lymph nodes. From the proximal anal canal, drainage follows the same pattern as for the lower third of the rectum, whereas below the dentate line, the drainage may lead to the deep and superficial inguinal lymph nodes.

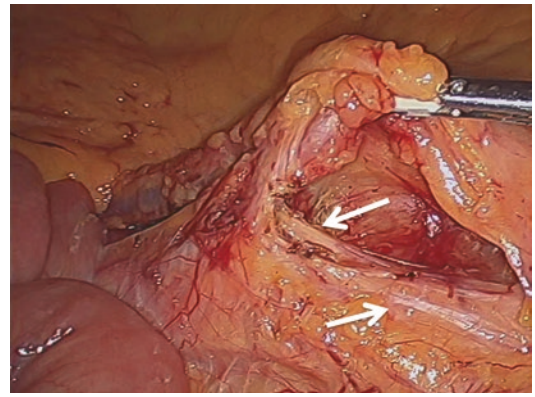

Fig. 1.27 Inferior mesenteric plexus (left and right side components)

Innervation

The colon, rectum, anus, and urogenital organs are innervated by sympathetic and parasympathetic fibers of the autonomic nervous system. The pelvic floor and the external sphincter are comprised of skeletal muscle and innervated by motor neurons, while the anus is also supplied by sensory nerve fibers.

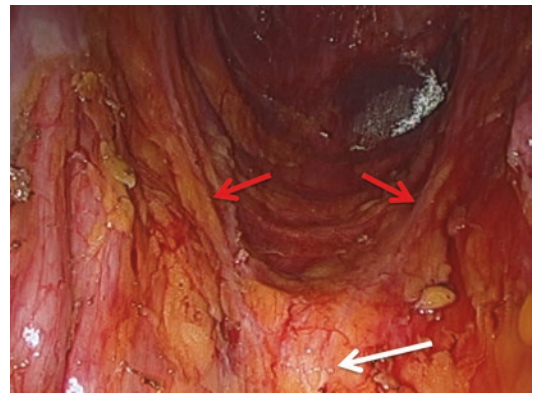

Fig. 1.28 Superior hypogastric plexus (*white arrow*) and hypogastric nerves (*red arrows*)

Inferior Mesenteric and Superior Hypogastric Plexus

The inferior mesenteric plexus and the superior hypogastric plexus (SHP) are the continuation of the preaortic sympathetic plexus, located on the anterior surface of the aorta with fibers originating from the spinal cord segments L1–L3. The inferior mesenteric plexus is situated around the origin of the inferior mesenteric artery (Fig. 1.27). The SHP is located between the aortic bifurcation and the sacral promontory. During surgical dissection, it is important to appreciate the continuous network of nerve fibers that form a distinct nerve layer on the anterior aortic surface and in front of the promontory. Along the left side of the aorta, this nerve layer runs close to the fascial reflection, separating the left mesocolon from the retroperitoneum. This proximity makes it vulnerable to injury while incising and entering this fascial reflection.

Hypogastric Nerves

The fibers of the SHP condensate at the sacral promontory to form two hypogastric nerves (Fig. 1.28). These structures run distally toward the deep posterior pelvis joining with the inferior hypogastric (pelvic) plexus and should be identified to avoid injury during rectal dissection. At the base of the rectosigmoid mesocolon, the hypogastric nerves are located underneath the peritoneum. The hypogastric nerves are created by sympathetic fibers, although they contain a few ascending parasympathetic fibers (from the sacral plexus). At the level of the mid-rectum, each hypogastric nerve joins the parasympathetic nerve fibers from the sacral plexus to form the inferior hypogastric (pelvic) plexus (Figs. 1.29).

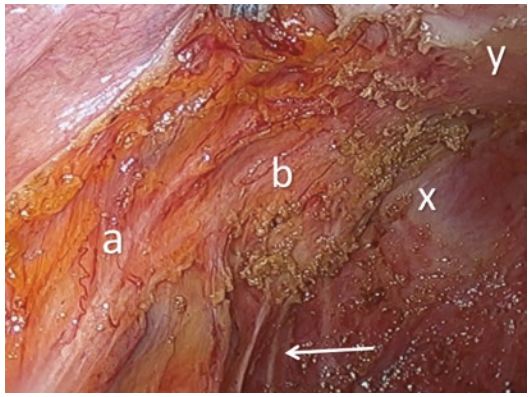

Fig. 1.29 Pelvic plexus (*b*) exposed after total mesorectal excision with the left hypogastric nerve (*a*) and sacral splanchnic nerves (*arrow*); dome of the left iliococcygeus muscle (*x*) and Denonvilliers' fascia (*y*)

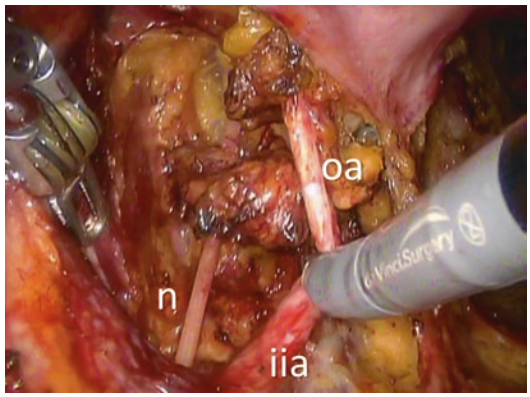

Fig. 1.30 Lateral pelvic compartment on the left side; obturator nerve (*n*), obturator artery (*oa*) and internal iliac artery (*iia*) [courtesy of Prof. G.S. Choi]

Inferior Hypogastric (Pelvic) Plexus

The pelvic plexus (PP) is the major autonomic coordinating center within the pelvis. Together with the SHP, it is frequently referred to as the "pelvic brain". The pelvic plexus is embedded within the parietal pelvic fascia just above the origin of the levators and associated with the LTS (Figs. 1.12, 1.13 and 1.29). The PP is formed by sympathetic and parasympathetic nerve fibers that supply the rectum and all other pelvic organs. The sympathetic component is delivered by the hypogastric nerve as well as the presacral sympathetic ganglia via the splanchnic sacral nerves running caudal and parallel to the hypogastric nerve (Fig. 1.16). The parasympathetic component is delivered by *nervi erigentes* that originate from the sacral plexus (S2–S4) and run in the posterior aspect of the lateral compartment [33]. The efferent nerves continue on within the neurovascular bundles along the posterolateral aspect of the prostate gland (or vagina), where they are particularly susceptible to injury during the anterior dissection of the distal rectum [34].

Lumbosacral Plexus

The lumbosacral plexus is a major neural structure that provides motor-sensory innervation to the lower leg, posterior thigh, and part of the pelvis through its contributions to the sciatic nerve. It is located on the anterior surface of the piriformis muscle in the posterolateral aspect of the upper pelvis [35]. Locally advanced tumors with posterolateral extension or those with neural invasion may require en bloc resection of the sacral nerve roots. Unilateral resection of S2 and below will produce minimal functional deficits.

Obturator Nerve

The obturator nerve that originates from the lumbar plexus enters the pelvis underneath the common iliac artery and just lateral from the internal iliac artery and ureter. It is easily identified in the lateral pelvic compartment running toward the obturator foramen and is a key anatomical landmark during lateral pelvic lymph node dissection (Fig. 1.30). This nerve carries the sensory fibers from the inner thigh and the motor fibers to the adductor muscles. It does not, however, innervate the internal obturator muscle.

Pudendal Nerve

The pudendal nerve is the main nerve of the perineum, ultimately involved in sensation, pelvic floor muscle innervation, and continence. It

originates from the fibers of the sacral plexus and leaves the pelvis between the piriformis and the coccygeus muscles, wrapping around the sacrospinous ligament to enter Alcock's canal where it accompanies the internal pudendal vessels (Figs. 1.16, 1.21). It ultimately supplies the sphincter and the inferior surface of the pelvic floor muscles. The pudendal nerve carries sensation from the anus and external genitalia and innervates the external anal and urethral sphincters.

Genitourinary Considerations

Identification and knowledge of the course of the ureter is paramount during surgery for rectal cancer. The ureter crosses the pelvic brim near the bifurcation of the common iliac artery and runs underneath the peritoneum and within the PF, anterior to the internal iliac vessels. Deeper in the pelvis, it runs above the hypogastric nerves and the pelvic plexus to enter the bladder. In men, it runs in front of Denonvilliers' fascia anteromedially, wrapping in front of the vas deferens before entering the bladder. In women, it continues its course toward the bladder through the cardinal ligament, crossing underneath the uterine artery. The mid ureter should be easily visualized during routine colonic mobilization and should remain lateral to the plane of dissection during rectal mobilization, unless extension by tumor necessitates en bloc ureteral resection.

The seminal vesicles spread in an arcuate fashion, conforming to the shape of Denonvilliers' fascia. Anterior dissection initiated approximately 1–2 cm above the peritoneal reflection allows for identification of the upper border of the Denonvilliers' fascia. From there, the plane of dissection can be carried in front of or posterior to the fascia depending on the location of the tumor. Bleeding during the anterior dissection results from dissection too close to the seminal vesicles and the associated parasympathetic nerve fibers. Exuberant cauterization in this area can therefore lead to erectile dysfunction. However, anterior tumors can become adherent or involve the seminal vesicles, periprostatic neurovascular bundle, or the prostate gland itself requiring en bloc resection.

Similarly, in women, locally advanced tumors may involve the uterus or vagina which should also be resected with the principle of complete, en bloc resection. There exists abundant blood supply to the vagina and an associated venous plexus. Dissection too close to the vagina can result in unexpected bleeding.

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Endorectal Ultrasound

2

Victoria Valinluck Lao and Alessandro Fichera

Abbreviations

CRT Chemoradiation therapy
ERUS Endorectal ultrasound

Introduction

Endosonography was first introduced in the 1950s and has since become a valuable tool for evaluation of both benign and malignant diseases of the anorectum. This chapter focuses on the use of endorectal ultrasound (ERUS) in rectal cancer. Rectal cancer is a significant health concern in the United States. There is approximately 40,000 new cases diagnosed per year in the United States, and it is a major cause of cancer-related deaths [1, 2]. Currently, ERUS is easily accessible and safe and is one of the first-line diagnostic modalities in the initial assessment of rectal cancer.

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History and Development of Endorectal Ultrasound

Prior to the development of endoluminal ultrasound by Wild and Reid in 1952 [3] and subsequent introduction of the technology into clinical practice in 1983 by Dragsted and Gammelgaard [4], evaluation of the rectum and anal canal was conducted using digital exam, anoscopy, and rigid or flexible sigmoidoscopy. The use of ERUS in clinical practice has made examination of the anorectum less subjective and has provided a means to evaluate the layers of the rectal wall as well as perirectal anatomy. Because of the ability of ERUS to distinguish layers of the rectal wall, it is particularly valuable in local staging of rectal tumors.

Physics of Ultrasonography

The clinical relevance of ultrasonography is based upon using the reflection of high-pitch sound waves off of tissues with different impedance to create an image that is interpreted by the practitioner. Sound waves are emitted from piezoelectric crystals within the transducer; they then travel through the tissues of interest and are reflected back to the transducer, which then creates an image [5]. The production of an echo image relies upon the relative acoustic impedance, or resistance to propagation of sound waves, of the materials that the sound waves

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travel through. A reflection, or echo, is produced at the boundary between two materials that have different impedance properties.

The sound wave frequency, or number of cycles of a sound wave per second, used in clinical practice ranges between 6 and 16 mHz and can affect resolution. Another important factor is the wavelength, or distance traveled by a sound wave in one wave cycle, used. Shorter wavelengths will be of higher frequency and, therefore, produce images with higher resolution. However, there is less tissue penetration with shorter wavelengths. Longer wavelengths on the other hand will have lower frequency and penetrate deeper into tissues. Longer wavelengths, however, will produce images with lower resolution. This implies that longer, low frequency wavelengths should be use for deeper structures, whereas shorter high frequencies should be used for more superficial structures. This also implies that for a higher resolution, shorter wavelengths with higher frequency should be used, but at the trade-off of decreased penetration. Gain can also be used as an adjunct to amplify the received sound wave in order to get a brighter, whiter image [5]. Understanding these factors and how to interpret ultrasound images, a practitioner can gain very useful clinical information from ERUS.

Current Uses for Endorectal Ultrasound

Currently endoluminal ultrasound is useful for evaluation of both malignant and benign anorectal lesions and has been expanded to include imaging of the anal sphincter, such as in the evaluation of fecal incontinence. It is currently accepted as a valuable method for initial evaluation of rectal tumors and is thought to be fast, well-tolerated, safe, and accurate for local staging [6].

ERUS has an important role in the evaluation of rectal cancer from the perspective of staging and preoperative treatment and planning. Accuracy of preoperative staging has become very important in the management of rectal cancers given the personalized approach to therapy in rectal cancer as well as the option of local excision in early rectal cancers. In essence, accurate preoperative staging allows for optimal treatment of the patient with regard to combined modality therapy and determining the appropriate extent of the operation. The first report of rectal cancer staging with ERUS was in 1985. This was dubbed uTNM staging by Hildebrant and Feifel [7].

Although current options for preoperative local staging currently include ERUS, CT, MRI, and PET CT, ERUS is a valuable method given its accuracy, lack of radiation exposure, and cost-effectiveness.

Endorectal Ultrasound Technical Basics

The Equipment

A handheld endorectal probe with an enclosed, rotating transducer is used to capture 360° of images. Generally, a multifrequency transducer is preferred due to its ability to provide specific images based on the pathology in question. Higher frequency provides better clarity of image; however, it is thought that the assessment of lymph nodes and perirectal tissues are better conducted with lower frequencies [8].

Imaging of the rectum requires a latex balloon covering the transducer for acoustic contact. The balloon is filled with water as this allows maintenance of contact between the rectal wall and the balloon without interposition of air between the probe and the rectal wall. As air is a non-conductive medium, the presence of air between the transducer and the rectal wall distorts the image. Note that endoanal imaging can also be conducted with the same basic equipment; however, the balloon is removed.

Patient Preparation and Positioning

Just prior to the procedure, the patient is administered enemas to clear the rectum of stool or mucus, which can interfere with the imaging obtained from the EUS in the form of artifact. There is no need for sedation for most patients, as most patients will tolerate the procedure with adequate verbal cues. The exception would be very large,

low, and necrotic tumors. Stenosis caused by the lesion prevents insertion of the probe and can cause discomfort. The patient is positioned the Sims position, left lateral decubitus for the procedure. To better interrogate the lesion, the position of the patient may be altered during the examination to place the target lesion in the dependent position in order to displace any air in the rectum away from the target lesion.

The Procedure

Prior to the ERUS, a digital rectal examination is conducted to assess the lesion. Furthermore, a flexible proctoscopy is performed to evaluate the tumor size, location, and distance from the anal verge. This also allows clearing of any residual debris in the rectum that did not evacuate with the enemas, prior to proceeding with the ERUS.

There are two basic methods of inserting the ultrasound probe into the rectum, through a proctoscope or blindly. Insertion using a proctoscope allows for examination of the rectum as well as placement of the proctoscope past the proximal portion of the lesion prior to inserting the probe. This ensures a complete examination of the lesion proximally by the transducer including the proximal mesorectum. Blind insertion can be done with experienced operators; however, it does have some limitations as distortion of the proximal extent of the lesion, and the proximal mesorectum can occur.

The operator then examines the images for abnormalities in the rectal wall and perirectal structures. The goal is to evaluate the lesions for depth of invasion of the rectal wall as well as to determine whether there is involvement of perirectal lymph nodes and structures. Both still images and videos of this process can be obtained.

Interpretation of the Images Obtained from ERUS

Five distinct layers can be identified in the images produced by ERUS when interrogating the rectal wall. The layers of the rectal wall can be visualized as alternating hyperechoic (white) and hypoechoic (black) layers. Typically, there are three hyperechoic (white) layers and two hypoechoic (black) layers that can be seen. Two models exist as to the interpretation of the layers seen on imaging with regard to the layers of the rectal wall. The first model was introduced by Hildebrant and Feifel [7], and it assumes that the mucosa, muscularis mucosa, and submucosa cannot be delineated. In this model, the layers from the transducer outward are as follows:

1. Interface between balloon and mucosa (hyperechoic)
2. Mucosa, muscularis mucosa, and submucosa (hypoechoic)
3. Interface between submucosa and muscularis propria (hyperechoic)
4. Muscularis propria (hypoechoic)
5. Interface between muscularis propria and perirectal fat (hyperechoic)

The second, most widely used model is where the mucosa and submucosa can be distinguished, and the five layers seen on the ERUS images correspond to the five anatomic layers of the rectal wall. This model was initially described by Beynon et al. [9] based upon an anatomic study (Fig. 2.1). In the Beynon model, the layers from the transducer outward are as follows:

1. Interface between balloon and mucosa (hyperechoic)
2. Interface between mucosa and muscularis mucosa (hypoechoic)
3. Submucosa (hyperechoic)
4. Muscularis propria (hypoechoic)
5. Interface between muscularis propria and perirectal fat (hyperechoic)

The accuracy of staging using the Beynon model as compared to the Hildebrant and Feifel model has minimally been studied; however, one study suggested that the Beynon model has greater accuracy [10]. At our institution, the Beynon model is favored, and generally, this is the model used by most practitioners today.

In addition to the layers of the rectal wall, ERUS can also be employed to visualize perirectal anatomy. Pelvic floor muscles and the sphinc-

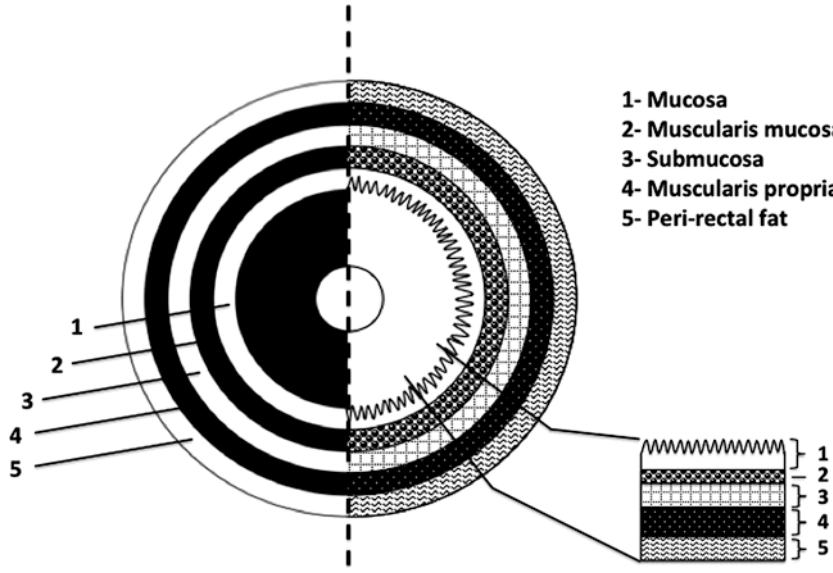

Fig. 2.1 Five-layer model of ERUS image (Beynon). Model image with ERUS layers seen on the left and corresponding layers of the rectal wall seen on the right

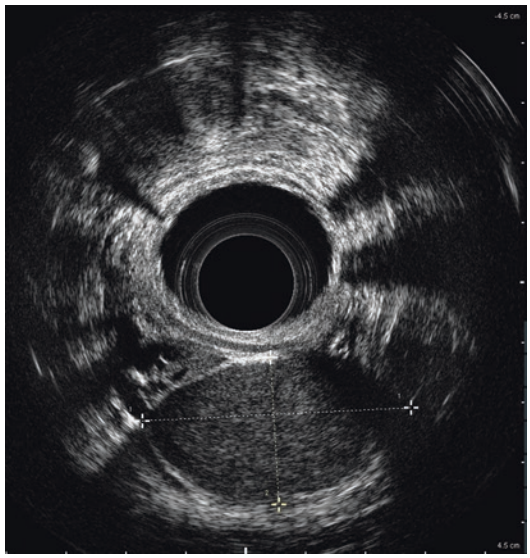

Fig. 2.2 Retrorectal cystic mass

ter complex can be seen on ERUS. Puborectalis can be seen using ERUS in the upper anal canal, whereas the internal anal sphincter (hypoechoic) is seen in the middle portion of the anal canal, and the external anal sphincter (hyperechoic) is seen in the lower anal canal [11]. Other structures that can be appreciated with ERUS in males include the seminal vesicles, the prostate, the bladder, and the urethra. In addition to perirectal fat and lymph nodes, loops of bowel may be appreciated. Retrorectal cystic masses can also be appreciated (Fig. 2.2).

Endorectal Ultrasound for Staging in Rectal Cancer

Endorectal ultrasound can be used to preoperatively stage rectal tumors according to uTNM staging initially introduced in the 1980s [7]. uTNM staging is based upon depth of tumor invasion as well as evidence of nodal metastasis. Currently, the uTNM staging is as follows:

- uT0 Lesion is confined to the mucosa.
- uT1 Lesion confined to the mucosa and submucosa.
- uT2 Lesion penetrates into but not through the muscularis propria.
- uT3 Lesion penetrates bowel wall into the perirectal fat.
- uT4 Lesion penetrates adjacent organs, pelvic sidewall, or sacrum.
- uN0 No evidence of lymph node involvement.
- uN1 Evidence of lymph node involvement.

T-Staging

uT0

Lesions classified as uT0 are considered noninvasive lesions or benign lesions. On ERUS, a uT0 lesion is confined to the mucosa and does not penetrate the submucosa. An irregular expansion of the hypoechoic layer that corresponds to the mucosa and muscularis interface will be seen, representing the tumor. However, the submucosa is completely intact (Fig. 2.3a). uT0 lesions can be treated with local excision therefore, any penetration invasion of the submucosa must be accurately excluded.

uT1

uT1 lesions on ERUS are lesions that have invaded the submucosa but not the muscularis propria. These lesions are considered early invasive rectal cancers. uT1 tumors will show an irregularity of the second hyperechoic layer, but no distinct break in this layer (Fig. 2.3b). This

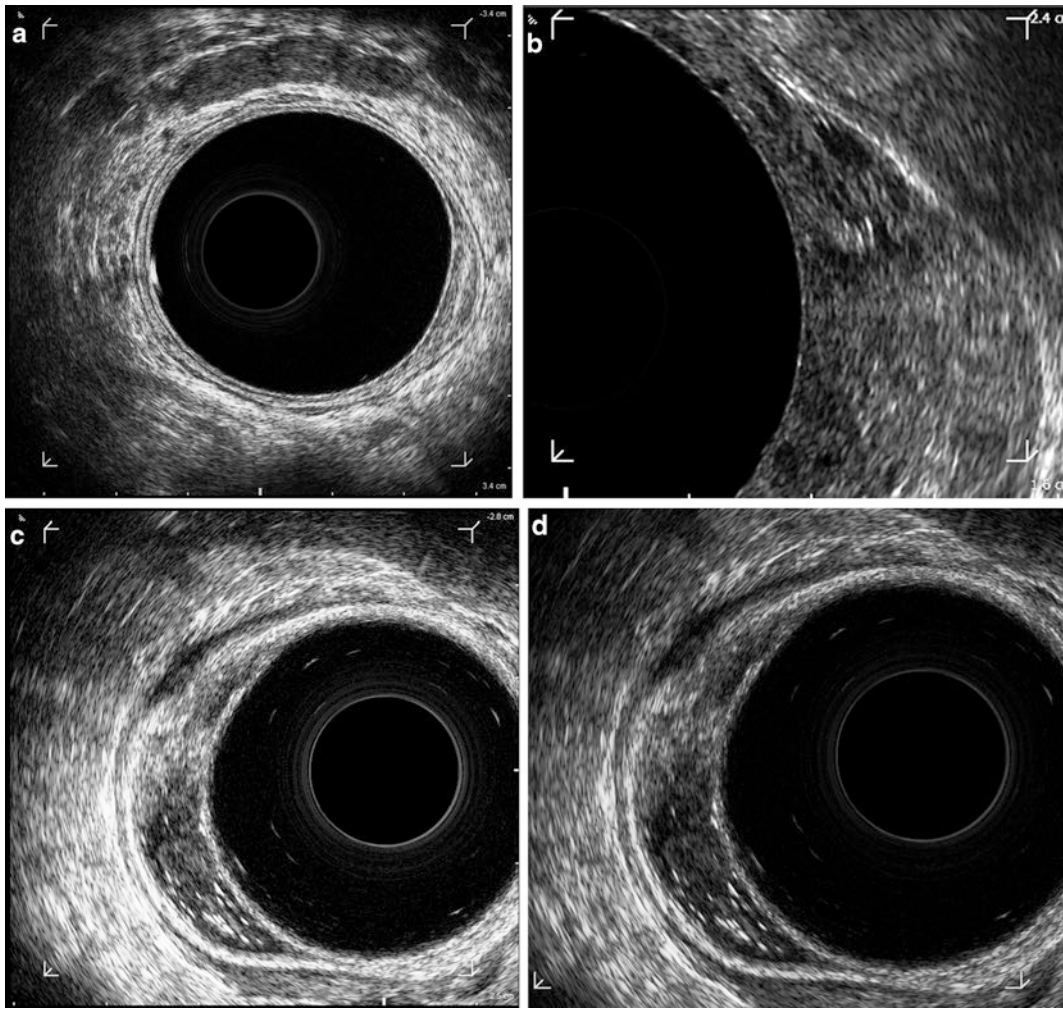

Fig. 2.3 T-stages based upon EUS. (**a**) uT0, noninvasive lesions or benign lesions, adenoma (**b**) uT1 lesion with invasion of the submucosa, but not the muscularis propria (**c**) uT2 lesion with complete disruption of the second hyperechoic layer, corresponding penetration of the tumor through the submucosa with invasion of the muscularis propria. (**d**) uT3 tumor with penetration through the muscularis propria and into the perirectal fat

indicates incomplete disruption of the submucosa, but not penetration of the tumor through the submucosa into the muscularis propria.

uT1 lesions can be treated with local excision with curative intent; therefore, staging these tumors correctly is critical due to the increased risk of local recurrence with preoperative understaging [12–14]. Favorable characteristics for local excision include well or moderate differentiation on histopathology, no evidence of lymphovascular invasion, no perineural invasion, no mucinous components, tumor size <3 cm, tumor involving <1/3 the circumference of the rectal wall, tumor <10 cm from the anal verge, and mobile lesion [15].

uT2

Sonographically, uT2 lesions show a complete disruption of the second hyperechoic layer, corresponding penetration of the tumor through the submucosa with invasion of the muscularis propria (Fig. 2.3c). The key feature of a uT2 tumor is a distinct break of the second hyperechoic layer seen on ERUS.

uT3

Penetration of the tumor into the perirectal fat, through the muscularis propria is indicative of a uT3 tumor. On ERUS, the image will show a disruption of all layers of the rectal wall, with extension of the lesion into the perirectal fat (Fig. 2.3d). Patients with uT3 lesions are not candidates for local excision and will need preoperative chemotherapy and radiation therapy prior to radical surgery.

uT4

uT4 lesions are locally advanced lesions that invade perirectal structures such as the prostate, seminal vesicles, pelvic sidewall, bladder, uterus, cervix, or vagina. Sonographically, there is loss of the plane between the tumor and adjacent organ of interest. Most uT4 lesions are confirmed using MRI. Usually, patients with uT4 tumors will require preoperative chemotherapy and radiation therapy prior to an operation involving en bloc resection of the involved organs when feasible and indicated.

N-Staging

ERUS can also be used to visualize perirectal lymph nodes and provide information about their disease involvement. N-staging is important given the decreased survival and increased local recurrence associated with nodal involvement. ERUS N-staging is classified into uN0 and uN1. uN0 denotes undetectable or benign appearing lymph nodes, indicating no lymph node involvement (Fig. 2.4a). Generally, normal non-enlarged lymph nodes are not detected by ERUS. uN1 indicates involvement of perirectal lymph nodes (Fig. 2.4b).

The involvement of the lymph nodes is usually suspected if the lymph nodes are greater than 5 mm in diameter, rounded, and hypoechoic [16–18]. However, metastatic foci have been reported in nodes that are smaller than 5 mm at a rate of 18% [19, 20]. Although the incidence of metastatic disease increases as the size of the lymph node increases, a definitive size threshold does not exist to distinguish nonmalignant from malignant lymph nodes [21]. Involved lymph nodes are usually seen adjacent to the primary tumor or in the mesorectum near the primary tumor. Note that hypoechoic lesions seen perirectally have also been found to be tumor deposits and very small hypoechoic spots have also been shown to correlate with significant venous or lymphatic invasion on histologic evaluation [22].

Inflamed lymph nodes can be distinguished from malignant lymph nodes as they are generally enlarged but not as large as malignant lymph nodes, and they are often slightly hyperechoic [16]. Both can have irregular borders. When confronted with lymph nodes that are of mixed echogenicity that are larger than 5 mm, these should be considered malignant.

Accuracy of uTNM Preoperative Staging

The overall accuracy of staging of ERUS for rectal cancer varies between studies. A recent meta-analysis shows that the overall accuracy of T-staging ranges from 88 to 95% [23] depending

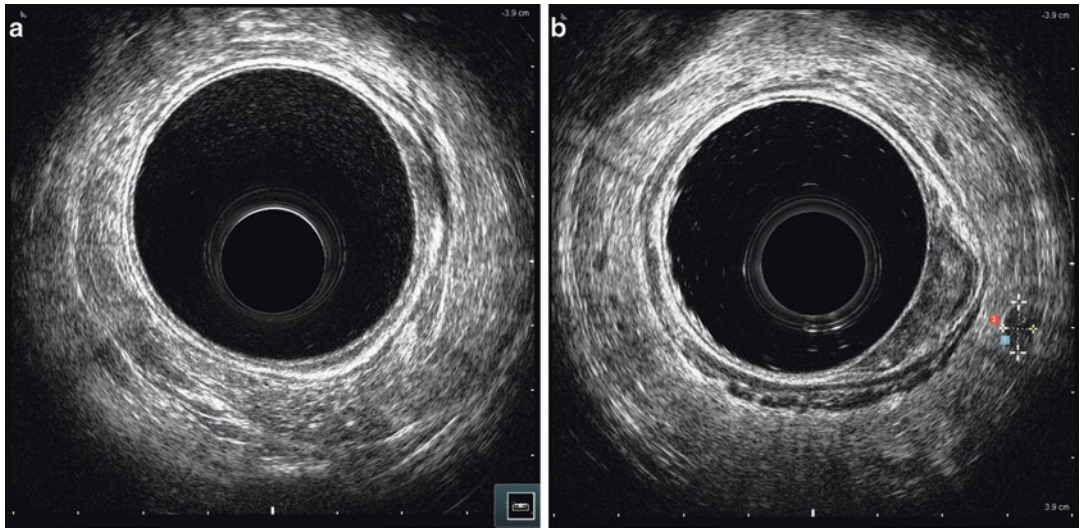

Fig. 2.4 Lymph node assessment with EUS (**a**) uN0, (T2) with no evidence of lymph node metastasis (**b**) uN1, (T2) evidence of lymph node metastasis as indicated by *dotted lines*

upon the T-stage. Other meta-analyses cite accuracy of T-staging ranging from 76 to 96% [20, 24] and another ranging from 75 to 87% [25]. More recent data suggest that ERUS is most accurate for early tumors, especially T0 and T1 tumors [26, 27]. Approximately a quarter of rectal adenomas can be misdiagnosed on initial biopsy with a finding of invasive adenocarcinoma on final pathology; however, ERUS is able to detect up to 81% cases with focal carcinoma identified on final pathology [28]. ERUS is recommended for staging early tumors, with excellent sensitivity (97.3%) and specificity (96.3%) in diagnosing T0 tumors [26]. When looking at rectal cancer as early versus advanced stage, ERUS also has high specificity and accuracy for staging advanced tumors, 96% and 94%, respectively [12]. ERUS is currently the most accurate modality for evaluating T1 rectal tumors [27], whereas it is least accurate for staging T2 tumors, often due to overstaging [29–31]. The accuracy of uT3 based upon meta-analyses is thought to be 88–96% [20, 24, 25, 29].

The accuracy of nodal metastasis assessment with ERUS is less than the accuracy for T-staging [32–34], with a mean accuracy for T-stage of 85% and a mean accuracy for N-stage of 75% in one study [35]. Its accuracy in excluding lymph node involvement may be better than confirming it [34]. With regard to the accuracy of ERUS for N-staging, it is thought that earlier tumors have smaller metastatic deposits, and therefore positive nodes are more likely to be missed by ERUS. In one study, the ability to correctly stage lymph node status drops from 84% in T3 tumors to 48% for T1 tumors [36]; this was attributed to a drop in the median size of the lymph nodes and metastatic deposits from 8 mm to 3.3 mm and 5.9 mm to 0.3 mm, respectively, when going from T3 to T1 tumors.

It has been proposed that ERUS be combined with a technique for obtaining specimens for further analysis when it is used to guide a needle biopsy or needle aspirate, allowing for further use in the evaluation of rectal cancer. This approach can provide diagnostic material for ancillary studies as well as allow the evaluation of perirectal lesions in a more accurate manner by combining both imaging and histology [37]. The use of this technology may help increase the specificity of nodal staging with ERUS; however, further studies are still needed to validate the role of ERUS with guided biopsy/FNA.

Other imaging modalities have been employed for preoperative staging, including CT scan, PET scan, and MRI. CT scans are considered the

standard of care for detecting widely metastatic disease. Its role, however, in local staging is minimal as it is unable to delineate the layers of the rectal wall. In a study comparing the accuracy for spiral CT and ERUS for T-staging, the results show 70.5% and 84.6%, respectively. With nodal staging, there seemed to be no difference in CT as compared to ERUS for evaluating nodal metastasis, with a reported accuracy of 61.5% and 64.1%, respectively [38]. Much like with CT scans, the lack of detailed anatomy provided by PET CT scans make local T-staging and lymph node involvement difficult to ascertain [39, 40].

Unlike ERUS, MRI does not provide excellent visualization of the layers of the rectal wall, which is key in local staging. It is thought that ERUS provides better visualization of superficial tumors or early stage, whereas MRI allows better assessment of locally advanced or stenotic tumors [25, 41]. When evaluating nodal metastasis, MRI and ERUS show similar results for muscularis propria invasion, but MRI has higher sensitivity for perirectal tissue invasion [42]. The overall sensitivity and specificity of MRI to assess lymph node involvement was 77% and 71%, respectively [43]. These data suggest that there may be a complimentary role for ERUS and MRI in the evaluation of lymph nodes [41]. Where MRI is thought to be clearly better than ERUS is for visualizing the circumferential resection margin after resection [44].

Currently, ERUS is routinely a first-line modality for imaging and local staging of rectal cancers and with good supporting data as reviewed in this chapter. Its adjunct is CT scan for distant metastasis. The use of multiple modalities for preoperative staging will give the most accurate results, especially if the images obtained by ERUS are not straight forward such as in the case of highly stenotic and locally advanced tumors.

Limitations of Endorectal Ultrasound

Evaluation of response to chemoradiation therapy (CRT) or restaging after CRT with ERUS is limited by the inflammation, necrosis, fibrosis, and post-radiation edema. Therefore, ERUS has a limited role in this arena with reported accuracies of 46–47% [45, 46]. The misinterpretation rate was found to be highest in responsive patients where accuracy rates were the lowest (29%) [47]. There are authors who feel that when there is residual tumor present, it is limited to the area of fibrosis, allowing for determination of the maximum possible determination of depth of invasion [48, 49]. However, further studies are needed to identify and confirm post-CRT sonographic changes, and better rates must be reported before ERUS is recommended for restaging post-CRT.

Operator dependence is also thought to be a limitation of ERUS. The learning curve for T-staging and N-staging are reported to be approximately 50 and 75 cases, respectively [18]. Accuracy is thought to vary with the level of experience of the operator [33, 50], allowing for some of the variations seen among different studies with regard to accuracy of ERUS.

Another limitation of the ERUS is the field of view of the transducer. This is most often seen when rigid ERUS probes are used to evaluate iliac lymph nodes. Flexible echoendoscopes allow for better evaluation of this area due to the ability to insert the probe in deeper. Even with this limitation, ERUS-FNA has been shown to better detect iliac nodal involvement than CT scan [51].

In the authors' practice and experience, ERUS and MRI are complimentary imaging tools, utilized based on tumor characteristics, location, and stage of treatment. When the patient first presents, for staging of local disease, we typically obtain a 3Tesla pelvic MRI for evaluation of mesorectal involvement as well as the pelvic sidewall. At the same time, flexible sigmoidoscopy and a 3D rigid ultrasound are obtained by the surgeon that will be performing the operation. Since ultrasound is clearly operator dependent, we believe it is mandatory that the operating surgeon performs the local staging. The information obtained will be extremely useful at the time of the operation. We see this also as an opportunity for the surgeon to improve his or her ultrasound skills as the findings will be further confirmed by the MRI or the pathology report if no additional neoadjuvant treatment is indicated. While the data in the literature are mixed on this topic, we

believe that for very low early rectal cancer, a rigid ultrasound following a thorough digital rectal examination by an experienced operator and flexible sigmoidoscopy offers superior and more detailed information in terms of planning operative intervention than an MRI. There is no doubt that when dealing with bulky lesions, stenosis, or threatened mesorectal fascia, MRI should be considered the imaging tool of choice. Following completion of neoadjuvant treatment local restaging, when indicated, is performed exclusively by MRI. Ultrasound does not adequately differentiate between residual cancer, fibrosis, and acute inflammatory edema and therefore is not routinely utilized.

Conclusion

Based upon the current standards of care, ERUS is indeed an effective diagnostic and preoperative local staging tool for rectal cancer and is an established modality for determining the integrity of the rectal wall. In an era where there are multiple options for therapy depending upon preoperative staging, including local excision, neoadjuvant CRT, as well as options for non-operative management, ERUS with its advantage of accurate local staging for early tumors, and distinction of early and late tumors, plays a major role in the treatment of rectal cancers.

As with most things, there are limitations to this technology; however, it is still first line for evaluation of rectal cancer. Other modalities such as MRI and CT scan are being optimized, and ERUS continues to be optimized with emerging technology. It is likely that the most accurate method will not be a single modality but a complement of imaging modalities for both preoperative staging and restaging for rectal cancer patients.

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Magnetic Resonance Imaging of the Rectum

3

Gina Brown

Introduction

In recent years preoperative staging and assessment of rectal cancer has moved away from reliance on clinical and ultrasonographic assessment to detailed prognostic assessment afforded by high-resolution MRI. As with surgery and other modes of treatment, the use of preoperative staging is variable, and a minimum standard for both the technique and interpretation in staging rectal cancer needs to be followed to obtain the best results for patients. This chapter aims to highlight the important standards to establish or maintain in rectal cancer staging and the techniques in interpretation that will enable consistently accurate assessment as demonstrated in published multicentre studies.

MRI Technique for Staging Rectal Cancer

MRI was first introduced in the early 1990s—the imaging parameters and techniques used for evaluating rectal cancer showed a wide variability in staging with a near-linear relationship between the accuracy achieved and the spatial T2-weighted resolution of the imaging utilised.

Schnall et al. showed that using an endorectal coil with a 12 cm field of view, 256 matrix and 3 mm slice thicknesses, in-plane resolution of 0.59 mm × 0.59 mm and a voxel size of <1 mm^3 could be achieved. The drawback of the endorectal coil, and indeed of any endoluminal technique for assessing rectal cancers, was an inherent inability to interrogate the whole mesorectum, the potential radial margins and tumour spread laterally and above the primary tumour site. In addition passage of an intraluminal probe for bulky or stricturing tumours was impossible.

The advent and ongoing improvement of modern multichannel surface phased array coils overcame reliance on intraluminal techniques to evaluate the rectum and perirectal structures. When optimal parameters were used, an in-plane resolution could be achieved which was similar to those obtained with the endorectal coil (0.6 × 0.6 mm with a voxel size of 1.1 mm^3). In order to meet these levels of resolution consistently, there needed to be a shift away from multiple noncontributory MRI sequences such as contrast enhancement, fat suppression and diffusion-weighted and T1-weighted scans to a more dedicated sequence that enabled clear delineation of the tumour with high-resolution depiction of the rectal wall, the mesorectum and the pelvic sidewall compartments in order to get genuinely prognostic and predictive staging information. The technique was developed and

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rolled out to radiologists at multiple institutions in the MERCURY trials and national training programmes. The scans are easily run on any generation 1.5–3T MRI system in conjunction with a multi-coil, multichannel surface array coil. The total examination duration is approximately 40 min and this is essential. Shortening the examination time by increasing the field of view, reducing the number of acquisitions or increasing the slice thickness inevitably reduces both the resolution and the consequent accuracy of the technique. The addition of further sequences also reduces the overall quality of the examination as well as prolonging patient discomfort in the scanner and for these reasons is not recommended. Figure 3.1 illustrates the difference between a high-resolution and suboptimal MRI scan. The difference in technique amounts to 3–4 min acquisition time to obtain high-resolution scans but can make a substantial improvement to staging accuracy and the ensuing appropriateness of treatment decisions.

Summary Points—for MRI Staging Technique

- The field of view and matrix parameters should not exceed a pixel size of 0.6 × 0.6 mm, e.g. 200 × 200 mm with 384 × 384 matrix or 160 × 160 mm with a 256 × 256 matrix (note pixel size (mm) is calculated as = field of view/matrix). Voxel size mm^3 = pixel size × slice thickness.
- The surface phased array coil should be placed correctly over the lower pelvis. For low rectal cancers the distal edge of the coil should lie 10 cm below the symphysis pubis to ensure that the distal rectum is in the centre of the image (Fig. 3.2).
- Scans should be obtained perpendicular to the rectal wall; the sagittal MRI scans are used to plan the oblique axial images (Fig. 3.3).
- Coronal images should be undertaken parallel to the anal canal to visualise the distal mesorectal plane (Fig. 3.3) and must also be performed using the same high-resolution parameters.
- The use of saturation bands reduces image degradation due to abdominal wall motion, and hyoscine butylbromide given as an i.m. injection or oral mebeverine reduces small bowel peristalsis, respectively (Fig. 3.4).
- High-resolution coverage should include at least 5 cm above the top of the tumour and to the L5/S1 level for all tumours to ensure that discontinuous tumour deposits are visualised (Fig. 3.3).
- T1-weighted imaging, contrast enhanced imaging and fat saturated sequences do not

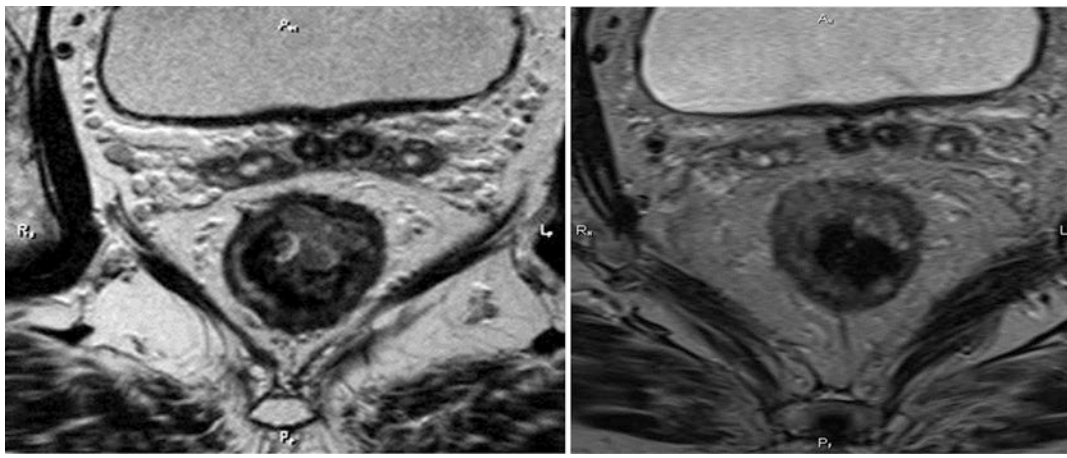

Fig. 3.1 Axial image showing the difference between a high resolution (*left*) and lower resolution scan in the same patient (*right*). The polypoidal tumour is much more clearly depicted on the high resolution scan. Similarly the anatomic layers of the bowel wall are also more clearly shown

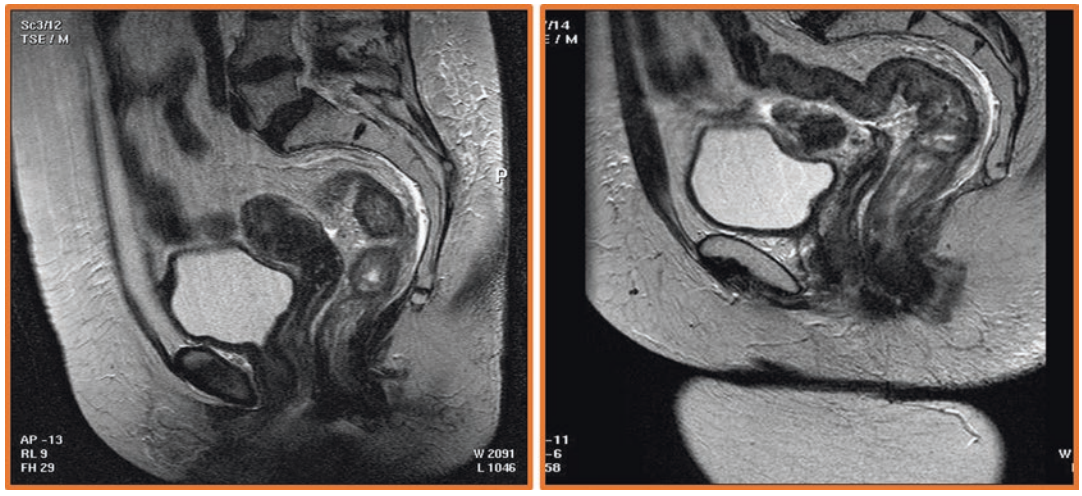

Fig. 3.2 The surface phased array coil should be placed correctly over the lower pelvis. The left hand image shows incorrect placement- the coil has been positioned too high so that there is insufficient signal from the lower third of the rectum. For low and mid rectal cancers the distal edge of the coil should lie 10 cm below the symphysis pubis to ensure that the distal rectum is in the centre of the image

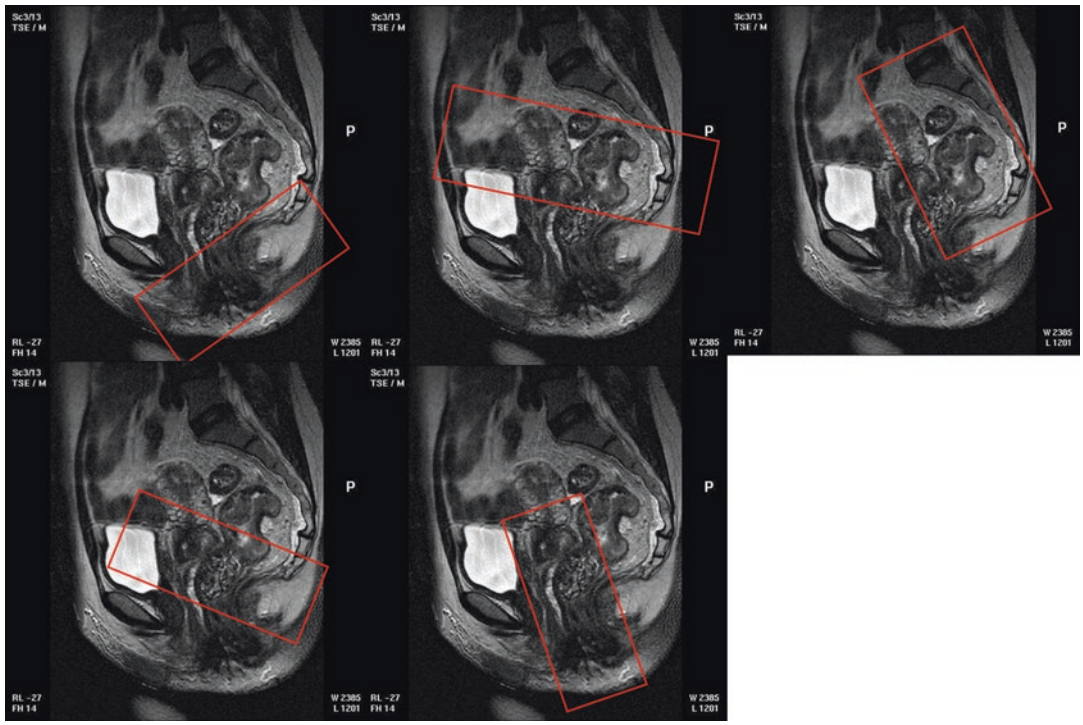

Fig. 3.3 Illlustrates how the sagittal scans can be used to plan the correct scan planes for oblique axial and coronal images that are perpendicular to the rectal wall and coronal to the anal canal

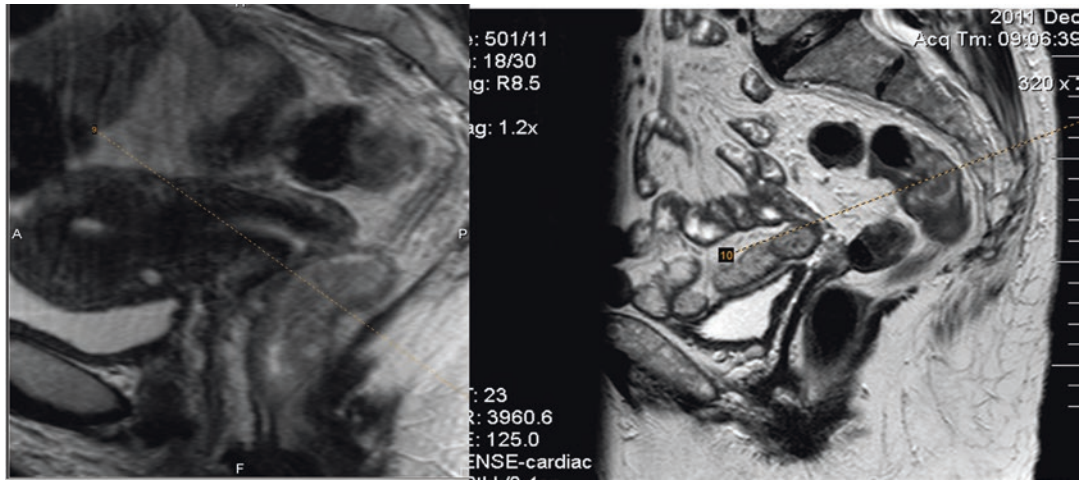

Fig. 3.4 The use of a "saturation bands" to suppress the signal from unwanted areas. For example the anterior abdominal wall produces movement degradation and so placing the saturation band over the abdominal wall (on the right hand image) reduces the image degradation. This is evident on the left hand image where no saturation band has been used

contribute and worsen staging accuracy and should not be used for primary rectal cancer staging.

- Caution when using diffusion-weighted imaging for rectal cancer as it does not improve accuracy when compared with high-resolution MRI techniques.
- The prolonged examination time caused by additional noncontributory sequences reduces the overall quality of the examination as well as prolongs patient discomfort.

Anatomic Considerations

The major utility of MRI lies in its ability to depict the surgical anatomic planes for preoperative road-mapping, thereby enabling a clear surgical approach that can be defined by the extent of tumour and its relationship to neighbouring structures.

Surgery for rectal cancers can be modified in accordance with the plane required to enable total clearance of the tumour. For the vast majority of patients presenting with rectal cancer, total mesorectal excision (TME) plane surgery enables the primary tumour and all the draining lymph nodes to be removed in an intact package with clear radial, distal and proximal margins. This approach has substantially reduced local recurrence rates from above 40% in non-TME series to 5% in patients where a clear margin is achieved and a good-quality TME specimen is shown. When all patients with rectal cancer are staged by MRI, the prevalence of potential involvement of the TME plane (mrCRM) is 26%, and the use of preoperative therapy enables tumour shrinkage that significantly reduces CRM positivity rates. For those patients that become either *mr* or *p*CRM negative as a result of preoperative therapy, the local recurrence rates are 7%, but for those with either persistence of tumour at the TME plane on imaging or pathologic involvement of the CRM, the rates of local recurrence are over 20%. Consequently, in a proportion of patients with persistence of tumour at the mesorectal margins, a beyond TME approach is required to achieve tumour-free resection margins. The major surgical landmarks for rectal cancer surgery are readily visualised using preoperative MRI.

The Mesorectum and Mesorectal Fascia

The rectum is somewhat unique having a mesenchyme that is encircled by a visceral fascial layer that encases the rectum, its draining nodes and neural and vascular structures. On MRI the fascial envelope is shown as a low signal intensity

structure that encircles the mesorectum from the level of the distal levator inferiorly to the sacral promontory posteriorly. Anteriorly, the mesorectum ends at the level of the anterior insertion of the peritoneum. Therefore, anteriorly above the peritoneal insertion, the rectum is devoid of a fascia and is covered by the peritoneal serosa which gradually widens until the point of the sigmoid is reached. At this point the mesorectum is no longer anchored to the sacral concavity and is instead posteriorly surrounded by a relatively mobile sigmoid mesentery rooted by the sigmoid vascular branches to their vascular origin/confluence at the IMA and IMV.

Anteriorly Infiltrating Tumours

The peritoneum separating the pelvic and abdominal visceral compartments is seen on high-resolution scans as a low signal intensity layer. Anteriorly the peritoneum can be traced over the surface of the bladder and seminal vesicles or uterus before its attachment to the rectum in the midline. This is well seen on the sagittal images. The peritonealised surface of the rectum does not form part of the circumferential surgical resection margin, and so anterior tumours above this level are not considered as potentially margin involved but can still be infiltrating through the peritoneum. Such tumours have a risk of pelvic recurrence through transperitoneal spread.

The Ureteric Plane/Pelvirectal Space

This space is devoid of lymph node tissue but contains neurovascular structures as they pass forward from the sacrum to the anterior pelvic organs. When tumour is evident in this space, this will either be from direct spread out of mesorectal compartment, from peritoneal spread or from venous invasion.

The Rectovaginal Septum and the Urogenital Compartment

Below the peritoneal insertion anteriorly, a condensation of the rectogenital septum is manifest as a focal low signal intensity band-like thickening of the anterior mesorectum in the anterior midline. In males the fascia forms the plane separating the anterior mesorectum from the prostatic capsule and can be followed inferiorly to the perineal body in the midline (Fig. 3.5).

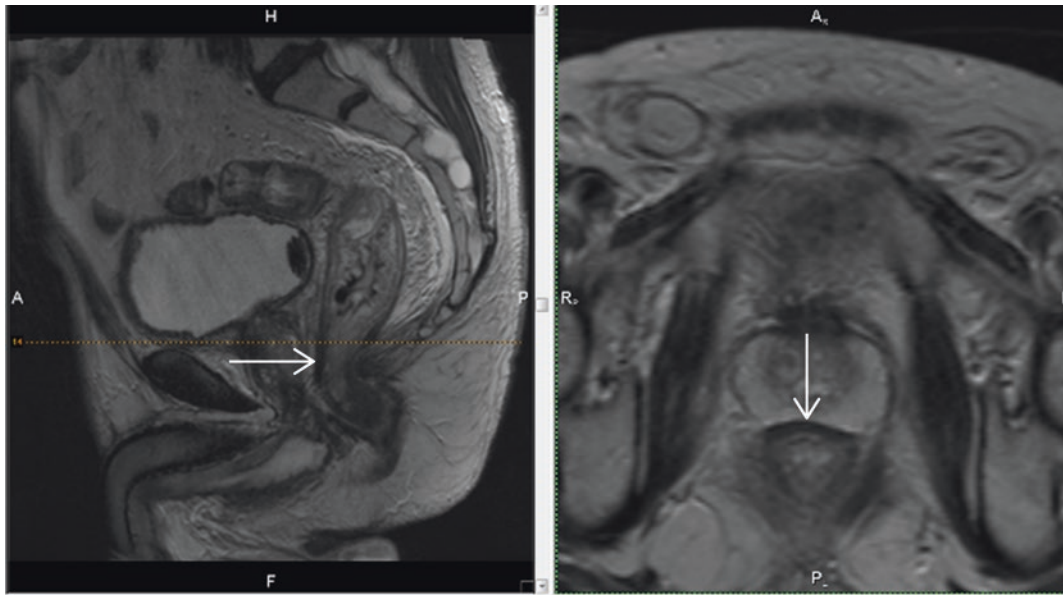

Fig. 3.5 The arrow points to the low signal intensity rectogenital septum which forms a band-like thickening that overlies the anterior mesorectum in the anterior midline

The pelvis can thus be divided into distinct anatomic compartments based upon the boundaries of the peritoneal reflection, the visceral (or mesorectal) fascia, the presacral fascia and the pelvic floor musculature.

The Parietal Fascia and the Pelvic Parietal Compartments (Presacral and Lateral Pelvic Compartments)

Where tumours extend beyond the conventional mesorectal compartment and beyond the mesorectal fascia, patients can then be appropriately referred for a therapeutic strategy that will enable clearance of tumour from undertaking beyond TME plane surgery that could range from adjacent organ removal to total pelvic exenteration depending on the compartmental distribution of tumour as shown on the preoperative MRI.

The Infralevator Compartment (Fig. 3.6)

The levator muscle forms a single sheet of muscle forming the pelvic floor. In the midline, its posterior proximal attachment is seen at the tip of the coccyx, and laterally it forms a 'hammock-like' structure on both sides around the mesorectum, with a further point of fixed attachment on both sides at the ischial spines (best seen on the coronal image—Fig. 3.6); laterally the muscle fuses with the obturator fascia, and inferiorly the fibres blend with the puborectalis sling whose anterior fibres attach to the inner surfaces of the upper pubic symphysis on either side of the midline. The lower third of the rectum is defined anatomically from the point of the levator attachment at the tip of the coccyx posteriorly to the levator's most distal point at the level of the puborectalis sling. This represents a surgically challenging portion of the TME dissection where the mesorectum starts to taper and the proximity of the rectum to the adjacent anterior urogenital compartment limits the space. For tumours arising in this lower third segment of the rectum, even minimal spread beyond the rectal wall, mesorectal fat plane is small and can result in potential CRM involvement.

MRI and Local Rectal Cancer Staging

The development of high-resolution MRI and carefully validated image interpretation criteria has created the unique advantage of identifying

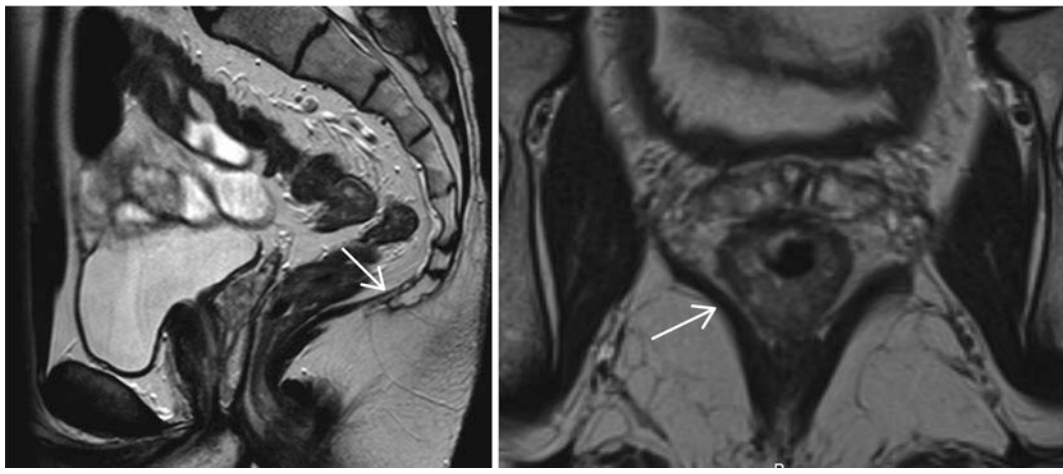

Fig. 3.6 The levator muscle is (*arrows*) a single sheet of muscle forming the pelvic floor. In the midline, its posterior proximal attachment is seen at the tip of the coccyx, and laterally it forms a 'hammock-like' structure on both sides around the mesorectum its most distal point is at the level of the puborectalis sling. The levator origin and its distal insertion effectively defines the anatomic lower third of the rectum where the mesorectum starts to taper resulting in the most challenging portion of surgical dissection in TME rectal cancer surgery

prognostic factors that predict for the risk of local and distant failure before treatment commences. This precision in preoperative staging was previously not available and can now be used for the benefit of all patients with rectal cancer. For the surgeons and oncologist managing the patient, there is a consequent opportunity to tailor the surgical and preoperative therapeutic approach to reduce the risk of recurrence.

T Classification

For all cancers, the direct relationship between depth of tumour spread and prognosis is a well-established basis for the TNM classification. For patients with rectal cancer, there is a near-linear relationship between outcomes and degree of spread into and beyond the rectal wall. The ability to closely reproduce the low power haematoxylin and eosin stained depiction of tumour of the resection with the high-resolution T2-weighted images can afford millimetre accuracy in stage assessment that enables far more precise prognostication than the broader T categories and stage categories of the traditional AJCC/TNM systems.

Preoperative Assessment of T1 Tumours

Tumour depth into the submucosa can be measured to the nearest millimetre, and the depiction of a preserved submucosal layer can now be used to select patients for a primary local excision approach that avoids the morbidity of major radical surgery. On high-resolution scans, the submucosal layer is of brighter signal than the tumour, and its preservation enables the identification of a patient with a likely T1 cancer (Fig. 3.7).

T2 Tumour Spread

The muscularis propria is characterised by the following features: low signal (dark) intensity relative to tumour. It is formed by two layers—the circular and longitudinal muscle coat. The latter is seen as a discontinuous layer with vertically arranged low signal intensity bundles and separated from the inner circular layer by a distinct high signal layer of the myenteric plexus. The degree of muscularis propria preservation enables differentiation between an early invasive T2 and deeper T2 tumour inseparable prognostically from an early T3 tumour (Fig. 3.8).

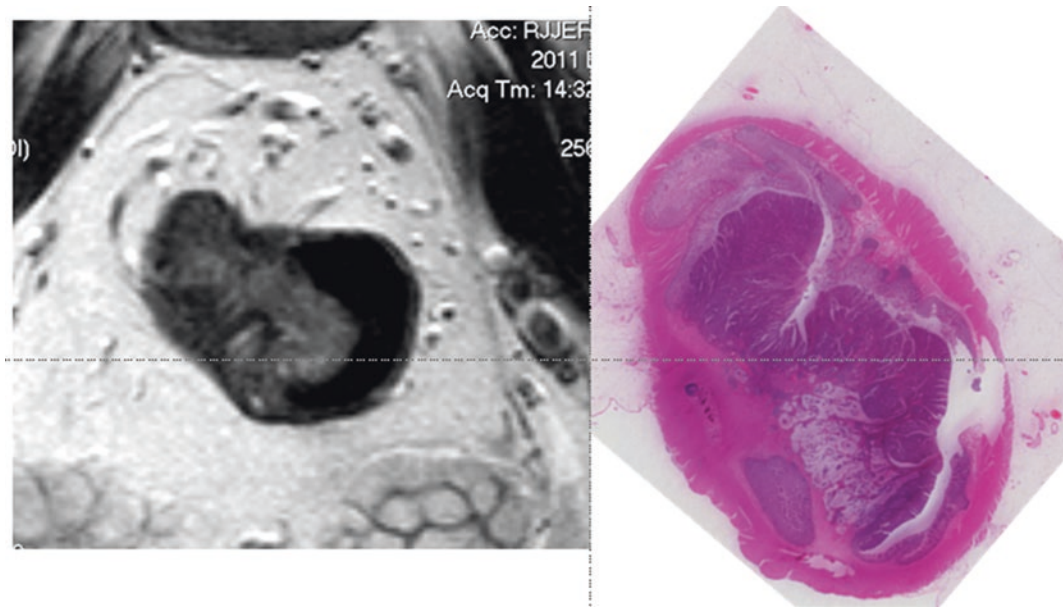

Fig. 3.7 MRI image and corresponding histopathologic section of a T1 tumour

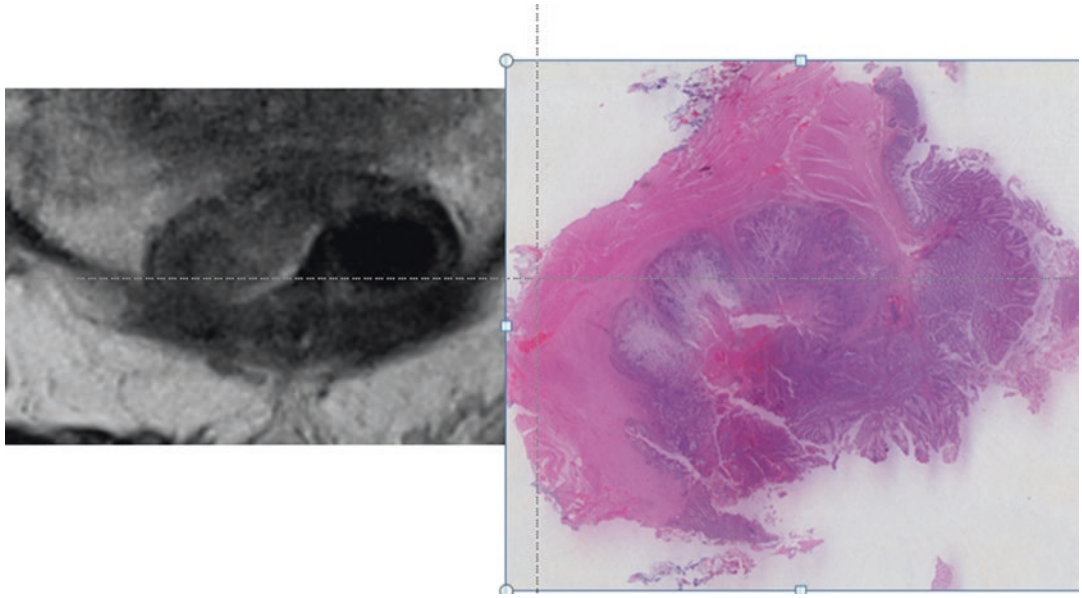

Fig. 3.8 MRI image and corresponding histopathologic section of the T2 tumour

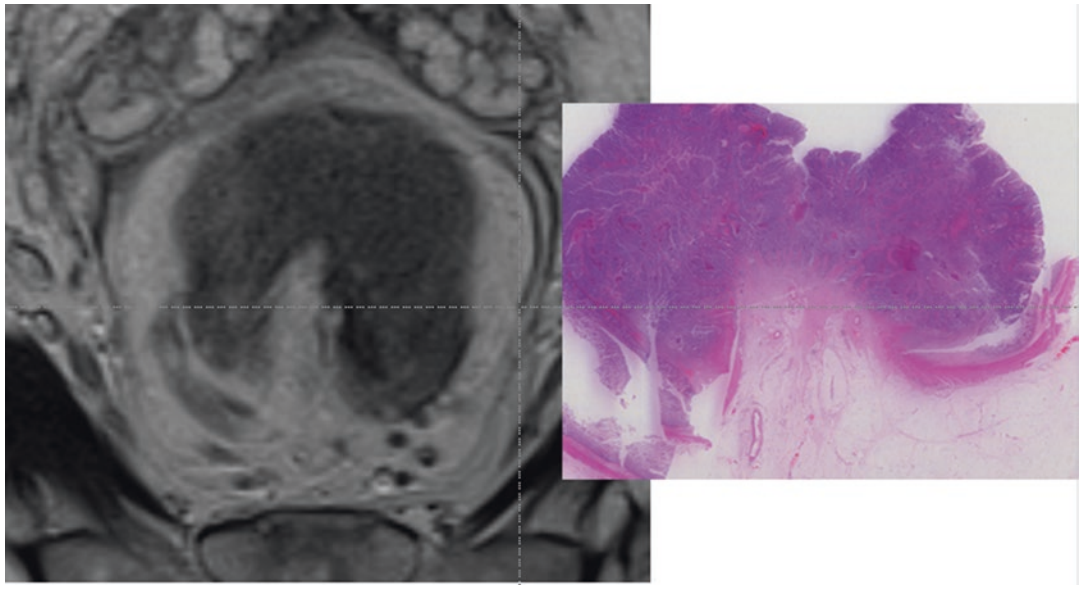

Fig. 3.9 MRI image and corresponding histopathologic section of a T3 tumour

Early T3 Tumours

As tumour advances, the degree of muscularis preservation diminishes until finally tumour is seen to completely replace the muscularis propria layer. Such tumours can be classified as full thickness T2 or T3 <1 mm. These are prognostically identical tumours with a low likelihood of spread to lymph nodes or distant spread and unless bordering the intersphincteric plane readily amenable to cure by primary surgical total mesorectal excision (Fig. 3.9).

When tumour has clearly spread beyond the muscularis propria, the depth of extramural invasion

is an independent prognostic factor [1, 2]. This is defined as the depth in millimetres of tumour spread beyond the outer edge of the muscularis propria. Tumours with less than 1 mm spread have exactly the same prognosis as T2 tumours. Spread between 1 and 5 mm is also associated with cancer-specific survival rates that are similar to T2 tumours regardless of lymph node involvement. For patients with tumour spread beyond 5 mm, there is a consistent reduction in cancer-specific survival, with an increased propensity to distant metastatic disease and local recurrence.

Since the majority of rectal cancers diagnosed comprise T3 tumours, there is merit in addressing the inherent heterogeneity by taking into account the depth of extramural spread. Merkel and others [3] showed that pT3 rectal cancers could be usefully subdivided according to depth of extramural spread as follows: pT3a minimal invasion, <1 mm beyond the border of the muscularis propria; pT3b-slight invasion, 1–5 mm beyond the border of the muscularis propria; pT3c-moderate invasion, >5–15 mm beyond the border of the muscularis propria; and pT3d-extensive invasion, >15 mm beyond the border of the muscularis propria [4]. This prognostic classification based on a study of 850 patients in the Erlangen Cancer Registry was proven to predict survival regardless of nodal stage. This was an important observation as of all parameters assessable on MRI, depth of tumour spread showed the greatest agreement with pathology showing a mean agreement of 0.5 mm when compared with pathology [5]. Since survival and local recurrence outcomes for T2 and early T3 tumours are identical and with increasing use of precision depth of spread measurements afforded by preoperative high-resolution MRI, preoperative decisions regarding chemoradiotherapy (CRT) are increasingly based on the 5 mm depth of extramural spread cut-off rather than the T2/T3 boundary. As further evidence to support this practice, a 5-year follow-up from the MERCURY study, Taylor et al. showed that MRI staged rectal cancers with <5 mm depth of spread 85% 5-year overall survival and 3% local recurrence rates, thus supporting the use of a more rigorous preoperative stratification of rectal cancer patients [6].

Circumferential Resection Margin (CRM)

The importance of tumour spread within 1 mm of the surgical circumferential resection margin (CRM) is well known [7, 8]. The appearance of the predicted CRM on MRI was first described in 1999 and was shown as a low signal intensity structure surrounding the mesorectum on high-resolution imaging. High-resolution MRI is the most accurate imaging modality for consistently identifying the mesorectal fascia and thus the CRM [9]. The first prospective study was conducted in 98 patients and showed that if the distance of tumour was 1 mm or less to the mesorectal fascia, this predicted pathological CRM involvement with 92% agreement (kappa = 0.81) [10]. The high-resolution technique needed to be strictly adhered to but was considered that if the protocol was adhered to and image interpretation criteria established by Brown et al. were followed, then this could be reproduced in a multicentre setting. In 2003, the MERCURY group comprising 11 hospitals in the UK and Europe prospectively tested the hypothesis that tumour depth and distance to CRM could agree with histopathology findings in a multicentre setting. Following TME surgery 327 (94%) patients were found to have clear margins on histopathology [11]. The specificity was 92% (CI 90–95%). The group showed a high risk of pCRM involvement if tumour distance to the mesorectal fascia was 1 mm or less. In a follow-up paper evaluating outcomes of these patients, MRI proved to be as likely to predict the risk of local recurrence as pCRM involvement. When the MRI suggested that the tumour was ≤1 mm from the mesorectal fascia, there was a 20% local recurrence rate compared with 7.1% in the mrCRM 'clear' group [6, 12]; the local recurrence rates were identical for patients with pCRM involvement. The group also showed that increasing the threshold for risk of CRM involvement by widening this distance to 2 mm or more did not improve the prediction of likely CRM involvement and would result in substantial overtreatment and toxicity for such patients.

Node Stage

In the pre-TME era, nodal involvement was unsurprisingly a predictor for pelvic recurrence [13]. Patients undergoing non-TME surgery experienced local recurrence rates that ranged from 20 to 40% that were strongly linked to mesorectal disease left in the pelvis after suboptimal surgery. The use of preoperative radiotherapy in such patients was associated with a reduction in local recurrence rates to 20%, but this was clearly not an effective compensatory approach for poor quality surgery. The Scandinavians subsequently adopted a nationwide training and accreditation programme of TME surgery spearheaded by Lars Pahlman [14]. When an approach that employed high-quality TME resection was adopted, the local recurrence rates dramatically reduced. Thus in the TME era, lymph node status per se does not confer any additional risk of local recurrence in patients provided that tumour does not extend to within 1 mm of the mesorectal fascia [15].

The assessment of lymph node status remains important in patients with early rectal cancer treated by local excision. The benefits of the reduced morbidity and organ preservation afforded by a less radical technique must be balanced against the potential risk of small volume disease remaining in the mesorectal nodes which may relapse. It is evident that relying on nodal size alone is highly inaccurate and likely to result in incorrect assessments of nodal positivity. Firstly the favoured cut-off of 5 mm fails as the majority of patients with rectal cancer have small (<5 mm) mesorectal lymph nodes that contain a tumour [16]. There is considerable overlap between the size of reactive nodes and nodes containing tumour metastases such that no size cut-off can be relied upon. By determining mixed intranodal signal and irregularity of the border, which are features evident on high-resolution imaging, MRI can determine lymph node involvement with 85% accuracy compared with histopathology reference standard [10]. Morphological assessment has the additional advantage of displaying the anatomic distribution of nodes both within and outside the mesorectum. Another crucial advantage that had previously been unavailable to patients following local excision is that MRI can be used to serially monitor the evolution of nodal morphology such that a progressive change in morphological appearances by close monitoring will enable early identification and resection in patients with residual mesorectal disease. Hence, node morphology and serial 3 monthly high-resolution MRI evaluation is a helpful assessment technique following local excision in patients desiring an organ preservation approach.

Extramural Vascular Invasion (EMVI)

Extramural vascular invasion (EMVI) is defined as the presence of tumour in the vasculature beyond the muscularis propria and was first described by Grinnell in the 1930s. In 1980 and 1981, Ian Talbot at St Marks undertook a comprehensive histological assessment of venous invasion in patients with rectal cancer with follow-up of outcomes. He concluded that tumour invasion into 'thick-walled' extramural veins occurred in 52% of 703 surgical specimens from patients with adenocarcinoma of the rectum, the corrected 5-year survival rate was significantly worse and liver metastases developed more frequently when venous invasion was present with only a 33% 5-year survival [17]. Several subsequent histopathological studies confirmed the relationship between venous invasion and the risk of local failure, distant metastases and reduced survival [18–20]. Metastatic disease in the liver is more strongly linked to EMVI than nodal status and is now the principle cause of death in patients treated with rectal cancer. Thus a preoperative search for this feature and careful systematic follow-up of patients is certainly warranted. Unfortunately the focus on lymph node involvement has resulted in relative neglect of this important prognostic marker, and in several histopathologic audits, the identification of extramural venous invasion is generally underreported [21–24]. The strict histopathologic definition is tumour involvement of a vascular structure with a smooth muscle wall that will contain elastin on elastic staining [25]. However many laboratories do not undertake this form of assessment, and pathologists do not universally recognise the

significance of an isolated tumour deposit seen close to an arterial structure, without an accompanying vein [26].

High-resolution MRI has an inherent advantage in being able to depict the anatomical course of veins as serpiginous structures that are of low signal intensity (signal void—due to flowing blood in large and small veins). Furthermore, multiplanar imaging enables tracking of the anatomic course and calibre of veins. The ability to identify EMVI on both CT and MRI had previously been unrecognised but now established as a significant prognostic indicator. The first imaging study to document this by imaging was carried out in 98 patients undergoing TME surgery with histopathologic correlation; the technique was shown to have a positive predictive value of 85% percent. The radiological characteristics of EMVI as seen on MRI have been described in detail [26]. Unlike nodal status, in TME specimens, tumour assessment of EMVI on MRI remains an important predictor of both local and distant failure [27] and will arguably make a better prognostic biomarker for the use of neoadjuvant chemotherapy.

Post-Treatment Assessment of Extramural Vascular Invasion (ymrEMVI)

A positive mrEMVI is associated with poor survival outcomes. The 3-year overall survival for mrEMVI-positive patients was 35% compared with 74% for mrEMVI-negative patients; mrEMVI-positive patients also had a fourfold increased risk of developing distant metastasis (52 vs. 12%) [26].

Yu et al. report that 78% (219/281) of patients had evidence of mrEMVI on the baseline MRI (96% of patients had ≥ mrT3c). These patients were significantly less likely to respond to CRT than mrEMVI-negative patients (OR 2.5 [CI 1.36–4.54] $p = 0.02$). However when preoperative chemotherapy was used with radiotherapy, mrEMVI was more likely to change from positive to negative and was associated with good overall outcomes. It is hypothesised that this subgroup of patients may benefit from the treatment intensification by the additional use of chemotherapy following chemoradiotherapy. These strategies for managing persistent ymrEMVI will be investigated as part of the phase III multicentre TRIGGER trial (NCT02704520).

Tumour Height: The Problem with Low Rectal Cancers

In determining the feasibility of sphincter preservation, a crucial assessment is the distal margin of clearance from the lowest portion of tumour to the anal verge and sphincter complex and the radial extent of tumour above the level of the sphincter complex. The height of rectal cancer is usually measured from the anal verge and can be readily assessed on clinical digital rectal examination, rigid sigmoidoscopy or endoscopic assessment. Radiological assessment permits an objective assessment of the lowermost edge of the tumour to the anatomic sphincter and anal verge.

For ease of classification, it is common to classify the rectum into three: the lower rectum 6 cm or less from the anal verge, the mid-rectum (from 7 to 11 cm) and the upper rectum (from 12 to 15 cm) [28]. These measurements are somewhat arbitrary and will be subject to usual variation depending on the patient's body habitus. For practical purposes, the majority of patients with tumours arising at 6 cm or less from the anal verge have tumours located in the distal, tapering portion of the mesorectum and located at the anatomically challenging portion of the conventional TME dissection due to the physical narrowing of the pelvis and proximity to nearby vital structures such as the prostate, vagina and neurovascular bundle that are all vulnerable to collateral damage. Thus we can anatomically define the lower third of the rectum as the portion arising below the level of the proximal origin of the levators [29]. These tumours have been shown to be at increased risk of an involved CRM, with routine abdominal perineal excisions being undertaken with TME plane surgery. In such patients CRM positivity rates of up to 30% had been reported in nearly all series [11, 30–32] with higher recurrence rates [33, 34], mortality rates [33], high permanent stoma rates [35] and poor function after sphincter conservation [36,

37]. A precise preoperative staging system that could enable assessment of the radial planes and feasibility of TME plane surgery in achieving clear radial margins was proposed as a way to improve the universally poor outcomes observed in such patients. An MRI staging system was derived which involved assessment of tumour at or below the puborectalis sling and an assessment of the degree of clearance to the intersphincteric plane. For tumours with >1 mm clearance, a TME plane could be considered with potential sphincter conservation, but for tumours that extended to within 1 mm of the intersphincteric plane or beyond, a more radical approach would be needed. In addition, assessment of other factors such as extramural spread, presence of EMVI on MRI and mesorectal fascia invasion could all be combined to provide an overall prognostic risk. By testing this staging system prospectively, the MERCURY group showed that CRM positivity rates could be reduced from 30% to <15%. Furthermore, an MRI prediction of a safe TME plane without adverse prognostic features was observed in 50% of patients and was associated with pCRM risk of <2%. On the other hand, preoperative identification of high-risk features combined with preoperative therapy and good tumour regression was associated with a low risk of pCRM involvement. Finally, patients with a poor response to treatment and persistence of tumour extension into the TME plane could be identified as having a maintained risk of CRM involvement, and more radical surgery was justified in this group [38].

Magnetic Resonance Tumour Regression Grade (mrTRG)

Following chemoradiotherapy a number of radiation-induced tissue changes occur. These include oedema, inflammation, necrosis and fibrosis. The assessment of postirradiated tissue is challenging with all imaging modalities. However, advances in MRI have enabled high-resolution (3 mm) slices to be oriented through the plane of the tumour; consequently the accuracy of MRI has increased. This improved appreciation of the reactive changes that occur in normal rectal tissue after chemoradiotherapy and led to a better understanding of the appearance of residual disease on the post-treatment MRI.

The T2-weighted sequences of high-resolution MRI have a unique ability to distinguish fibrosis from tumour based on the signal intensity differences. Tumour characteristically maintains both its high signal intensity and its disruption of the anatomical layers, whereas fibrosis is characterised by low (dark) signal intensity. By examining the proportion of tumour to fibrotic signal intensity after treatment, it is possible to derive an MRI-based tumour regression grade. This scoring system is based on the pathological tumour regression grade systems and most closely resembles the Mandard pTRG [39]. In an analysis of 111 patients undergoing preoperative radiotherapy in the MERCURY trial, mrTRG was compared to other staging factors. The group reported a significant difference in disease-free survival (DFS) and overall survival (OS) between mrTRG 1–3 (good response) and mrTRG 4–5 (poor response) ($p < 0.001$); the 5-year DFS was 72% and 27%, respectively. Our own single-centre experience has also found a significant difference in DFS and OS: mrTRG 1 and 2 (good response), mrTRG 3 (intermediate response) and mrTRG 4–5 (poor response) had a 3-year DFS of 82%, 72% and 61%, respectively. In these independent series, mrTRG identifies prognostically distinct groups. This suggests that mrTRG can distinguish between ‘good’ and ‘poor’ responders to chemoradiotherapy.

Patients with mrTRG 4 and 5 have relatively little response to preoperative therapy. As expected this group has a significantly higher risk of CRM involvement, distant failure and poor overall survival compared with patients that have mrTRG 1–3 [40, 41]. On the other hand, mrTRG 1 and 2 are strongly predictive of pathological complete response (pCR). If surgery is performed immediately, mrTRG 1 and 2 are associated with an identical survival outcome to pCR [40]. In two further series, the interobserver reliability between radiologists has been reported as moderate to substantial with kappa values of 0.55–0.65, compared with 0.41 (a slight to fair agreement) for the ymrT

assessment [40, 41]. Finally, mrTRG 1 and 2 are associated with a high probability of either no residual tumour or tumour of uncertain viability—this has been used to good effect in two scenarios: (1) in predicting clear CRM in patients with advanced low rectal cancers having a good mrTRG response as 0/33 patients with mrTRG 1–2 had involved CRM and (2) in identifying patients achieving radiological complete response as being suitable for a deferral of surgery approach. The latter is being tested in a prospective phase III trial where patients randomised to an mrTRG-based treatment pathway will be offered deferral of surgery. Comparison with pathologic complete response has shown that radiological complete response based on mrTRG 1–2 identified four times more patients with a similar outcome to pCR.

Conclusion

High-resolution dedication rectal magnetic resonance imaging plays a central role in the management of patient with rectal cancer. It is reliable for evaluating the risk for circumferential margin involvement at surgery and can identify patients who may be safely treated with surgery without radiotherapy or those requiring extended resection beyond the TME plane. The presence of MRI features such as EMVI can identify patients at high risk for systemic failure who may benefit from systemic treatment. Finally, post-treatment MRI can help to identify patients with complete treatment response who may be candidates for surgery deferral.

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4 Local Excision: Transanal Endoscopic Microsurgery and Transanal Minimally Invasive Surgery

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Background

TME and Transanal Excision (TAE) for Rectal Cancer

Originally described by Heald and colleagues in 1982, total mesorectal excision (TME) refers to en bloc removal of the rectum and mesorectum along the mesorectal fascia and has been established as the gold standard in the surgical management of rectal cancer [1, 2]. Wide adoption of TME technique, in combination with stage-appropriate neoadjuvant chemoradiation, has dramatically reduced local recurrence rates in resectable rectal cancer. This is true whether TME is performed with sphincter-preserving low anterior resection (LAR) or abdominoperineal resection (APR) [3]. However, these oncologic resections are associated with significant postoperative mortality and morbidity. Across large trials, TME-related mortality ranges from 2 to 4% [4, 5], while morbidity ranges from 35 to 40% and includes infectious, anastomotic, and wound-related complications, as well as urogenital dysfunction and defecatory disturbances [6–9]. Even when TME is performed for stage I rectal cancer, perioperative morbidity remains between 20 and 25%, which does not reflect the surgical and psychological impact of stoma creation [10]. Long-term complications related to ileostomy and colostomy creation include parastomal hernia and stomal prolapse, which are associated with significant morbidity and often require surgical correction [11]. Even when a sphincter-preserving low anterior resection is feasible for low rectal tumors, the functional disturbances associated with the low anterior syndrome and coloanal reconstruction can be debilitating. Cumulatively, the morbidity associated with radical rectal cancer resections is substantial, negatively impacts quality of life measures, and is largely unaffected by the use of minimally invasive laparoscopic or robotic abdominal approaches [12].

Historically, the high morbidity and mortality rates associated with TME have driven the quest for less invasive local surgical approaches. Conventional transanal local excision (Park's operation, or TAE) was developed as a strategy to treat lesions in the distal rectum that could be accessed and removed under direct visualization through the anus. Local excision can also be undertaken via a transsphincteric (e.g., York-Mason) or transcoccygeal (e.g., Kraske) approach. The morbidity of TAE has been shown

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to be substantially lower than that of radical resection, with complication rates ranging from 10 to 17%, mostly consisting of bleeding, transient urinary retention, and fecal incontinence [13, 14]. However, this type of local excision only allows access to lesions within 6–8 cm of the anal verge, with limited exposure and visualization of the surgical field and increased risk of specimen fragmentation and positive resection margins [15].

As local excision techniques gained popularity in the management of early rectal cancer due to their considerable lower-risk profile, concerns arose regarding the oncologic adequacy of local excision relative to radical resection, particularly due to reports of higher local recurrence rates. Mellgren et al. retrospectively evaluated oncologic outcomes of 260 patients with T1 or T2 rectal cancer treated with either TAE or radical resection [16]. Patients with T1 tumors treated with local excision had an 18% rate of local recurrence, as compared to no recurrence in the radical resection group. However, 5-year survival was similar in both groups. Paty et al. retrospectively evaluated 74 patients with T1 rectal cancer treated with local excision and reported a similarly high local recurrence rate of 17%, with a 74% 10-year survival [17]. You et al. used the National Cancer Database to retrospectively compare 765 patients treated with local excision to 1359 patients treated with TME and found that after adjusting for patient and tumor characteristics, the 5-year local recurrence for local excision was 12.5% as compared to 7% for radical resection among T1 tumors [18]. Again, the 5-year survival was comparable for both groups. Confounding most of these earlier retrospective studies is the lack of patient selection, which introduced significant heterogeneity in histopathological features and stage of tumors, as well as in the type of local excision techniques employed.

Transanal Endoscopic Surgery (TES): TEM, TEO, and TAMIS

Transanal endoscopic microsurgery (Richard Wolf Company, Tubingen, Germany) was developed by Gerald Buess in 1982 as an endoscopic approach for local excision of low and mid-rectal lesions [19]. This approach represented a significant technical advancement relative to conventional TAE and endoscopic piecemeal polypectomy, with improved visualization and exposure of lesions, particularly those in the proximal rectum. The original TEM platform, which has been minimally modified over the last 20 years, employs a rigid metal 4-cm wide proctoscope available in two lengths to target the low to middle and middle to upper rectum (Fig. 4.1a). The proctoscope has an external multiport faceplate through which CO_2 is insufflated to achieve distention of the rectum and which accommodates a magnifying stereoscope and adapted dissection instruments. Once positioned transanally, the proctoscope is anchored to the operating table using a locking arm, which achieves a stable operating platform and videoscopic setup. TEM allows for either submucosal or full-thickness rectal dissection with hemostasis achieved with electrocautery, bipolar energy, or clips. Superficial rectal defects can be left open or closed in a fashion similar to full-thickness defects using laparoscopic suturing instruments. The original TEM technique and platform were adapted for the use with conventional laparoscopic equipment and a 2D laparoscopic camera, termed the transanal endoscopic operation (TEO, Karl Storz GmbH, Tuttlingen, Germany, Fig. 4.1b).

Until recently, adoption of transanal endoscopic surgery was confined to a few high volume and centers of expertise. Wider adoption was limited by the prohibitively high costs of the rigid TEM and TEO platforms, scarcity of training centers, and long learning curve required to achieve technical expertise in these procedures. In 2009, at the height of popularity of single-incision laparoscopy, an alternate transanal endoscopic setup using single-incision laparoscopic disposable transanal ports was reported, which was called transanal minimally invasive surgery (TAMIS) [20, 21].

TAMIS has popularized transanal endoscopic approaches through improved access, as disposable equipment is more readily available, less expensive, and compatible with standard laparoscopic equipment [21]. TAMIS platforms are shorter and pliable, thereby increasing the free-

Fig. 4.1 TES (transanal endoscopic surgery) platforms. Rigid platforms include (**a**) TEM (transanal endoscopic microsurgery) (Richard Wolf Medical, Vernon Hills, IL, USA). (**b**) TEO (transanal endoscopic operation) (Karl Storz Endoscopy-America, Inc. El Segundo, CA, USA). TAMIS (transanal minimally invasive) platforms include (**c**) SILS (single incision laparoscopic surgery, Covidien, Mansfield, MA, USA). (**d**) GelPOINT path (Applied Medical, Rancho Santa Margarita, CA, USA)

dom of motion and limiting instrument collision (SILS Port, Covidien, Mansfield, MA, Fig. 4.1c; GelPOINT Path, Applied Medical, Rancho Santa Margarita, CA, Fig. 4.1d). The shorter length, however, limits the extent of proximal rectal wall retraction and exposure, particularly beyond the second or third haustral valves [22]. Rather than using an anchoring arm to stabilize the platform and the stereoscope, a standard laparoscopic camera and scope are used. TAMIS procedures therefore require two operators, a camera holder and an operating surgeon. While a number of case series have been published demonstrating the preliminary feasibility and safety of TAMIS, these studies are relatively small and the data short-term, with no long-term oncologic results of TAMIS yet described.

TES as Compared to TAE and TME

TEM has long been considered an ideal minimally invasive approach to resect large rectal adenomas not amenable to complete endoscopic resection with a colonoscope, incompletely resected adenomas with dysplasia or intramucosal adenocarcinoma, small low-risk carcinoids, and other miscellaneous benign rectal pathologies. Until recently, however, the use of TEM for cancer was most widely accepted for the resection of rectal cancers in patients refusing more oncologically appropriate radical resection, radiation, or abdominoperineal resection and for palliative resection in patients considered medically unfit to undergo radical resection (Fig. 4.2). Routine use of TEM in the curative resection of T1 and T2

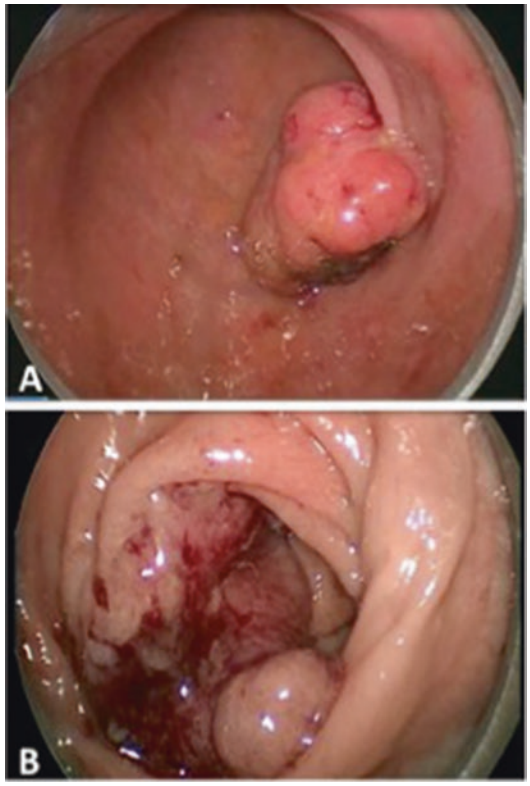

Fig. 4.2 TES resection of malignant rectal lesions: (**a**) Full-thickness curative resection of a 3 cm upper rectal polyp with a small focus of well-differentiated invasive adenocarcinoma (pT1, sm1, LVI). (**b**) Full-thickness for a mid-rectal bleeding T2 rectal cancer in a patient with dementia and major medical comorbidities, not eligible for radical resection of CRT

rectal cancers has been controversial because of unacceptably high rates of local recurrence reported in early series on local excision using TAE and TEM relative to radical resection rates. More contemporary published series, however, have demonstrated that local excision via TEM/TEO may be used with a curative intent in carefully selected cases of T1 rectal cancer with acceptable oncologic outcomes.

Several studies have demonstrated equivalent or superior outcomes of TEM for rectal cancer as compared with other methods of local excision [13, 23]. A recent meta-analysis by Clancy et al. reviewed six studies that compared outcomes from TAE and TEM. Cohorts were highly heterogeneous and included a mix of adenomas and adenocarcinomas as well as tumors of various stages. There were no differences in overall complication rates, but TEM was associated with higher negative margin rates (OR 5.28), reduced specimen fragmentation (OR 0.10), and lower rates of local recurrence (OR 0.25) when compared with conventional transanal excision [15]. However, studies included in this meta-analysis were retrospective, with varying definitions of specimen fragmentation and local recurrence. Although randomized studies comparing local excision techniques are lacking, superior oncologic outcomes with TEM are presumably secondary to the better visualization and more precise dissection that can be accomplished with this approach as compared to TAE. Despite this evidence, TAE is still more commonly used than TEM or TAMIS in many centers because of lack of specific training in TES, low volume of cases, and higher costs related to these procedures [13].

Although originally developed to treat benign disease, indications for TEM have expanded over the last 30 years to include the curative treatment of rectal adenocarcinoma via full-thickness endoscopic excision in select cases. Selection of appropriate tumors for local excision rather than radical resection remains a topic of controversy [24–27]. Unacceptably high local recurrence rates in heterogeneous cohorts treated with TEM alone are still quoted, despite their inherent biases. These earlier retrospective case series reported mixed data from TAE and TEM cohorts and did not use current staging modalities including pelvic MRI. Further, T1 tumors were not sub-analyzed based on histopathologic features that are now known to be of prognostic significance for lymph node metastasis and local recurrence. More contemporary TEM series have demonstrated comparable oncologic outcomes in select cohorts with low-risk T1 tumors relative to radical resection with TME [28]. Authors have adopted standard preoperative staging and detailed pathologic review in order to identify patients with very low risk of occult nodal disease who would in effect likely be overtreated by radical surgery, thus incurring unnecessary morbidity. These carefully selected T1 rectal tumors can usually be safely offered

TEM alone as curative therapy. Moreover, there is mounting evidence to support the potential use of TEM in combination with adjuvant or neoadjuvant chemotherapy for more advanced lesions, when carefully selected [29, 30].

Indications for TES

Benign Disease

TEM was originally developed as an alternative minimally invasive endoscopic approach for rectal adenomas and is currently the preferred approach to resect large or carpeting adenomas that cannot be removed via conventional colonoscopy, particularly in centers that do not use endoscopic mucosal resection (EMR) or endoscopic submucosal dissection (ESD) techniques [13, 24, 25]. In such cases, when an underlying malignancy is not suspected, TEM with submucosal dissection can be used in a manner similar to endoscopic submucosal dissection, in order to avoid large full-thickness rectal defects [31, 32]. TEM is also commonly used in the setting of incomplete resection by piecemeal polypectomy or EMR, when a focus of high-grade dysplasia or intramucosal adenocarcinoma with unascertainable or positive deep margins of resection is discovered upon pathology review. In such cases, full-thickness excision of the polypectomy scar by TEM, TEO, or TAMIS is not only diagnostic of any residual tumor or more advanced disease but also therapeutic, as it achieves definitive resection of the lesion [33]. TEM has also been used for a variety of other tumors including early-stage rectal carcinoid, GIST tumors, and presacral tumors, as well as other benign conditions including repair of complex rectourethral and rectovaginal fistulas, stricturoplasty, and repair of colorectal anastomotic complications [34].

T1 Rectal Cancer

Selection of appropriate patients for treatment of rectal cancer with TES alone remains a topic of controversy. Of particular concern are the overall high rates of local recurrence following TEM for unselected T1 tumors, with some early studies reporting rates of local recurrence as high as 26% [35]. Such unacceptably high rates of local recurrence have driven efforts to identify risk factors for lymph node involvement and local recurrence of T1 rectal tumors and better identify T1 tumors that may be suitable for excision by TEM.

Several studies have sought to determine histopathological risk factors for local recurrence. One of the most important risk factors identified has been the degree of submucosal invasion. As described by Kikuchi et al., T1 lesions can be further classified by the level of penetration of tumor into the submucosa, with sm1 representing invasion into the upper third, sm2 into the middle third, and sm3 into the deepest third [36]. The depth of submucosal invasion according to this classification is predictive of local recurrence following TEM, with depth greater than sm1 being highly predictive of local recurrence [37]. In one cohort of 48 patients who underwent TEM for T1 cancer, 10.4% experienced local recurrence at a median follow-up of 54 months. Of these, none of 26 patients with sm1 lesions developed recurrence, while 5 of 22 patients with sm2–sm3 lesions recurred. This suggests that T1 sm2–sm3 lesions may behave more like T2 tumors and are not suitable for treatment with TEM alone. This finding is not surprising given that the degree of submucosal invasion is highly associated with the likelihood of positive lymph nodes, with sm1 lesions having a 0–3% chance of lymph node positivity, whereas T1 sm2–sm3 and T2 lesions have 15–25% lymph node positivity [38].

Additional important histopathologic risk factors for local recurrence following local excision include poor differentiation grade, lymphovascular invasion (LVI), positive resection margins (R1 resection), large tumor size, and the presence of tumor budding [39]. Doornebosch et al. have reported on the importance of tumor size in predicting local recurrence [40]. Out of 62 patients with T1 tumors, the overall 3-year local recurrence following TEM was 31%, with significantly higher local recurrence for tumors larger than 3 cm relative to tumors smaller than 3 cm (39% versus 11%). Local recurrence was lowest

in the subgroup of tumors less than 3 cm with no evidence of sm3 submucosal invasion (7%).

Tumor budding refers to the presence of small discrete clusters of tumor cells (less than five cells) at the invasive tumor edge [41]. Tumor budding has been consistently demonstrated in multivariate analyses to be an independent adverse prognostic factor associated with local recurrence and metastases, as well as significantly worse overall and disease-free survival in colorectal cancer [42]. For submucosally invasive colorectal carcinomas that are candidates for endoscopic resection by EMR or ESD, several large studies have shown tumor budding to be an independent prognostic factor associated with lymph node metastases, local recurrence, and cancer-related death [43]. In a series of 251 submucosally invasive colorectal carcinomas that were ultimately resected using radical resection, high tumor grade, LVI, and tumor budding were the three factors independently associated with lymph node metastases [44]. Compared to patients without any of those risk factors, patients with 1, or 2–3 of those risk factors, had a significantly higher rate of nodal metastases (1% versus 21% versus 36%). This suggests that local excision with polypectomy or TEM with negative resection margins would be sufficient treatment for early T1 colorectal carcinoma with no such risk factors [44, 45]. In the series of 62 T1 rectal cancers resected using TEM by Doornebosch et al., the 3-year local recurrence for tumors less than 3 cm without budding was 10% compared with 38% in tumors greater than 3 cm and with budding [40].

With respect to current consensus and guidelines for the management of early rectal cancer, the 2015 NCCN guidelines currently recommend TEM as an alternative approach for the management of select T1 cancer [46]. According to these guidelines, adenocarcinoma that is to be treated with TEM should have no radiographic evidence of lymph node involvement based on preoperative endorectal ultrasound (ERUS) and/or pelvic MRI, be less than 3 cm in diameter and less than 30% of the rectal circumference, be well to moderately differentiated, and be within 8 cm of the anal verge. These guidelines are based on several recent series that have reported local recurrence rates following TEM of T1 rectal cancers selected using the above selection criteria comparable to those following radical resection. Despite this evidence, there remains considerable controversy with regard to whether TES is a valid alternative to TME for T1 cancer. For example, in a review of 11 national or international guidelines on management of rectal cancer, only eight recommended the use of TES in the treatment of low-risk early rectal cancer [47].

This debate is particularly relevant given the increasing adoption of EMR and ESD for en bloc resection of superficial colorectal cancer (intramucosal adenocarcinoma or T1 sm1 cancers), which has been associated with good short- and long-term oncologic outcomes [25, 48, 49]. In a recent European Association for Endoscopic Surgery (EAES) consensus statement on early rectal cancer, full-thickness excision down to the mesorectum was considered the procedure of choice in order to achieve R0 en bloc resection for T1 tumors determined preoperatively to be well to moderately differentiated, without lymphovascular and perineural invasion, less than 4 cm in diameters and involving <30% of the rectal wall circumference [50]. With regard to ESD, the EAES consensus quoted two recent studies, including one which retrospectively compared 30 ESD and 33 TEM patients for resection of non-polypoid rectal mucosal adenocarcinomas or submucosally invasive adenocarcinomas. No significant differences were noted in en bloc resection rates or R0 resection rates (96.7% versus 97%), procedural or postoperative complications, or need for additional treatment such as radical resection or adjuvant treatment. ESD was associated with shorter operative time and length of hospital stay, and no local recurrence or distant metastases were noted over the study period [48].

T2 Rectal Cancer and Locally Invasive Tumors

While TEM, TEO, and TAMIS are considered acceptable alternatives for curative resection of carefully selected T1 rectal tumors, TES as a

unimodal treatment for T2 or T3 cancer—outside of the palliative setting—is considered oncologically inadequate, due to the higher rates of lymph node metastasis, ranging 12–28% and 36–66% in T2 and T3 disease, respectively [16]. In an early study, Lee et al. retrospectively evaluated 17 patients treated with TEM and 83 patients treated with radical resection for T2 lesions [51]. No patients received adjuvant therapy. Local recurrence was 19.5% in the TEM group as compared to 9.4% in the radical surgery group ($p = 0.035$), although disease-free survival was similar in the two groups. Borschitz et al. reviewed their experience with 40 T2 patients treated with TEM [52]. Of these, 20 patients underwent TEM alone with no further surgery or adjuvant therapy. Over a median follow-up of 59 months, 35% developed local recurrence and 30% systemic metastases. Among patients with high-risk histopathological features such as poorly differentiated tumors or evidence of LVI, the local recurrence rate was as high as 50%. Local recurrence in the case of T3 disease treated with TEM alone is as high as 100% in some case series [53].

The use of neoadjuvant chemoradiation therapy (CRT) prior to full-thickness TEM excision of high-risk T1, T2, and even more advanced rectal cancers, specifically in patients demonstrating clinical downstaging during chemoradiation, has shown particular promise as an alternative treatment strategy to radical rectal cancer resection with TME. Lezoche et al. recently published long-term results from a randomized control trial of patients with preoperatively staged T2 N0 tumors on the basis of ERUS and/or pelvic MRI [30]. A total of 100 patients who underwent neoadjuvant treatment were then randomized to undergo either TEM or laparoscopic TME. At a median follow-up of 9.6 years, the local recurrence rate in the TEM group was comparable to that of the radical surgery group (6% versus 8%, respectively). Moreover, complications and morbidity were lower in the TEM group. Other groups, however, have cautioned early adopters of this strategy about the high incidence of wound-related complications noted in radiated patients undergoing TEM excision of residual tumors or scars. Complications include rectal wound dehiscence which has been associated with severe and refractory pain [54].

Most recently, advocates of organ-preserving strategies have gone one step further and investigated the outcomes of non-operative management of rectal cancers that have demonstrated complete clinical regression following neoadjuvant therapy. This so-called watch-and-wait approach has been evaluated by Dr. Habr-Gama's group in 70 patients with T2 to T4, N0 to N2 rectal cancers without evidence of metastases. Intensive chemoradiation achieved a 68% rate of complete clinical response 10–12 weeks following completion of treatment, as demonstrated by the lack of gross evidence of residual tumor or other mucosal irregularity on endoscopy or imaging following CRT [55]. These patients were subsequently observed and a sustained complete clinical response was observed in 51% of the entire cohort at 3-year posttreatment. The remaining 49% with evidence of recurrent disease underwent immediate or salvage surgery with either TEM or radical surgery. Several European series have corroborated the findings from the Habr-Gama group [29, 56, 57]. With more aggressive CRT regimens, the rates of complete clinical response have surpassed the historical 20% rate, although this has occurred at the expense of increase toxicity and possibly overtreatment early rectal tumors.

While the possibility of multimodal treatment with chemoradiation and local excision for T2 lesions shows promise, current NCCN guidelines recommend that this treatment regimen be used only in the experimental setting [46]. While not currently indicated for curative intent, TEM with or without chemoradiation is still frequently used as compromised or palliative treatment for more advanced lesions in patients who are considered medically unfit to undergo radical resection using either an open or laparoscopic approach. Palliative treatment with TEM is also pursued in those who refuse surgery that could result in permanent colostomy.

Tumor Location and Tumor Size

Prior recommendations considered tumor distance greater than 8–10 cm from the anal verge to be a contraindication to TEM, particularly for anterior tumors of the upper rectum, due to the increased risk of peritoneal entry during full-thickness resection [58]. Inadvertent peritoneal entry during full-thickness TEM excision was previously considered to be a complication requiring immediate conversion to laparotomy with low anterior resection or fecal diversion in order to mitigate the risk of leak and infection [59, 60]. From an oncologic standpoint, peritoneal entry during TEM excision of a rectal tumor was also thought to increase the risk of tumor cell spillage and thus the risk of peritoneal tumor implants [61]. Several contemporary studies from experienced TEM operators have demonstrated that peritoneal entry occurred more commonly during full-thickness resection of lesions located in the upper rectum, anteriorly or laterally along the rectal wall [62–64]. These studies showed that in experienced hands, peritoneal defects could be sutured closed transanally without increase in morbidity. Finally, several studies have demonstrated no adverse short or long-term oncologic outcomes in patients in whom peritoneal entry occurred during TEM excision of rectal tumors [61, 65]. Based on these studies, tumor location 10 cm or more from the anal verge is no longer considered a contraindication to TEM surgery, as long as full-thickness suture closure of rectal defects can be achieved transanally by experienced operators [62, 63, 65–67]. It is important to note that with respect to more complex rectal lesions, the TAMIS published experience with upper rectal lesions is limited, with only three small series reporting on seven cases of peritoneal entry during TAMIS for upper rectal tumors, with conversion to laparoscopy or laparotomy required in six out of seven cases. This has raised the concern that shorter TAMIS platforms may not be adequate to perform full-thickness resection for high-risk rectal tumors [20, 22, 68]. Overall, only lesions within reach of the 15–20 cm rigid proctoscope, and otherwise amenable to resection with TEM, should be considered or full-thickness endoscopic excision.

At the other extreme end of the rectum, TAMIS platforms do not permit access to rectal polyps located within 4 cm of the anal verge [69]. For lesions partially or entirely located within the distal 4 cm of the anorectal canal, the TEM and TEO platforms can often be pulled back maximally to permit exposure without losing excessive pneumorectum. This is in contrast to TAMIS where resection must be combined with a standard TAE approach for the distal-most dissection.

With respect to rectal tumor size, near-obstructing, near-circumferential, and circumferential tumors constitute a contraindication for transanal endoscopic resection with TES. This is in large part because of the difficulty encountered in removing bulky lesions intact with clear margins, suturing large defects with the TEM instrumentation, as well as high risk of rectal stenosis or incomplete closure with this method [26].

Technical Considerations for TES

Preoperative Workup and Staging

Comprehensive preoperative workup is essential in selecting patients who are appropriate candidates for TES as a curative surgical approach. Preoperative assessment consists of complete clinical evaluation including digital rectal examination to assess anal sphincter tone, tumor location with respect to the anal sphincters, and anorectal ring, as well as tumor fixation. Preoperative workup also includes a colonoscopy to evaluate for synchronous lesions and careful pathology review of the biopsied rectal lesion to confirm eligibility for TES. Rigid or flexible proctoscopy is also performed preoperatively by the operating surgeon to accurately determine the distance from the anal verge, tumor size and extent of rectal wall involvement, and orientation along the rectal wall [26, 66]. This assessment is essential in order to assess feasibility of the resection and select the positioning on the operating table.

Standard rectal cancer staging is performed and includes carinoembryonic antigen (CEA) serum levels, CT scans of the chest, abdomen, and pelvis to rule out distant spread, and a pelvic

MRI and/or endorectal ultrasound (ERUS). While the T-stage accuracy of ERUS is largely operator dependent, ERUS is limited in its accuracy in assessing nodal status, with accuracy rates ranging 65–81% [70]. The reported T-stage accuracy of ERUS ranges from 63 to 95% across studies [66]. The accuracy reported in multi-institutional studies is usually lower than that reported in single-institution or single-operator studies, which may relate to variations in equipment as well as the steep learning curve and operator-dependent expertise required to achieve consistency in performance and interpretation of ERUS. Overall, ERUS is relatively less accurate at differentiating between T1 and T2 lesions, with one multi-institutional study reporting only 57% accuracy, as compared with individual studies reporting up to 88% accuracy in identifying T1 lesions with this modality [71, 72]. Despite the accuracy obtained by highly skilled practitioners, a recent study showed that the results of ERUS rarely changed the management plan for patients undergoing TES when used in conjunction with other preoperative staging modalities [73].

Pelvic MRI has supplanted ERUS as the preferred modality for rectal cancer staging. Although standard MRI imaging has comparably low sensitivity (66% versus 67%) and specificity (76% versus 78%) for lymph node assessment, it provides assessment of the circumferential radial margin (CRM), as well as detailed measurements of the tumor relative to sphincters, prostate, vagina, and even the peritoneal reflection [74]. Recent studies have highlighted 3 Tesla MRI imaging as a promising technology to improve nodal staging in rectal cancer. This technology may provide morphologic details beyond nodal size, which is not a reliable predictor of lymph node involvement. When nodal size is combined with other characteristics such as spiculation, indistinct borders, and heterogeneity of internal structure, great accuracy in predicting lymph node involvement may be achieved. In one study that investigated 437 lymph nodes in 42 patients, the sensitivity and specificity for identifying positive nodes were 85% and 97%, respectively, when using 3 Tesla MRI [75]. There is hope that accuracy of preoperative staging will continue to improve with new developments in radiographic technology [66].

Instrumentation

The original transanal microsurgery platform was developed by Gerhard Buess with support from the Richard Wolf Company (Tubingen, Germany). It consists of a rigid beveled proctoscope, 4 cm in diameter, with two lengths (12 and 20 cm) to allow for ease of operation in different parts of the rectum (Fig. 4.1a). The rectal lesion is visualized through a binocular stereoscope that allows for 3D visualization of the rectal lesion with up to sixfold magnification. The proctoscope also accommodates three 5 mm channels for specialized instruments that are angled at their tip. The 20 cm TEM proctoscope is the longest transanal platform commercially available, providing access to the upper rectum and even the rectosigmoid colon. The narrow diameter and rigidity of the metal proctoscope complicates instrument maneuvering through the platform and limits hand movement of the surgeon and instrument separation, resulting in collisions and crossing of instruments. The operating surgeon must rely on rotational movements as opposed to the typical retraction and levering of laparoscopic surgery. For this reason, the specialized laparoscopic tools used in TEM are angled at their tip to facilitate transanal dissection [24].

The system is secured to the operating table with a multi-jointed clamp, creating a stable operating platform. The scope is inserted through a dedicated port built onto the platform, which provides a stable view during dissection. The Wolf TEM setup includes its own combined pump and insufflation system to maintain consistent distention of the rectum, even during smoke evacuation and fluid suctioning [76]. The proctoscope has a detachable faceplate that provides an airtight seal and allows insufflation of the rectum. Pneumorectum is typically accomplished with pressures of 8–16 mmHg, although pressures as high as 20 mmHg are described to maintain adequate visualization in the face of rectal collapse [20].

The transanal endoscopic operation (TEO) platform, from Karl Storz GmbH (Tuttlingen, Germany), has been modified from the original TEM platform to allow for use with a 5 mm laparoscopic camera (Fig. 4.1b) [25]. This system also provides a 4 cm beveled rigid proctoscope that comes in two lengths (7.5 and 15 cm), with a faceplate with three ports in addition to the dedicated camera port (12, 5 and 5 mm), that accommodate conventional laparoscopic instruments. The system also includes an articulated proctoscope holder to secure the system to the operating table. Insufflation is provided with a standard CO_2 insufflator and tubing, and the scope is compatible with the standard laparoscopic camera and laparoscopic tower. The TEO system does not have a built-in system for smoke evacuation, which is achieved by standard laparoscopic suctioning or venting through small valves on the platform itself. This system is lower in cost than the more specialized Wolf TEM system and seeks to decrease the operating room setup time and lessen the learning curve for TEM with the use of more familiar laparoscopic equipment [77]. It should be noted that because of the similarity between TEM and TEO rigid metal platforms, recent studies do not necessarily distinguish between the two rigid platforms and may use the terms TEM and TEO interchangeably, or refer to them as TEM or TES rigid platforms.

In 2009, transanal minimally invasive surgery (TAMIS) was described as an alternative minimally invasive endoscopic setup to resect rectal lesions [20, 21]. The original report is described using a single-incision laparoscopic port, typically used for single-incision laparoscopy, and inserting it transanally in combination with a standard laparoscopic camera, scope, and instruments, to perform submucosal or full-thickness rectal resection. Since this first report, two commercial devices, the GelPOINT Path (Applied Medical, Rancho Santa Margarita, CA) and SILS Port (Covidien, Mansfield, MA), have been FDA-approved for the use in TAMIS (Fig. 4.1c, d). Other single-incision laparoscopic platforms have been used for TAMIS, including several platforms that are not currently commercially available in the United States. One group described using a simpler and cost-effective transanal access device consisting of a surgical glove assembled onto a wound retractor inserted transanally, in combination with laparoscopic trocars and instruments [78]. TAMIS has the advantage of disposable equipment that is more widely available, less expensive, and faster to set up in the operating room than the TEM or TEO platforms. The disposable port will sometimes be sutured to the surrounding perianal tissue to avoid dislodgement [21]. The available devices have three channels that can accommodate standard laparoscopic instruments ranging from 5 to 15 mm, including both rigid and flexible-tipped scopes [22]. The use of extra-long straight laparoscopes, deflectable-tip laparoscopes, and conventional endoscopes can help overcome some of the limitations of maneuvering a rigid scope through TAMIS platforms and reduce instrument collision [79]. High definitions and 3D imaging can also be incorporated to improve image quality and depth of perception. In addition, articulating laparoscopic instruments that were designed for the use in single-incision laparoscopy can be incorporated in TEM, TEO, and TAMIS procedures in an effort to facilitate reaching difficult angles.

Recently, high-flow CO_2 insufflation units (Olympus, Center Valley, PA and Stryker, San Jose, CA) have been used in conjunction with TEM/TEO and TAMIS platforms for active smoke and mist evacuation. These insufflators provide automatic smoke evacuation and high-speed CO_2 insufflation that responds quickly to CO_2 leaks resulting from suctioning and maintaining a stable pneumorectum and stable field of view. The Airseal® insufflation system (SurgiQuest, Inc., Milford, CT, USA) uses a cannula though which a continuous flow circuit occurs, evacuating CO_2 and smoke, recirculating filtered and high-pressure CO_2, and maintaining a stable pneumorectum. The 5–12 mm cannula can only be used through TAMIS platforms and has been described as a useful tool to maintain a stable pneumorectum [80].

Robotic technology has recently been combined with TAMIS, with the first clinical case of robotic transanal endoscopic resection reported in 2012 [81]. A handful of small case series have

since reported preliminary outcomes of robotic transanal endoscopic resection of rectal lesions using a glove port technique, which allows for greater working angles for the robotic arms [82, 83]. Despite a cumbersome perianal setup, and increased costs associated with robotic procedures, the preliminary data demonstrates feasibility of this approach with proposed advantages of ergonomically favorable dissection and suturing.

Preoperative Preparation and Operating Room Setup

Patients typically undergo full mechanical bowel preparation and/or administration of enemas prior to surgery in order to clear the rectum and to allow for adequate visualization. Some surgeons will use enemas or full mechanical bowel preparation selectively, based on anticipation of the possibility of full-thickness excision with peritoneal entry. Most surgeons also use standard perioperative parenteral antibiotic prophylaxis as well as thromboembolic prophylaxis. General anesthesia with complete muscle paralysis is usually recommended for TES in order to avoid abdominal wall contractions during procedures and minimize CO_2 leakage. One recent case report and one case series have demonstrated the safety of performing TAMIS under spinal anesthesia [69, 84].

Regarding patient positioning, patients are either placed in the supine, prone jackknife, or lateral decubitus position (Fig. 4.3). Standard

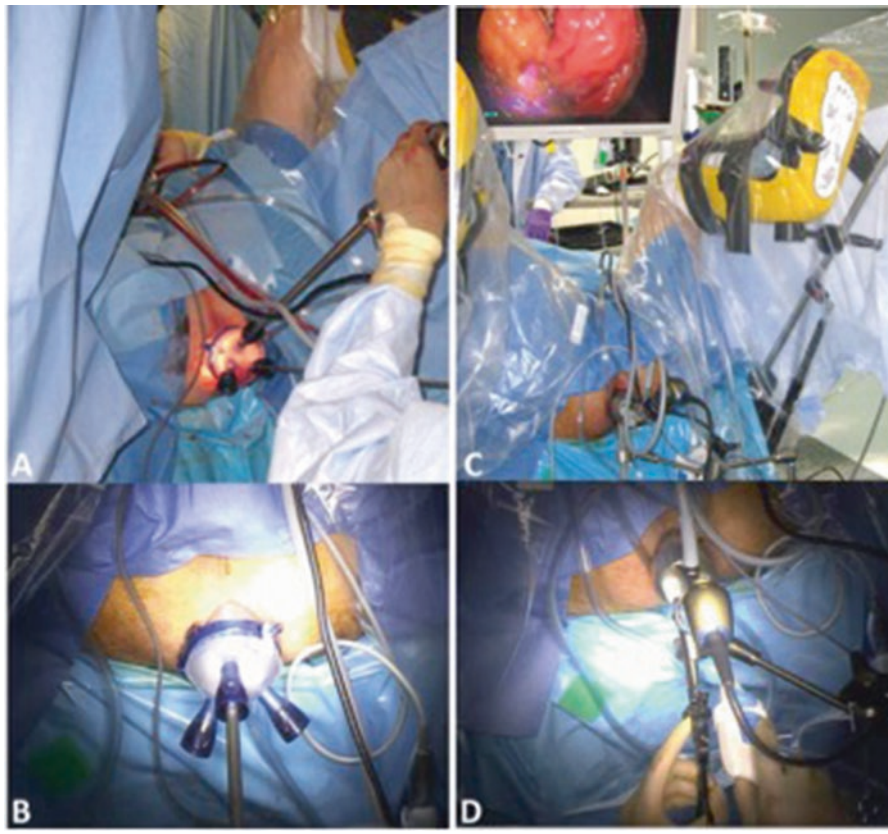

Fig. 4.3 TES setup. The patient is positioned in lithotomy position and the monitor is placed in between the patient's legs for improved ergonomics. The TAMIS platform is inserted transanally and procedures are performed by an operator and an assistant to hold the camera (**a**, **b**). The TEM/TEO rigid platform is inserted transanally, and the platform is secured to the OR table using a U-shaped platform holder. The procedure is performed by a single operator (**c**, **d**)

operating tables are used in combination with leg stirrups or, alternatively, split leg operating tables can be used. The TEM and TEO platforms traditionally require rectal lesion to be in a dependent position for ease of operation. This preference is based on the original design of both platforms, which are beveled at their tip, with the angled camera fixed at the superior aspect of the platform. Thus, for anterior rectal lesions, the patient is typically placed in the prone jackknife position, whereas for posterior lesions, the patient is placed in dorsal lithotomy. For lateral lesions, the traditional teaching is to place patient in the lateral decubitus positioning. Most experienced TEM and TEO surgeons will perform these procedures routinely in dorsal lithotomy regardless of the location of the lesion [76]. TAMIS is usually performed in the dorsal lithotomy position, and the use of a deflectable-tip scope and articulating instruments greatly facilitates exposure and visualization during these procedures [20].

One relative indication for placing patients in prone position includes preoperative anticipation of peritoneal entry during full-thickness excision of high-risk rectal lesions [65]. High-risk lesions for peritoneal entry include anterior and lateral lesions located in the upper rectum or rectosigmoid, as well as circumferential or near-circumferential lesions [61–64]. Peritoneal entry through large rectal wall defects can result in the rapid accumulation of CO_2 into the abdominal cavity and collapse of the rectum. In such cases, closure of the rectal wall defect can be very difficult due to poor exposure. Preemptively positioning the patient in prone position prior these cases limits the amount of CO_2 leakage into the abdominal cavity and helps maintain a stable pneumorectum throughout the case [65].

Dissection

Following patient positioning, transanal platform insertion, and CO_2 distention, the lesion is localized and dissection is initiated (Fig. 4.4). By convention, the lesion is scored circumferentially with electrocautery marks to map out the planned resection margins. In the case of suspected or proven rectal invasive adenocarcinoma, this is followed by full-thickness circumferential dissection through the rectal wall until the mesorectum, or perirectal fat is reached. A 5–10 mm resection margin is usually achieved in order to maximize the likelihood of R0 resection [25, 26, 85]. Submucosal and full-thickness dissection is traditionally accomplished with monopolar cautery, using conventional reusable laparoscopic hooks, spatulas, or articulating disposable instruments based on surgeon's preference and availability. Bipolar energy devices and ultrasonic shears can also be used to improve hemostasis and reduce dissection time. Hemostasis can also be achieved using laparoscopic clips or sutures. Some surgeons routinely excise a portion of the mesorectum attached to the segment of rectum removed in order to increase the chance of including some lymph nodes in their specimen for improved staging. Others have performed rectal sleeve resections for near-circumferential and circumferential rectal tumors. However, more extensive rectal dissection may be associated with higher morbidity, including bleeding, suture line dehiscence and leak, complex perirectal infections, and inadvertent injuries to surrounding organs, as well as postoperative urinary retention [86, 87]. In their series of 196 TEM cases, Guerrieri et al. reported two urethral injuries in male patients which occurred during wide anterior rectal dissection [86]. In addition, wider-than-indicated rectal dissection, including mesorectal dissection, may complicate or compromise the safe performance of salvage TME if warranted based on final pathology results from the TEM procedure. Scarring and inflammation form along the mesorectal plane after prior rectal dissection, which can significantly impact TME procedures.

Following full-thickness dissection, the specimen is oriented with sutures and mounted on a hard surface with pins or sutures for accurate pathologic assessment of resection margins (Fig. 4.5).

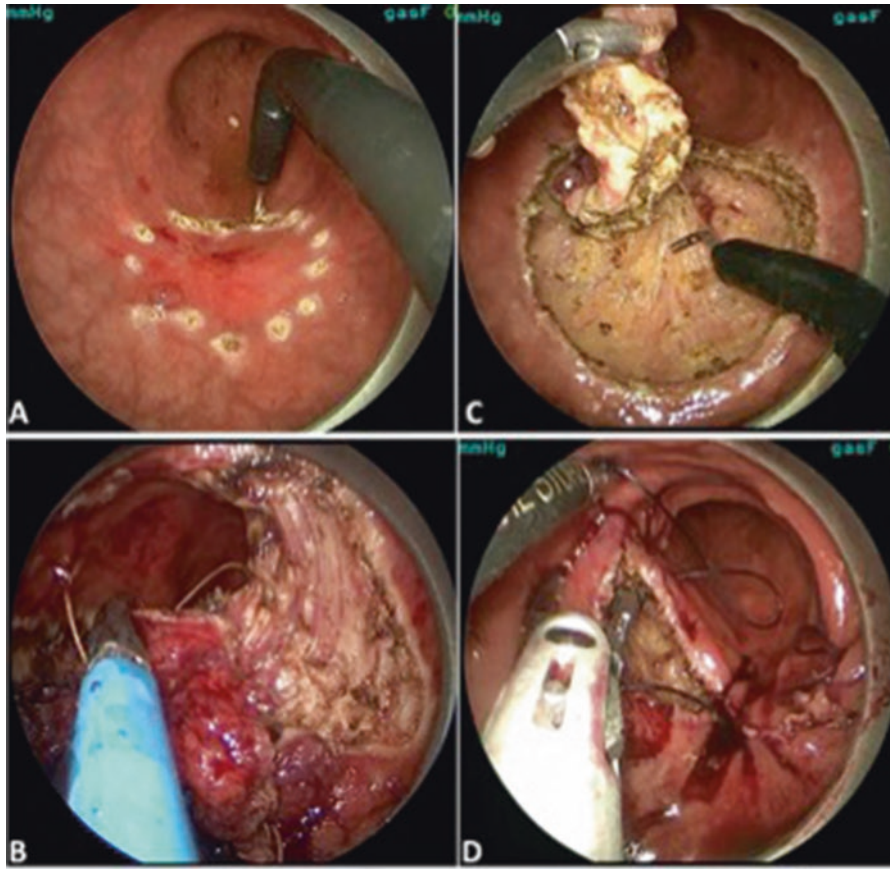

Fig. 4.4 Procedural steps for TES. Following setup and insufflation of the rectum, the lesion is scored with monopolar cautery circumferentially (**a**). The lesion is dissected endoscopically either along the submucosal plane (**b**), or full-thickness, down to the mesorectum or perirectal fat (**c**). Full-thickness rectal defects are closed with sutures (**d**)

Loss of Pneumorectum and Peritoneal Entry

As previously mentioned, peritoneal entry is not an uncommon occurrence during TEM and is no longer considered a complication. Overall, the reported rate of peritoneal entry during TEM ranges from 0 to 32.3% [62, 88] but across large contemporary series with more than 300 patients, that rate is lowered to 5–10.7% [89, 90]. To date, only three TAMIS series of 32–75 patients have reported a 2–9.4% incidence of peritoneal entry [20, 22, 68]. Entry into the peritoneal cavity, with subsequent difficulty maintaining adequate pneumorectum and visualization, presents a considerable technical challenge to the surgeon (Fig. 4.6). For this reason, surgeons will routinely place patients with high anterior lesions, where the risk of accidental peritoneal entry is greatest, in the prone position to mitigate the impact of CO_2 leakage into the peritoneal cavity on successful closure of rectal wall defects [65]. This allows the surgeon to minimize gas losses and maintain a stable pneumorectum. Other strategies to maintain pneumorectum include complete muscle paralysis, minimizing CO_2 leakage, increasing the pressure of CO_2 insufflation, and decompressing the pneumoperitoneum with a Veress needle or trocar [20]. Over time, and in experienced centers as demonstrated in

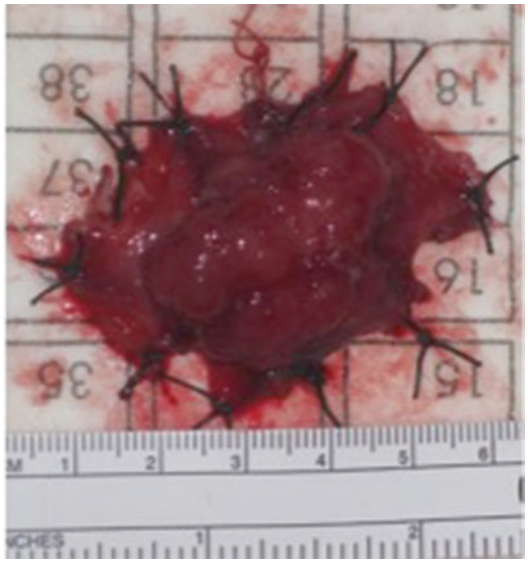

Fig. 4.5 Orientation of the TES specimen. Following exteriorization of the resected specimen, it is oriented with sutures for accurate pathologic assessment of all resection margins

large contemporary TEM series, conversion rates following peritoneal entry have steadily decreased, with conversion rates ranging from 0 to 40% but averaging 10% or less [65]. Interestingly, among the three TAMIS series that reported a total of seven cases of peritoneal entry during TAMIS for upper rectal tumors, six required conversion to laparoscopy or laparotomy from inability to effectively close the rectal wall defect. This may reflect the long learning curve required for managing these complex rectal lesions, and the currently small experience with TAMIS to date. But it may also reflect technical limitations of shorter TAMIS platforms, which do not always permit adequate retraction and exposure of the proximal rectum.

With regard to the morbidity associated with peritoneal entry, several studies have reported no increase in the rate of postoperative complications relative to TEM cases without peritoneal entry [61–65]. Notably, there has been no demonstrated

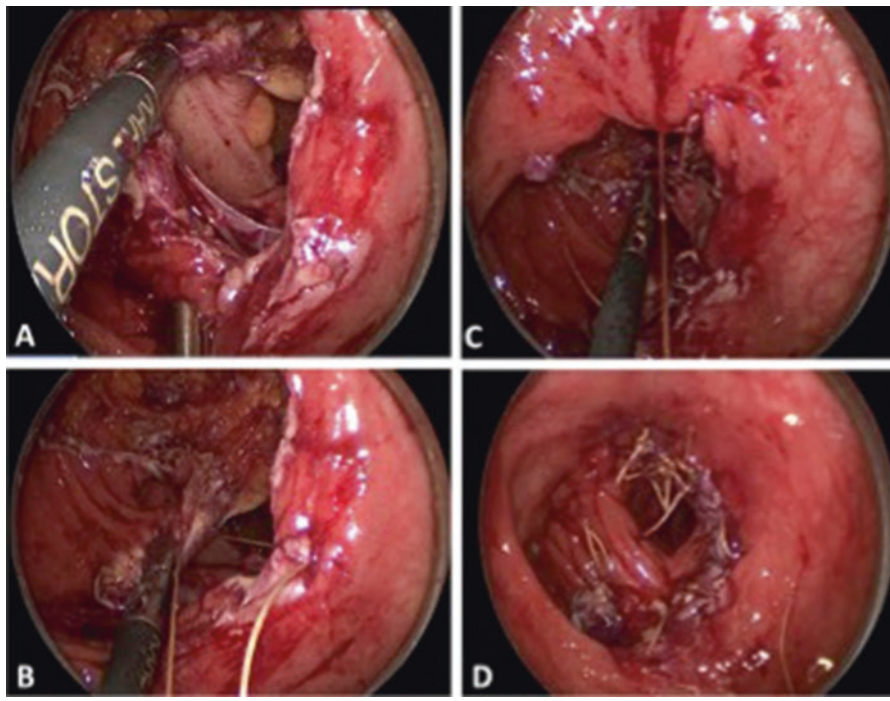

Fig. 4.6 Peritoneal entry during TES. Full-thickness resection of a rectal lesion located anterolaterally in the upper rectum results in peritoneal entry with visualization of the rectosigmoid (**a**). The adverse consequences of CO_2 leakage into the abdominal cavity are mitigated by the prone position (**b**). The rectal defect is closed using interrupted and continuous absorbable sutures without adverse outcomes (**c**, **d**)

increased risk of pelvic sepsis or abscess formation following peritoneal perforation. Fewer studies have evaluated the oncologic impact of peritoneal entry during TEM performed for rectal cancer. Morino et al. followed 13 patients with rectal adenocarcinoma in whom peritoneal perforation occurred during TEM [65]. At a median follow-up of 48 months (range 12–150), no cases of liver or peritoneal metastasis occurred. Two patients with T2 and T3 tumors developed local recurrence and subsequently died of lung metastases.

Rectal Defect Closure Techniques

Many techniques and devices can be employed for closing rectal wall defects during TES. In some select cases, particularly for low or posterior rectal lesions, or in cases of partial-thickness excision, the rectal wall defect can be left open, as there is some evidence that leaving the defect open does not increase complications for such lesions [91]. In a recent study by Hahnloser et al., 35 patients underwent TAMIS for lesions located at a mean of 6.4 ± 2.3 cm from the anal verge, with the rectal defect left open. This group included both full-thickness and partial-thickness defects. No increase in complications was noted between this group and the 38 patients in whom rectal defects were closed [68]. Of note, only 6% of the 35 open rectal wall defects were located anteriorly compared to 28% of 38 closed rectal wall defects. Clearly, for larger, full-thickness lesions, and in particular for high-risk lesions where peritoneal entry has occurred or is suspected, complete and airtight closure is required to decrease the risk of leak and intra-abdominal abscess formation [76, 92]. Prior to closure, particularly in the event of an incomplete bowel preparation and ongoing fecal contamination of the rectal wound, the area can be irrigated with dilute iodopovidone. Most TES surgeons close the defect with running or interrupted absorbable monofilament sutures. A variety of suture materials are described including glycolide and trimethylene carbonate (Maxon), polydioxanone (PDS), and polyglactin (Vicryl) [76]. Intracorporeal suturing devices and techniques can be used, including extracorporeal knot tiers. In order to overcome the technical difficulty of knot tying through a transanal rigid platform, the TEM instruments include an angled needle holder, and sutures can be secured with specialized silver bullets (Richard Wolf, Knittlingen, Germany). Alternatively, a V-loc barbed absorbable suture (Covidien) can be used to avoid having to make a knot. Finally, disposable automated suturing devices can facilitate knot tying including the Endo Stitch™ device (Covidien) and the Cor-Knot device (LSI Solutions, Victor, NY). If peritoneal entry occurs, some authors advocate closing the defect in two layers [76]. In cases where there is concern that the closure is not airtight, further investigation with a gastrografin enema would be recommended in order to rule out a leak.

Postoperative Management and Follow-Up

Following submucosal and low-risk full-thickness TES cases, patients are routinely discharged home on the same day [93]. Patients who have undergone full-thickness excision with peritoneal entry, or patients with extensive medical comorbidities, are typically admitted overnight for observation. Administration of postoperative antibiotics is not routinely recommended, nor is routine imaging, in the absence of clinical indications.

There are no specific guidelines for postoperative surveillance specific to patients who have undergone TES for rectal adenocarcinoma [47]. Current practice follows standard NCCN guidelines for rectal cancer surveillance, including clinical evaluation, CEA, and endoscopic surveillance by flexible sigmoidoscopy every 3–4 months for the first 3 years and every 6 months until year 5 [26, 94]. Other standard testing includes yearly CT scans until year 5 as well as surveillance colonoscopy at 1 year followed by 3 years post-resection. There is no NCCN guideline for surveillance pelvic MRI. However, following TES excision of T1 rectal tumors, particularly T1 tumors with borderline or high-risk features that were or were not treated with TME or adjuvant chemoradiation, most surgeons will recommend bi-annual or annual pelvic MRI for 5 years to rule out locoregional pelvic recurrence.

Outcomes of TES

Operating Time

The average operating time reported in large TEM and TEO case series for rectal neoplasms ranges from 70 to 95 min [28, 53, 86, 95–98]. Some smaller series have reported mean operative times as low as 45 min [35, 99]. Variations in OR time relate to size of the lesion, submucosal versus full-thickness dissection, distance from the anal verge, closure versus non-closure of rectal defects, complexity of the rectal defect closure, and management of intraoperative complications such as bleeding, CO_2 leakage, and peritoneal entry. Additionally, there is a clear learning curve for TEM, with possible improvement in operative time as the surgeon becomes more experienced with the equipment [90].

A small randomized study by Serra-Aracil et al. comparing TEM and TEO in 34 eligible patients with rectal lesions found no differences in lesion characteristics, postoperative morbidity, and final pathology between the platforms used. Although there was a trend toward shorter operative time with TEO, including time to mount the equipment and perform the excision and suture closure, this difference was not statistically significant [98].

Reduced operating time from shorter operative setup and faster procedure completion are commonly cited as one of the main advantages of TAMIS over TEM/TEO as reported by its many adopters. The initial report of TAMIS reported a mean operative time of 86 min which has progressively decreased with a recent series reporting mean operating time of 57 min [21, 100]. Another series reported a median operating time as low as 45 min [69]. To date, no prospective comparative or randomized trial of TEM, TEO, and TAMIS procedures has been published comparing operating time and other perioperative variables.

Mortality and Morbidity

A major advantage of TES is the improved safety profile relative to TME [51, 101–103]. Mortality is well under 1% across most series, even in patients with multiple comorbidities who are deemed unable to tolerate a radical operation [104]. The overall complication rate following TEM is also relatively low relative to standard colorectal resections, with most complications being minor and transient. Published 30-day morbidity rates range from 6 to 23% in the largest TEM/TEO series with cohorts ranging from 262 to 693 patients [25, 53, 88, 89, 100, 101, 105]. Major complications are noted in less than 10% of cases [13, 76, 106]. The most commonly reported surgical complication following TEM is hemorrhage, which is reported in 1–13% of patients, and is usually managed non-operatively [76]. The most common nonsurgical complication is urinary retention, with incidence reported around 5% on average (range, 5–10%) [53, 89]. Other surgical complications include suture line dehiscence, which can range from minor defects usually managed non-operatively with antibiotics and bowel rest, to major defects with leakage and sepsis, requiring return to the operating room for washout and fecal diversion. Additional major TES complications include perirectal and presacral abscess, fistulas, and rectal stenosis. Rare complications include organ injury, with two cases of urethral injury reported following TEM resection of anterior-based lesions [107]. In the largest multicenter series published to date, among 693 combined TEM and TEO cases, conversion to conventional TAE or abdominal procedures was required in 4.3%, and the 30-day morbidity was 11.1%, with hemorrhage and suture dehiscence being the most common surgical complications and urinary tract infections being the most common nonsurgical complication [90].

The relatively low morbidity following TEM procedures is reflected in the short hospital stay and minimal postoperative analgesic requirement. Up to 50% of patients undergoing TEM for rectal cancer are safely discharged on the day of surgery as reported in several recent series [93]. When patients are admitted for observation, average length of hospital stay ranges from 0 to 5 days, with reasons for admission ranging from management of major medical comorbidities to observation following complex cases involving peritoneal entry [24].

In the more limited literature on TAMIS, the published incidence of postoperative complications range from 0 to 25%, with bleeding and urinary retention reported as the most common complications [22]. One review of published TAMIS outcomes between 2010 and 2013 reported a total of 29 complications among 367 patients (7.9%) treated for rectal neoplasms [108]. Bleeding occurred in 2.7% of patients and suture dehiscence in 0.5% of patients. There were no deaths reported following TAMIS, and the average length of hospital stay was only 1.9 days. In the absence of comparative studies evaluating rigid metal versus TAMIS platforms, there is no data on differences in morbidity, mortality, or length of stay between approaches.

Functional Outcomes

By virtue of the prolonged dilation of the anal sphincter by the 4 cm wide rigid and semirigid anal platforms, there is some concern that TEM, TEO, and TAMIS procedures might not only transiently impact anorectal function but might cause permanent deterioration in fecal continence, particularly in patients with compromised anal sphincter tone at baseline. Interestingly, while multiple small TEM studies have documented a transient decrease in sphincter resting pressures on anal manometry that was proportional to the duration of the procedure, resting pressures were noted to return to baseline value 12 months postoperatively [109–111]. Other objective functional measurements, such as mucosal electrosensitivity and rectal compliance, were found not to be generally affected [110]. More importantly, changes in resting anal sphincter pressures did not translate into any detrimental effects on continence. Indeed, a majority of patients reported no change and even some improvement in anorectal function following TEM for rectal lesions. In a study of 41 patients who underwent TEM, Cataldo et al. found no significant changes in the Fecal Incontinence Severity Index (FISI) or the Fecal Incontinence Quality of Life (FIQL) scores reported 6 weeks postoperatively relative to preoperative scores [112]. A recent study that longitudinally assessed anorectal function and quality of life score in 102 TEM patients at 6, 12, 26, and 52 weeks postoperatively relative to baseline values found that the general quality of life scores (EQ-5D) was significantly lower at 6 and 12 weeks but returned toward baseline at 26 weeks. Similar to prior studies, anorectal function as assessed by colorectal functional outcome (COREFO) was worse at 6 weeks postoperatively but returned to baseline at 12 weeks postoperatively [113].

Because of the less rigid design of the transanal ports used in TAMIS, the procedure has been hypothesized to potentially result in less damage to the anal sphincter during transanal surgery. On the other hand, there is also concern that functional outcomes might be worse as compared to traditional rigid platform TES because of more extreme movements and stretch allowed by the flexible platform. Thus far, although published data is limited, short-term functional results following TAMIS have been comparable to historical TEM reports. One small prospective study conducted by Schiphorst et al. assessed functional outcomes in 37 patients following TAMIS using FISI score completed at 3, 6, 9, and 12 months relative to preoperative scores [114]. Interestingly, among 17 patients with decreased preoperative fecal continence at baseline, improved FISI scores were noted in 88%, while among 18 patients with normal continence at baseline, no change in FISI scores were noted in 83%, suggesting preserved long-term anorectal function following TAMIS procedures.

Positive Margins and Specimen Fragmentation

Positive resection margins are an important predictor of local recurrence for both benign and malignant rectal lesions and, along with specimen fragmentation, constitute an important metric of the efficacy of local excision including TAE and TEM. There is a clear association between the risk of local recurrence and the rates of positive resection margins for adenomas. Speake et al. reviewed their series of 80 patients

with adenomas treated with TEM and found that no recurrence occurred in patients with negative margins; however, 10% of patients with positive margins recurred [115]. With respect to rectal cancers resected using TEM, positive margin rates range across series from less than 2% to as high as 8.8% [53, 89, 95, 103, 116, 117].

Clancy et al. recently performed a meta-analysis that included six retrospective studies comparing outcomes of TEM versus TAE for indications ranging from adenomas to adenocarcinomas and other pathologies [15]. Of these studies, five compared rates of negative resection margins and specimen fragmentation in a total of 798 lesions, including 439 TEM and 359 TAE cases. Overall, TEM was associated with a significantly higher rate of R0 resection compared to TAE, with an odds ratio of 5.281 ($p < 0.001$). With respect to rectal cancer specifically, one study included in the meta-analysis by Christoforidis et al. retrospectively compared 42 TEM and 129 TAE procedures performed for pT1 or pT2 rectal cancers [23]. A significantly higher rate of positive margin positivity was demonstrated for TAE, with a 16% incidence of positive margins as compared with 2% with TEM. No tumors removed by TEM demonstrated specimen fragmentation, whereas 9% of TAE specimens were fragmented. However, the authors commented that there was a significant difference in location of the tumors in this study, with tumors resected by TAE primarily located in the lower rectum, whereas tumors resected by TEM were generally more than 5 cm from the anal verge.

Across TAMIS series, which are far fewer in number, rates of positive margins have varied but have generally been less than 6% for larger series including both benign and malignant pathologies [20, 22, 68].

Oncologic Outcomes for T1 Rectal Cancer

Published long-term rates of local recurrence for T1 tumors treated with TEM range from 0 to 26% (Tables 4.1 and 4.2) [121]. This is in comparison with local recurrence of 6% or less for T1 tumors treated with radical TME [125]. As previously detailed, wide variations in published oncologic outcomes following TEM reflect heterogeneous selection criteria including histopathological tumor analysis (grade, submucosal extent, size, lymphovascular invasion, tumor budding), staging methods (ERUS, pelvic MRI), surgical techniques used (TAE versus TEM), the use of adjuvant or neoadjuvant CRT, and outcome measures reported (positive resection margins, fragmentation versus en bloc resection,

Table 4.1 Summary of local recurrence rates for series of T1 tumors treated with TEM. Included series reported on at least 40 patients treated with TEM alone

Study	Location	Year	Criteria for TEM	Number of patients	Mean follow-up time (months)	Local recurrence (%)
Mentges [118]	Germany	1997	Primarily G1/2	64	29	4
Floyd [119]	United States	2006	None specified	53	34	8
Borschitz [120]	Germany	2006	G1/2, no LVI, R0 resection	66	74	6
Baatrup [121]	Denmark	2009	None specified	72	Not stated	13
Tsai [53]	United States	2010	Prior excision, metastatic disease	51	54	10
Doornebosch [116]	Netherlands	2010	None Specified	81	Not stated	21
Morino [122]	Italy	2011	None specified	48	54	10
Ramirez [95]	Spain	2011	G1/2, no LVI	54	71	7
Amann [123]	Germany	2012	G1/2, no LVI, R0 resection	41	34	10
Stipa [117]	Italy	2012	R0 resection	86	85	12
Guerrieri [28]	Italy	2014	<3 cm, G1–3, <8 cm from anal verge	110	82	0

Table 4.2 Summary of studies comparing TEM to radical resection for T1 rectal cancer

Author	Year	Study type	Criteria	Number of patients		Follow-up (months)		Local recurrence		5-year overall survival	
				TEM	RR	TEM	RR	TEM	RR	TEM	RR
Winde [124]	1996	Randomized control	Excluded patients >pT1 on final histology, poorly differentiated tumors	24	26	41	46	4.2	0	96	96
Heintz [102]	1998	Retrospective	Tumors were well or moderately differentiated, without lymphovascular invasion	46	34	52		4.4	2.9	79	81
Langer [14]	2002	Retrospective	Excluded poorly differentiated tumors, no limitations on diameter of tumor	20	18	22	34	10	0	100[a]	96.3[a]
Lee [51]	2003	Retrospective	Excluded poorly differentiated tumors, positive margins (R1)	52	17	31	35	4.1	0	100	93
Palma [103]	2009	Retrospective	Excluded poorly differentiated tumors, any evidence of lymphovascular invasion	34	17	87	93	5.9	0	88	82
de Graaf [101]	2009	Prospective	Any pT1 tumor, no limitations on diameter or tumor grade stated	80	75	42	84	24	0	75	77

[a]2-year overall survival

local recurrence, overall survival, etc.). Variance in surgeon experience may also account for differences in outcomes. As previously detailed, in series where T1 tumors were carefully selected based on well-defined histopathological features, local recurrence rates have been shown to approach those of radical surgery with TME. Heintz et al. conducted a retrospective study of all TEM cases performed between 1985 and 1996 and classified T1 tumors as low risk versus high risk, where low-risk features included good to moderate differentiation and the absence of LVI [102]. Using these strict criteria, they were the first to demonstrate a 4.4% local recurrence rate with TEM relative to 2.9% following radical surgery. On the other hand, in the same study, TEM for high-risk tumors was associated with a 33% risk of recurrence following TEM, relative to 18.2% following radical resection. Several similar studies have demonstrated local recurrence rates ranging from 0 to 10% when strict selection criteria for TEM excision of T1 tumors were used [28, 95, 118, 120, 123]. In a prospective series of 66 T1 rectal cancer cases, Borschitz et al. reported similar differences in local recurrence rates when T1 tumors were stratified according to histopathological features following TEM [120]. Local recurrence rates were 6% versus 39% in low- versus high-risk tumors. Another prospective cohort of 110 patients with T1 rectal cancers selected for TEM on the basis of good to moderate differentiation, size less than 3 cm, and distance of 8 cm or less from the anal verge demonstrated no local recurrence at a median follow-up of up to 82 months (range 48–144) [28, 96, 107].

Few TAMIS series have reported on short-term oncologic outcomes given the comparatively recent and limited experience with this approach in rectal cancer (Table 4.3). In a series of 50 TAMIS cases, 1 patient out of 16 patients (6.3%) with pT1 rectal cancer developed a local recurrence over a median follow-up of 20 months [20]. In the largest series of 75 TAMIS cases, 13 T1 rectal cancers were resected with no recurrence at a median follow-up of 385 days [68].

Table 4.3 Summary of data for TAMIS surgery

Study	Year	Number of patients	Port type	Final pathology	Operative time (min)	LOS (days)	Positive margins (%)	Morbidity (%)
Atallah [21]	2010	6	SILS	adenoma (3) pTis (1) pT1 (1) carcinoid (1)	86	1	17	0
Van den Boezen [126]	2011	12 (two converted to TAE)	SILS	adenoma (9) pT1 (1) pT2 (2)	55	1	0	8.3
Barendse [100]	2012	15	SSL	adenoma (7) pT1 (1) pT2(3) carcinoid (1) fibrosis (1)	57	1.5	13	7.7
Lim [127]	2012	16	SILS	pT1 (3) pT2–3 (8) mucocele (1) carcinoid (4)	86	3.0	0	0
Ragupathi [128]	2012	20	SILS	adenoma (14) unspecified malignant (6)	79.8	1.1	5	5
Albert [20]	2013	50	SILS/ GelPOINT	adenoma (25) hyperplastic (2) pTis (1) pT1 (16) pT2 (3) pT3 (3)	74.9	0.6	6	6
Seva-Periera [129]	2013	5 (one converted to LAR)	SSL	pTis (2) pT2 1) fibrosis (1)	52	1	0	25
Bridoux [130]	2014	14	Endorec	adenoma (10) pT1 (3) pT2 (1)	60	4.0	7.1	21
Lee [69]	2014	25	SILS	adenoma (6) pT1 (9) carcinoid (9) GIST (1)	45	3	0	0
Schiphorst [114]	2014	37 (one converted to LAR)	SILS	adenoma (23) pTis (7) pT1 (4) pT2–3 (2)	64	1	16	8
McLemore [22]	2014	32	GelPOINT/ SILS	adenoma (10) pTis (1) pT1 (6) pT2 (4) carcinoid (2) fibrosis (9)	132	2.5	3	25
Gorgun [131]	2014	12	GelPOINT	adenoma (10) pT2 (1) carcinoid (1)	79	1	0	25
Hompes [83]	2014	16 (one conversion)	Transanal glove port, da Vinci robot	adenoma (6) pT1 (2) pT2 (1) pT3 (1) fibrosis (5)	108 (36 min docking)	1.3	13	13
Hahnloser [68]	2015	75	SILS	adenoma (35) pTis (11) pT1 (13) pT2(9) pT3 (1) carcinoid (1) hamartoma (1)	77	3.4	4	19

Table 4.4 Summary of local recurrence rates for series of T2 tumors treated with TEM with or without adjuvant therapy

Study	Location	Year	Treatment Strategy	Number of patients	Follow up	Local recurrence
Lezoche [134]	Italy	1998	TEM + adjuvant RT	20	35	10
Maslekar [104]	United Kingdom	2008	TEM ± adjuvant or neoadjuvant CRT	22	32	18
Baatrup [121]	Denmark	2009	–	47	–	26
Ramirez [95]	Spain	2011	TEM + adjuvant CRT	22	71	9
Allaix [135]	Italy	2012	TEM ± neoadjuvant or adjuvant RT	42	70	22
Stipa [117]	Italy	2012	TEM ± neoadjuvant or adjuvant RT or CRT	38	85	37
Guerrieri [28]	Italy	2014	Neoadjuvant RT or CRT + TEM	185	53	13[a]

Included studies reported on at least 20 patients
[a]This represents both local recurrence and distant metastases

Across 15 TAMIS series including a total of 348 patients, margin positivity rates for lesions ranging from benign rectal lesions to T3 rectal tumors range from 0 to 17%, which is comparable with historical R1 resection rates following TEM, supporting the preliminary conclusion that TAMIS is a likely a safe alternative to TEM for carefully selected T1 lesions [20, 68, 69, 100, 108, 126, 128, 130, 132]. However, large series with longer oncologic outcomes are lacking.

Oncologic Outcomes for T2 Rectal Cancer

With the exception in palliative cases, TES excision of T2 rectal cancer without the use of adjuvant chemoradiation is considered unacceptable, given reports of local recurrence rates as high as 43% in small TEM series [133]. A review of oncologic outcomes following TEM excision of T2 tumors in larger series (Table 4.4) demonstrates local recurrence rates ranging from 5 to 40%, reflecting variations in the use of neoadjuvant or adjuvant CRT and specific regimen used. Overall, the use of adjuvant and/or neoadjuvant treatment in conjunction with local excision of T2 rectal cancers using TEM is associated with a trend toward improved local control. Guerrieri et al. reported outcomes in 88 patients with preoperatively staged T2N0 tumors on the basis of ERUS with or without pelvic MRI [86]. Patients were treated with neoadjuvant therapy followed by full-thickness TEM excision, with nearly 50% tumor downstaging to pT1 or pT0 lesions on final pathology. Over a median follow-up of 81 months, 6% of patients developed local recurrence, 3% developed distant metastases, and overall disease-free survival was 90%. Of note, no recurrent disease occurred in patients who were downstaged or who showed significant downsizing of the tumor on final pathology. Lezoche et al. reported long-term outcomes of the same cohort, and at a median follow-up of 97 months, the local recurrence rate was 5%, and the rate of distant metastases was 2%, with a 93% disease-free survival [96]. In a randomized trial of 70 T2 rectal tumors treated with neoadjuvant CRT followed by either full-thickness TEM or radical surgery, at a median follow-up of 84 months, Lezoche et al. reported no significant differences in local recurrence rates (5.7% versus 2.8% in the TEM and radical resection groups, respectively). There was no difference in overall survival, which was 94% in both groups [30, 136]. These results, as well as those from a number of case series, suggest that neoadjuvant treatment followed by TEM excision may be considered in preoperatively staged and selected T2N0 low rectal tumors. Using this strategy, local recurrence rates range 0–10% [52, 137–141]. However, it is important to consider that chemoradiation is associated with substantial morbidity and may also complicate

completion of TEM and result in increased wound-related complications, as suggested by several reports describing an increased incidence of suture line dehiscence, delayed TEM wound closure, and rectal pain [54, 107]. The ACOSOG Z6041 prospective phase II trial is assessing oncologic outcomes of preoperatively staged T2N0 rectal cancer treated with neoadjuvant CRT followed by local excision [29]. A total of 72 patients completed protocol treatment with 64% of tumors downstaged with CRT and 44% with evidence of a complete pathologic response. However, complications from CRT were substantial, with 39% of patients developing grade 3 or greater adverse events during the course of neoadjuvant treatment. At a median follow-up of 56 months, the 3-year disease-free survival was 86.9% in the per protocol group [142]. These high rates of adverse events led to revision of the protocol with dose reductions for both chemotherapy and radiation. Overall, in the absence of long-term oncologic data from ACOSOG Z6041 and other similar trials, this approach should be considered only in the setting of clinical trials.

Multiple authors have evaluated the combination of local excision of rectal cancer, including TAE and TEM, and adjuvant chemoradiation. Borschitz et al. reviewed the cumulative results from 267 patients with T2 rectal cancer from 13 case studies treated with TEM followed by adjuvant radiation (RT) or CRT [52]. Among a total of 64 patients treated with local excision and RT alone, 18% experienced local recurrence, whereas among 107 patients treated with both chemotherapy and radiation, this figured dropped to 11%.

Radical Resection Following TES

In patients with locally advanced rectal cancer, multiple studies have shown no difference in oncologic outcomes when TEM is followed by immediate salvage radical resection compared to initial radical resection. In many instances, accurate staging of suspected rectal cancers can be difficult based on location low in the rectum, difficulties with tumor sampling for an accurate diagnosis, and the current limitations of imaging modalities. This has led to the increasing use of TES to provide an excisional biopsy for suspected and early rectal cancers in order to guide further therapy. In a case-matched study, 25 patients who underwent TEM followed by immediate radical surgery based on unsuspected adverse pathological findings were compared to 25 patients who underwent TME as primary therapy [143]. No differences in operative time or intraoperative complications were noted between the groups, suggesting that prior TEM does not greatly increase the technical difficulty of future TME. More importantly, no differences in local and distant recurrence rates were noted between the groups.

However, when radical resection is undertaken later as salvage therapy for local recurrence following TEM, outcomes are generally poor [144, 145]. Baron et al. evaluated 21 patients who underwent immediate APR following TEM because of adverse histopathological features and compared this group to 21 patients who underwent salvage APR for local recurrence [146]. The disease-free survival for the immediate reoperation group was 94%, but in the salvage group, it was only 56%.

Obstacles and Limitations of TES

Training

A major obstacle to widespread adoption of TES has been the relative technical complexity of the operation and long learning curve given the relatively low volume of eligible patients with early rectal tumors suitable for TES, even at larger institutions. Although similar to single-incision transabdominal laparoscopy, transanal minimally invasive surgery is more challenging from an ergonomic standpoint as a result of the very narrow and shallow working space within the rectum. The transanal surgeon must overcome a steep learning curve, learning how to mazimize the working space for precise dissection and stable visulation and master their suture skills in this environment. The impact of the learning curve

for TEM has been investigated. Koebrugge et al. reviewed 105 TEM cases performed between 2002 and 2007 and demonstrated a significant decrease in the operative time, incidence of postoperative complications, and length of stay between patients treated during the later years of experience as compared to patients treated earlier in their experience with TEM [147]. Barendse et al. reviewed the cumulative experience of four colorectal surgeons who performed a total of 693 TEM resections of rectal lesions and demonstrated that conversion rate, operative time, and complication rates all decreased with increasing surgeon experience [90]. There is speculation that the adoption of TAMIS, with its use of ports and equipment that are familiar to surgeons skilled in laparoscopic surgery, may shorten the learning curve; however, this hypothesis has yet to be investigated.

Cost of TES

Multiple studies have attempted to address the cost of TEM, particularly in relation to the cost of radical resection. Of note, these studies include all indications for TEM, including resection of adenomas. In comparison to radical resection, the cost of TEM per procedure performed is certainly cheaper than radical resection. Cocilivo et al. performed an analysis of the cost of TEM and found that the cost per patient of TEM was $7775 USD as compared to $34,018 for low anterior resection [148]. This analysis did not include the cost of the TEM device, which is significant and certainly mitigates the cost savings associated with TEM, particularly if the procedure is not frequently performed. Maslekar et al. performed a case-control study to consider cost of TEM at a single institution [149]. A total of 124 TEM procedures were performed over 5 years and compared to 124 radical resections performed during the same time period where patients were matched on the basis of tumor and patient characteristics. The cost saving associated with TEM was found to be more than ten times the initial cost of TEM equipment during this time period.

Some studies have also attempted to address the cost of TEM in comparison to TEO or TAMIS. TAMIS, in particular, uses a disposable transanal platform which is less expensive relative to the capital investment costs of the specialized TEM and TEO platforms. This is particularly important when considering the relatively limited oncologic indications for TEM and the small proportion of patients who are appropriate for this approach. In a high-volume institution where TEM is performed frequently, the initial cost of the reusable metal platform and equipment may be offset by the number of cases performed, which may ultimately be cost-effective. Serra-Aracil et al. estimated the cost per procedure with 50 TEM procedures performed per year, taking into account fixed costs (non-reusable equipment) and variable costs (operating time, length of stay, and disposable equipment). Under these assumptions, the cost of TEM was 2310 euros, compared to 2220 euros for TAMIS and 1920 euros for TEO [26]. However, 50 procedures may overestimate the typical number of TEM procedures performed per year, even at those institutions with the largest experience.

Conclusion and Future Directions

Transanal endoscopic surgery is a minimally invasive approach to the rectum that has expanded in indications since its introduction over 30 years ago. The recent introduction of disposable transanal platforms and equipment may reduce operating time and cost of these procedures and facilitate widespread adoption of this approach by surgeons familiar with laparoscopic techniques in other settings. TES can be used in the curative treatment of rectal adenomas and select T1 rectal adenocarcinoma with oncologic results that are equivalent to TME. Moreover, TES results in much lower mortality and morbidity than TME, as well as improved functional outcomes. Currently, the use of TES for more advanced rectal cancer is limited to the experimental and palliative settings, but there is increasing evidence that in combination with neoadjuvant and/or adjuvant chemoradiation, TES may facili-

tate organ preservation and serve as an acceptable alternative to radical surgery for T2 or even T3 tumors in the future.

Furthermore, TEM and TAMIS represents an exciting new medium for the advancement of natural orifice transluminal endoscopic surgery (NOTES). A transanal endoscopic approach offers the possibility of "incisionless" transanal colorectal resection, whereby rectal and/or colon dissection followed by specimen extraction is performed primarily through the anus. The first case of transanal NOTES rectosigmoid resection with TME for a locally invasive rectal cancer was reported in 2009 with laparoscopic assistance [150]. Since then, a growing number of series on hybrid and pure transanal TME (taTME) cases have been published, demonstrating the feasibility and procedural and preliminary oncologic safety of taTME in carefully selected patients, with promising oncologic results [151, 152]. Future advances in surgical optics, multiport transanal platforms, and endoscopic instrumentation will help further the extent and scope of procedures that can be performed through a primarily transanal endoscopic route.

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Radiation Therapy for Rectal Cancer

5

Prajnan Das and Bruce D. Minsky

Radiation therapy plays an important role in the management of patients with rectal cancer. Radiation therapy can improve local control and increase sphincter preservation rates. Preoperative chemoradiation and preoperative short course radiotherapy are now considered standards of care for appropriate rectal cancer patients. Specific radiation therapy techniques such as reirradiation and intraoperative radiation therapy may also improve outcomes in selected patients with rectal cancer. This chapter will discuss the various roles of radiation therapy for rectal cancer and review modern approaches for radiation therapy delivery.

Postoperative Chemoradiation

Several years before the widespread adoption of preoperative chemoradiation, multiple clinical trials established the role of postoperative chemoradiation for rectal cancer. In the Gastrointestinal Tumor Study Group trial, 227 patients with resected Dukes B2-C (current T3–T4 and/or node-positive) rectal cancer were randomized to no adjuvant therapy, postoperative radiotherapy, postoperative chemotherapy with fluorouracil and semustine, or postoperative radiotherapy and chemotherapy [1, 2]. Patients treated with a combination of postoperative radiotherapy and chemotherapy had significantly improved overall survival (58 vs. 48%, $P = 0.005$) and disease-free survival (70 vs. 46%, $P = 0.009$) compared to patients receiving no adjuvant therapy. Furthermore, patients treated with postoperative radiotherapy and chemotherapy had a trend toward improved locoregional control. The North Central Cancer Treatment Group conducted a trial on 204 patients with resected T3–T4 and/or node-positive rectal cancer, who were randomized to postoperative radiation therapy alone, or radiation therapy with concurrent fluorouracil, along with fluorouracil and semustine before and after radiation [3]. The use of chemotherapy and radiation significantly reduced the overall death rate by 29%, distant metastasis by 37%, and local recurrence by 46%, compared to radiation alone. In the National Surgical Adjuvant Breast and Bowel Project R-02 trial, 694 patients with Dukes B or C rectal cancer were randomized to either postoperative chemotherapy alone or postoperative chemotherapy and radiation therapy [4]. Patients treated with postoperative chemotherapy and radiation therapy had significantly lower locoregional relapse rate (8 vs. 13%, $P = 0.02$), but no difference in the disease-free or overall survival rate, compared to patients treated with postoperative chemotherapy alone. Together, these three randomized trials showed that the combination of chemotherapy and radiation

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therapy provided the best outcomes after resection of rectal cancer, with increases in overall survival, disease-free survival, and local control. Hence, these trials provided strong level I evidence for the use of postoperative radiation therapy and chemotherapy for rectal cancer.

Preoperative Chemoradiation

For over a decade, preoperative chemoradiation has been widely accepted as a standard of care for rectal cancer (Fig. 5.1). The German CAO/ARO/AIO-94 trial was the landmark trial that established the role of preoperative chemoradiation for rectal cancer [5, 6]. In this trial, 823 patients were randomized to receive either preoperative chemoradiation or postoperative chemoradiation, along with total mesorectal excision and adjuvant chemotherapy with bolus fluorouracil and leucovorin. The radiation dose was 50.4 Gy in the preoperative arm and 55.8 Gy in the postoperative arm; concurrent chemotherapy consisted of infusional fluorouracil in the first and fifth weeks of radiation. Patients in the preoperative chemoradiation arm had significantly lower rates of local relapse (5-year rates 6 vs. 13%, $P = 0.006$). Preoperative chemoradiation led to tumor downstaging, with pathologic complete response in 8% of patients. Preoperative chemoradiation also led to increased rates of sphincter preservation. Among patients that were initially deemed to be not suitable for sphincter preservation, 39% in the preoperative arm and 20% in postoperative arm were able to undergo sphincter preservation. In addition to increased efficacy, preoperative treatment was also associated with decreased toxicity. Rates of both acute and chronic toxicity were significantly lower in the preoperative arm compared to the postoperative arm (grade 3–4 acute toxicity 27 vs. 40%, grade 3–4 late toxicity 14 vs. 24%). However, there was no significant difference in overall or disease-free survival between the two arms. Updated results from the German trial were published recently [6]. Even after a median follow-up of 11 years, patients in the preoperative chemoradiation arm showed persistent and statistically significant reductions in rates of local relapse (10-year rates 7 vs. 10%, $P = 0.048$).

The National Surgical Adjuvant Breast and Bowel Project R-03 trial also provides support for the use of preoperative chemoradiation [7]. In this trial, patients were randomized to either preoperative or postoperative chemoradiation, with a radiation dose of 50.4 Gy. Patients in both arms received a cycle of bolus fluorouracil and leucovorin before radiation, two cycles with radiation, and four additional adjuvant cycles. This trial was underpowered since it was not able to

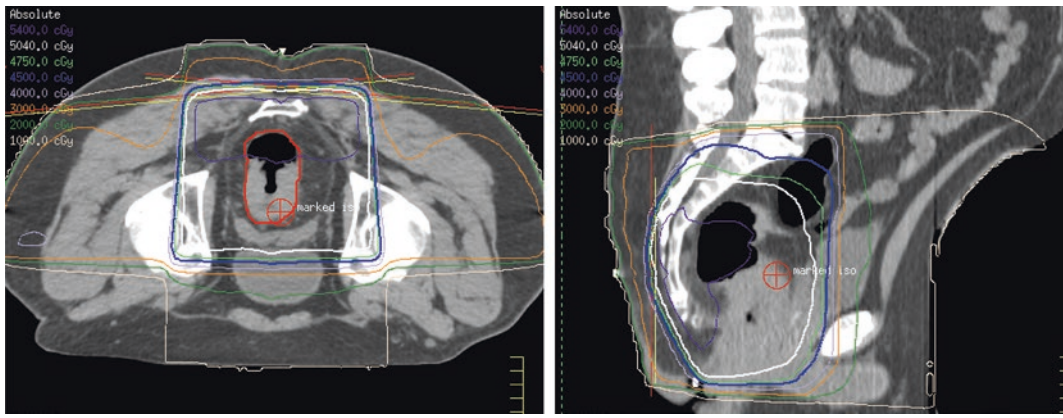

Fig. 5.1 3D conformal radiation therapy treatment plan for preoperative chemoradiation in a man with T3N1 distal rectal adenocarcinoma. The patient was treated using a prone belly board technique, with a dose of 45 Gy (*blue*), followed by a boost to the rectal tumor and adjacent high-risk areas with a cumulative dose of 50.4 Gy (*white*)

meet its accrual goals and enrolled only 267 out of a planned 900 patients. Unlike in the German trial, there was no significant difference in local control or toxicity between the two arms. However, there was a significant improvement in disease-free survival (65 vs. 53%, $P = 0.011$) and a trend toward improvement in overall survival (75 vs. 66%, $P = 0.065$) in patients in the preoperative arm, compared to the postoperative arm. The specific results of this trial should be interpreted cautiously, given its limited accrual. However, this trial does provide general support to the preoperative approach.

A potential downside of preoperative treatment is the possible overtreatment of some patients. Since pretreatment staging may not be completely accurate, some patients may be overstaged and given unnecessary preoperative treatment. For example, in the German rectal cancer trial, 18% of patients in the postoperative arm were found to have stage I disease at surgery instead of stage II–III disease and were, therefore, not administered postoperative treatment [5]. This indicates that around 18% of patients in the preoperative arm likely had stage I disease and were overtreated with preoperative chemoradiation. Hopefully, improvements in staging methods with time will decrease the proportion of overstaged patients, thereby reducing the inappropriate use of preoperative therapy.

Two randomized trials have compared preoperative chemoradiation and preoperative long course radiation for rectal cancer. In the European Organization for Research and Treatment of Cancer (EORTC) 22,921 trial, 1011 patients were randomized to preoperative chemoradiation or radiation and also to adjuvant chemotherapy or no chemotherapy [8, 9]. Patients treated with preoperative chemoradiation had a higher rate of pathologic complete response (14 vs. 5%), smaller tumors, and less advanced T and N stages on surgical pathology, compared to those treated with preoperative radiotherapy alone. Furthermore, those treated with radiation and concurrent and/or adjuvant chemotherapy had significantly lower rates of local recurrence compared to those treated with radiation and no chemotherapy (8–10 vs. 17%, $P = 0.002$). Similarly, in the Federation Francophone de Cancerologie Digestive (FFCD) trial, 762 patients were randomized to receive either preoperative radiation or preoperative chemoradiation [10]. Patients treated with preoperative chemoradiation had significantly higher rates of pathologic complete response (11 vs. 4%) and significantly lower rates of local recurrence (17 vs. 8%, $P < 0.05$). Hence, preoperative chemoradiation has been shown to have increased efficacy, with somewhat increased toxicity, compared to preoperative long course radiotherapy alone.

The German trial, along with the other trials discussed above, has established preoperative chemoradiation as a standard of care for patients with stage II and III rectal cancer (Table 5.1). Preoperative chemoradiation has been rapidly and widely adopted in clinical practice, following publication of these results. For instance, a study based on the Surveillance, Epidemiology, and End Results (SEER) tumor registry showed that the use of preoperative radiation therapy increased from 33% in 2000 to 64% in 2006, among those treated with radiation therapy [11]. Multiple trials have evaluated different concurrent chemotherapy regimens for preoperative treatment; these trials have been discussed elsewhere in this textbook.

Short Course Radiotherapy

Short course radiotherapy, consisting of five treatments of 5 Gy each in a single week, has long been established as another standard of care for rectal cancer (Table 5.2). A landmark trial on this treatment approach was the Swedish Rectal Cancer Trial, in which 1168 patients were randomized to undergo either surgery or preoperative short course radiotherapy followed by surgery [12]. Long-term results from the trial with a 13-year median follow-up show persistent and statistically significant improvements in overall survival (38 vs. 30%, $P = 0.008$), cancer-specific survival (72 vs. 62%, $P = 0.03$), and local recurrence (9 vs. 26%, $P < 0.001$) in the preoperative radiotherapy arm, compared to the surgery alone arm [13].

Table 5.1 Randomized trials on preoperative chemoradiation for rectal cancer

Trial/arms	*N*	Pathologic complete response (%)	5-year local recurrence (%)	≥ Grade 3 acute toxicity (%)
German (CAO/ARO/AIO-94) [5, 6]	823			
Preop chemoradiation		8	6	27
Postop chemoradiation		NA	13	40
NSABP R-03 [7]	267			
Preop chemoradiation		15	11	41
Postop chemoradiation		NA	11	49
EORTC 22921 [8, 9]	1011			
Preop radiation		5[a]	17	7[a,b]
Preop radiation + postop chemo			10	
Preop chemoradiation		14[a]	9	14[a,b]
Preop chemoradiation + postop chemo			8	
FFCD [10]	762			
Preop radiation		4	17	3[b]
Preop chemoradiation		11	8	15[b]

NA not applicable, *NSABP* National Surgical Adjuvant Breast and Bowel Project, *EORTC* European Organization for Research and Treatment of Cancer, *FFCD* Federation Francophone de Cancerologie Digestive
[a]Combined rates for the groups with and without postoperative chemo
[b]Toxicity rates during preoperative radiation/chemoradiation only

Table 5.2 Randomized trials on short course radiotherapy with total mesorectal excision

Trial/arms	*N*	Local recurrence (%)
Dutch [14, 15]	1861	
Preop short course + surgery		5[a]
Surgery		11[a]
MRC/NCIC [16]	1350	
Preop short course + surgery		4.7[b]
Surgery + selective postop chemoRT		11.5[b]

MRC Medical Research Council, *NCIC* National Cancer Institute of Canada
a10-year rates
[b]5-year rates

While the Swedish Rectal Cancer Trial was conducted in an era prior to the advent of total mesorectal excision, subsequent randomized trials have evaluated the role of short course radiotherapy in patients treated with total mesorectal excision. In the Dutch Colorectal Cancer Group trial, 1861 patients were randomized to undergo either total mesorectal excision or short course radiotherapy followed by total mesorectal excision [14, 15]. In this trial, short course radiotherapy reduced local recurrences by over 50% compared to the surgery alone group (10-year rate 5 vs. 11%, $P < 0.0001$). While overall survival was not significantly different between the two arms of the entire trial, overall survival was improved with radiotherapy in stage III patients that underwent surgery with negative circumferential resection margin.

Preoperative short course radiotherapy was also evaluated in the Medical Research Council (MRC) CR07/National Cancer Institute of Canada (NCIC) C016 trial [16]. In this trial, 1350 patients were randomized to either short course radiotherapy followed by surgery or initial surgery followed by selective postoperative chemoradiation. Selective postoperative chemoradiation consisted of 45 Gy with concurrent fluorouracil and was administered only to patients with positive circumferential resection margin, who comprised only 12% of patients in that arm. Patients in the preoperative short course radiotherapy arm had significantly lower rates of local recurrence (3-year rates 4 vs. 11%, $P < 0.0001$) and significantly higher rates of disease-free survival (3-year rates 78 vs. 72%,

$P = 0.013$). Importantly, the benefit from preoperative radiotherapy did not seem to differ depending on the plane of surgery (mesorectal or intramesorectal or muscularis propria plane) [17]. The combination of preoperative radiotherapy and surgery in the mesorectal plane appeared to yield the best local control, with a 3-year local recurrence rate of just 1%. Thus, the Dutch and MRC/NCIC trials both support the use of preoperative short course radiation therapy in patients undergoing total mesorectal excision.

The use of short course radiotherapy varies between countries, ranging from widespread use in selected European countries to relatively low rates of adoption in North America. Based on radiobiology principles, some radiation oncologists have expressed concerns that the large fraction size of radiotherapy in short course could potentially lead to high rates of long-term toxicity. Data from the Dutch and MRC/NCIC trials do provide some support for such concerns. Long-term quality of life questionnaires among patients in the Dutch trial showed increased fecal leakage rate, stool frequency, and erectile problems among patients in the preoperative radiotherapy arm compared to the surgery alone arm [18]. Similarly, quality of life questionnaires from the MRC/NCIC trial showed higher rates of male sexual dysfunction and fecal incontinence in the preoperative radiotherapy arm [19].

Short course radiotherapy and long course chemoradiation may both be considered standard of care for the preoperative treatment of rectal cancer. Randomized trials have compared these two approaches (Table 5.3). In a trial from Poland, 316 patients were randomized to either short course radiotherapy (5 Gy × 5), followed by surgery in a week, or long course radiotherapy (50.4 Gy) with concurrent fluorouracil and leucovorin, followed by surgery after four to 6 weeks [20]. Patients in the long course chemoradiation arm showed higher rates of pathologic complete response (16 vs. 0.7%) and lower rates of positive circumferential resection margin (4 vs. 13%, $P = 0.017$). The 4-year rate of local recurrence was 10.6% in the long course chemoradiation group and 15.6% in the short course group ($P = 0.21$). There was no significant difference in sphincter preservation, disease-free survival, or overall survival between the two groups. There was also no difference in the rate of severe late toxicity between the two groups. In the Trans-Tasman Radiation Oncology Group (TROG) trial 01.04, 326 patients were randomized to short course radiotherapy (5 Gy × 5), followed by surgery in a week, or long course radiotherapy (50.4 Gy) with concurrent infusional fluorouracil, followed by surgery in four to 6 weeks, with both groups receiving adjuvant fluorouracil and leucovorin [21]. Patients in the long course group showed significantly higher rates of pathologic downstaging (45 vs. 28%, $P = 0.002$) and pathologic complete response (15 vs. 1%). The 3-year local recurrence rate was 7.5% in the short course group and 4.4% in the long course group ($P = 0.24$). There was no significant difference in the rates of sphincter preservation, distant recurrence, or overall survival between the two groups, nor was there a significant difference in the rate of grade 3–4 late toxicity between the two groups. Although the Polish and TROG trials did not show a signifi-

Table 5.3 Randomized trials comparing short course radiotherapy and long course chemoradiation

Trial/arms	*N*	Pathologic complete response (%)	Local recurrence (%)	Severe late toxicity (%)
Polish [20]	312			
Preop short course		1	15.6	10
Preop chemoradiation (long course)		16	10.6	7
TROG [21]	326			
Preop short course		1	7.5	6
Preop chemoradiation (long course)		15	4.4	8

TROG Trans-Tasman Radiation Oncology Group

cant difference in local recurrence rates between the long course and short course groups, these trials were relatively small and may have been underpowered to detect a small but clinically relevant difference in local control. The local recurrence rates do appear to be numerically 3–5% higher in the short course groups, whereas the TROG trial was designed to detect a 10% difference in local recurrence. Furthermore, while the Polish and TROG trials did not show any differences in late toxicity, much longer follow-up would be needed to fully evaluate the impact of radiotherapy on long-term bowel and sexual function, as suggested by the quality of life studies from the Dutch and MRC/NCIC trials discussed above. Finally, in both the Polish and TROG trials, long course radiotherapy was associated with enhanced pathologic response, but this may have arisen partly from the longer interval between radiotherapy and surgery in the long course arms of these studies. Combining short course radiotherapy with delayed surgery could potentially enhance pathologic response [22, 23]. The Stockholm III trial is currently comparing short course radiotherapy with surgery in 1 week, short course radiotherapy with surgery in 4–8 weeks, and long course radiotherapy with surgery in 4–8 weeks [24]. Results from this trial will further add to our understanding of the role of short course radiotherapy for rectal cancer.

Radiotherapy for Watch and Wait and Local Excision Approaches

Since chemoradiation can lead to pathologic complete responses in a proportion of patients, selected patients could potentially be treated with chemoradiation and local excision, or even chemoradiation alone. The strategy of trying to avoid surgery altogether has been termed the watch and wait approach. Avoiding surgery could potentially lead to better functional outcomes and better quality of life. The largest systematic study on this approach was from Brazil [25, 26]. In this study, 361 patients were treated with radiation therapy (50.4 Gy) and concurrent fluorouracil and leucovorin; 122 patients attained clinical complete response and 99 (27%) had sustained complete regression for at least 1 year. Patients were required to have no residual mass or ulcer on clinical evaluation and endoscopy, as well as no residual tumor on imaging studies, to be considered to have clinical complete response. Of the 99 patients with sustained complete regression, only 5% developed endoluminal recurrences, none developed pelvic regional recurrence, and 8% developed metastatic disease. Of the five patients that developed endoluminal recurrences, three underwent salvage abdominoperineal or low anterior resections, while two refused radical surgery and underwent local excision or brachytherapy. The 5-year rates of overall and disease-free survival were 93% and 85%, respectively. This study suggests that watch and wait could be a reasonable option in carefully selected and closely followed patients.

In a prospective Dutch trial, 192 patients were treated with radiation therapy (50.4 Gy) with concurrent capecitabine, of whom 21 (11%) attained clinical complete response [27]. Response was assessed based on magnetic resonance imaging (MRI) and endoscopy, and patients were followed closely with MRI, endoscopy, digital rectal examination, and carcinoembryonic antigen (CEA) levels. At a mean follow-up of about 2 years, only 1 of the 21 patients had an endoluminal recurrence. The 2-year rates of overall and disease-free survival were 100% and 89%, respectively. In contrast, some prospective and retrospective studies have reported high rates of local recurrence, ranging from 20 to 80%, with the watch and wait approach [28–31].

Many questions remain unanswered about the watch and wait approach, such as the optimal methods for assessing response to chemoradiation, the optimal methods and timing for follow-up evaluations, and the long-term functional outcomes and quality of life associated with this treatment. Patients treated with watch and wait need to be followed systematically and closely, since many of these patients may develop local recurrences that need salvage surgery. The wide range in local recurrence rates between studies raises some concerns about the efficacy of this approach. Additional prospective studies with

Table 5.4 Selected studies on watch and wait and local excision

Study	Treatment	*N*	Results
Brazil (Habr-Gama) [25, 26]	Radiation + watch and wait	99	5% endoluminal recurrence, 85% 5-year DFS
Dutch [27]	Radiation + watch and wait	21	89% 2-year DFS
MD Anderson [32]	Radiation + local excision	47	49% pCR, 10.6% 10-year local recurrence
ACOSOG Z6041 [35]	Radiation + local excision	77	44% pCR

ACOSOG American College of Surgeons Oncology Group, *DFS* disease-free survival, *pCR* pathologic complete response

adequate follow-up will be needed before this approach can be accepted as a standard.

Preoperative chemoradiation could also be used in combination with local excision for selected patients. A number of retrospective studies have shown excellent local control rates in patients treated with preoperative chemoradiation and local excision [32–34] (Table 5.4). These studies primarily evaluated patients that were not candidates for radical excision or patients that declined radical excision. A retrospective study from MD Anderson reported outcomes in 47 patients with T3 rectal cancer treated with preoperative radiation (45–52.5 Gy) with concurrent fluorouracil [32]. Of these patients, 49% had pathologic complete response and 36% had microscopic residual disease after chemoradiation. The 10-year actuarial risk of local recurrence was 10.6% in these patients, in comparison to a rate of 7.6% in a cohort of 473 patients treated with total mesorectal excision at the same institution. Similarly, a retrospective study from Korea showed 89% 5-year local relapse-free survival in 27 patients with mostly T3 rectal cancer that were treated with preoperative chemoradiation and local excision [33]. Another retrospective study reported outcomes in 44 patients with T2–T3 rectal cancer treated with preoperative chemoradiation and local excision [34]. Pathologic complete responses were seen in 43% of patients. Only two patients developed isolated local recurrences, and two developed local and distant recurrences. The results of these studies should be interpreted cautiously given their retrospective nature. Careful selection of patients likely contributed to these results, as suggested by the high proportion of patients with pathologic complete responses in some of these studies.

A recent phase II prospective trial has investigated the combination of preoperative chemoradiation and local excision for T2N0 patients [35]. In the American College of Surgeons Oncology Group (ACOSOG) Z6041 trial, patients with clinical T2N0 rectal cancer were treated with preoperative radiation therapy with a dose of 54 Gy, along with concurrent capecitabine and oxaliplatin, followed by local excision. Of 77 eligible patients that completed protocol-based chemoradiation and local excision, 44% had pathologic complete response and 99% had negative margins. However, the rate of grade 3 or higher complications was relatively high (39%) with this regimen. Information on local recurrence and disease-free survival is not yet available from this study.

Based on the studies discussed above, at this time, the combination of preoperative chemoradiation and local excision for T3 patients appears appropriate mainly for patients that are medically unfit for radical surgery or patients that refuse radical surgery, though good oncologic outcomes have been reported for selected patients in multiple retrospective studies. Preoperative chemoradiation and local excision could be a potential treatment option for T2N0 patients; however, long-term oncologic outcomes will be needed from the ACOSOG Z6041 trial to support this approach.

Selective Use of Radiotherapy

There exists considerable variation among rectal cancer patients in their risk for local recurrence and, therefore, in the magnitude of their benefit from radiation therapy. While the randomized

trials on preoperative and postoperative chemoradiation discussed above typically included all stage II and III patients, certain patient subgroups have relatively low risk of local recurrence and could potentially be treated without radiation therapy, thereby sparing them from the acute and late side effects of radiation therapy.

A pooled analysis of 3791 patients from five randomized trials evaluated survival and relapse rates in patient subgroups, based on T and N classification [36]. This study identified an intermediate-risk group of patients, with stages T1-2N1 and T3N0. Patients in the intermediate-risk group had 5-year local relapse rates of 12–14% with surgery alone, 5–11% with surgery and chemotherapy, and 5–10% with surgery and chemoradiation. While this was a pooled analysis and not a planned prospective or randomized comparison between these treatment approaches, the data from this study suggests that certain patients may have low risk of local recurrence without radiation therapy, especially if they receive chemotherapy.

A prospective European trial, called the MERCURY study, evaluated the role of MRI in identifying patients at low risk of local recurrence who could be treated with surgery without radiation therapy [37]. MRI was used to identify good prognosis patients, based on the following imaging criteria: safe circumferential resection margin with tumor >1 mm from the mesorectal fascia; no extramural venous invasion; stages T2, T3a, and T3b, i.e., extramural spread <5 mm; and no encroachment into intersphincteric plane or levators for low rectal tumors. Among 374 patients in the MERCURY study, 122 (33%) met the good prognosis criteria and were treated with surgery alone. Patients in the good prognosis group had only 3% local recurrence rate. Moreover, the 5-year rates of disease-free survival and overall survival in this group were 85% and 68%, respectively. The MERCURY study suggests that MRI can be used to select patients that can be treated without radiation therapy. The success of this approach depends on the availability of good-quality MRI and appropriate interpretation of the images by highly trained radiologists. In certain regions such as the United Kingdom, MRI-based selective use of radiotherapy has now been accepted as a standard of care.

A small prospective trial at Memorial Sloan Kettering Cancer Center investigated the use of preoperative chemotherapy without radiation therapy for rectal cancer [38]. In this trial, 32 patients with stage II–III rectal cancer who were candidates for low anterior resection underwent preoperative chemotherapy with FOLFOX (fluorouracil, leucovorin, and oxaliplatin) and bevacizumab. Two patients were not able to complete chemotherapy and received preoperative chemoradiation. All patients underwent R0 resection. The pathologic complete response rate to chemotherapy was 25%. The 4-year rates of local recurrence and disease-free survival were 0 and 84%. This trial suggests that preoperative chemotherapy could be a potential alternative to preoperative chemoradiation for selected patients. It should be noted this was a relatively small, single-institution trial, and patient selection may have contributed to these results. A large phase II/III randomized multi-institutional trial is currently underway to further study the role of preoperative chemotherapy as an alternative to preoperative chemoradiation. In the Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT) trial, patients with T2N1, T3N0, and T3N1 rectal cancer with distal edge 5–12 cm from the anal verge are being randomized to either routine preoperative chemoradiation or preoperative chemotherapy with FOLFOX, along with selective chemoradiation. In a few years, results from the PROSPECT trial may help us better understand whether radiation therapy can be used more selectively in rectal cancer patients.

Reirradiation

Traditionally, only one course of pelvic radiation therapy was administered to rectal cancer patients, because of the potential risk of toxicity with reirradiation. However, even after preoperative chemoradiation or short course radiotherapy

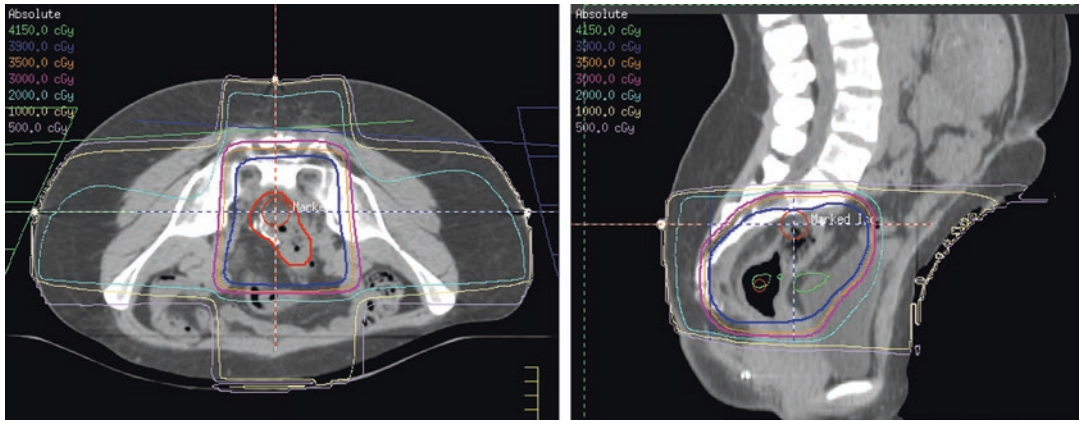

Fig. 5.2 3D conformal radiation therapy treatment plan for preoperative reirradiation in a woman with an anastomotic recurrence of rectal adenocarcinoma. The patient was previously treated with a dose of 50.4 Gy 3 years ago and was given reirradiation with a dose of 39 Gy (*blue*) in 1.5 Gy twice-daily fractions

and surgery, rectal cancer patients have 5–10% risk of local recurrence [6, 8, 10]. Reirradiation could play a role for palliation or definitive salvage therapy in these patients, albeit at a higher risk of toxicity (Fig. 5.2).

The earliest reports on reirradiation for rectal cancer were from the University of Kentucky [39–42]. The most recent study from this group reported on 103 patients with recurrent rectal cancer treated with a median initial radiation dose of 50.4 Gy and a median reirradiation dose of 34.8 Gy, with a median 19-month interval between initial treatment and recurrence [42]. Patients were treated with either 1.2 Gy twice-daily fractions ($N = 43$) or 1.8 Gy daily fractions ($N = 60$), and all patients received concurrent infusional fluorouracil. Of the 103 patients, 34 underwent surgical resection in addition to reirradiation. Patients tolerated treatment relatively well, with 15 (15%) patients requiring treatment breaks or early treatment termination due to grade 3 or higher acute toxicities, such as diarrhea, moist desquamation, or mucositis. Twenty-two (21%) patients had late complications including chronic severe diarrhea in 17%, small bowel obstruction in 15%, fistula in 4%, and coloanal stricture in 2%. The rate of late toxicity was significantly lower in patients treated with twice-daily fractions compared to those treated with daily fractions and was also significantly lower in patients with a retreatment interval over 2 years. The median survival was 26 months for all patients, 44 months for patients undergoing surgery, and 14 months for patients undergoing reirradiation without surgery.

In a multicenter phase II trial in Italy, 59 patients with recurrent rectal cancer and prior pelvic radiotherapy (median dose 50.4 Gy) were treated with reirradiation with a dose of 40.8 Gy in 1.2 Gy twice-daily fractions, with concurrent infusional fluorouracil [43]. The median interval between the two courses of radiotherapy was 27 months. Treatment was well tolerated, with only 5% grade 3 lower gastrointestinal acute toxicity. Seven (12%) patients developed late toxicity including skin fibrosis, impotence, urinary complications, and small bowel fistula. The overall response rate was 44%, including complete response in 9%. Thirty (51%) patients underwent surgical resection, with R0 resection in 21 (36%) patients. The 5-year survival was 39% for all patients, 67% for patients with R0 resections, and 22% for patients with non-R0 surgeries or no surgeries.

Investigators from MD Anderson Cancer Center reported a retrospective study on 50 patients with prior pelvic radiotherapy who were treated with 30 Gy ($N = 3$) or 39 Gy ($N = 47$) in

Table 5.5 Selected studies on reirradiation for rectal cancer

Study	Reirradiation dose and fractionation	*N*	Survival	Late complications (%)
University of Kentucky [42]	Median 34.8 Gy, 1.8 Gy daily or 1.2 Gy twice daily	103	5-year survival 19% for all patients, 22% with surgery	21
Italian phase II trial [43]	40.8 Gy, 1.2 Gy twice daily	59	5-year survival 39% for all patients, 67% for R0 resections	12
MD Anderson [44]	30–39 Gy, 1.5 Gy twice daily	50	3-year survival 39% for all patients, 66% with surgery	26
Peter MacCullum [45]	Median 39.6 Gy, 1.8 Gy daily	56	Median survival 19 months for all patients, 39 months with surgery	2
Catharina Hospital [46]	30–30.6 Gy, 1.8–2 Gy daily	135	5-year. survival 35% with surgery	39[a]

[a]Total complications, including postoperative complications

1.5 Gy twice-daily fractions, with concurrent chemotherapy in 96% of the patients [44]. Of the 50 patients, 48 had recurrent rectal cancer, and 2 had primary rectal cancer with history of prior pelvic radiotherapy for other malignancies. Reirradiation was well tolerated with grade 3 acute toxicity in 3 (6%) patients and grade 3–4 late toxicity in 13 (26%) patients. Eighteen (36%) patients underwent surgical resection after reirradiation. The 3-year freedom from local progression was 33% for all patients, 47% for those who underwent resection, and 21% for those who did not undergo resection. The 3-year overall survival was 39% for all patients, 66% for those who had resection, and 27% for those who did not have resection.

While the studies discussed above have provided data supporting the use of twice-daily reirradiation, other recent studies have evaluated the safety and efficacy of once-daily reirradiation. A retrospective study from Peter MacCullum Cancer Center reported on 56 patients with rectal cancer who had prior pelvic radiotherapy [45]. Patients were treated with a median dose of 39.6 Gy in 1.8 Gy daily fractions, with concurrent chemotherapy in 80% of patients and surgery in 23% of patients. Only seven (13%) patients developed grade 3 acute toxicity and one patient developed significant late toxicity. The median survival was 39 months in patients who underwent surgical resection and 15 months in patients who only had reirradiation.

In a large study from the Catharina Hospital in the Netherlands, 135 patients with recurrent rectal cancer and prior pelvic radiotherapy were treated with reirradiation and surgical resection [46]. Of these patients, 62% had previously received short course radiotherapy, and 38% had received long course radiotherapy. The median interval between initial surgery and recurrence was 34 months. Reirradiation was given in doses of 30–30.6 Gy in 1.8–2 Gy daily fractions, with concurrent fluorouracil and capecitabine. In addition, intraoperative radiation therapy was given to 96% of patients, at doses of 10–15 Gy. Patients tolerated reirradiation well, with grade 3–4 diarrhea in 5% and grade 3–4 neutropenic sepsis in 1%. Late complications included fistula in 10% and ileus in 14%. The 5-year local recurrence-free and overall survival rates were 51% and 35%, respectively. Patients treated with reirradiation had higher survival compared to a historical control group of 24 patients treated without radiation.

The studies above suggest that reirradiation is a feasible treatment approach in rectal cancer patients who have received prior pelvic radiotherapy (Table 5.5). The rates of acute and late toxicity appear to be reasonable. However, it must be noted that most of these studies were conducted in high-volume, experienced centers. The safety of reirradiation depends on the details of radiotherapy planning. Efforts must be made to minimize the radiotherapy treatment volume and avoid reirradiation to sensitive normal structures.

Intraoperative Radiation Therapy

Intraoperative radiation therapy (IORT) involves the delivery of radiation therapy to high-risk areas of the operative bed, typically using either electron beams or high-dose rate (HDR) brachytherapy applicators (Fig. 5.3). IORT is delivered using a single, large dose of radiation that is biologically equivalent to 2–3 times its nominal dose [47]. IORT allows the delivery of radiation therapy to a small, selected volume that is at highest risk of recurrence, taking advantage of direct visualization of the treated area and operative mobilization of normal structures away from the radiation field. IORT is frequently given in conjunction with a course of preoperative external beam radiation therapy.

A number of retrospective studies have evaluated the use of IORT for locally advanced and recurrent colorectal cancers (Table 5.6). A study from the Mayo Clinic evaluated 146 patients with locally advanced colorectal cancers fixed to critical structures, such as the inferior vena cava or pelvic sidewall [48]. These patients were treated with external beam radiation therapy, surgical resection, and electron beam IORT, with a median IORT dose of 12.5 Gy. The surgical resection was R0 with a close margin in 68%, R1 in 19%, and R2 in 13%. The 5-year rates of local control, disease-free survival, and overall survival were 86%, 43%, and 52%, respectively.

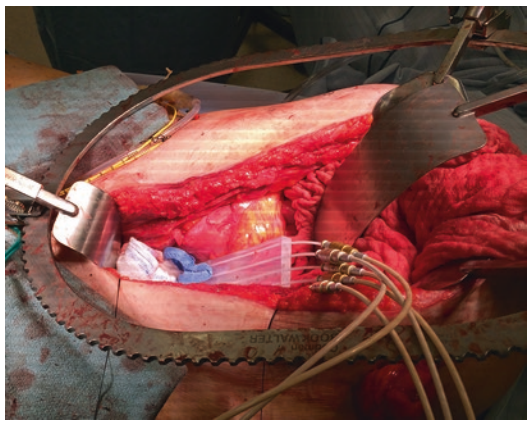

Fig. 5.3 Intraoperative radiation therapy (IORT) with high dose rate brachytherapy

Grade 3–4 late complications occurred in 32 (22%) patients, including small bowel obstruction in 10%, ureteral obstruction in 6%, wound complication in 3%, and peripheral neuropathy in 2% of patients. Another study from the Mayo Clinic evaluated 607 patients with recurrent colorectal cancers treated with surgical resection and electron beam IORT, with a median IORT dose of 15 Gy [49]. Of these patients, 96% were also treated with external beam radiation therapy. The surgical resection was R0 in 37%, R1 in 37%, and R2 in 26%. The 5-year local recurrence rate was 28%, while the 5-year rate of recurrence in the IORT field was only 14%. The 5-year overall survival rate was 30% for these patients with recurrent colorectal cancers. Grade 3 or higher IORT-related complications included wound complications or fistulas in 8%, ureteral obstruction in 3%, and neuropathy in 3% of patients.

Investigators from the MD Anderson Cancer Center reported a study on 100 patients with locally advanced primary (30%) or recurrent (70%) colorectal cancer, treated with resection

Table 5.6 Selected studies on intraoperative radiation therapy (IORT)

Study	IORT dose	N	5-year rates
Mayo Clinic, locally advanced	Median 12.5 Gy	146	LC 86%, OS 52%
Mayo Clinic, recurrent	Median 15 Gy	607	LR 28%, OS 30%
MD Anderson	Median 12.5 Gy	100	LC 94% for primary tumors, 56% for recurrences
			OS 61% for primary tumors, 56% for recurrences
Erasmus MC	10 Gy	95	LR-free survival 70% for R0, 84% for R1 with IORT
			LR-free survival 79% for R0, 41% for R1 without IORT
European multicenter	10–12.5 Gy	605	LR 12%, OS 67%

LC local control, *OS* overall survival, *LR* local recurrence

and IORT, using an HDR brachytherapy system with median dose of 12.5 Gy [50]. Of these patients, 37% received preoperative chemotherapy and 82% received preoperative chemoradiation. The resection was R0 in 54% and R1 in 46%; 75% had multivisceral resections. The 5-year local control rate was 94% for primary tumors and 56% for recurrent tumors. The 5-year local control rate was 72% for those with R0 resection and 60% for those with R1 resection; however, the resection status was not significantly associated with the local control rate. The 5-year overall survival was 61% for patients with primary cancers and 56% for patients with recurrent tumors. Grade 3 or higher postoperative complications were seen in 33% of patients, but long-term toxicity rates were not reported.

A retrospective study from the Erasmus MC Cancer Institute compared local recurrence rates in 95 locally advanced rectal cancer patients treated with and without IORT [51]. All patients were treated with either preoperative short course radiotherapy or long course chemoradiation. IORT was delivered using HDR brachytherapy with a dose of 10 Gy. Among patients with clear but narrow circumferential resection margins, there was no significant difference in the local recurrence-free survival rate between those treated with IORT ($N = 21$, 5-year rate 70%) and those treated without IORT ($N = 22$, 5-year rate 79%). However, among patients with microscopically involved circumferential resection margins, the local recurrence-free survival rate was significantly higher in those treated with IORT ($N = 31$, 5-year rate 84%), compared to those treated without IORT ($N = 17$, 5-year rate 41%). Moreover, among patients with microscopically involved circumferential resection margins, the overall survival was significantly higher for those treated with IORT (5-year rates 41 vs. 13%). There was no significant difference in perioperative complication rates between patients treated with and without IORT.

A pooled analysis from four major European centers evaluated outcomes in 605 patients with locally advanced rectal cancer treated with preoperative radiotherapy or chemoradiation, surgery, IORT, and adjuvant chemotherapy [52]. The clinical stage was advanced T3 in 71% and T4 in 29%. IORT was delivered using electrons, typically with doses of 10–12.5 Gy. The 5-year local recurrence and overall survival rates were 12% and 67%, respectively.

In a French multi-institutional phase III trial, 142 patients with T3–T4 rectal cancer were treated with preoperative radiotherapy (40 Gy) and were then randomized either to surgery alone or surgery with IORT. There was no significant difference in local control (5-year rates 92 vs. 93%) or overall survival (median 106 vs. 88 months) between patients treated with and without IORT. There was also no significant difference in the rate of postoperative complications between the two groups. However, this study has a number of limitations. Most importantly, 90% of patients enrolled in the trial had clinical T3 disease and would not be expected to benefit from the addition of IORT. The sample size was low, and the number of local failure events was also much lower than anticipated during the design of the study, thus limiting the power of the study to detect a difference. While this is the only randomized trial to evaluate the role of IORT, no conclusions about the role of IORT can be drawn from this trial because of its limitations.

A recent systematic review and meta-analysis on IORT evaluated 29 studies with a total of 3003 patients with locally advanced or recurrent colorectal cancer [53]. Comparative data were available on local control from six studies ($N = 482$), on disease-free survival from four studies ($N = 288$), and on overall survival from five studies ($N = 370$). The meta-analysis indicated significant increases in local control (OR 0.22, $P = 0.03$), disease-free survival (HR 0.51, $P = 0.009$), and overall survival (HR 0.33, $P = 0.001$) with the addition of IORT. The meta-analysis also showed a significant increase in wound complications (OR 1.86, $P = 0.049$) with IORT, but no significant difference in total complications, urologic complications, or anastomotic complications.

Thus, the evidence for IORT comes largely from multiple retrospective studies that have shown good rates of local control and survival in high-risk locally advanced or recurrent colorec-

tal cancer patients. When given in combination with systemic therapy, external beam radiation therapy, and surgery, IORT appears to result in favorable oncologic outcomes with acceptable rates of perioperative and long-term toxicities. Many large volume centers that specialize in treating locally advanced and recurrent colorectal cancers have adopted IORT as part of their standard of care in appropriately selected high-risk patients.

Intensity Modulated Radiation Therapy

Intensity modulated radiation therapy (IMRT) allows the delivery of more conformal radiation therapy, potentially leading to increased sparing of normal tissues (Fig. 5.4). A number of dosimetric studies have indicated that IMRT for rectal cancer spares more normal tissues, such as small bowel, bladder, pelvic bones, and femurs, compared to conventional 3D conformal radiation therapy [54, 55, 56]. However, the clinically relevant issue is whether IMRT can lead to a reduction in acute or late radiation-related toxicities compared to 3D conformal radiotherapy. A retrospective study from the Mayo Clinic compared 61 patients treated with 3D conformal radiotherapy and 31 patients treated with IMRT for rectal cancer, mostly with preoperative treatments [57]. Patients treated with IMRT had significantly lower rates of grade 2 or higher acute gastrointestinal side effects (32 vs. 62%, $P = 0.006$), grade 2 or higher diarrhea (23 vs. 48%, $P = 0.02$), and grade 2 or higher enteritis (10 vs. 30%, $P = 0.015$). Another retrospective study from Boston compared 28 patients treated with 3D conformal radiotherapy and 20 patients treated with IMRT for preoperative treatment of rectal cancer [58]. Patients treated with IMRT had significantly lower grade 2 or higher acute gastrointestinal toxicity rate (30 vs. 61%, $P = 0.036$), lower grade 2 or higher diarrhea rate (10 vs. 43%, $P = 0.14$), and required less time needed to complete radiation (35 vs. 39 days, $P < 0.0001$). Similarly, a retrospective multi-institution study compared 56 patients treated with preoperative 3D conformal radiotherapy and 30 patients treated with preoperative IMRT [59]. Patients treated with IMRT had significantly lower grade 3 or higher toxicities, fewer hospitalizations and emergency department visits (2 vs. 14%, $P = 0.005$), and fewer treatment breaks (0 vs. 20%, $P = 0.0002$).

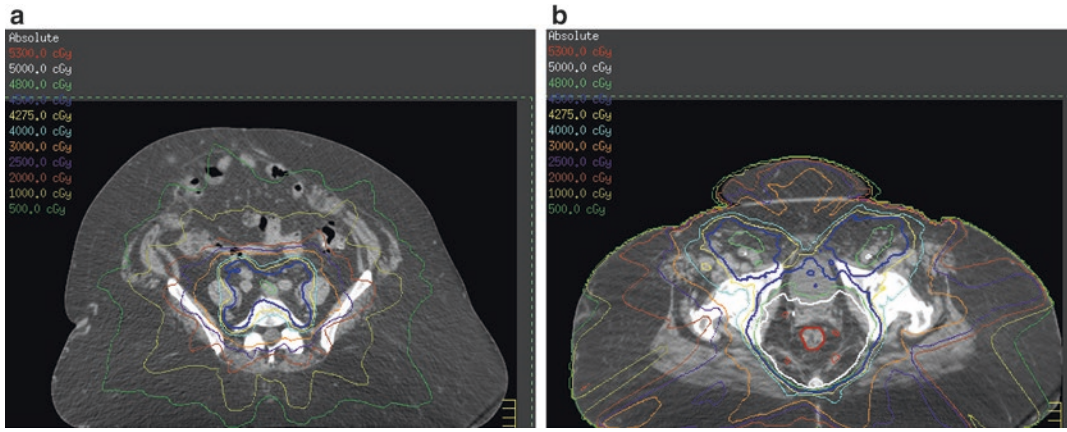

Fig. 5.4 (**a**, **b**) Intensity modulated radiation therapy (IMRT) treatment plan for preoperative chemoradiation in a woman with T3N1 distal rectal cancer with perianal involvement. IMRT was used to include the inguinal nodal regions in the treatment volume while sparing normal structures such as the small bowel, femurs, and genitalia. Pelvic and inguinal regions were treated to 45 Gy (*blue*) in 25 fractions, with a simultaneous integrated boost of 50 Gy (*white*) in 25 fractions to the rectal tumor and adjacent high-risk areas

Although these retrospective studies suggest that IMRT may reduce acute gastrointestinal toxicity, a prospective phase II trial by the Radiation Therapy Oncology Group (RTOG) did not confirm this finding [60]. In this trial, 68 patients were treated with preoperative IMRT with concurrent capecitabine and oxaliplatin [60]. There was no statistically significant reduction in grade 2 or higher gastrointestinal toxicity, compared to that in a prior trial of 3D conformal radiotherapy with concurrent capecitabine and oxaliplatin (51 vs. 58%, $P = 0.31$). At this time, there is no clear consensus about whether IMRT should be used routinely for rectal cancer. However, some radiation oncologists believe that IMRT could play a role in reducing toxicity in patients at the highest risk for toxicity, such as those with resected rectal cancer with a large amount of fixed small bowel in the pelvis. IMRT may also play a role in other selected cases, such as for treating the inguinal regions in patients with low rectal cancers or for radiation therapy dose escalation to the primary tumor or involved nodes.

Radiation-Related Toxicity

Radiation therapy for rectal cancer can lead to both acute and long-term toxicities. Many of the studies discussed above have reported toxicities related to radiation therapy. For instance, the German CAO/ARO/AIO-94 trial reported grade 3–4 acute toxicities in 27% of patients in the preoperative chemoradiation arm and 40% of patients in the postoperative chemoradiation arm [5]. These toxicities included diarrhea, hematologic toxicity, and dermatologic toxicity. Moreover, the German CAO/ARO/AIO-94 trial reported grade 3–4 long-term toxicities in 14% of patients in the preoperative arm and 24% of patients in the postoperative arm. The most common long-term toxicities included chronic diarrhea, small bowel obstruction, anastomotic strictures, and bladder problems. A study from Norway compared late side effects and quality of life in 199 patients treated with surgery and preoperative or postoperative radiation and 336 patients treated with surgery without radiation [61]. Patients treated with radiation were found to have higher rates of increased bowel frequency, stool incontinence, and urinary incontinence. Patients treated with radiation also had worse social function scores on quality of life studies. Other studies on the same cohort of patients have shown increased rates of erectile dysfunction in males and increased rates of dyspareunia and vaginal dryness in females after radiotherapy, compared to those treated with surgery alone [62, 63].

Many studies have investigated radiation treatment planning parameters associated with the risk of toxicity. Multiple studies have shown that the volume of small bowel exposed to radiation therapy is significantly associated with the risk of acute gastrointestinal toxicity, especially at doses of ≥15 Gy to the small bowel [64–66]. Hence, special attention should be paid to reducing the volume of small bowel exposed to radiation therapy. Prone positioning and belly board devices help in achieving anterior and superior displacement of small bowel away from the radiation treatment field, thereby reducing radiation exposure to the small bowel [67]. Treatment with a full bladder can lead to further displacement and sparing of small bowel [67]. In selected patients, IMRT may also help in reducing radiation exposure to normal structures.

Along with optimal radiation therapy treatment planning and delivery, toxicity management plays a critical role in the treatment of rectal cancer patients undergoing radiation therapy. A low-fiber diet can help reduce the risk or severity of diarrhea. Many patients need treatment with antidiarrheal medications such as loperamide and diphenoxylate/atropine. Patients receiving concurrent chemotherapy may need antiemetic medications such as ondansetron and prochlorperazine. Appropriate skin care with topical emollients is necessary for patients that develop dermatologic toxicity. Patients may develop tumor-related or treatment-related pain and may therefore require pain management. Careful attention must also be paid to the hydration and nutritional status of patients undergoing radiation or chemoradiation.

Summary

Radiation therapy represents a key component in the multidisciplinary management of rectal cancer patients. For most patients with stage II and III rectal cancer, the two most widely accepted approaches at this time are preoperative long course radiation with concurrent chemotherapy and preoperative short course radiotherapy. Selected patients could potentially be treated with radiation therapy followed by watch and wait or local excision, but these treatment strategies remain investigational. Radiation therapy could potentially be used selectively rather than routinely for stage II and III rectal cancer patients; MR is now used in some regions to identify patients that could be excluded from radiotherapy. Reirradiation has a role in salvage therapy or palliative therapy in patients with locally recurrent rectal cancer. Similarly, IORT is useful in the management of patients with locally advanced or recurrent rectal cancers. IMRT may help reduce radiation-related toxicity in selected patients, though there is no current consensus about its role for rectal cancer. In all patients treated with radiotherapy for rectal cancer, careful radiation therapy planning and delivery, and appropriate management of toxicities, are essential parts of clinical care.

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Preoperative and Postoperative Chemotherapy for Rectal Cancer

6

Katherine Van Loon and Alan P. Venook

No cancer represents the successes of multidisciplinary management as well as rectal cancer. Over the past decades, technical advances have clarified the optimal surgical approaches and have refined the delivery of radiation therapy. Well-conducted trials have rearranged the sequence of successive therapies. Most remarkably, ongoing trials are now looking to subtract, rather than to add, elements to the treatment algorithm. While the use of perioperative radiation therapy continues to evolve, the role for chemotherapy has remained essentially constant. Fluoropyrimidines remain at the center of treatment strategies, both as radiosensitizers and for systemic disease control.

Concurrent Chemotherapy with Radiation

In 1969 of Moertel et al. first described that administration FU in combination with radiation therapy increased the survival of patients with locally advanced gastrointestinal tumors, compared to radiation therapy alone [1]. From 1975 until 1989, postoperative pelvic radiation therapy in combination with FU-based chemotherapy was evaluated in patients with Dukes B and C rectal cancer, with the conclusion that the combination of chemotherapy with radiation resulted in a significant benefit for local control, distant metastases, and overall survival compared with surgery alone [2–4]. In 1991, the National Institutes of Health disseminated a "Clinical Announcement" reflecting a Consensus Conference and recently published data, which stipulated that postoperative chemoradiation—not radiation alone—become the new standard of care for patients with stage II and III rectal cancer [5].

In 1993, the European Organisation for Research and Treatment of Cancer (EORTC) initiated a randomized phase III study (EORTC 22921) with a 2 × 2 factorial design to examine the value of adding chemotherapy to preoperative radiation for patients with T3 or T4 rectal cancer and the value of additional postoperative chemotherapy versus none in the same patient group. This study demonstrated that the use of 5-day bolus 5-FU/leucovorin during weeks 1 and 5 of radiation enhanced tumoricidal effect of preoperative radiation [6]. Use of combined chemoradiation resulted in higher rates of pathologic complete response (14 versus 5%) and significant reductions in tumor size, pTN stage, and rates of lymphatic, vascular, and perineural invasion, compared with the use of radiation and surgery alone [6]. However, mature results from this trial, after a median follow-up of 10.4 years, ultimately failed to demonstrate that the addition of a fluoropyrimidine, either as a radiosensitizer to

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neoadjuvant radiation or as postoperative adjuvant therapy, had a significant effect on disease-free or overall survival; however, this trial did demonstrate a decreased incidence of local relapse in patients who were treated with neoadjuvant radiation and chemotherapy [7]. At 10 years, the cumulative incidence of local relapse was 22.4% (95% CI 17.1–27.6) in the group that was treated with neoadjuvant radiation alone versus 11.8% (95% CI 7.7–15.6) in the group that received neoadjuvant radiation and chemotherapy. Our review would be incomplete without mention of the controversy generated by the unexpected outcome of this study. Notably, a major limitation is that the concurrent 5-FU was administered at a reduced dose of 350 mg/m^2 per day via intravenous bolus during weeks 1 and 5 of radiation, rather than as a continuous infusion as is generally accepted as standard in the US.

Limitations and controversies aside, a number of systematic reviews support the findings. A summation of four studies [8] and a Cochrane review of six randomized trials [9] suggested that radiosensitizing chemotherapy reduced the risk of local recurrence in stage III rectal cancer patients but had no effect on overall survival, 30-day mortality, sphincter preservation, or late toxicity. A separate Cochrane review of five clinical trials that randomized resectable stage II or III rectal cancer patients to at least one arm of preoperative radiation therapy alone or at least one of arm of preoperative chemoradiation similarly concluded that no differences were observed in disease-free or overall survival [10]. These analyses also showed that despite the fact that preoperative chemoradiation significantly increased the rate of complete pathologic response (OR 2.12–5.84, $P < 0.00001$), this did not translate into a higher rate of sphincter preservation, although the incidence of local recurrence was significantly lower in the group that received chemotherapy in combination with radiation therapy (OR 0.39–0.72, $p < 0.001$). Another meta-analysis of five relevant trials similarly concluded that chemoradiation improved local control compared to radiation therapy alone (0.53; 0.39–0.72), without a significant impact on long-term survival [11].

Although the relationship between pathologic stage after neoadjuvant chemoradiation has been shown to be associated with survival outcomes in both clinical trials and a meta-analysis [12–14], the reason why higher rates of pathologic complete response have not translated into a survival advantage is not obvious. Nevertheless, the addition of chemotherapy to radiation therapy has become a standard approach to neoadjuvant therapy.

Attention has more recently been focused on optimizing delivery of fluoropyrimidine radiosensitization. Early randomized trials largely explored postoperative radiation with bolus 5-FU for practical rather than scientific reasons. Radiation was delivered following surgery to allow for the careful planning, central review, and frequent redrawing of the radiation ports, which took many weeks to accomplish in the pre-digital era. Chemotherapy was commonly administered in the immediate postoperative period while awaiting radiotherapy planning and was typically given via bolus injection due to practical limitations. In that era, the pumps that now allow for continuous infusion of the drug were rare and often malfunctioning, relegating infusional 5-FU largely to an inpatient setting.

However, in vitro models that demonstrated that the radiosensitizing effects of 5-FU are maximized with exposure of at least 24 h and up to 48 h following radiation exposure [15] eventually prompted evaluation of alternate delivery schedules in a variety of gastrointestinal cancers, including rectal cancer. In 1994, a landmark trial conducted by the North Central Cancer Treatment Group (NCCTG) clarified the importance of the 5-FU administration schedule [16]. This study randomized 660 stage II and III rectal cancer patients, following curative surgery, to receive intermittent bolus injections or protracted venous infusions of 5-FU during postoperative radiation to the pelvis. Infusional 5-FU (225 mg/m^2 per day for the entire course of radiation) was shown to be associated with improved overall survival, compared to two 3-day courses of bolus 5-FU during the first and last weeks of radiotherapy ($p = 0.005$).

Conversely, a US Intergroup trial (INT 0144), conducted 12 years later to investigate the benefit

of continuous infusion 5-FU before, during, and after radiation therapy, demonstrated no significant differences in relapse-free survival or overall survival from three different schedules of postoperative fluorouracil, with or without folinic acid modulation, when administered with radiation [17]. Although both bolus and infusional 5-FU administration schedules can be considered, we favor continuous infusion 5-FU based upon the results of the earlier NCCTG study and in consideration of lower rates of hematologic toxicity with this approach [16, 17].

Capecitabine, an oral prodrug of 5-FU, was designed to mimic continuous infusion 5-FU while avoiding the cost, inconvenience, and risks associated with maintaining a central venous line for continuous infusion. Conversion of capecitabine to 5-FU relies on three enzymes, including thymidine phosphorylase which is present in higher concentrations in colorectal tumors than in normal tissue. As a result of tumor selectivity, higher tumor to plasma ratios of 5-FU can be reached with capecitabine than with infusional 5-FU [18, 19]. Available clinical trial data support the therapeutic equivalence of daily oral capecitabine compared with continuous intravenous FU during neoadjuvant radiation for rectal cancer. A phase III trial of 401 patients with stage II or III rectal cancer which randomized patient to receive capecitabine versus infusional 5-FU-based chemoradiation either pre- or postoperatively demonstrated that capecitabine was non-inferior to infusional 5-FU with regard to overall survival (75.7 vs. 66.6%; $p = 0.0004$) [20]. Although no difference was seen in overall survival, secondary efficacy endpoints favored capecitabine, with a higher rate of tumor downstaging and pN0 status. A trend was also seen toward an improvement in 3-year disease-free survival in this study (75.2 vs. 66.6%; $p = 0.07$). In this trial, patients who received capecitabine experienced significantly more palmar-plantar erythrodysesthesia but less neutropenia.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 trial also explored the role of capecitabine, randomizing patients with clinical stage II or III rectal cancer to radiation in combination with one of four chemotherapy regimens in a 2 × 2 factorial design: continuous infusion 5-FU, with or without intravenous oxaliplatin, or oral capecitabine with or without oxaliplatin. Mature results from this trial established that continuous infusion 5-FU or oral capecitabine combined with radiation therapy was associated with similar rates of pathologic complete response (18% and 21%, respectively), similar rates of locoregional control and overall survival, and comparable toxicity profiles [21].

NSABP R-04 also demonstrated that adding oxaliplatin to a fluoropyrimidine during concurrent radiation therapy adds toxicity without improving patient outcomes [21]. This result was corroborated by ACCORD 12, which compared capecitabine plus radiation (45 Gy) to capecitabine and oxaliplatin (CAPOX) plus radiation (50 Gy) [22]. The primary endpoint of pathologic complete response was similar in the two groups (13.9 versus 19.2%, $p = 0.09$). While patients treated with oxaliplatin and 50 Gy of radiation had a higher rate of minimal residual disease, this did not impact local recurrence rates, disease-free survival, or overall survival at three-year follow-up.

The German CAO/ARO/AIO-04 trial also assessed the addition of oxaliplatin to fluoropyrimidine-based radiation [23]. This is the exceptional trial that showed higher rates of pathologic complete response in the arm that received oxaliplatin (17 vs. 13%, $p = 0.030$) [23]; however, this difference was possibly confounded by different 5-FU administration schedules [24]. The addition of oxaliplatin to fluorouracil-based neoadjuvant chemoradiation and adjuvant chemotherapy resulted in a small but significant difference in 3-year disease-free survival (75.9 vs. 71.2%, $p = 0.03$) [25].

Meanwhile, we await results from the primary endpoints of overall survival and local tumor control from the STAR-01 trial which randomized 747 patients with resectable, locally advanced adenocarcinoma of the mid-low rectum to receive pelvic radiation and concomitant infused fluorouracil (225 mg/m^2 per day) either alone or in combination with weekly oxaliplatin. In a planned interim analysis, no difference in pathologic responses in the two treatment groups

was detected (16% in both arms; $p = 0.904$) [26]. Grade 3 and 4 adverse events occurred more frequently in patients receiving infusional 5-FU and oxaliplatin plus radiation than in those receiving 5-FU plus radiation (24 vs. 8%, $p < 0.001$). Moreover, data from NSABP R-04 similarly demonstrated added toxicity in the patients receiving oxaliplatin, without improvements in rates of a pathologic complete response, sphincter-saving surgery, and surgical downstaging [21]. While additional follow-up of STAR-01 and NSABP R-04 is needed to evaluate any benefit in terms of local recurrence rates or progression-free survival, based upon currently available data, the addition of oxaliplatin to neoadjuvant chemoradiation is not recommended.

Although nonrandomized trials suggested benefit from the addition of irinotecan to the chemoradiation [27–29], this benefit was not substantiated in a multi-institutional Radiation Therapy Oncology Group (RTOG) trial in which patients with T3 or T4 distal rectal cancers were randomized to continuous infusional 5-FU (225 mg/m^2 daily) concurrent with hyperfractionated RT (55.2–60 Gy at 1.2 Gy twice daily) or to infusional 5-FU (225 mg/m^2 daily 5 days per week) plus irinotecan (50 mg/m^2 once weekly for 4 weeks) and concurrent conventional fractionation RT (50.4–54 Gy in daily 1.8 Gy fractions) [30]. Moreover, the rate of pathologic complete responses was similar in both arms (30 versus 26% with irinotecan), as were acute and late toxicities.

Early studies conducted to evaluate the addition of epidermal growth factor receptor (EGFR) antibodies yielded similarly underwhelming results. SAKK 41/07 was a multicenter, phase II trial which randomized patients with KRAS wild-type locally advanced rectal cancer to receive chemoradiation with or without panitumumab [31]. While the addition of panitumumab to neoadjuvant chemoradiation in patients with KRAS wild-type locally advanced rectal cancer resulted in a higher pathologic complete or near-complete response rate (53 vs. 32% in the group who did not receive panitumumab), this study did not meet the primary endpoint of pathological near-complete or complete tumor response. Moreover, patients who received panitumumab experienced more grade ¾ toxicities.

Phase II studies evaluating the addition of bevacizumab to conventional 5-FU-based chemoradiotherapy provided encouraging rates of pathologic complete responses. However, the results of safety analyses have been mixed, with concerns raised regarding increased risk of anastomotic leaks and/or wound healing complications [32–34]. At the time of this writing, we await the completion of phase III studies to completely delineate the impact of adding targeted therapies to chemoradiation on both long-term outcomes and posttreatment complications. However, based on the activity profile demonstrated in other settings, we do not expect the results of these ongoing studies to change current treatment algorithms.

In conclusion, concurrent use of a fluoropyrimidine during radiation therapy is recommended, with potential benefits including radiosensitization, systemic disease control, and increased rates of pathologic complete response or sphincter preservation. 5-FU should be administered via an infusional schedule at a dose of 225 mg/m^2 per 24 h 5 or 7 days per week, during radiation. For patients who are able to tolerate oral therapy, data support the use of capecitabine as an acceptable alternative to infusional 5-FU, albeit with a unique toxicity profile. A capecitabine dose of 825 mg/m^2 twice daily, 5 days per week during radiation is recommended as a starting dose.

In terms of toxicity differences, one concern is that metabolism and bioavailability of oral fluoropyrimidine is highly variable [35]. Thus, clinical discretion and a careful patient-centered conversation regarding risks and benefits of the two delivery options is necessary. In particular, for patients who have required a diverting ileostomy in the setting of obstruction at presentation or who have baseline diarrhea or malabsorption, there could be an argument against relying on the oral bioavailability and proper absorption of capecitabine. Additionally, increased risk for toxicity from capecitabine in the elderly, possibly due to decreased renal clearance, should be considered.

The Role for Adjuvant Chemotherapy

In the era preceding total mesorectal excision, postoperative 5-FU was shown to improve overall survival in patients with Dukes B and C rectal cancer [36]. In the modern era, however, there is little to no data supporting the current guideline recommendation of adjuvant chemotherapy for all patients with stage II and III rectal cancer, following neoadjuvant chemoradiation and total mesorectal excision, regardless of surgical pathology results. Yet, this has remained the standard of care. In truth, this guideline should be considered an extrapolation of data from the NSABP C-07 and MOSAIC trials demonstrating the benefits of 5-FU plus oxaliplatin for patients following curative resection for node-positive colon cancers [37, 38].

The best, albeit imperfect, data pertaining specifically to adjuvant therapy for rectal cancers come the EORTC Radiotherapy Group Trial 22921. In a preliminary analysis this study and that the addition of 5-FU adjuvant chemotherapy to preoperative chemoradiation did not decrease local recurrence but that there was a trend toward improvement in disease-free survival (HR 0.87; 95% CI 0.72–1.04; $p = 0.13$) among patients who received adjuvant chemotherapy (with or without radiation) following preoperative radiation (with or without concurrent FU-based chemotherapy) [39]. Further follow-up showed that there was no survival benefit from 5-FU chemotherapy, and the disease-free survival benefit was diminished in comparison to the earlier analysis (HR 0.91; 95% CI 0.77–1.08; $p = 0.29$) [7]. A major limitation of this trial was that only 43% of participants completed the full course of adjuvant chemotherapy, possibly compromising the ability to detect any benefit. The failure to deliver the full course of adjuvant chemotherapy in 57% of patients in this trial could explain the lack of a detectable survival benefit, representing either poor decision-making by the treating physicians or the reality of difficulties with tolerance of chemotherapy after chemoradiation and surgery. Additionally, adjuvant chemotherapy was delivered at reduced doses by comparison to US standards. Critics also argue that this trial was underpowered to detect a small difference, which might explain the discrepant findings compared to a large meta-analysis of 9785 participants with locally advanced rectal cancer who participated in 21 randomized controlled trials, between 1975 and 2011, which demonstrated improvement in both overall survival and disease-free survival with the addition of postoperative FU-based chemotherapy [40].

Additional smaller studies have also attempted to address the role of postoperative chemotherapy, following preoperative radiation or chemoradiation. Cionini et al. randomized 655 patients with cT3 or cT4 disease who underwent chemoradiation followed by surgery to six cycles of adjuvant 5-FU/leucovorin versus observation [41]. This study reported overall survival at 5-year follow-up of 68% in the group who received adjuvant 5-FU versus 69% in the observation group. No difference in distant metastases was detected (24.3 versus 23.9% in the observation arms). This study was similarly limited by the reduced-dose bolus delivery of 5-FU.

The Dutch Colorectal Cancer Group conducted a trial that evaluated patients who received preoperative radiation or chemoradiation followed by total mesorectal excision [42]. This study randomized 470 patients to adjuvant chemotherapy with either 5-FU/leucovorin or capecitabine versus observation. Despite a high proportion of pathologic stage III disease in both arms (75.6% and 78.4%, respectively), no differences in overall survival or disease-free survival were detected after a median of 4 years of follow-up. This study was also limited by its small sample size and underpowered to detect a small survival benefit.

The Chronicle study was a small phase III study that randomized patients with locally advanced rectal cancer who received neoadjuvant chemoradiation to receive either 6 months of postoperative chemotherapy with capecitabine/oxaliplatin versus observation [43]. Although this study was closed early due to poor accrual, an analysis of the 113 patients who were randomized demonstrated no trend towards improved outcomes in those who received adjuvant chemotherapy.

The phase III ECOG E3201 trial attempted to investigate the benefits of adding either oxaliplatin or irinotecan to 5-FU-based adjuvant chemotherapy following preoperative or postoperative chemoradiation; however, this study was suspended in lieu of an alternative trial evaluating bevacizumab. Analysis of the 165 patients who were enrolled prior to suspension provided support for the safety profile of FOLFOX regimen in this setting. The phase II ADORE trial randomized 321 patients who had previously completed neoadjuvant therapy followed by TME for rectal cancer to receive either adjuvant 5-FU/leucovorin or FOLFOX. An improvement in DFS was seen in the arm that received FOLFOX compared to 5-FU/leucovorin alone (71.6 versus 62.9%; $p = 0.047$) [44]. In the CAO/ARO/AIO-04 trial, an improvement in 3-year disease-free survival was seen when oxaliplatin was added to 5-FU in both the neoadjuvant and adjuvant setting (75.9 vs. 71.2%; $p = 0.03$) [25].

Suffice it to say, the role for adjuvant chemotherapy for patients with stage II or III rectal cancer who are treated with neoadjuvant chemoradiation remains an unanswered question. The controversy surrounding this issue highlights a number of challenges in clinical trial design specific to this disease, including the broad range of outcomes for patients with clinical stage II and III rectal cancer, which may make detection of a 10% overall survival benefit nearly impossible. Moreover, the challenges of evaluating true stage in rectal cancer are myriad. Notably, in the ADORE study that randomized patients with ypT3–4 or ypN(+) disease to 5-FU/leucovorin versus FOLFOX, an improvement in disease-free survival was seen among the patients with pathologic stage III disease who received adjuvant FOLFOX [44].

It must be highlighted that EORTC 22921 is not an outlier in terms of the tolerance and compliance with postoperative chemotherapy that could contribute to the lack of convincing evidence to support its benefit [39]. In an analysis of SEER data, only 61.5% of patients in the general population treated for a diagnosis of locally advanced rectal cancer between the years of 1998 and 2007 received any postoperative chemotherapy [45]. Even at specialty cancer centers, a sizable proportion of patients (17%) treated with curative intent chemoradiation followed by total mesorectal excision did not complete postoperative chemotherapy [46]. In a multivariate analysis, factors associated with not receiving adjuvant chemotherapy include: age, lower performance status, uninsured or insured by Medicaid, a complete pathologic response, postoperative complications, and no closure of an ileostomy or colostomy [46].

Initiation of adjuvant chemotherapy within 8 weeks of the total mesorectal excision is recommended. This recommendation is based upon a meta-analysis of 15,410 patients with colon and rectal cancers that reported that each 4-week delay in initiation of adjuvant chemotherapy resulted in significant decreases in both overall survival (HR, 1.14; 95% CI 1.10–1.17) and disease-free survival (HR, 1.14; 95% CI, 1.10–1.18) [47]. While some have interpreted this to mean that adjuvant therapy should be administered as soon as a patient is medically able, others have cautioned against overinterpreting this data due to the possibility that worse outcomes in patients starting chemotherapy at later times could be biased by significant comorbidities or surgical complications that portend a poorer prognosis to begin with [48]. It is known that among patients who do receive adjuvant chemotherapy, postoperative complications are linked to delays in initiation following surgery and also linked to worse overall survival [49]. Acknowledging potential confounding from age and comorbidities, we do recommend starting chemotherapy as soon as practical but first allowing for full recovery from surgery.

Finally, the optimal duration of adjuvant chemotherapy remains undetermined. Extrapolating from the MOSAIC trial, from which 6 months of FOLFOX emerged as the standard of care for patients with locally advanced colon cancer, the NCCN Guidelines currently recommend a cumulative 6 months of perioperative chemotherapy in the management of rectal cancer. Counting the approximately 2 months of fluoropyrimidine chemotherapy administered with radiation towards the sum, our standard practice is to attempt to administer a 4-month course of adjuvant FOLFOX.

However, we admonish that there is no evidence that combination therapy is superior to fluoropyrimidine therapy alone in the adjuvant setting for rectal cancer, nor is there data to support the optimal duration of adjuvant chemotherapy. Given our historic reliance on adjuvant colon cancer trials to inform guidelines for adjuvant therapy in rectal cancer, current guidelines regarding duration of adjuvant chemotherapy could plausibly be impacted should the current IDEA collaboration show non-inferiority of six cycles of FOLFOX, compared to 12 cycles, in the adjuvant treatment of stage III colon cancer patients.

The Role for Neoadjuvant Chemotherapy

As a result of the current standard-of-care paradigm of neoadjuvant chemoradiation, followed by total mesorectal excision, followed by adjuvant systemic therapy, local recurrences have become a rare complication, with rates of less than 10%. In the modern era, patients more commonly succumb to rectal cancer as a result of distant metastatic disease, with greater than 25% of stage II and III rectal cancers developing metastatic recurrences. Although neoadjuvant chemoradiation has been shown to decrease the incidence of local recurrence, overall survival and risk of distant metastases are not impacted by radiation therapy [4, 36].

The current paradigm for trimodality therapy delays delivery of systemic chemotherapy until 3 or 4 months following diagnosis. This delay may be theoretically disadvantageous by allowing undetected micrometastatic disease to remain untreated. Moreover, as noted above, adherence to guidelines for postoperative systemic therapy, following chemoradiation and resection, is low. In effort to reduce distant recurrences and thereby increase the long-term cure rate, the role for optimizing the benefits of systemic chemotherapy through earlier introduction is under investigation. Putative benefits include: earlier protection against dissemination of micrometastatic disease; delivery of chemotherapy to the primary tumor with undisrupted vasculature; tumor downstaging, possibly eliminating the need for pelvic radiation in a subset of patients; and less toxicity with better adherence.

A British study treated 77 patients who met MRI criteria for poor-risk rectal cancer (e.g., tumors within 1 mm of mesorectal fascia, T3 tumors at or below levators, tumors extending ≥5 mm into perirectal fat, T4 tumors, and N2 tumors) with 12 weeks of neoadjuvant capecitabine and oxaliplatin, followed by concomitant capecitabine and radiotherapy, followed by an additional 12 weeks of postoperative capecitabine. The radiographic response rate following neoadjuvant chemotherapy alone was 88%, and 86% of patients had symptomatic responses in a median of 32 days. After chemoradiation, the tumor response rate was increased to 97%. Only 3 of 77 patients were inoperable. Although small and nonrandomized, this trial demonstrated substantial tumor regression, rapid symptomatic response, and achievement of R0 resection with incorporation of neoadjuvant chemoradiation [50].

The Spanish GCR-3 phase II study randomized 108 patients with locally advanced rectal cancer to induction chemotherapy with CAPOX versus the existing standard-of-care paradigm of neoadjuvant chemoradiation with postoperative CAPOX [51]. Outcomes were comparable in the two arms with a pathologic complete response rate of 13 versus 14%. Mature follow-up data recently reported comparable 5-year disease-free survival (60.7 versus 64.3%), without a significant difference in local recurrence (7.1 versus 1.9%, $p = 0.36$) [52]. Incidence of grade 3/4 toxicity was notably lower in patients who received preoperative chemotherapy versus those who received postoperative chemotherapy (19 versus 54%). Moreover, the proportion of patients who completed four cycles of chemotherapy was higher in the arm that received preoperative chemotherapy (94 versus 57%).

Based upon demonstration of high response rates and favorable outcomes [50, 51], Schrag et al. undertook a pilot study that enrolled 32 participants with clinical stage II or III rectal cancer who were candidates for a low anterior resection with total mesorectal excision. Patients were treated with six cycles of neoadjuvant FOLFOX,

with bevacizumab added for cycles 1 through 4. Chemoradiation prior to total mesorectal excision was planned only for patients with stable or progressive disease following chemotherapy, whereas responders proceeded directly to TME. All 32 of 32 (100%) of participants underwent R0 resections. Of the 30 patients who completed neoadjuvant chemotherapy, all had tumor regression and underwent resection without preoperative chemoradiation. The pathologic complete response rate to chemotherapy alone was 25% (95% CI 11–43%). The four-year local recurrence rate was 0% (95% CI 0–11%). The 4-year DFS was 84% (95% CI 67–94%). The limitation of this study was that it was a single-institution trial performed at a highly specialized center with dedicated high throughput colorectal surgeons; therefore, the generalizability of results is unknown.

The phase II/III Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT) trial, which will evaluate this treatment paradigm at multiple centers with a target accrual of 1060 patients is ongoing. This study randomizes patients to neoadjuvant FOLFOX followed by low anterior resection with TME if ≥20% tumor regression is observed versus the current standard of care. In patients in whom ≥20% tumor regression is not achieved after chemotherapy, chemoradiation will be administered prior to surgery. The primary endpoint for the phase II component is percent of patients unable to undergo R0 resection and will be assessed after 360 patients have been accrued. If expanded to phase III, the primary endpoint study will be disease-free survival. This study is now open to accrual through the US cooperative group network (NCT01515787) (Fig. 6.1).

The role for preoperative chemotherapy is being evaluated in both Europe and China as well. The BACCHUS trial is a phase II trial that is evaluating the efficacy and toxicity of six cycles of neoadjuvant FOLFOX plus bevacizumab versus six cycles of FOLFOXIRI plus bevacizumab (NCT01650428). Chemoradiation will be selectively utilized. In addition, a three-arm phase II study is being conducted in China which will

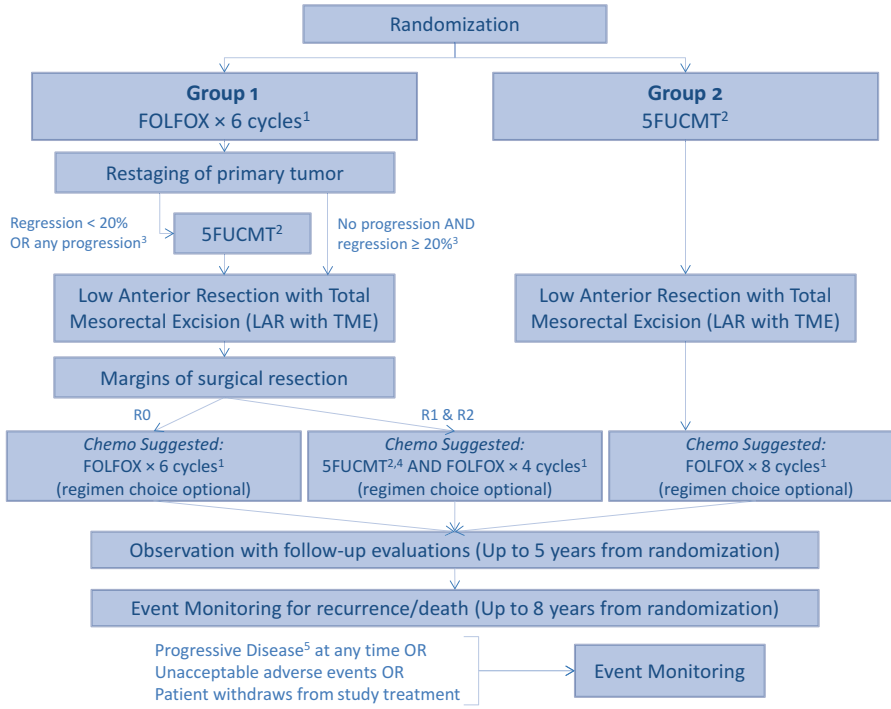

Fig. 6.1 Protocol schema for the phase II/III Preoperative Radiation or Selective Preoperative Radiation and Evaluation Before Chemotherapy and TME (PROSPECT) trial

randomize patients to four cycles of neoadjuvant FOLFOX versus FOLFOX-based chemoradiation versus radiation with 5-FU alone (NCT01211210). The results of the aforementioned trials are likely to either reaffirm our current treatment paradigm or reshape the face of treatment for locally advanced rectal cancer.

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Total Mesorectal Excision

7

Abhi Sharma and John Monson

Total mesorectal excision (TME) is a term coined by Professor Richard J (Bill) Heald from Basingstoke, UK, in the late 1970s. He initially described TME as the excision of the rectum along with the fascia covering it on all sides. TME is now a well-established procedure and a concept that is recognised all over the world to have increased rates of sphincter preservation and reduced the risk of local recurrence in rectal cancer.

Anatomy of the Mesorectum

Understanding the anatomy of the mesorectum is essential to performing a TME. Mesorectum itself as a term has not been a standard term used in anatomical textbooks in the past. It describes the fat around the rectum, which encloses lymphatics and vessels and in turn is enclosed by a thin but well-defined fascial layer. The word "meso" is used even though the rectum is not thought to have a mesentery in the classical sense. This is justified as the mesorectum contains the blood supply and lymphatic drainage of the rectum just like the mesentery of the rest of the small and large bowel. The superior rectal artery continues downwards as continuation of inferior mesenteric artery (IMA) into the mesorectum and supplies most of the rectum and upper anal canal. Similarly, lymphatics from these areas drain to lymph nodes in the IMA territory. All the fat, along with the vessels and lymphatics, is enclosed in a fascial layer, which can be clearly seen on magnetic resonance imaging (MRI) scans and during open or laparoscopic surgery or anatomical dissection. This anatomy of the mesorectum was described over 100 years ago by the Romanian surgeon Jonnesco, although he did not refer to the perirectal tissue by this name [1, 2] and the term mesorectum owes its popularity largely to Bill Heald [3].

One of the most important facets of mesorectal anatomy is the distribution of nerves. Understanding this distribution of the nerves is critical to reducing the urogenital complications associated with TME (Figs. 7.1, 7.2, 7.3, 7.4, 7.5, and 7.6).

The ventral and lateral aspects of upper two third of the rectum is covered by peritoneum which then reflects on to the bladder in males (rectovesical pouch) and the uterus in females (rectouterine pouch). The remainder of the rectum including the ventral aspect of the lower third and all of dorsal aspect of rectum is not

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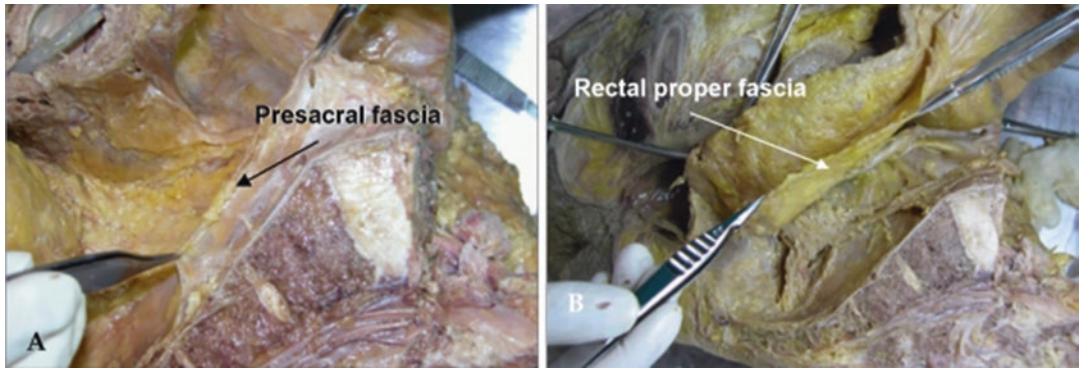

Fig. 7.1 Cadaveric dissection of hemisectioned pelvis. (**a**) Presacral fascia covers the presacral vein over the sacrum. (**b**) The fascia picked up by the forceps is the rectal proper fascia enveloping the mesorectum and the rectum

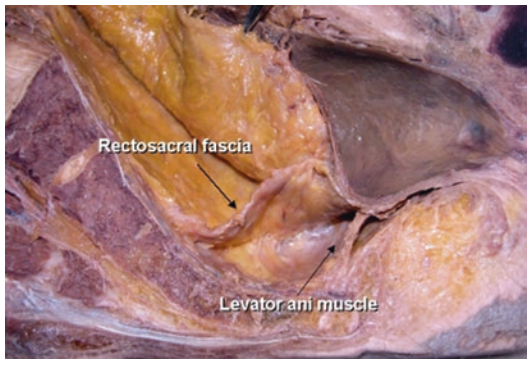

Fig. 7.2 Cadaveric dissection of hemisectioned pelvis; the retrorectal space. The rectosacral fascia is noted in the retrorectal space at the level of 4th sacrum when dissection proceeds along the rectal proper fascial plane

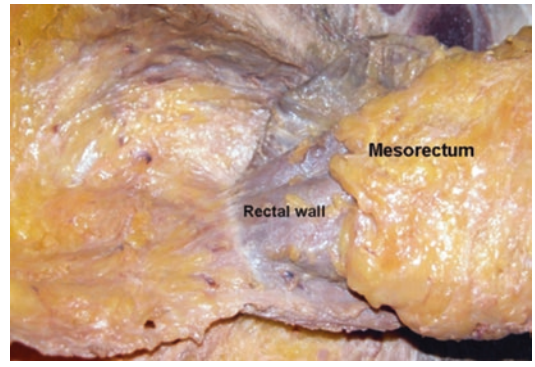

Fig. 7.3 The mesorectum is well developed at the posterolateral side of the rectum. The mesorectum is tapered down, and it ended 2–3 cm above the level of the levator ani muscle

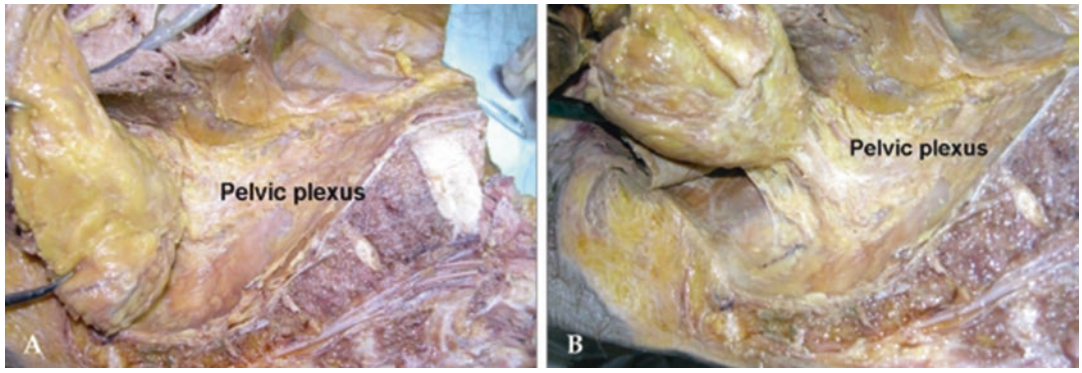

Fig. 7.4 (**a**) The rectal proper fascia is adhesed to the mesh-like pelvic plexus at the lateral pelvic wall. (**b**) The fine branches from pelvic plexus enter the rectal wall. The rectum was attached to the lateral pelvic wall by adhesed pelvic plexus

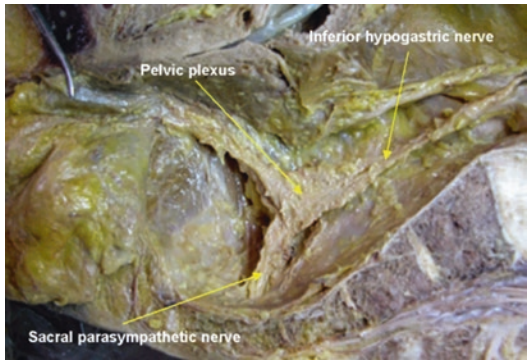

Fig. 7.5 Cadaveric dissection on hemisectioned pelvis shows the inferior hypogastric nerve descend into the pelvic cavity and meet sacral parasympathetic nerve arising from S2th, 3th, 4th foramen nearby the piriformis muscle. The inferior hypogastric nerve forms the pelvic plexus at the lateral pelvic wall after merging the sacral parasympathetic nerves. Nerve bundles from pelvic plexus go to the genitourinary organ along the seminal vesicle in male

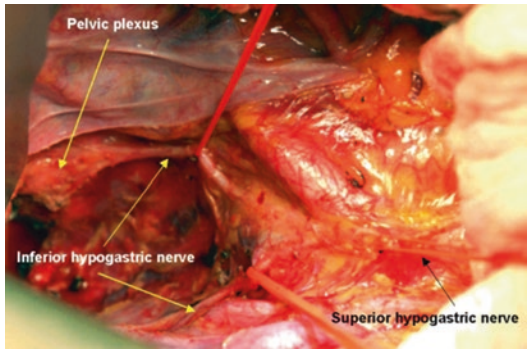

Fig. 7.6 On operative field, bifurcation of the superior hypogastric nerve was noted at the aortic bifurcation. The inferior hypogastric nerve descends along the pelvic side wall. The pelvic plexus forms after merging with the sacral parasympathetic nerve

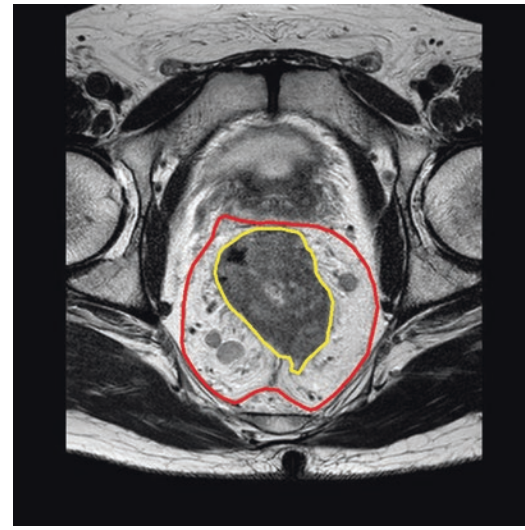

Fig. 7.7 MR pelvis with rectal tumour and mesorectum outlined. The mesorectum is well developed on the posterolateral aspect

Fig. 7.8 Rectal specimen: dissection in TME plane

covered by the peritoneum. However, the rectum and the mesorectum are covered in its entirety by mesorectal fascia. The mesorectal tissue is most obvious and bulky in the dorsal aspect and produces the classically described buttock cheeks on surgical dissection (Figs. 7.7 and 7.8). This fascia separates the mesorectum from the presacral fascia, which covers the sacrum and encloses the hypogastric and splanchnic nerves forming the inferior hypogastric plexus (Figs. 7.1, 7.2, 7.3, and 7.4). The retrorectal space, which is a thin space between the mesorectal and the presacral fascia, constitutes the often described "holy plane" or angel's hair appearance during TME.

The retrorectal space is obliterated as dissection is continued posteriorly at the level of fourth sacral vertebrae where it fuses with the presacral

fascia and forms the Waldeyers' fascia. The retrorectal space constitutes an avascular space and is also free of nerves up to this level.

On the ventral aspect, the upper two thirds of the rectum and mesorectal fascia are covered by peritoneum. The mesorectum itself is thin and less distinct. TME plane is accessed by division of the peritoneum between the rectum and the genital organs. This gives access to the rectogenital septum also known as the Denonvilliers' fascia. It is a thick and distinct fascial structure that can be identified after division of the rectovesical or rectouterine/vaginal peritoneum. The TME plane can be in front of or behind Denonvilliers' fascia. Dissection below Denonvilliers' fascia leaving the fascia on the genital organs is protective of branches of the inferior hypogastric plexus which lie underneath the Denonvilliers' fascia and supply the genital organs. There is some unresolved debate regarding the preferred choice of dissection plane when performing a TME for cancer excision.

Another area of potential nerve injury is on the lateral aspect of the rectum (Fig. 7.4).

Laterally mesorectal fascia is relatively indistinct as it appears to form lateral ligaments. These lateral ligaments are reflections of the mesorectal fascia towards the pelvic sidewall to allow vessels and nerves to reach the rectum. The inferior hypogastric plexus, which is present between the lateral aspect of the presacral fascia and the lateral mesorectal fascia, can be tented in and injured during this lateral dissection (Fig. 7.5). This can be avoided by sharp dissection in this area. If posterior dissection has been completed, sharp circumferential dissection close to the rectal wall will minimise the risk of nerve injury in this area. Occasionally this dissection will encounter the middle rectal vessels. These are branches of the internal iliac artery but are only present in a minority of patients and can be controlled on most occasions by monopolar or bipolar energy devices [4, 5].

Magnetic resonance imaging (MRI) has become an integral part of staging for rectal cancer and helps plan rectal cancer management in the current preferred setting of multidisciplinary team (MDT) management. Current high-resolution MRI techniques help identify all the important anatomical structures around the rectum including mesorectal, presacral and Denonvilliers' fascia. Anatomic landmarks important to the performance of rectal cancer surgery, in particular the mesorectal fascia, can be defined on MRI, and this is of critical importance in the staging of tumours, assessing resectability, planning surgery and selecting patients for preoperative neoadjuvant therapy (Fig. 7.7) [6].

TME History and Literature

TME appears to have been described by Abel in 1931 [7] well before Heald brought it to worldwide attention. Rectal cancer surgery was considered morbid and difficult surgery with high rates of Abdominoperineal excision of rectum (APER), high rates of local recurrence and poor long-term survival [8, 9]. Heald first published the Basingstoke experience in 1979 describing proctectomy with an emphasis on sharp dissection and complete removal of the mesorectum and called it TME [10]. Heald went on to publish the first series of TME for rectal cancer with an extremely low local recurrence rate of 2.7% and an overall 5-year survival of 87.5% [11]. The low recurrence rates have since been verified, and similar results have been reported in other series [12–14].

In addition to reducing recurrence rates, TME has also contributed to improved rates of sphincter preservation. Historically the majority of rectal cancers were treated with APER due to the high risk of local recurrence and the difficulty of creating low anastomoses. A distal margin of 5 cm was used as a minimum margin for rectal cancer resection. This has changed significantly with histopathological and surgical studies showing that cancers rarely show distal intramural spread of more than a centimetre [15–19] and furthermore that no improvement existed in local recurrence or survival if the distal margin was more than a centimetre. The development of linear and circular staplers has also contributed significantly to the technical ability to create a low anastomosis after TME. The data available

therefore supports the use of low coloanal or colorectal anastomosis if the estimated distal margin of resection is more than a centimetre from the sphincter complex and there are no other contraindications to the procedure. The main contraindication to an anterior resection at this level is the presence of preexisting faecal incontinence or the risk of developing incontinence after surgery. This is discussed in more detail under patient selection.

There are other areas that need to be discussed when reviewing TME in 2017. Neoadjuvant radio and/or chemotherapy now have a prominent place in the current management of rectal cancer. Increasingly it is appreciated that tumour-specific partial mesorectal excision for upper rectal tumours may also be an oncologically safe operation with lower risks of complications including nerve injury.

Unsurprisingly, one of the largest single surgeon series of TME has been published by Heald and colleagues [20] who have reviewed their experience with TME at a single centre over a 20-year period. this series included 519 cases of rectal cancer and included curative and palliative resections. Less than 10% of patients received preoperative radiotherapy. One hundred and two patients were Dukes A, 167 Dukes B, 142 Dukes C, and 108 had Dukes D disease (residual or metastatic disease). Four hundred and sixty five anterior resections were performed. The 5-year survival rate was 81%, and the 10-year survival rate was 80% after a curative TME anterior resection in this series. The local recurrence rate in this group was only 2% for curative anterior resections at 5 and 10 years. The study also reported low clinically evident anastomotic leak rate of 6.5% with a further 5.5% radiological leak rate. In this series radiotherapy was used sparingly and did not appear to change the extremely low recurrence rates [20].

Other large series have also shown low local recurrence rates of 6–8% and good long-term survival around 70% [21]. As a result of these multiple series, TME is now accepted all over the world as standard surgery for rectal cancer and has been shown to improve outcomes. Several countries in Europe established training and audit programmes for TME in the 1990s, and improvements in outcomes of rectal cancer have followed. For example, implementation of TME in Norway resulted in a reduction of local recurrence rates from 12 to 6% and improvement in 4-year survival from 60 to 73%. Radiotherapy was only used in 5% of this group of patients [22]. A similar reduction in local recurrence has also been shown in the Netherlands along with a higher survival rate [23].

The use of radiotherapy in other series has been shown to reduce local recurrence rates. The Dutch Colorectal Cancer Group study investigated the efficacy of preoperative short course radiotherapy in conjunction with TME [24]. Curative rectal cancer surgery was undertaken, and patients were randomised to short course radiotherapy (5 Gy over 5 days) followed by TME or straight to TME. The Dutch TME trial included 1861 patients with 924 patients in the radiotherapy followed by TME group and 937 in the TME alone group. There was a significant difference in local recurrence rate in the two groups (2.4% in the radiation and surgery group vs. 8.2% in the surgery alone group, $p < 0.001$). This difference in recurrence was most pronounced for low rectal cancers (<5 cm from anal verge). This study showed that further reduction in local recurrence rate can be obtained with addition of radiotherapy to TME and this benefit is most pronounced in low rectal cancers.

The CR07 study which was a UK- and Canadian-based trial further showed that a good plane of surgery combined with short course radiotherapy further reduced the local recurrence rates. The 3-year local recurrence rate in patients who had good quality TME and short course radiotherapy was only 1% in this study [25].

Neoadjuvant long course chemoradiotherapy has also been compared with postoperative chemoradiotherapy in a German trial (CAO/ARO/AIO-94) [26] in patients undergoing TME for locally advanced rectal cancer (T3, T4 or node positive). The neoadjuvant group showed lower local recurrence rates with no difference in complications or survival. Recently 11-year follow-up results of this trial have been published and show continuing benefit of lower local recurrence rates

in the preoperative neoadjuvant therapy group compared to postoperative group [27]. This study has not shown any survival benefit, although in a nonrandomised trial Delaney et al. demonstrated a survival benefit in their cohort of T3, node-negative patients who received preoperative radiotherapy [28].

The current challenge is to develop better selection criteria for the use of neoadjuvant therapy so that oncologic benefit can be maximised, while cost and complications are reduced. MRI is increasingly being used to determine the stage of rectal cancer along with the risk of involvement of the radial margin. The identification of so-called threatened margins is being increasingly used to select patients for neoadjuvant treatment [29–31].

Neoadjuvant radiotherapy also offers the possibility of allowing sphincter preservation by reducing the size of the tumour. Reduction in the size of tumour may also allow a TME and low anastomosis mitigating the need of a permanent colostomy. This approach also is controversial as some patients who respond may still have microscopic nests of cancer cells which may lead to an inadequate resection [32].

The incidence of anastomotic leak and neural injury is significant with TME and may be related to the level of anastomosis. Surgeons [33] in Hong Kong reported their results on selective use of PME in 622 rectal cancer patients. Patients with mid or low rectal cancers were treated with TME; rectosigmoid and upper rectal cancers were treated with PME, where the rectum was transected 4–5 cm below the tumour. TME was performed in 396 and PME in 226 patients. TME was associated with longer operative times, higher blood loss, longer hospital stays and a higher incidence of stoma formation. The rate of anastomotic leaks was significantly higher with TME compared with PME (8.1 versus 1.3%). TME was an independent risk factor for anastomotic leak on multivariate analysis. The authors recommend a selective use of TME based on this data which also shows similar oncological outcomes with the two techniques. This data has been replicated in other studies showing similar local recurrence rates in TME and PME [34].

In summary therefore, TME produces superior control of local recurrence as compared with conventional surgical techniques; however, PME in the same plane is appropriate in selected cases. The benefits of TME appears to be additive with the effects of neoadjuvant radiotherapy in most published series.

Complications of TME

It is clear that TME is the standard surgical approach to rectal cancer and has become widely accepted. TME, however, is associated with some complications. As noted earlier, there is a concern that anastomotic leak rate after TME may be significantly higher compared to non-TME dissection. TME leads to a low anastomosis and studies confirm a higher leak rate in lower anastomosis.

The use of neoadjuvant chemoradiotherapy may contribute to devascularisation of the anorectal stump leading to higher leak rates [35]; however, if a defunctioning stoma is used, it does not seem to increase the risk of other complications [36], and several authors recommend formation of a routine diverting stoma after TME after neoadjuvant therapy.

As a follow-up to the Dutch TME trial, the [23] short- and long-term outcomes of patients from the Dutch TME trial [24] were compared with data from the previous trial of cancer recurrence and blood transfusion (CRAB). Rectal cancer resection involved non-TME dissection in the CRAB trial. The patient population included was older and included more women. Tumour features were however similar between the two studies. The incidence of anastomotic leaks was higher in the TME trial on univariate analysis in this comparison, but this was not significant on multivariate analysis. Anastomotic leak rates of 7–15% and other morbidity of up to 40% have also been described in other studies [37, 38].

Elsewhere, a prospective study of 1958 patients undergoing TME for rectal cancer showed that the risk of leakage was significantly higher in men, in patients undergoing neoadjuvant radiotherapy and in anastomoses that were ≤6 cm from the anal verge [35].

There is also some evidence that leak rates may reduce as surgeon experience builds up [39] and the clinical incidence and detrimental effects of anastomotic leakage are lower if a defunctioning stoma is used [40].

Lower leak rates have also been described in PME for higher rectal cancers, and this is an argument for utilising PME in selected cases [33].

Functional Outcome After TME

TME can lead to increase in bowel frequency, urgency and associated faecal incontinence. This results from the removal of rectal reservoir function and is exacerbated by possible sphincter and neural injury resulting from rectal and pelvic dissection. Anorectal function is compromised after TME with or without the use of preoperative radiotherapy though functional symptoms are worse after neoadjuvant radiotherapy. Anorectal function appears to improve after 12 months especially in the absence of neoadjuvant radiotherapy [41]. In patients who receive preoperative radiotherapy, the effects on anorectal function persist for the longer term. The long-term follow-up of patients from the Dutch TME trial has shown significantly more bowel dysfunction and increased use of incontinence material in patients who received neoadjuvant radiotherapy after a median follow-up of over 14 years [42].

The use of adjuvant radiotherapy can also cause postoperative deterioration of anorectal function. Kollmorgen et al. [43] compared 41 patients who received postoperative radiation to 59 patients who did not. The patients who received radiotherapy had a significantly higher number of incontinent episodes compared to the surgery alone group.

Anastomotic leakage with associated fibrosis also results in poorer function in the long term. Indeed anterior resection syndrome is well recognised and significantly impairs quality of life [44].

Older age and poor baseline anorectal function may lead to poor post TME function. It may be prudent to consider an end stoma in selected patients who are at high risk of poor postoperative functional results, but this has to be a joint decision along with the patient discussing all the risk factors and the effect on their quality of life [45]. This is especially relevant as some studies have shown no difference in post TME bowel function in older (pt > 65 years) compared to younger patients [46, 47].

Preoperative anorectal function may be more relevant compared to age in predicting postoperative anorectal function. Yamana et al. [48] concluded that patients who had a longer anal high-pressure zone, larger maximum tolerable rectal volume and lower rectal sensory threshold had improved postoperative evacuatory function after anterior resection. In summary, a significant number of patients will experience significant reduction in continence scores after surgery alone. This functional damage is further worsened by the addition of radiotherapy [49].

Urinary and Sexual Function After TME

Identification and protection of autonomic nerve fibres is an essential part of TME. The anatomy of nerves is now well described along with an understanding of areas during dissection where there is an increased risk of neural injury. Precise dissection in TME plane, dissection close to the rectum laterally and dissection behind Denonvilliers' fascia are all protective of urogenital nerves [4, 50]. In anterior tumours, dissection is needed in front of Denonvilliers' fascia, and nerve protection can be achieved in these patients with sharp dissection through Denonvilliers' fascia before it fuses with the prostatic fascia [51]. Careful identification and protection of pelvic nerves results in improved postoperative urogenital function after TME. In a study by Junginger et al. [52], complete or partial identification of pelvic nerves was achieved in 82% of patients. Postoperative bladder function was significantly better in patients in whom nerves were identified.

Even though TME may be a more radical procedure compared to non-TME dissection, the sharp dissection with the understanding of anatomy and concerted attempt to preserve the autonomic nerves may lead to less urogenital dysfunction

compared to traditional surgery. Maurer et al. compared 29 patients with non-TME dissection to 31 patients after TME and described a lower incidence of postoperative sexual dysfunction in the TME group [53]. Shirouzu et al. reported similar results in a review of 403 patients undergoing proctectomy over a 20-year time span, with some patients having a nerve-sparing approach and some not [54]. Urinary and sexual function was better preserved in the nerve-sparing group. Another study by Kim et al. also compared nerve sparing approach with non-nerve sparing in 69 men and showed a higher rate of preserved sexual and urinary function in the TME group [55].

Neoadjuvant radiotherapy also leads to higher rates of sexual dysfunction and result in a decrease in health-related quality of life (HRQoL). Marijnen et al. studied the HRQL and sexual function of 990 patients who underwent TME and were randomly assigned to either surgery alone or neoadjuvant short course radiotherapy. Overall HRQoL was similar between the two groups, but neoadjuvant radiotherapy had a negative impact on sexual and urologic function in this study [56].

Bowel Reconstruction After TME

Several techniques are used to restore bowel continuity after TME. Bowel continuity may be restored by a straight (end to end) colorectal/coloanal anastomosis. This may be achieved using a stapler or by a hand-sewn anastomosis. Bowel continuity may also be restored by a side to end anastomosis or by formation of a neorectum by coloplasty or a colo pouch. Colonic pouch formation is shown to result in better functional outcome compared to a straight anastomosis in several studies—at least in the relative short term [57]. The benefit appears to persist in the longer term although the difference in functional outcome is reduced at 12 months post-surgery [58, 59].

Meta-analysis of studies comparing pouch to straight anastomosis has suggested that the pouch option provides better functional outcomes than coloanal anastomosis, including reduced urgency rates and the reduced need for antidiarrheal medications. Leak rates have been shown to be as low as 3% in colonic pouches compared to up to 15% in patients with straight anastomosis [58, 60, 61].

Interestingly, other studies have shown a higher risk of anastomotic leak in colonic pouches compared to coloplasty [62]. Transverse coloplasty may reduce the evacuatory problems described in colonic pouches with an equivalent functional result. [63]. Remzi et al. also reviewed the complication rates, functional outcomes and quality of life in patients undergoing anterior resection with a low anastomosis comparing coloplasty ($n = 69$), a colonic J-pouch ($n = 43$) or a straight coloanal anastomosis ($n = 50$). The patients with a straight anastomosis had a worse quality of life and functional outcome than did patients who underwent a coloplasty or colonic J-pouch, both of which had similar QoL outcomes [64].

Defunctioning Stoma After TME

Anastomotic leak is a devastating complication after TME, and one strategy to reducing the morbidity of an anastomotic leak is by creating a defunctioning stoma. It has been shown in a systematic review that defunctioning ileostomy reduces the incidence of clinically relevant anastomotic leakage reducing the need for reoperation [65].

On the other hand, ileostomy formation and closure are also associated with a significant incidence of complications [66], and some ileostomies may never be closed resulting in long-term effects. In the Dutch TME trial, 19% of ileostomies were never closed mainly due to postoperative complications [67].

The decision of perform an ileostomy can therefore be difficult and often is a subjective choice. Several authors recommend blanket defunctioning ileostomy for all mid and low rectal cancers after TME [65], whereas others utilise a more selective approach. Wolthius et al. performed an audit of their approach of selective use of defunctioning ileostomy and showed that in 65% of TME defunctioning stoma can be avoided

without increasing risk. According to their data, their leak rate in patients without defunctioning stoma was 10.1% (19/266), and 15 out of the 19 (78%) patients with anastomotic leakage required a secondary stoma in addition to 78 patients who were defunctioned primarily due to the presence of risk factors [68]. Avoidance of stoma also improves quality of life and also reduces costs in the long term [60]. Quality of life is poorer in patients with stoma and appears to improve soon after reversal [69].

Difficult resections, excessive bleeding (>1 l), presence of advanced disease, radiation enteritis, male gender, obesity, incomplete donuts and positive leak test have all been cited as predictors of leaks needing defunctioning stoma in various series [60, 68] and should be considered in the decision-making process.

The evidence suggests that selective use of ileostomy is justifiable in the absence of risk factors. In our practice, we continue to use a defunctioning ileostomy in majority of TME resections. We will usually close the ileostomy within 3 months in patients who do not require postoperative chemotherapy.

Open vs. Laparoscopic vs. Robotic TME

The initial description of TME was as an open operation. Laparoscopic TME was first described in case series by enthusiastic surgeons, and early trial data was disappointing showing a higher risk of positive circumferential margin involvement with laparoscopic TME [70]. Studies in the ensuing period however have shown that laparoscopic rectal surgery is oncologically equivalent to open TME. In addition laparoscopic TME has significant short-term benefits with lower pain, quicker recovery and lower incidence of some complications [71].

Robotic-assisted TME is a relatively new technique, and evidence supporting robotic resection consists mainly of case series. Robotic TME has been shown to be an oncologically safe operation in these series though cost and duration of surgery are higher compared to laparoscopic TME [72]. A recent randomised controlled trial (ROLARR) has been completed comparing laparoscopic and robotic surgery. The published data is awaited, but recent presentations have shown robotic resections to be equivalent with some possible short-term benefits.

Conclusion

TME has become the standard approach for rectal cancer surgery worldwide. This has led to a significant reduction in local recurrence rates with no significant increase in surgical morbidity. TME has also led to a better understanding of anatomy of the rectum and pelvis, and this has allowed surgeons to perform sharp dissection in the TME plane allowing sparing of urogenital nerves. Neoadjuvant radiotherapy appears to be complementary to TME surgery and reduces local recurrence rates further but increases some postoperative complications. Laparoscopic TME has been shown to be oncologically equivalent to open TME while reducing the short-term morbidity.

Surgical Technique

Preoperative Assessment

All patients should be investigated prior to surgery to stage the tumour and rule out synchronous disease. All patients should be discussed in the colorectal MDT with a review of clinical findings along with histology, dedicated MRI of pelvis and CT of the chest and abdomen. Current standard of care is to use neoadjuvant long course chemoradiotherapy if the circumferential margin is threatened or short course radiotherapy for T3 cancer in upper or mid rectal tumours without potential margin involvement. Increasingly, induction chemotherapy alone is being evaluated as a way of being more selective in the use of radiotherapy. All patients also undergo preoperative fitness assessment depending on their medical history and exercise tolerance. Selected patients are referred for cardiopulmonary exercise testing (CPEX). Patients are seen in a clinic with colorectal

nurse practitioners and reviewed by stoma nurses prior to surgery for education and training with respect to likely ileostomy formation.

Although we recognise the data is unclear on this matter, we have recently reverted back to using mechanical bowel prep for all patients who are likely to need a defunctioning ileostomy. This at present includes all patients with mid or lower rectal cancer requiring TME and any patient receiving neoadjuvant radiation therapy.

Patients are placed in Lloyd Davies position and are catheterised prior to procedure. A Foley catheter is inserted and rectum is washed out with povidone iodine solution. Patients also receive broad-spectrum antibiotics and low molecular weight heparin prior to skin incision.

Our default is to perform laparoscopic rectal resections unless there are obvious contraindications. These may include high BMI or previous abdominal surgery both of which are only relative contraindications. Rarely we will consider significant cardiac morbidity, which may be a contraindication to pneumoperitoneum. We have also started performing transanal TME (taTME) in selected cases, and this technique is described elsewhere.

We use a four (or rarely five)-port technique. The first port is placed in the supraumbilical region, and we use an 11 mm port at this site. A 12 mm port is introduced in the right iliac fossa to facilitate the endoscopic stapler. One 5 mm port is inserted in the right middle quadrant and a 5 mm port in the left middle quadrant.

Diagnostic laparoscopy is performed to rule out obvious metastatic disease. For most patients, the first step will be formal mobilisation of the splenic flexure as this has to be performed regardless of the subsequent operative procedures. The greater omentum is separated from transverse colon to enter the lesser sac, and the dissection is carried on to mobilise the flexure completely. The mesocolon is not divided at this stage.

A standard medial to lateral dissection is carried out, dividing the peritoneum above the sacral promontory and letting the pneumoperitoneum aid the dissection in this area. Obvious gas dissection usually indicates that the initial incision is in the right place! The right ureter can be easily identified in most patients at this stage. The plane is developed between the mesocolon and retroperitoneal fat using primarily traction and blunt dissection to push the retroperitoneal fat. The left ureter is identified at this early stage crossing the common iliac artery. Dissection is carried upwards identifying the inferior mesenteric artery (IMA). The ureter is again identified in this area prior to dividing the IMA. This is also an area of potential nerve injury, and we dissect the IMA fully and push all surrounding tissue backwards clearing the artery completely before its division. This is followed by high division of the IMV ideally at the lower border of the pancreas or adjacent to the duodeno-jejunal junction. Medial to lateral dissection is carried out until above the upper pole of the kidney and laterally up to the abdominal wall where the peritoneal incision will meet that from the previous splenic flexure mobilisation. The lateral peritoneal reflection (white line of Toldt) can be visualised in the medial to lateral dissection and helps to ensure a bloodless dissection plane. Finally the dissection is completed from lateral to medial side and should consist of division of a thin layer of peritoneum to enter the plane of previous dissection. For the superior part of the lateral to medial mobilisation, vision may be aided by a left side up tilt on the operating table. The previous medial to lateral dissection is useful if it has been carried out to above the superior pole of the kidney.

The pelvic stage of the operation is started by lifting the rectosigmoid junction and following the plane posterior to the IMA by sharp dissection. The peritoneum is initially divided only on the right side, and mesorectal plane is identified. The classic Angel hair appearance is identified, and TME is carried down over the sacral promontory and into the pelvis. Sharp dissection of the mesorectal plane is performed using a hook dissector. This ensures a smooth mesorectal dissection and allows identification of important adjacent structures and avoids inadvertent injury to the neural structures. Sharp dissection allows dissection in a bloodless plane. Hypogastric nerves are identified at this point and preserved. The posterior plane is developed first, but it is

important to avoid tunnelling in the lowest part where the sacrum turns forward; otherwise, sudden bleeding from presacral veins may lead to a loss of view. Walderyers fascia is divided to get access to the lower rectum and mesorectum to ensure complete TME. The risk of sacral venous injury is high in this area if the curve of the sacrum is not identified leading to division of the presacral fascia. The dissection is then carried to the lateral aspect staying close to the mesorectum to avoid damaging the inferior hypogastric plexus at the site of the so-called lateral ligaments. Dissection is circumferential from posterior to lateral aspect to ensure that the lateral dissection is at the same level as posterior dissection. Anterior dissection is started at this stage and our approach depends on the location of the tumour. In case of anterior tumours, if CRM is threatened, we divide the peritoneum anterior to the peritoneal reflection to reach the plane in front of Denonvilliers' fascia. The plane is developed between the Denonvilliers' fascia and prostate or vagina, and an incision is made in the fascia just before it inserts into the prostatic fascia to expose rectum. Our default however is to develop the dissection plane behind Denonvilliers' fascia by making the initial incision posterior to the peritoneal reflection. This technique has a better chance of preserving the hypogastric nerves which lie in front of Denonvilliers' fascia.

Complete mobilisation of rectum is achieved when the levator muscles of the pelvic floor are seen "jumping" when touched by a monopolar current. The rectum is divided at this stage. This is another stage where we vary our approach depending on the patient anatomy. A laparoscopic stapler is used in most patients if we can achieve division using two or less reloads. On the rare occasions where this appears to be difficult to achieve, we divide the rectum after making a Pfannenstiel incision and using open transverse stapler. Colorectal/coloanal end-to-end anastomosis is fashioned using a circular stapler. The final anastomosis is actually best performed laparoscopically following reinflation of the abdomen rather than struggling to gain access through a small suprapubic incision.

Pfannenstiel incision is also utilised to deliver the specimen. We routinely use a small wound protector during the specimen delivery to ease the specimen delivery, reduce wound infection and reduce the theoretical risk of implantation. We do not routinely check the vascularity of the colon by assessing bleeding from marginal vessels though this has been described in the literature. Majority of patients having TME also get a defunctioning ileostomy.

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Abdominoperineal Excision

8

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History

The story of abdominoperineal resection (APR) is one of surgical pioneers and innovators who not only developed revolutionary techniques to optimize outcomes but also contributed to our progressive understanding of rectal cancer biology. Prior to the introduction of surgical treatment, rectal cancer was a uniformly fatal disease. During the nineteenth and early twentieth centuries, extirpation of rectal tumors generally involved a perineal approach. In 1826, Jacques Lisfranc described a technique of blunt circumferential dissection through a perianal incision and subsequent amputation of the tumor-containing portion of the rectum. The transected rectum was allowed to retract and the wound packed for hemostasis and left open to drain [1]. Various modifications were adopted by Aristide Verneuil, Emil Kocher, and Paul Kraske using first coccygectomy and later sacrectomy to improve exposure and thus allow for more radical transperineal excisions [1–3]. Unfortunately, these approaches were associated with frequent incontinence, rectocutaneous fistulae, a mortality rate of approximately 20%, and a recurrence rate of 80% [1, 2].

Not until the advent of Joseph Lister's principles of surgical asepsis and the introduction of combined spinal and gas anesthesia near the turn of the century that laparotomies were able to be performed [3]. The first combined abdominoperineal approach for the excision of a rectal cancer is attributed to Vincenz Czerny, a student of Theodor Billroth and head of surgery at the Universities of Heidelberg and Freiberg. During a sacral approach to excise a rectal cancer in 1884, Czerny was unable to complete the resection requiring him to reposition the patient supine and complete the operation through an abdominal incision [2, 3].

While several other surgeons began to explore the idea of a combined abdominoperineal approach for rectal cancer resection, the formal one-stage APR wasn't described until 1908 by William Ernest Miles. Miles trained at St. Bartholomew Hospital in London under the tutelage of Harrison Cripps, a renowned rectal surgeon in the late 1800s. Rather than de novo lesions explaining metastatic malignancies, as was the common belief at the time, Cripps and, subsequently, Miles supported the emerging concept that metastases represented tumor cells disseminated from the primary tumor through the blood and lymphatics [3]. In his landmark publication [4], Miles reported his personal experience of treating rectal carcinoma with perineal excisions. Out of 57 patients, 54 had developed

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local recurrences within 3 years. Postmortem examinations revealed a "zone of upward spread of cancer from the rectum" where metastases were found in the pelvic peritoneum and mesocolon extending to lymph nodes situated over the left common iliac artery. Given that these areas were clearly "beyond the scope of removal from the perineum," Miles proposed an extensive mesenteric lymphadenectomy in order to prevent recurrence. He later went on to describe "zones of downward and lateral spread [5]" creating the foundation for the concept of wide perineal dissection during APR.

The resultant operation, known as the Miles procedure, was a one-team combined abdominoperineal approach with en bloc removal of the rectum, sigmoid, and associated lymph nodes [4]. Through a supraumbilical celiotomy, the proximal sigmoid was transected and the proximal end externalized and secured to the abdominal wall. The inferior mesenteric artery was divided distal to the left colic artery, and the sigmoid, mesocolon, and rectum were completely mobilized down to the pelvic floor. The celiotomy was closed, and the patient was then placed in the right lateral, semiprone position. The perineum was incised widely, the coccyx removed, and the levator ani muscle divided as laterally as possible. The specimen was dissected off the prostate or vagina and removed through the perineal opening. The skin edges were sutured closed over large drains. Lastly, a small colotomy was made in the externalized colon. The entire operation was usually performed by Miles in less than an hour and a half [6]. In his original description, Miles emphasized several essential principles of his operation, including (1) resection of the rectum and sigmoid with their blood supply, (2) complete pelvic mesocolon excision, and (3) wide perineal margins with resection of the levator ani muscle [4]. While the technique of total mesorectal excision, not described until 1982, largely disproved Miles' postulate of downward and lateral spread [7], many of Miles' oncologic principles still hold true today.

Despite its potential oncologic advantages, an initial mortality rate of over 40% contributed to the reluctance of most contemporary surgeons to readily adopt APR for rectal cancer [4]. Yet, convinced that curative resection was only possible by APR, Miles and others continued to refine the technique. In 1912, William Mayo, one of the founders of the Mayo Clinic in Rochester, Minnesota, first described a two-stage APR, which was quickly adopted by others. This modification involved mobilization of the rectum through a laparotomy with creation of an end colostomy followed by transperineal rectal resection several weeks later. Within a few years, operative mortality had been cut to approximately 20%, and with further improvements in patient selection, anesthesia, and the development of blood transfusion, mortality dropped to less than 10% by the end of World War II [1–3]. By this time, Miles had reported a recurrence rate of 30% in his earliest survivors [2], and the theorized oncologic basis of the Miles procedure was substantiated by the histologic description of local and lymphatic metastases by Cuthbert Dukes, a renowned pathologist from St. Mark's Hospital in London [8]. In 1938, Oswald Lloyd-Davies of St. Mark's Hospital in London reintroduced the one-stage radical APR with patients placed in lithotomy-Trendelenburg position and used a synchronous, two-team, combined abdominal and perineal resection, which greatly improved the speed and efficiency of the procedure [2].

By the mid-twentieth century, the reduced recurrence rate, acceptable mortality, and improved efficiency led to the acceptance of APR as the standard of care for all rectal cancers (and those of the distal sigmoid) irrespective of tumor location. Nonetheless, APR remained a morbid operation for patients due to the need for a permanent colostomy and its frequent sequela of genitourinary dysfunction. This led to the interest in exploring sphincter-preserving surgical approaches for the treatment of rectal cancer. Beginning in the 1930s, Claude F. Dixon began to challenge the necessity of APR for proximal rectal and distal sigmoid cancers, describing sphincter-preserving anterior resection with end-to-end colorectal anastomosis [9]. He later reported an experience of 426 cases with an operative mortality of 5.9% and 5-year survival of 68% [10]. The acceptance of anterior resection

over APR for mid and proximal rectal cancers was further established by a large multicenter review of 829 patients comparing APR to segmental resection for proximal rectal cancers which showed an equivalent recurrence rate (22%) but lower 5-year survival (27% vs. 49%) among patients treated with APR [11].

Inspired by such results, surgeons sought alternate surgical techniques which could achieve sphincter preservation for low rectal cancers while maintaining satisfactory oncologic outcomes. End-to-end anastomosis (EEA) staplers were first introduced in 1977 making ultra-low pelvic anastomoses possible [2]. At the same time, the previously accepted requirement of a 5-cm distal margin was challenged. Authors began to report equivalent survival and recurrence rates for resections with less than 2-cm distal margins [3, 12], further promoting sphincter-preserving anterior resection over APR for all but the lowest rectal tumors invading the anal sphincter. In the 1970s and 1980s, several reconstructive techniques including rectal pull-through with coloanal anastomosis and various colonic pouch configurations were introduced. More recently, transanal endoscopic microsurgery techniques have allowed select T1 rectal cancers with favorable features to be treated by local excision. Laparoscopic and robotic techniques, along with advances in neoadjuvant chemoradiation and systemic chemotherapy, have also influenced the role of APR over the past two decades. As a result of these pioneering advances, the rates of APR for the surgical treatment of rectal cancer have fallen to less than 15%, while at the same time the rates of local recurrence and long-term survival have steadily improved (Fig. 8.1) [3].

Indications

The indications for APR have evolved significantly over the past century. As noted above, due to advances in surgical technique, technology, and understanding of rectal cancer biology, fewer and fewer patients require APR to achieve adequate local control. The primary objective of rectal cancer surgery remains oncologic cure with the preservation of sphincter and sexual and urinary function as desirable secondary goals. As such, the choice of surgical procedure depends on the surgeon's ability to achieve histologically negative proximal and distal margins and to perform a total mesorectal excision to obtain adequate radial clearance and lymph node dissection. The selection of APR over a less morbid sphincter-sparing operation is most often determined by the distal extent of disease. Inability to clear distal disease, resulting in a positive margin, is associated with a local recurrence rate approaching 40% (HR = 16.8, 95% CI 4.8–5.9) [13] and decreased 5-year survival (HR = 2.35, 95% CI 1.08–5.11) [14].

Defining the adequate distal surgical margin in rectal cancer has been the source of significant investigation over the past half century. In the 1950s, Robert Grinnell of Columbia University in New York City recommended a 5-cm distal margin for rectal cancer based on histologic examinations of distal intramural extension [15]. Subsequent studies have demonstrated that distal intramural spread beyond 1 cm occurs in less than 20% of specimens [16, 17]. And when present, distal intramural spread is associated with a poorly differentiated, aggressive cancer and portends a poor prognosis from *distant* failure regardless of distal margin status [16–18]. A 2-cm negative distal margin was established in the 1980s by multiple retrospective studies [19–21] and a secondary analysis of patients from the randomized National Surgical Adjuvant Breast and Bowel Project (NSABP) R-01 trial. In this study, no significant differences were identified in relative risk of local failure or relative risk of death when comparing distal margins of <2 cm, 2–2.9 cm, and >3 cm [22]. Subsequent studies confirmed acceptable and equivalent recurrence and survival rates using 2-cm distal margins [18, 23–25]. However, the 2-cm distal margin rule was largely established before the routine use of total mesorectal excision (TME) and neoadjuvant chemoradiation [26]. The most recent studies evaluating acceptable distal margins in the setting of current treatment practices have shown that microscopically negative margins, even

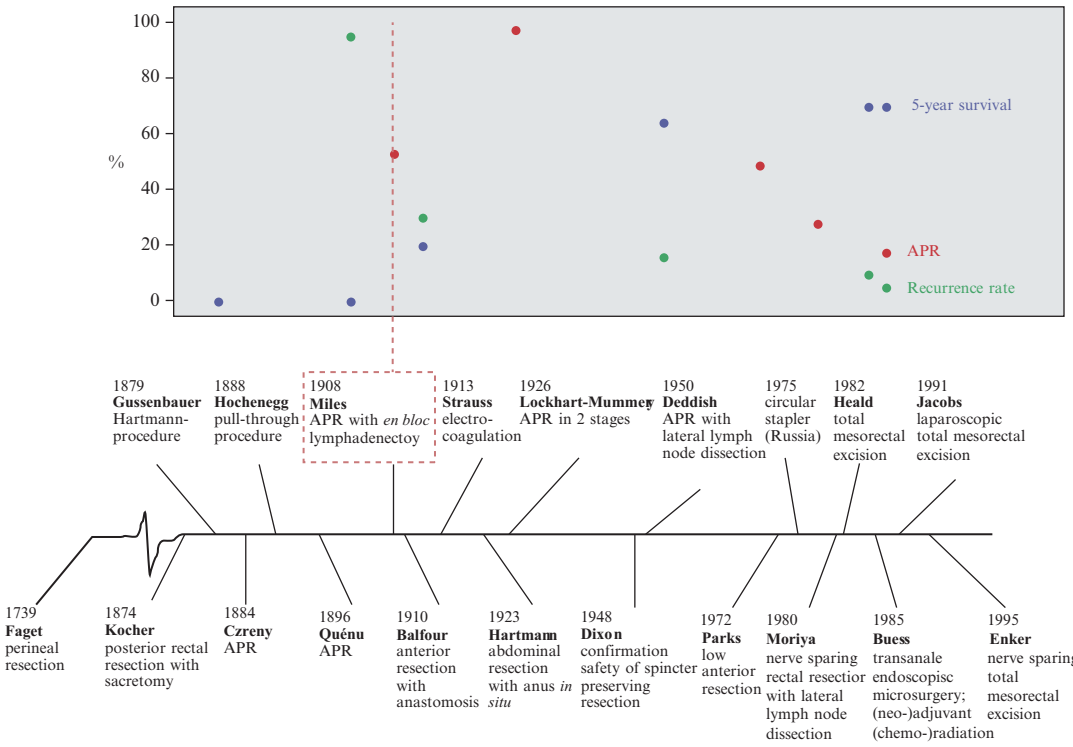

Fig. 8.1 Estimated 5-year survival and recurrence rates of rectal cancer patients over time as they relate to the proportion of rectal cancer operations comprised by abdominoperineal resections

when <1 cm, are associated with low local recurrence rates [14, 27–29]. In a meta-analysis of 3680 patients from 13 studies treated with sphincter-saving resections with or without chemoradiation, no significant difference in local recurrence rates were found among cases with a negative distal margin less than 1 cm compared to greater margins [30].

Based on these data, most specialized centers are able to apply sphincter-sparing techniques for the majority of low rectal cancers and reserve APR for malignancies with significant direct involvement of the sphincter complex or bulky tumors which preclude a negative distal margin. Certainly, in cases of impaired preoperative sphincter function, such patients may be better served by APR even if sphincter preservation is technically feasible (see Quality of Life section below).

Techniques

Principles

Regardless of operative technique, the oncologic surgical principles remain the same. The concept of total mesorectal excision (TME), as originally described by Richard Heald in the early 1980s, includes meticulous surgical dissection of the rectal mesentery and has been shown to increase overall survival and decrease local recurrence [31]. The open operation begins with mobilization of the descending and sigmoid colon from the lateral attachments at the white line of Toldt. The colon and its mesentery are mobilized medially off the retroperitoneum as the ureter is identified and protected. The splenic flexure is not usually taken down since an anastomosis will not

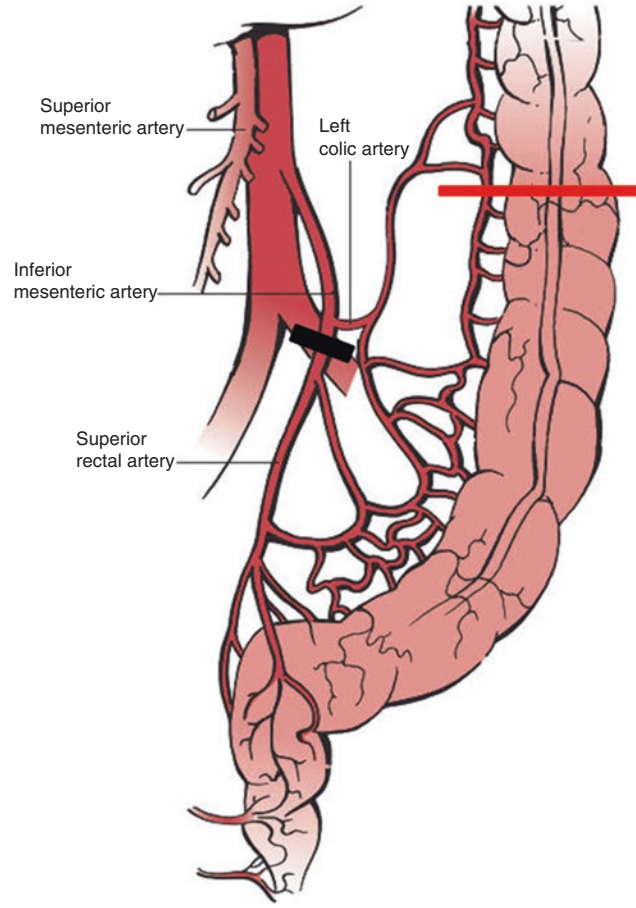

Fig. 8.2 Relevant vascular anatomy of the rectosigmoid. Ligation of the superior rectal artery at its origin off the inferior mesenteric artery preserves the left colic artery optimizing perfusion to the descending colon and eventual end colostomy. From Fischer's *Mastery of Surgery* textbook, sixth ed

be created. If additional length is required, the splenic flexure may be taken down and the inferior mesenteric vein ligated near the duodenal-jejunal flexure medially. The origin of the superior rectal artery off of the inferior mesenteric artery (IMA) is identified and is ligated at this point. The corresponding point on the descending colon represents the proximal resection margin, and the colon and adjacent mesentery are divided at this level (see Fig. 8.2). For minimally invasive approaches, a medial to lateral approach is often taken to isolate the superior rectal pedicle. This then facilitates a complete submesenteric dissection prior to the division of the remaining lateral attachments of the sigmoid and descending colon. Frequently, the descending colon is not immediately divided to allow traction on the rectum during minimally invasive pelvic dissection.

At this point, attention is directed toward pelvic dissection, and the patient is positioned in Trendelenburg position with the small intestines packed away for improved visualization. The rectal dissection is begun at the sacral promontory, and the retrorectal space is identified. A circumferential dissection of the rectum and mesorectum is performed as described in the chapter on total mesorectal excision. Laterally, care is taken to avoid injury to the internal iliac vein as well as the ureters at the pelvic brim. Posteriorly, care is taken to identify the hypogastric nerves as they course from the midline laterally; injury to these structures can result in retrograde ejaculation. Anteriorly, the anterior rectal wall is separated from the bladder and, in men, the prostate and seminal vesicles and, in women, the posterior vaginal wall along the fascia of Denonvillier (see Fig. 8.3). In most cases, dissection can be carried

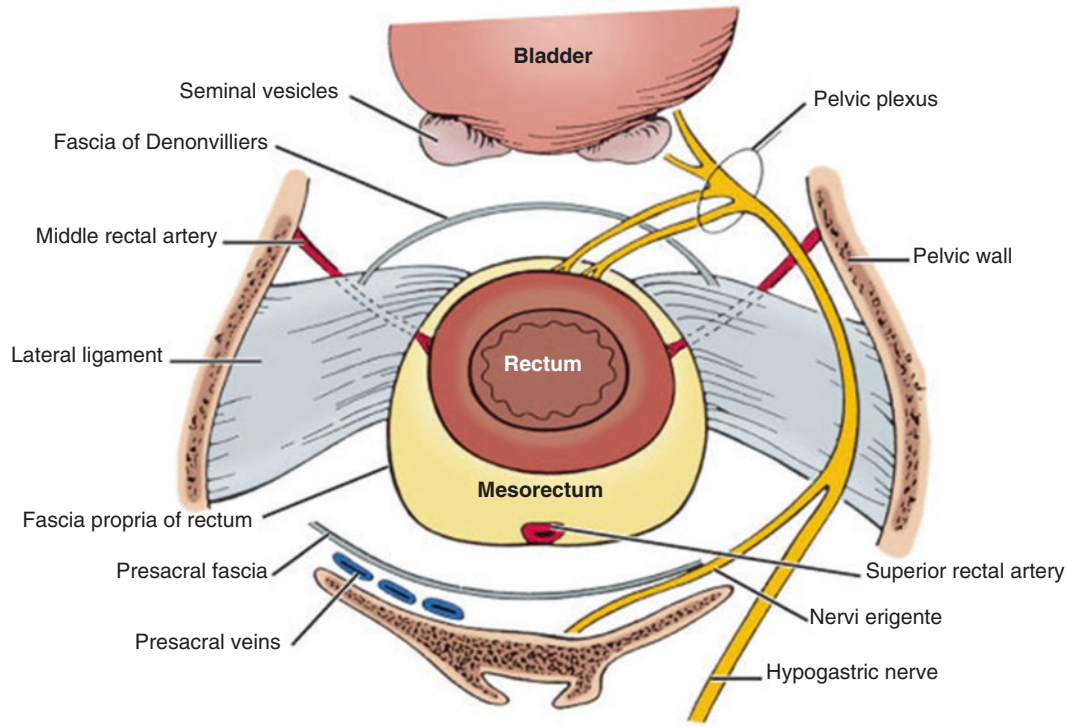

Fig. 8.3 Pelvic anatomy as it relates to the technique of total mesorectal excision during abdominoperineal resection

out posterior to Denonvillier's fascia, but anterior dissection may be indicated to optimize circumferential margin for anterior-based rectal lesions.

Circumferential rectal dissection is then carried down to the pelvic floor at the level of the levator ani muscles. The lateral attachments are divided close to the mesorectum to avoid injury to the lateral nerve plexuses which could potentially contribute to impotence in men and bladder dysfunction. At this point, a critical technical step in APR must be considered. The historical literature typically demonstrates a significantly greater degree of radial margin positivity and corresponding rate of local recurrence in APR as compared to LAR [32, 33]. It has been theorized that this may be due to inadequate wide excision at the level of the pelvic floor.

Indeed circumferential rectal margin (CRM) status is a predictor of outcome and is considered an important surgical quality indicator. Of the 455 patients who underwent APR as part of the Dutch Rectal Cancer Trial, 29.6% had a positive CRM. Location of tumor was the most important predictor of CRM with anterior tumors being the most likely to have a positive CRM when compared to laterally located tumors (44% vs. 21%, $p < 0.0001$) [34]. Local recurrence rates of ~22 and ~5% have been reported for patients with positive and negative CRM, respectively [35]. Positive CRM has also been associated with increased rates of distant metastasis [35]. Quirke et al. found that the combination of a negative CRM and optimal TME offers the lowest chance for local recurrence (1% at 3 years) [36].

As such, there has been greater emphasis placed on achieving wide local excision of the levator ani muscles via a "cylindrical dissection" via what has been referred to as extralevator abdominoperineal excision (ELAPE) [37]. From a procedural standpoint, the wide division of the levator ani muscles can be achieved from either the abdominal or perineal approach. Regardless of approach, the deep dissection should maintain a cylindrical shape to avoid "waistcoating" of the mesorectum at the level of the levator ani muscles (see Fig. 8.4). ELAPE has been shown to

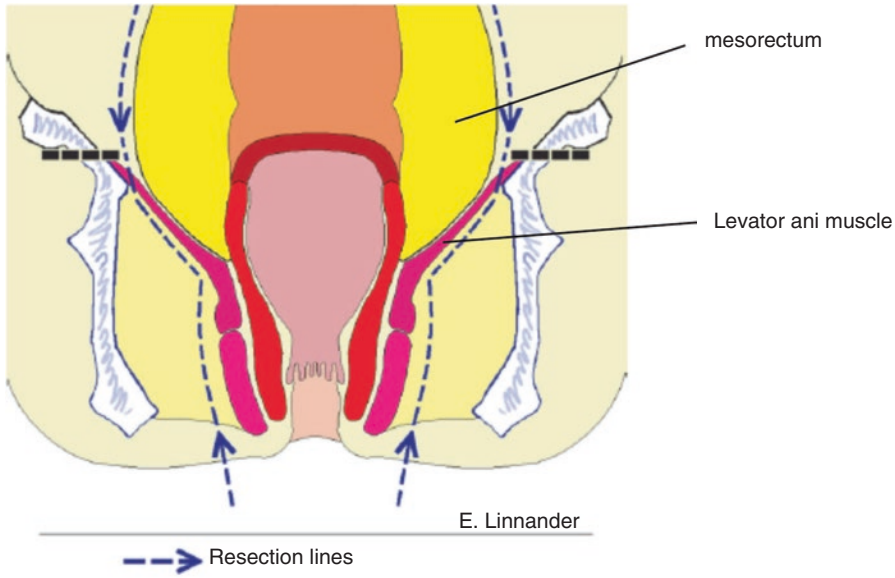

Fig. 8.4 Lines of dissection during an extralevator abdominoperineal excision (ELAPE). Note that the levator ani muscles are divided near their insertion on the pelvis. This technique allows for a wider "cylindrical" dissection avoiding "waistcoating" of the distal mesorectum

have improved CRM at the expense of a potential increase in wound and other complications [38].

The perineal portion of the procedure can be performed with the patient in either the lithotomy (Lloyd-Davies) or prone jackknife (Kraske) position. For the prone approach, upon completion of the abdominal portion, pelvic drains are placed, the wound closed, and the colostomy matured prior to repositioning the patient. Some authors claim that in prone position, exposure is improved along the anterior dissection plane and prostatic urethra leading to decreased operative time and blood loss [39, 40]. The lithotomy position requires no additional repositioning and offers the advantage of simultaneous access to both the abdomen and perineum, which in turn also offers the ability for a time-efficient two-team synchronous approach. Regardless, effective and safe extralevator resection is possible from either patient position and are considered equivalent [41–43].

The landmarks of the perineal resection are the coccyx posteriorly, the prostatic urethra anteriorly, and the ischiorectal fossae laterally (see Fig. 8.5). An extrasphincteric circumferential incision is made at the perineum, and an extralevator dissection continues the cylindrical shape. Posteriorly, the perineal dissection is first connected to the previously completed abdominal dissection immediately anterior to the coccyx. Subsequently, circumferential perineal extralevator dissection continues by transecting the levator ani muscles at their origin. The anterior rectal dissection is generally performed last to improve visibility and reduce chances for injury to the urethra in men and the vagina in women. Upon removal of the specimen, the perineal defect may be closed primarily or with flap reconstruction (see below) as indicated. The authors prefer the placement of a transabdominal closed suction drain. Some surgeons prefer transperineal placement; however, this has been associated with increased patient discomfort [44]. If not already completed, the midline incision is closed and the colostomy matured.

Maturing the End Colostomy

Unlike emergent situations when a colostomy is potentially temporary and reversible, the colostomy performed at the time of APR is permanent.

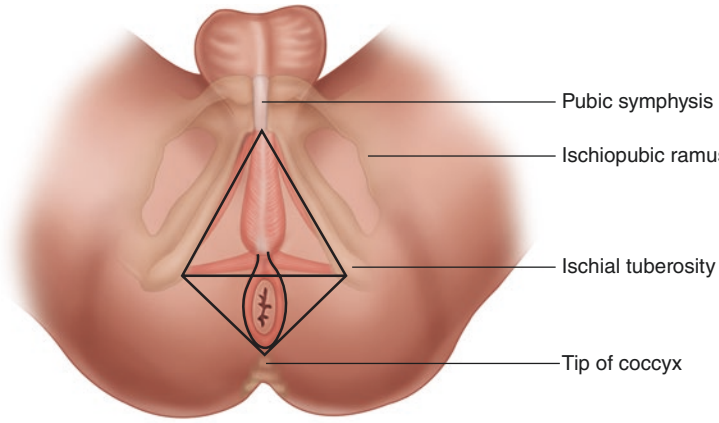

Fig. 8.5 Landmarks of the perineal dissection during abdominoperineal resection. An extrasphincteric elliptical incision is performed as illustrated. The posterior dissection proceeds anterior to the coccyx and laterally in the ischiorectal fossae. The anterior extent of the dissection is the prostate in men and vagina in women

As such, patients may live decades following curative APR, and special care should be given to perform a technically precise and meticulous end colostomy in order to avoid both short-term and lifelong complications.

Choosing a practical and functional location of the colostomy on the patient's abdominal wall is essential to avoid the morbidity and diminished quality of life associated with poorly functioning ostomy appliances. The left-sided location should be chosen prior to surgery taking into consideration body habitus, skin folds when sitting, and patient preferences. The colostomy should be well within reach of the patient so he/she can independently empty and change the ostomy appliance. It should be located either above or below the belt line and skin folds, and previous scars should be avoided to prevent leakage from the appliance. Preoperative education and marking provided by a trained enterostomal therapist is valuable and can help prepare the patient for this life-altering situation.

Prior to closing the abdominal fascia, a 2–3-cm circular incision is made, the skin excised, and the tissues dissected down to the fascia. A fascial defect is made through the anterior and posterior rectus sheath. The distal colon is extracted through the rectus sheath, and the muscle fibers are split, rather than transect. As the distal colon is brought through the fascia to the skin, special care must be taken to avoid twisting of the colon or avulsion of the mesentery which may result in devascularization. The fascial opening should allow a snugly fit finger in addition to the bowel and its mesentery. The bowel should be externalized without tension to a point approximately 3 cm above the level of the skin.

Once the abdominal wall and skin closure is complete, the colostomy is matured by removing the staple line from the externalized bowel. The mucosa and mesentery are assessed to ensure preserved perfusion and viability. The mucosa is secured to the subcuticular layer of the skin using interrupted 3-0 or 4-0 absorbable sutures. The bowel wall should be everted such that the colostomy protrudes 1–2 cm above the skin to facilitate placement of the ostomy appliance.

Approach

Surgical approaches include open, laparoscopic-assisted, and robot-assisted techniques. Pivotal early studies such as the COST and the MRC CLASICC trials showed that the

laparoscopic approach for colon cancer is oncologically comparable to open colon surgery [45–47]. However, given the additional complexity of rectal surgery, the data showing benefits for the laparoscopic approach for rectal cancer are not as definitive. The COLOR II trial has reported on the long-term results of laparoscopic rectal cancer surgery and shown no difference in the rates of local recurrence between laparoscopic and open surgery, overall. One interesting finding in the study was the fact that the rate of CRM positivity was significantly lower in the laparoscopic arm for patients with distal rectal cancer. However, this might be explained by the notably higher than expected rate of CRM positivity in the open arm. Long-term results of the ACOSOG Z6051 and ALaCaRT trials are awaited; however, neither study could establish the oncologic noninferiority of laparoscopic surgery in the short term. However, short-term non-oncologic benefits of laparoscopic surgery have been demonstrated, including less intraoperative blood loss (200 vs. 400 ml, $p < 0.0001$), shorter hospital stay (8 vs. 9 days, $p = 0.036$), and decreased time for return of bowel function (2 vs. 3 days, $p < 0.0001$) [48]. The COREAN trial randomized patients with mid-rectal cancers to laparoscopic or open surgery and showed no difference in surgical specimen quality as measured by lymph node harvest, CRM, and macroscopic quality of TME [49]. They also showed shorter hospital stay and faster return of bowel function following laparoscopic rectal surgery. Despite the current data from prospective randomized control trials, there remains great interest for considering laparoscopic surgery for low rectal cancer with the caveat that long-term oncologic equivalency to open surgery has not been established.

Robot-assisted minimally invasive approaches to rectal cancer surgery have gained popularity in recent years due to the improved instrumentation and visualization. A meta-analysis by Yang et al. evaluated 16 studies comparing laparoscopic to robotic rectal cancer surgery and found that the robotic approach had lower blood loss and conversion rates but higher costs when compared to the laparoscopic approach. The two techniques were similar in terms of complications and early markers of surgical quality including CRM and lymph node harvest [50]. Nonetheless, large-scale prospective analyses that examine both clinical outcomes and cost-effectiveness remain necessary.

Extended APR

For patients who have locally advanced, nonmetastatic primary, or recurrent tumors, multivisceral resections may offer the best chance for cure. Pelvic exenteration traditionally involves en bloc removal of the rectum along with its adjacent pelvic organs which include the bladder and prostate in men and the bladder and uterus in women. Additional extended resections may also involve partial sacrectomy or partial vaginectomy. Yamada et al. demonstrated that 5-year survival rates were higher among patients with locally recurrent rectal cancer treated by curative-intent exenteration as compared to those who underwent palliative non-oncologic resection (22.9% vs. 0%, $p = 0.0065$) [51]. Law et al. observed that pelvic exenteration was associated with a high risk of perioperative morbidity (54%) and an overall 5-year mortality rate of 44% [52]. Multivisceral resection including sacropelvic resection can have good oncologic outcomes with 5-year disease-free survival rates in the range of 43% [53]. The preoperative evaluation should include high-quality imaging of the pelvis. Any concern for extra-rectal sacral, prostatic, bladder, or vaginal involvement warrants further investigation with MRI.

Sacral resection may be indicated in cases of primary or recurrent rectal cancer with posterior bony extension. Tumors at or below S3 are amenable to standard partial sacrectomy. Milne et al. reviewed 100 cases and found a high complication rate (74%) with 43% of these classified as major morbidity. Neurologic complications were

increased if the resection was above the S3 level [54]. Among patients from Memorial Sloan Kettering who presented for abdominosacrectomy because of recurrent disease, their complication rate was 59%, and disease-free survival was 20% at 5 years [55]. For tumors at or above S2, a high sacrectomy is possible but carries a higher risk of neurologic complication, increased morbidity, and decreased disease-free survival [56, 57].

The use of a coordinated multidisciplinary team approach is critical for the management of rectal cancer and particularly important in the setting of locally advanced primary or recurrent rectal tumors. The integrated surgical team often includes involvement of specialists from urology, gynecology, plastic surgery, and/or neurosurgery.

Use of Ureteral Stents

The routine use of ureteral stents for the identification and prevention of ureteral injury during APR is controversial. There are no randomized trials evaluating the prophylactic use of ureteral stents during colorectal cancer surgery owing to the fact that the incidence of ureteral injury is so low [58]. A recent nationwide analysis using data from the Healthcare Cost and Utilization Project Nationwide Inpatient Sample reported that among all patients who suffered an iatrogenic ureteral injury, rectal cancer was the most common indication for surgery, yet ureteral injury only occurred in 7.6 per 1000 cases during APR [59]. Comparison studies have not shown a decrease in the incidence of ureteral injuries during colorectal surgery with the use of ureteral stents [58, 60], but some authors suggest that ureteral stents allow for more apparent intraoperative recognition of an injury [61, 62]. Furthermore, ureteral stent placements are not without complications. Complications from ureteral stents include transient hematuria, urinary tract infections, hydronephrosis, and reflex anuria [63, 64]. One study of 66 patients reported that hemodialysis was required in two patients due to anuria following ureteral stent placement [65]. In addition to potential complications, ureteral stent placement adds cost and operative time to each procedure [64, 65]. It is our practice to selectively use ureteral stents in those cases when dense pelvic adhesions are expected, such as in cases of prior pelvic surgery, remote pelvic radiation (external beam or brachytherapy), or recurrent bulky disease which appears to involve one or both ureters.

Reconstruction of the Perineum

Perineal wound complications (including bleeding, infection, dehiscence, fistulae, perineal herniation, chronic pain, and delayed wound healing) occur in 16–41% of patients following APR [66, 67] and are, consequently, a major source of morbidity. These complications are exacerbated by neoadjuvant radiation, which roughly doubles the rate of perianal complications [66]. Patients with obesity and significant comorbidities are also at increased risk for perineal wound complications [67, 68]. Furthermore, depending on the location and extent of involvement, rectal tumors can invade the vagina, prostate, bladder, and/or coccyx, and en bloc resections can result in substantial soft tissue defects too large for primary closure. These issues are particularly pertinent in patients with recurrent anal cancer, as these patients almost universally receive external beam radiation as part of their primary treatment and often require wide perineal soft tissue excisions to obtain negative margins. That said, most perineal wounds following APR are amenable to primary closure; however, large perineal defects require plastic surgery reconstruction. While a complete discussion of the reconstruction techniques used is beyond the scope of this book, the four most common methods are introduced here.

V-Y Advancement Flap Reconstruction

Some perineal wounds are too large for a tension-free primary closure but do not require myocutaneous flaps to close the soft tissue defect. In these situations, a V-Y advancement flap of skin and subcutaneous tissue is a common technique to allow for a tension-free closure. This is performed by incising the skin in a wide “V” shape

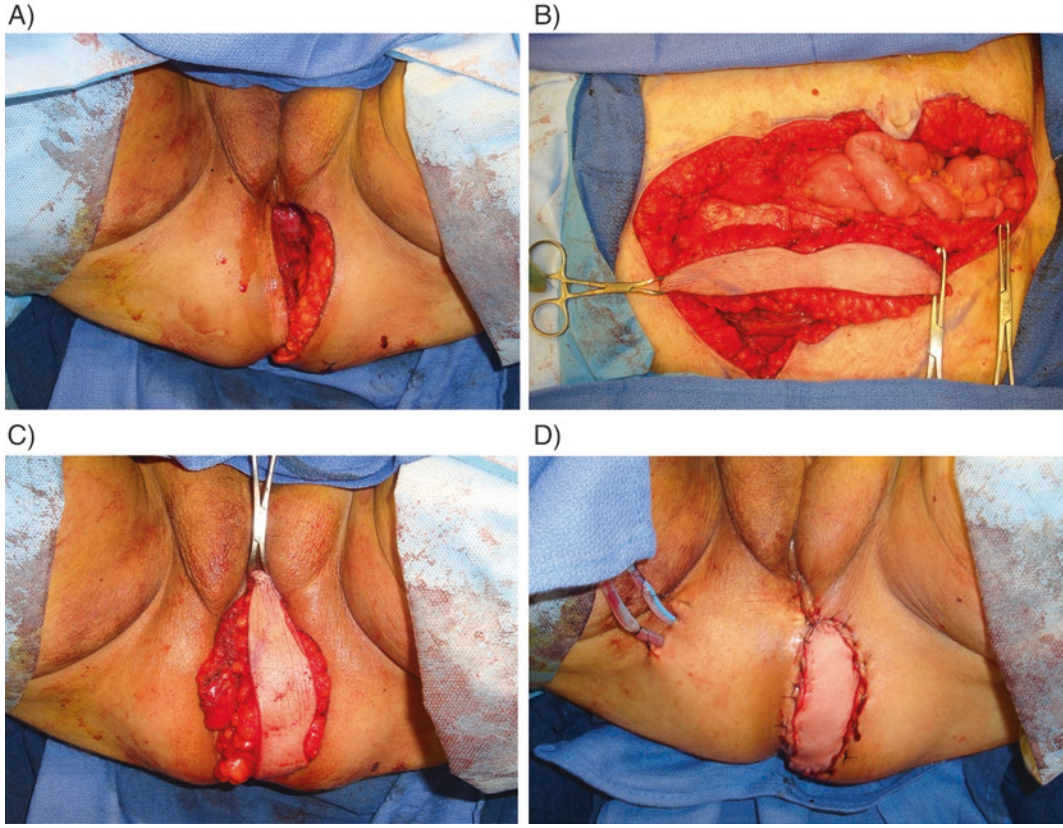

Fig. 8.6 Reconstruction of the perineal defect using a vertical rectus abdominis myocutaneous (VRAM) flap. (**a**) Perineal defect following abdominoperineal resection. (**b**) Harvested right rectus abdominis muscle with vertically oriented elliptical overlying fasciocutaneous tissue. (**c**) VRAM flap rotated into position to fill the perineal defect. (**d**) Flap sutured in place with perineal drains

extending from the anterior and posterior perineal incision laterally. The soft tissue is mobilized off the underlying muscle as needed preserving perforating vessels and the flap is advanced medially until the perineal wound can be closed without tension. The remaining incisions are closed in a "Y" configuration [69].

Vertical Rectus Abdominis Myocutaneous (VRAM) Flap Reconstruction

VRAM flaps rely on the inferior epigastric artery and are created by harvesting the rectus abdominis muscle off of the posterior rectus sheath with inclusion of a vertically oriented elliptical strip of overlying fasciocutaneous tissue [70]. Often an obliquely curved overlying skin paddle extending to the costal margin is incorporated to increase length. The flap is transposed and rotated into the pelvis (see Fig. 8.6). If a partial vaginectomy was performed, a neovagina can be constructed by folding the skin paddle on itself and recreating the vaginal wall. While the preferred method of perineal reconstruction following APR by most plastic surgeons, a VRAM cannot be used in patients with a prior abdominoplasty, and may need careful consideration in a patient requiring exenteration with placement of bilateral ostomies.

Primary healing has been reported in greater than 85% of VRAM flap reconstructions with nearly 100% healing during follow-up [71–73]. The incidence of wound complications following VRAM flap reconstruction is 18–29% and includes wound infection, bleeding, partial or complete flap necrosis, disunion, vaginal stenosis, and perineal or abdominal hernia [72, 73].

Controlled studies have shown that when compared to primary closure, VRAM flap reconstruction demonstrates lower incidences of wound complications including abscesses, dehiscence, and delayed wound healing [74–76] despite the fact that VRAM flaps were used in higher-risk wounds.

Gracilis Flap Reconstruction

Gracilis myocutaneous flaps maintain their blood supply from the medial circumflex branch of the profunda femoris artery. The cutaneous flap is harvested from the medial thigh over the proximal and middle third of the gracilis muscle (see Fig. 8.7). In general, gracilis flaps are used for smaller defects or if a VRAM is unavailable [70]. Gracilis flap reconstruction results in primary healing in over 94% of patients [71] and is associated with fewer perineal complications compared to primary closure [77, 78]. In a study of locally recurrent, highly radiated cases of rectal cancer, 11 out of 24 patients who underwent APR with primary perineal closure developed a major infection requiring hospitalization and/or reoperation compared to 2 out of 16 patients following gracilis flap reconstruction [78].

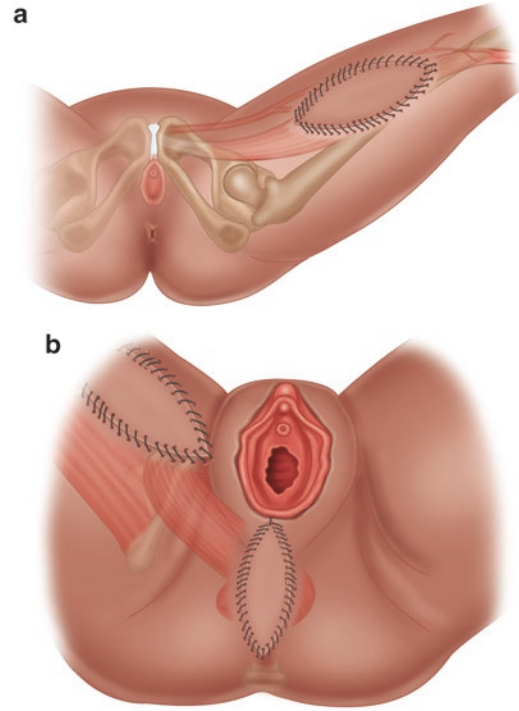

Fig. 8.7 Gracilis flap reconstruction. (**a**) The blood supply of the gracilis myocutaneous flap branches off the profunda femoris artery. The skin pedicle is harvested over the middle of the gracilis muscle. (**b**) The flap is rotated superiorly to fill the perineal defect

Gluteal Flap Reconstruction

Gluteus maximus myocutaneous flaps are based on the superior and/or inferior gluteal arteries and are rotated medially to fill the perineal defect. Perineal reconstruction using unilateral or bilateral gluteal flaps is often performed following extralevator abdominoperineal excision or extended APR where the levator muscles and/or involved adjacent organs are resected en bloc (see above) creating larger perineal soft tissue defects. In one recent report of 28 gluteal flap reconstructions, 86% of patients had complete primary wound healing, while four patients developed local wound infections or partial wound rupture [79]. Another study reported perineal wound complications in 42% of 65 patients following gluteal flap reconstruction, although 91% had completely healed by 1 year [80].

Other Reconstruction Techniques

There is evidence to suggest that the use of mobilized greater omentum to fill the pelvic dead space following APR decreases the incidence of perineal wound complications. One study analyzed the complication rates among 70 primary or myocutaneous perianal reconstructions with or without omentoplasty and found major pelvic complications occurred less frequently when an omental flap was used to buttress the perianal closure (21% vs. 61%, $p < 0.01$) [81]. Another study reported less perineal dehiscence following omentoplasty (5% vs. 16%, $p = 0.04$) [82]. In a recent meta-analysis, omentoplasty added a

median of 20 min to the operation but was associated with a higher rate of primary wound healing (67% vs. 50%, $p = 0.05$) and a lower incidence of wound infection (14% vs. 19%, $p = 0.03$) [83].

Placement of biologic mesh to reinforce the pelvic floor has received some attention as an alternative to myocutaneous flap reconstruction to reduce operative time, costs, and the morbidity of flap harvest. Its use has preliminarily been supported by several small case series [84–86], but a multicenter, randomized trial is currently underway [87] comparing outcomes with and without the use of porcine-derived biologic mesh. Christensen et al. [88] compared perineal biomesh ($n = 24$) to gluteal flap reconstruction ($n = 33$) and reported higher but nonsignificant infection rates (17% vs. 6%, $p = 0.26$), lower rates of perineal hernia (0% vs. 21%, $p < 0.01$), and shorter hospital stay (9 vs. 14 days, $p < 0.05$) with the use of biomesh. In another small comparison study, VRAM reconstruction ($n = 5$) was associated with longer median operative times (405 vs. 259 min, $p < 0.01$), longer length of stay (20 vs. 10 days, $p = 0.07$), and almost double the median costs ($p < 0.01$) as compared to biologic mesh reconstruction ($n = 10$), while early complication rates were similar (80% vs. 70%, $p = 0.37$).

APR-Specific Complications

Overall Rates of Morbidity and Mortality

As noted previously, during its infancy, APR was associated with substantial rates of perioperative morbidity and mortality. However, as with many complex operative procedures, the evolution of surgical, anesthetic, and antimicrobial techniques has resulted in substantial improvements in outcomes. In modern series, perioperative mortality rates are generally less than 2%. Nonetheless, APR remains a relatively morbid procedure with an overall complication rate of approximately 50% [89–91].

Intraoperative Complications

Presacral Bleeding

A dreaded complication of posterior rectal mobilization is presacral hemorrhage resulting from inadvertent traversal of the presacral fascia and injury to the presacral venous plexus or sacral basivertebral veins [92]. Pollard et al. described this complication as occurring in approximately 3% of patients undergoing either APR or LAR [91]. Simple suture ligation or cautery is generally unsuccessful and may in fact exacerbate bleeding [93]. Consequently, over the years, a variety of operative techniques have been described including compression methods (e.g., sterile thumbtacks [93], tamponade with saline bag [94], or tissue expander [95]), use of hemostatic agents (e.g., fibrin, cyanoacrylate glue [96], rectus abdominis muscle welding [97]), and endoscopic stapling devices [98]. Despite the availability of numerous such technologies, it must be emphasized that in the face of patient instability, packing of the pelvis allowing patient stabilization with interval return to the OR remains a sometimes necessary and highly sound approach.

Urethral Injury

Inadvertent injury to the membranous portion of the urethra can occur in males during anterior perineal dissection during APR. In older series, it has been reported that this complication may occur in 1–5% of cases [99–101]. Close attention and palpation of the urinary catheter within the urethra can help to avoid this complication. Fortunately, urethral injury can often be recognized immediately by visualization of the urinary catheter in the dissected field. This can often be managed successfully by primary repair and/or prolonged urethral stenting and drainage with a urinary catheter. Unsuccessful management or unrecognized injury may result in urinoma and/or urethrocutaneous fistula to the perineal wound which may ultimately require more complex reconstructive techniques [102].

Ureteral Injury

It is estimated that surgical procedures involving the colon and rectum account for approximately

5–15% of iatrogenic ureteral injuries [102]. Among colorectal procedures, APR is the most commonly associated with ureteral injury with frequencies reported as high as 5% [99]. Careful visualization of the left ureter is critical prior to transection of the colonic mesentery. As discussed previously, ureteral stenting can facilitate the identification of the ureters and also of an injury but generally do not prevent ureteral injury. The use of ureteral stenting can be performed at the discretion of the surgeon taking into account factors such as reoperative surgery, complexity, uncertain anatomy, and experience. Mechanisms of ureteral injury include laceration and/or transection, ligation, devascularization, and thermal injury. Suspected ureteral injury can be diagnosed intraoperatively with intravenous injection of colored dyes such as methylene blue or indigo carmine and observation for extravasation. Subsequent management depends on timing of diagnosis as well as the extent and anatomic location of the injury [102]. For injuries to the middle third of the ureter, the preferred method of repair is a spatulated ureteroureterostomy over a ureteral stent. Occasionally, ureteroneocystostomy is required with the aid of a psoas bladder hitch or Boari flap [102]. Ureteroneocystostomy techniques are the procedures of choice for the more common distal one third ureteral injuries [102].

Vaginal Injury

During APR in women, posterior vaginal defects can occur as a result of planned resection for directly invading anterior-based rectal tumors or by inadvertent injury during anterior perineal dissection. Smaller defects may be closed by primary repair in a tension-free fashion. However, it should be recognized particularly in cases treated with neoadjuvant radiation that breakdown of the repair may occur. This, in turn, may lead to vaginal stenosis, scarring, and in some cases vaginocutaneous fistula to the perineal wound or in association with persistent perineal sinus [103]. Larger defects are best managed with myocutaneous flap reconstruction as previously discussed with VRAM flaps being most preferable [73].

Perineal Wound Complications

Short Term

Immediate nonhealing of the perineal wound represents a spectrum of clinical significance ranging from superficial wound separation to pelvic abscess and sepsis and thus requires different management strategies [104]. Despite general improvements in surgical outcomes, postoperative perineal wound healing complications following APR remain a significant problem with rates ranging from 14% to as high as 50% [83, 105, 106].

Perineal wound complications are associated with substantial additional medical costs as a result of increased length of stay, hospital readmission, and home nursing care needs [104]. Additionally, Hawkins et al. noted by multivariate analysis that perineal wound dehiscence following APR was associated with a 1.7 times increase in the adjusted risk of death [107].

Risk Factors

Extirpation of the rectum and anus (and other pelvic organs for exenteration) results in a large dead space that is fixed by the surrounding bony pelvis. This cavity facilitates the accumulation of fluid and/or hematoma that increases the risk of wound leakage/infection, pelvic abscess, and wound sinus tracts. The ELAPE approach (as compared to conventional APR) and the use of neoadjuvant radiation therapy are generally associated with an increase in perineal wound complications [37, 105, 106, 108]. Indications for surgery such as malignancy and inflammatory bowel disease contribute to increased rates of nonhealing, while additional patient-specific risk factors include diabetes mellitus, anemia, obesity, and smoking [68].

Prevention

As noted, numerous approaches have been described with varying degrees of success to help mitigate the issue of nonhealing and/or infection of the perineal wound and its subsequent sequelae. In addition to reconstructive options

cited above, additional maneuvers include closed suction drainage [109, 110] and pelvic placement of a gentamicin-impregnated collagen sponge [111]. Notably, the historical practice of closing the pelvic peritoneum has been associated with delayed wound healing presumably as a result of creating a significant closed pelvic dead space [112]. The addition of irrigation to closed suction drainage has been shown not to add any additional benefit [113].

Where possible, it is the authors' practice to employ primary closure with omental pedicle flap placement in combination with transabdominal closed suction drainage. Flap closure is generally reserved for larger or extended defects (e.g., exenteration, posterior vaginectomy) particularly in the setting of presurgical radiation treatment (e.g., advanced anal squamous cell cancer).

Management

Superficial and uncomplicated wound separation may be treated with simple packing with normal saline wet-to-dry dressings. Occasionally excessive granulation tissue may require topical treatment with silver nitrate. Traditional initial management of complete perineal wound dehiscence has consisted of debridement of devitalized tissue and wet-to-dry dressing changes. However, in the setting of abundant fibrinous exudate and/or low-grade infection, the use of one fourth strength Dakin's solution or silver-impregnated preparations may be used [104]. With these routine wound care measures, it is estimated that almost 90% of wounds will heal within 6 months [104]. It is important to emphasize that complete dehiscence does require careful examination to ensure that there is no evidence of small bowel evisceration which may require urgent operative intervention.

Recently, the use of vacuum-assisted closure (VAC) devices has become relatively commonplace to accelerate healing by secondary intention particularly for large abdominal wounds [114]. The use of VAC dressings for perineal wounds following APR has been described [115, 116]; however, the perineum is inherently a difficult anatomic location to maintain an airtight seal necessary to allow for the application of suction. The authors have found VAC therapy for perineal wounds to be highly effective but have noted that success depends on the involvement of a dedicated and experienced wound care team.

Fever and pelvic pain with or without perineal wound drainage may be a manifestation of a pelvic fluid collection and/or abscess and should prompt CT imaging. Pelvic abscesses are most often treated by placement of percutaneous CT-guided drainage catheters and broad-spectrum antibiotics. Occasionally, in the acute setting, narrow-mouthed sinus tracts from the perineal wound may require operative intervention to enlarge the wound opening to allow for adequate drainage and more effective wound packing [104].

Long Term

Persistent Perineal Sinus

A perineal wound that remains unhealed for more than 6 months after surgery is defined as a persistent perineal sinus (PPS) and may occur in up to 30% of patients undergoing APR for rectal cancer. Development is often associated with preceding sepsis (particularly in the setting of neoadjuvant radiation) with subsequent chronic inflammation and fibrosis which in turn contribute to reduced tissue oxygenation and poor healing capacity [117]. The sinus is typically a long fibrous tract lined with granulation tissue with a narrow external opening at the perineal wound and often extending into a presacral cavity. PPSs can be associated with pain and foul-smelling and/or bloody discharge. Evaluation can include sinography, CT scan, and/or MRI to define the sinus anatomy and to exclude underlying causes such as undrained abscess, foreign body, recurrent cancer, or perineal enterocutaneous fistula [117].

Conservative management with wound care and/or topical agents such as fibrin glue may assist in palliating symptoms but are unlikely to effectuate complete healing [118]. Topical metronidazole ointment has been reported to reduce both associated foul odor and perineal discomfort

[117]. In addition to use in acute, nonhealing wounds, there have been reports that VAC can either promote outright closure of PPSs or increase granulation beds to allow for improved take of skin grafts [119, 120].

Surgical management of the nonhealing PPSs can range from minor local debridement to major reconstructive procedures. Debridement and sinus tract curettage alone are rarely sufficient for complete healing [117]. Successful healing of PPSs in 8 of 8 patients has been reported by use of wide local excision of the sinus, partial coccygectomy, primary wound closure, and closed suction drainage [121]. Of note, it has been suggested that the healing rate of this approach is substantially reduced without accompanying coccygectomy [122]. Several local modifications can be used when primary closure without tension is not possible. These include a skin flap cleft closure technique as described by Branagan et al. which was successful in 7 of 8 patients [123] or the use of split thickness skin grafts to the wound bed which was able to effect immediate healing in 5 of 9 patients [124].

More aggressive reconstructive approaches may be required for larger excised defects. The most commonly used approaches include VRAM and gracilis muscle myocutaneous flaps as described above. In the setting of chronic pelvic sepsis and/or PPS, a systematic review of the literature demonstrated complete healing within 12 months in 84% and 64% of VRAM and gracilis muscle flaps, respectively. Gluteus maximus V-Y advancement flap closure has also been described but has limited capacity to fill a pelvic defect [125].

Chan et al. recently described a limited experience of applying hyperbaric oxygen therapy prior to, and in some cases after, rectus abdominis myocutaneous flap closure in patients with highly refractory PPS following proctectomy for IBD. In this small case series of four patients, all perineal wounds completely healed within 3 months [126]. This approach may have promise for expanded study.

Perineal Enterocutaneous Fistula

Without adequate filling of the pelvic dead space following APR, the small bowel will often reoccupy the perineal space. In the setting of pelvic sepsis, chronic inflammation, and/or nonhealing of the perineal wound, erosion into the small intestine can occur resulting in an enterocutaneous fistula. Due to the anatomic location, control and conservative management of a perineal enterocutaneous fistula is very difficult and may be extremely problematic for the patient. Initial conservative management, as indicated for enterocutaneous fistulae at abdominal sites, is recommended and includes bowel rest to reduce output, TPN to enhance nutrition, and broad-spectrum antibiotics as needed to control local sepsis [127]. Local skin protection measures are particularly essential in these cases. As with other enterocutaneous fistula sites, the application of somatostatin analogs to reduce output may be considered [128]. It is the experience of the authors that spontaneous closure of such fistulae can occur but is uncommon. As such, reoperative surgery is often necessary, and although a several months interval is desirable for reduced intra-abdominal inflammation and adhesions, timing may be influenced by inability to achieve fistula control at the perineal site. Operative intervention often includes laparotomy, takedown of the fistula, and resection of the affected segment of bowel. Filling of the pelvic cavity (e.g., with the omentum, uterus, etc.) to serve as a barrier between the intestine and perineal wound to prevent recurrence is critical.

Perineal Hernia

Perineal wound hernia is a relatively rare complication that is estimated to occur in less than 1% of cases although rates as high as 8% have been reported [108, 129]. Although it has been theorized that reduced adhesions may predispose patients to slippage of small bowel into the pelvis, the incidence of perineal hernia following laparoscopic APR is unclear [129, 130]. It is likely that a number of post-APR perineal hernias are asymptomatic and undetected. When present,

symptoms may range from bulging, discomfort and/or pain, urinary symptoms, and intestinal obstruction to skin erosion [131]. Much like at other sites, perineal hernias can present with incarceration and/or strangulation [132, 133]. Risk factors include female gender, smoking, previous hysterectomy, chemoradiation, long small bowel mesentery, and perineal infection. Surgical approaches are varied and include open transabdominal, laparoscopic, transperineal and combined abdominoperineal repairs [131, 134, 135]. The most durable results appear to be achieved with the use of nonabsorbable synthetic or absorbable biologic mesh [129, 131, 134–138]. The use of myocutaneous flaps for reinforcing repairs has also been described but may be reserved for the setting of failure of other approaches [139, 140].

Colostomy-Related Complications

Complications arising from the colostomy are the greatest source of long-term morbidity and reduced quality of life for patients following APR. It is estimated that over 50% of patients will develop a colostomy-associated complication [141–144] with ischemia, stenosis, prolapse, retraction, parastomal herniation, obstruction, and skin irritation being the most common. Fortunately, much of the morbidity associated with colostomies can be managed with good enterostomal care. Nonetheless, surgical management may be necessary with frequently unsatisfying results and potentially requiring multiple revisions [143, 145].

Ischemia and Stenosis

Ischemia of the colostomy is a technical complication at the time of the operation caused by disruption of the blood supply to the distal bowel. As previously discussed, meticulous care must be given when externalizing the bowel to prevent mesentery twisting, devascularization, and congestion. Venous congestion or patchy mucosal necrosis can often be managed expectantly, while full-thickness bowel necrosis can cause functional obstruction, sepsis, or subsequent stenosis and is an indication for surgical revision.

Stomal stenosis can be the long-term sequela of ischemia and occurs in 1–7% of cases [141, 143, 146]. As long as the colostomy is otherwise functional, the stenosis can be treated with serial dilation and bowel function optimized with laxatives. Surgical revision may be required and can often be accomplished by excising the mucocutaneous junction and freeing the bowel from the subcutaneous tissue enough to mature a new colostomy without mobilizing it from the fascia [145]. Other approaches include laparotomy with full mobilization and revision [143] or stomaplasty [146].

Retraction

Retraction of the stoma is often a result of mesenteric tension preventing adequate bowel externization at the time of surgery. Retraction can result in poorly fitting appliances leading to skin irritation and ulceration. While local revision can be attempted, symptomatic stomal retraction usually requires a laparotomy with further bowel mobilization and complete colostomy revision and/or resiting.

Prolapse

Fortunately, prolapse from an end sigmoid colostomy is uncommon [143, 147] but can result from a very redundant sigmoid or extensive splenic mobilization. While alarming to the patient, a prolapsed colostomy normally remains functional but can lead to difficulties with appliance fitting. If revision is necessary it can be done by mobilizing and externalizating the distal colon through the colostomy site as much as possible followed by amputating the prolapsed segment and maturing a new colostomy. While less morbid than a revision via a laparotomy, recurrent prolapse following this conservative approach is a common problem [145].

Parastomal Hernia

Parastomal hernia may occur in over a third of patients with an end colostomy [143, 147, 148] and in up to 75% of obese patients [149]. While most cases are relatively benign, parastomal hernias can be a source of chronic abdominal pain, intestinal obstruction/strangulation, and ostomy appliance malfunction. A comprehensive discussion of the

surgical management of parastomal hernia is beyond the scope of this chapter except to say that recurrence following parastomal repairs is high [145] and the most efficacious method of repair is yet to be determined.

Different approaches of colostomy maturation to prevent parastomal hernias have been described. The placement of the stoma lateral to the rectus sheath has been proposed; however, most studies conclude that there is no difference in the rate of parastomal herniation between transrectal and lateral pararectal placement [150–152]. The Goligher extraperitoneal colostomy [153], which involves tunneling the distal colon between the parietal peritoneum and the posterior fascia starting from the lateral retroperitoneum until it is brought through the abdominal wall and matured at the skin, is another proposed technique aimed at reducing parastomal hernias [154–156]. A recent meta-analysis of 1071 patients showed a lower rate of parastomal hernias following extraperitoneal creation compared to the traditional transperitoneal method (odds ratio, 0.41; 95% CI, 0.23–0.73) [157]. Neither the lateral pararectal nor the extraperitoneal techniques have been subjected to prospective randomized controlled trials.

The use of synthetic mesh to reinforce the fascia defect at the time of colostomy creation in an effort to prevent parastomal hernias has received attention recently. In a small randomized trial, the incidence of parastomal hernia following traditional colostomy creation was compared to colostomy reinforced with a prosthetic mesh positioned between the rectus abdominis muscle and the posterior rectus sheath. At 5-year follow-up, fewer parastomal hernias occurred in surviving patients following the placement of mesh compared to traditional colostomy without mesh (13% vs. 81%, $p < 0.001$) [158]. Several meta-analyses have also concluded that peristomal mesh placed at the time of colostomy formation can decrease the rate of parastomal hernias [159, 160]. Further large-scale prospective studies will be needed to validate the routine application of this approach.

Quality of Life

The negative psychosocial impact of a permanent colostomy necessitated by APR has long been the driving force behind developing sphincter-sparing alternatives. Indeed an abdominal stoma has an undeniable impact on body image, sexual intimacy, social relationships, and emotional well-being. However, the misconception of most patients and physicians is that restoring intestinal continuity (e.g., by LAR) invariably results in a better quality of life compared to that associated with a permanent colostomy. Less appreciated are the sequelae of suboptimal bowel function associated with LAR. These are grouped under a constellation of symptoms of commonly described as "low anterior syndrome" (increased frequency, urgency, soilage, incontinence, inability to distinguish flatus from stool, perianal irritation, and evacuatory difficulties) which occur in varying degrees following sphincter-sparing techniques. Progressively lower anastomoses with corresponding shorter rectal remnants correlate with worsening anorectal function, especially at levels below 5–8 cm from the anal verge [161–163].

The impact on patient quality of life following rectal cancer surgery has been intensely studied with conflicting and often difficult to interpret results [162–168]. Some studies suggest better quality of life following sphincter-sparing anterior resections [162, 164, 165], while others found improved quality of life after APR. [163, 166] In a recent meta-analysis including 1443 rectal cancer patients from 11 studies [169], there was no difference seen in global quality of life following APR compared to anterior resection. However, when analyzing individual assessment tools, patients who underwent APR appeared to have higher psychological, cognitive, emotional, and future perspective scores, while better physical, sexual function, and pain scores were seen in patients following anterior resection.

The perception that avoiding a permanent colostomy results in superior quality of life is not conclusively supported by available data. As

such, the choice between APR and a sphincter-sparing operation for patients with low rectal cancer is complex and must be individualized. Even if technically feasible, sphincter-sparing surgery should be avoided in patients with poor preoperative function, diarrheal disorders, neurologic dysfunction, or significant risk factors for incontinence (elderly, females, history of birth trauma). Preoperative assessment of anorectal function and a frank discussion of expected outcomes are imperative prior to the surgical management of rectal cancer.

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Laparoscopic Rectal Surgery

9

David W. Larson

Abbreviations

APR	Abdominoperineal resection
AR	Anterior resection
CAA	Coloanal anastomosis
HA	Hand assisted
ISR	Intrasphincteric resection
LA	Laparoscopic assisted
MIS	Minimally invasive surgery
RCT	Randomized controlled trial
RS	Robotics
SP	Single port
TEMS	Transanal endoscopic microsurgery

Introduction

The short-term benefits of minimally invasive surgery (MIS) for patients and systems are clear and irrefutable [1–8]. However, for the colorectal surgeon, rectal cancer represents one of the most complex technical challenges in the field. These challenges are either magnified or ameliorated by minimally invasive approaches (laparoscopic assisted, LA; hand assisted, HA; single port, SP; and robotics, RS). Given the complexity of this challenge, controversy persists regarding the long-term outcomes and safety profile of this technique.

Colorectal carcinoma remains the second leading cause of cancer-related deaths in the USA. In 2011 it was estimated that more than 39,000 new cases of rectal cancer would be diagnosed [9]. However, only a small percentage of all colorectal cancers benefit from a laparoscopic approach. Between 2005 and 2010, only 6–10% of all colorectal cancers in the USA were completed by this technique [10–13]. Recently, Fox's et al. [14] review of the national inpatient sample determined that more than 40% of colon cancers are treated with a laparoscopic approach, yet its use in rectal cancer is far lower. The American College of Surgeons National Surgical Quality Improvement Program recently evaluated 5240 patients undergoing rectal cancer surgery and demonstrated that 19.2% are performed laparoscopically. Some surmise that the lack of training and experience in addition to concerns about oncologic safety has contributed to poor adoption [15–17]. Despite the low incidence and penetration of laparoscopic techniques, it is well known that MIS results in fewer blood transfusions, shorter length of stay, and lower morbidity [10, 18].

Historically, questions were raised regarding the feasibility and oncologic outcomes of laparoscopic surgery. Over the past 15 years,

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multiple randomized controlled trials (RCTs) have demonstrated oncological equivalence with open surgery in colon cancer. To date, the evidence is incomplete to suggest that minimally invasive surgery for rectal cancer become the standard of care. Multiple studies have demonstrated that MIS approaches in rectal cancer are safe and associated with postoperative morbidity rates comparable to conventional open surgery [9]. If history however is to teach us anything, we must prepare for the probability that MIS will become the dominant surgical technique for all of surgery including cancer. The realization of this potential truth has been held at bay by two fundamental principles. First, the long-term oncologic and safety outcomes of minimally invasive rectal cancer have not been substantiated to the same degree as colon cancer. To date, there are only two large multicenter RCTs, which have reported long-term, greater than 3 years, oncologic outcomes [19–21]. Secondly, the technical demands of pelvic surgery and the potential risks to the patient lead the surgeon scientist to demand more convincing evidence. It is in this mindset that this chapter hopes to inform the well-trained minimally invasive colorectal surgeon.

The Data

The safety and feasibility of laparoscopic colectomy for colon cancer has been established by large RCT (Barcelona trial, COST, COLOR, and CLASICC) [4, 6, 22–24]. This degree of level 1 data is currently unavailable in the field of rectal cancer. However, the belief in innovative technical advancement and the commitment to base surgical principles allow many high-volume rectal cancer surgeons to support the use of MIS in the field. In fact the current recommendations from ASCRS [25] and NCCN [26] allow for minimally invasive treatment of rectal cancer when performed in experienced hands. In the following paragraphs, the details behind the science and the technique of laparoscopic surgery for rectal cancer will be discussed.

Short Term

Morbidity and Mortality

The short-term morbidity and mortality of MIS rectal cancer has largely been demonstrated to have equivalent or improved outcomes when compared to open surgery. Systemic reviews and meta-analysis have shown laparoscopic surgery to benefit from lower wound infection rates, decreased overall morbidity, and decreased length of stay [1, 27, 28]. In 2006 a Cochrane review including 48 studies, with a total number of 4224 patients, reviewed laparoscopic rectal cancer surgery [1]. Positive findings include faster time to diet, less blood loss, pain, and narcotic use. The randomized controlled European COLOR II trial reported short-term outcomes from 30 hospitals across eight countries. The 699 laparoscopic patients had improved outcomes over the 364 open surgical patients in terms of length of stay, blood loss, and GI recovery [8] (Table 9.1).

Large population-based data, which may provide insight into the generalizability of these procedures, has led to a more confusing picture. A French series based on 22,359 laparoscopic procedures in 62,165 open resections revealed significantly lower mortality rates after laparoscopy (2 vs. 6%) [29]. This finding remained positive after multivariate analysis (OR 0.59; 0.54–0.65) [29]. In contrast a German series concluded that open resection would be the preferred approach given the observed worse outcomes in converted laparoscopic patients [30]. Trials like CLASICC have echoed the German series by demonstrating significantly worse overall survival in converted patients (open 58.5%, laparoscopic 62.4%, converted 49.6% $p = 0.005$) [19]. Other challenges for the approach include longer operative time and higher costs [1]. Alternatively, other series have lent credibility and support to widespread adoption of these less invasive procedures. For one, laparoscopy appears to benefit the frailest in society undergoing surgery. Stocchi [31] and colleagues found lower rates of morbidity, decreased narcotic use, shorter length of stay, and lower rates of postoperative ileus in elderly

Table 9.1 Operative outcomes for laparoscopic versus open resection of rectal cancer in major randomized trials and meta-analyses

Trial	Assigned group	No. of patients	Conversion rate (%)	Operative time (min)	Estimated blood loss (ml)	Lymph node (mean)	CRM + rate (overall, AR, APR) (%)
COLOR II	Laparoscopic	699	16	240	200	13	10/9[a]/8[a]
	Open	345	–	188	400	14	10/22/25
CLASICC	Laparoscopic	242	34	180	–	8	16/12/20
	Open	113	–	135	–	7	14/6/26
COREAN	Laparoscopic	117	1.2	245	200[a]	17	3/3/5
	Open	170	–	197[a]	218	18	4/3/8
Meta-analyses							
Arezzo[b]	Laparoscopic	1566	13	219	307	13.1	7.9
	Open	1093	–	175	444	14.5	6.9

CLASICC conventional versus laparoscopic-assisted surgery in colorectal cancer, *COLOR II* colon cancer laparoscopic or open resection II, *CRM* circumferential radial margin, *AR* anterior resection, *APR* abdominoperineal resection

[a]Is a significantly lower rate

[b]Only RCT evaluated

patients undergoing laparoscopic colectomy. Moreover, these elderly patients had higher independence after their surgery [31]. Other authors have demonstrated similar short-term benefits in elderly patients [32–35].

Oncologic Markers

Surrogate measures of oncologic outcome have been the currency by which most series have measured initial success. To date nearly every series has consistently demonstrated equivalent outcomes in this regard. In the COLOR II trial, the lymph node harvest was found to be equivalent [8]. Potential concerns did arise in the short-term outcomes of the CLASICC trial, which demonstrated positive circumferential radial margins occurring in 12% of laparoscopic anterior resection versus 6% of open resection [24, 36]. These differences did not reach statistical significance and have not led to any long-term difference in local recurrence [19]. Even more interesting and potentially profoundly positive for laparoscopy were the findings of the CLASICC trial, which demonstrated overall rates of TME that were actually better in the laparoscopic group (77 versus 66%) [20]. Likewise, in contrast to CLASICC's CRM findings, the COLOR II trial demonstrated a lower CRM positivity rate in laparoscopic surgery, specifically for the subgroup of distal rectal cancers (22 vs. 9%, $P = 0.014$) [8]. This benefit of laparoscopy may have been confounded in the COLOR trial by the exclusion of T4 tumors and T3 tumors, which were within 2 mm of the endopelvic fascia [8]. More recent randomized studies included patients with rectal cancer after completion of neoadjuvant chemoradiotherapy. The COREAN trial [21, 37] as an example evaluated 170 patients per arm and found no difference in circumferential margin positivity. Rates for CRM positivity ranged from 4.1% for open to 2.9% for laparoscopic resections with no difference in complete mesorectal resection across the board. These rates of CRM positivity are much lower than the earlier RCT with rates ranging from 6 to 26% depending on the type of operation and location of tumor (anterior resection vs. abdominoperineal) [8, 24]. Two smaller randomized controlled trials found CRM positivity rates of 2.6–4% in the laparoscopic arms [38, 39]. Over the years there have been several single-center randomized controlled trials of limited size and scope, which have demonstrated comparable lymph node harvest, circumferential resection margin positivity rate, and distal margin in both techniques [38–42]. Together these randomized controlled data suggest that short-term outcomes are no different between approaches.

Nonrandomized, systemic reviews and meta-analysis have found similar equivalence between approaches. Aziz et al. [27] meta-analysis

demonstrated no difference in CRM between laparoscopic and open surgeries. A meta-analysis from Anderson [43] incorporating 17 different trials did find a small but significant difference in lymph nodes between laparoscopic (mean = 10) and open (m = 11) surgery. This difference did not translate into any significant difference in proximal/distal or radial margin [43]. A 2014 meta-analysis by Arezzo et al. [2] included eight randomized controlled trials (2659 patients) and 19 prospective or retrospective studies (8202 patients) in which they reported their results. Their outcome endpoints were un-phased by surgical technique with CRM positive rates of 10.3% lap and 11.6% open, and TME completeness was 85% overall (85% lap and 86% open) for those tumors within 12 cm of the anal verge. Two large meta-analyses of randomized controlled laparoscopic versus open colorectal cancer trials found no difference in total lymph node count. This included lymph node counts for both colon and rectal cancers when evaluated independently [44, 45].

Lujan et al. [46] multicenter series involving more than 4970 patients showed no statistical difference in TME rates, circumferential margins, or number of lymph nodes. Multiple individual series have demonstrated no difference in lymph node count when comparing techniques [42, 47–49]. A retrospective review of 579 patients following laparoscopic proctectomy showed a CRM positivity rate of 2% [47]. Other recent series have actually suggested that MIS may be an improvement over open approaches. Several series have demonstrated better total mesorectal excision (TME) in those undergoing laparoscopic approach [46, 50]. Moreover, these lower rates of positive resection margin in laparoscopic surgery have been discovered as an improving trend over time in a systemic review of laparoscopic rectal cancer including 97 studies [51].

One particularly controversial and historically challenging technical and oncological issue has been in the surgical treatment of the most distal rectal cancers. Historically over the last 30 years, the issue of abdominoperineal resection and its oncologic outcomes has been debated in earnest. It remains an interesting fact that the three large randomized controlled trials, the CLASICC, COREAN, and COLOR trials, have demonstrated a consistently lower rate of positive circumferential margins in the laparoscopic group [8, 24, 37]. It is uncertain whether improvements in overall surgical technique or the laparoscopic approach itself has been the inciting event for this improvement. Recent meta-analysis of three randomized trials and five nonrandomized studies demonstrated significantly lower local recurrence rate (OR 2.73; 95% CI 1.137–6.548) and distant recurrence rate (OR 1.994; 95% CI 1.062–3.742) [22] after laparoscopic APR compared to an open surgery [52]. Historical dogma may be challenged by these intriguing yet controversial findings. In conclusion, this robust short-term data should provide surgeons confidence that laparoscopic surgery for rectal cancer is a safe operation.

Recovery Pathways

The importance of postoperative pathways in the recovery profile and complication risk of surgical patients cannot be understated [53]. In our institution this is achieved by effectively coordinating minimally invasive approach with best practice enhanced recovery pathway (ERP) principles [54]. Enhanced recovery pathways include multimodal pre-, intra-, and postoperative elements, which place the patient in a more normal physiologically state. Multiple randomized controlled trials of demonstrated improvements in not only length of stay but complications as well [55]. The LAFL trial [56] specifically demonstrated the shortest length of hospital stay in those patients undergoing laparoscopic surgery in combination with an enhanced recovery pathway [57, 58]. By optimizing postoperative pain control, postoperative nausea, euvolemic state, and early feeding, one can effectively combine modern surgical techniques with best practice process [53, 59–61].

Long Term

Oncologic Outcomes

Level 1 long-term oncologic outcomes in rectal cancer have not fully matured to date. Although the safety of the technique has been demonstrated by multiple randomized trials [8, 19–21, 24, 37],

the long-term oncologic outcomes have limited results to report.

Two large multicenter randomized controlled trials have demonstrated 3- to 5-year oncological results [19, 21]. The first of such trials includes the CLASICC trial, which demonstrated no difference in 5-year oncologic disease-free survival outcomes in its 794 patients [19]. This study had a significant proportion of patients with T3 disease (63%) and N-positive disease (34%) [19, 24, 36]. Surgery is a local therapy; therefore it is important to note that local recurrence rates were also comparable [19]. This may be surprising given the fact that laparoscopic anterior resection group had a nonsignificant difference in radial margin positivity of 12 vs. 6% compared to open anterior resection. Despite this finding it did not translate into a statistically significant adverse local recurrence rate at either 3 years (9.7 versus 10.1%) or at 5 years (17.7% for laparoscopic vs. 8.9% for open) [36, 62]. The COREAN trial, which evaluated rectal cancers after neoadjuvant chemoradiation therapy, has reported 3-year results [21, 37]. Three-year disease-free survival was 79.2% (95% CI 72.3–84.6) in patients undergoing laparoscopic surgery and 72.5% (65.0–78.6; $p = 0.0001$) in those undergoing open surgery. Three-year overall survival was also equal between treatment arms (90.4% [95% CI 84.9–94.0] vs. 91.7% [86.3–95.0]). Likewise local recurrence-free survival was no different at 3 years (90.4% [95% CI 84.9–94.0] vs. 91.7% [86.3–95.0]) (Table 9.2).

The limited data regarding long-term outcomes in large randomized controlled trials can be contrasted to the large volume of single-institutional randomized and nonrandomized data. Long-term oncologic outcomes for rectal cancer have been determined in a meta-analysis including six randomized controlled trials with 1033 patients to be unaffected by approach [63]. Ng et al. [38] demonstrated no oncological difference even after 10 years of follow-up. A 2014 meta-analysis by Arezzo et al. [2] included eight randomized controlled trials (2659 patients) and 19 prospective or retrospective studies (8202 patients). Local recurrence was 3.5 and 5.6% for laparoscopic and open surgery patients with cancers within 12 cm of the anal verge. In addition, there have been multiple prospective trials incorporating 886 patients, which showed no difference in disease-free or overall survival between laparoscopic and open surgery. These trials' follow-up ranged between 37 and 113 months [36, 42, 64–66]. Moreover, multiple single-center trials demonstrate comparable 5-year local recurrence rates, disease-free survival, and overall survival [38–42]. Current ongoing large randomized controlled trials, the Australasian Laparoscopic Cancer of the Rectum Trial, the American College of Surgeons Oncology Group Z6051 trial, and the Japan Clinical Oncology Group (JCOG0404) trials, are awaiting completion and long-term follow-up.

Beyond the technique of laparoscopic surgery, it must be recognized that the individuals who

Table 9.2 Long-term outcomes for laparoscopic versus open resection of rectal cancer in major randomized trials and meta-analyses

Trial	Assigned group	No. of patients	Local recurrence rates (%), overall/anterior rsxn/APR	Disease-free survival (%)	Overall survival (%)
CLASICC	Laparoscopic	253	–/9.4/–	53	60
	Open	128	–/7.6/–	52	53
COREAN[a]	Laparoscopic	170	2.6	72.5	91.7
	Open	170	4.9	79.2	90.4
Meta-analyses					
Arezzo[b]	Laparoscopic	1566	4.1	–	–
	Open	1093	5.0	–	–

CLASICC conventional versus laparoscopic-assisted surgery in colorectal cancer, *CRM* circumferential radial margin
[a]Is based on 3-year follow-up
[b]Only RCT evaluated

perform these operations across the various medical centers in the USA impact care. Although sphincter preservation is high on the list of preferred outcomes for rectal cancer, it has been shown in a large population-based series [67] (8219 cases) that those patients having an elective proctectomy by colorectal surgeons obtained higher sphincter preservation rates as compared to those operated by general surgeons (OR = 1.42; $P = 0.018$). Even more important are the higher cancer-free 5-year survival rate when the operation is performed by a colorectal surgeon (HR = 1.5; $P = 0.03$) [68]. A retrospective study [69] with 384 consecutive rectal cancer patients resulted in significant survival advantage when operated on by a colorectal surgeon. After a multivariate analysis, the 5-year survival was 77 versus 68% for the patients operated by general surgeons. Here too local control was improved as well as sphincter preservation. In addition, a recent review and meta-analysis [70] demonstrated that colorectal surgeons were able to accomplish proper cancer operations with a lower rate of permanent ostomy (*RR* = 0.7; 95% CI, 0.53–0.94). Collectively these issues suggest that there is additional long-term data required to make a definitive conclusion. Moreover, if one is to undergo an MIS approach to rectal cancer, it should be performed in a high-volume center by an experienced colorectal surgeon.

Costs

The economic impact of surgical technique is difficult to fully elucidate. The literature is mired in contradictory reports with heterogeneous patient cohorts with difficult to interpret conclusions. Jensen's meta-analysis using data for randomized controlled trials suggested that laparoscopic surgery was indeed a net savings of more than $4283 per patient with no difference in quality-adjusted life years [71]. However others have suggested laparoscopy due to its higher inventory expenses in the operating room lead to higher overall costs. A Cochrane review of 48 studies (4224 patients) demonstrated higher overall costs in laparoscopic TME [1]. Other systemic reviews from the UK's NICE [72] demonstrated higher overall costs and laparoscopic surgery of colorectal cancer due to longer operative times and inventory expense. It was noted that shorter hospital stays and reduced morbidity may compensate for these higher operative costs. Other more recent reports suggest that laparoscopy may ultimately be more cost-effective [73–75].

Patient-Related Concerns

For patients the long-term functional consequences of control, frequency, and sexual and urinary dysfunction dominate the debate over approach for rectal cancer. The gastrointestinal functional consequences of low anterior resection can be significant. With a loss of the rectal reservoir, patients may experience the so-called anterior resection syndrome (soiling, urgency, frequency). It is widely recognized that the functional outcomes of intra-sphincteric resection as an extreme example (ISR) are suboptimal with more than 50% of patients maintaining fecal continents at 2 years [76, 77]. Therefore, the GI consequences of rectal surgery must be considered to assure patients are well informed prior to surgery.

There has been no shortage of controversy related to the sexual function of patients undergoing pelvic surgery. The autonomic plexus to avoid includes the superior hypogastric plexus (SHP) (sympathetic), the inferior hypogastric plexus (IHP) (mixed), and the pelvic splanchnic nerves (PSN) (parasympathetic) [78]. This controversy has been renewed by the use of minimally invasive surgery. Despite surgeon efforts to identify and preserve nerves during open TME, the incidence of bladder and sexual dysfunction ranges from 0 to 12% and 10 to 35% of patients, respectively [79]. Kim et al. [80] studied sexual dysfunction risk prospectively in 68 men undergoing rectal cancer surgery. In this study 6% of patients could not successfully obtain or maintain an erection, and 13% experienced retrograde ejaculation postoperatively [80]. Therefore, even in open surgery, these functional impairments can be significant, and it leads surgeons to question whether MIS could possibly improve these well-known risks.

The answer to this question has only recently become available in large level 1 trial. Jayne et al.

used the international prostate symptom score (I-PSS), the International Index of Erectile Function (IIEF), and the female sexual function index (FSFI) to evaluate patients [62]. The MRC CLASICC trial reported on sexual function with a trend toward worse sexual function and erectile function in men after laparoscopic rectal surgery (41% in lap, 23% in open; $P > 0.05$) [62]. This finding was similar in the female population with 28% of laparoscopic patients experiencing decreased sexual function (vaginal dryness during intercourse or pain) vs. 17% in the open group. The authors of CLASICC conclude that this may have been influenced by the learning curve [62] given the 34% conversion rate in this cohort. The recent COREAN trial with much lower conversion rates demonstrated no differences in male sexual function in its two arms [37].

Two small series actively investigated ejaculatory dysfunction after laparoscopic surgery and found no significant difference in dysfunction after either procedure (pooled OR 0.59; 95% CI 0.01 to 32.75; $Z = 0.26$; $p = 0.79$) [81, 82]. Likewise there were no differences in erectile dysfunction (pooled OR 1.30; 95% CI 0.02–69.13; $Z = 0.13$; $p = 0.90$) [79]. Five series have evaluated females specifically for postoperative sexual dysfunction [62, 81–84]. Overall these series have demonstrated similar risks. A systematic review identified three additional nonrandomized trials reporting sexual function after minimally invasive pelvic surgery demonstrating better sexual function in the laparoscopic arms [37]. McGlone [84] et al. used the female sexual function index and found better outcomes in women's libido in the laparoscopic group as well as lubrication, orgasm, and dyspareunia after surgery [85]. Given this mix of data, it is likely that MIS provides neither an advantage nor disadvantage to sexual function.

Urinary dysfunction is another long-term potential issue after pelvic surgery. The CLASICC trial [62] reported equivalence for bladder dysfunction with the most common compliant being weak stream. The COLOR II [8] and COREAN trial [37] used the QLQ–CR38 to evaluate micturition problems. Both trials found significantly less issues in patients who underwent laparoscopic surgery [8, 37]. Four studies have reported no significant differences and urinary function after laparoscopic approaches to pelvic tumors [81–84]. In fact, Yang et al. [83] reported fewer micturition problems at 3–6 and then again at 12–18 months compared to open. In conclusion it appears that there is no distinct advantage of the laparoscopic technique in preserving autonomic function for sexual or urinary complications.

Technical Challenges

The technical challenges of laparoscopic rectal surgery have limited the diffusion of this technique. In the United States, it has been estimated that minimally invasive rectal resection makes up less than 20% of the overall resection practice [17]. In addition high rates of conversion (46.2%) to open surgery persist without any significant recent improvement [17]. For these reasons groups such as the National Comprehensive Cancer Network and the American Society of Colon and Rectal Surgeons continue to recommend laparoscopy for rectal cancer within study protocols or high-volume specialized centers [26].

The technical risks and pitfalls of minimally invasive approaches to rectal cancer can be defined by two basic principles: those of patient and tumor biology and those of intrinsic anatomy. Known patient and tumor risk factors for a laparoscopic conversion in the literature include obesity [86–88], elevated patient age, ASA score, advanced tumor stage, and emergency setting [22]. These patient and tumor factors can lead to the inability to complete cases through a laparoscopic approach. Multiple studies have demonstrated increased complication rates, length of hospital stay, and overall costs associated with conversion [20, 89]. These disappointing trends may be improving as recent series have reported conversion rates that are much lower, ranging from 5 to 8% [90–92]. The impact of conversion must be met with serious consideration as level 1 evidence has suggested increased local recurrence rates and decreased overall survival [33, 74]. The CLASICC trial found significantly lower overall

5-year survival in those with conversion but similar disease-free survival [19]. Similar findings were found in a 10-year retrospective single-institution review of rectal cancer surgery [89]. Alternatively, other recent series with more than 100 laparoscopic rectal resections revealed no negative oncologic consequences with a mean follow-up of 35.8 months [93]. However, even these authors concluded that given the technical challenges and the potential high conversion rates that expert teams should perform minimally invasive approaches to rectal cancer [93].

The type of operation a surgeon can achieve is dependent on the tumor characteristics. General tumors, which involve the anal canal or pelvic floor musculature, are typically best treated with a classical abdominoperineal resection (APR). Very distal tumors, which are amenable to retaining intestinal continuity, may be treated with techniques such as coloanal anastomosis (CAA). It is acceptable for tumors located very distantly to have only a 1 cm distal margin based on good evidence that tumor spread beyond 1 cm in only 4–10% of cancers [25]. Such techniques can be completed transanally, with direct visualization and hand-sewn anastomosis. Alternative approaches to reconstruct very low tumors have been described in which the intersphincteric resection (ISR) of either part of or the entire internal anal sphincter muscle in order to obtain appropriate radial margins [76]. Rullier and colleagues recently standardized the surgical treatment of these low tumors proposing a new classification according to degree of sphincter invasion. They used for classifications for these low tumors the following: "Type I (supra-anal tumor): inferior tumor board located more than 1 cm from the anal ring; Type II (juxta-anal tumor): inferior tumor board is located ≤ 1 cm distant from the anal ring; Type III (intra-anal tumor): there is internal sphincter invasion; and Type IV (transanal tumor): when there is external sphincter or levator any muscle invasion" [66, 76]. Type I and type II included partial and complete resection of the internal sphincter muscle. Type IV lesions of course are treated with classical APR resection. In this study more than 404 patients were evaluated with local recurrence rates of 6%, 5%, 9%, and 17%, respectively, for each of the type of resections I–IV ($p = 0.186$) [76].

The operative techniques needed to successfully complete an operation for rectal cancer are many. For all tumors of the middle and lower third of the rectum, it would be an expectation that total mesorectal excision would be employed [25, 26]. For tumors in the upper third of the rectum, a margin of at least 5 cm should be typical [26, 94]. It is important to note that tumor deposits can be found up to 4 cm beyond the distal tumor within the mesorectum [94, 95]. Radial margins or circumferential resection margin (CRM) is a critical component to rectal cancer surgery and profoundly important as a predictor of local recurrence and survival [25, 96, 97]. Many centers include the quality of the surgical TME as part of their overall cancer quality metrics [25]. The controversy over circumferential margin in APR resection has been significant. However, multiple series have actually shown improvement in APR circumferential margin positivity exclusively within laparoscopic trials [22]. (The important take-home message, when performing an APR resection, includes that need for wide on-block resection of the levator muscles with the rectum and anal canal). The techniques for accomplishing this are multiple, but at least one will be described below.

Achieving vascular control, on-block resection of T4 tumors, and a full and appropriate lymph node dissection can be challenging to even the best technical surgeon. All surgical resections should include proximal vascular ligation at the origin of the main feeding artery [25]. There is little convincing evidence that high ligation of the IMA is required in the setting of no obvious tumor above or proximal to the superior rectal artery [25]. However, in order to achieve a proper tension-free anastomosis, this higher-level dissection may enable additional mesenteric length. It is important to recognize that any clinically suspicious node should be removed including periaortic [25, 26]. It goes without saying that this is a technical challenge. It can be daunting for many surgeons to perform these resections and is certainly more difficult when performing it with an MIS approach. Equally difficult is dealing with

adjacent organs involved by T4 cancers. These too require aggressive on-block techniques, to achieve published survival rates of up to 50% at 5 years [25]. These facts must be considered when contemplating a laparoscopic approach for the most complex of rectal cancers.

Operative Technique for a Laparoscopic Operation

Patient and Positioning

For a patient undergoing rectal resection, a modified lithotomy position is chosen to provide access to the perineum and anal canal.

Trocar Placement

Abdominal access can be obtained by a variety of methods. We prefer the use of a modified open technique, using an Optiview® trocar (Ethicon Endo-Surgery, Inc.) placed under direct visualization in the midline just superior to the umbilicus. The Optiview® trocar has been especially beneficial in the obese patient. Ideally, the 30-degree camera is positioned 15 cm from the target anatomy and 30-degree down angle.

It is critical to consider the boney aspects of the pelvic sidewall and sacral promontory when planning surgical dissection. Trocars placed too cephalad will make the presacral dissection toward the pelvic floor difficult secondary to reach. Likewise, the sacral promontory acting as a fulcrum can lead to an improper angle of dissection into the presacral space. Finally, trocars placed too laterally (particularly in a male patient) will ensure collisions with the lateral pelvic sidewall (Fig. 9.1).

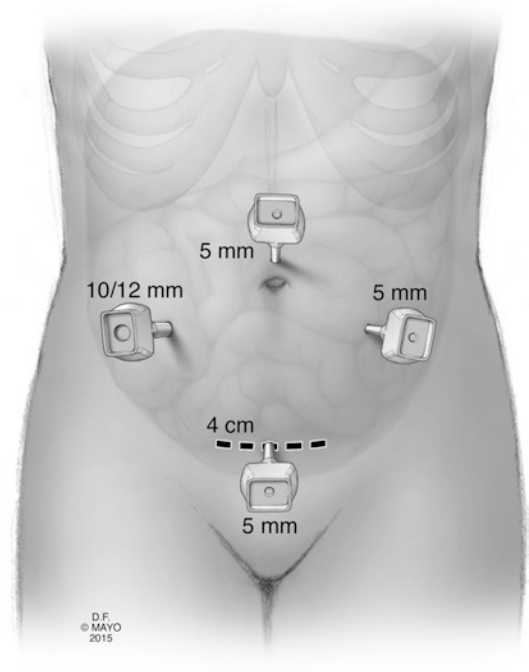

Fig. 9.1 Trocar placement and laparoscopic

Step 1: Initial Exposure

In order to free up, space in the lower abdomen and pelvis is prudent to reflect the greater omentum over the transverse colon toward the liver and the small bowel retracted out of the pelvis. In a female patient, it may be necessary to suspend the uterus to obtain an unobstructed view into the deep pelvis. We place a suture transabdominally around the round ligaments to suspend the uterus anteriorly or directly through the fundus of the uterus.

Step 2: Control of the Inferior Mesenteric Artery (IMA) and Inferior Mesenteric Vein (IMV)

Depending on the length of colon needed, vessel ligation may include any combination of inferior mesenteric artery (IMA), proximal or distal to the left colic artery, as well as inferior mesenteric vein (IMV) ligation. The initial step to vessel ligation begins with placing the patient in steep Trendelenburg position. At this point the assistant grasps the rectosigmoid junction and retracts the rectum superiorly out of the pelvis. Monopolar-curved scissors are used in the right lower quadrant trocar, and a retracting instrument is used in the other trocars to displace key anatomy. It is critical that the upper rectum be elevated to stretch the peritoneum overlying the right pelvic gutter, as well as the superior rectal artery to help separate the vessels from the sacral promontory. Electrocautery is then used to incise the peritoneum along the right side of the rectum, caudal to the sacral promontory. This exposes and opens the presacral space (Fig. 9.2).

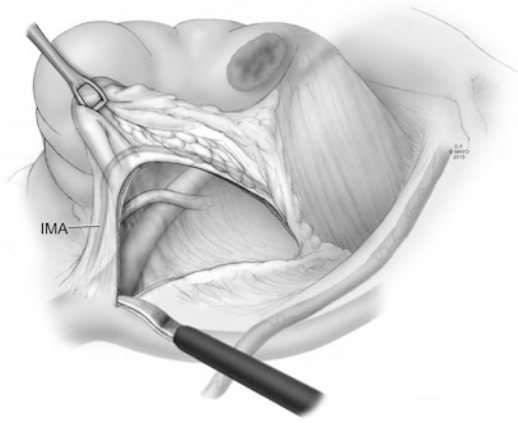

Fig. 9.2 Presacral dissection of the rectum with exposure of the superior rectal artery and inferior mesenteric artery

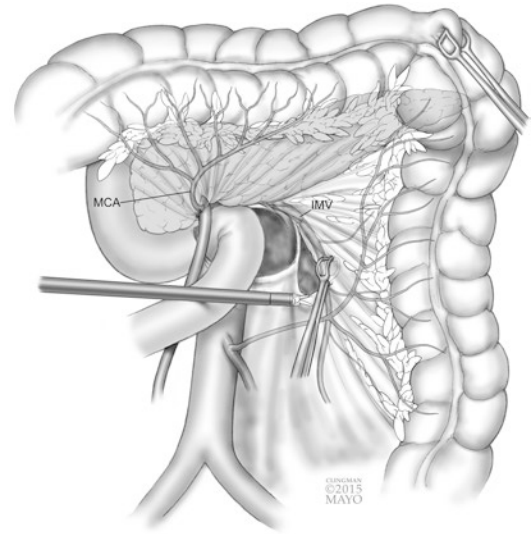

Fig. 9.3 Dissection of the inferior mesenteric vein and medial approach

This initial dissection is carried cephalad along the posterior border of the mesorectum toward the IMA (Fig. 9.2). Care must be taken to not breach the fascia propria of the rectum and avoid injury to the superior hypogastric nerve plexus (SHP). To avoid the SHP, one must locate it anterior to the body of L5 vertebra and typically slightly displaced to the left anterolateral side of the aorta and its bifurcation [78, 79]. Alternatively, the left and right hypogastric nerves (HN) can be identified underneath the promontory. Injury to the SHP or the HN may cause loss of nerve function resulting in retrograde ejaculation, urgency, urinary incontinence, and orgasm dysfunctions [78, 79]. As one dissects directly below the superior rectal artery and above the retroperitoneal fascial planes, the left ureter and gonadal vessels can be easily swept bluntly posteriorly to maintain their position within the retroperitoneum, posterior and lateral to the IMA.

While there is no oncologic benefit to high versus low ligation of the IMA, we prefer to ligate this vessel at its origin to obtain maximal length for a potential low pelvic anastomosis and to minimize tension. Once the IMA is isolated at its origin, we ligate this using a 5 mm blunt tip LigaSure (Covidien Surgical Solutions, Mansfield, MA) vessel sealer. Other methods of vascular control include the use of endoscopic staplers, clips, or sutures.

The colonic mesentery can now be elevated off the retroperitoneum proximally and laterally. Much of this dissection can be carried out bluntly. The extent of dissection is superior to the inferior border of the pancreas and laterally overlying Gerota's fascia. The cut edge of the colonic mesentery can continue to be transected superiorly, lateral to the duodenum to include the IMV. An alternative method to IMV ligation involves placing the patient into reverse Trendelenburg position, with the left side elevated. The greater omentum is reflected superiorly, and the transverse colon is retracted anteriorly and superiorly. The ligament of Treitz is identified, and the IMV can usually be seen coursing within the colonic mesentery just lateral to the fourth portion of the duodenum (Fig. 9.3). To enter the lesser sac through the transverse mesocolon, the peritoneum of the transverse mesocolon, just superior to the IMV and lateral to the duodenum, is incised. Dissection is carried through the mesocolon and into the lesser sac. The pancreas should be identified posteriorly. To achieve enough length for any coloanal anastomosis, the IMV generally needs to be divided at the inferior border of the pancreas. This medial approach to the vein flows into the lesser sac dissection and facilitates complete mobilization of the splenic flexure. Any remaining colonic mesentery between the region of dissection of the IMA and IMV is then also transected with the vessel sealer.

Our typical approach at this point includes taking the colonic mesentery from the primary feeding vessel of the rectum to the edge of the sigmoid or descending colon. This allows for complete vascular isolation of the target anatomy and provides an estimate as to the proximal area for anastomosis. In general, we prefer to use the more compliant descending colon for any low anterior resection. Once the mesentery has been divided, we do not divide the bowel as it provides a fantastic opportunity for retraction during the pelvic dissection.

If an abdominoperineal resection (APR) is to be performed, the splenic flexure is not mobilized. The colonic mesentery is instead transected with a vessel sealer to the border of the sigmoid colon, and the colon is divided with an endoscopic stapler.

Step 3: Medial-to-Lateral and Splenic Flexure Mobilization

If the splenic flexure is to be mobilized, the mesentery and lateral attachments of the descending and sigmoid colon are all that remain to be divided. From the medial side, the appropriate avascular plane can be quickly and easily separated in a blunt manner. It is imperative to ensure that Toldt's fascia is preserved, and the retroperitoneum is not violated, doing so places the retroperitoneal structures (kidney, ureter, and gonadal vessels) at risk of injury. This dissection is complete when all that remains of the colonic attachments are the lateral peritoneal attachments. Without changing the position, these attachments can be cut with electrocautery. Alternatively, one may place the patient in reverse Trendelenburg position with the left side slightly elevated. One can quickly detach the lateral peritoneal attachments to the left colon and sigmoid by starting at the pelvic brim and continued proximally toward the splenic flexure.

Step 4: Rectal Dissection

The dissection begins in the avascular mesorectal plane. We typically start this dissection along the posterior, right side and proceed caudally; in this case one retracts the rectum toward the patient's left side with the surgeon performing the dissection. This dissection is carried posterior to the rectum as far to the left pelvic sidewall as possible to decrease the amount of dissection necessary from the patients left side. The surgeon may need to switch sides to complete the dissection along the left side of the rectum. When one has reached the lateral stakes, the posterior dissection is continued distally, including the lateral stalks, which are taken with monopolar cautery. If a middle rectal vessel is present within the lateral stalks and not controlled with cautery, this may be controlled with either bipolar or the vessel sealer. Dissection that is too lateral in the region of the lateral stalks places the nervi erigentes at risk for injury, which can lead to erectile dysfunction [78]. Distally the pelvic splanchnic nerves (PSN) are responsible for erection, detrusor contractility, vaginal lubrication, and arousal [78]. These fibers running inside the piriform muscles covered by the parietal fascia then cross the retrorectal space forming the IHP together with the HN.

The anterior dissection is then undertaken. The assistant pulls the rectum down and out of the pelvis to provide proper tension on the anterior structures. The assistant aids the dissection by placing a suction device or grasper anterior at the level of the seminal vesicle or posterior vagina and lifting anteriorly. This countertraction anterior to the rectum allows the dissection to progress to the level of the pelvic floor. In patients with an anterior tumor, our dissection plane is always anterior to Denonvilliers' fascia. During this part of the dissection, the nerves are especially at risk near the lateral edges where adhesions to the facial attachments can obscure the true and correct plane of dissection. It is at this level that the autonomic nerves (the Walsh bundles) are at particular risk as they lie laterally and anterior to Denonvilliers' fascia. If one wishes to ensure the nerves' integrity, one should proceed with the dissection by keeping contact with the propria fascia [78]. Below on this level of dissection, one enters the rectoprostatic fascia and the mesorectum ends with the correct plane of dissection along the wall of the rectum. The periprostatic nerve plexus carries both sympathetic and parasympathetic fibers which may be injured during this maneuver [78]. A small triangular-shaped space bordered by the prostate or vagina anteriorly, the rectum posteriorly, and the levator

ani muscle laterally is a critical landmark for this nerve plexus [78].

A total mesorectal excision is completed circumferentially to the pelvic floor for patients undergoing coloanal anastomosis. For more proximal tumors, the dissection proceeds to a level that includes a 5 cm distal mesorectal margin. In this case, the mesorectum at the distal transection point is ligated using a handheld vessel sealer in order to isolate the rectum and prepare it for transection in a proper tumor-specific mesorectal excision.

Step 5: Anastomotic Technique

In patients undergoing APR, the rectal dissection proceeds to the pelvic floor in a cylindrical manner. The bare area of the rectum distal to the mesorectum must not be unroofed. In this scenario, the pelvic floor musculature can even be incised from the pelvis and the ischioanal space entered, exposing the ischioanal fat. The perineal portion of the resection is then conducted in the usual open fashion, and the rectum is extracted through the perineum. Finally, the abdomen is insufflated after closure of the perineal incision, and the end colostomy is identified and matured usually in the left lower quadrant.

For those patients with a low rectal tumor and undergoing a coloanal anastomosis, a mucosectomy is completed just proximal to the dentate line. Placement of a Lone Star retractor (CooperSurgical, Trumbull, CT) generally provides adequate visualization. The mucosectomy is carried proximally to just above the anorectal ring. The pelvis is then entered from the perineal side just anterior to the coccyx. A finger placed into the pelvis, transanally, is then utilized to identify the correct plane of dissection to free the rectum circumferentially with electrocautery. When performing this dissection anteriorly, one must take care not to injure the urethra in males or the vagina in females. Once completely mobilized, the rectum may be extracted transanally and divided at the previously identified proximal transection point on the descending colon. A single-layer hand-sewn coloanal anastomosis is then fashioned with interrupted absorbable sutures placed circumferentially.

For tumors that are slightly higher within the rectum, the opportunity does exist for a low purse string to be placed and a single stapled anastomosis to be fashioned in this low position. Finally, it must be noted that on rare occasion for tumors which are too low or space occupying in a narrow pelvis for proper or safe dissection from above, one can complete a bottom-up approach in order to meet the superior dissection from below. This is typically accomplished with traditional anal instrumentation and/or devices traditionally used for transanal endoscopic microsurgery (TEMS) and dissection through the rectal wall after purse string placement just above the anorectal ring. Once through the rectal wall, one must dissect in the correct anatomical planes up to the point of the abdominal dissection. This bottom up approach may allow one to complete a very complex tumor with an MIS approach and avoid conversion to open surgery.

Patients undergoing low anterior resection can have the rectum and colon transected, once the mesorectum/colon has been cleared with the vessel sealer, either intracorporeally using the stapling device (Figs. 9.4 and 9.5) or transabdominally, through a small Pfannenstiel incision. An end-to-end stapled anastomosis is then fashioned (Fig. 9.6). An alternative to a straight colorectos-

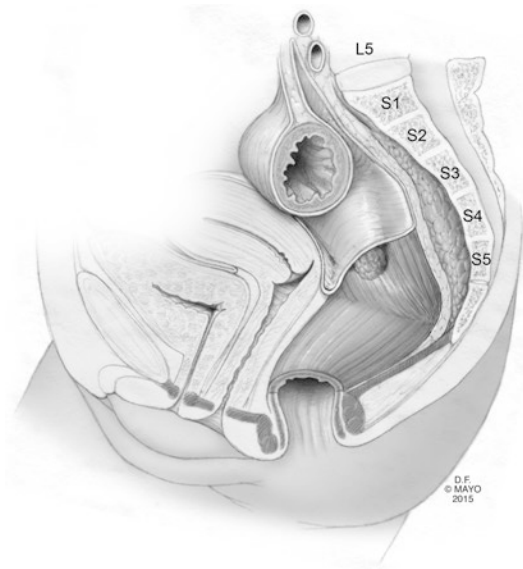

Fig. 9.4 Anatomy of a mid-rectal cancer

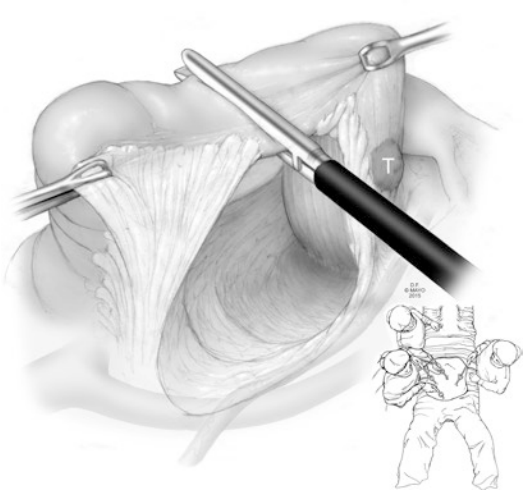

Fig. 9.5 Proximal division of the colon with an intracorporeal stapling device

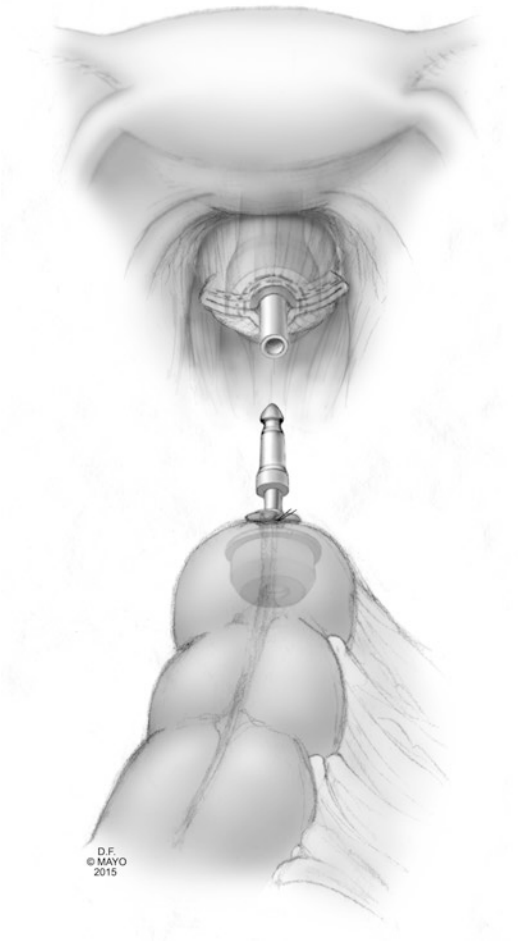

Fig. 9.6 Anastomotic technique for low anterior resection

tomy, a colonic J-pouch or a transverse coloplasty, may be fashioned to increase the reservoir capacity of the colon [98, 99].

A diverting loop ileostomy is routinely used in patients with low (below the anterior peritoneal reflection) anastomoses or those patients who received preoperative radiation therapy. Consideration for ileostomy reversal occurs 3 months after the index operation or once any potential adjuvant therapy is completed.

Conclusion

The use of MIS in the treatment of rectal cancer is dependent on the surgeon and their associated surgical technique and training. Following standards of care including best evidence is likely one of the many reasons NCI-designated cancer centers is associated with lower mortality [68]. Moreover, hospitals, specialty focus, and surgeon volume continue to be important predictor of lower mortality, better survival, and higher rates of restorative procedures [67–70]. These facts, in concert with the clinical and scientific evidence, that MIS of rectal cancer is both challenging and to date incomplete in its defined results of long-term outcomes lead this author to a simple conclusion. Until further long-term data can be obtained, it is prudent and appropriate to suggest that the laparoscopic treatment of rectal cancer be left in the hands of well-trained experts along with their multidisciplinary teams and highly capable institutions.

The future and the generalizability of minimally invasive approaches to rectal cancer rests in the hands of surgeons who to date through reported data appear to fulfill all the technical criteria of appropriate surgery. Although long-term outcomes from multiple level 1 trial remain unpublished, we have a large plethora of small level 1 and larger level 2 trials, which support its use. In fact to date there is little evidence that MIS for rectal cancer is any worse than open surgery in either RCT or single- or multi-institutional nonrandomized trials. It goes without saying that the principles of surgery must be maintained regardless of approach or tool used in the surgical

treatment of this disease. Just as energy devices replaced sharp dissection, minimally invasive approaches and tools will replace open surgery. It remains as it always has that the technical skill and the ability of the operating surgeon will continue to advance and change as the technology they use advances. High-volume centers with specialized interest and rectal cancer will continue to expand the techniques of minimally invasive surgery. However its implementation in the general community remains limited secondary to steep learning curves, high entrance costs, training, and long-term oncologic controversy.

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Robotic Rectal Resection

10

Sunil Patel and Martin R. Weiser

Abbreviations

3-D	Three dimensional
ACOSOG	American College of Surgeons Oncology Group
COLOR II trial	Color carcinoma laparoscopic or open trial
COREAN trial	Open versus laparoscopic surgery for mid or low rectal cancer after neoadjuvant chemoradiotherapy
CRM	Circumferential resection margin
MRC CLASSICC trial	Conventional versus laparoscopic-assisted surgery in patients with colorectal cancer
ROLARR trial	Robotic vs. laparoscopic resection for rectal cancer
TME	Total mesorectal excision

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Introduction

Minimally invasive surgery for colorectal disease has become increasingly popular over the last 20 years. Advances in the quality and function of laparoscopic equipment, and greater experience on the part of clinicians, have resulted in increased utilization of minimally invasive surgery for malignant as well as benign colorectal disease. The robotic surgical platform represents a new generation of useful tools for the clinician, improving the surgical treatment of rectal cancer. The robot offers several advantages over traditional laparoscopic equipment, including articulating instruments with a stable camera platform and high-quality three-dimensional (3-D) vision that restores and enhances the eye-hand-target axis. The robot also appears to facilitate training in minimally invasive surgical procedures, enabling clinicians to gain experience more quickly. This chapter presents the current evidence for robotic surgery in rectal cancer, and describes our preferred surgical techniques as of March 2015.

Short-Term Outcomes of Laparoscopic Rectal Cancer Surgery

As of March, 2015, a number of large trials have investigated the short-term outcomes of laparoscopic versus open surgery in the treatment of

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rectal cancer. These include the MRC CLASICC trial [3], the COREAN trial [4], and the COLOR II trial [5]. The short-term outcomes reported by these trials are outlined in Table 10.1. In general, the investigators detected no difference in short-term outcomes between traditional laparoscopic versus robotic resection, with respect to positive circumferential resection margin (CRM) or intra-operative complications. Two of the three studies found that patients undergoing laparoscopic surgery had a shorter length of in-hospital stay. The conversion rate to open surgery in these studies ranged from 1.2% to 32.4%. Two major trials are currently investigating the safety of laparoscopic surgery in patients with rectal cancer. The American College of Surgeons Oncology Group (ACOSOG) has completed enrollment of rectal cancer patients and short-term results from this trial (ACOSOG Z6051) are expected shortly. The Australasian Laparoscopic Cancer of the Rectum Trial (A La CaRT) is also ongoing and anticipates accrual of 470 patients.

In addition to the major trials listed above, a recently published Cochrane review [6] assessed 11 large and small trials involving 3812 patients. The Cochrane group found no differences in rates of positive CRM, 30-day morbidity, 30-day mortality, or number of lymph nodes retrieved. Patients undergoing laparoscopic surgery had a decreased risk of wound infection (OR 0.68, 95% CI 0.50–0.93, $P = 0.015$), decreased use of analgesia (−0.60 doses, 95% CI −0.93 to −0.27, $P < 0.001$), decreased length of stay (−2.16 days, 95% CI −3.22 to −1.10, $P < 0.001$), decreased time to diet (−0.53 days, 95% CI −0.80 to −0.23, $P < 0.001$), and decreased time to defecation (−0.86 days, 95% CI −1.17 to −0.54, $P < 0.001$), compared to patients undergoing open surgery.

Long-Term Outcomes of Laparoscopic Rectal Cancer Surgery

Two of the large rectal cancer trials (the MRC CLASICC trial and the COREAN trial) [3, 7] have reported long-term outcomes comparing laparoscopic to open surgery. The results are summarized in Table 10.2. No differences between laparoscopic and open surgery have yet been observed with respect to the risk of local recurrence, distant metastasis, or overall survival. However, both the COLOR II and ACOSOG Z6051 trials have yet to publish long-term outcomes at the time of preparation of this summary.

Table 10.1 Short-term outcomes of laparoscopic vs. open surgical trials

Author, year	Trial name	Laparoscopic patients	Open patients	Conversion rate (%)	Positive margin RR	Complications	Hospital stay
Guillou 2005 [3]	MRC CLASSIC trial[a]	253	128	32.40	1.08 (0.60–1.97)	1.08 (0.83–1.43)	Favored laparoscopic surgery
Kang 2010 [4]	COREAN trial	170	170	1.20	0.71 (0.23–2.21)	0.90 (0.61–1.34)	No difference
van der Pas 2013 [5]	COLOR II trial	699	345	17	0.95 (0.63–1.45)	1.08 (0.91–1.27)	Favored laparoscopic surgery

RR risk ratio, presented with (95% confidence intervals)
[a]Rectal cancer subgroup, MRC Classic trial included both colon and rectal cancer patients

Table 10.2 Long-term outcomes from RCT assessing laparoscopic vs. open surgery

	3-year disease-free survival		3-year overall survival		3-year local recurrence	
	Laparoscopic	Open	Laparoscopic	Open	Laparoscopic	Open
COREAN Trial	79.2%	72.5%	88.0%	85.0%	2.6%	4.9%
MRC CLASICC Trial	66.3%	67.7%	68.4%	66.7%	7.9%	8.6%

A Cochrane review of both colon and rectal cancer patients found no differences in 5-year overall survival (OR 1.15, 95% CI 0.87–1.52, $P = 0.32$), 5-year local recurrence (OR 0.94, 95% CI 0.49–1.81, $P = 0.32$), distant recurrence (OR 0.97, 95% CI 0.70–1.32, $P = 0.80$), or port site/wound recurrence (2.76, 95% CI 0.75–10.20, $P = 0.13$) [8] between open and laparoscopic surgery. Thus, the currently available data appear to support minimally invasive surgery for rectal cancer, reporting short-term benefits similar to those seen in colon cancer.

Trends in Minimally Invasive Surgery

In light of the observed short-term benefits of minimally invasive surgery compared to open surgery—as well as increased technical expertise on the part of clinicians and improvement in technique and devices—the use of laparoscopic colon surgery has increased dramatically during the past two decades. Kang et al. compared the frequency of laparoscopic surgery from 2007 to 2009 using the National Inpatient Sample. They found that the proportion of patients undergoing a laparoscopic right colectomy increased from 13% in 2007 to 49% in 2009 [7]. A large increase was also seen in laparoscopic sigmoid resection (18% in 2007 to 55% in 2009). In addition, the rates of conversion in sigmoid resection dropped dramatically between 2007 and 2009, indicating significant advances along the surgical learning curve, as well as improved instrumentation. However, during this time there was very little increase in the use of laparoscopic surgery for low anterior resection of rectal cancer (12% in 2007 to 16% in 2009) [9] (Figs. 10.1 and 10.2).

The difficulty in adapting laparoscopic techniques to rectal cancer surgery stems from the anatomical restrictions imposed by the operative field and the technical demands of these procedures. The narrow, bony pelvis can inhibit proper visualization of anatomical landmarks and restrict surgical movement; furthermore, it is hardly an ideal space for the straight, rigid instruments used in traditional laparoscopy. The limitations inherent in maneuvering laparoscopic instruments and the difficulty in achieving proper retraction are a challenge. The proximity of other pelvic organs adds a layer of difficulty not encountered in segmental colon resection. In addition, there is the potential for collision of instruments within the small pelvic working space. In rectal cancer surgery, the need for complete and total mesorectal excision (TME) ,

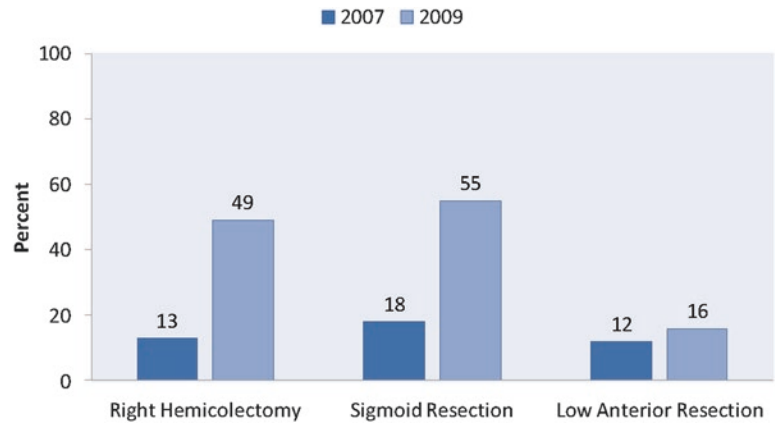

Fig. 10.1 Proportion of surgeries performed laparoscopically. Proportion of colon and rectal resections (right hemicolectomy, sigmoid resection, low anterior resection) performed laparoscopically from 2007 to 2009. (Adapted from Kang CY, Halabi WJ, Luo R, Pigazzi A, Nguyen NT, Stamos MJ. Laparoscopic colorectal surgery: a better look into the latest trends. Arch Surg. 2012;147(8):724–31)

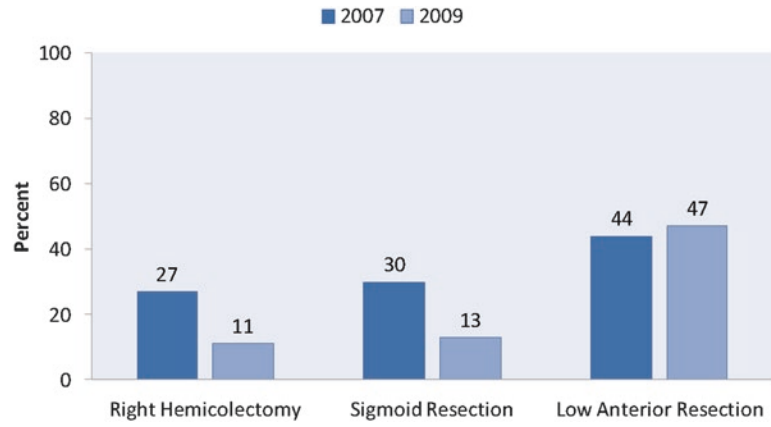

Fig. 10.2 Conversion from laparoscopic to open surgery. Proportion of laparoscopic colon and rectal resections (right hemicolectomy, sigmoid resection, low anterior resection) requiring intraoperative conversion from 2007 to 2009. (Adapted from Kang CY, Halabi WJ, Luo R, Pigazzi A, Nguyen NT, Stamos MJ. Laparoscopic colorectal surgery: a better look into the latest trends. Arch Surg. 2012;147(8):724–31)

entailing exact and sharp dissection of the mesorectal fascia, is paramount. Achieving nerve preservation in order to maintain the patient's postoperative bladder and sexual function, whenever possible, is also an important goal.

Many of the limitations of laparoscopic pelvic dissection can be eliminated when using the robotic surgical platform. The robot's articulating instruments facilitate dissection within the difficult confines of the pelvis. A stable camera platform, and the ability of the surgeon to control camera location, provides greatly enhanced 3-D visualization of the operative field—far superior to the two-dimensional visuals provided by the laparoscope. Retraction with the third robotic arm—so difficult to achieve with traditional laparoscopic instruments—can be controlled directly by the operating surgeon without impingement on the working space. In addition, the articulating instruments decrease the risk of collision.

Laparoscopic vs. Robotic Surgery for Rectal Cancer: A Review of the Literature

The safety and efficacy of robotic rectal surgery has been assessed in a number of observational studies as well as in several small randomized, controlled trials. The largest trial, robotic vs. laparoscopic resection for rectal cancer (ROLARR trial), is currently open to accrual and anticipates enrolling 400 rectal cancer patients. The primary outcome will be conversion to open surgery. Secondary outcomes include circumferential radial margin and other margin positivity. The investigators will also examine morbidity and mortality, 3-year disease-free survival, and postoperative sexual function [10].

Currently, several meta-analyses have been completed [11–13]. The findings are summarized in Table 10.3. These studies consistently reported a lower risk of conversion to open surgery in the robotic group (OR 0.26, 95%CI 0.12–0.57) (Fig. 10.3). A meta-analysis of randomized, controlled trials [14] focused on four studies comparing robotic to laparoscopic surgery in colorectal cancer. The conversion rate was found to be lower in the robotic group (OR 0.26, 95% CI 0.12–0.57) (Fig. 10.4). There was no difference in length of stay, rate of complications, or number of harvested lymph nodes. A large population-based study [9] also compared rates of conversion between laparoscopic and robotic surgery, with similar findings (Fig. 10.5). Unlike laparoscopic rectal resection, patient obesity and low-lying tumors are not strongly associated with conversion in robotic surgery [15, 16].

Table 10.3 Findings from meta-analyses comparing robotic to laparoscopic surgery

Author	Number of studies	Blood loss	Operative times	Conversion to open surgery	Complications	Length of stay	Cost	Lymph node yield	CRM
Yang et al.	16	Robotics	Laparoscopic	Robotics	No difference	No difference	Laparoscopic	No difference	No difference
Trastulli et al.	8		No difference	Robotics	No difference	No difference		No difference	No difference
Memon et al.	7		No difference	Robotics	No difference	No difference		No difference	No difference
Lin et al.	8	No difference	No difference	Robotics	No difference	No difference		No difference	No difference
Xiong et al.	8	No difference	No difference	Robotics	No difference	No difference		No difference	Robotics

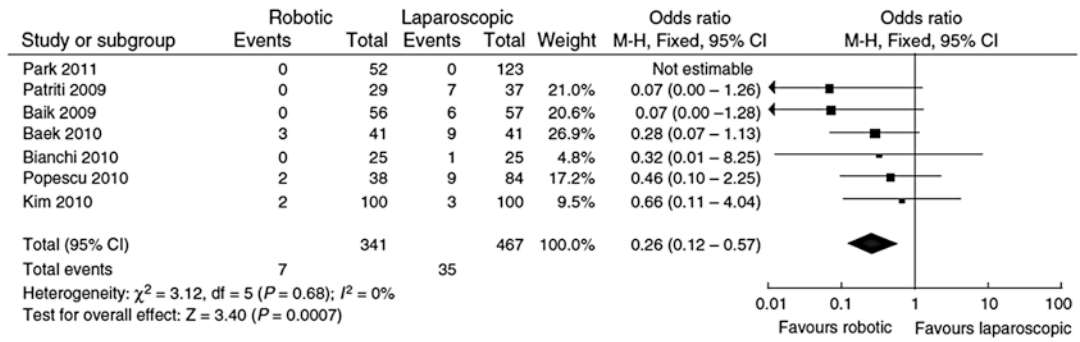

Fig. 10.3 Robotic vs. laparoscopic surgery conversion rates, as reported by randomized and nonrandomized trials. (From Trastulli S, et al. Robotic resection compared with laparoscopic rectal resection for cancer: systemic review and meta-analysis of short-term outcome. Colorectal Dis 2012;14(4):e134–56. Publisher: Wiley. Used by permission)

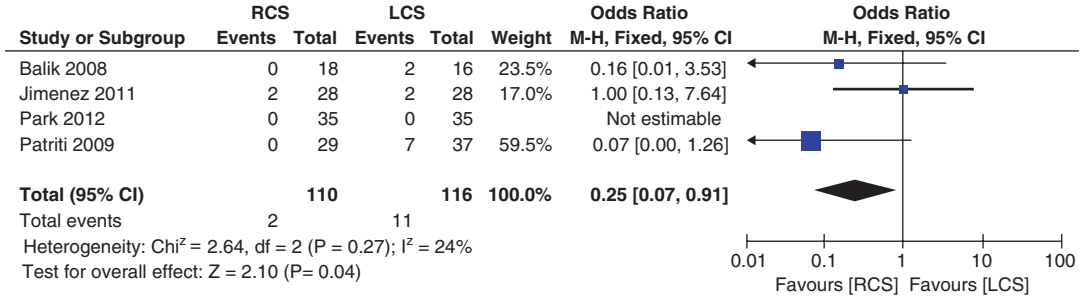

Fig. 10.4 Robotic vs. laparoscopic surgery conversion rates (randomized controlled trials only). Robotic versus laparoscopic surgery rates of intraoperative conversion, as reported by randomized trials. (From Liao G, et al. Robotic-assisted versus laparoscopic colorectal surgery: a meta-analysis of four randomized controlled trials. World J Surg Oncol 2014;12:122. Publisher: Springer. Used by permission)

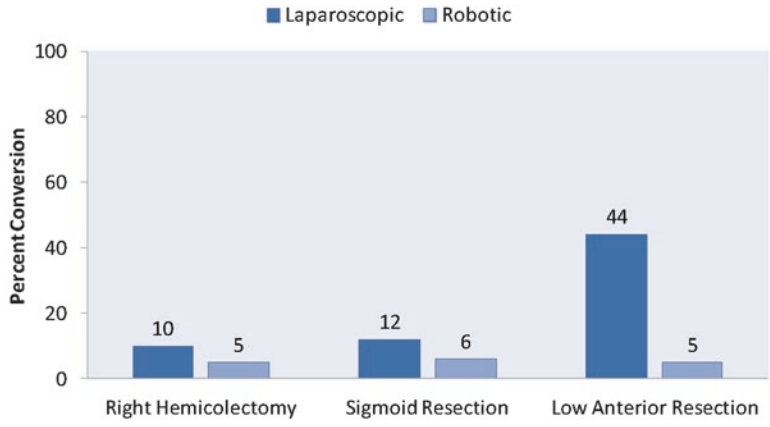

Fig. 10.5 Conversion rate, 2007–2009. Laparoscopic vs. robotic surgery rates of intraoperative conversion from 2007–2009 (right hemicolectomy, sigmoid resection, low anterior resection). (Adapted from Kang CY, et al. Laparoscopic colorectal surgery: a better look into the latest trends. Arch Surg 2012;147(8):724–31. Publisher: Springer. Used by permission)

Total Mesorectal Excision

Poor quality TME is associated with local recurrence. This phenomenon has led to a grading system for surgical quality [17, 18]. In a comparison of 56 robotic and 57 laparoscopic rectal resections, the robotic resection group had a higher proportion of complete TME compared to the laparoscopic group (93 vs. 75%, $P = 0.01$): there were no incomplete excisions in the robotic group, but two in the laparoscopic group [19].

Learning Curve

Several studies have examined the learning curve in robotic surgery [20–22]. In one study [22] operative time was monitored over case volume. Robotic surgery took longer for the surgeon to master compared to laparoscopic surgery (Fig. 10.6). After 21 cases, however, robotic TME dissection became dramatically faster than laparoscopic TME (based on ten-case moving averages) (Fig. 10.7). The authors concluded that robotic rectal surgery was associated with a quicker learning curve than laparoscopic surgery.

Two other studies also examined operative time as a function of case number [20, 21]. Both studies reported three phases of the learning curve. The first phase was defined by rapidly decreasing operative time, corresponding to the surgeon's greater familiarity with the robotic platform. The second phase was defined as a plateau, while the surgeon mastered less complex cases. The third phase was defined by the surgeon's ability to approach more difficult tumors robotically, with a subsequent increase in, followed by a stabilization of, operative time (Fig. 10.8). Docking time also decreased rapidly during the first series of patients, eventually reaching a sustained plateau. (Fig. 10.9).

Cost

The current robotic platform is associated with significant equipment and maintenance costs. Understanding hospital costs and charges can be difficult. In a study assessing National Inpatient

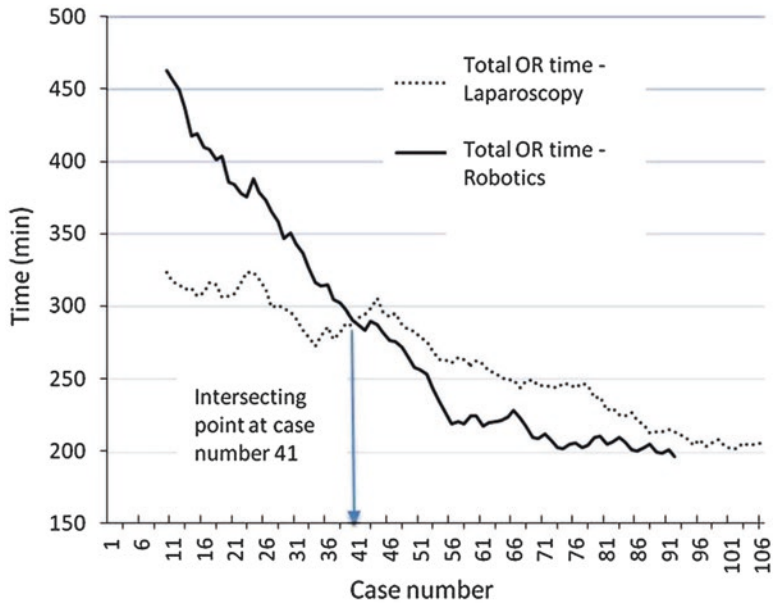

Fig. 10.6 Total OR time. Total operating room time, laparoscopy, and total operating room time, robotic surgery, with respect to number of cases. (Adapted from Melich G, Hong YK, Kim J, Hur H, Baik SH, Kim NK, Sender Liberman A, Min BS. Simultaneous development of laparoscopy and robotics provides acceptable perioperative outcomes and shows robotics to have a faster learning curve and to be overall faster in rectal cancer surgery: analysis of novice MIS surgeon learning curves. Surg Endosc. 2015;29(3):558–68)

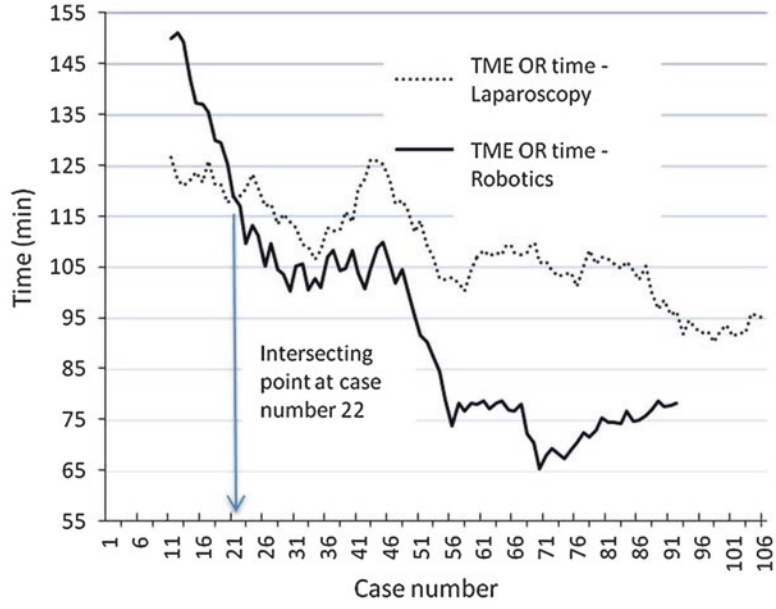

Fig. 10.7 TME time. Total operating room time, laparoscopy, and total operating room time, robotic surgery, for completion of total mesorectal excision, with respect to number of cases. (Adapted from Melich G, Hong YK, Kim J, Hur H, Baik SH, Kim NK, Sender Liberman A, Min BS. Simultaneous development of laparoscopy and robotics provides acceptable perioperative outcomes and shows robotics to have a faster learning curve and to be overall faster in rectal cancer surgery: analysis of novice MIS surgeon learning curves. Surg Endosc. 2015;29(3):558–68)

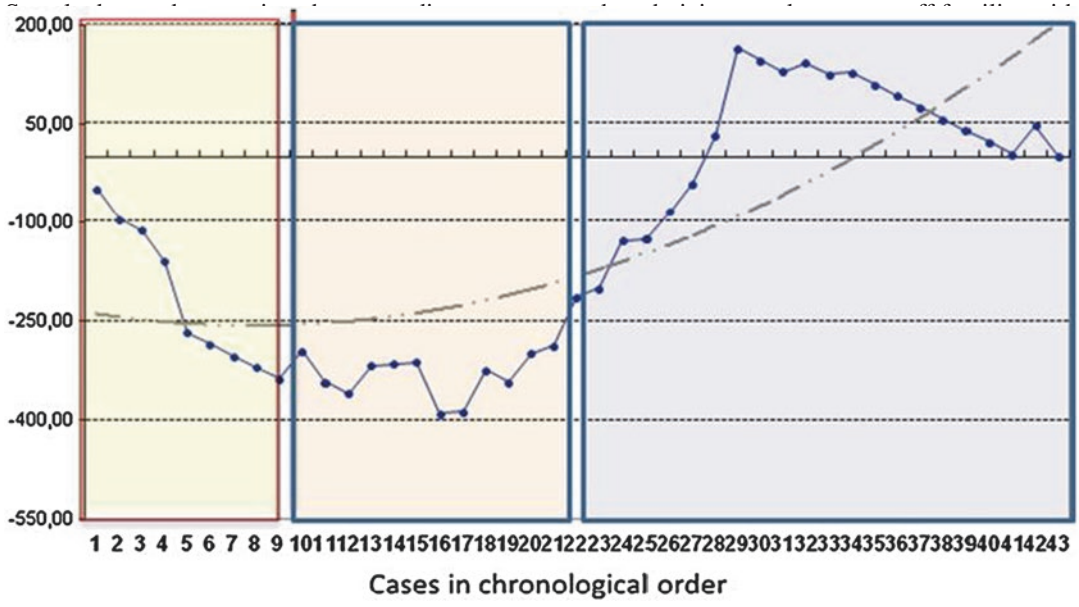

Fig. 10.8 Operative time vs. case number. Total operating room time, with respect to number of cases. (Adapted from Sng KK, Hara M, Shin JW, Yoo BE, Yang KS, Kim SH. The multiphasic learning curve for robot-assisted rectal surgery. Surg Endosc. 2013; 27(9):3297–307 and Jiménez-Rodríguez RM, Diaz-Pavon JM, de la Portilla de Juan F, Prendes-Sillero E, Dussort HC, Padillo J. Learning curve for robotic-assisted laparoscopic rectal cancer surgery. Int J Color Dis. 2013;28(6):815–21)

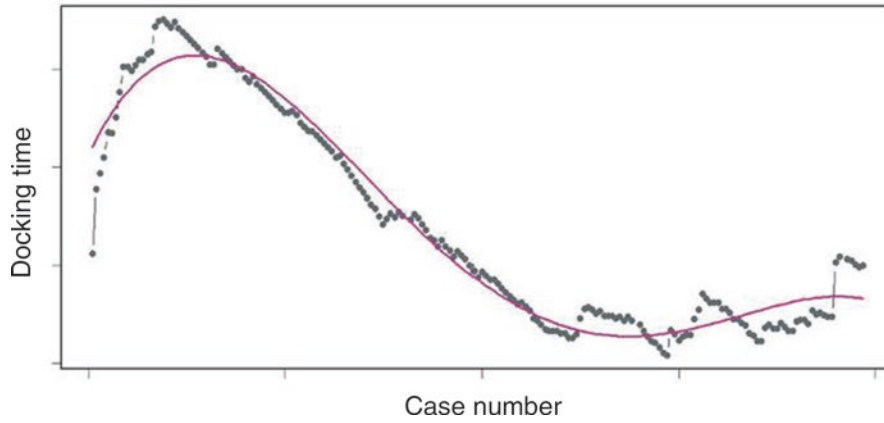

Fig. 10.9 Docking time vs. case number. Total docking time, with respect to number of cases. (Adapted from Sng KK, Hara M, Shin JW, Yoo BE, Yang KS, Kim SH. The multiphasic learning curve for robot-assisted rectal surgery. Surg Endosc. 2013; 27(9):3297–307 and Jiménez-Rodríguez RM, Diaz-Pavon JM, de la Portilla de Juan F, Prendes-Sillero E, Dussort HC, Padillo J. Learning curve for robotic-assisted laparoscopic rectal cancer surgery. Int J Color Dis. 2013;28(6):815–21)

points, with arms tucked. The current robotic platform does not allow table movement while the robot's arms are docked; therefore, it is beneficial to identify the proper position before attaching the arms. For a total robotic procedure, we first position the patient in lithotomy with right-side down and slight Trendelenburg. This provides access to the vascular pedicle, left colon, and splenic flexure. In patients with elevated BMI, additional Trendelenburg and tilt can be helpful.

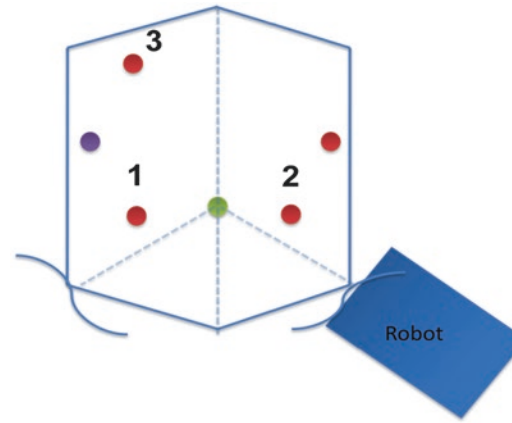

Fig. 10.10 Splenic flexure mobilization, vascular pedicle ligation, and pelvic dissection: port placement and location of the robot for the Si platform

Port Placement and Robot Positioning

For the Si platform, we typically use three robotic arms and one or two assistant ports. In all cases, the initial camera port is 12 mm and is placed at the umbilicus using the Hasson technique. For surgeons planning to utilize the robot for splenic flexure mobilization, vascular pedicle ligation and pelvic dissection, port placement, and location of the robot are shown in Fig. 10.10. This setup allows for the initial vascular pedicle ligation and splenic flexure mobilization.

Two 8 mm robotic ports are placed to the left of the umbilicus. These should be at least 10 cm from the camera port. The most lateral port should be 10 cm lateral to the more medial port and placed superiorly, to prevent arm collisions during pelvic dissection.

The right lower quadrant port should be at least 12 mm, allowing for insertion of the stapling device. It should be placed at least 15 cm from the target anatomy and 10 cm from the camera port. An 8 mm robotic port should be placed in the right upper quadrant. This port is utilized in splenic flexure mobilization and pedicle ligation and can be used as an assistant port during pelvic dissection. One or two 5 mm

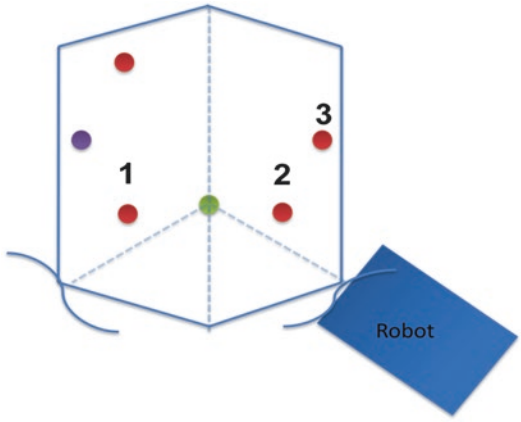

Fig. 10.11 Pelvic dissection: Arm #3 of the robot is moved to the lateral left port from the right upper quadrant port for the Si platform

laparoscopic ports can be placed for the assistant, to aid in retraction. These should be at least 5 cm from the robotic ports and can be placed in a location convenient to the assistant. For the pelvic dissection, Arm #3 is moved to the lateral left port from the right upper quadrant port (Fig. 10.11). The robot is brought obliquely over the patient's left hip.

After ports are placed and insufflation has been achieved, we find it easiest to sweep the small bowel medially and superiorly prior to docking the robot. To facilitate this, the patient is placed in Trendelenburg with a right tilt. As noted above, it is important to position the patient properly before docking.

Vascular Pedicle Ligation

We identify, dissect, and ligate the vascular pedicle first. To achieve this, we begin resection medial to the inferior mesenteric artery. The sigmoid colon can be grasped by Arm #2 in either of the setups described above. The sigmoid colon is then elevated anteriorly; this tents up the vascular pedicle for identification. We then incise the peritoneum medially at the level of the sacral prominence. With insufflation through this opening, the plane becomes easily identifiable. The retroperitoneal fat can then be gently pushed posterior using a combination of blunt and sharp dissection, separating the retroperitoneum from the mesentery of the sigmoid colon. The sympathetic nerves are swept posteriorly. The superior aspect of the posterior mesorectal plane is identified and serves as an important point of reference. Dissection proceeds cephalad; the ureters and gonadal vessel are identified posteriorly and laterally, and these are protected.

With the ureter and gonadal veins identified, the plane between the retroperitoneum and the mesentery can be further developed from medial to lateral and superiorly along the inferior mesenteric artery (IMA). The IMA can be followed proximally and then isolated near the takeoff from the aorta, for ligation either above or below the takeoff of the left colic pedicle. If the IMA is ligated below the left colic artery, the lymph nodes overlying the base of the IMA are swept inferiorly and resected en bloc with the specimen. It is often helpful to dissect, in a medial to lateral fashion, underneath the left colonic mesentery to further define the takeoff of the IMA. To ligate the vessel, we skeletonize it from the surrounding fat and ligate it with the robotic vessel sealer. A stapling device may also be used.

The inferior mesenteric vein (IMV) is identified and ligated at this point or dissected closer to the pancreas. To divide the vein, we skeletonize it using the vessel sealer. It is often helpful to dissect the IMV early in the procedure, as this can aid in the identification of the IMA.

The left colon mesentery is divided to the proposed proximal dissection point of the left colon.

Splenic Flexure Mobilization

Splenic flexure mobilization, with ligation of the IMV adjacent to the pancreas, should be used liberally, permitting rotation of the left colon into the pelvis for a tension-free anastomosis. In order to mobilize the splenic flexure, we continue to separate the retroperitoneum from the colonic mesentery superiorly. Once the pancreas is identified, dissection continues anteriorly, with entry into the lesser sac.

The omentum is then dissected from the transverse colon, from medial to lateral. As dissection is carried out laterally, the splenic flexure will

begin to drop. Once the omentum is completely mobilized off the transverse colon, a clear plane is established posterior to the colonic mesentery. The vessel sealer can be used to maneuver around the corner of the splenic flexure, dissecting medial to lateral, and then inferiorly along the white line of Toldt. If the medial to lateral resection is adequate, the line of Toldt can be easily dissected. The left colon is then freed completely from the retroperitoneal attachments, and full mobility to the level of the rectosigmoid is achieved.

Pelvic Dissection

If the robot was set up for both splenic flexure mobilization and pelvic dissection, Arm #3 must now be moved from its initial position to the left lateral position (Fig. 10.11). We pass the umbilical tape around the rectosigmoid and grasp it for retraction. In female patients, a Keith needle is passed through the abdominal wall and through the uterus; this can be tightened to retract the uterus out of the surgical field.

The assistant retracts the specimen anteriorly, using the umbilical tape. Two operating arms can be utilized to dissect in the alveolar plane of the mesorectum between the visceral and parietal planes of the endopelvic fascia. The third arm is used for additional retraction. Dissection continues in the posterior midline. The mesorectal fascial plane is easily visualized and can be dissected circumferentially. The dissection can be taken down through Waldeyer's (rectosacral) fascia to the planned distal resection margin. A flexible sigmoidoscope may be used to confirm that the proper level of dissection has been achieved. At this position, for tumors located in the mid-rectum, the rectum can be skeletonized off the mesorectum. For distal cancers, dissection can be taken to the level of the bare rectum at the pelvic floor.

In low anterior resection, distal resection may be completed using the robotic stapler. Typically, two firings of the 45 mm stapler are required to come across the rectum. The specimen may be retrieved through the proposed ileostomy site or an alternative extraction site. An end-to-end stapled anastomosis is then completed. An appropriate loop of ileum is identified to complete the defunctioning loop ileostomy.

In abdominoperineal resection, we advocate division of the pelvic floor (the levator ani) from above, under direct robotic visualization. Depending on the location of the tumor, extralevator (cylindrical) resection can be performed to improve margin-negative resection. The proximal colon is stapled prior to completion of the perineal dissection, permitting easy passage of this portion of the bowel to create an end colostomy in the left lower quadrant. The dissection can then be completed via the perineal approach, as is done in both laparoscopic and open procedures.

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Combined Transanal/Laparoscopic Total Mesorectal Excision

11

Antonio M. Lacy and Marta Jiménez Toscana

The Evidence for Current Approaches: Historical and Up-to-Date Perspective

The management of rectal tumors has changed significantly in the last century. The radical abdominoperineal resection proposed by Miles in 1908 has evolved to less aggressive approaches to reduce the associated morbidity and mortality and to preserve sphincters as had been proposed by Abel in 1931. On the other hand, the introduction of the total mesorectal excision in 1979 by Heald as the standard care for rectal cancer, with or without neoadjuvant adjuvant treatment [1, 2], led to the reduction of the local recurrence rate from 20 to 45% described before the 1990s in literature [3] to 4.7% described nowadays [4]. With this slowly but progressive evolution, we could achieve sphincter preservation surgeries, in very low rectal cancer, with acceptable oncological and functional outcomes. The introduction of laparoscopic surgery in the last decades has further improved these results, thanks to the improvements in the quality of the surgical technique and the advances in equipment and instruments. The laparoscopic approach lets us reduce the hospital stay and recovery time with equivalent oncological results. These new approaches, in combination with neoadjuvant and adjuvant protocols, have improved oncologic outcomes and have increased the rate of sphincter preservation.

Rectal cancer management has also focused on the development of transanal procedures since TEM (transanal endoscopic microsurgery) was first introduced by Buess et al. in 1983 and the subsequent introduction of the transanal minimally invasive surgery (TAMIS) technique, which could achieve better outcomes and reduce the morbidity of the ancient techniques. With the multiport transanal device, combined with the standard laparoscopic equipment, we carried out endoluminal excisions of benign lesions or early-stage rectal cancer with the limitation of local recurrences and metastasis rates in case of T2 or advance tumors [5]. Nowadays, the increasing interest in natural orifice surgery has produced an interesting evolution of the transanal natural orifice and minimally invasive surgery allowing a transanal endoscopic surgical resection of the rectum [6]. The fusion of the abdominal and transanal techniques carried Marks et al. to develop in 1984 the combined approach for low-lying rectal cancer. Since then, the advances of this kind of surgery let us develop the transanal minimally invasive surgery for total mesorectal excision (TAMIS-TME) that allows the entire rectal and mesorectal dissection using a transanal approach [7–9]. The feasibility and reproducibility of this approach has been demonstrated first in swine survival experiments [10–12] and

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after in human cadaver series [13–15]. So we proposed a double approach, abdominal and transanal, to perform the rectal cancer surgery offering technical advantages [16–20], beyond the ability to remove the specimen transanally [2]. The transanal approach, with CO_2 insufflation and direct endoscopic visualization, permits a perfect visualization and a precise resection of the distal margin and presacral mesorectal plane, which is essential in very low tumors (in order to allow a sphincter preservation) or in difficult sceneries (e.g., narrow pelvis, males, IBM >30, visceral obesity, prior radiation, low rectal tumors) with the safety in descending the splenic flexure, dissecting the vessels, mobilizing the proximal colon, and retracting the tissue, especially in the setting of a bulky uterus and redundant sigmoid colon [2, 16] that conferred the abdominal approach, meeting the oncologic requirements. Laparoscopic assistance allows us to compensate the limitations of current NOTES instrumentation to ensure the safety and adequacy of oncologic resection [17]. The TAMIS-TME is particularly well suited for patients with locally advanced distal rectal cancer and obesity, where the abdominal approach is challenging [21]. With this technique, we also minimize the need for sizeable abdominal incisions with the secondary reduction of wound infection and hernia formation.

Several studies have been published in literature about this innovative technique in the last several years. All of them have demonstrated the safety and feasibility of the procedure as well as the high quality of the mesorectum obtained [6, 22] (Fig. 11.6), even the heterogeneity of the studies and patients selected makes it difficult to find the evidence. Authors including Zorron et al. [9], Dumont et al. [19], Sylla [10], and ourselves [11] included low and mid-rectal tumors (although Sylla specifically exclude node-positive tumors and those with radiochemotherapy), while Velthuis et al. [24] focused on mid-rectal cancer and Atallah et al. [21] on distal cancers. Most of series excluded bulky tumor [11, 24]; however, Dumont et al. [19] and Rouanet [25] specifically included patients with anatomical difficulties or high-risk tumors (T4, recurrent, large anterior tumor, predicted CRM ≤1 mm on MRI) where the dissection was expected to be difficult. In our series, there are no specific exclusion criteria, and all the patients with rectal cancer are proposed for TAMIS-TME. The overall complication rate published for this procedure is approximately 27%, which is comparable to those described following laparoscopic TME. In addition, postoperative mortality has not been reported [26].

Most of series describe short-term oncological outcomes, and they are comparable to the results obtained after standard laparoscopic TME. Rouanet [26] described the longest follow-up, with a median of 21 months (range 10–40). During this period, 40% of patients were treated for local (four patients) or distant recurrence, and 13% died of cancer-related causes although overall survival rates were 96.6% and 80.5% and relapse-free survival rates were 93.3% and 88.9% at 12- and 24-month follow-up, respectively. Dumont et al. [19], Lacy [17], and Sylla [10] reported no recurrence at an average follow-up of 4.3 months, 30 days, and 5.4 months, respectively.

Long-term oncological outcomes, local recurrence, functional results, and quality of life analysis have to be demonstrated with this technique, but the results are already encouraging and the TAMIS-TME may revolutionize the rectal cancer treatment in the following years being a promising alternative to open and laparoscopic TME [6, 27].

Patient Evaluation and Selection

Indications and Contraindications for Operations

It should be noted that any patient may benefit from TAMIS-TME to treat malignant tumors of the rectum up to 3–4 cm from the anal verge, but this procedure is especially advantageous in patients where the intervention is expected to be complex as in those patients who are male, are obese, or have a narrow pelvis.

There are no absolute contraindications described, although some authors exclude from their series patients with a body mass index over 35 kg/m^2, presence of T4 disease, or recurrent tumors. These factors should be considered relative contraindications, and the only exclusion criterion that we take into account is the patient's previous medical history that could be a contraindication for pneumoperitoneum.

Preoperative Workup

The management of the patients with rectal cancer should begin with a complete study of the patient, tumor characteristics (stage, evaluation of distal metastasis, etc.), and functional anorectal study. Our preoperative evaluation does not differ from the one that is performed for open or laparoscopic approach. The complete evaluation is comprised of:

- Clinical evaluation: family history, defecatory changes, weight loss, rectal bleeding, abdominal and rectal examination, assessment of baseline sphincter function
- Carcinoembryonic antigen levels
- Laboratory analysis: hemoglobin, liver function, prothrombin time
- Nutritional status: albumin, prealbumin
- Complete colonoscopy with histopathologic confirmation of the diagnosis
- Thoracoabdominal tomography (CT)
- Endoanal ultrasound or high-resolution magnetic resonance imaging (MRI)
- Consideration for neoadjuvant chemoradiotherapy if indicated
- Anorectal manometry in low rectal tumors

Perioperative Preparation

The perioperative preparation of the patient begins several days before surgery when a liquid low-fiber diet is recommended for 4 or 5 days prior to surgery. Twenty-four hours prior to surgery, a mechanical anterograde bowel preparation is administered as well as diazepam 5 mg the night before and early in the morning of the intervention day. Correct ostomy positioning is essential; therefore, a specialized nurse marks the optimal ileostomy or colostomy sites the day prior to surgery.

Finally, there are some important considerations for management at resection, which include:

- Administration of prophylactic intravenous antibiotics
- Use of thoracic epidural catheter for pain control
- Insertion of central venous catheter (when indicated)
- Use of Foley catheter bladder drainage
- Use of a warming blanket
- Application of intermittent lower extremity compression stockings and adjustable leg stirrups
- Lithotomy position utilizing Lloyd-Davies or Allen stirrups
- Irrigation of the rectal stump with 1% diluted iodine solution
- Two teams of nurses and surgeons

Technique Description (Key Technical Details)

Patient Position (Fig. 11.1)

The patient is placed in a Lloyd-Davies lithotomy position, and the arms are tucked at the patient's side. The abdomen is prepared with a standard antiseptic solution. There should be three monitors; one is placed on the left side of the patient at the patient's hip level for the surgeon and another on the right side at the same level for the first assistant on the abdominal approach. The third one should be on the head of the patient for the team assisting the transanal approach. There are also two teams of nurses. The first operating nurse's instrument table should be on the right of the patient for the abdominal surgery and the second one down on the left for the transanal surgery.

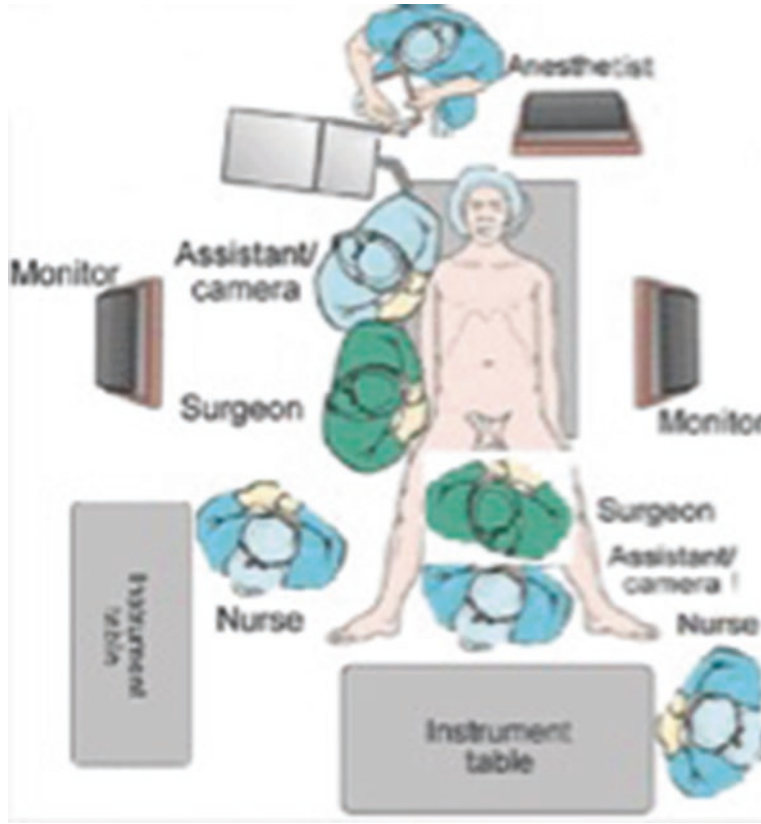

Fig. 11.1 Theater organization

Transabdominal Approach

The surgeon works from the patient's right with the camera assistant on the surgeon's left side and the first assistant on the patient's left. To create a more comfortable working position, there should be a monitor on each side of the patient. Pneumoperitoneum is made by a Veress needle insertion on the left upper quadrant, and the abdomen is insufflated with CO_2 to a pressure of 12 mmHg. A 12-mm port is introduced next to the umbilicus for a 30°-angled scope (e.g., 3D EndoEye 10-mm videolaparoscope; Olympus KeyMed, Europe), and two 5-mm trocars are introduced through the ileostomy or colostomy sites, being cautious to avoid the inferior epigastric vessels. Finally, a 5-mm trocar is introduced in the right lower abdominal region (Fig. 11.2). Additional trocars can be introduced as needed.

Firstly, a complete laparoscopic exploration of the abdominal cavity should be performed to

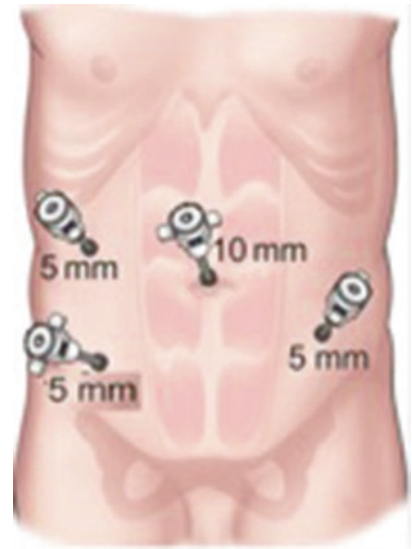

Fig. 11.2 Trocar position in abdominal approach

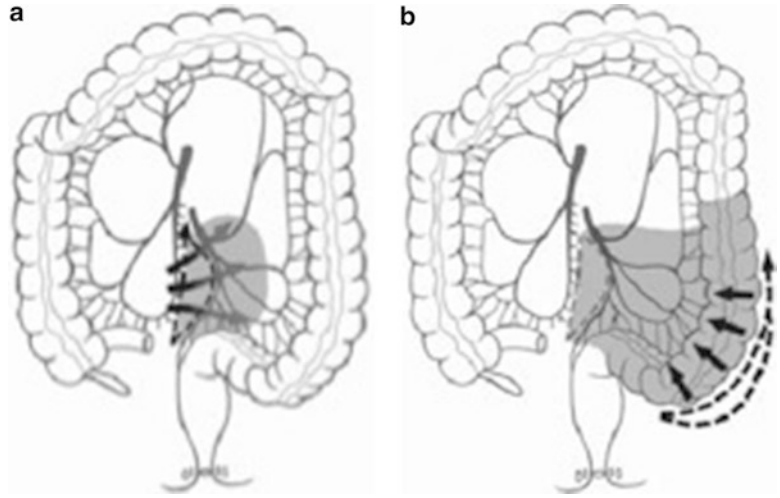

Fig. 11.3 Sigmoidectomy scheme. (**a**) Development of the medal-to-lateral dissection. Division of the IMA after identification of the ureter and gonadal vessels. (**b**) Incision of Toldt's fascia until splenic flexure is mobilized

identify tumoral implants or occult liver lesions. The patient is placed in Trendelenburg (head down) and right side down positions, and the small bowel is retracted to the upper right quadrant of the abdominal cavity. To perform the procedure, we use a 5-mm LigaSure device (Covidien, Ireland) as hemostatic device and monopolar energy, mainly with the hook. A laparoscopic sigmoidectomy is performed in a medial-to-lateral fashion (Fig. 11.3). The assistant makes a gentle skyward traction of the sigmoid colon, holding the mesentery or an epiploic appendage with a grasping forceps, so the inferior mesenteric vessels are retracted. The surgeon incises the anterior layer of the mesentery, and a blunt dissection is performed between the vessels and the retroperitoneum, until the left ureter is localized well down into the pelvis over the common iliac artery and gonadal vessels, before cutting the mesenteric vessels. The inferior mesenteric artery and the vein are dissected separately. The inferior mesenteric artery is divided 1 cm from its origin with a white 35-mm Endo GIA stapler or with the LigaSure device after applying two clips on the proximal side. The inferior mesenteric vein is found next to the pancreas, and it is divided with the LigaSure device with two clips proximally when necessary. All of the mesosigmoid is released up to the left side of the colon and cephalad to the left colonic artery. Care should be taken to avoid injuries to the mesenteric arcades to guarantee an intact blood supply to the descending colon. Gauze could be used for the hemostasis to protect the ureter and gonadal vessels and as a reference to complete the dissection from the left side. The first assistant draws the sigmoid colon medially to expose the left lateral peritoneal gutter. Toldt's fascia is incised down to up as far as splenic flexure.

After sigmoid liberation, we can begin the pelvic dissection, combining our surgery with the one that the transanal team is making from below. With an upward retraction, the surgeon begins to delineate the mesorectum. Thanks to traction-countertraction and the pneumoperitoneum, the proper presacral plane in entered. At this point, the surgeon can bluntly separate the mesorectum (fascia propria of the rectum) from the fascia propria of the sacrum by pushing it anteriorly to the retrorectal space. This way, we can identify the hypogastric nerve trunks and more distally the pelvic nerve plexus avoiding potential injury. After that, the dissection is continued, first along the right side and then along the left, down to the peritoneal reflection in the cul-de-sac through the lateral ligaments. The position of both ureters and hypogastric nerves should be checked at this point and preserved. Meticulous dissection permits identification of the sacral venous plexus. Finally, the peritoneum of the rectovesical pouch or the rectouterine pouch in female patients is incised to expose Denonvilliers' fascia.

By continuing with this dissection plane, the surgical team can rendezvous the team from the transanal approach. This way we can avoid dissection to the levator ani muscle in a narrow pelvis. Once the dissection is completed, the CO_2 pressure of the abdominal cavity is reduced to allow repressurization from the CO_2 that is coming from the transanal approach. We can complete now the surgery with both approaches at the same time.

Transanal Approach

The perineal team initiates transanal approach, while the abdominal team proceeds with the anterior resection. For this approach, we use a flexible single incision platform (GelPoint Advanced Access Platform, Applied Medical), noting an excellent maneuverability and triangulation of instruments, and a 10-mm 3D flexible endoscope (3D EndoEye 10-mm flexible tip videolaparoscope; Olympus KeyMed, Europe) to minimize the movement inside the rectum. The 3D laparoscopy system allows us to perceive depth within the pelvis. On the other side, the innovative use of GelPoint for transanal access is a perfect alternative, from our point of view, to rigid transanal endoscopic platforms (Atallah), being that the device is universally available and its learning curve is shorter according to its similarity to laparoscopic manipulation.

First, the GelSeal cap (GelPoint Path Transanal Access Platform, Applied Medical, European Union) is prepared and upon it is introduced three 10-mm sleeves making a triangle, with a distance of 2 cm between them. This cap is connected to the CO_2 infuser and to a piston valve to exteriorize the smoke. The surgery is begun with a low pressure of 8–10 mmHg that is slowly increased to 12 mmHg in the middle rectum up to 14 mmHg when we perform the rendezvous with the abdominal approach.

The patient is placed in a Lloyd-Davies position with the surgeon and the assistant between the legs. Digital examination is performed to confirm the location of the tumor and the LoneStar Retractor System (CooperSurgical, USA) is applied on the anal verge to expose the anal canal. Depending on the height of the tumor from the anal verge, we can begin the surgery without or with the single port device to develop an intersphincteric resection (ISR) in very low cancers (for tumors located 1–1.5 cm from the anorectal ring) or a higher resection for medium or high rectal tumors in each case. To develop an ISR, the mucosa and the internal sphincter muscle are dissected circumferentially starting at least 1 cm below the distal margin of the tumor and proximately for 1–2 cm until a purse-string suture can be performed to occlude the rectum. This partial or complete excision of internal sphincter extends the distal resection margin and expands the possibility of restorative surgery. To apply the GelPort, the Alexis wound retractor is first introduced and the cap connected on it after removing the LoneStar device. The device is seated just above the anorectal ring, and then it is sutured to the skin to keep in place during the TAMIS-TME procedure. The camera is introduced initially through the 10-mm lower trocar; the left 10 mm is used for an exposure grasper and the right one is used for the dissection instrument (bipolar, monopolar electrocautery, LigaSure, etc.) changing the position as needed, with the help of the pneumorectum to find the correct plane. This device allows us to take the cap out quickly and introduce gauze to clean mucus or bleed as many times as needed. Impregnate the gauze with atropine could help us in the hemostasia for a better visualization.

The first step in the transanal dissection is to place a purse-string 2/0 prolene suture to occlude the proximal lumen of the rectum, at least 1 cm below the lower tumor margin (Fig. 11.4). Small marks are made with monopolar diathermy circumferentially into the mucosa, just distal to the purse string, to delineate the distal resection line not to lose the references. We can now incise all the layers of the rectum radially to obtain a full-thickness transection, and the mesorectum is dissected up to the presacral fascia until identification of the correct plane of dissection (mesorectal plane), using a monopolar cautery hook and bipolar dissecting instruments, in accordance with total mesorectal excision (TME) principles.

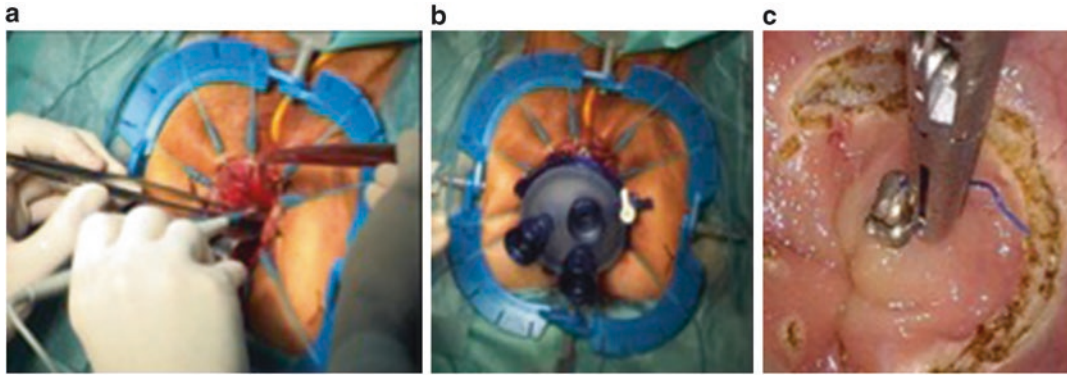

Fig. 11.4 Transrectal dissection. (**a**) LoneStar Retractor positioned to explore the tumor and begin transanal dissection in ISR. (**b**) View of GelPoint device to get access to the lumen and develop transanal TMR surgery. (**c**) Full-thickness rectal transaction below the purse string

The dissection is continued sharply down to up within the pelvis along the proper mesorectal fascial and the visceral pelvic fascial plane until an increase of the abdominal pressure is detected, which indicates that rendezvous with the abdominal approach has (Fig. 11.5). The dissection is carried out posteriorly along the presacral avascular plane to mobilize the mesorectum and then anteriorly along the plane posterior to the vagina or prostate until the peritoneal reflection is divided. After this dissection, it is easier to incise the lateral attachments of the colon, alternatively along the right and left sides until the specimen is completely freed, taking care to preserve the lateral pelvic nerve bundles. Once the peritoneal cavity is entered, the CO_2 is equalized to 15 mmHg from both insufflation sites. At this moment, we can continue the surgery with two teams simultaneously, using a combined transanal and laparoscopic approach, until the whole specimen is dissected and the specimen is removed transanally (Fig. 11.6). In our experience, it is really helpful to develop the combined surgery with two teams simultaneously, for example, the assistance with retraction that a team is making in its side results in a great advantage for the one who is on the other side; it permits also retraction of a bulking uterus or redundant sigmoid colon and can significantly reduce the operative time.

The most important principle for the management of complications during surgery is anticipation of the possible difficult steps of the surgery in order to prevent these complications. Here we describe some potential complication and how to deal with them:

- Presacral hemorrhage and prostatic bleeding. Usually can be stopped with local pressure using a gauze sponge.
- Anastomotic bleeding. The transanal approach permits achievement of hemostasis with bipolar cautery or Vicryl sutures.
- Trauma to rectal stump during presacral resection. In our experience, with a transanal approach, we minimize the traction over the rectum comparing with conventional laparoscopy or open technique so the potential risk for rectal perforation is reduced. In case this complication does occur, it can be repaired with single sutures or by including this area within the specimen.
- Ureteral damage that precise catheterization and primary suture when it is possible or a reimplantation of the ureter in the bladder.
- Iliac vessels damage that should be repaired with conversion to open surgery and a prolene suture of 4–5/0.

Anastomotic Technique

Depending on patient and tumor characteristics, we can complete the surgery intra-abdominally or

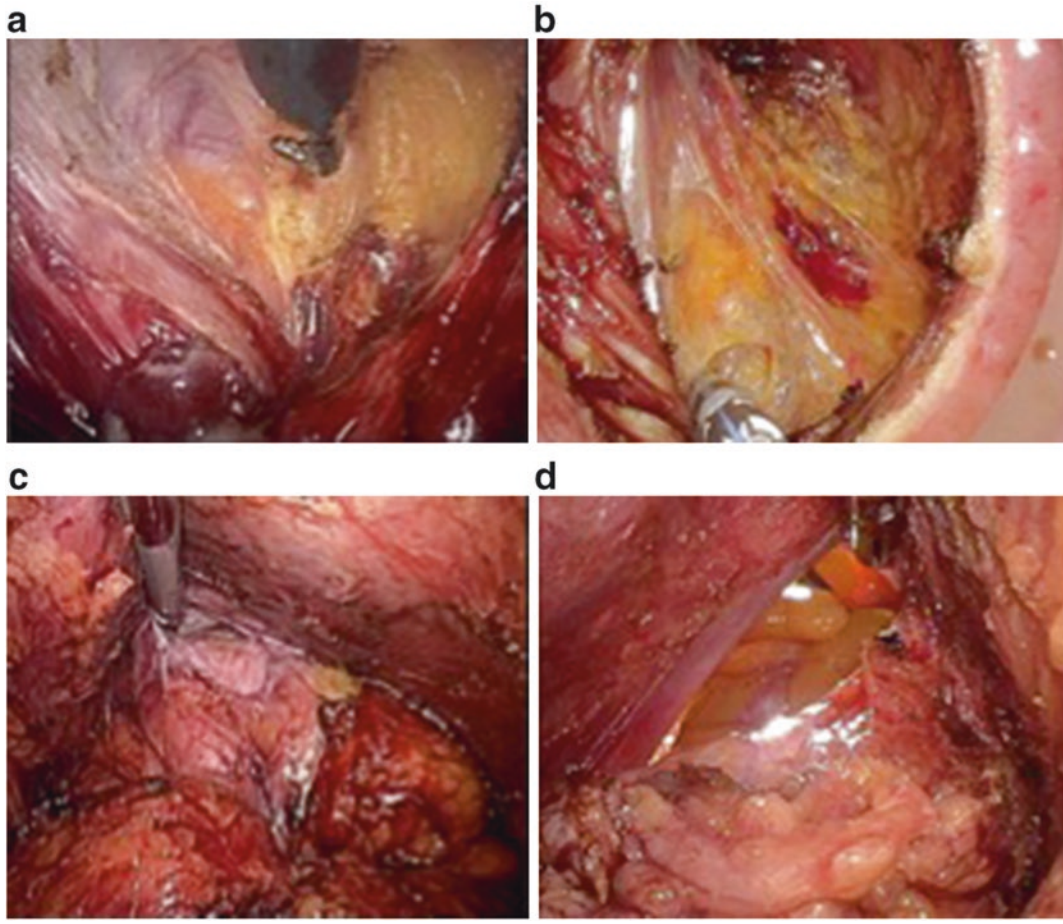

Fig. 11.5 Circumferential view of TME transanal dissection. (**a**) Posterior view, (**b**) lateral view, (**c**) anterior view, (**d**) peritoneal reflection

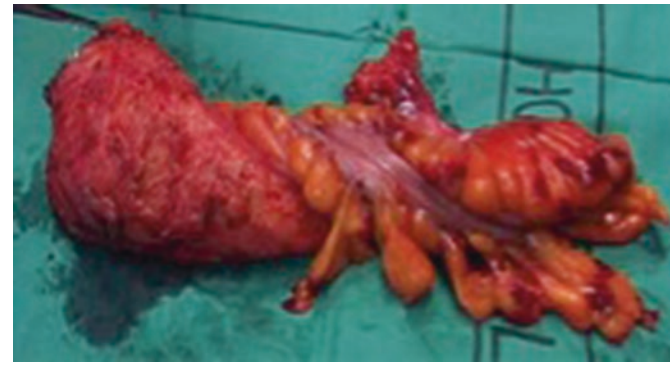

Fig. 11.6 Specimen with intact mesorectum

with a Pfannenstiel incision with a mechanical or hand-sewn anastomosis (Fig. 11.7). It is important to note that the target of this procedure is not only to avoid the skin incisions but to improve the quality of the surgery thanks to a better retraction and better visualization of the surrounding structures. With this idea in mind, we describe in the following different techniques for anastomosis.

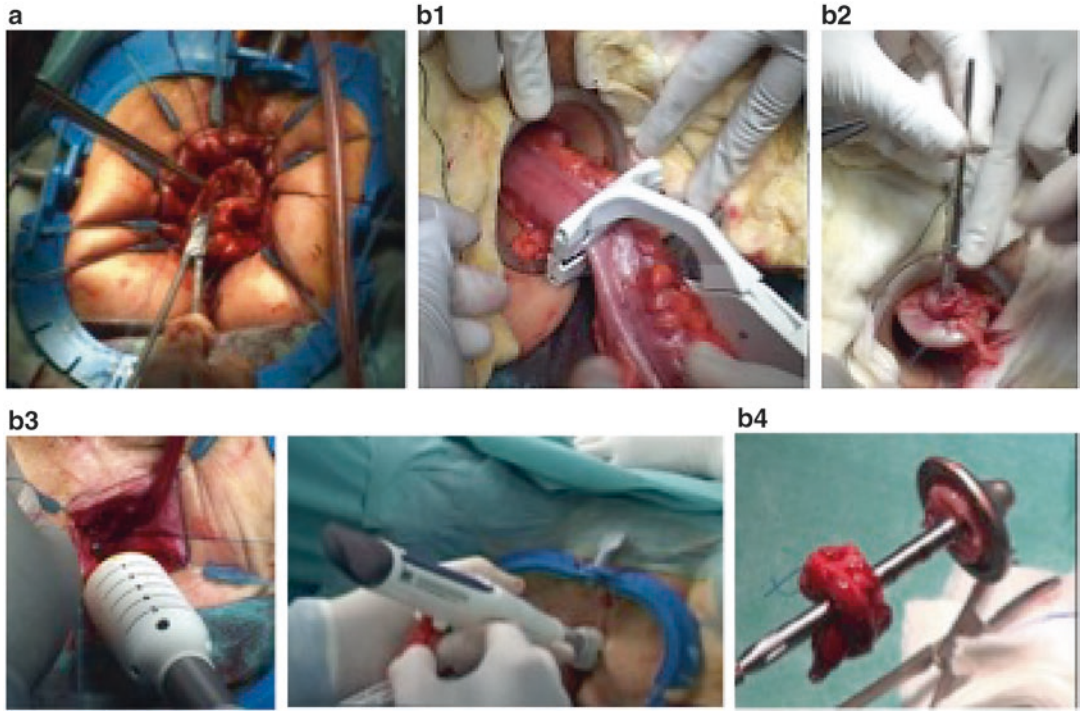

Fig. 11.7 Anastomosis. (**a**) Hand-sewn coloanal anastomosis, (**b**) Mechanical anastomosis. (*b1*) Transanal specimen extraction view with placement of purse-string suture; (*b2*) anvil positioned; (*b3*) transanal position of circular stapler (EEA hemorrhoid and prolapse stapler DST series; Covidien, AutoSuture); (*b4*) rectal donuts

Mechanical Anastomosis

To develop a mechanical anastomosis, we prefer to use a procedure for prolapse and hemorrhoid 33-mm circular stapler, which allows us to add approximately 1 cm to the distal resection margin and eliminates the need for multiple stapler firings required to transect the rectum. With this kind of stapler, there is no need to dissect the perirectal tissue of the rectal stump.

In large bulky tumors, we prefer to exteriorize the sigmoid and rectum by a Pfannenstiel incision. The specimen is drawn out of the peritoneal cavity after protecting the wound, using a plastic ring drape or wound protector, and it is resected proximally with scissors after applying a purse-string device (AutoSuture Purstring 45; Covidien). We then check for adequate vascularization of the proximal colon. The anvil of a 33-mm circular stapling device (AutoSuture EEA hemorrhoid and prolapse stapler DST series; Covidien) is inserted and fixed with the purse-string suture of prolene 2/0. The fat is cleaned and the bowel is returned to the abdomen closing the fascia behind. The pneumoperitoneum is reestablished to finish the colorectal anastomosis. We usually attach a small catheter to the anvil to facilitate the exteriorization of the proximal colon through the anus.

If the size of the tumor allows it or with very low rectal tumors, we complete the surgery intra-abdominally. First of all, we should confirm that sufficient length of the colon has been freed, the GelPoint is removed, and the LoneStar Retractor is positioned again. The specimen is exteriorized through the anus until the proximal descending colon is localized. After allocation of a purse-string device, the colon is cut with scissors. The anvil head is put on the extreme, and the prolene suture is knotted. When it is possible, a side-to-end anastomosis is performed in order to obtain better functional results. From this point, the technique is common for both intra-abdominally or Pfannenstiel incision. The spike of the circular stapler is connected transanally with the anvil, and the prolene suture of the distal rectum is knotted around the stapler. The stapler device is

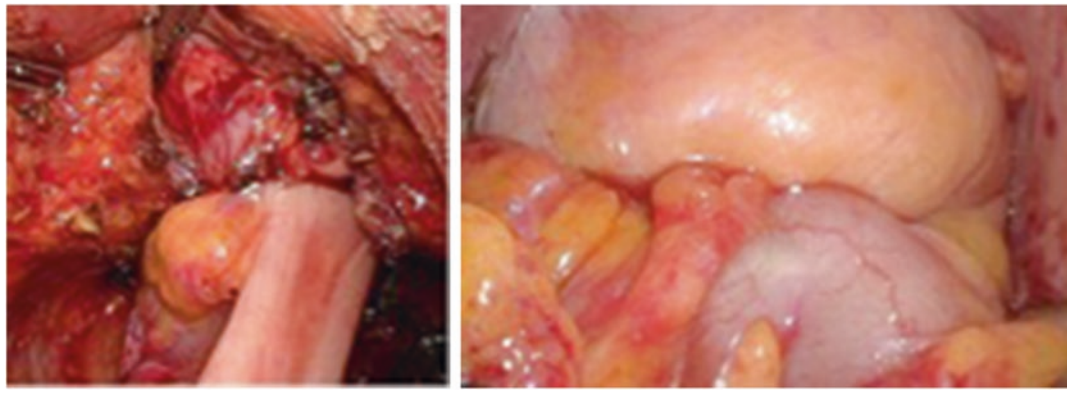

Fig. 11.8 Laparoscopic assistance during anastomosis

slowly closed without tension or torsion by a visual control from the abdominal side checking that the surrounding tissues (vagina, lateral pelvic tissues) are not caught in the anastomotic site. If there is some bleeding of the anastomosis, we can make hemostasia and strengthen it with single knots of Vicryl through transanal approach. The tissue rings removed by the circular stapler are inspected for completeness.

Before closing the stapler, we confirm the correct position of the colon by following the colonic taenia and the cut edge of the mesentery (Fig. 11.8). The splenic flexure is mobilized from its attachments to the spleen and to the left kidney over the Gerota's fascia as needed to ensure a tension-free anastomosis. The flexure is approached by elevating the omentum and dissecting off from the transverse colon. This way, we can enter to the lesser sac, expose the stomach, pancreas, and retroperitoneum, and finish the dissection of the splenic flexure. Sometimes, long instruments, other 5-mm trocars, or allocate the surgeon between the legs are needed.

Hand-Sewn Anastomosis

In very low tumor, a hand-sewn end-to-end coloanal anastomosis is needed. First, four cardinal stitches are made. Usually, we prepare these stitches on the distal side of the anastomosis before exteriorizing the specimen to be prepared, and the anastomosis is completed when we open the proximal side of the colon. A LoneStar Retractor is positioned at this point to facilitate the view and development of the anastomosis. After these four sutures are knotted, we complete the anastomosis with single stitches of 3/0 monofilament suture.

Before closing, hemostasis is confirmed and the abdominal cavity is cleaned with 1% povidone-iodine. A closed suction drain is introduced from the left port and positioned in the pelvis close to the colorectal anastomosis. From the anus, a rectal drainage is placed through the anastomosis.

Port Site Closure

Usually we do not close the 5 mm port sites. If one of them is bleeding or we have to enlarge them for any reason, they will be closed with a Vicryl suture using a Reverdin needle.

Diverting Ileostomy

When a low anastomosis is developed, we realize a defunctioning loop ileostomy in a standard Brooke fashion. The distal small bowel is localized by laparoscopy, and the afferent and efferent bowel is identified. The 5-mm port on the right side is enlarged to get the bowel out. A diverting loop ileostomy is performed with 3-0 Vicryl leaving the afferent bowel on the cranial side. It can be closed from 8 weeks depending on the need for adjuvant chemotherapy, after checking the anastomosis with a contrast enema test.

Postoperative Management

At the end of the intervention, the nasogastric tube is removed, and the rectal tube is removed as soon as possible with the passage of flatus or stool. The bladder is drained with a Foley catheter, which is also removed on the first day if the patient has adequate urine output. The pelvic drainage catheter is removed on the third day when the output is below 50 cc and there is no evidence of bleeding. If it is necessary, the patient could be discharged with the drainage catheter for removal during ambulatory follow-up. Oral liquids intake is initiated on the first day after surgery, especially if an ileostomy is used. The epidural catheter is removed on the second postoperative day, and pain is adequately controlled with oral analgesia. The patient is discharged home when a soft diet can be tolerated and with a functioning stoma.

The main potential complications after surgery include:

- Anastomotic failure and pelvic sepsis: Depending upon the magnitude of the defect and the clinical presentation, an anastomosis leak could be treated in different ways. In case of small leaks with clinical stability without leukocytosis, the failure may be managed in a conservative manner with antibiotics and with percutaneous drainage in case of abscess formation. If not previously performed, a diverting ileostomy should be created. Finally, if the patient develops feculent peritonitis, reoperation with washout may be necessary in addition to antibiotic therapy and resuscitation maneuvers. A TAMIS approach visualization of the anastomosis and closure of a leak with sutures if possible.
- Autonomic dysfunction: Urinary retention results from inflammation around or injury to the hypogastric plexus. A urinary catheter may be needed for some weeks. Inflammation around or injury to the pelvic parasympathetic plexus along the lateral pelvis can cause sexual dysfunction, particularly in men.
- Fecal incontinence: Loss of the rectal reservoir function or the distal rectal sensory zone or partial sphincter resection may be associated with fecal incontinence. This complication may be at least in part improved with pelvic floor strengthening maneuvers.

Key Steps

1. Patient is placed in a Lloyd-Davies position, rotated slightly to the right and in Trendelenburg position.
2. Transanal approach (steps 2 and 3 may be developed simultaneously):
   a. Preparation of the GelSeal cap with its three 10 mm ports.
   b. Application of the LoneStar Retractor System to expose the anal canal.
   c. Distal rectal incision (at the internal anal sphincter or rectal wall if tumor is more proximal) until the mesorectal plane is identified and a full-thickness dissection of the rectum is effected.
   d. Placement of purse-string 2/0 prolene suture to occlude the proximal lumen (at least 1 cm below the tumor).
   e. Apply the GelPort device and suture it to the skin.

Note: c, d, and e sections can be modified in its order depending on the high of the tumor to facilitate the surgery as needed.

   f. Sharp dissection is continued down to up to the pelvis circumferentially until the specimen is freed.
   g. Rendezvous with the abdominal team.
3. Transabdominal approach:
   a. Pneumoperitoneum to 15 mm Hg.
   b. Insertion of trocars: 10-mm umbilical port and three 5-mm ports, one in the left iliac fossa and two on the right iliac fossa (the signals for the future possible ileostomy and colostomy are used).
   c. Abdominal exploration and reflection of the small bowel and omentum toward right upper quadrant.
   d. Ligation of the inferior mesenteric artery near its origin after identifying the left ureter.

e. Medial-to-lateral mobilization of the descending and sigmoid colon.
f. Division of the inferior mesenteric vein.
g. Mobilization of the splenic flexure.
h. Rectal mobilization beginning with the dissection of the presacral plane according to TME fashion.
i. Dissection of peritoneal attachments on right and left sides of the rectum and, finally, on the anterior peritoneal resection until rendezvous with the transanal team is achieved.
j. Exteriorization of the specimen through a Pfannenstiel incision; resection of the proximal colon and introduction the anvil of the circular stapler at the proximal colon. Alternatively, the specimen is exteriorized transanally; the proximal limit is transected and is prepared for the anastomosis.

4. Anastomosis: Hand-sewn coloanal anastomosis vs. mechanical anastomosis with circular stapler (EE hemorrhoid and prolapse stapler DST series).
5. Irrigation of the pelvis and confirmation of hemostasis.
6. Closure ports of 10–12 mm size.
7. Diverting ileostomy in right iliac fosse.

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Intersphincteric Resection and Coloanal Reconstruction

12

Nam Kyu Kim, Young Wan Kim, and Min Soo Cho

Abbreviations

APR	Abdominoperineal resection
CRT	Chemoradiation therapy
CRM	Circumferential resection margin
CAA	Coloanal anastomosis
ISR	Intersphincteric resection
MRI	Magnetic resonance imaging
3-D	Three-dimensional
TME	Total mesorectal excision
TRUS	Transrectal ultrasonography
uLAR	Ultralow anterior resection

Introduction

The primary goal for the surgical treatment of rectal cancer is to achieve an oncologic cure while preserving function. Total mesorectal excision (TME) is the standard surgical procedure for rectal cancer. The concept of TME is the elimination of potential sources of local recurrence by completely excising the mesorectum through sharp pelvic dissection [1]. TME has evolved to include the tailored removal of the mesorectum with adequate mucosal margins that are determined according to the distance of the tumor from the anal verge [2]. However, surgical treatment for low rectal cancer remains challenging, particularly with regard to the preservation of the anal sphincter. Anatomically, the mesorectum disappears at a distance of 1–2 cm above the anorectal sling, and only the rectal wall remains to the anal hiatus. Thus, there are greater risks of direct tumor invasion of the adjacent structures and of a positive circumferential resection margin (CRM) in low rectal lesions.

Traditionally, a distal resection margin of at least 5 cm has been recommended for anal sphincter-preserving surgery [3]. However, numerous reports have established that rectal tumors rarely spread more than 1–2 cm distally and that oncologic outcomes are not compromised with a 2 cm distal margin in rectal cancer patients who are undergoing surgery alone [4–7]. Moreover, findings from recent studies support the oncologic safety of a shorter distal margin of only 1 cm when it is combined with multimodality treatment and clear radial margins [8].

Advances in surgical techniques and multimodal treatment have led to the possibility of sphincter preservation in patients who have traditionally required abdominoperineal resection (APR) in the past. In this regard, intersphincteric resection (ISR) has been described by Schiessel

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et al. [9] as the definitive surgical technique for anal sphincter preservation, and now, ISR in combination with preoperative chemoradiation therapy (CRT) is increasingly being performed in patients with low rectal cancers. In this chapter, we will discuss ISR and coloanal reconstruction in terms of its surgical indications, the operative techniques, and its oncologic and functional outcomes.

History

In 1977, Lyttle and Parks [10] used the term "intersphincteric excision" in the context of surgical treatment for inflammatory bowel disease, and the authors described the dissection of the anal canal and rectum via the intersphincteric plane. In 1981, Shafik [11] also described a technique for anorectal mobilization through the intersphincteric plane for the treatment of benign and malignant rectal diseases. In 1982, Parks and Percy [12] described an ultralow anterior resection (uLAR) with a coloanal anastomosis (CAA) for low rectal cancers. This technique involves dissecting away the mucosa from just above the dentate line, followed by a hand-sewn anastomosis within the anal canal. With improvements in technique, double-stapled CAA can also be performed within a wide pelvis using a circular stapler.

In 1994, Schiessel et al. [9] described ISR for low rectal cancers. The underlying concept is a proctectomy based on the TME technique and the extension of the dissection through the intersphincteric plane. This technique involves a *per anal* approach through the intersphincteric plane, the partial or complete removal of the internal anal sphincter, and the restoration of intestinal continuity by a hand-sewn anastomosis.

Several surgical options now exist for low rectal cancer. The uLAR and CAA without ISR includes a total proctectomy to the level of the anorectal ring just above the level of the puborectalis muscle and the restoration of bowel continuity using either a double-stapled or a hand-sewn anastomosis [13]. ISR can be considered for low rectal cancers that are close to the dentate line unless the tumor involves the external sphincter. The ISR procedure includes the partial or complete removal of the internal sphincter by dissecting within the intersphincteric plane [14–17]. After resection, coloanal reconstruction is performed using an end-to-end CAA, a J-pouch, coloplasty, or an end-to-side CAA, using either a hand-sewn or a stapled anastomosis. Because of technical advances and greater surgical experience, a combined resection of the external sphincter or levator ani muscle can be performed in highly selected patients in whom the tumor has invaded the external sphincter or the levator ani muscle [18–22].

Definitions

The ISR procedure should be differentiated from uLAR and CAA based on whether the internal sphincter is removed. The ISR procedure is classified according to the amount of the internal sphincter that is removed. Schiessel et al. [9] described two types of ISR that involved either the complete or partial excision of the internal sphincter. Rullier et al. [14] proposed three types of ISR, namely, the total, subtotal, and partial ISR (Fig. 12.1). In Japan, three subtypes of ISR are defined. A total ISR occurs at the level of the intersphincteric groove, a subtotal ISR occurs between the dentate line and the intersphincteric groove, and a partial ISR occurs at the level of the dentate line [23]. These classifications are supported by the histological observations of Akagi et al. [24] who measured the lengths of the resected internal sphincters in specimens from CAA, ISR, and APR procedures. The mean lengths of the internal sphincters were 1.3 mm in the CAA, 11.5 mm in the partial ISR, 17.1 mm in the subtotal ISR, 21.3 mm in the total ISR, and 28.4 mm in the APR specimens. In recent years, ISR in combination with resection of the deep or superficial external anal sphincter is described in selected cases [18–20, 22].

Preoperative Staging

The preoperative staging workup includes digital rectal examinations, transrectal ultrasonography (TRUS), colonoscopy, abdominopelvic computed

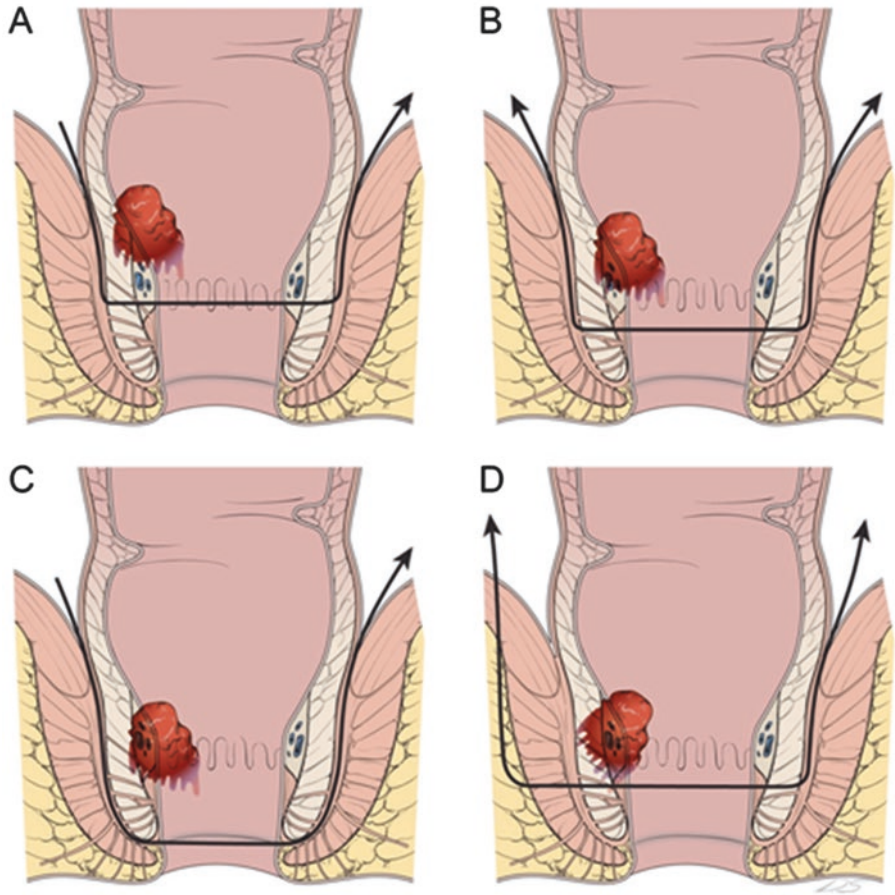

Fig. 12.1 Types of intersphincteric resection (ISR). (**a**) Partial ISR, (**b**) subtotal ISR, (**c**) total ISR, (**d**) ISR in combination with resection of deep or superficial external anal sphincter in selected cases [18–20, 22]

tomography scanning, pelvic magnetic resonance imaging (MRI), and positron emission tomography scanning. Preoperative CRT is considered for patients with bulky and/or tethered tumors that TRUS and pelvic MRI determine to be at clinical stages T3–T4 or if clinically positive lymph node metastases are detected. Pelvic MRI is widely used for preoperative regional staging of rectal cancer to determine the depth of rectal wall invasion, the presence of nodal metastases, and CRM involvement. The coronal and axial MRI planes reveal whether the anal sphincter or the levator muscle is involved in low rectal cancer that is very close to the anorectal ring around the level of the levator ani muscle [25, 26].

It is important to assess the depth of tumor invasion in low rectal cancer using MRI. T1 is defined as a tumor that is confined to the mucosa and submucosa, T2 is defined as a tumor that is confined to the muscularis propria, and T3 is defined as a tumor that has penetrated the rectal wall and involves the mesorectal fat. T4 is defined as a tumor that involves the visceral peritoneum (T4a) or the adjacent tissues (T4b), including those of the prostate, vagina, sacrum, and the pelvic side wall. Caution should be exercised when interpreting the depth of tumor invasion located at or below the levator muscles. Tumor invasion of the external anal sphincter is interpreted as stage T3, and tumor invasion of the levator muscles is interpreted as stage T4 [27–29]. To standardize MRI reporting, the MERCURY group suggested that low rectal cancer is defined when the lowest margin of the tumor is located at or below the upper border of the puborectalis muscle [29, 30].

Accurate restaging of tumors after preoperative CRT may help to determine optimal treatment strategies and reduce positive surgical margins. Unlike initial tumor staging, it is difficult to distinguish viable tumors from radiation-induced inflammation, necrosis, or fibrosis. Thus, the restaging accuracy of MRI is unsatisfactory, and in terms of the restaging accuracy of the T stage, the mean sensitivity and specificity have been reported to be 50.4% and 91.2%, respectively [31].

TRUS is useful when determining T1 or T2 disease because the higher-frequency sonoprobe has a higher resolution [32]. Katsura et al. [33] reported that the positive predictive values were 96.2% and 85.7% for T1 and T2 disease, respectively. Three-dimensional (3-D) ultrasound has become popular in recent years [34]. The 360° rotating ultrasound transducers have higher frequencies (6–16 MHz), and the system has an automated image reconstruction function. Multiplanar images can be obtained with 3-D TRUS, and it provides more comprehensive information with respect to the depth of tumor invasion and the relationships among the adjacent structures [35] (Fig. 12.2).

Indications

The ISR procedure is primarily indicated for patients with low rectal tumors within the surgical anal canal and where the tumor involves the internal sphincter [16, 24, 36–52]. If the tumor is located at the level of the puborectalis muscle and involves the external anal sphincter or levator ani muscle, APR remains the gold standard for surgical treatment. However, in some specific cases, more extensive resection techniques, including levator muscle excision and external sphincter excision, have been explored to preserve the anal sphincter [18–20, 22].

Good surgical outcomes can be anticipated when the tumor is staged at T1–T3, mobile, confined to less than 50% of the rectal circumference and has well-to-moderately differentiated histological grade and when the patient has a good performance status, with an Eastern Cooperative Oncology Group score of 0–2, and good anal function.

Standard management of locally advanced rectal cancer now is comprised of preoperative

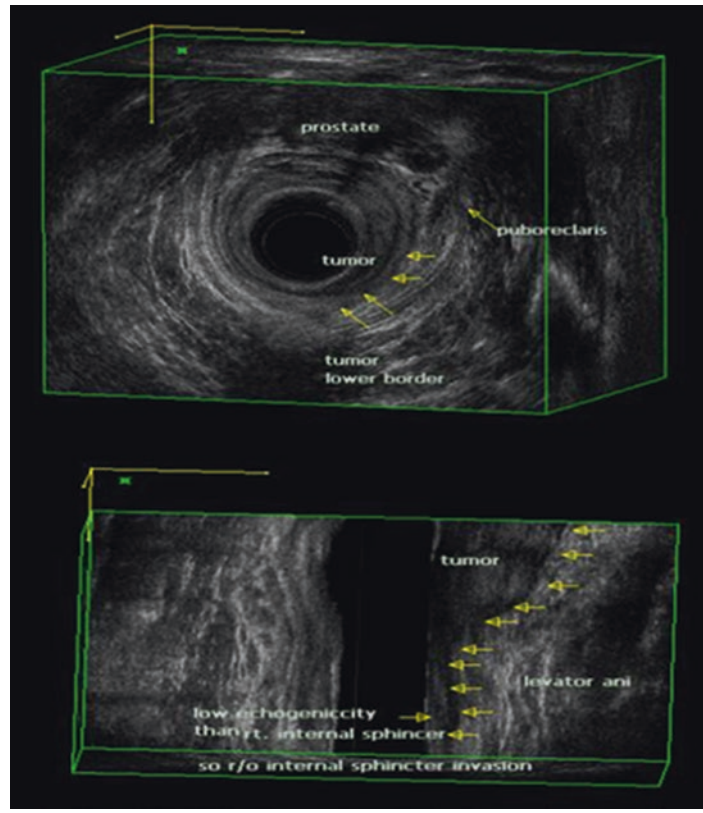

Fig. 12.2 Three-dimensional (3-D) transrectal ultrasonography (TRUS) in a male patient. The relationship between rectal tumor and anal sphincter is well visualized by 3-D TRUS (BK Medical Systems, Herlev, Denmark). uT2 tumor at left lateral side shows a hypoechoic lesion representing disruption of the internal anal sphincter muscle

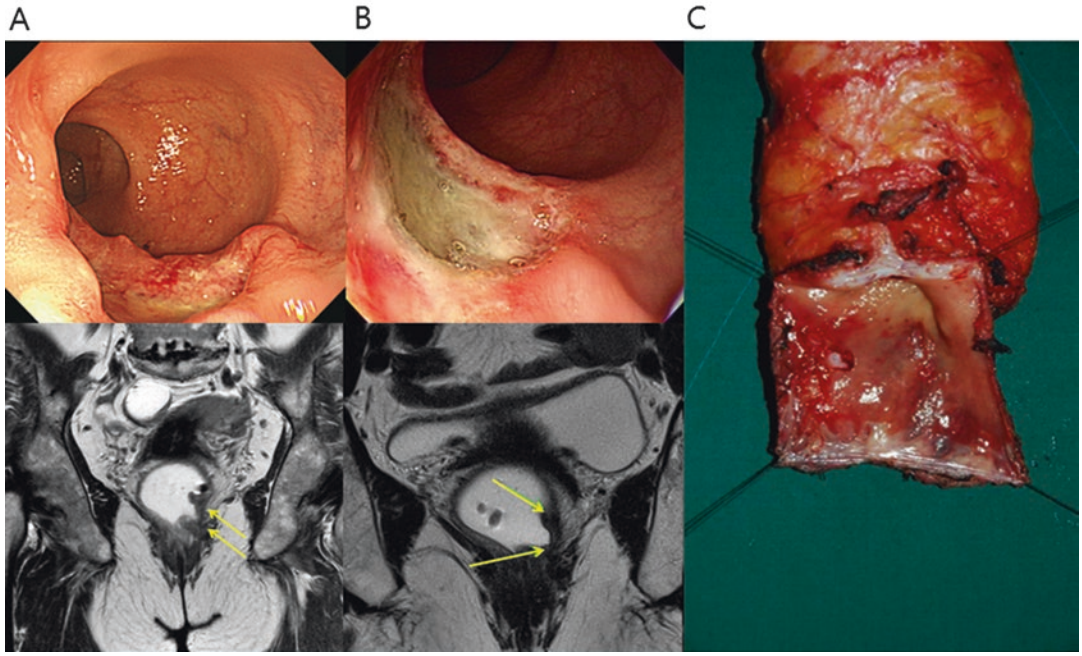

Fig. 12.3 Preoperative chemoradiation therapy (CRT) and intersphincteric resection (ISR) in a 64-year-old female patient with low rectal cancer. (**a**) Before preoperative CRT, the rectal tumor was located 3 cm from the anal verge, and pretreatment magnetic resonance imaging (MRI) shows suspected tumor invasion to the internal anal sphincter muscle on T2-weighted coronal image. (**b**) After preoperative CRT, the depth of main tumor invasion was downstaged based on posttreatment colonoscopy and MRI. T2-weighted coronal image shows posttreatment fibrosis with decrease in signal intensity. (**c**) Surgical specimen after ISR. Suspicious invasion on preoperative MRI was replaced with fibrosis. Final pathology report confirmed 4 mm tumor-free circumferential margin

CRT followed by radical resection [53, 54]. Preoperative CRT reduces tumor bulk and increases the probability of sphincter preservation surgery. Indeed, sphincter-preserving surgery can be achieved in a large proportion of patients who undergo CRT [55]. Preoperative CRT is associated with a pathologic complete response rate of 4–31%, which is associated with good oncologic outcome in terms of both recurrence and survival [56] (Fig. 12.3).

Coloanal Reconstruction

To date, several methods for coloanal reconstruction after proctectomy have been described (Table 12.1). In terms of the shape of the proximal colon, the current options for coloanal reconstruction include straight CAA (end-to-end), J-pouch reconstruction, coloplasty, and side-to-end anastomoses, and either hand-sewn or stapled anastomoses are performed. When performing a stapled anastomosis, 10–15 mm of distal remnant anoderm is incorporated into the circular stapler. In addition, the external anal sphincter may become entrapped within the stapler, and the pelvic cavity should be wide enough for the creation of a stapled anastomosis. Accordingly, the hand-sewn anastomosis is the gold standard following subtotal or total ISR. A hand-sewn anastomosis has the advantages of being easy, simple, and familiar to surgeons. In addition, it can be performed conveniently in a narrow and deep pelvis.

Since its first description by Parks and Percy [12], the straight (end-to-end) anastomosis has been the most commonly used method for CAA. In their study, 69 of the 70 patients were either fully continent (n = 39) or they had only minor bowel dysfunction (n = 30), and only one patient was incontinent. The main symptoms of

Table 12.1 Methods of coloanal reconstruction

	Colon configuration	Anastomosis	Fecal diversion (%)	Type of stoma
Schiessel et al. [9]	End-to-end	Hand-sewn	100	Colostomy
Braun et al. [52]	End-to-end	Hand-sewn, stapled	NS	Colostomy, ileostomy
Rullier et al. [14]	End-to-end, J-pouch	Hand-sewn, stapled	100	Colostomy, ileostomy
Teramoto et al. [57]	End-to-end	Hand-sewn	100	Colostomy
Watanabe et al. [58]	End-to-end	Hand-sewn	100	Ileostomy
Akasu et al. [59]	End-to-end, J-pouch, coloplasty	Hand-sewn	87	NS
Kim et al. [60]	End-to-end, J-pouch	Hand-sewn	100	Ileostomy

NS not specified

bowel dysfunction were frequency and irregular bowel movements. Anterior resection syndrome refers to a broad spectrum of bowel habit changes that range from irregular bowel movements to fecal incontinence or defecation difficulty following low anterior resection. The incidence of anterior resection syndrome has been reported to be about 30% among patients who have undergone low anterior resection, and the quality of life is likely to be impaired in affected individuals [61, 62]. A reduction in the reservoir capacity is thought to be one reason for anterior resection syndrome; therefore, a colonic pouch is devised to increase the neorectal reservoir capacity [63, 64].

A colonic pouch is a surgically constructed neorectal reservoir. A J-shaped pouch is commonly used because it is simple and easy to construct. Lazorthes et al. [63] observed that a colonic J-pouch increased the maximum tolerated volume and reduced the frequency of bowel movements. In their study, 60% of the patients with pouches and 33% of the patients without pouches produced one or two stools per day during the first year. After 1 year, 86% of the patients with pouches and 33% of the patients without pouches had one or two bowel movements per day. Parc et al. [64] evaluated the functional results from 31 patients who had J-pouches, and they found that there was no incontinence and that the mean number of bowel movements was 1.1 per day; however, 25% of the patients eventually required enemas to defecate.

Some controversies remain regarding the use of J-pouches in relation to the optimal length of the pouch, the use of the sigmoid colon, and long-term functional outcomes. The length of the J-pouch has varied from 5 cm [65], 6 cm [63], 7 cm [66], 8 cm [64], 9 cm [67], 10 cm [65], to 12 cm [63]. However, lengthy pouches develop defecation dysfunction, including the inability to evacuate bulky stools, tenesmus, or the need for regular enemas [63, 64, 66–71]; hence, the length has been reduced to 5–6 cm. Indeed, Ho et al. [72] demonstrated that small J-pouches that are 5 cm long retain liquid stools well, and 6–8-cm-long pouches are now recommended.

The use of the sigmoid colon for the creation of J-pouches is another issue. Traditionally, both the sigmoid and descending colon have been used; however, disadvantages associated with the use of the sigmoid colon have been suggested, and these include diverticular disease, bulky mesentery, and motility problems. Seow-Choen [73] suggested that the sigmoid colon contributes to evacuatory dysfunction because defecation difficulties were observed in 25% of patients who had pouches created using the sigmoid colon [74], but these difficulties were not seen in patients who had pouches created using the descending colon [70, 75].

It is unclear whether the beneficial effects of J-pouches on bowel function are maintained in the long term [76, 77]. Defecatory function improves with time, even after straight CAA, because of an increase in the neorectal reservoir volume, the improvement in sphincter function, the recovery of the rectoanal inhibitory reflex, and improvements in neorectal sensations [78, 79]. Ho et al. [80] observed that stool frequency and the incidence of incontinence were lower at 6 months in patients with pouches, but that the benefit was not sustained 2 years after surgery.

Meanwhile, Harris et al. [81] demonstrated that 5–9 years after surgery, patients with J-pouches had better long-term outcomes with respect to their Kirwan continence scores, their evacuation difficulties, and urgency associated with defecation compared with patients with straight CAA.

The colonic J-pouch is created as described next. The two loops of the descending colon are anastomosed in a "J" configuration using a linear stapler. The appropriate pouch length is 5–8 cm, and the linear stapler may be inserted through the uppermost or lowermost parts of the J-pouch. The enteroenterostomy site is carefully inspected for any bleeding along the staple line, and hemostatic sutures are applied at the site of any bleeding. Then, hand-sewn or stapled anastomoses are performed.

Coloplasty refers to a colonic reservoir that is created by a longitudinal incision with a transverse closure using a method that is analogous to that of the Heineke-Mikulicz pyloroplasty. Z'graggen et al. [82, 83] originally described this technique in a pig model, and Fazio et al. [84, 85] applied it to low colorectal or coloanal anastomoses. A reservoir for the coloplasty is made by a longitudinal incision, which is 8–10 cm long, along the teniae coli on the antimesenteric side. The colonic incision is stopped 4–6 cm proximal to the distal end of the colon, the colostomy is closed transversely using absorbable sutures, and then a stapled or hand-sewn anastomosis is performed with a prepared reservoir. Remzi et al. [86] demonstrated that the coloplasty group had fewer night bowel movements, fewer bowel movements per day, less clustering, and less antidiarrheal agent use than the straight anastomosis group. Coloplasty is a good alternative technique when a colonic J-pouch is technically difficult; however, there is more limited support of its benefit when compared to straight reconstruction than there is for a colonic J-pouch.

The side-to-end anastomosis was described for colorectal anastomoses in 1950, and its theoretical advantages include technical ease, a blood supply, and a larger anastomosis lumen [87]. Huber et al. [88] compared colonic pouches with side-to-end anastomoses after low anterior resections. The defecation frequencies were 2.2 and 5.4 per day at 3 months and 2.3 and 3.1 per day at 6 months in the pouch and side-to-end anastomosis groups, respectively. The investigators pointed out that the side-to-end anastomoses showed satisfactory long-term function and that the major benefit associated with the colonic pouches was seen during the immediate postoperative period. Machado et al. [89] observed that the colonic J-pouch and side-to-end anastomosis had comparable functional outcomes 2 years after low anterior resections.

When considering coloanal reconstruction, a straight (end-to-end) CAA is an easy, simple, and convenient reconstruction method, which is preferred after ISR. While J-pouch construction is performed to improve defecation function, it is not always possible, particularly in patients who have a narrow pelvis or bulky mesentery. Accordingly, surgeons should be cautious about the selection of the optimal coloanal reconstruction technique. While the J-pouch may be the first choice as opposed to the end-to-end CAA, alternatives such as a side-to-end CAA can be also considered.

Some additional technical considerations deserve mention. The use of irradiated sigmoid colons may cause anastomotic strictures or leakages [90]. Kim et al. [91] suggested that hand-sewn sutures between the levator muscles and the distal anorectal stumps may improve postoperative defecatory function. Yamada et al. [38] reported that 4 out of 20 patients who underwent total ISR experienced postoperative mucosal prolapses of the neorectum, and mucosal excisions were later performed in all 4 patients. In our opinion, a redundant proximal colon may be a source of a prolapse, and the appropriate length of the proximal colon is just beyond the symphysis pubis (Fig. 12.4). Furthermore, anchoring sutures between the proximal colon and the levator muscles may prevent prolapse.

Excision of the External Anal Sphincter or Levator Ani Muscle

More extensive resections in addition to ISR have been described in the literature (Fig. 12.5). In 2002, Fucini et al. [22] described the excision of the

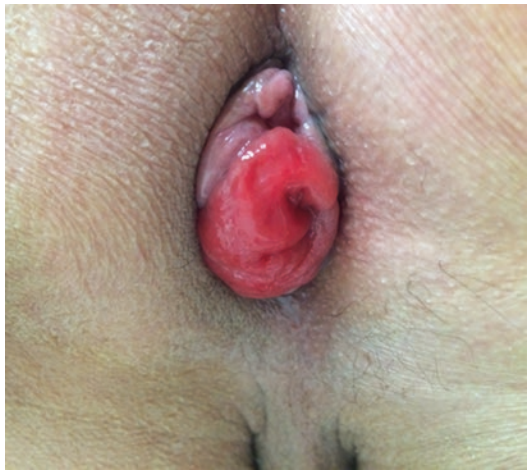

Fig. 12.4 Postoperative mucosal prolapse after intersphincteric resection

levator muscles and the preservation of the part of the internal sphincter and the external sphincter and its innervation for low T4 rectal cancers. Shirouzu et al. [18] described the excision of the puborectalis muscle, deep and superficial external sphincter, and the internal sphincter muscles while preserving the subcutaneous external sphincter muscle. Cong et al. [20] described the partial longitudinal resection of the anorectal and sphincter muscles. This technique involves the unilateral removal of the sphincter complex as occurs in APR. Alasari et al. [19] described a hemi-levator excision through the intersphincteric plane by removing the levator ani and the deep external sphincter muscles. All of these new techniques need to be scrutinized with respect to oncologic efficacy and functional outcomes.

Applied Anatomy of the Anal Canal

The anal canal is the last part of the digestive tract, and the anatomical anal canal refers to a zone between the dentate line and the anal verge, and it is approximately 2–3 cm long. The surgical anal canal refers to the zone between the anorectal ring and the anal verge. It is about 4–5 cm long and is shorter in women. The anorectal ring refers the site where the rectum goes into the pelvic floor. The levator ani muscle forms the pelvic floor and it is attached to the pelvic sidewall. The levator ani muscle is composed of the puborectalis, puborectalis, and iliococcygeus muscles. During rectal dissections, the U-shaped puborectalis muscle and the surrounding levator ani muscles are easily seen in the form of a membranous sheet, and they sometimes adhere to the rectal proper fascia [92]. The anorectal ring is angled by the puborectalis muscle and is pulled anteriorly by the contraction of the puborectalis muscle [93]. The levator ani muscle is innervated by branches of the pudendal, inferior rectal, perineal, and sacral nerves [94, 95]. The anal canal is surrounded by the internal sphincter and the longitudinal rectal muscle layer, the external sphincter [96] and the coccyx are located posteriorly, the ischiorectal fossa is located laterally, the urethra is located anteriorly in men, and the lower part of the vagina is located anteriorly in women.

The internal sphincter is connected from the inner circular smooth muscle of the rectum supplied by autonomic nerve. The length of the internal sphincter muscle is about 2 cm and 3 cm on the anterior and posterior sides, respectively [97]. The mean thickness is 4.5–5.9 mm [98], and the internal sphincter muscle ends with a thickened edge that is 1–1.5 cm from the anal verge and constitutes the intersphincteric or Hilton's groove. The intersphincteric groove is an important surgical landmark for rectal cancer surgery that is well palpated during digital rectal examination. The outer longitudinal muscle of the rectum gets thinner in the distal rectum and meets the fibers from the puborectalis muscle and forms a thin band. This band runs between the internal and external sphincters, and it spreads radially and penetrates the subcutaneous portion of the external sphincter and finally ends as a supporting structure for the hemorrhoidal plexus. The external sphincter muscle is a striated muscle that forms a cylinder around the internal sphincter. While it acts in concert with the puborectalis muscle, its innervation is different. The anal canal receives both sympathetic and parasympathetic innervation that controls the action of the internal anal sphincter. The external sphincter is innervated by the perineal branch of the sacral nerve and the inferior rectal branch of the internal pudendal nerve [99].

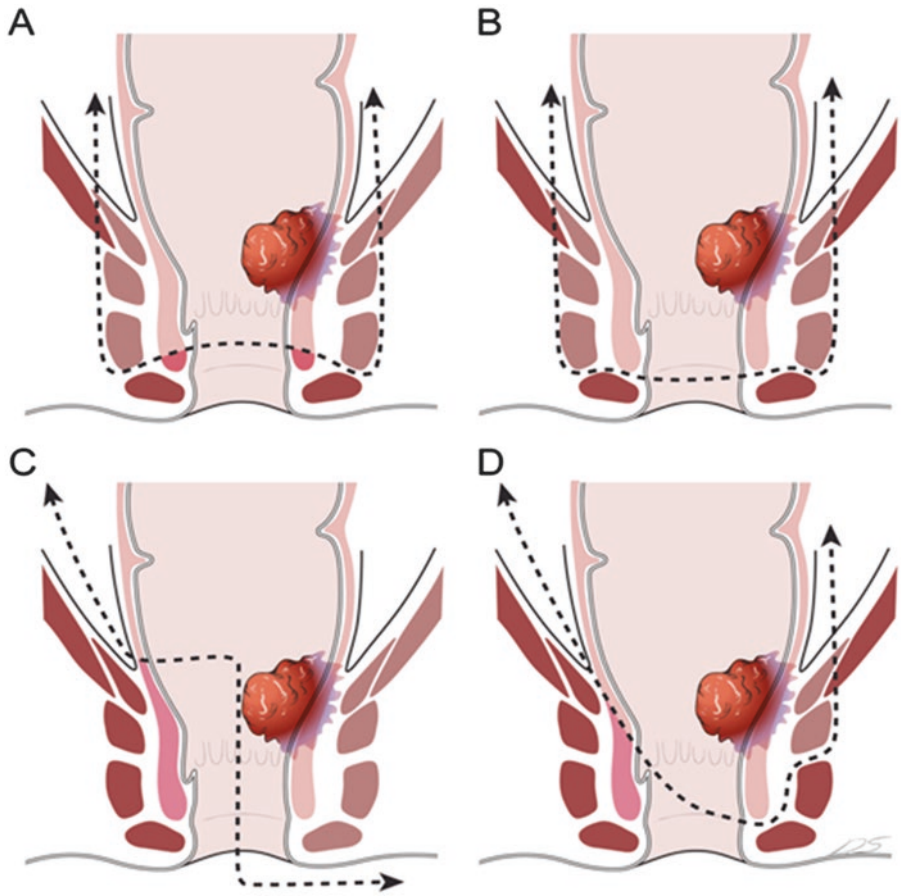

Fig. 12.5 External anal sphincter resection and levator muscle excision. (**a**) Excision of the levator and internal and external anal sphincter muscles while preserving distal parts of the internal and external sphincters and its innervation for low T4 rectal cancers described by Fucini et al. [22]. (**b**) Excision of the puborectalis muscle, deep and superficial external sphincter, as well as internal sphincter muscles while preserving subcutaneous external sphincter muscle described by Shirouzu et al. [18]. (**c**) Partial longitudinal resection of the anorectum and sphincter muscles described by Cong et al. [20]. This technique involves removal of all sphincter complex unilaterally such as abdominoperineal resection. (**d**) Hemilevator excision through the intersphincteric plane by removal of the levator ani and deep external sphincter muscles described by Alasari et al. [19]

During operations for low rectal cancer, the anterior dissection is the most difficult part, and sometimes, surgeons may miss the proper dissection plane. Uchimoto et al. [100] emphasized the importance of the rectourethralis muscle based on a histologic study. They demonstrated that Denonvilliers' fascia is absent at the level of the rectourethralis muscle and that the rectal wall is directly attached to the rectourethralis muscle. The anorectal veins and cavernous nerve are present around the rectourethralis muscle; thus, deeper dissection to the anterior surface of Denonvilliers' fascia may cause unwanted bleeding or nerve injury. Neurovascular bundles cross the seminal vesicles in the 10 o'clock and 2 o'clock directions; therefore, unless the tumor is located anteriorly, the correct dissection plane is between the posterior side of Denonvilliers' fascia and the rectal fascia proper [101–104]. Kinugasa et al. [105] highlighted that surgeons may overlook the correct surgical plane that lies between the ventral and dorsal layers of the anococcygeal ligament during per anal dissections (Fig. 12.6).

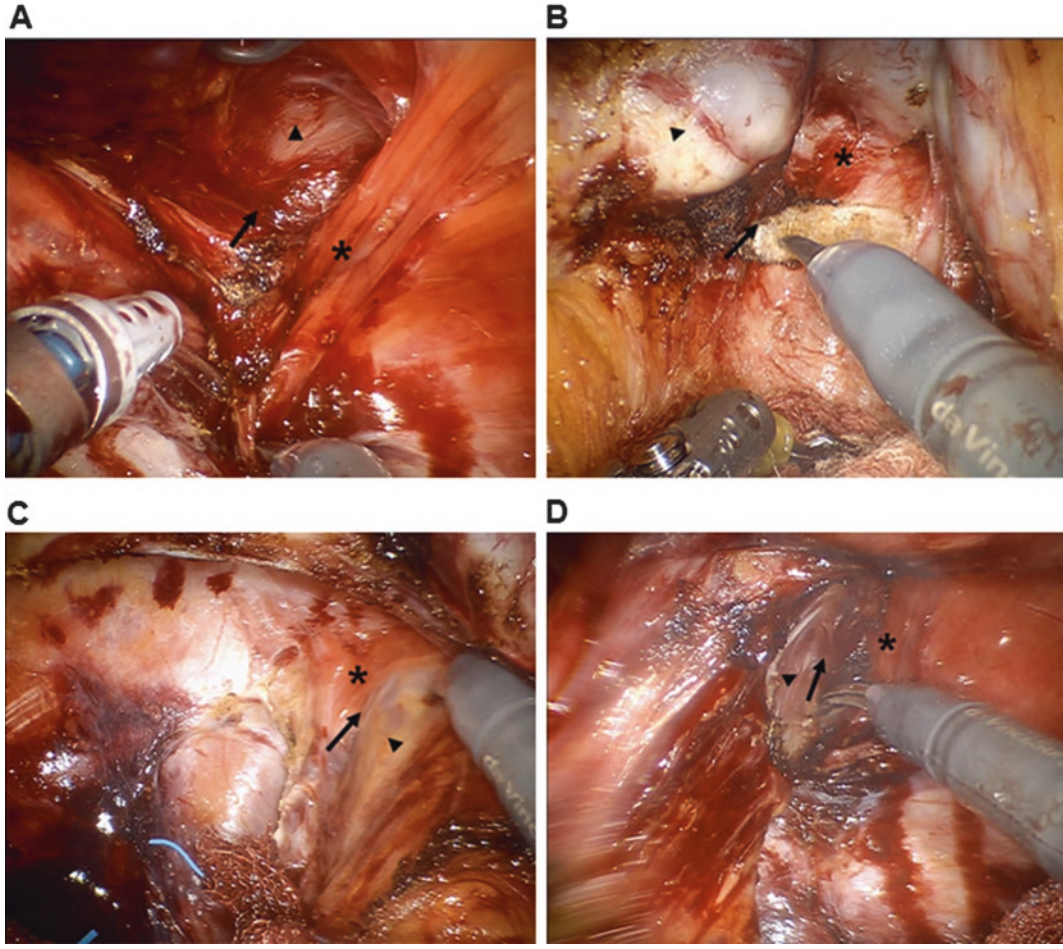

Fig. 12.6 Essential surgical anatomy for intersphincteric resection. Operative pelvic anatomy by robotic three-dimensional vision. (**a**) Posterior dissection through the intersphincteric plane (*arrow*) between the rectum (*arrowhead*) and the puborectalis muscle (*asterisk*). (**b**) Anterior surgical plane (*arrow*) behind the Denonvilliers' fascia (*asterisk*). Seminal vesicle (*arrowhead*). (**c**, **d**) Left and right lateral dissection around the anal hiatus. Intersphincteric plane (*arrow*) is identified between the rectum (*arrowhead*) and the medial side of the puborectalis muscle (*asterisk*)

Preoperative Preparation

Mechanical bowel preparation is performed 1 day before surgery. The patient is fasted for 1 day before surgery and ingests 4 L of polyethylene glycol solution. A rectal glycerin enema is performed twice, once in the afternoon and once during the evening before the day of surgery. A first-generation cephalosporin is used as a prophylactic antibiotic and is administered just before surgery begins. Antibiotic treatment is maintained for 24–48 h after surgery. Preoperative chemical bowel preparation using antibiotics is not performed. Sequential compression stockings and subcutaneously administered low-molecular-weight heparin are considered for venous thrombosis prophylaxis.

Role of the Diverting Stoma

A diverting stoma is created by either a loop transverse colostomy or an ileostomy after ISR with CAA for rectal cancer. Although a diverting

stoma does not prevent anastomotic leakages, the use of a diverting loop stoma does reduce symptomatic anastomotic leakages [2, 106]; thus, fecal diversion is cautiously considered after ISR.

Operative Technique

Details of the Operative Procedures

The operative procedures comprise three essential steps, namely, the first abdominal procedure, the second per anal procedure step, and the third step that comprises a second abdominal procedure.

Abdominal Procedure

Patient Position and Skin Incision

The patient is placed in the lithotomy-Trendelenburg position with the legs supported by stirrups. The laparotomy for the ISR procedure begins with a midline abdominal skin incision. After abdominal exposure, a mechanical self-retaining retractor is placed in position.

Ligation of the Inferior Mesenteric Artery

An incision is made at the level of the sacral promontory. A peritoneal incision extends along the right side of the rectal mesentery, and the avascular plane is exposed. The pedicle of the inferior mesenteric vessel is visualized, and the colonic mesentery is separated from the underlying fascia propria of the rectum and the inferior hypogastric nerves. The superior hypogastric plexus is carefully preserved around the aortic bifurcation, the inferior mesenteric artery is ligated at the root of its origin from the abdominal aorta, and the lymph nodes along the inferior mesenteric artery are cleared from just above the superior hypogastric nerves overlying the aorta. The inferior mesenteric vein is divided immediately beneath the pancreas. Older patients or patients with questionable blood supplies may be candidates for low ties of the inferior mesenteric artery.

Descending and Sigmoid Colon Mobilization via the Medial to Lateral or Lateral to Medial Approaches

During mobilization of the descending colon and the sigmoid colon, the locations of the ureter and the gonadal vessels are assessed and preserved.

Splenic Flexure Mobilization

The splenic flexure of the colon is routinely mobilized to gain a sufficient length for coloanal anastomosis. After ligation of the inferior mesenteric vein just below the inferior border of the pancreas, an avascular retroperitoneal space between the mesentery and Gerota's fascia, including the perirenal fat, is developed. The loose attachment of the transverse mesocolon is separated from the lower border of the pancreas, and the lesser sac is entered. The left paracolic gutter is dissected, and the previously dissected retroperitoneal plane of Toldt's fascia is identified. The greater omentum overlying the transverse colon is divided to enter the lesser sac, and the previous surgical plane is met at this point. Finally, any loose connective tissue is freed to complete the colonic mobilization, and the medial part of colonic mesentery is divided carefully, avoiding any injury to the marginal artery.

Total Mesorectal Excision

The pelvic dissection is continued along the parietal pelvic fascia, leaving the hypogastric nerve intact over the aorta. The proper rectal fascia enveloping the mesorectum should remain intact during the pelvic dissection. The autonomic pelvic plexus is also preserved. The rectum is sharply dissected to the anal hiatus of the pelvic diaphragm. The posterior rectal dissection is performed in the retrorectal avascular space along the visceral pelvic fascia plane. The rectosacral fascia or Waldeyer's fascia is encountered at the S4 level between the presacral fascia and the rectal proper fascia. Division of the rectosacral fascia enables the surgeon to reach down to the level of the coccyx. The anterior rectal dissection

involves the identification of Denonvilliers' fascia in males.

Techniques to preserve the autonomic nerves are performed to preserve postoperative sexual and voiding function. A U-shaped incision during the excision of Denonvilliers' fascia in the anterior part of the rectum helps to avoid injury of the genitourinary neurovascular bundles. In females, the rectum and the vaginal wall should be dissected carefully. The lateral part of the rectum is mobilized after the anterior and posterior dissections, while avoiding excessive traction of the rectum. The pelvic plexus and the arising sacral nerves are assessed and preserved [93]. The three common sites of nerve injury are the superior hypogastric plexus, the inferior hypogastric plexus, and the pelvic plexus.

Dissection to the Anal Canal Through the Intersphincteric Plane

The puborectalis muscle sling is exposed laterally, and the anococcygeal ligament is divided at the posterior side of the anal canal. The intersphincteric space is identified between the puborectalis muscle and the rectal wall. The dissection continues through the puborectalis muscle and in the deep part of the external anal sphincter at the intra-anal canal.

Per Anal Procedures

Assessment of the Lower Margin of the Tumor and the Distal Resection Margin

A Lone Star retractor (Lone Star Medical Products, Inc., Houston, TX, USA) is applied to the anus, and a rectal washout is performed using a solution of Betadine and saline. Then, 0.25% bupivacaine mixed with epinephrine is injected below the dentate line. The lower tumor margin is assessed, and a distal resection margin that is at least 1–2 cm long is obtained whenever possible.

Determination of Extent of ISR (Partial, Subtotal, or Total) and Circumferential Incision Around the Distal Margin

A digital rectal examination is performed to identify the intersphincteric groove, and the circumferential incision is made (Fig. 12.7). For more proximal lesions, the incised distal rectum may be closed to prevent contamination of the intraluminal contents.

Complete Mobilization of the Rectum to the Level of the Levator Ani Muscle

The posterior dissection begins at the level of the dentate line for partial ISR cases, between the dentate line and the intersphincteric groove for subtotal

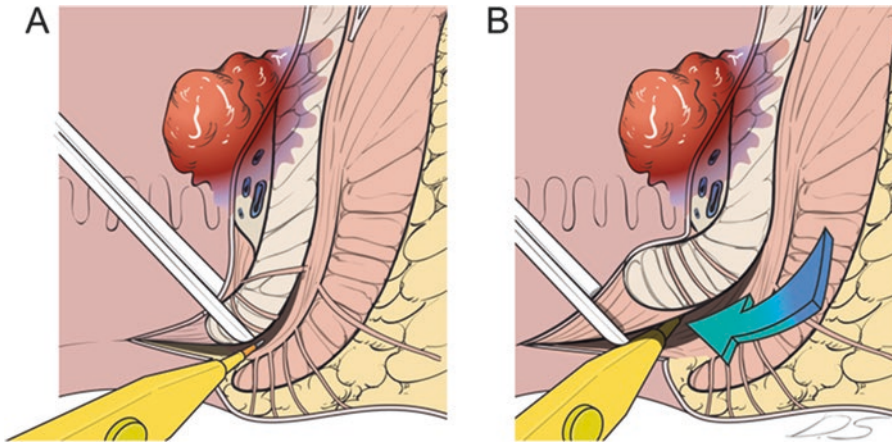

Fig. 12.7 Perianal procedure for intersphincteric resection (ISR). Lower margin of the tumor is assessed, and proper type of ISR (partial, subtotal, or total) is selected. Digital rectal examination is performed to identify intersphincteric groove, and 0.25% bupivacaine mixed with epinephrine is injected below the dentate line (a). Circumferential incision is made along the intersphincteric groove (b)

ISR cases, or at the intersphincteric groove for total ISR cases. The lateral and anterior dissections continue through the intersphincteric plane. Further posterior and lateral dissections continue, and the anterior attachment of the prostate or the vagina is eventually dissected. The rectal wall and the internal sphincter are sharply dissected just above the puborectalis sling along the surgical plane developed via the abdominal approach. The muscular rectal wall is freed using cautery at the level of the anorectal ring, and full mobilization is confirmed using the index finger.

Specimen Delivery

The specimen can be delivered either through the anus or through the abdominal wound. Care should be taken to avoid sphincter injury or tumor violation during specimen extraction. For patients with a bulky mesorectum or narrow pelvis, it may be difficult to deliver the specimen via the anus. The specimen is then transected with an adequate proximal margin.

Coloanal Reconstruction

The reconstruction type (J-pouch, end-to-end, side-to-end, or coloplasty) and method (hand-sewn or stapled) are selected. Splenic flexure mobilization is beneficial to ensure the acquisition of a sufficient colonic length. Anastomotic tension should be avoided. The mesocolon should not be twisted when the pouch is delivered into the pelvic cavity. The prepared proximal colon is pulled down through the anus. For hand-sewn anastomoses, a CAA is performed using absorbable 3-0 sutures placed in an interrupted fashion. Each suture should incorporate either external or internal sphincter muscles to provide anastomotic strength (Fig. 12.8). The proximal colon is then anastomosed to the anal mucosa or the external sphincter. For a stapled technique, a manual purse-string suture is made around the anoderm to facilitate the use of the circular stapler. The stapling technique is quick and technically convenient compared with hand-sewn anastomoses. However, as mentioned previously, stapled anastomoses may not be feasible in subtotal or total ISR cases.

Abdominal Procedure

1. Placement of pelvic and colonic drains before closure of the abdominal wall.
2. A temporary protective stoma is made in the right lower quadrant area using the terminal ileum. A diverting ileostomy is closed 2–3 months later or when the planned adjuvant chemotherapy is completed.

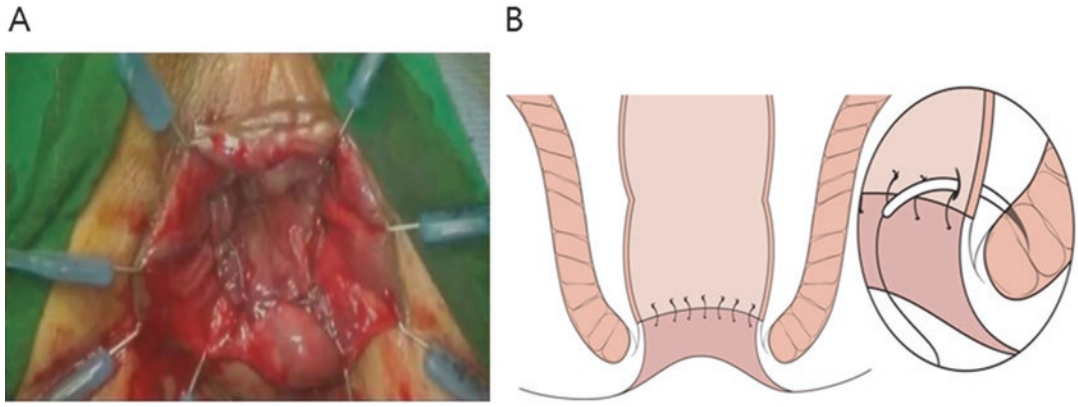

Fig. 12.8 Hand-sewn coloanal anastomosis. Lone Star retractor (Lone Star Medical Products, Inc., Houston, TX, USA) is applied to the anus. End-to-end coloanal reconstruction with hand-sewn anastomosis is performed by absorbable 3-0 sutures in interrupted fashion. Anastomosis is positioned at the level of intersphincteric groove, not at the dentate line (a). Each suture should incorporate either external or internal sphincter muscles to provide anastomotic strength (b)

Laparoscopic Approach

The operative principles underlying the laparoscopic approach are the same as ISR through laparotomy. The patient is placed in the lithotomy-Trendelenburg position, and five trocars are positioned after a carbon dioxide pneumoperitoneum has been established at 12 mmHg. One camera port with an 11 mm trocar is placed in the umbilicus using the open technique, one 12 mm port is placed in the left lower quadrant area, one 12 mm port is placed in the right lower quadrant area, and two 5 mm ports are placed in the left and right upper quadrant areas. High or low ligation of the inferior mesenteric artery, splenic flexure mobilization, total mesorectal excision, and intersphincteric dissection are then performed sequentially. After the per anal procedures, the specimen is brought out through the anus or through a minilaparotomy wound. Coloanal reconstruction is undertaken in the same manner as that used for ISR through laparotomy.

Robotic Approach

There is growing interest in the da Vinci Surgical System (Intuitive Surgical, Sunnyvale, CA, USA), and the robotic approach to rectal cancer surgery is becoming more widely adopted. The robotic surgical system provides a 3-D view of the surgical site, tremor filtering, and more ergonomic instrumentation compared with conventional laparoscopic surgical systems [107].

We evaluated outcomes after robotic (n = 47) and laparoscopic (n = 37) uLAR with CAA [108]. The demographic and operative data did not differ significantly between the two patient groups, but the rate of conversion to open surgery was lower in the robotic surgery group (2.1%) compared with the laparoscopic surgery group (16.2%, p = 0.02). In addition, the mean duration of the hospital stay was shorter in the robotic surgery group (9 days) than in the laparoscopic surgery group (11 days). No postoperative mortality occurred.

For robotically assisted ISR with CAA, the perianal approach is performed first before docking the robotic system [13]. The per anal dissection is performed at the beginning of the operation. After an injection of bupivacaine, the dissection begins at the intersphincteric groove. A meticulous dissection is performed from the intersphincteric groove to the lower rectum. After suturing the dissected rectum, the gauze is packed into the anal canal to maintain the pneumoperitoneum during the robotic procedure.

The robotic procedure then begins, and the surgical principles include high or low ties of the inferior mesenteric vessels and routine splenic flexure mobilization. Next, a total mesorectal excision is performed. The robotic arms provide solid and stable anterior and lateral traction. Rectal retraction is performed using cotton tape with an endosuture device. The anatomical pelvic dissection is performed using the robotic instruments. It is important not to injure the neurovascular bundles. After completing the total mesorectal excision, further dissection continues within the pelvic floor. The pelvic dissection is completed when the previously packed gauze is seen at the puborectalis sling. The muscular wall of the rectum is divided at the level of the puborectalis muscle. While performing ISR with CAA, a secure and meticulous dissection through to the pelvic floor is critical for oncological safety, and this can easily be achieved with the aid of the robotic ergonomic instruments and the magnified 3-D view, even in a narrow pelvic cavity. The specimen is delivered through the anus or through an additional minilaparotomy wound. Caution should be exercised when patients have a bulky mesocolon or mesorectum because it can make it difficult to pull the specimen through the anal route. The hand-sewn coloanal reconstruction is then performed.

Recently, Kim et al. [109] described a ISR technique with a completely abdominal approach, whereby some or all of the intersphincteric dissection is performed from the pelvis. They pointed that a robotic approach facilitates visualization of the embryonic intersphincteric plane between the rectum and the surrounding pelvic floor musculatures in the abdominal side.

In-Hospital Care

Postoperative management following ISR is the same as that for low anterior resections for rectal cancer. The discharge criteria include stable vital signs, controllable pain, stool passage, toleration of a liquid or soft diet, no nausea or vomiting, and independent ambulation. The routine use of nasogastric tubes is not recommended. The pelvic drain is removed 2–3 days after surgery.

Postoperative Follow-Up

All patients are regularly followed up in the outpatient department. The evidence suggests that there are benefits for patients when they undergo intensive follow-up assessments.

Postoperative Morbidity and Mortality

TME for rectal cancer is associated with risk for postoperative morbidity and mortality. It has been reported that the wound infection rate is 7%, the anastomotic leak rate is 11%, and the postoperative mortality rate is 2% [110]. The overall morbidity rate associated with ISR is reportedly 4.8–65%, while the anastomotic leak rate is 5.1–25.8%, the anastomotic stricture rate is 3–15.8%, and the mortality rate is 0–5% [111].

Oncologic Outcomes

Schiessel et al. [9] reported a local recurrence rate of 10% and a disease-free survival rate of 83.2%. Rullier et al. [16] reported a local recurrence rate of 2% and a disease-free survival rate of 70%. Saito et al. [46] analyzed data from several Japanese institutions and reported that the local recurrence rate was 5.8% and that the overall and disease-free survival rates were 91.9% and 83.2%, respectively.

Portier et al. [44] compared outcomes between CAA without ISR (n = 105) and CAA with ISR (n = 173) over a mean follow-up period of 66.8 months. The 5-year local recurrence rate did not differ between the CAA without ISR (6.7%) and the CAA with ISR (10.6%) groups. Furthermore, the 5-year overall survival rate did not differ between the CAA without ISR (80%) and the CAA with ISR (86.1%) groups.

Weiser et al. [39] compared outcomes from three surgical techniques, namely, CAA, ISR, and APR, for low rectal cancer, and they determined that the local recurrence rates were 2% (2/28), 0% (0/44), and 9% (6/63) in the CAA, ISR, and APR groups, respectively. The 5-year recurrence-free survival rates for the CAA, ISR, and APR groups were 85%, 83%, and 47%, respectively, and the 5-year disease-specific survival rates for the CAA, ISR, and APR groups were 97%, 96%, and 59%, respectively. They concluded that sphincter preservation in combination with preoperative CRT for low rectal cancer did not compromise the oncologic outcomes. In addition, Saito et al. [40] compared the oncologic outcomes between ISR and APR. They found that the local recurrence rates were 10.6% (14/132) and 15.7% (11/70) in the ISR and APR groups, respectively; the 5-year local relapse-free survival rates were 83% and 80% in the ISR and APR groups, respectively; and the 5-year disease-free survival rates were 69% and 63% in the ISR and APR groups, respectively. They also found that the 5-year overall survival rates were 80% and 61.5% in the ISR and APR groups, respectively. Saito et al. [40] suggested that ISR is an oncologically acceptable surgical approach compared with APR for very low rectal cancers (Table 12.2).

Functional Outcomes

Functional outcomes, for example, defecation, are important clinical outcome measures following ISR for low rectal cancer. We reviewed the literature and found that the mean stool frequency varies from 2.2 to 5.1 times per day and that urgency was noted in 2–50% of patients. Perfect continence was achieved in 30–80%, but fecal soiling was observed in 11–63%, and incontinence of flatus was observed in 9–88% of patients

Table 12.2 Oncologic outcomes

	Year	*N*	FU (month)	R0 (%)	LR (%)	CSS or OS (%)	DFS (%)
Braun et al. [52]	1992	63	80	100	11	62	–
Bannon et al. [51]	1995	109	40	NR	11	87	–
Kohler et al. [50]	2000	31	82	100	10	79	–
Rullier et al. [16]	2005	92	40	89	2	81	70
Schiessel et al. [17]	2005	121	94	96.7	5.3	88	NR
Saito et al. [46]	2006	228	41	98.7	5.3	92	83
Hohenberger et al. [47]	2006	65	70	92	23	–	–
Chamlou et al. [45]	2007	90	56	94	7	82	75
Akasu et al. [43]	2008	120	42	96.7	6.7	91	77
Krand [41]	2009	47	68	98	2	85	82
Han [42]	2009	40	43	100	11	62	NR
Weiser [39]	2009	44	47	92	0	96	83
Yamada [38]	2009	107	41	100	2.5	92	87
Baek [108]	2013	84[a]	32	100	6	87–91	81
Akagi et al. [24]	2013	83	60	100	11	87	74
Saito et al. [112]	2014	199	78	100	14	78	67

FU follow-up, *LR* local recurrence, *CSS* cancer-specific survival, *OS* overall survival, *DFS* disease-free survival, *NR* not reported

[a]Including ultralow anterior resection with coloanal anastomosis

[9, 24, 38, 41, 42, 45, 48, 50, 52, 60, 112]. Saito et al. [46] evaluated functional outcomes in 110 patients using the Wexner score, and the mean score was 7.8 after a 24-month follow-up period. Using the Kirwan classification, perfect continence was observed in 36 patients, incontinence of flatus was observed in 32 patients, occasional minor soiling was observed in 25 patients, and frequent major soiling was observed in seven patients. None of the patients needed a colostomy for fecal incontinence. In a recent study by the same group [112], the median Wexner score at 5 years was 8 and 10 in the surgery alone and in the surgery plus preoperative CRT groups, respectively. Risk factors for poor postoperative functional outcomes were being a man and the use of preoperative CRT (Table 12.3).

We analyzed 21 patients who underwent ISR for low rectal cancer at our institute between 2004 and 2008. At a mean follow-up period of 12.9 months, two patients had local recurrences, and perfect continence was evident in 50% of the patients who underwent ileostomy reversals. Furthermore, those patients who underwent preoperative CRT sometimes suffered from anastomotic strictures, stool frequency, urgency, fragmentation, soiling, and fecal incontinence [60]. When planning ISR, surgeons can determine a patient's anorectal sphincter integrity and function from TRUS, anorectal manometry, and comprehensive history.

Conclusions

ISR is a safe and effective surgical technique for low rectal cancer. Now, patients who have undergone APR in the past can be treated with ISR. In addition, preoperative CRT induces tumor downstaging and facilitates anal sphincter-preserving surgery. To achieve good oncologic outcomes, appropriate patient selection based on MRI is important, because MRI provides accurate information about the extent of tumor invasion and the anal canal structures. On top of all, a meticulous surgical technique based on anatomical dissections is essential. Recent developments in robotic technology provide an enhanced surgical view

Table 12.3 Functional outcomes

	Year	N	Stool frequency/day	Urgency (%)	Perfect continence (%)	Soiling (%)	Incontinence of flatus (%)
Braun et al. [52]	1992	63	2.2	22	75	15	17
Kohler [50]	2000	31	3.3	–	30	63	11
Schiessel et al. [17]	2005	121	2.2	–	86	14	–
Chin [48]	2006	10	[a]	50	30	20	20
Chamlou et al. [45]	2007	90	2.3	19	41	59	25
Krand et al. [41]	2009	47	2.3	2	80	11	9
Han et al. [42]	2009	40	2.2	31	43	29	29
Yamada et al. [38]	2009	107	3.7	–	42	28	–
Kim et al. [60]	2009	21	[b]	0	50	25	25
Akagi et al. [24]	2013	83	5.1	33	60	16–22	88
Saito et al. [112]	2014	104	4	32	–	26–30	55

[a]50% had less than three times per day
[b]75% had less than two times per day

and ergonomic instrumentation; hence, fine dissections with effective traction are possible. Future investigations should be directed to improve functional outcomes after ISR.

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Management of Lateral Pelvic Lymph Nodes

13

Toshiaki Watanabe and Soichiro Ishihara

Abbreviations

AJCC	American Joint Committee on Cancer
CRM	Circumferential resection margin
CRT	Chemoradiotherapy
CSS	Cancer-specific survival
DFS	Disease-free survival
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasonography
LPLN	Lateral pelvic lymph node(s)
OS	Overall survival
RCT	Randomized controlled trial
TME	Total mesorectal excision

Introduction

The abdominoperitoneal resection reported in 1908 by Miles was the first systematic curative surgery performed on a patient with rectal cancer and significantly improved the prognosis of patients with the condition [1]. Subsequently, extended surgery involving dissection of the periaortic and lateral pelvic lymph nodes (aortopelvic lymphadenectomy) began to be implemented in the 1950s in the USA [2], with Bacon and Stearns reporting that extended dissection may further improve prognosis [3, 4]; however, increased hemorrhage, problems with urinary function, and sexual dysfunction resulted in extended dissection gradually coming into disuse [5]. In 1982, Heald et al. proposed the principle of complete resection of the mesorectum, called a total mesorectal excision (TME) [6]. Quirke et al. demonstrated that the pathological circumferential resection margin (CRM) is important in the local control of rectal cancer [7, 8], with acceptance of the principle of TME significantly contributing to a reduction in local recurrence. During the 2000s, various reports of clinical studies noted a reduction in local recurrence as a result of the use of preoperative chemoradiotherapy (CRT) [9–13], with TME + preoperative chemoradiotherapy becoming the gold standard in the surgical treatment of rectal cancer. Generally speaking, interest was almost completely lost in the significance of lateral pelvic lymph node (LPLN) dissection.

The surgical treatment of rectal cancer in Japan, however, has taken a completely different route to that in Europe and the USA, with LPLN dissection being implemented actively since the 1970s. The importance of LPLN dissection has been reported by Hojo and Moriya et al. [14–16], and extended surgery, including LPLN dissection but not CRT, has become the standard surgical procedure for locally advanced rectal cancer.

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Recently, a retrospective study by Sugihara et al. indicated the possibility that LPLN dissection may reduce local recurrence and improve survival rates [17, 18]; however, there has so far been no randomized controlled trial (RCT) studying the effectiveness of LPLN dissection to date. In this way, regional differences in the handling of the LPLN in rectal cancer cases (in particular, the differences between Europe/the USA and Japan) are significant, with much still unknown in terms of the significance of LPLN dissection.

Definition of the Rectal Lymphatic Flow and Lateral Pelvic Lymph Node

The rectal lymphatic flow is categorized into the three categories of an *upward lymphatic flow*, which moves upward in line with the inferior mesenteric artery and collects in the para-aortic lymph node; a *lateral lymphatic flow*, which passes through the pelvic plexus in line with the middle rectal artery before reaching the lymph node below the aortic bifurcation after passing through the internal iliac lymph node and common iliac lymph node; and a *downward lymphatic flow*, which moves in line with the lower rectal artery, from the proctodeum, subcutaneously via the peritoneum, toward the superficial inguinal lymph node (Fig. 13.1). Research into lateral lymphatic flow began with Gerota's writings on lateral rectal lymphatic flow in 1895, while in 1904 Poirier described lateral lymphatic flow from the rectum in line with the pelvic wall to the aortic bifurcation, and in 1925 Villemin confirmed that lateral lymphatic flow only occurs from the lower rectum. In Japan in 1924, Senba distributed pigment into the obturator lumen of stillborn babies in line with the internal iliac artery, practically demonstrating rectal lateral lymphatic flow as it reaches the internal and external iliac artery bifurcation [19].

The American Joint Committee on Cancer (AJCC) Cancer Staging Manual categorizes the internal iliac lymph node and external iliac lymph node as rectal cancer region lymph nodes, but does not give a clear definition of LPLN [20].

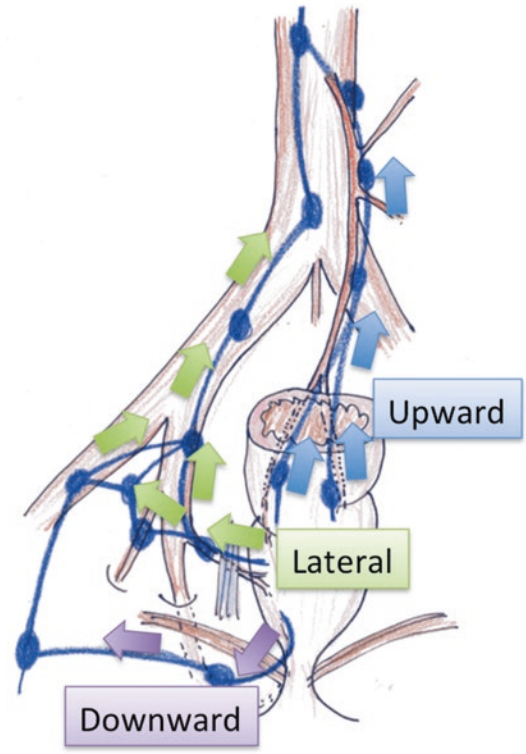

Fig. 13.1 Lymphatic flow of the rectum. The rectal lymphatic flow is categorized into three categories including an *upward lymphatic flow*, which moves upward in line with the inferior mesenteric artery and collects in the para-aortic lymph node; a *lateral lymphatic flow*, which passes through the pelvic plexus in line with the middle rectal artery before reaching the lymph node below the aortic bifurcation after passing through the internal iliac lymph node and common iliac lymph node; and a *downward lymphatic flow*, which moves in line with the lower rectal artery, from the proctodeum, subcutaneously via the peritoneum, toward the superficial inguinal lymph node

In Japan, the LPLN is defined as in Fig. 13.2 in the Japanese Classification of Colorectal Carcinoma, based on the experience of treatment utilizing LPLN dissection [21]. In other words, the *internal iliac lymph node* (#263), the lymph nodes that exist on the outside of the rectal ligament and pelvic plexus, in line with the internal iliac artery; the *obturator lymph node* (#283) which exists within the obturator lumen held between the external iliac artery and the internal iliac artery; the *external iliac lymph node* (#293), which is positioned in line with the external iliac artery; and the *common iliac lymph node* (#273),

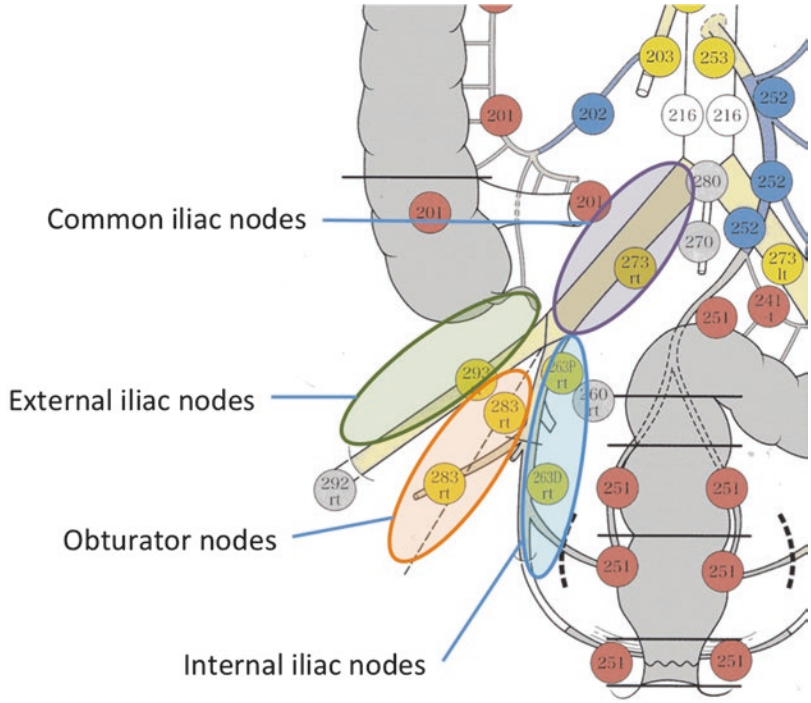

Fig. 13.2 Lateral pelvic lymph nodes according to the Japanese classification. The Japanese Classification of Colorectal Carcinoma defines the *internal iliac lymph node* (#263), the lymph nodes that exist in line with the internal iliac artery; the *obturator lymph node* (#283) which exists within the obturator lumen held between the external iliac artery and the internal iliac artery; the *external iliac lymph node* (#293), which is positioned in line with the external the external iliac artery; and the *common iliac lymph node* (#273), which is positioned in line with the common iliac artery, as lateral pelvic lymph nodes

which is positioned in line with the common iliac artery are defined as LPLN.

The Status of Lateral Pelvic Lymph Node Metastasis

Sugihara et al. retrospectively gathered data from rectal cancer cases at multiple facilities in Japan and reported on the status of LPLN metastasis [17]. Of 1977 cases in which curative surgery had been performed, lateral dissection was performed in 930 (47%), with LPLN metastasis confirmed in 129 (13.9%) of the cases undergoing LPLN dissection. The frequency of LPLN metastasis has been reported elsewhere as between 10.6% and 25.5%, with most reports suggesting it is somewhere around 15% [22–28] (Table 13.1). Of these, the proportion of cases testing positive for LPLN metastasis among cases of lymph node metastasis within the mesorectum (upward) was high, at 23.5%. When the tumor location was studied, LPLN metastasis was found in 8.2% of

Table 13.1 Rates of pelvic lateral lymph node metastasis and survival [17]

Study	Year	Positive lateral nodes (%)	5-year overall survival (%)[a]
Moriya et al. [23]	1997	14.0	49.3
Mori et al. [24]	1998	25.5	43.0
Ueno et al. [25]	2001	15.5	39.0
Shirouzu et al. [26]	2001	15.5	<3 positive nodes: 60 ≥3 positive nodes: 16.7
Shimoyama et al. [27]	2003	13.6	38.9
Ueno et al. [28]	2005	17.3	42.0
Sugihara et al. [17]	2006	13.9	47.7

[a]Patients with positive lateral nodes

cases when the tumor was intraperitoneal (proximal to the peritoneal reflection) (the *upper rectum*, defined as Ra in the Japanese classification), but that in 14.9% of cases—a significantly higher rate—when the tumor was extraperitoneal (between the peritoneal reflection and the anus) (the *lower rectum*, defined as Rb in the Japanese classification). Kanemitsu et al. studied the tumor location in terms of its distance from the anal verge, demonstrating that in cases where distance from the anal verge was over 9 cm, the frequency of LPLN metastasis was low, at 1.4%, while in cases where it was 9 cm or smaller, the rate of metastasis suddenly increased (to 9.1% between 8.1 and 9.0 cm, 12.5% between 6.1 and 8.0 cm, 20.3% between 4.1 and 6.0 cm, 18.8% between 2.1 and 4.0 cm, and 23.3% between 0.0 and 2.0 cm). An analysis of the depth of tumor invasion by Sugihara et al. showed that the frequency of LPLN metastasis was 7.1% in cases T2 and shallower, but it was significantly higher (16.6%) in cases T3 or deeper [17]. Based on this analysis of metastasis frequency, the indication criteria for LPLN dissection according to Japan's colorectal cancer treatment guidelines were set as "cases in which the lower border of the tumor is located distal to the peritoneal reflection and the tumor has invaded beyond the muscularis propria" [29]. Other risk factors in LPLN metastasis are reported to include being female, histologic types other than well-/moderately differentiated adenocarcinoma, etc. [17, 18, 28]. It is assumed that the reason being female is an independent risk factor in LPLN metastasis is due to some sort of oncological or anatomical difference between men and women; however, this has not been clarified.

Frequency of metastasis by location within LPLN has been examined and reported. As above, the Japanese Classification of Colorectal Carcinoma divides the LPLN broadly into four defined areas [21] (Fig. 13.2). According to Kobayashi et al., a study of 117 cases of lower rectal cancer (Rb) cases testing positive for LPLN metastasis showed the highest rate of metastasis in the internal iliac lymph node [18]. The frequency of metastasis in these lymph nodes differs significantly on either side of the superior vesical artery, which is the branch of the internal iliac artery, occurring in 26% among lymph nodes on the proximal side of the superior vesical artery (#263P), but 47% on the distal side (#263D). Obturator lymph node cases (#283) had the next highest rate of metastasis frequency (38%). The frequency of metastasis in other areas was much lower than those in the internal iliac lymph node and obturator lymph node (external iliac lymph node (#293), 6%; common iliac lymph node (#273), 3%; aortic bifurcation lymph node (#280)/midline sacrum lymph node (#270), 6%). Based on analysis of these metastasis frequencies, lymph nodes defined in the Japanese Classification of Colorectal Carcinoma as LPLNs include the internal iliac lymph node and obturator lymph node within the scope of D3 dissection, with the common iliac lymph node and external iliac lymph node not included in D3 dissection.

Image Diagnosis of Lateral Pelvic Lymph Node Metastasis

Image diagnosis of rectal cancer lymph node metastasis is performed using endoscopic ultrasonography (EUS), CT, or MRI. According to meta-analysis, the sensitivity and specificity of each method is 67% and 78% with EUS, 55% and 74% with CT, and 66% and 76% with MRI, respectively, revealing no significant difference between the methods [30]. EUS is considered useful for diagnosing lymph nodes within the mesorectum, but is not suitable for the diagnosis of LPLN metastasis for anatomical reasons. MRI gives better contrast resolution for soft tissue than CT and is a more specific method of diagnosis. The European Society for Medical Oncology (ESMO) guidelines stress the importance of correctly diagnosing lymph node metastasis both within and outside the mesorectum for rectal cancer staging, and as a result, MRI is considered the first choice [31].

Cross-sectional images using CT or MRI depict the LPLN in the deep part of the pelvis, surrounded by the external iliac artery as the ventral border, the internal iliac artery as the dorsal border, the psoas major muscle and internal obturator muscle

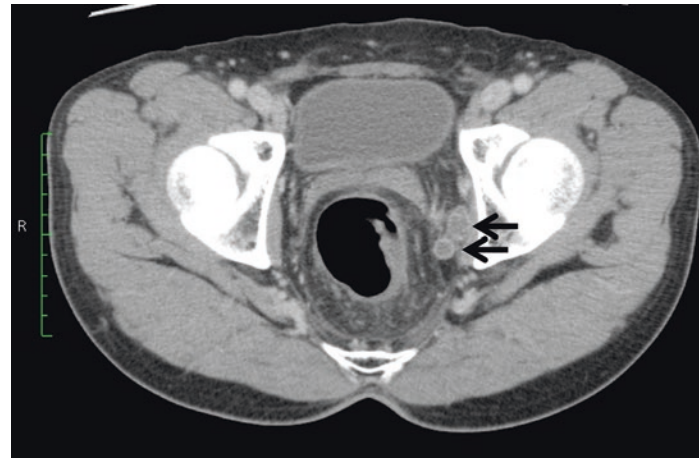

Fig. 13.3 CT findings of lateral pelvic lymph node metastasis. Uneven swelling noted in the left lateral pelvic lymph nodes (*arrow*)

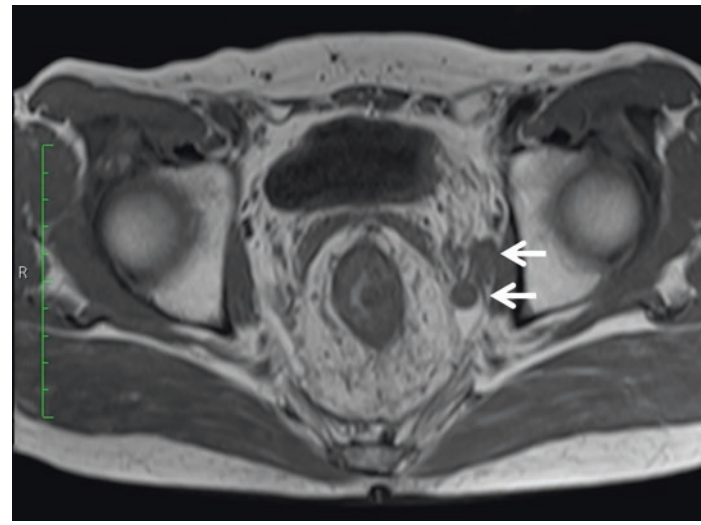

Fig. 13.4 MRI findings of lateral pelvic lymph node metastasis. Uneven swelling noted in the left lateral pelvic lymph nodes (*arrow*)

as the outer (pelvic wall side) border, and the proper rectal fascia as the inside (organ side) border (Figs. 13.3 and 13.4). While a range of diagnostic criteria have been reported for use in diagnosing lymph node metastasis, the method most generally accepted is the size of the lymph node depicted. Metastatic lymph nodes tend to be bigger than nonmetastatic lymph nodes [32]. When the maximum diameter of lymph nodes is compared on a histogram, however, there is a significant amount of crossover between metastatic and nonmetastatic lymph nodes [33], making it difficult to establish a strict cutoff value. For this reason, signal heterogeneity and irregular border are used, among other non-size-related morphological criteria, with reports suggesting that they are useful [34, 35]. Morphological determinations become more difficult, however, the smaller the size of the lymph node, and at present, it is believed difficult to diagnose lymph node metastasis merely using criteria relating to size and morphology.

More recently, diagnostic methods including qualitative elements, such as MRI diffusion-weighted imaging and FDG-PET, have proven useful in regard to diagnosing lymph node metastasis. In particular, FDG-PET has a sensitivity of between 40 and 50%, which is slightly lower than that of EUS, CT, and MRI, but an extremely high

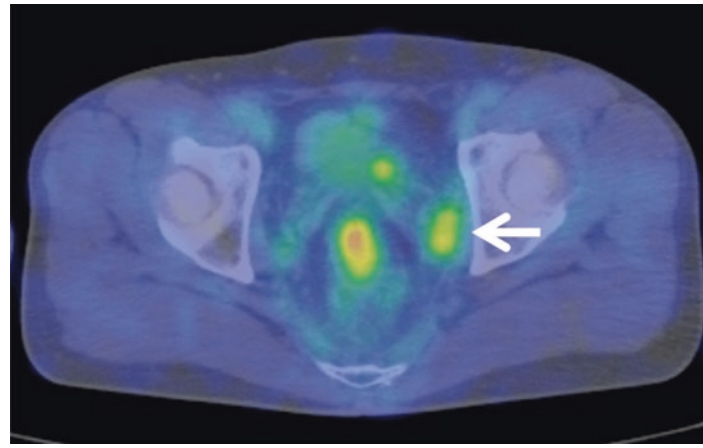

Fig. 13.5 FDG-PET findings of lateral pelvic lymph node metastasis. High accumulation image noted in the left swollen lateral pelvic lymph nodes (*arrow*)

level of specificity at 90% [36], suggesting it may be a potentially effective supplementary method of morphological diagnosis (Fig. 13.5).

Prognosis in Cases with Lateral Pelvic Lymph Node Metastasis and the Effect of Dissection

Sugihara et al. analyzed multicenter data in Japan and found that among cases in which LPLN dissection was implemented, the 5-year overall survival (OS) rate among patients with LPLN metastasis was 45.8%, which is significantly worse than the 71.2% of stage III cases with no LPLN metastasis (where lymph node metastasis was only inside the mesorectum) [17]. Furthermore, assuming that local recurrence occurs when LPLN metastasis is not removed and left, leading to the cause of death, it is calculated that LPLN dissection would have reduced T3–T4 rectal cancer local recurrence by 50%, improving the 5-year survival rate by 8%. Fujita et al. report [37] that upon analysis of 91 cases of LPLN metastasis in which dissection was performed, the 5-year OS rate was 39%, while the 5-year disease-free survival rate (DFS) was 27%. Japanese reports of this type state that the 5-year OS for cases of LPLN metastasis in which dissection was performed is around 40% (Table 13.1).

Akiyoshi et al. retrospectively analyzed more than 10,000 cases of lower rectal cancer, dividing the LPLN into the internal iliac lymph node (internal LPLN) and categorizing everything else as the external LPLN (obturator lymph node, external iliac lymph node, common iliac lymph node, lymph node below the aortic bifurcation, and midline sacrum lymph node) and then studying the prognoses in cases that metastasized. The 5-year OS and cancer-specific survival (CSS) in metastasized internal LPLN cases were 45% and 49%, respectively, which was comparable to the 5-year OS (45%) and 5-year CSS (51%) for cases in which lymph node metastasis was confined to the inside of the mesorectum with the number of metastasized node between 4 and 6, defined according to the AJCC Cancer Staging Manual as N2a. Furthermore, the 5-year OS and CSS for cases in which metastasis occurred in the external LPLN were 29% and 34%, respectively, which was worse than cases in which metastasis remained in the internal LPLN, but roughly the same as the 5-year OS (32%) and CSS (37%) of cases defined by AJCC as N2b, and significantly better than the 5-year OS (24%) and CSS (27%) of stage IV rectal cancer cases undergoing R0 resection. These results indicate that even if there is metastasis in the LPLN, provided it is removed, the prognosis is comparable to cases in which it is limited to the inside of the mesorectum and better than stage IV cases; in other words, they lead to the conclusion that LPLN metastasis is not a systemic disease, but should rather be considered a regional disease, and that it is important that it be removed if at all possible [38]. Furthermore, analysis of the prognostic factors

indicates that LPLN dissection is an independent prognostic factor, equivalent to the stage and number of dissected lymph nodes, and that LPLN dissection can improve OS and CSS. Therefore, while cases with LPLN metastasis have a relatively poor prognosis in reports from Japan, there are indications that removal can improve prognosis. The USA Guidelines 2000 for Colon and Rectal Cancer Surgery also state that if LPLN metastasis is suspected clinically, then dissection should be attempted if it is considered possible [39].

Prophylactic Dissection of Lateral Pelvic Lymph Node

The indications above are that dissection may improve prognosis in cases of metastasis to the LPLN. The fact that the rate of metastasis to the LPLN is around 15% means that there are no oncological benefits to LPLN dissection for the majority of patients. It is, however, impossible to make a 100% accurate diagnosis of LPLN metastasis either preoperatively or from intraoperative findings. For this reason, we need to consider whether or not there is any meaning in prophylactic LPLN dissection for cases in which it is determined that there is no LPLN metastasis. An RCT (JCOG0212 trial) is currently being carried out in Japan in order to answer this question [40]. This study involves patients with advanced lower rectal cancer, in whom it has been clinically determined that no LPLN metastasis has occurred, and is a trial to validate the non-inferiority of TME alone without prophylactic LPLN dissection to TME with prophylactic LPLN dissection. Cases of rectal cancer in which the lower edge was between the peritoneal reflection and the anus, in clinical stages II–III, and with no swelling of the LPLN equal to or greater than 10 mm observed upon CT or MRI, which were operated on without any preoperative treatment such as CRT, with macroscopic R0 resection, and in which it was determined based on intraoperative findings that no LPLN metastasis had occurred, were randomly divided into those in whom a LPLN dissection was performed and those in whom it was not. The primary endpoint was the relapse-free survival, with an analysis expected to be conducted in 2015. The secondary endpoints are overall survival, local recurrence-free survival, occurrence of adverse events, surgery time, hemorrhage volume, and the occurrence of sexual dysfunction/urinary function problems. A report was made in 2012 of the short-term results [40], which indicated that the LPLN dissection group had significantly longer surgery time than those not undergoing LPLN dissection (360 min vs. 254 min, $p < 0.0001$), as well as greater blood loss (576 ml vs. 337 ml, $p < 0.0001$). There was no significant difference in the incidence of grade 3–4 adverse events, although the group undergoing LPLN dissection had slightly more (22% vs. 16%, $p = 0.07$). In terms of the primary endpoint of relapse-free survival, if the non-inferiority of TME without LPLN dissection is proven, it will be possible to determine that TME without LPLN dissection is an effective therapy for cases in which it is determined that LPLN metastasis has not taken place.

Preoperative Chemoradiotherapy and Lateral Pelvic Lymph Node Dissection

Preoperative CRT in cases of locally advanced rectal cancer has been demonstrated in multiple clinical trials to reduce postsurgical local recurrence [9–13]. In these clinical trials, TME was the basic surgery, with no routine LPLN dissection carried out. In Japan, on the other hand, TME accompanied by LPLN dissection has become standard, without preoperative CRT, and reports indicate that it achieves a similar or lower rate of local recurrence to that of TME after CRT in Europe and the USA [17, 18, 41] (Table 13.2). Given this, discussions are now underway regarding whether or not it is oncologically acceptable to omit LPLN dissection if preoperative CRT has been implemented. However, few reports exist that consider this clinical question.

Watanabe et al. divided patients with advanced lower rectal cancer on which curative removal had been implemented into four groups, depending on whether or not they had undergone preop-

Table 13.2 Impact of treatment modalities on local recurrence and survival

Study	Year	Design	Treatment	5-year local recurrence (%)	p	5-year overall survival (%)	p
Western series							
Swedish trial [10]	2005	RCT	Surgery alone	26[a]	<0.001	30[b]	0.008
			sRT	9[a]		38[b]	
Dutch trial [57]	2001	RCT	Surgery alone	10.9	<0.001	63.5	NS
			sRT	5.6		64.2	
EORTC22921 [12]	2006	RCT	RT	17.1	0.002	64.8	NS
			CRT	8.7		65.8	
FFCD9203 [13]	2006	RCT	RT	16.5	0.0004	67.9	NS
			CRT	8.1		67.4	
Japanese series							
Moriya et al. [41]	1995	Retrospective	Surgery alone[c]	9.3	–	70.0	–
Sugihara et al. [17]	2006	Retrospective	LLND (−)	5.4	<0.0001	76.9	0.0017
			(+)	10.9		82.6	
Kobayashi et al. [18]	2009	Retrospective	LLND (−)	7.4	NS	79.5	NS
			(+)	10.5		75.8	

RCT randomized controlled trial, *(s)RT* (short-course) radiotherapy, *CRT* chemoradiotherapy, *LLND* lateral pelvic lymph node dissection
[a]13-year local recurrence
[b]13-year overall survival
[c]Including LLND (+) cases

erative radiotherapy and whether or not they had undergone LPLN dissection, and retrospectively compared their prognoses. Overall, while an improvement in disease-free survival (DFS) was noted in patients undergoing preoperative radiotherapy, the fact that there was no difference in DFS between the group undergoing lateral dissection without radiotherapy and those undergoing radiotherapy, but no lateral dissection, indicates that preoperative radiotherapy may be a replacement for LPLN dissection [42].

Nagawa et al. compared prognosis and function between random groups comprising rectal cancer patients in whom no LPLN metastasis was diagnosed prior to surgery, who were given radiotherapy and then underwent rectal resection and then either underwent or did not undergo LPLN dissection [43]. There was no difference in either OS or DFS between the two groups. Furthermore, the group undergoing LPLN dissection had significantly higher rates of urinary function disorders and male sexual dysfunction. Given these results, it is possible that there is no need for patients diagnosed with rectal cancer and no LPLN metastasis to undergo LPLN dissection following radiotherapy. This clinical study is the only RCT verifying the preventative effects of LPLN dissection following radiotherapy; that said, it involved only 45 cases, and as such, the results thereof need to be interpreted with caution.

Kim and Takahashi et al. studied the additional oncological benefits of LPLN dissection and postsurgical CRT on TME in facilities in Japan and Korea. While there was no difference in OS or DFS, local recurrence occurred in 2.2 times the number of cases in the LPLN dissection compared with the postsurgical CRT group. From this result, it appears that postsurgical CRT is more effective in controlling local recurrence than LPLN dissection, that LPLN dissection alone is insufficient, and that the group on which LPLN dissection was performed also requires CRT. This trial, however, has several identified problems, including the fact that CRT was performed postsurgically and that the definition of lower rectal cancer differed between the institutions [44].

Kim et al. analyzed the local recurrence patterns in rectal cancer patients who were given CRT prior to TME and found that LPLN recurrence was the most common form of local recurrence. Local recurrence was noted in 7.9% of patients, and of these, it occurred in the LPLN in 82.7% of cases. Risk factor analysis was implemented for LPLN recurrence, with the result that, assuming that ypN+ and LPLN swelling are risk factors in recurrence, discussions are now ongoing regarding the potential benefits of lateral dissection after CRT for patients with these risk factors.

Akiyoshi et al. implemented selective LPLN dissection on post-CRT rectal cancer patients in whom LPLN metastasis was suspected based on pretreatment imaging examinations, but did not implement prophylactic LPLN dissection on cases in which no metastasis was suspected, and then compared the treatment results of the two groups. The rate of pathological metastasis in the lateral dissection group was high, at 66%, indicating that it is difficult to control LPLN metastasis even with CRT. There was almost no difference, however, in the rate of local recurrence between the LPLN dissection group (0%) and the non-dissection group (3.4%), indicating that even for cases in which LPLN metastasis is suspected, CRT and selective lateral dissection can achieve good local control [45].

From these reports, it is believed that there is a high probability that LPLN dissection can be omitted after preoperative CRT, at least for cases in which it is determined in pretreatment that no LPLN metastasis has occurred. The effectiveness of prophylactic LPLN dissection itself for cases in which pretreatment has not been carried out is unclear, forcing us to wait for the results of the aforementioned RCT (JCOG0212 trial). While some metastasized LPLNs are sterilized by CRT, a high rate of residual cancer is reported, and the fact that it is difficult to diagnose this from preoperative image diagnosis means that it is difficult to anticipate a similar level of effectiveness against metastasized lymph nodes from CRT as from resection. It is now considered that CRT is not always necessary in all rectal cancer cases, with reports from the USA and Europe suggesting that surgery alone can achieve good local control in low-risk cases [46]. CRT and LPLN dissection should not be treated as opposing treatment modalities, but rather used in the future in the optimum combination for the treatment of individual cases.

Procedure for Lateral Pelvic Lymph Node Dissection

From the point of view of metastasis frequency, the internal iliac lymph node and obturator lymph node are important in LPLN dissection. The Japanese Classification of Colorectal Carcinoma also defines this dissection as a D3 dissection involving both, so the following is an explanation of the dissection procedure for the internal iliac lymph node and obturator lymph node.

Approach

Ordinarily, once TME on the primary lesion in the rectum has been completed, the procedure moves onto LPLN dissection. If open surgery is being performed, since exposure of the deep areas of the pelvis is poor using an approach from the abdominal cavity alone, the paravesical space is also exposed, and the LPLN area should be extraperitoneally approached. Recently, methods have been reported involving laparoscopic LPLN dissection [47, 48] and robotic assistance [49, 50]; however, they are only being carried out in a few facilities and are not yet established procedures. LPLN dissection performed using a laparoscope or robot, however, gives an excellent view of the deep part of the pelvis, allowing detailed movement as a result of the expanded view, and it is anticipated that it will become a more commonly selected minimally invasive procedure.

Landmarks in Lateral Pelvic Lymph Node Dissection

a. Ureter, hypogastric nerve-pelvic plexus: inner edge of dissection

b. External iliac artery: outer edge of dissection
c. Internal/external iliac artery bifurcation: cranial edge of dissection
d. Vesicohypogastric fascia (sheath including internal iliac artery and its branches, such as umbilical artery (ligament), superior vesical artery, and inferior vesical artery): formation of a screen that demarcates the LPLN external region (obturator lymph node) and internal region (internal iliac lymph node)
e. Sacral plexus: dorsal edge of internal iliac lymph node dissection
f. Pudendal canal (Alcock canal): caudal edge of internal iliac lymph node dissection
g. Psoas major muscle, inner obturator, obturator foramen: dorsal-caudal edge of obturator lymph node dissection

Dissection

The authors implement LPLN dissection with the proactive assistance of robots. The following is an explanation of the procedure, using images from a robot-assisted left LPLN dissection:

1. Tape and separate the ureter and hypogastric nerve to determine the inner edge of the dissection (Fig. 13.6).
2. Using the internal/external iliac artery bifurcation as the cranial edge of the dissection, expose the anterior surface of the external iliac artery (determine the external edge of the dissection). Continue to separate in line with the external iliac artery and the external iliac vein behind it, to reach the surface of the psoas major muscle (Fig. 13.7).
3. Continue to separate inward and downward, in line with the psoas major muscle—inner obturator.
4. Confirm obturator nerve and obturator artery/vein at the obturator foramen (Fig. 13.8).
5. Proceed with separation caudally, from the internal/external iliac artery bifurcation in line with the internal iliac artery (Fig. 13.9), and confirm the bifurcation consisting of the obturator artery, umbilical artery (ligament), superior vesical artery (in many cases formed from the same stem as the umbilical artery), and the inferior vesical artery. The obturator artery (vein) should be dissected at the origin (bifurcation from the

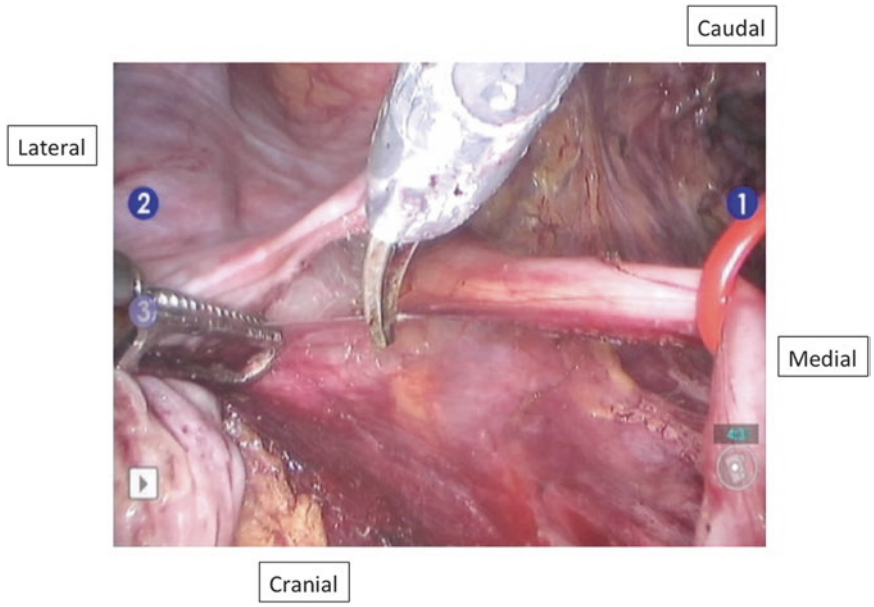

Fig. 13.6 Taping and mobilization of the ureter. The ureter (*left*) is taped, to clarify the inner edge of the dissection as well as prevent damage

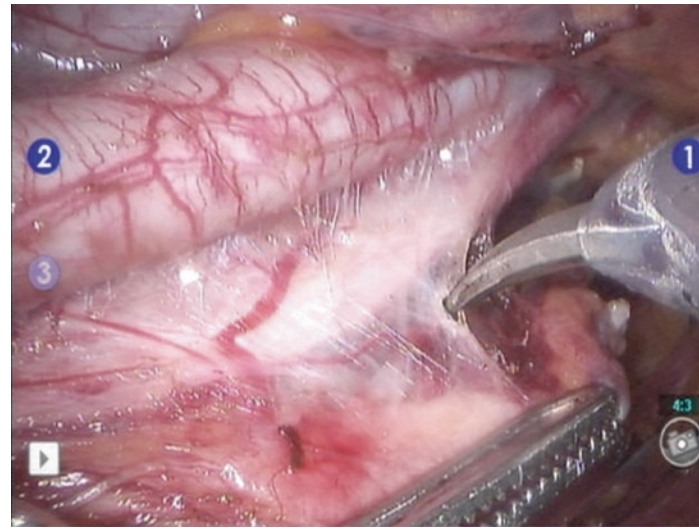

Fig. 13.7 Lateral border of lateral pelvic lymph node dissection. The external iliac artery is the outer edge of the lateral pelvic lymph node dissection

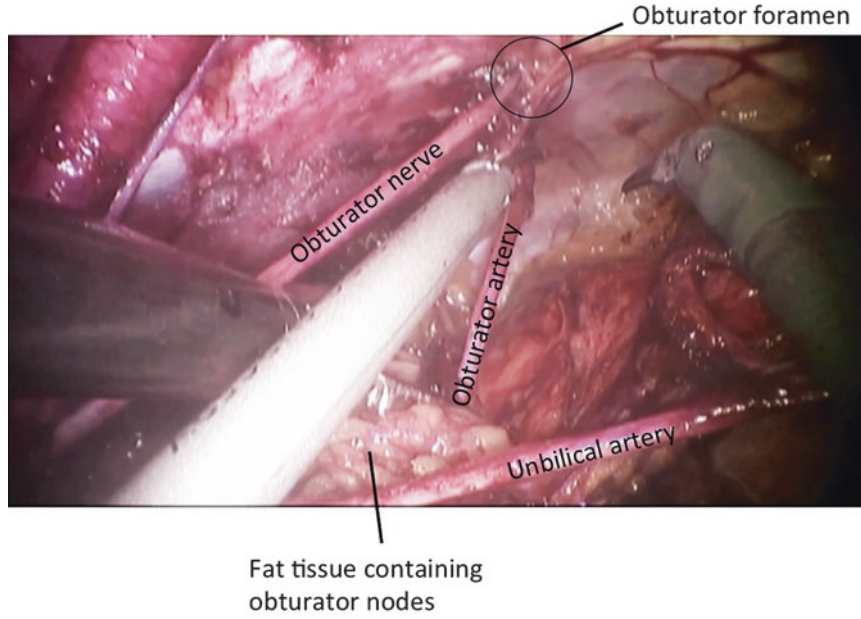

Fig. 13.8 Exposure of the obturator foramen. In obturator lymph node dissection, the obturator foramen is confirmed at the caudal end, and the obturator artery/vein is usually separated for dissection

internal iliac blood vessels) and peripherally (obturator foramen) in order to achieve sufficient dissection of the obturator lymph node.

6. When dissecting the internal iliac artery and its branches, confirm that the umbilical artery, superior vesical artery, and inferior vesical artery form a fascia-like structure, which is known as the vesicohypogastric fascia. This should be pulled to the center and the deep part of the obturator lymph node region exposed (Fig. 13.10). Separate the fatty tissue, including the obturator lymph node, from the vesicohypogastric fascia (inner edge of the obturator lymph node region). The obturator nerve pen-

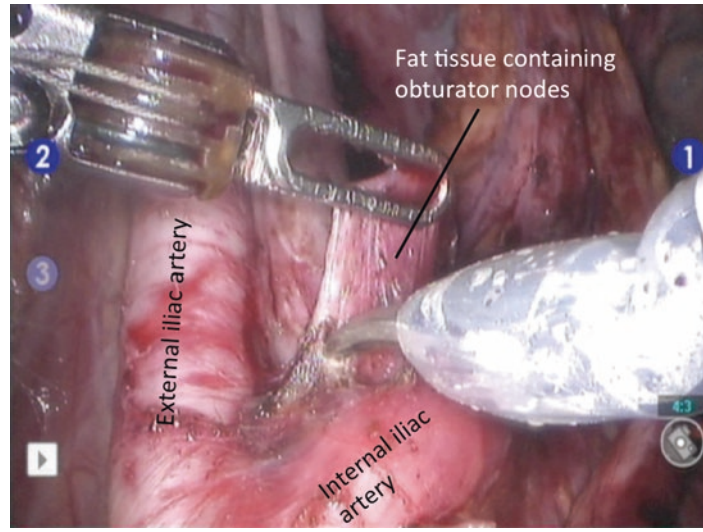

Fig. 13.9 Dissection of the cranial edge of the obturator nodes. The internal/external iliac artery bifurcation is the cranial edge of the dissection

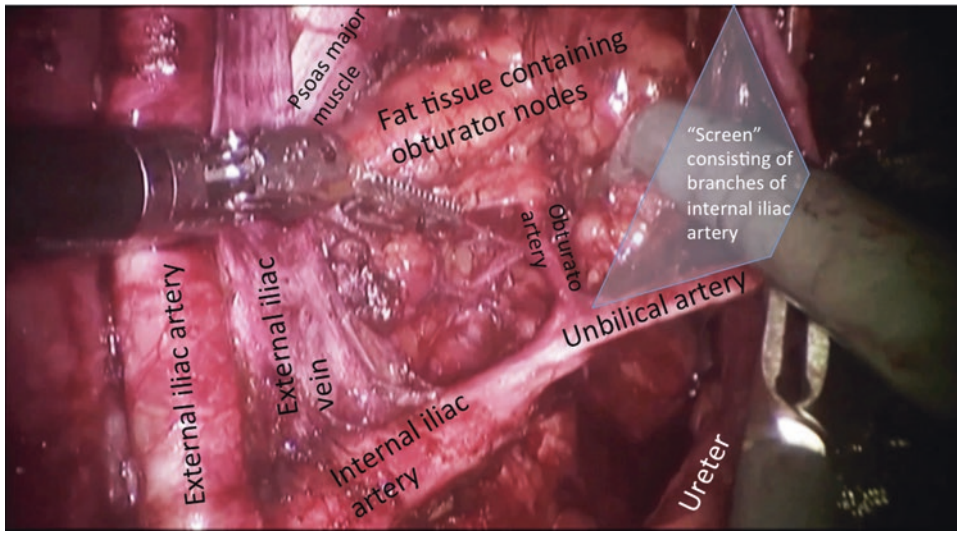

Fig. 13.10 Dissection of the deep part of the obturator nodes. The umbilical artery, superior vesical artery, and inferior vesical artery form a fascia-like structure (vesicohypogastric fascia). Confirm this and pull it to the center in order to expose the obturator lymph node deep part

etrates the fatty tissue, including the obturator lymph node, and can be confirmed at the cranial (deep part of the internal/external iliac artery bifurcation) or caudal (obturator foramen) side. Split up this fatty tissue and preserve the obturator nerve during dissection.

7. Dissect at the part where the fatty tissue, including the obturator lymph nodes, continues into the inguinal lymph node region to complete the dissection of the obturator lymph node.
8. Next, perform the internal iliac lymph node dissection (Fig. 13.11). If possible, the branches of the internal iliac artery such as the inferior vesical artery should be preserved; however, it can be resected if required for dissection. Dissect as far as the part where the internal pudendal artery enters the pudendal canal (Alcock canal)

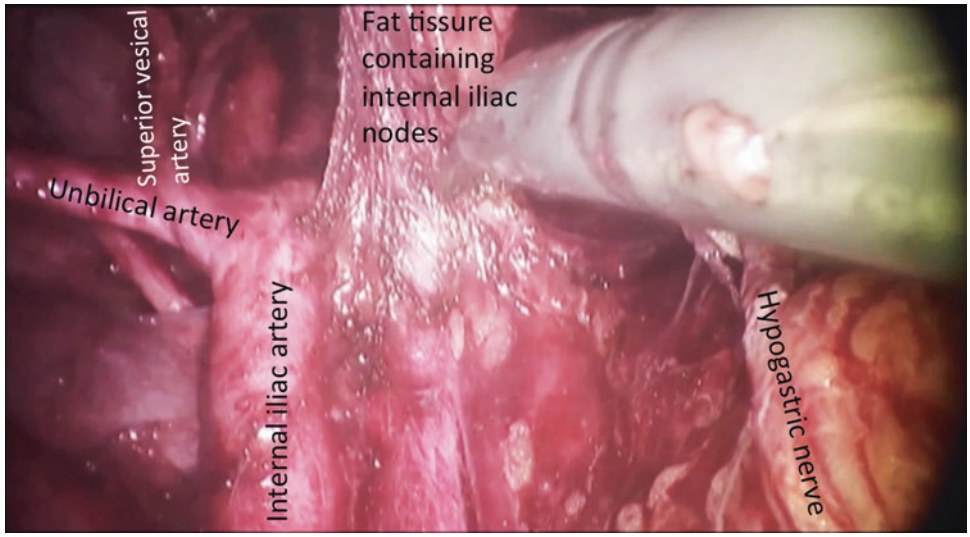

Fig. 13.11 Dissection of the internal iliac nodes. Dissect the lymph nodes in line with the internal iliac artery to the part where the internal pudendal artery enters the pudendal canal (Alcock canal)

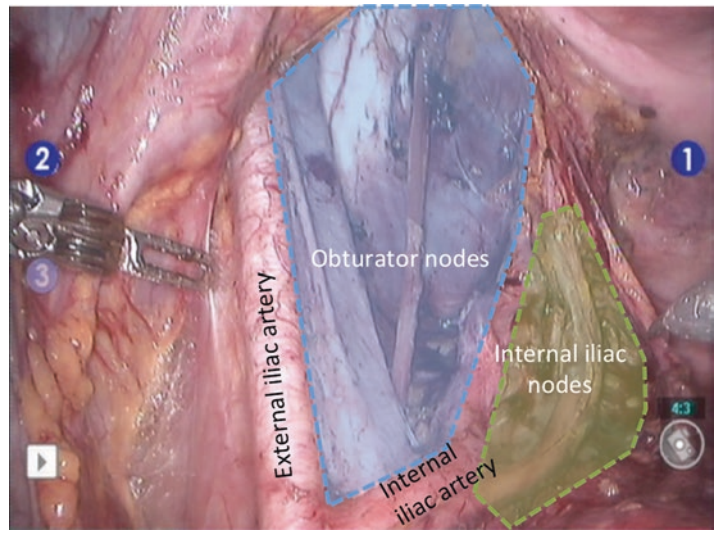

Fig. 13.12 Completion of lateral pelvic lymph node dissection. Left lateral pelvic lymph node dissection completed

(Fig. 13.12). The Japanese Classification of Colorectal Carcinoma categorizes the internal iliac lymph node along the superior vesical artery into proximal (#263P) and distal (#263D) sides, with exposure of #263D poor due to the deep part of the pelvis; however, some data suggests that among LPLNs, #263D has the highest rate of metastasis [18], and as such, it is important to ensure that sufficient dissection is carried out. The internal iliac vessels are also sometimes dissected due to invasion of internal iliac lymph node metastasis.

9. Autonomic nerves should be preserved as much as possible in order to preserve function during LPLN dissection. If they have been invaded by lymph node metastasis, they will be jointly dissected; however, reports suggest that functional disorders occur in proportion to the extent of preservation of the autonomic nerves.

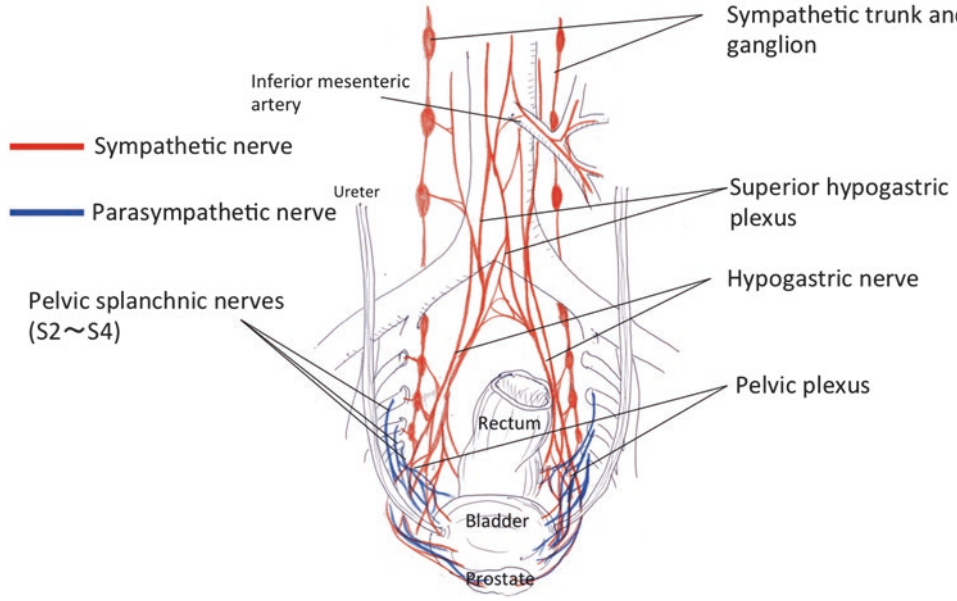

Fig. 13.13 Autonomic nerves around the rectum. The hypogastric nerve and sympathetic nerve trunk are formed from the sympathetic nerves, while the pelvic splanchnic nerves are formed from parasympathetic nerves. The two together form the pelvic plexus on both sides of the rectum

Lateral Pelvic Lymph Node Dissection and Functional Disorders

The LPLNs are located close to the pelvic autonomic nerve, and it goes without saying that for cases in which LPLN dissection involves removal of the autonomic nerve, as well as those in which it is preserved and dissected, there is a possibility of autonomic nerve disorders occurring. In Japan during the 1970s, extended surgeries on rectal cancer cases involving the removal of the autonomic nerve were reported as achieving good oncological results; however, in many cases, patients were left with urinary function disorders and sexual dysfunction [51]. In response to the experience of urinary function disorders and sexual dysfunction, during the 1980s, a significant amount of research was conducted into the operation and movement of the pelvic autonomic nerve, facilitating the autonomic nerve-preserving surgeries that are now performed as standard. The autonomic nerves distributed throughout the pelvic organs form the pelvic plexus. The pelvic plexus is formed from sympathetic and parasympathetic nerves. The sympathetic nerves follow either the lumbar splanchnic nerve, which runs from the left and right lumbar sympathetic nerves, forming the superior hypogastric nerve plexus in front of the aorta, before splitting into the left and right hypogastric nerves approximately 3 cm below the aortic bifurcation and entering the upper corner of the pelvic plexus, or descend the left and right sympathetic nerve trunks from the sacral splanchnic nerves to the pelvic plexus. The parasympathetic nerves, on the other hand, are formed from the pelvic splanchnic nerves, which enter the lower corner of the pelvic plexus from the 2nd–4th (S2–S4) sacral foramen (Fig. 13.13). Regarding the urinary function, the sympathetic nerves contribute to urinalysis by the reduction of pressure within the bladder and increase in pressure within the ureter, while the parasympathetic nerves are considered to contribute more to the contraction of the bladder and the emission of urine. Damage to the parasympathetic nerves, therefore, has more of an impact on urinary function, with almost no urinary disorders being clinically associated with

Table 13.3 Functional disturbance after nerve-preserving surgery for rectal cancer

Study	Year	Degree of preservation	Urinary function	Sexual disturbance (%)	
				Erection	Ejaculation
Moriya et al. [41]	1995	Total	Poor, 2%	10	32
		Partial			
		Bilateral PP[a]	Poor: 4%	68	89
		Unilateral PP	Poor: 4%	73	100
Masui et al. [52]	1996	Total	–	7	18
		Partial			
		Unilateral HN and PP	–	18	53
		Partial PP	–	39	100

PP pelvic plexus, *HN* hypogastric nerve
[a]Hypogastric nerve resected

damage to the sympathetic nerves. In male sexual function, the sympathetic nerves contribute to ejaculation, while the parasympathetic nerves contribute to erection. Compared with their contribution to male sexual function, the contribution of these nerves to female sexual function has not yet been sufficiently explained.

Nowadays, surgical methods that completely preserve these autonomic nerves are the basic methods used in rectal cancer surgery. Table 13.3 shows reports relating to functional disorders subsequent to surgeries designed to preserve the autonomic nerves [41, 52]. All these reports note good results in the preservation of urinary and erectile function after autonomic nerve-preserving surgery. In 20–30% of cases, ejaculation function disorders were noted even where autonomic nerves had been preserved. Urinary function disorders occurred in more than half of cases where the autonomic nerves were completely removed; however, if part of the pelvic nerve (particularly S4) was preserved on one side, it appears that severe dysfunction can be avoided in many cases. Male sexual function is preserved in line with the extent of nerve preservation; however, in general, there is a higher rate of ejaculatory dysfunction than erectile dysfunction. Ejaculation is mainly controlled by the sympathetic nerves; however, if the hypogastric nerve is damaged, then reverse ejaculation may occur into the bladder, since the internal ostium of the urethra cannot be closed.

Recurrence in Lateral Pelvic Lymph Nodes

Postoperative recurrence of rectal cancer in the LPLN is categorized according to local recurrence. Prior to the acceptance of TME, reports suggested high rates of 5-year local recurrence (as much as 30%) [53]; however, the wide use of TME and, furthermore, the introduction of preoperative CRT, has resulted in the rate of local recurrence falling to below 10% [9–13, 54]. Among incidences of local recurrence, LPLN recurrence accounted for around 10% of cases prior to TME, with most occurring outside the lateral region, either anastomotically or to the front or rear (anterior aspect of the sacrum) [53, 55]. Since the implementation of TME and CRT began, anastomotical and other non-LPLN recurrence has reduced, with recent reports by Kim et al. suggesting that the majority (80%) of local recurrence after CRT + TME occurs in the LPLNs [56].

Roughly half of postoperative local recurrences of rectal cancer are discovered as systemic disease, accompanied by distant metastasis, with roughly half recurring only locally [56, 57]. In some of these cases, repeat surgery is possible, improving prognosis [58–60]. Kuster et al. studied the results of multidisciplinary treatment of local recurrence cases, combining CRT and radiation during surgery with surgical resection, according to the location of the local recurrence [59]. Their results

showed that recurrence in the lateral regions showed that curative resection was performed in 64% of cases, that the 5-year re-recurrence rate was 56%, and that the 5-year cancer-specific survival rate was 36%, treatment results that indicate to an extent that long-term survival is almost impossible without resection, although these results were poorer than those gained in cases with only anastomotical local recurrence (at 77%, 28%, and 60%, respectively). Kanemitsu et al. also studied surgical resection of local recurrence (with around half of cases also receiving radiotherapy) and demonstrated that R0 resection cases had a 5-year CSS (43.3%) that was significantly better than R1 (19.5%) or R2 (10%) resection. Lateral region recurrence, however, is frequently irresectable and, if resected, is reported as an independent risk factor for local re-recurrence and distant recurrence [58]. In other words, while salvage surgery offers some hope of long-term survival in cases of recurrence in LPLNs, the condition has poor treatment results when compared with recurrence localized to anastomotic parts. As such, now that anastomotic recurrence can be reduced by TME and CRT, it is increasingly important to control recurrence in the LPLNs.

Summary

- The frequency of LPLN metastasis in rectal cancer cases is approx. 15%.
- The 5-year overall survival rate of resected LPLN metastasis cases is approx. 40%.
- There are indications that prognosis in cases of LPLN metastasis with no distant metastasis may be improved by resection.
- Accurate preoperative image diagnosis of LPLN metastasis is difficult, and it is unclear whether the omission of prophylactic dissection in cases diagnosed as negative for metastasis actually worsens prognosis. An RCT is underway in Japan.
- It is currently under discussion whether the implementation of preoperative chemoradiotherapy enables the omission of dissection (both curative dissection and prophylactic dissection).

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Evaluation of Treatment of Locally Recurrent Rectal Cancer

14

Tarik Sammour and John M. Skibber

Introduction

Locally recurrent rectal cancer is defined as recurrence, progression, or development of new sites of rectal tumor within the pelvis after previous resection for rectal cancer [1]. The rate of local recurrence after primary treatment of rectal cancer with curative intent varies between 2.4 and 10% in modern series [2] and is dependent on a multitude of variables including patient-specific factors, tumor biology, and surgical and oncology practices [3, 4]. Multiple classification systems for local recurrence have been proposed [5–7]. The simplest and most useful system involves categorization into four anatomical groups: central (involving the rectum and/or urogenital organs), posterior (sacral), lateral (pelvic sidewall), or composite (combination of the above) [8]. Of patients who develop a recurrence, 70% will do so within 2 years of surgery and 85% within 3 years [9], although recurrence after more than 6 years has been reported [10].

The management of locally recurrent rectal cancer is complex as this particular subset of colorectal cancer patients is heterogeneous in their presentation, and the standard of care in their management is rapidly evolving. In addition, the available literature mainly consists of prospective and retrospective case series and consensus statements, with a heavy focus on survival outcomes and anatomical aspects of surgical resection [11]. Despite this, it remains of paramount importance to tailor management to individual patients, with the primary aim of achieving acceptable patient-centered outcomes such as quality of life, pain control, freedom from disability, and a return to premorbid functional status [12]. Locally recurrent rectal cancer also represents a clinical situation where the balance between achieving long-term survival versus major complications and treatment failure approaches equipoise. Therefore, good patient selection is vital in order to minimize the risk of overtreatment in cases which will not benefit, and management is best undertaken in a high-volume specialist center with multidisciplinary expertise to prevent and minimize the risk of complications which occurs at a high rate (REF).

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Patient Assessment

History

A full account of the patient's medical, surgical, and social history is obtained. Previous medical documentation is very useful to supplement the patient account. Of specific importance in the setting of locally recurrent rectal cancer are the following points:

- Does the patient have any of the following symptoms: pain, weight loss, leg swelling, neurology, obstructive symptoms, urinary symptoms, or gynecological symptoms in females? Importantly, symptoms present at the time of diagnosis may have implications for prognosis, extent of resection required, need for consultants, and the potential for an R0 resection [12].
- When and where was the primary surgery undertaken? Did the patient have any intraoperative or postoperative complications that could affect the resection or reconstruction?
- What neo-adjuvant and adjuvant therapy has the patient had? Details of doses, duration, and patient tolerance are required to enable planning of future chemotherapy and radiotherapy regimens.
- Review of initial histology, looking specifically at primary staging, nodal status, whether there was a positive margin or tumor perforation, and quality of total mesorectal excision (TME) if available. In addition, previous details of immunohistochemistry, microsatellite instability, and genetic testing are helpful. These details may affect considerations about the extent of surgical resection.
- What postoperative surveillance has the patient undergone so far? Details of carcinoembryonic antigen (CEA) levels, colonoscopy, and cross-sectional imaging are useful to indicate rate of progression.
- Review of systems to enable determination of medical fitness for further treatment. Lack of mobility or independence indicating frailty can impact the decision to proceed with extensive surgical procedures.
- Social history including functional status, cognitive ability, quality of life, and patient preferences is required to facilitate shared decision-making discussions.

Examination

While physical examination may not aid in diagnosis, it can often help to establish the true extent of the recurrence and help plan the extent of resection. Nevertheless, a digital rectal exam may still afford the surgeon a sense of fixity and a measurement of height from the anal verge if the recurrence is intraluminal. In female patients, a per-vaginal examination can also help to determine vaginal or urethral involvement. Rectal and vaginal examination may have to be performed in the operating room under general anesthetic if discomfort does not permit adequate assessment in the outpatient setting, and this may also allow preemptive cystoscopy and ureteric stenting if required. Palpation of nodal basins is not often useful, but assessment of the abdominal wall, looking specifically for incisional hernia, previous stoma sites, and the state of the rectus abdominis muscle on both sides, is important if there is likely to be a need for soft tissue reconstruction or stoma placement. For the same reason, the state of the perineum should also be assessed.

Imaging

The purpose of cross-sectional imaging is to establish two important facts regarding the anatomy of the recurrence which will determine whether curative treatment is an option: (1) whether there is distant metastatic disease or (2) local resectability (predicted R0 resection) [1].

Up to 50% of patients with local recurrence will have metastatic disease at the time of diagnosis [13]. In many cases this may preclude resection of a local recurrence. Multiphase contrast-enhanced computed tomography (CT) of the chest, abdomen, and pelvis is commonly used for the detection of metastatic tumor deposits [1]. In some institutions, including our own,

fluorodeoxyglucose [^{18}F] positron emission tomography with computed tomography (PET/CT) is utilized as part of the initial assessment as there is some evidence that it alters management in a subset of patients (up to 14%) with small deposits of distant metastatic disease that would otherwise be undetected by CT alone (Fig. 14.1) [10, 14–16]. However, the evidence for routine use of PET/CT remains limited and is extrapolated from other settings [17, 18]. Further research into the added value and cost-effectiveness is required [1, 19].

High-resolution magnetic resonance imaging (MRI) with or without diffusion-weighted imaging (DWI) is the current standard of care for evaluation of pelvic resectability [1, 20, 21]. Good-quality T2-weighted images are essential (Fig. 14.1) [22], preferably accompanied by standardized reporting on involvement of any residual mesorectum, other pelvic viscera, pelvic

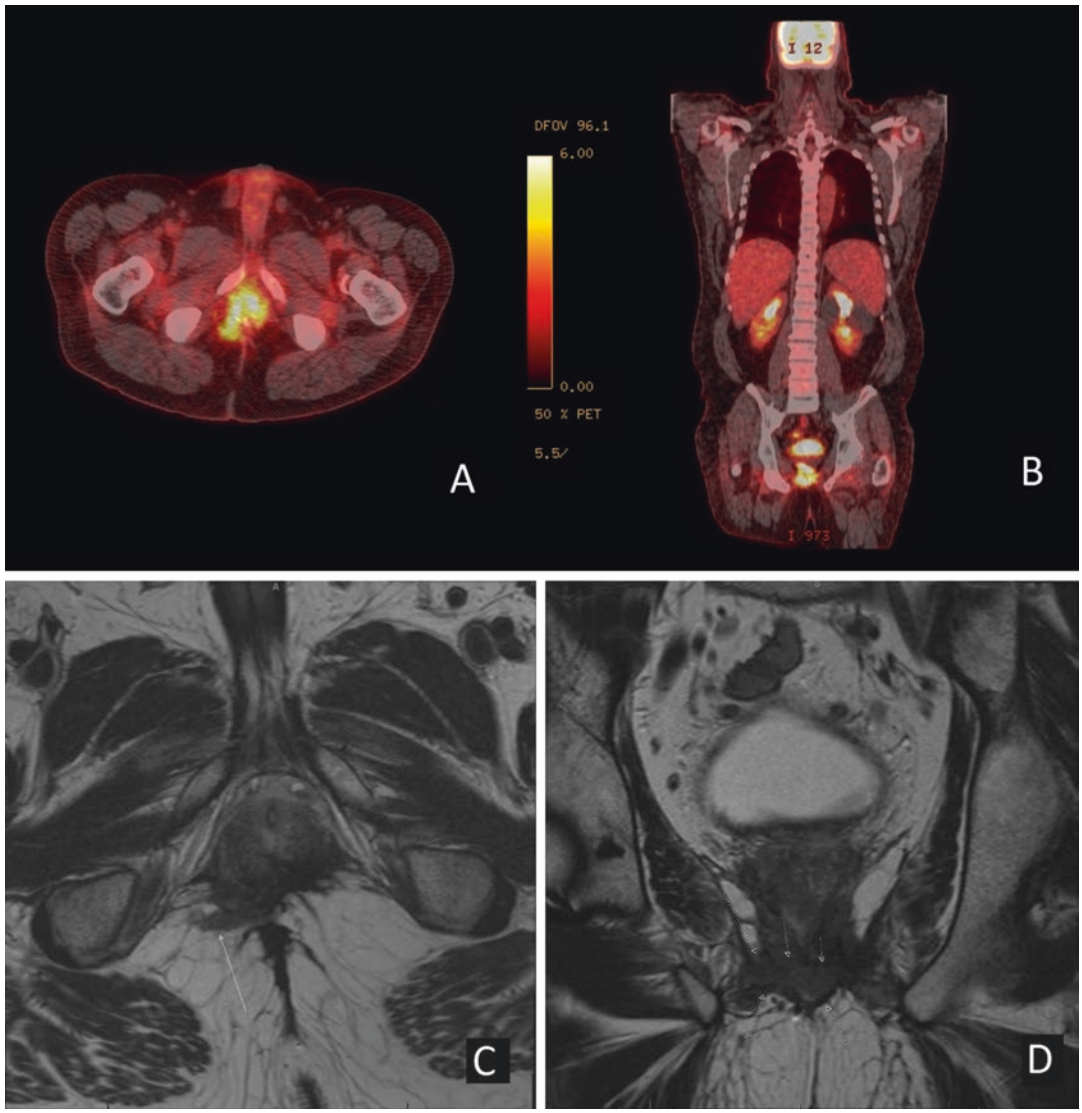

Fig. 14.1 (**a**) PET/CT scan axial, (**b**) PET/CT scan coronal, (**c**) MRI axial, and (**d**) MRI coronal. Note these images are all taken from the same patient at presentation, demonstrating the utility of PET in highlighting areas of active disease

bones, nerve roots, and major vascular structures [23, 24]. While some assessment can be made of residual superior rectal and pelvic sidewall nodal disease [25], it is worth noting that nodal size and appearance in the pelvis do not necessarily correlate directly with tumor positivity, especially in the context of previous surgery [26]. Dedicated bone nuclear medicine scans and brain imaging are required only if the patient has specific symptoms that warrant this and are not requested routinely [1].

Confirmation

Confirmation of rectal cancer recurrence is obtained by formal tissue biopsy and histological assessment. For intraluminal recurrences, the biopsy can be achieved using rigid or flexible endoscopy. For extra-luminal recurrence, radiologically guided percutaneous biopsy is performed. According to the Beyond TME Collaborative Consensus Statement, where tissue biopsy is not possible or is negative, serial enlargement of a PET-CT enhancing lesion or a serially rising CEA level can be accepted as sufficient proof of recurrence, but only after multidisciplinary team consensus [1]. At our institution, however, histological confirmation is mandatory prior to undertaking major extirpative surgery, radiotherapy, or chemotherapy treatment in this setting [27]. It is rare that biopsy of recurrence cannot be obtained and confirmation will prevent error.

Multidisciplinary Considerations

After the above assessment and investigations are performed, the patient's case is reviewed at a multidisciplinary tumor board meeting, and the options for management are discussed (Fig. 14.2). Treatment options can be broadly categorized as: palliation or treatment with curative intent.

Palliation may involve proximal fecal diversion if soiling or obstruction is an issue, but usually reserved for patients with limited distant metastatic disease load. A defunctioning loop sigmoid colostomy via a minimally invasive surgical approach is ideal if this is technically achievable. Palliative pelvic exenteration has been performed, but this should only rarely be considered in highly selected patients due to the morbidity of the surgery and no demonstrable benefit in terms of pain control or survival [12, 28, 29]. Chemotherapy and/or radiotherapy with palliative intent may also be considered. Involvement of the pain management team and dedicated palliative care services is important at an early stage, once the decision for palliation has been made. Recently, radiofrequency ablation under CT guidance has been described and appears to induce tumor necrosis and reduce pelvic pain [30].

Treatment with curative intent mandates surgical resection of all known disease, which can range from repeat total mesorectal excision to complete pelvic exenteration with multi-visceral resection, sacrectomy, and reconstruction. If the patient has not had pelvic radiotherapy previously, then neo-adjuvant long course chemoradiotherapy is given (50·4 Gy in 28 fractions and concurrent 5-Fluorouracil (5FU)/capecitabine). In situations where previous radiotherapy had been given, then hyperfractionated radiation therapy is recommended to limit late toxicity (39 Gy in 26 fractions of 1·5 Gy twice daily, with concurrent capecitabine on days of radiotherapy) [31, 32]. These regimens may improve long-term disease-free and overall survival outcomes after surgery, although tumor response rates are lower than in the primary rectal cancer neo-adjuvant setting [27, 33]. Restaging with repeat pelvic imaging should be performed 6–8 weeks after neo-adjuvant treatment, preferably with repeat DWI-MRI and PET-CT [17, 18]. The optimal timing of surgery is unclear, but 6–8 weeks after neo-adjuvant treatment is generally recommended based on data from primary rectal cancer treatment [1]. After surgery, all patients are offered adjuvant treatment with 5FU-based chemotherapy or combined treatment with 5FU, oxaliplatin, and leucovorin (FOLFOX).

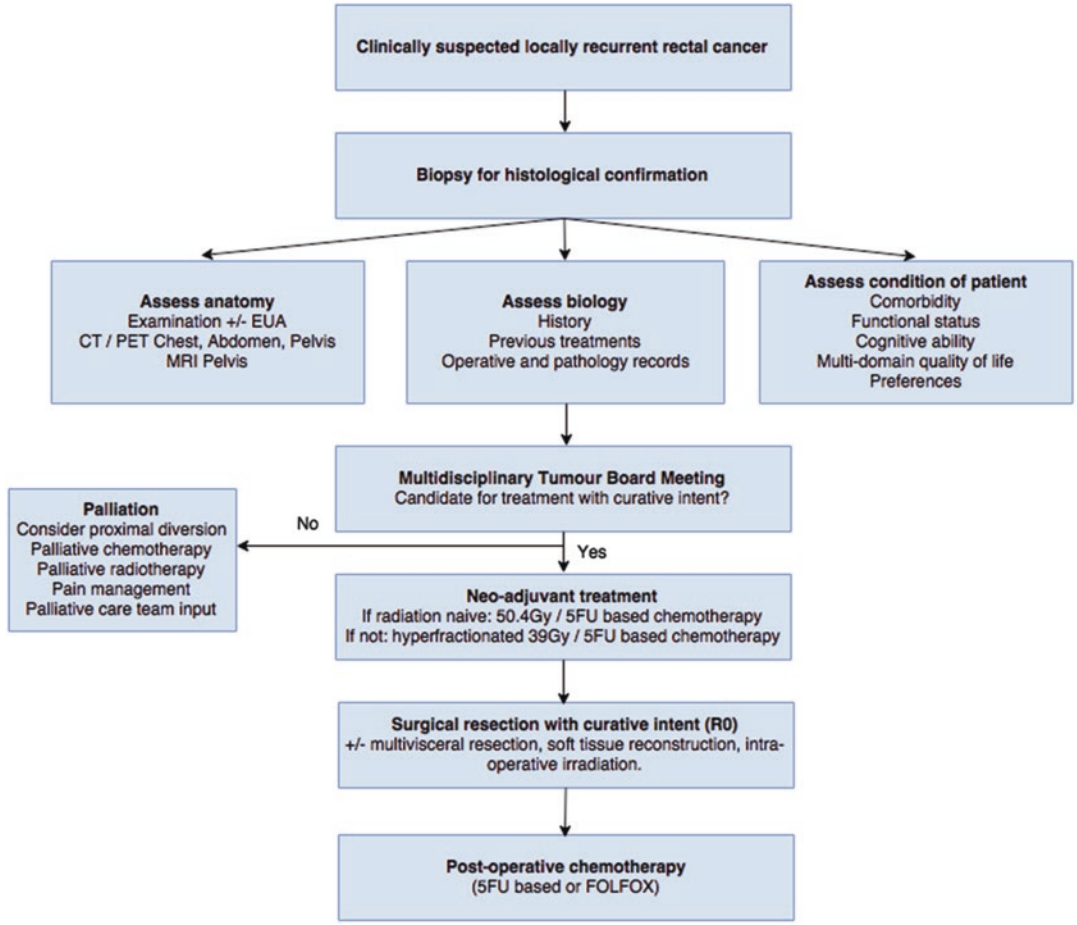

Fig. 14.2 Management algorithm for recurrent rectal cancer at the University of Texas MD Anderson Cancer Center (Adapted with permission from You et al.) [27]. *EUA* examination under anesthesia, *Gy* gray, *5FU* 5-fluorouracil, FOLFOX 5FU, oxaliplatin, and leucovorin

Patient Selection for Surgery

"The conundrum for exenteration surgery in the past two decades has been: what can be done safely? Presently, the conundrum presently is not what *can* be done but what *should* be done?" [34] Patients with locally recurrent rectal cancer should only be offered surgery if all of the following criteria are fulfilled:

1. Complete R0 resection is technically possible based on imaging.
   a. Absolute technical contraindications to resection are unresectable extra-pelvic disease, para-aortic node involvement, bilateral sciatic nerve involvement, circumferential bone involvement, and lumbar spine involvement (above L5/S1) [1].
   b. Relative contraindications are tumor extension through the sciatic notch, encasement of external iliac vessels, and high sacral involvement (sacrectomy above S2/S3 junction is controversial but can be performed in selected centers) [35–40]. Multifocal disease.
2. There is no unresectable distant metastatic disease.
3. The patient is medically fit to undergo the procedure.

4. The patient is cognitively able to engage in a shared decision-making discussion and give reasonable informed consent [23].

Preparation for Surgery

Informed Consent

After multidisciplinary tumor board recommendations have been finalized, a face-to-face meeting between the primary colorectal surgeon and the patient accompanied by a support person (such as a close family member) is scheduled, and formal informed consent is obtained. There may be multiple options offered to the patient, and each of these needs to be discussed fully outlining the benefits and risks. The consent discussion should also include details of planned (and potentially unplanned) stomas and the possibility of the surgeon finding unexpected metastatic disease intraoperatively which is unresectable and would lead to the procedure being abandoned. As alluded to previously, a shared decision-making process on the part of the attending surgeon and the patient is required and should be clearly documented.

It is usual for the patient to also discuss their management with a medical oncologist, a radiation oncologist, and any other surgical services that are expected to be involved during the operation. Involvement of a cancer nurse specialist or care coordinator, an ostomy nurse, and relevant allied health staff such as cultural support workers and interpreters is prudent.

Medical Optimization

Given the magnitude of the surgery to be undertaken, the management of all relevant medical comorbidities should be optimized, with the help of perioperative care physicians and the involvement of anesthetists, preferably with experience in this type of surgery. In patients who require it based on screening assessments, preoperative nutritional support and pre-habilitation programs should be undertaken [41]. There is a high risk of intraoperative hemorrhage, and any anticoagulants the patient is on preoperatively should be managed accordingly.

Coordination of Multidisciplinary Team

Depending on the anatomy of the surgery to be performed, a multidisciplinary team of surgeons may be required. Anticipated involvement based on preoperative assessment should result in the patient being seen and consented by the relevant service ahead of time in the outpatient setting. This may result in requests for further imaging required for planning such as a CT angiogram to look at major vascular structures and the inferior epigastric vessels for use in future tissue flap reconstructions or renal excretion scans. Unanticipated need for other surgical services is also possible, but should be avoided by optimal planning, with relevant teams placed on standby ahead of time. The frequent involvement of the urinary bladder and distal ureters necessitates involvement of a dedicated urology service, the members of which will often perform a cystoscopy and place bilateral ureteric stents at the beginning of surgery if this has not been done already. Involvement of the iliac arteries or veins may necessitate reconstruction by a vascular surgeon and sacral, iliac bone, or pubic bone involvement resection and reconstruction by a neurologic or orthopedic surgeon. Finally, abdominal wall and perineal defects may require flap and mesh closure by plastic surgeons. The patient should be marked by an experienced stoma nurse before he or she changes into a hospital gown to facilitate assessment of stoma location in standing, supine, and sitting positions and when the patient is in his or her usual clothes. The patient should be marked bilaterally, and if they already have a stoma on one side, the other side should be marked. Given the lengthy nature of exenteration surgery, it is important that delays are minimized by effective coordination. All consultants should communicate their expectations, roles, and plans ahead of the day of operation.

Operating Room Setup

Some important elements of the operating room setup are a radiolucent operating table in the correct orientation with the ability to perform angiography; vascular loops and clamps; ureteric stents of different sizes; a selection of prosthetic, biological, and composite mesh of different sizes; and intraoperative radiotherapy equipment. Ideally, all of these tools should be made available for every case as their use may not have been anticipated prior to surgery being undertaken. Equipment requirements should be communicated to the nursing staff ahead of the procedure. Patient safety requires a high degree of teamwork among the professionals undertaking these procedures. Preoperative antibiotics and pharmacologic DVT prophylaxis are used. Blood product availability is confirmed. The nature of procedure and potential concerns are reviewed prior to the procedure.

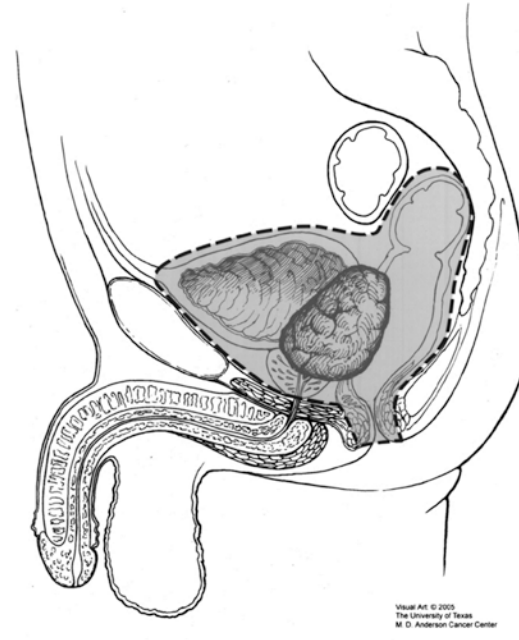

Fig. 14.3 Total pelvic exenteration (Reproduced with permission from Pawlik et al. [42])

Surgery

The primary goal of surgery is to achieve an R0 resection, with preservation of function and soft tissue coverage. Total pelvic exenteration is defined as the removal of the rectum, distal colon, genitourinary viscera including lower ureters, internal reproductive organs, draining lymph nodes, and pelvic peritoneum (Fig. 14.3). A sacrectomy may also be included. Anterior pelvic exenteration in the context of rectal cancer surgery is defined as the removal of the upper rectum, reproductive organs, and bladder, but sparing the lower rectum. Posterior pelvic exenteration is the removal of the reproductive organs and rectum, sparing the bladder [43]. Clearly the exact surgery undertaken will depend on the current anatomy and what has been done previously, but the following will present a general overview of salient points.

Patient Position

The patient is usually placed in modified Lloyd-Davies position, with provision for undertaking part of the procedure via a perineal or posterior approach if necessary. Calf compression devices and precautions against pressure areas are routinely used. A folded towel or roll may be placed under the sacrum to improve access to the perineum. If the patient already has a colostomy, this can be sutured, covered with a swab and plastic adhesive dressing so that it is excluded from the wound in the early stages of the procedure. Draping is performed taking into account not only the needs of the primary surgeon but also the optimal exposure and prepping for the other members of the multidisciplinary surgical team. For example, if vein harvest is anticipated for an interposition graft or patch, then the patient's groin and thigh are prepped. Both thighs maybe prepped circumferentially to allow a lateral thigh or gracilis flap.

Technical Aspects

The first step is digital rectal examination and bimanual examination in women to reestablish tumor height, position, and fixity followed by an exploratory laparotomy. All four quadrants of the abdomen, including the liver, the diaphragm, and

the small and large bowel and their mesentery, are visually inspected and palpated. A finding of unexpected metastatic disease which is unresectable should be confirmed with intraoperative frozen section, and the procedure should be abandoned and saved for palliative defunctioning stoma if deemed beneficial by the operating surgeon [44].

In the absence of unresectable metastatic disease, the next step is a complete adhesiolysis, noting that any small bowel adhesions in the region of the recurrent tumor are usually taken en bloc with the specimen. Next, inspection and palpation of the area of local recurrence is performed. Often local resectability is difficult to confirm at this stage, and the preoperative imaging is relied upon to determine this. It is important, however, to avoid making any irreversible decisions or operative maneuvers early in the procedure and before progress is made on mobilizing the tumor. Instead, identification of any "normal" or previously "untouched" planes and dissecting within these is usually the best start. Dissection then continues from easier and softer tissues toward more difficult and rigid areas, with wider margins taken as necessary. Identification of the ureters (which are often more medial in reoperative surgery than usual) and a decision regarding whether one or both can be preserved can often be the defining step in this operation. Ureteric catheters are a useful aid to assist in palpation and identification of the ureters which, if free, can be slung with a vascular loop and preserved. The site of previous inferior mesenteric artery transection is located, and if this was not taken high at the original surgery, then re-resection of is warranted and may provide a lead into the correct posterior plane if this is not invaded directly. Dissection is then extended distally as far as required posteriorly in the total mesorectal excision plane, although often there is little remaining mesorectum, and dissection therefore proceeds in the plane deep to the endopelvic fascia.

Preservation of the integrity of the anal sphincter complex is considered whenever possible based on adequacy of margins and anticipated acceptable functional outcomes. Anterior resection with primary colorectal or colo-anal anastomosis may be performed for high central recurrences where adequate distal margins can be attained; however, it should be noted that functional outcomes may be suboptimal in this setting. In areas of clear tumor invasion, wider excision will be necessary, and abdominoperineal resection is performed with end colostomy. Options for ureteric reconstruction include ureteroureterostomy with or without psoas hitch, ureteric reimplantation, or Boari flap repair. If the situation is not directly reconstructible, then the urologist may proceed with a radical cystectomy ± prostatectomy and subsequent ileal or colonic conduit reconstruction after the specimen is removed. [27].

In cases with extensive lateral pelvic sidewall involvement, iliac vessel identification and dissection are required. If the common, external veins are invaded by tumor, then en bloc resection and reconstruction by a vascular surgeon is required to achieve R0 resection [45]. The detailed technique of lateral pelvic compartment excision has been described in the literature [46]. First, the internal iliac artery and its branches are ligated, ideally distal to the superior gluteal artery to minimize buttock claudication and preserve supply to any potential gluteal flaps. Lymph node dissection is performed including nodal tissue overlying the aortoiliac bifurcation down to the origin of the internal iliac. Proximal and distal control of the internal iliac vein is achieved, and smaller branches are divided prior to division of the main trunk. The lateral and middle sacral vein branches are also ligated and divided, and dissection is continued along the pelvic sidewall bilaterally down to the pelvic floor, with the dissection completed from below if required. Extended lateral pelvic sidewall excision which includes resection of the sciatic nerve may also be necessary [47].

En bloc sacrectomy can also be performed if necessary with neurologic or orthopedic surgeon involvement. Resections above S3 require conversion to the prone position, whereas below S3 a combined abdominal/perineal approach can be used [48]. All gluteus muscular attachments to the posterior aspect of the coccyx and sacrum are

dissected free up to a point above the planned site of sacral transection. The sacrococcygeal ligaments are divided off the sacrum, and the anterior sacrum is scored with diathermy at the level of planned transection. Division is possible with the patients still in the supine position using two osteotomes, one placed posterior to the sacrum to protect the skin and the other anteriorly for transection. For sacrectomy above the level of S3, temporary or permanent closure of the abdomen is required prior to turning the patient prone. A posterior midline incision is made from L5 down to the perineal scar or anus. Again the gluteus muscles are dissected away from the sacral attachments, and the sacrospinous and sacrotuberous ligaments are divided, taking care not to injure the sciatic and pudendal nerves which are seen at this point. If the piriformis is involved, this can be excised en bloc before the sacrum is transected at the appropriate level using osteotomes.

If possible, an omental pedicle flap based on the right gastroepiploic artery is fashioned and used to fill the dead space in the pelvis [49]. At least one intra-abdominal drain is often used and placed in the pelvis as well.

Intraoperative Radiotherapy (IORT)

Any margins which are not obviously macroscopically clear are confirmed with intraoperative frozen section. Intraoperative radiotherapy (IORT) is administered selectively with consultation with the radiation oncologist if any resection margins are microscopically positive (R1) based on intraoperative frozen pathology assessment or if the margins were negative but 2 mm or less [50]. At our center, IORT is administered using high-dose rate iridium-192 brachytherapy using a Harrison-Anderson-Mick applicator, with a dose of 10–15 Gy at 1 cm from the radiation source [27]. Level one evidence to support the use of IORT is not yet available [51], but comparative studies have demonstrated improved local control, disease-free survival, and overall survival with no increase in total complications [52–56].

Soft Tissue Reconstruction

There are two wounds that may require reconstruction: the anterior abdominal wall and the perineum, with the latter usually requiring greater consideration. The size of the defect depends on the extent of the resection (determines lateral dimensions) and the patient's body habitus (determines depth). The complexity of the reconstruction can be compounded by the presence of stomas, ileal conduits, previous incisions and hernias, as well as vascular supply to tissue flaps or lack thereof. Close consultation with experience plastic surgical services is therefore required at all stages.

Flap closure of perineal defects reduces wound complications compared with attempts at primary closure, particularly after radiation treatment [57, 58]. It is possible to use absorbable or biological mesh to reconstruct the pelvic floor, but this technique may still require additional soft tissue coverage, as primary skin closure is not always possible without tension [59]. Selection of which flap to use is based on the size of the defect, the availability of tissue, the characteristics of the patient, and the local expertise available. The most common technique utilized for perineal reconstruction is the vertical rectus abdominis myocutaneous (VRAM) flap based on the inferior epigastric artery, which is a robust flap which usually affords significant tissue bulk [60]. Harvesting of this flap leaves a defect in the anterior abdominal wall which usually requires repair with synthetic mesh or component separation techniques [61]. Other options include gracilis muscle flaps [62], inferior gluteal artery myocutaneous (IGAM) flap [63], gluteal fold flaps [64], anterolateral thigh flaps [65], and full-thickness local advancement flaps [66]. In female patients, vaginal reconstruction can be attempted using modifications of the above flaps, or including local rotation flaps such a modified Singapore flap [67].

Postoperative Care

All patients are managed in a high dependency unit setting immediately after surgery and transitioned to standard ward care as possible.

Principles of enhanced recovery after surgery are applied as closely as possible while taking into account the magnitude of surgery undertaken and the unique considerations that go along with this [68]. Median day stay after pelvic exenteration surgery for locally recurrent rectal cancer is 14.5 days [3]. It is critical to monitor for bleeding in the immediate postoperative period followed by the issues of poor wound healing or infection. Urinary tract complications require prompt management to avoid long-term renal deterioration.

Outcomes

Short Term

The complication rate after surgery for locally recurrent rectal cancer is very high, with a meta-analysis published in 2012 documenting an overall major complication rate of 51% [3]. Common complications included wound infection; intra-abdominal and pelvic collections; urinary tract infections; intestinal obstruction; fistulae; incisional, perineal, and para-stomal hernias; urological complications; renal failure; venous thrombosis; pulmonary embolus; and pressure ulcers [69]. In the same study, the median 30-day mortality rate was 4% [3]. When sacrectomy is performed, the morbidity rate increases corresponding to the level of sacrectomy [43].

Long-Term Survival

The median rate of R0 resection in the recent published literature is just over 60% (see Table 14.1) [3, 70]. Five-year overall and disease-free survival after aggressive therapy with curative intent are currently 30% and 36%, respectively, but these have been improving with time due to advances and standardization of adjuvant and neo-adjuvant treatment and better patient selection [27, 74]. Patients who previously received radiotherapy for their primary rectal cancer treatment have worse oncologic outcomes than those who were radiotherapy naive [75], as do patients with multiple sites of fixation in the pelvis [76], but the most important prognostic factor is the completeness of resection [3]. Patients with an R1 resection have an overall 5-year survival of approximately 20%, whereas R2 resection offers no survival benefit compared to palliative treatment [3]. In terms of median survival times, patients with an R0 resection survive on average 38 months longer than those undergoing R1 resection and 53.0 months longer than those undergoing R2 resection (median survival time approximately 1 year) [3].

Another determinant of outcome is whether re-resection is possible after a second recurrence. In approximately 15% of patients who recur a second time, the recurrence is locoregional only [27, 70], and recent data suggests that re-exenteration has almost identical results as the initial exenteration, with high R0 resection rates (up to 60%) and almost equivalent 5-year survival [77–79].

Quality of Life

Quality of life has been defined as the patient's appraisal of, and satisfaction with, their current level of functioning as compared to what they perceive to be possible or ideal. Several aspects of quality of life are impaired for a variable time after treatment of recurrence of rectal cancer [80], but there is evidence that patients that undergo resection experience an improvement in quality of life scores compared to those who do not undergo surgery [81, 82]. Patients can in fact achieve quality of life comparable to nonrecurrent cancer survivors, although full recovery may take up to 3 years [83]. Thus far, however, patients have only been evaluated using generic quality of life tools, which may not necessarily be applicable to this unique patient group [84]. The development of a locally recurrent rectal cancer-specific patient-reported outcome measure is currently underway to address this [85, 86].

As expected, the impact on urogenital function is significant. At a median of 14 months after surgery, a 48% rate of new voiding dysfunction

Table 14.1 Summary of the most recent reported data on long-term survival after planned curative surgery for recurrent rectal cancer

Author	Demographics	Year	*n*	*R*0 (%)	5-year OS (%)	5-year DFS (%)
Harris [70]	Five centers (UK, Australia, New Zealand)	2015	533	59	28	37
You [27]	Single center (USA)	2016	229	80	43	47
Alberda [71]	Single center (Netherlands)	2015	165	55	32	nr
Neilsen [72]	Single center (Denmark)	2015	115	61	30	nr
Selvaggi [16]	Three centers (Italy)	2015	100	61	28	35
Denost [73]	Multiple sites (France)	2015	72	60	29	12
Total/median			1214	61	30	36

n number of planned curative resections, *5-year OS* 5-year overall survival for all patients (*R*0, *R*1, *R*2), *5-year DFS* 5-year disease-free survival for all patients (*R*0, *R*1, *R*2), *nr* not reported

has been reported. In the same subset of patients, the preoperative ability to achieve orgasm disappeared in 57% of patients [87].

Regardless of whether patients are treated with palliative or curative intent, a substantial proportion has significant pain that is directly attributable to the neoplastic process or to the surgery itself [28]. This symptom alone can become a major determinant of quality of life and should be aggressively managed [12].

Surveillance and Follow-Up

There is no data available on the utility of active surveillance on outpatient follow-up. However, given the amount of time already invested by these patients and the managing healthcare team, as well as the possibility of re-exenteration in a proportion of patients with local failure, most authors advocate intensive and extended follow-up for patients treated with curative intent [88]. This involves three monthly clinical examination and CEA levels and annual PET-CT imaging.

Future Research

The incremental improvement in outcomes after treatment of recurrent rectal cancer is likely to continue with several potential advances in care on the horizon. Standardization of management of rectal cancer in general is expanding due to concerted efforts of groups like the OSTRiCh Consortium [89] and the Beyond TME Collaborative [1]. There is recognition that improving quality in primary surgery and higher rates of neo-adjuvant treatment should lead to a reduced incidence of local recurrence. The development of risk-adjusted nomograms will facilitate inter-institution comparisons and assist in quality control efforts [90]. Similar nomograms could also facilitate patient selection for more intensive adjuvant treatment and postoperative surveillance, improving our ability to identify recurrences early [2].

Our understanding of tumor biology is rapidly improving, and it is conceivable that in the near future, patient selection for exenterative surgery, as well as choice of and sequence of adjuvant treatment, will be determined not just by disease anatomy, but by expected tumor behavior based on genetic markers [91]. The ability to predict propensity for distant metastatic recurrence more accurately will enable better patient selection and allow avoidance of futile surgery. Finally, induction chemotherapy prior to surgery and the addition of novel therapeutic agents in the adjuvant or neo-adjuvant setting may improve overall disease-free survival outcomes by improving systemic disease control, downstaging the pelvic lesion [92–95], and perhaps even ameliorating the need for surgery entirely in a subgroup of patients with complete response [96].

Summary

The management of locally recurrent rectal cancer is complex, and the balance between achieving acceptable outcomes versus major complications and treatment failure approaches equipoise. It remains of paramount importance to select patients carefully and tailor management, with the primary aim of achieving acceptable patient-centered outcomes such as quality of life and pain control. Management is best undertaken in a high-volume specialist center with multidisciplinary expertise. Recent improvements in survival outcomes are encouraging.

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Reconstruction of the Pelvis and Perineum

15

Nicholas Calotta and Justin M. Sacks

Keys to Preventing Complications

1. Communication is essential. Surgical oncology, medical and radiation oncology, and plastic and reconstructive surgery will be working closely to care for the pelvic oncology patient. Effective communication empowers teams to carry out optimal preoperative planning and postoperative care. Moreover, open discussion permits full disclosure of potential morbidity to the patient and the family.
2. Identifying structures with an absolute need for vascularized tissue coverage is of chief importance. Specifically, the pelvis features abundant dead space and numerous hollow viscous organs that are well suited for coverage with local soft tissue flaps.
3. Hematoma and seroma formation are common complications in perineal reconstruction, especially when attempting primary closure of large perineal wounds. The use of vascularized tissue and closed suction drains minimizes dead space, effectively reducing rates of wound dehiscence, seroma, and infection.
4. Sharp debridement of devitalized adipose and fascia, as well as scar tissue, is necessary for preventing infection. These tissues are a nidus for infection.
5. Significant attention should be paid to the postoperative care of the wound. Reducing the pressure load on the wound combined with early, consistent ambulation helps reduce the risk of ischemic pressure necrosis of the reconstruction.

Keys to Managing Complications

1. In the early postoperative period, venous congestion may lead to flap ischemia. A surgical team must evaluate the wound in the operating room for reversible etiologies to prevent total or subtotal flap loss.
2. Prompt recognition of infectious signs and symptoms related to the reconstructive site should lead to radiographic assessment. The presence of hematoma, seroma, or abscess must be treated appropriately and timely.
3. Perioperative nutrition is important. Enteral or parenteral nutrition with protein supplementation aids in wound healing.
4. Large reconstructions are prone to small areas of dehiscence. Conservative management with dressing changes and negative pressure wound therapy is appropriate.
5. Extensive wound dehiscence should lead to operative evaluation. Consideration of the integrity of the flap and the need for reoperation are paramount.

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Introduction

Malignancy of the anorectum is a common indication for perineal resection. Various approaches can be employed, including the traditional abdominoperineal resection (APR), intersphincteric resection, pelvic exenteration, and low anterior resection (LAR). Contemporary surgical care prioritizes sphincter preserving surgery for rectal cancer; despite this, up to 25% of surgical candidates may be treated with APR [1].

Reconstruction of defects of the pelvis and perineum is a challenge (Fig. 15.1). In patients who necessitate reconstruction due to malignancy, there is often a history of neoadjuvant chemotherapy and/or radiotherapy. Though important for downstaging disease, these treatments will negatively affect future wound healing capacity. Furthermore, significant dead space volume, close proximity of local organs, increased bacterial susceptibility, and extended periods of direct wound pressure (i.e., sitting, lying in bed) all serve to complicate surgical efforts. Consequently, wound complications can be common, with rates reported as high as 65% [2].

Primary closure is the ideal choice for perineal defects. However, in many cases, this is not possible due to the size of the defect or other constraining factors, leading to primary wound closure complication rates of nearly 65% [2]. Hematoma, seroma, fistula formation, nonhealing wound, and abdominal/perineal hernia are other frequent issues. These can lengthen hospital stays, cause significant morbidity, decrease mobility, and delay adjuvant therapy.

Because of potential issues with primary wound closure, many reconstructive surgeons rely on pedicled, vascularized soft tissue flaps for coverage of extensive perineal defects [3]. Vascularized soft tissue provides the nourishing effects of consistent blood flow such as increased oxygenation, delivery of growth factors, and higher cytokine concentrations. These flaps further assist wound healing by obliterating dead space and decreasing incisional tension.

In this chapter, we will provide a comprehensive overview of the reconstructive options for perineal defects (Fig. 15.2). With this information, the reader will understand the principles for the multidisciplinary management of post-resective

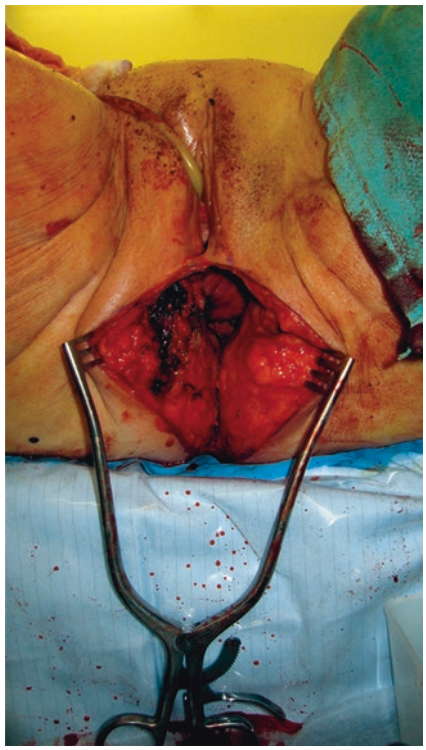

Fig. 15.1 Perineal defect exposing pelvic organs and creating significant dead space

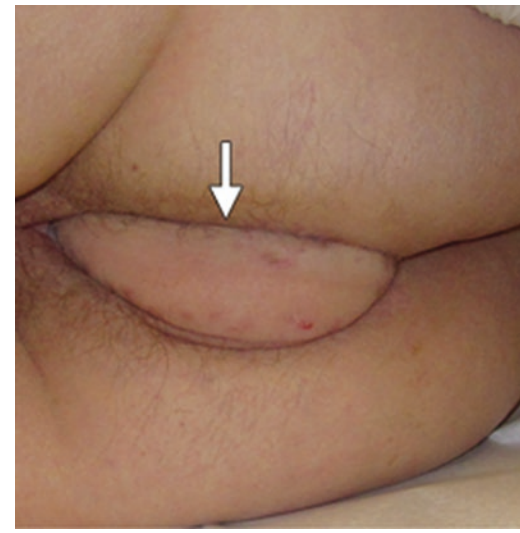

Fig. 15.2 Perineal reconstruction, with arrow indicating healing soft tissue reconstruction

perineal wound defects and prevention of associated complications, facilitating maximized patient outcomes despite the challenging nature of these cases.

Preoperative Assessment

The need for reconstruction must be balanced with the physiological state of the patient. Overall determination of the patient's health is key to planning the operative repair of a perineal defect; a patient too sick for surgery will not benefit from even the best reconstructive effort. For those patients healthy enough for surgery, accurate assessment of the surgical site should be performed, perhaps under anesthesia if necessary, as in the case of prior failed primary closure. The long term prognosis of the patient is also a contributor to this equation. Reconstruction will have tremendous positive impacts on quality of life so it may be considered in palliative cases too.

Medical Comorbidities

Preoperative risk stratification by pre-existing health conditions or environmental factors (e.g., smoking) must be undertaken to understand patient-specific relative risks for wound complications. One major element that must be addressed is smoking. The effects of smoking on the microcirculation can severely compromise soft tissue healing, and the patient should cease smoking at least 4 weeks before surgery [4]. Nutrition is another modifiable factor that must be optimized prior to undertaking major reconstructive surgery [5, 6]. Ideally, pre- and postoperative enteral feeding with supplemented protein will be ordered.

Radiation Therapy

Many rectal cancer patients will be treated with pelvic radiation prior to tumor resection and reconstruction. The exposure of the perineum to radiation can be problematic to the reconstructive effort. Radiation therapy injures healthy tissue which will not be resected, especially in the microcirculation of the defect and the surrounding areas. This effect produces decreased perfusion and diminished wound healing capacity [3]. Knowledge of the timing, dosage, and location of prior or planned radiation therapy is crucial to the reconstructive surgeon as he or she plans for debridement of irradiated tissue or recruitment of tissue outside the irradiated field for the reconstruction.

Chemotherapy

Neoadjuvant chemotherapy is often necessary in patients undergoing perineal reconstruction for oncological conditions. Similarly to radiation therapy, this treatment mainstay can compromise wound healing. Close, frank communication with the medical oncology team facilitates an accurate determination of if and when neoadjuvant chemotherapy is needed and how to address potential wound complications.

Imaging

Some cases may require imaging with computed tomography (CT) and/or magnetic resonance imaging (MRI). Radiographic studies are primarily used to understand the integrity of surrounding tissue and local vascular anatomy. Reconstructive surgeons can rely on these images to formulate more precise preoperative plans.

Timing of Reconstruction

Reconstruction of perineal defects should be done immediately, if possible. Rates of wound complications have been shown to be more favorable following immediate reconstruction in other anatomical locations [7]. The feasibility of immediate reconstruction is most frequently dictated by the status of the tumor and surgical excision margins. Other factors, such as advanced age, multiple comorbidities, or further need for adjuvant radiotherapy, will also influence the practicality

of immediate reconstruction. Some instances will require delayed reconstruction, such as in cases of patient instability or extensive soft tissue defects. For these scenarios, negative pressure closure devices are the preferred intermediate treatment.

Reconstructive Surgical Tenets

The most fundamental goal of the reconstructive surgeon is to replace missing tissue with the most similar tissue possible—replace "like with like," as the saying goes. Reconstructive efforts proceed from simple to complex schemes, as dictated by the nature of the wound. The functional aim of any reconstruction is to fill dead space and provide a tension-free closure.

Local flaps are a desirable option for surgeons to recapitulate form and function with similar tissue. Axial pattern flaps are the backbone of perineal reconstructions and are supplied by named blood vessels. They may be prepared as myocutaneous (muscle with skin), fasciocutaneous (deep muscle fascia with skin), or myofasciocutaneous (muscle, deep fascia, and skin) depending on the surgeon's needs for restoring resected tissue.

Microvascular free tissue transfer is similar to local flaps in that the tissue used for reconstruction is supplied by a named blood vessel. The key difference is that this tissue originates from elsewhere in the body; in the process of the reconstruction, the native blood supply will be severed, and a new anastomosis will be created at the site of the defect, using the named recipient blood vessels and the flap's donor vessels. Again, the nature of the defect will determine the specific origin and tissue composition (skin, adipose, fascia, muscle) of the donor flap. Microvascular free tissue transfer provides a handful of advantages, chief among them being the ability to recruit similar tissue from distant body sites, increasing the odds of a favorable functional and esthetic outcome. Another important advantage is as a source of viable, vascularized tissue for repair of previously irradiated or infected defects with compromised tissue. Limitations of this approach derive from donor-site morbidity and extended operation times. Pedicled soft tissue flaps are always the first line of therapy for the reconstruction of perineal wounds. Free flap microvascular transfer of soft tissue flaps to the perineum is a final option if all other local and pedicled options are exhausted.

Classification of Defect

As mentioned earlier, the most important aspect of reconstructive surgery is replacing "like with like". Classifying a defect through identification of which structures are missing and/or compromised is the first step toward remediating the defect and recapitulating normal form and function. Perineal defects are organized according to the scheme presented in Table 15.1.

For male patients with advanced rectal cancer, the penis, scrotum, and pelvic floor musculature are at risk of disruption during resection. Fortunately, total penile resection is rarely necessary. In those uncommon instances in which it is necessary, the goals of reconstruction are threefold: provide acceptable cosmesis, allow for normal urination, and facilitate normal sexual activity. Local flaps have been shown to be ineffective so free tissue approaches have been devised with greater success [9, 10]. Female patients have similar susceptibility to pelvic floor musculature injury along with potential need for vaginal vault reconstruction. The construction of a neovagina is aimed at providing a sexually functional vagina while closing the perineal wound and providing bulk fill-

Table 15.1 Classification of perineal defects

Anatomic structure(s) involved	Missing tissue components
Vaginal vault	S, MS, ST
Vulvoperineal surface	MS, ST
Scrotum	S, ST
Penis	S, MS, ST
Perineum and pelvic floor	S, ST
Sacrum/bony pelvis	S, ST, ± osseous involvement

S skin, *MS* mucosal surface, *ST* soft tissue
Adapted from [8]

ing to the pelvis to prevent bowel herniation. Many techniques have been used in the past with marginal success including skin-only grafts, intestinal grafts, and omental flaps [11]. The preferred approach is myocutaneous or fasciocutaneous flaps, such as vertical rectus abdominis myocutaneous (VRAM) flap or anterolateral thigh (ALT) flap, as discussed below [12].

Once a defect has been identified and appropriately classified, the quality of the tissue must be assessed. Viable vascularized tissue is essential for a successful reconstruction. Local flaps are the ideal, first-line reconstructive options. Potential donor sites will require adequate rotational lengths and soft tissue coverage of donor defects. Abdominal wall, thigh, or buttocks sites are frequently adequate donors. Should free tissue transfer be necessary, the patency of recipient vessels will need to be verified; failing this, appropriate planning for an arteriovenous loop should be undertaken. This can be performed using a saphenous vein graft anastomosed to femoral vessels or lumbar perforators.

Adjuncts to Flap Surgery

Negative Pressure Wound Therapy

In cases of delayed reconstruction, negative pressure wound therapy can bridge the time gap between tumor resection and reconstruction. When indicated, this treatment can enhance neovascularization and decrease edema, encourage granulation tissue formation, and stimulate circumferential wound contraction [13]. Beyond its use as a temporary measure in delayed reconstruction, negative pressure wound therapy facilitates healing by secondary intention in partial-thickness defects.

Tissue Expansion

Tissue expansion is a process by which local and regional tissues are slowly coaxed into controlled growth that will eventually enable them to be advanced into the wound and participate in the healing process. An inflatable prosthetic with a silicone shell is implanted at the time of tumor resection or during a second procedure; at subsequent office visits, serial saline injections are used to expand the implant and direct tissue growth. Once adequate growth has occurred, surgery is performed to definitively repair the defect with this expanded tissue. An unavoidable limitation of this method is that it cannot help in immediate reconstruction or in cases of exposed hollow viscous or neurovascular structures. Risks include infection or prosthetic damage leading to extrusion or rupture [14]. Some patients may additionally find the expansion process to be uncomfortable. For patients with immediate reconstructive needs for acquired defects following rectal cancer resection, this is not a commonly utilized form of reconstruction.

Biological Tissue Matrices

Biological tissue matrices are commercially available allograft or xenograft products. These can be derived from human (dermis), porcine (dermis and small intestine submucosa), or bovine (dermis and pericardium) sources [15]. In the setting of perineal reconstruction, biological tissue matrices are chiefly used to create pelvic diaphragms intended to limit visceral herniation and to reinforce abdominal donor site defects against bulges/herniations, especially in the context of prior radiotherapy or future ostomy placement. These biologic or acellular dermal matrices need to be placed next to well-vascularized soft tissue. Seromas in these regions can lead to infection. Closed suction drains need to be used in these types of reconstruction.

Characterization of Axial Pattern Flaps

Rectus Abdominis Muscle

The rectus abdominis muscle is harvested as the pedicled vertical rectus abdominis myocutaneous (VRAM) flap. It is supplied by the deep inferior

epigastric system. This flap can be utilized as a muscle only, myocutaneous, or perforator flap with a large skin paddle, making it versatile for perineal reconstruction. Further increasing its utility is the ability to close all but the largest donor sites primarily, oftentimes with the help of a biological tissue matrix. Several studies have shown the VRAM is indispensable in eliminating large amounts of dead space, as would be seen in extensive APR defects [16, 17]. One group also found that despite VRAM complication rates being comparable to primary closure complication rates, defects repaired with VRAM flaps experienced drastically reduced rates of major wound dehiscence (9% vs 30%) and perineal abscess (9% vs 37%) [18]. This is secondary to reducing the dead space in the pelvis and recruiting vascularized soft tissue.

Reconstruction with the VRAM provides the surgeon ample vascularized tissue derived from non-radiated tissue (Fig. 15.3). The size and versatility of this flap are its primary advantage. Further endearing it to reconstructive surgeons is its close proximity to the perineum; during extirpation procedures, a second incision is ordinarily not required to harvest the VRAM, so donor-site morbidity is essentially eliminated.

On the other hand, the anatomy of this flap also contributes to its major drawbacks. In patients not being operated on via a midline incision (e.g., following a minimally invasive approach to rectal resection), utilizing the VRAM may necessitate a second incision via an anterior approach. Consequently, there is an increased risk of herniation and bulging along with the typical donor site risks of poor wound healing and injury to surrounding structures. Some authors have proposed a modified VRAM, either muscle-sparing VRAM (ms-VRAM) or fascia-sparing VRAM to prevent some abdominal complications [19]. The use of VRAM flaps is also more complicated in patients who have an ostomy or will have one placed on the side of the flap procurement (e.g., after pelvic exenteration); a pre-existing ostomy can disrupt the vascularity of the VRAM flap, and a new ostomy is ideally placed within the rectus abdominis for anchorage. Coordination with the oncological surgeon is critical for preoperative planning. The requirement for both a colostomy and a urostomy does not preclude the potential for the use of a VRAM flap, however, it will be inhibited, as oftentimes the rectus muscle is required to anchor the ostomy.

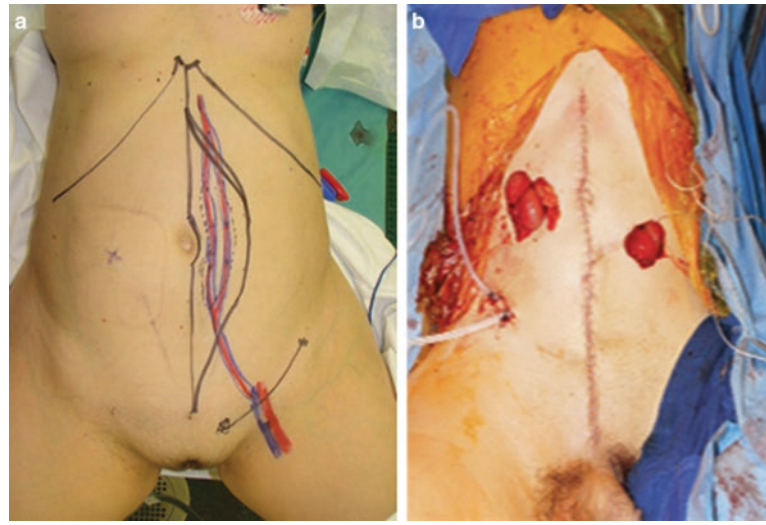

Fig. 15.3 (**a**) Surgical planning of a VRAM flap. (**b**) Bilateral ostomies make VRAM unfeasible

Gracilis Muscle Flap

The gracilis muscle is a long, slender muscle in the adductor compartment of the medial thigh and is supplied by the medial circumflex femoral artery proximally (Fig. 15.4). Its versatility stems from its ability to be harvested unilaterally or bilaterally as a muscle-only or myocutaneous flap with a small skin paddle. This flap is most often utilized in cases where a laparotomy is not being performed and the defect to be repaired is limited in size. In cases of anorectal cancer, gracilis is especially effective in remediating rectovaginal or rectourethral fistulas [20].

Reconstruction with a gracilis flap is desirable due to the low incidence of donor-site morbidity, owing to the simple anatomy of the muscle and the lengthy pedicle. Avoidance of the abdomen is also a positive aspect, especially in obese patients. In cases of prior or neoadjuvant perineal radiotherapy, this flap can provide healthy tissue from outside the radiation field [20].

The limited size of the gracilis flap severely limits its use in perineal reconstruction. Even in cases of bilateral harvesting, this muscle simply cannot adequately cover large defects. Additionally, the distal third of the muscle/skin paddle can have unreliable vasculature, predisposing to wound healing problems. The proximal portion of the muscle with its skin paddle can be used for vaginal reconstruction.

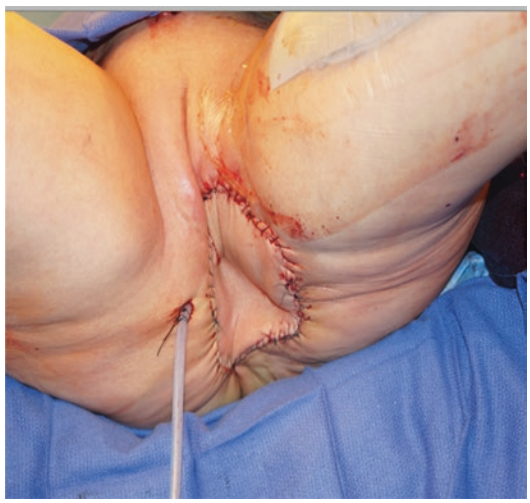

Fig. 15.4 Vaginal reconstruction with visible surgical drain

Gluteus Maximus Muscle

The gluteus maximus is a large muscle of the buttocks supplied by the superior gluteal artery. As a flap, it can be used as a myocutaneous flap but is often encountered as a muscle-only preparation. In perineal reconstruction, this muscle is somewhat limited by a restricted axis of rotation. Consequently, gluteus maximus is best suited for posterior perineal defects [21]. In cases with concomitant sacral defects, the superior aspect of the muscle can provide adequate coverage. For patients requiring ipsilateral ischium coverage, the inferior portion of gluteus maximus is desirable [22].

Reconstructive surgeons rely on this flap for its sizable vascularized muscle and fascia components that are well suited to repair large defects. Additionally, the donor site can be easily closed with a simple V to Y advancement. This flap is limited in use by four main issues, however. First, the sheer size of gluteus maximus predisposes it to denervation atrophy. Second, harvesting the flap impairs the native functionality of the muscle, significantly increasing the morbidity rate [23]. Third, the sciatic nerve courses adjacent to the muscle so care must be taken in harvesting the flap. Finally, the rotational arc is restricted to such an extent that anterior coverage is not feasible.

Pudendal Flap

Based off the posterior labial vessels, the pudendal flap is fasciocutaneous flap that serves as a valuable option for the reconstructive surgeon when perineal coverage is needed with minimal volumetric requirements. The most unique quality of this flap is the availability of the posterior labial branches of the pudendal nerve, allowing the flap to be harvested and used as sensate tissue. The pudendal flap is thus well suited for vaginal vault reconstruction and repair of small anterior or lateral defects [24] (Fig. 15.5).

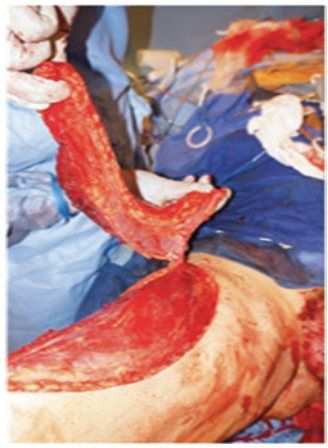

Fig. 15.5 ALT flap with a visible pedicle

The major advantage of this flap is the availability of sensate tissue. Other factors such as minimal donor-site morbidity further enhance its usefulness. Drawbacks of using a pudendal flap stem from size limitation and its proximity to the perineum; in cases of large defects, the pudendal flap is too small to provide complete coverage whereas a history of perineal radiation will likely compromise the tissue that would be harvested as the pudendal flap.

Anterolateral Thigh Flap

The pedicled anterolateral thigh (ALT) flap can be harvested as skin, fat, and fascia, all supplied by the lateral circumflex femoral artery. Traditionally, the ALT flap has been used as a fasciocutaneous flap in free tissue transfer to reconstruct the pelvis, perineum, and lower abdomen [25]. The relative ease of dissection allows for extensive recruitment of skin and fascia without significant donor-site morbidity [26]. In cases where VRAM cannot be utilized, the ALT flap is a suitable alternative [27].

As mentioned, the ALT flap has been used widely due to a reliable, simple dissection that provides copious soft tissue for coverage. When used as a pedicled flap, the generous length of the pedicle enables the surgeon to easily maneuver the flap through a rotational arc. Moreover, the ALT can be adapted as a myofasciocutaneous flap if it is harvested along with vastus lateralis. This is especially useful when even larger volumes of soft tissue are required.

Drawbacks of the ALT flap become most apparent in obese patients. Excessive adipose tissue can limit the mobility of the flap and inhibit ideal placement in the perineum. Larger flaps, whether due to increased adipose tissue or for filling a larger dead space volume, are at higher risk for poor wound healing secondary to their bulkiness and associated venous flow derangement. For large ALT flaps, the donor site from the thigh is typically covered with a skin graft.

Peforator Flaps

With the recent advancement of the cylindrical abdominoperineal excision technique, abdominal wall morbidity has decreased. Thus, reconstruction with less donor-site morbidity has become essential. One attractive option to this end is a perforator flap [28]. Perforator flaps rely on small musculocutaneous perforator arteries to supply skin and subcutaneous fat without a muscular component to the flap. For the reconstructive surgeon, perforator flaps represent an opportunity to capture the vascular reliability of musculocutaneous flaps with the minimal morbidity of a typical skin flap [29]. Perforator flaps require the time of additional dissection. Not bringing muscle with the soft tissue flap reduces the ability to obliterate dead space in the pelvis. However, the potential for donor-site morbidity is decreased. Currently, investigations are ongoing to evaluate the utility of these pedicled perforator flaps.

Perineal reconstruction is well suited for perforator flaps due to the richness of the perforators in the gluteal region. Some authors have used superior and inferior gluteal artery perforator flaps for reconstructions of the pelvis and perineum while others have suggested the usefulness of “freestyle” flaps, ones that are not known a priori and are specifically designed for a certain case [30, 31]. Perforator flaps do not have the robust body of supporting literature that axial

pattern flaps enjoy, so further study is warranted to ascertain their effectiveness in these patients.

Postoperative Care

Ambulation

Early ambulation is key for progressive recovery from surgery. At a basic level, ambulation reverses the thrombotic effects inherent to surgery. More specifically for perineal reconstruction, mobilization off-loads pressure from the closure and the flap itself. This population of patients is more susceptible to ischemic pressure ulcers as well; mobilization or every-other-hour turning in immobilized patients mitigates this risk. A general approach that incorporates early ambulation and excludes sitting in a chair for at least 2 weeks is a reasonable plan for most patients. The overall goal of these procedures is to reduce the odds of flap necrosis and reoperation.

Surgical Drains

Drains are necessary in perineal reconstructions. Even the most experienced surgeon with the best-designed flap will not be able to entirely eliminate anatomic dead space. Whereas the flap does most of the work in obliterating this dead space, closed circuit suction drains further play a role in preventing hematoma and seroma formation. All drains should be left in place until drainage is less than 30 mL per day for 3 consecutive days, and the patient is ambulating. When the decision is made to remove drains, sequential removal is preferred. Simultaneous removal is not recommended.

Complications

Surgical complications are an unfortunate occurrence and can be devastating for the cancer patient and the surgical team. Most often, soft tissue reconstructions of the perineum are complicated by hematoma, seroma, wound infection, or flap failure. Flap failure is the most serious and can be a surgical emergency.

In the case of soft tissue fluid collections or infections, investigation with CT or MRI is indicated. Knowledge of the size, location, and qualities of the fluid will help guide further care. If there is concern that fluid has collected in the setting of an infectious process, cultures and broad-spectrum antibiotics should be ordered. Surgical debridement can be considered for invasive infection. When appropriate, transition to culture-directed antimicrobial therapy.

Flap failure manifests as a pale, cool flap with poor capillary refill time. Failure can be partial or complete. The underlying cause of failure must be investigated with operate evaluation. The goal is to identify reversible causes and swiftly counteract them. For small wounds, conservative treatment with dressing changes and/or negative pressure therapy is appropriate. More extensive defects with larger wounds may require long-term wound care protocols. These reconstructions will more frequently necessitate debridement and additional flap closure efforts. Regardless of wound size, those that are reoperated upon should be vigorously debrided of necrotic tissue followed by attentive wound care and antimicrobials. Most wounds will successfully heal secondarily after flap reoperation. Special consideration is given to wounds in previously irradiated areas; complication rates are higher, especially chronic wound drainage and fistulization. For these patients, specialized reconstructive techniques and wound analysis can help mitigate long-term side effects.

Conclusion

Reconstruction of the pelvis and perineum in the setting of the oncological defect is often a challenging proposition. With appropriate preoperative planning and surgical technique, reconstruction of the pelvis and perineum can be performed safely with excellent clinical outcomes.

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Optimizing Primary Tumor Management in Stage IV Rectal Cancer

16

Jane Y.C. Hui and Elin R. Sigurdson

Abbreviations

FLR	Future liver remnant
NCCN	National Comprehensive Cancer Network
RECIST	Response evaluation criteria in solid tumors

Introduction

It is estimated that in 2014, 40,000 new cases of rectal cancer will be diagnosed in the United States [1]. Of these, 16–18% will present with distant metastases [1, 2] (i.e., stage IV disease [3]). The liver is the most common site of metastasis (60%), followed by the lungs (39%), the non-regional lymph nodes (22%), and the peritoneum (19%) [4]. The prognosis and management of these patients are dependent on the extent of metastatic involvement, but the aggregate 5 years survival for patients with stage IV rectal cancer is reported to be around 13% [1]. Because there are multiple sites of disease that demand attention, the clinician must take into consideration the management options for each site while keeping in mind the bigger picture of the patient as a whole.

Management of the rectal cancer primary in the absence of metastatic disease has been relatively clearly defined. The use of preoperative chemoradiation has become the standard of care for clinical T3, T4, or node-positive disease due to a significant reduction in locoregional recurrence compared to surgery alone [5, 6] or to the use of postoperative chemoradiation [7]. However, longer-term follow-ups have not borne out any overall survival benefits [8, 9], although other studies have suggested an advantage in disease-free survival [10]. Nonetheless, in the setting of metastatic disease, local control becomes less of a priority when considering therapeutic strategies.

Metastasectomy in selected patients has been shown to be beneficial in the metachronous literature. The 5 years overall survival following hepatic resection for disease confined to the liver has been reported at approximately 40% [11, 12] compared to less than 5% with best supportive care [13]. Surgical resection is currently the most effective form of treatment for colorectal liver metastasis. In a meta-analysis, the 5 years survival rates after pulmonary metastasectomy were found to range from 11% to 61% [13]. When combined hepatic and pulmonary metastases are present, the 5 years survival rates have been reported at around 30% [14] and even at 64% in a highly selected population [15].

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Given the outcomes with increasing indications for surgical resection and increasingly improved chemotherapy and chemoradiation regimens, the complex multimodality management plan of a patient presenting with stage IV rectal cancer should be based on (1) whether all of the disease is resectable with a curative intent and, (2) if not, whether the patient is symptomatic from the primary (Fig. 16.1). This approach will help to guide the clinician in determining the goals of therapy, as well as the modalities of therapy that are most appropriate.

All Sites Resectable at Presentation: Curative Intent

In those with resectable primary and metastatic disease, the goal of therapy is curative. The resectability of liver metastases was historically defined by the characteristics of the tumor deposit(s), including size, number, and location within the liver. However, newer resectability criteria focus on the remaining liver following metastasectomy and have increased the number of patients eligible for liver resection. These criteria must all be met and are (1) R0 resections (i.e., complete resection with microscopically clear margins) of all disease sites, including the primary and the intra- and extrahepatic metastatic disease sites, (2) sparing of at least two adjacent liver segments, (3) preservation of the vascular inflow and outflow and the biliary drainage of the remaining liver segments, and (4) preservation of a minimum of 20% future liver remnant (FLR) in normal livers, 30–60% FLR for livers injured by chemotherapy, steatosis, or hepatitis and 40–70% FLR for liver cirrhosis [16, 17]. Further strategies to increase the number of patients eligible for hepatic resection include portal vein embolization [16].

For pulmonary disease, resectability criteria are less well defined and mainly include the ability to achieve an R0 resection. In the metachronous literature, some have noted that patients with three or more pulmonary metastatic deposits are twice as likely to experience a recurrence [18]. In a recent meta-analysis of retrospective single-center experiences, multiple lung metastases, thoracic lymph-node involvement, and elevated pre-thoracotomy carcinoembryonic antigen levels all increased the risk of death [13].

There are numerous strategies in existence that vary in the timing of surgery for the primary and metastases, systemic chemotherapy, and chemoradiation. Timing and sequencing of therapy remain debated and controversial. Early involvement and discussion with surgeons, in conjunction with medical oncologists and radiation oncologists in a multidisciplinary fashion, is crucial. The most recent iteration of the National Comprehensive Cancer Network (NCCN) 2014 guidelines recommend preoperative combination chemotherapy for 2–3 months, with or without subsequent chemoradiation, followed by surgery [19]. Resection of the primary and

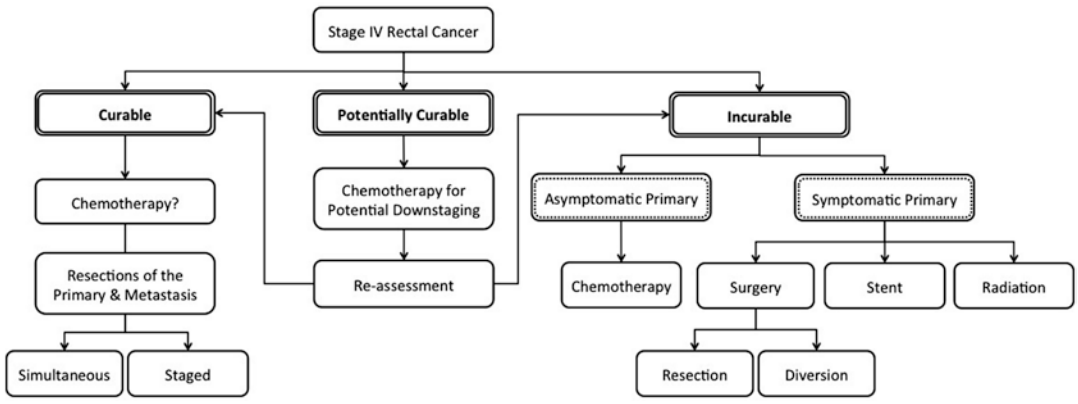

Fig. 16.1 The approach to patients with stage IV rectal cancer

metastasis can then be undertaken simultaneously or in a staged fashion. Chemoradiation can be considered postoperatively if not given preoperatively [19].

5-Fluorouracil-based chemotherapy (with oxaliplatin or irinotecan) has been shown to improve median overall survival for patients with metastatic colorectal cancer in randomized controlled trials [20, 21]. In particular, the trial by De Gramont et al. included patients with synchronous disease (i.e., stage IV at presentation), who accounted for 66% of the study population [20]. More recently, the addition of the antiangiogenic agent bevacizumab has further improved median overall survival in metastatic colorectal cancer [22]. Because of its antiangiogenic properties, there have been concerns surrounding impaired wound healing leading to increased perioperative morbidity with the addition of bevacizumab to preoperative chemotherapy regimens. However, if stopped at least 8 weeks prior to surgery, bevacizumab does not seem to increase morbidity [23]. Additional recent randomized trials also examined the use of anti-epidermal growth factor receptor agents cetuximab and panitumumab in the setting of metastatic colorectal cancer. Ye et al. found that for colorectal liver metastases, the addition of cetuximab to oxaliplatin- or irinotecan-based chemotherapy significantly improved the overall response rate from 29% to 57% compared to chemotherapy alone [24]. The overall response rate in this study included both complete and partial response according to the response evaluation criteria in solid tumors (RECIST) guidelines [25].

If considering upfront chemotherapy followed by surgery, the severity of symptoms relating to the primary must be taken into consideration. In cases of clinical obstruction, surgical diversion with an ostomy or endoluminal stent placement may be appropriate prior to initiating chemotherapy. Unfortunately, there are also known risks of hepatotoxicity relating to preoperative chemotherapy, specifically with oxaliplatin and irinotecan [26], and prospective data to support preoperative chemotherapy in clearly resectable liver metastases is lacking [27].

Timing and Sequence of Surgery

The goal in this subgroup of stage IV patients is complete surgical resection of all disease sites. Thus, the different surgical strategies include (1) rectal resection first, followed by hepatic resection; (2) hepatic resection first, followed by rectal resection (the "liver first" approach); or (3) simultaneous rectal and hepatic resections. The first two strategies are often collectively termed "staged resections." Rectal resection-first approach has traditionally been the path most taken. However, more recently, investigators have suggested the liver-first approach as a strategy to ensure that resectable metastases are treated without delays caused by potential complications from rectal surgery.

While there are no randomized prospective studies, several retrospective series have reported on the feasibility of the liver-first approach. The majority of these studies included both colon and rectal cancer patients [28–31]. Verhoef et al., along with Ayez et al. in a follow-up study, reported on their experience with the liver-first approach specifically in patients with locally advanced rectal cancer and synchronous liver metastases [32, 33]. These patients received a median of five cycles of oxaliplatin- or irinotecan-based chemotherapy with or without bevacizumab, then underwent hepatic resection, followed by long-course radiotherapy with or without capecitabine, and then completed the protocol with rectal resection. Of the 42 patients identified, 31 completed their protocol, with 11 remaining patients developing progressive disease precluding rectal surgery. More recently, Buchs et al. reported their experience with a similar liver-first strategy for rectal cancer [34]. Of the 34 patients included, 33 completed their protocol. With respect to the rectal cancer surgery, the rate of a positive distal margin in this study was 6.1% (seen in two patients). Neither of these patients received the long-course chemoradiotherapy prior to their rectal cancer surgery due to the acute development of obstruction and perforation. They both experienced a pelvic recurrence. There were no patients with a positive

circumferential resection margin. Three patients experienced a complete rectal pathologic response. Overall, five of 33 patients experienced a pelvic recurrence. The 5 years overall survival was 52.5% in this cohort.

There have also been some retrospective reports of simultaneous colorectal and hepatic resections. A case series from the Mayo Clinic described 45 patients who received simultaneous R0 resections with a 5 years overall survival of 32% [35]. There were no significant differences in local recurrence rates between the 18 patients who received neoadjuvant (i.e., preoperative) pelvic radiotherapy and the 27 patients who did not. There were no perioperative mortalities. There were 26 postoperative complications in this group. In another retrospective series, patients who underwent simultaneous resections were compared to patients who underwent staged resections in a multi-institutional analysis [36]. There were more patients in the simultaneous group (40%) with rectal primaries than in the staged group (23%). Simultaneous resections resulted in a significantly shorter combined length of hospital stay compared to staged resections. In the subgroup of minor hepatectomies (resection of less than three Couinaud hepatic segments), the mortality and major morbidity rates were similar between the simultaneous and staged resection groups. However, simultaneous resections with major hepatectomies (resection of at least three Couinaud hepatic segments) had significantly increased mortality and major morbidity when compared to staged resections. The authors concluded that simultaneous resections with minor hepatectomies are safe but that consideration should be given to simultaneous resections with major hepatectomies. Interestingly, there was not a similar subgroup analysis comparing the impact of colonic resections to rectal resections.

On a national level, a recent retrospective study using the American College of Surgeons National Surgical Quality Improvement Program data demonstrated that patients who underwent simultaneous resection had more perioperative adverse outcomes, longer operative time, and longer length of stay than colorectal resection or hepatic resection alone [37]. However, the authors were unable to perform a direct comparison of these outcome variables in the simultaneous group to the cumulative outcome variables of the staged colorectal and hepatic resections.

Thus, true comparisons between the simultaneous and the staged resections are not readily available. Currently, the strategy employed in the surgical management of the rectal primary and liver metastasis is determined by the review of the individual patient and by the surgeon(s)' level of comfort with simultaneous resections.

The Role of Pelvic Radiation

The role of pelvic radiation in the treatment of rectal cancer is thought to lie mainly in local control [5, 7, 8]. In those with clearly resectable stage IV rectal cancer, neoadjuvant treatment of the primary with 6 weeks of chemoradiotherapy followed by an 8-week wait before rectal resection can mean delays in the administration of systemic chemotherapy or in the surgical management of the metastatic disease. Butte et al. retrospectively examined the patterns of failure in stage IV rectal cancer patients with resectable liver metastases managed at the Memorial Sloan Kettering Cancer Center [38]. After the complete resection of all sites of disease and a median follow-up of 44 months, 70% of the entire cohort developed a recurrence. Ten percent of the cohort developed a pelvic recurrence in combination with recurrence at other sites, and 4% developed an isolated pelvic recurrence. Approximately half of the patients in this series received perioperative pelvic radiation, with the majority of these patients receiving neoadjuvant radiation. The receipt of pelvic radiation was not found to be associated with the rate of pelvic recurrence. The disease-specific survival at 5 years was 51%. It was not associated with pelvic recurrence or with the receipt of pelvic radiation.

Some authors have also examined the utility of adjuvant (i.e., postoperative) pelvic radiation in the setting of stage IV rectal cancer. In Korea, there are several retrospective series comparing the use of

adjuvant chemotherapy to adjuvant pelvic chemoradiotherapy in stage IV rectal cancer [39–41]. In one of these studies, following simultaneous rectal and hepatic resections, there was no difference in median disease-free survival or in overall survival between patients who received adjuvant chemotherapy compared to patients who received adjuvant chemoradiotherapy. Approximately 42% of the adjuvant chemotherapy group received oxaliplatin- or irinotecan-based chemotherapy, with the remaining receiving fluoropyrimidine therapy alone. The groups were not equal, as there were higher proportions of patients with abdominoperineal resections and node-positive disease in the chemoradiotherapy group than in the chemotherapy group. The majority of recurrences were distant only (67%), as compared to locoregional only (3%), and distant plus locoregional recurrence (2%). A second retrospective series revealed similar findings of a lack of difference in overall survival or disease-free survival between adjuvant chemotherapy and adjuvant concurrent chemoradiotherapy [40]. These two series stand in contrast to the third retrospective series demonstrating a benefit in pelvic-failure-free survival in stage IV rectal cancer patients receiving adjuvant radiation compared to patients receiving adjuvant chemotherapy [41]. However, no overall survival benefit was seen.

When managing the benefits of local control, clinicians may be able to predict who will derive the most benefit from pelvic radiation. The MERCURY study has suggested a sensitivity of 64% and specificity of 91% for the use of pelvic MRI in predicting a positive circumferential resection margin [42]. A positive circumferential margin was predicted on MRI if tumor is seen to be within 1 mm of the mesorectal fascia on MRI. When followed prospectively, a significant difference in overall survival was observed between patients with an MRI-predicted positive circumferential resection margin compared to those with an MRI-predicted negative margin. A similarly significant difference in local recurrence rates was also observed between these two groups. A recent meta-analysis of the diagnostic accuracy of pelvic MRI for assessing T and N stages and circumferential resection margin included the MERCURY study along with 20 other studies, nine of which were retrospective [43]. The pelvic MRI was found to be most accurate for circumferential resection margin status. In addition, T stage assessment by pelvic MRI has a sensitivity and specificity of 87% and 75%, respectively. Accuracy for *N* stage was found to be relatively poor.

In the stage IV setting, the use of pelvic MRI can be helpful for determining the patients with locally advanced disease who will benefit the most from pelvic radiation in addition to surgery as a means for local control (i.e., those most likely to have a positive circumferential resection margin). In these patients, "short-course" radiotherapy can be used to decrease the concerns of delaying surgery and systemic chemotherapy that is seen with the traditional neoadjuvant chemoradiation regimen (6 weeks of chemoradiation followed by an 8-week wait) that is typically given in North America. Short-course radiotherapy is used more commonly in Europe and consists of 5 days of 5 Gy pelvic radiation per day, with rectal surgery taking place within a week of completion of pelvic radiation [5, 6, 9]. Alternatively, postoperative chemoradiation may be employed for local control. However, in general, pelvic radiation likely plays a diminutive role in the curative management of stage IV rectal cancer given that the majority of these patients recur distantly.

Patients with Potentially Curative Disease

Approximately 70–80% of patients with colorectal liver metastases are considered unresectable at initial presentation. However, a proportion of patients with initially unresectable disease can potentially be converted to resectable disease. In such cases, it is still possible to approach these patients with a curative intent. Select patients treated with modern chemotherapy regimens can be "downstaged" and converted to resectable disease with improvements in survival. The NCCN recommends restaging studies to reassess resectability every 2 months while on chemotherapy.

The resection rate following chemotherapy for initially unresectable colorectal liver metastases was reported to be 32.5% in a series from Italy [44]. Two-thirds of the study population had synchronous disease. A total of 40 patients received irinotecan, 5-fluorouracil, and folinic acid therapy with assessments for response every 6 cycles (12 weeks). Patients underwent resection as soon as their disease was reassessed and deemed converted to resectable. The presenting factors most favorable for resection after chemotherapy were small number of metastases, right lobe involvement only, and presence of large lesions. The median disease-free survival in the patients who were resected was 14.3 months, while the median progression-free survival in unresected patients was 5.2 months.

Another group reported treatment with oxaliplatin, 5-fluorouracil, and leucovorin resulting in a lower conversion rate of 13%: 138 colorectal cancer patients underwent hepatectomy out of an initial 1104 patients with unresectable metastatic disease after an average of ten courses of chemotherapy [45]. Assessments were performed every four courses of chemotherapy. Perioperative mortality and morbidity were 0.7% and 28%, respectively. The 5 years survival of patients with rectal primaries who were successfully downstaged to receive metastasectomy was 25%.

Therefore, in those successfully downstaged, there are reported survival benefits to subsequent surgical resection. Relatively frequent reassessments to determine treatment response are important in selecting for these patients. In order for a patient to be successfully downstaged and considered for treatment with a curative intent, all apparent sites of disease at diagnosis must be amenable to complete surgical resection.

Patients with Unresectable Disease and Symptomatic Rectal Primaries

In patients presenting with unresectable metastatic disease, the goal of therapy is palliative, and not curative, in nature. Metastatic disease that is unlikely to become resectable even with upfront chemotherapy treatment includes diffuse extrahepatic and extra-thoracic disease including peritoneal carcinomatosis, mediastinal involvement, miliary hepatic, or pulmonary involvement. In addition, patients who are not surgical candidates due to medical comorbidities also fall in this category. On the other hand, when patients present with symptoms or complications related to their primary tumor, resection may be appropriate despite the presence of unresectable metastatic disease. These complications include bleeding, obstruction, perforation, and pelvic pain. Surgical management in this situation must be tailored to the patient's symptoms and ability to tolerate the resection, as well. Other non-resection strategies for management of the symptoms include systemic chemotherapy, chemoradiotherapy, diverting ostomy, and endoscopic stent placement. Symptoms of obstruction may be relieved with diverting ostomy, surgical resection, or endoscopic stent placement. However, pelvic pain and/or bleeding is best managed with chemoradiotherapy or surgical resection. The strategy chosen should minimize morbidity while providing maximal symptom relief, with minimal delays to systemic chemotherapy administration, if possible.

Pelvic Radiation for Palliation

There is some evidence that radiotherapy is a reasonable alternative to surgical management (resection or diversion with an ostomy) of symptomatic rectal primaries. A phase II study enrolled previously untreated stage IV rectal cancer patients with symptomatic primaries who had obstruction (53%), bleeding (27%), and pain (20%) to receive short-course radiotherapy followed by capecitabine and oxaliplatin [46]. The short-course radiotherapy consisted of five fractions of 5 Gy pelvic radiation given over 5 consecutive days. Twenty percent of patients required palliative surgery secondary to local symptom progression. Seven patients received diverting ostomies (five for obstruction and two for perianal fistulae), and one patient required local tumor excision for bleeding. On a quality of life questionnaire, 30% reported complete symptom resolution, and 35% reported significant improvement in their symptoms during

the course of follow-up. The remaining 35% reported poor palliative effect.

Thus, for patients who would not otherwise tolerate a resection and who wish to avoid a diverting ostomy, pelvic radiation may be an option for palliation of pelvic symptoms, including obstruction, bleeding, and pelvic pain.

Endoluminal Stents

In the setting of acute malignant obstruction, the surgical options again include resection or diversion. More recently, the use of self-expanding metallic stents to palliate obstructive symptoms from rectal cancer has been reported in the literature. Stents are typically placed and deployed using a combination of endoscopy and fluoroscopic guidance. There are typically two broad indications for endoscopic stent placement: (1) palliation and (2) bridge to surgery. In the first setting, the self-expanding metallic stents are placed for definitive symptom (usually obstruction) control (see Fig. 16.2) for palliation. These stents are not removed, and should tumor ingrowth occur, a repeat endoscopic procedure is performed, if possible. In the second setting, as a bridge to surgery, stents are placed for patients who are acutely obstructed but are candidates for surgical resection. Therefore, the stent is placed in order to allow for temporary relief from the obstruction and preparation for surgery. The patient then undergoes definitive surgical resection shortly after stent placement. In this setting of stage IV rectal cancer with unresectable disease that is managed with a palliative intent, the stents are typically placed for the first indication.

A Japanese phase II study evaluated 33 patients with unresectable obstruction of the rectum or sigmoid colon treated with stenting [47]. The stent was effective in 82% of the patients. One stent was removed secondary to anal pain. The level of the tumors treated in this study was proximal to 5 cm above the anal verge. No stent migration was observed; however, the medial duration of follow-up was only 78 days.

In a prospective study in Italy, Fiori et al. randomized 22 patients with obstruction and unresectable rectosigmoid cancer to either endoscopic stenting or colostomy [48, 49]. None of these 22 patients required urgent surgery. Endoscopic and fluoroscopic guidance were used for inserting and deploying the self-expanding metallic stents. In the endoscopic group, all patients resumed oral intake within 24 h; in the colostomy group, all except one resumed oral intake by postoperative day 3. In the stenting group, 27% complained of abdominal pain during follow-up. On repeat colonoscopy, two patients were found to have fecal impaction at the stent, and one had near-complete

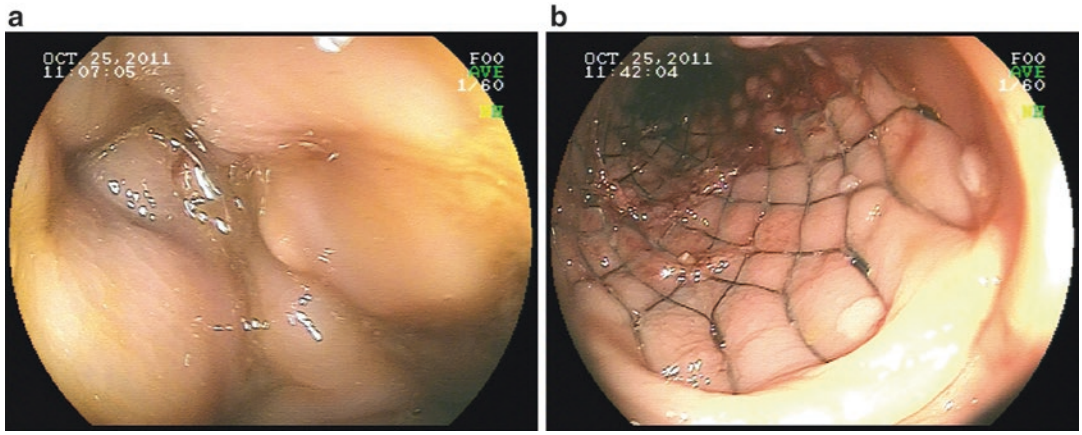

Fig. 16.2 The use of endoluminal self-expanding metallic stent for obstructing primary lesion. Before (**a**) an obstructing lesion was found on colonoscopy. After (**b**) the obstruction was relieved with the placement of a self-expanding stent. Mucosal abnormalities consistent with the primary lesion can be seen abutting the stent

obstruction by tumor ingrowth. There were no reports of stent migration or perforation related to stent placement. No patient went on to require surgery. There were no differences between the two groups in median overall survival, which was just under 300 days. There were no bleeding complications in this study, which would typically not be addressed by stents.

With regards to the safety of stent placement, complications such as stent migration, perforation, re-obstruction, and bleeding have been reported. A meta-analysis by Watt et al. suggested a median stent migration rate of 11% over 54 studies, with a range of 0–50% [50]. Similarly, the median perforation rate as a result of endoluminal stent placement was 4.5% (range 0 to 83%) over 50 studies. However, this meta-analysis included patients with colonic and rectal obstructions and also included stents placed for palliation and as a bridge to surgery. Rates of colonic re-obstruction in palliation cases were reported in 31 studies, yielding a median rate of 12%, with a range of 1–92%. Bleeding, pain, and tenesmus were reported to be relatively rare; however, once again, the proportion of patients with rectal obstructions specifically was not known. In a small retrospective study comparing the use of stents in patients with malignant rectal obstruction within 5 cm of the anal verge with that more than 5 cm away from the anal verge, a significantly higher proportion of patients (62.5% versus 7.1%) reported anal pain, with a proportion of these patients requiring narcotic analgesics [51].

Large-scale studies featuring the use of endoluminal stents for palliation of obstructive symptoms from a stage IV primary rectal cancer are lacking. There exist some data that suggest the relative safety of endoscopic stent placement. Obstruction from low rectal primaries poses potential problems in the use of endoluminal stents; stents have the ability to cause anal pain and tenesmus at this location and should be used with caution.

Asymptomatic Patients with Unresectable Disease

When the goal is palliation, the predominant argument for resection of the primary rectal tumor is for dealing with complications due to the presence of the tumor. Similarly, in those who present with an asymptomatic fashion, the rationale for resection of the primary lesion would be to prevent these complications.

There are currently no randomized prospective data that compare the benefits of primary resection to chemotherapy in those who present with asymptomatic but unresectable stage IV rectal cancer. Two attempts at randomized controlled trials have closed due to poor accrual [52]. There are several retrospective analyses that combine colon and rectal cancer together, some of which suggest a survival benefit in those who have undergone a palliative primary resection. Tebbutt et al. found that those with stage IV colorectal cancer who underwent primary resection and those who were treated primarily with chemotherapy had similar incidence of intestinal obstruction (14% in each group) [53]. The median survival in the resected group was 14 months compared with 8.2 months in the chemotherapy group. The main limitation, however, is that 80% of the patients received 5-FU-based chemotherapy and not the newer regimens of oxaliplatin- or irinotecan-based chemotherapy with antiangiogenic agents such as bevacizumab.

Watanabe et al. reported, in a retrospective series, their experience of primary tumor management in unresectable stage IV colorectal cancer [54]. One hundred and fifty-eight patients with asymptomatic primaries received chemotherapy (112 patients) or surgical resection (46 patients). The determining factor for surgical resection was the inability of the endoscopist to pass the colonoscope beyond the primary tumor. There was a 17% postoperative complication rate in the surgical group. Between the two groups, there was no difference in median survival (24 months in resection group versus 18 months in chemotherapy group, $P = 0.79$).

Furthermore, recent retrospective analyses of two large randomized studies suggested a survival advantage to primary resection in patients with stage IV colorectal cancer [55, 56]. However, in both studies, the resection of the primary was performed prior to randomization in the trials, suggesting a selection bias of patients who did and did not receive resection of their primaries. This suggestion is reflected in the fact that in both papers, there is a higher proportion of patients

with rectal cancer (than patients with colon cancer) in the non-resection group as compared to the resection group.

In another retrospective analysis, no advantages in median survival were noted between the resected and non-resected group in asymptomatic stage IV colorectal cancer [57]. Nine percent of the non-resected group developed obstruction requiring surgery while 30% of the resected group experienced perioperative complications. The authors concluded that elective primary resection in asymptomatic stage IV disease confers no advantage and nonoperative management with early chemotherapy should be pursued in these patients.

More recently, Poultsides et al. examined the rate of primary-related complications in those who received upfront chemotherapy in a single-center retrospective analysis [58]. The patients in this study received oxaliplatin-based chemotherapy (60%), irinotecan-based chemotherapy (40%), and bevacizumab (48%). Of the 233 asymptomatic synchronous stage IV colorectal cancer patients, 89% never experienced complications from their intact primary. Eleven patients out of 233 experienced obstruction, while five out of 233 experienced a perforation. Seven percent of the entire cohort was managed surgically: eight resections, one bypass, and seven ostomies were performed. It is important to note that this study included both colon and rectal cancers; 34% of the study patients had rectal cancers. Finally, 20% of the study population went on to have elective curative resection of both the primary and metastatic disease at a median of 8 months following the initiation of chemotherapy.

For those patients who present with unresectable metastatic disease and an asymptomatic primary rectal cancer, a reasonable approach is upfront systemic chemotherapy. The likelihood of symptom development in this patient population is low, and the primary lesion could still be managed if symptoms were to develop. There is little high-level evidence to support a definite survival benefit to upfront resection of the primary tumor. Moreover, initial surgical management of an asymptomatic primary rectal cancer may unnecessarily delay systemic chemotherapy should complications develop postoperatively. Upfront systemic chemotherapy also offers the potential to downstage to a point where both the primary and metastatic disease may become resectable—and potentially curable.

Conclusions

Although stage IV rectal cancer historically was associated with a poor overall survival, modern-day 5-fluorouracil-based chemotherapy has improved the outlook for a proportion of these patients. There are now patients who can undergo surgical resection with a curative intent, even in the metastatic setting. The approach to the patient with stage IV rectal cancer hinges on whether or not all diseases are considered resectable and whether the primary is symptomatic at presentation. Patients who present with resectable disease should be managed with a curative intent, by offering multimodality therapy. While the sequence of such therapy is controversial, these patients should be managed with a combination of chemotherapy and complete surgical resection of all disease sites, including the primary lesion and the metastatic disease. In patients who present with initially unresectable disease, there is a potential for downstaging and conversion to resectable disease. Therefore, these patients should not necessarily be placed into the palliative category immediately. Finally, in patients who present with symptomatic primaries, a number of management options exist for relief of those symptoms, including resection, diversion, pelvic radiation, and endoluminal stents. The management strategy is based upon the individual patient and his/her tumor biology; and treatment decisions should only be made after careful consideration by a multidisciplinary care team involving surgeons, medical oncologists, and radiation oncologists.

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17 Histopathologic Evaluation of Neoadjuvant Treatment Response and Tumor Regression Grade

Dipen Maru

The standard of care treatment for advanced locoregional (cT2-T4 and/or cN+) rectal adenocarcinoma includes preoperative chemoradiation composed of fluoropyrimidine (5-fluorouracil or capecitabine) with radiation (45 gy) to the tumor bed in the rectal wall and regional lymph nodes and soft tissue. This treatment has demonstrated substantial improvement in downstaging of the tumor and higher likelihood of sphincter-preserving surgery and negative margin of resection after total mesorectal excision approach for rectal cancer. Addition of neoadjuvant therapy has also demonstrated improvement in disease-specific and overall survival in patients with resectable rectal cancer [1, 2]. Histopathologic parameters of response to neoadjuvant therapy are major determinant factors to predict tumor biology and long-term disease-specific outcome for patients with rectal adenocarcinoma and a valid endpoint to assess response to investigational therapeutic approach applied in neoadjuvant setting [3]. The clinical relevance and impact on patient management of histopathologic response demand that surgical pathologists are proficient in gross and microscopic examination of the rectal resection specimens and report required pathology data points in a surgical pathology report.

Macroscopic Examination and Sampling

A meticulous and systemic approach to examine the rectal resection specimen in a fresh state and after fixation is the foundation of providing reliable, reproducible, and high-quality histopathology information about response to neoadjuvant therapy.

Macroscopic Examination in Fresh State

It is easy to identify important anatomical landmarks like mesorectal fascia and intactness of mesorectum (Fig. 17.1), highest vascular or inferior mesenteric artery lymph nodes, adherent organs (vaginal wall, seminal vesicles, bone, etc.), distal, proximal, radial, and other margins and measure dimensions of the specimen and distance of tumor to the margins in a fresh state. It is recommended that the specimen is evaluated for completeness, to identify any surgical defects in the integrity of the mesorectum and to assess plane of surgical dissection, and then inked and opened in the fresh state, and distance of distal and proximal margin from tumor is measured in fresh state without stretching the wall. The presence of any defects

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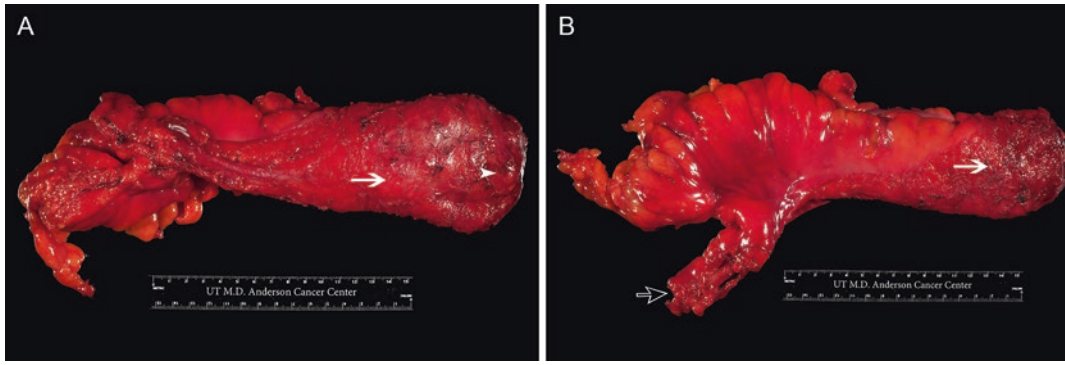

Fig. 17.1 Photomicrograph showing low anterior resection specimen with total mesorectal excision (TME). **a** shows posterior surface with good bulk of mesorectum (indicated with *an arrow*) with smooth surface and small superficial defect (indicated with *an arrowhead*), indicating a good TME. **b** shows anterior aspect of the specimen (indicated with *an arrow*) and highest vascular pedicle (indicated with *dark arrow*)

in the integrity of the mesorectal envelope or areas of tumor extension beyond the mesorectal plane should be identified and recorded for subsequent multidisciplinary review and quality assurance [4]. Formalin fixation causes shrinkage of the rectal wall leading to lower than actual distances of the mucosal margins from tumor. An effective communication between surgeon and pathologist or pathology assistant grossing specimen is very helpful in providing high-quality macroscopic examination. Ideally, the operating surgeon should help orient the specimen and identify the critical anatomical landmarks and unique issues specific to the specimen, such as at-risk margins, to the pathologist grossing specimen at the grossing bench in pathology laboratory. Assessment of margins by the grossing pathologist and operating surgeon facilitates optimal assessment of distal and other margins and helps in sampling of the margins for intraoperative frozen section pathology assessment.

Macroscopic Examination of Fixed Specimen

Tumor bed configuration and tumor boundaries are better observed after formalin fixation. Sectioning of the tumor with surrounding tumor is easy and does not produce disruptions or tissue curling after formalin fixation. Tumor dimensions, presence and dimension of other lesions, and status of nonneoplastic colorectal wall and adjoining organ should be assessed in the fixed state.

Sampling for Microscopic Examination

It is recommended that entire tumor bed or scar should be submitted for microscopic examination. In specimens with distinct grossly identifiable tumor, majority of gross tumor should be sampled for microscopic examination. There is more than one approach for sampling tumor for optimal assessment of residual tumor and status and distance of tumor from radial distal and other margins.

The approach of macroscopic examination being followed by majority of the pathology laboratories includes inking, examining, and opening the specimen in the fresh state followed by fixation and sampling in the fixed state. Tumor and adjacent nonneoplastic rectum are submitted by longitudinal or transverse sectioning of tumor to include tumor, rectal wall, mesorectum, and adherent organs. The tumor is serially sectioned in multiple slices, and each slice is divided into multiple sections to accommodate the tissue in a traditional paraffin block. A 5-micron thick section is procured and stained with H&E from each block. This sampling approach identifies discontinuous foci of tumor cells in tumor bed for appropriate pathologic tumor stage. In addition,

Table 17.1 Macroscopic features required in a pathology report

Specimen type	Low anterior resection, abdominoperineal resection, reresection of locally recurrent tumor
Specimen dimension	Length × diameter in cm
Location/epicenter of tumor	Rectosigmoid, upper/mid and distal rectum, anterior/posterior/lateral wall
Tumor	Length × width in cm
Tumor configuration	Ulcerated, exophytic, annular, no definite tumor; scar or ulcer only
Tumor distance from margins	Proximal, distal, radial, other soft tissue, adherent organ margins
Macroscopic depth of tumor invasion	Muscularis propria, perimuscular soft tissue, infiltrating the serosa/radial margin, invading into adherent organs
Other lesions and their distance from primary tumor and margins	Polyps, ulcer, diverticula
Grossly positive lymph nodes or soft tissue tumor deposits	Distance from primary tumor, radial margin, vascular pedicle margin
Highest vascular pedicle	Lymph node involvement Possible margin
Inferior mesenteric artery lymph nodes	Lymph node involvement
Section codes	Tumor, margins, lymph nodes, other lesions

this method is helpful in accurately measuring distance between tumor and radial or adherent organ margin under a microscope and status of peritumoral lymph nodes. In addition, due to each section derived from the paraffin block that has tissue thickness of <5 mm, the amount of tumor available for microscopic assessment is higher in the H&E-stained sections as compared to having >5 mm thick sections.

Approach for sampling distal margin depends upon the distance between tumor/scar and distal margin. When the distance between the distal edge of the tumor/scar and distal margin is ≤2 cm, perpendicular sections of tumor and corresponding margin should be submitted so that exact distance between tumor cells and/or acellular mucin and distal margin can be measured under the microscope. For specimens with broad distal margin, it is acceptable to submit part of distal margin which is in line with and closest to the tumor/scar in perpendicular sections and peripheral part of the margin as shaved sections with an en face margin. Highest vascular pedicle and proximal colonic margins should be submitted separately as shaved section for en face margins.

Major challenge for pathologic rectal cancer resection specimen evaluation of after neoadjuvant chemoradiation is finding adequate number of lymph nodes. Although processing by chemicals like Bouin's solution has shown to increase yield of lymph nodes, there is no alternative to meticulous dissection of mesorectal and other soft tissue to identify as many lymph nodes as possible. Not infrequently, the lymph node loses the rounded contour and soft consistency due to radiation, so nodular firm area should be felt and visualized and if suspicious should be sampled. Any lymph node which grossly appears positive should be sampled in its entirety because not infrequently these lymph nodes show reaction to the therapy and/or acellular mucin and not tumor cells. Due to independent prognostic value, inferior mesenteric artery lymph nodes should be identified in advance and sampled separately [5]. It is also essential to make sure that lymph nodes suspected to be positive in the preoperative scans are sampled for microscopic assessment. A review of the preoperative scan by the pathologist is helpful in identifying need of search for specific positive lymph nodes.

Sampling of additional focal lesions such as polyps, ulcers, and diverticula along with random section of nonneoplastic rectum is routinely performed as for any other colorectal resection specimen. Table 17.1 lists the essential components to be included in the gross/macroscopic description of rectal resection specimens.

A different approach of sampling originally described by Quirke et al. [6] includes whole

mount processing of the slices of the tumor and adjoining mesorectal and other soft tissue. In this method, the tumor is serially sliced in a transverse plane into 5–10 mm thick slices. The slice with maximal lateral spread of tumor is identified as "primary slice" and is blocked into multiple paraffin blocks with maintenance of orientation. A 5-micron thick section is procured and stained with H&E from each paraffin block. Remaining slices with tumor and mesorectal soft tissue are obtained, and the slices are whole mounted on paraffin blocks, and a 10-micron thick section is procured by sledge microtome followed by H&E staining. The strength of this approach is ability to consistently measure the distance between deepest extent of the tumor to radial margin and tumor extension beyond muscular layer and correlating the extent of the residual tumor with preoperative imaging findings. The limitations include training of the pathologist grossing these specimens and more demand on histology laboratory due to whole mount of the sections and less sampling of the tumor bed in the vicinity of the tumor epicenter as compared to the method described above, due to the fact that the amount of tissue remaining in the FFPE block and not assessed under microscope is higher than what is described in the first approach.

Histopathologic Assessment and Pathologic Parameters of Response to Neoadjuvant Therapy

Optimal histopathologic examination includes all the histopathology findings which are assessed in any adenocarcinoma of colon or rectal resection specimen including pathologic tumor stage, nodal stage, distant metastases, presence (or absence) of lymphovascular and perineural invasion, and distance of tumor to the margins. In addition, histologic regression of the tumor characterized by reduction of tumor cells and replacement of the tumor bed by fibrosis with or without necrosis, granulation tissue, and inflammation is one of the essential parameters required to be reported in the pathology report.

Pathologic Tumor Stage (ypT)

More than one study have shown that downstaging of tumor stage (ypT < cT) is an independent prognostic factor of disease-free survival in node-positive and node-negative rectal adenocarcinoma [7]. Pathologic T stage is decided based on the depth of invasion of tumor in rectal wall and/or adherent organs. Only difference as compared to the specimens without neoadjuvant therapy is that presence of tumor cells is required in a layer of rectal wall or adjacent organ for appropriate ypT stage designation. Presence of acellular mucin, necrosis, or fibrosis without tumor cells is not considered to be a histologic evidence of tumor for ypT. Radiation-induced injury also includes thinning of the colon wall with partial destruction of submucosa and/or muscularis propria which can lead to an understaging of ypT3 to ypT1 or ypT2.

Pathologic Nodal Stage (ypN)

Pathologic nodal stage is based on the number of lymph nodes involved by the tumor, similar to the specimens without neoadjuvant therapy. Presence of tumor cells is required in a lymph node to identify lymph node as positive for metastatic carcinoma. However, it is important to identify and report the lymph nodes which show features of preoperative therapy like necrosis, fibrosis, calcification, and acellular mucin. These findings help in identifying any lymph node which would have been reported as positive on preoperative imaging and explain cN+ disease. Location of positive lymph node is independently important if it is present at the margin of highest vascular pedicle (R1 resection) or identified as separate (e.g., inferior mesenteric artery) lymph nodes by the operating surgeon.

Histopathologic Tumor Regression

Tumor regression or pathologic response is identified as an excellent surrogate marker of efficacy of the neoadjuvant therapy and tumor biology in

rectal adenocarcinoma. The macroscopic findings of response to neoadjuvant chemoradiation therapy range from an exophytic tumor mass to an ulcer without any gross tumor to a well-healed scar with only minimal mucosal irregularity. With increasing efficiency in delivering radiation, rectal specimens with a grossly identifiable tumor mass are decreasing, and majority of the specimens show either ulcer or a fibrotic scar. Grading system of response to neoadjuvant therapy based on macroscopic examination is not well characterized and unlikely to be reproducible. Microscopic findings indicative of changes secondary to neoadjuvant chemoradiation are reduction of tumor cells and replacement by the granulation tissue, fibrosis, mononuclear inflammation, necrosis, calcification, and radiation-induced vascular changes like intimal thickening and medial muscular hypertrophy. The histopathologic response is graded under microscope by semiquantitative or quantitative assessment of fibrosis and/or residual tumor burden in the rectal wall and contiguous perirectal soft tissue.

More than one system of assessing histopathology regression (Table 17.2) have shown clinical relevance in predicting disease-specific survival in patients with advanced locoregional rectal adenocarcinoma [8–14].

The definition of complete pathologic response is uniform with all the systems for assessing histopathologic regression. Complete pathologic response (Fig. 17.2) characterized by absence of residual tumor cells in rectal wall and perirectal soft tissue has been observed in ~20% of patients in majority of the prior studies. These groups of patients with complete pathologic response are likely to have more than 95% or higher 5-year disease-free survival [15, 16], so it is imperative that generous sampling and meticulous histopathologic approach are applied before reporting complete pathology response in a rectal resection specimen. Presence of residual tumor cells in lymph nodes or presence of discontinuous soft tissue deposits without residual tumor cells in rectal wall (ypT0N1) is also classified as complete response by majority of grading systems. The significance of ypT0N1 as an independent prognostic factor is poorly defined due to small number of patients with ypT0N1.

Dhadda et al. [9] demonstrated that Mandard 3-point system has similar prognostic relevance to disease-free survival as compared to Mandard 5-point system [8]. Simplified 3-tier Dowrak et al. system [11] is also a good prognostic indicator with similar disease-free survival as Dowrak/Rodel et al. 5-point system [10].

For the AJCC category of TRG 1 or equivalent in other grading systems, disease-free survival ranges from 80 to 90% with 90% in AJCC TRG 1, 86–99% response in MSKCC system [14] near-complete response in UTMDACC system [13], and 80% in comparable grades in Mandard and Dowrak/Rodel grading systems [9, 11].

For the AJCC category of TRG 2 of or equivalent in other grading systems, the disease-free survival ranges from 68 to 77% with Mandard 3-point and <85% response in MSKCC systems showing lowest (68%) and Dowrak 3-point system showing highest (77%) disease-free survival.

For AJCC tumor regression 3 and equivalents in other systems, the disease-free survival ranges from 47 to 68%. The Dowrak/Rodel systems demonstrated lowest disease-free survival (47%), while other systems showed disease-free survival ranged from 61 to 73%.

Interobserver variability among pathologists' assessment for Mandard et al. showed strong linear correlation between the two independent measurements of quantified pathologic response ($R^2 = 0.77$), and moderate to substantial agreement was observed between the two pathologists for the categories of quantified pathologic response ($k = 0.72$) in UTMDACC system. In the Dowrak/Rodel, MSKCC, and UTMDACC systems, a quantitative approach was utilized to grade the response. These approaches require additional effort of quantifying percentage tumor cells and/or fibrosis in each section followed by the sum of these percentages in all sections from tumor bed. In majority of the classification systems, the pathology review was performed by pathologists with special interest or expertise in gastrointestinal or rectal pathology, and reproducibility was higher. However, data about reproducibility with general surgical pathologists is not well documented, and likelihood of poor reproducibility with tumors showing higher percentage of residual tumor cells is possible and should be considered in assessing a

Table 17.2 Histopathologic regression grading systems

Tumor regression grade (TRG), Ryan et al.	AJCC 7th[TR] edition (TRG) system	Mandard five-tier system	Modified Mandard three-tier system	Dowrak/Rodel five-tier system	Dowrak/Rodel three-tier system	MSKCC system	UTMDACC system
No tumor cells (1)	No residual tumor cells (0)	Absence of histologically identifiable tumor cells in rectal wall	Absence of histologically identifiable tumor cells in rectal wall	No regression	Complete regression	100% tumor response	Complete pathologic response
Single tumor cells or small groups of tumor cells (2)	Single tumor cell or small groups of tumor cells (1)	Rare residual tumor cells scattered through the fibrosis	Rare residual tumor cells scattered through the fibrosis	Dominant tumor mass with obvious fibrosis and/or vasculopathy	Fibrosis occupying 25–99% of tumor mass	86–99% tumor response	Near-complete pathologic response
Residual cancer outgrown by fibrosis (3)	Residual tumor outgrown by fibrosis (2)	Increased number of tumor cells but fibrosis predominant	Increased number of tumor cells but fibrosis predominant to absence of regressive changes	Dominant fibrosis with few tumor cells (easy to find)	Fibrosis occupying <25% of tumor mass	<85% tumor response	Major response
Significant fibrosis outgrown by tumor (4)	Minimal or no tumor cell kill (3)	Residual cancer outgrowing fibrosis		Very few (difficult to find) tumor cells in fibrotic tissue			Minor response
No fibrosis with extensive residual cancer (5)		Absence of regressive changes		No tumor cells, only fibrotic mass (total regression or response)			
Kappa = 0.64 for 5-grade system Kappa = 0.84 for 3-grade system (TRG2 + 3 = TRG2, TRG 4 + 5 = TRG3)		Kappa = 0.84	Kappa = 0.89 m $p < 0.001$				$r^2 = 0.77$ Kappa = 0.72

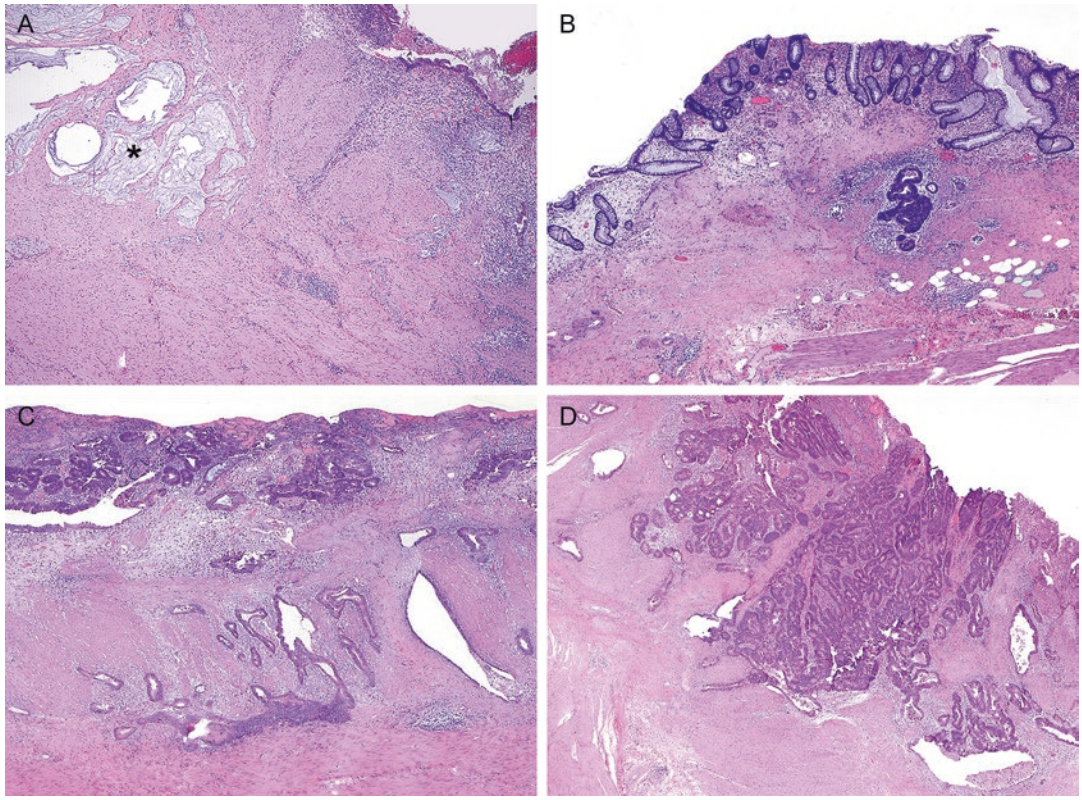

Fig. 17.2 Images of hematoxylin and eosin sections of rectal resection specimens with different grades of histopathologic response to neoadjuvant therapy. **a** shows complete pathologic response with acellular mucin and no tumor cells. **b** shows very good response (TRG 1 or near-complete response) with a single cluster of tumor cells in a fibrotic tumor bed. **c** shows TRG 2 with fibrosis slightly more than tumor cells. **d** shows TRG 3 with minimal fibrosis and dominant component of tumor cells

response to neoadjuvant chemoradiation in rectal cancer with poor responders in particular. Primary reason of likelihood of poor reproducibility is that the histologic changes are frequently patchy and more pronounced in the mucosa and submucosa followed by perimuscular soft tissue and least in the muscularis propria. Generous sampling and assessing the response for each section from the tumor bed followed by combining the measurement of all the slides from the tumor bed is the best approach for optimal assessment of pathologic response or histopathology regression after neoadjuvant chemoradiation in rectal cancer resection specimens.

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18 Maximizing Neoadjuvant Treatment Response and Watch and Wait

Oliver S. Chow and Julio Garcia-Aguilar

Neoadjuvant therapy has been a keystone supporting the advances we have made in the treatment of rectal cancer. The reason for maximizing tumor response to neoadjuvant treatment is clear: as response improves, the consideration of less invasive treatment options such as local excision and "watch-and-wait" (nonoperative) strategies can be explored. Tumor response is closely correlated with long-term oncologic outcome, and the optimization of tumor response to neoadjuvant therapy is thought to improve long-term outcomes as well [1–3]. Maximizing neoadjuvant treatment response is therefore expected to have profound effects on both oncologic outcomes and quality of life.

In this chapter, we will focus primarily on the maximization of neoadjuvant therapy for locally advanced rectal cancer (LARC), widely accepted to be clinical stage II (T3–4, N0) or stage III (any T, N1–2) invasive adenocarcinomas of the rectum, for which neoadjuvant treatment is the standard of care. While neoadjuvant treatment is sometimes considered and has been explored in the context of clinical trials for early rectal cancers, its use in those settings is controversial and will only be discussed briefly.

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Historical Context

At the outset of the twentieth century, abdominoperineal resection following the principles of oncologic surgery as outlined by Halsted was introduced by Dr. William Ernest Miles and considered a curative procedure for patients with rectal cancer. However, with the tools and techniques available at that time, this was a major operation. In Halsted's first 12 patients, there was an operative mortality of 50%. Not surprisingly, safer alternatives were sought.

Dr. Henry Janeway, the first Director of the Radium Department at Memorial Sloan Kettering Cancer Center (MSK), reported the first case of rectal cancer treated by radium in the United States. He used a flexible bougie to apply radium. In the 1920s, Dr. George Binkley, the first Chief of the Colorectal Service at our institution, reported the techniques for both external and interstitial application of radium. He noted that the implantation of gold radon seeds prompted a dramatic response in some tumors, which could be made even more durable when combined with surgical resection. Therefore, Binkley stated that radiation should be considered a preferable method for treating rectal cancers [4].

By the late 1920s and 1930s, however, it had become clear that radiation could not be considered curative except in a small number of patients. Even so, the combination of radiation and surgical approaches continued to be explored, and in

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1959 a large report on over 1700 patients treated with preoperative radiation therapy was published by Drs. Stearns, Deddish, and Quan. This became an influential paper in the field of neoadjuvant radiation for rectal cancer [5].

It was in this context that a large number of trials accumulated evidence demonstrating the effectiveness of radiation therapy in decreasing local recurrence. Four of the more notable trials include the Stockholm I/II trials, the Swedish rectal cancer trial, the UK MRC2 trial, and the Northwest England trial, each showing significant reductions in local recurrence. However, only the Swedish trial showed an improvement in survival through the use of radiation therapy. From the 1970s through the 1990s, the use of radiation for treatment of rectal cancer evolved, consisting primarily of external beam radiotherapy [6, 7].

Around the same time, surgical techniques were also improving our ability to provide local control. Total mesorectal excision (TME) was being adopted as the surgical standard for LARC. After introducing the principles of TME in 1982, Heald and colleagues reported that the rates of 5-year local recurrence dropped to 2.7% in their cohort, and throughout the 1990s, others began reporting similar results [8]. These two concurrent advances in the management of LARC successfully reduced rates of local recurrence from well above 30% to the range of 5% by the 2000s. Having observed improvement in local recurrence with TME surgery, in order to assess the potential benefit of TME and radiation therapy versus TME alone, the Dutch rectal cancer trial compared TME with and without radiation, demonstrating that radiation provided a further decrease in 5-year local recurrence; however, they were not able to identify a change in survival [9]. This trial proved critical in determining whether radiation therapy provided any additional benefit over optimal surgery alone.

Further reductions in the rate of local recurrence were achieved by adding chemosensitizing agents to radiotherapy [10, 11]. The German rectal cancer study group then shifted the routine postoperative use of chemoradiation treatment (CRT) to the preoperative setting, showing a decreased rate of local recurrence and no increase in perioperative morbidity in their randomized trial [12]. This cadre of clinical trials and a number of others we will review in this chapter have brought about a widely adopted current standard consisting of neoadjuvant chemoradiation, followed by TME in 6–8 weeks, with the consideration of adjuvant therapy afterward. Overall, progress has been extremely encouraging; a disease with high morbidity and mortality has now been met with therapies that almost completely mitigate the risk of local recurrence (Fig. 18.1) [8, 9, 12–21]. The coming years of research and clinical practice will be directed toward improving control of distant recurrence and tailoring therapy to groups of patients based upon the aggressiveness or molecular characteristics of their rectal cancers. An important goal will be to isolate and tailor therapies, selecting treatments that can be expected to benefit a particular group of patients, while minimizing or eliminating the use of treatments that will not provide additional benefit.

Radiosensitizing Agents

Numerous chemotherapeutic agents—most of which have shown some radiosensitizing effects in preclinical studies—have been tested in the neoadjuvant setting to accompany radiotherapy (Table 18.1). Some, like irinotecan, have been tested in LARC primarily because of its observed benefit in metastatic colorectal cancer. With the exception of fluoropyrimidines, however, none have been effectively validated in prospective trials.

Fluoropyrimidines

5-Fluorouracil (5-FU) is the primary chemotherapeutic agent used in the radiosensitization in rectal cancer. While its potential to create a state of radiosensitivity was recognized early on, studies eventually led to the understanding that the benefit of 5-FU was inextricably linked to the schedule of its administration. 5-FU must remain

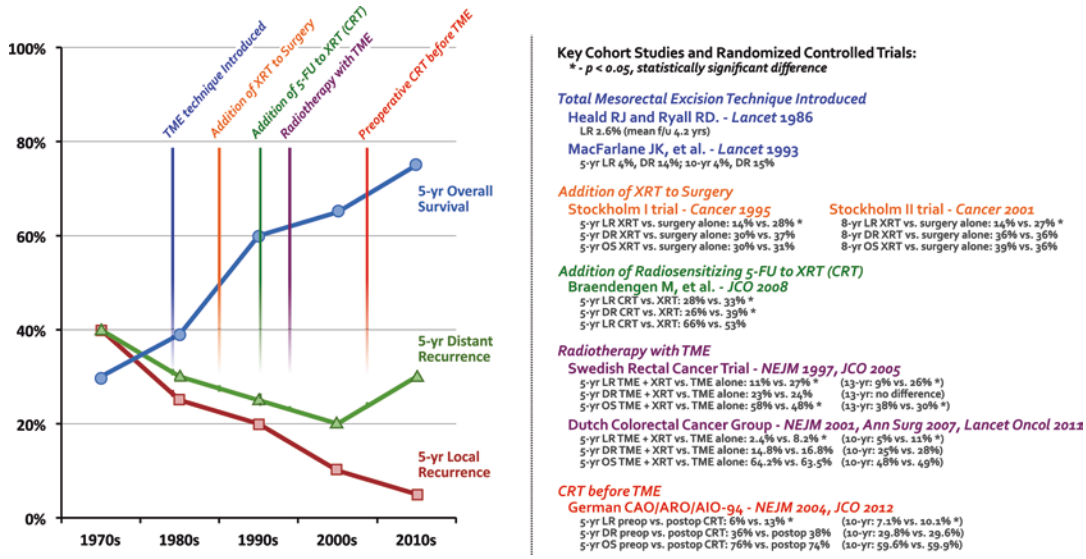

Fig. 18.1 Historic progression toward the current standard of care for locally advanced rectal cancer: chemoradiotherapy before total mesorectal excision. *XRT* radiotherapy, *CRT* chemoradiation therapy, *TME* total mesorectal excision, *LR* local recurrence, *DR* distant recurrence, *OS* overall survival

Table 18.1 Chemotherapeutic agents considered and explored as radiosensitizers or for total neoadjuvant therapy approaches

Agents	Mechanism	Common side effects
5-FU	Pyrimidine analog, thymidylate synthase (TS) inhibitor	GI, mucositis
Folinic acid (leucovorin)	Enhances 5-FU effects and contributes to TS inhibition	–
Irinotecan	Topoisomerase I inhibitor	GI, leukopenia
Capecitabine	Prodrug of 5-FU	GI, mucositis
Oxaliplatin	Platinum-based agent, DNA cross-linking	Peripheral neuropathy, GI
Cetuximab/ panitumumab	Anti-EGFR monoclonal antibody (for use with KRAS wild-type tumors only)	Skin rash
Bevacizumab	Anti-VEGF monoclonal antibody	Compromised wound healing[a]

[a]Recommend discontinuation 6 weeks prior to surgery, given its T1/2 of approx. 3 weeks

present after radiation exposure to establish and maintain the radiosensitive state; for this reason, bolus 5-FU quickly fell out of favor, and continuous venous infusion (CVI) of 5-FU 225 mg/m^2 daily became the standard [22].

The overall benefit of combining chemotherapy with radiation therapy (RT) was proven by several randomized trials by the North Central Cancer Treatment Group (NCCTG) and the Gastrointestinal Tumor Study Group (GITSG) that compared postoperative radiotherapy alone versus radiotherapy with 5-FU administered either as a bolus or by CVI [23, 24]. From other studies that followed in the NCCTG and the Intergroup consortia, it became apparent that CVI 5-FU was associated with lower hematologic toxicity and longer overall survival compared to bolus 5-FU [25, 26]. The European Organization for Research and Treatment of Cancer (EORTC) protocol 22921 was developed to assess the effect of adding chemotherapy to preoperative RT and the value of postoperative chemotherapy in LARC [11, 27]. They randomized 1011 patients across four arms: (a) preoperative radiotherapy, (b) preoperative radiotherapy plus bolus 5-FU and leucovorin, (c) preoperative radiotherapy followed by postoperative chemotherapy, and (d) preoperative radiotherapy and bolus 5-FU and leucovorin

followed by postoperative chemotherapy. Five-year local recurrence was significantly lower in all three arms receiving any form of chemotherapy (pre- or postoperative) compared to radiotherapy alone, though survival was not significantly altered. More recently, in a randomized phase III trial, Hofheinz and colleagues showed non-inferiority of capecitabine, the oral prodrug of fluorouracil, when compared to 5-FU. This provided a convenient treatment alternative for reliable and motivated patients [28]. The equivalence of capecitabine and 5-FU has also been corroborated with the NSABP-R04 cohort [29].

Oxaliplatin

A number of large phase III trials have evaluated the potential role of oxaliplatin in increasing radiation sensitivity. The STAR-01 [30], the ACCORD 12/0405-PRODIGE2 [31], and the NSABP-R04 [29] trial each investigated the addition of oxaliplatin to a fluoropyrimidine. This combination, however, appeared to result in greater toxicity with no improvement in response or therapeutic benefit. Conversely, the CAO/ARO/AIO-04 trial [32] found that the inclusion of oxaliplatin to a 5-FU-based CRT regimen led to a higher pathologic complete response (pCR) rate, with no increase in toxicity. While encouraging, their 5-FU dosing and schedule differed between the control arm and the arm with oxaliplatin, which may have affected the outcomes. At this point, oxaliplatin is not routinely included in the neoadjuvant regimens currently used for rectal cancer. Together, these four trials have also demonstrated that neoadjuvant chemoradiation using a fluoropyrimidine-based chemosensitization agent achieves a pCR rate between 13% and 19%.

EGFR Inhibitors

The success and efficacy of anti-EGFR agents like cetuximab, panitumumab, and nimotuzumab in KRAS wild-type metastatic colorectal cancer prompted a number of studies evaluating its use in the preoperative treatment of LARC. Response rates with the addition of EGFR inhibitors to 5-FU and radiotherapy have been inconsistent; increased response is seen in some studies [33], but most studies have demonstrated equivocal results [34, 35]. The EXPERT-C trial randomized 165 patients to four cycles of capecitabine/oxaliplatin before chemoradiotherapy, with or without weekly cetuximab during the CAPOX and CRT regimens. While cetuximab was shown to have an increase in radiologic response and overall survival in KRAS/BRAF wild-type rectal cancers, the primary endpoint of improved pCR was not met [36]. Some studies have reported a worse response, which suggests there may be mechanisms of response in tumors to these combined modality treatments that are not yet understood [37]. In a review of multiple phase I/II trials that included cetuximab in the neoadjuvant regimen, Glynne-Jones et al. measured a pooled pCR for cetuximab-based regimens across 11 studies at 10.71%, compared with a pCR rate of around 13% with other standard fluoropyrimidine-based CRT schedules [37]. Given these findings, EGFR inhibitors are not used in the neoadjuvant setting as a radiosensitizer at this time.

Irinotecan

This topoisomerase inhibitor has shown significant antitumor activity in metastatic colorectal cancer. While there have been small phase II trials showing that irinotecan may be effective and safe as an adjunct to traditional 5-FU and radiotherapy [38, 39], there have not been any phase III trials assessing its relative efficacy compared to 5-FU and radiotherapy alone.

Other Agents

Urick and colleagues reported enhanced radiosensitization when MEK inhibition by selumetinib was added in both in vitro settings and in vivo HCT116-derived xenografts [40]. Kleiman and colleagues focused on KRAS mutant rectal cancers that are widely reported to be more resistant to CRT and tested multiple

small molecular inhibitors for potential radiosensitizing capability. They found a Chk1/2 inhibitor and a PI3K/mTOR inhibitor to be particularly promising, as these had a synergistic effect combined with 5-FU [41]. Other experimental approaches have attempted to increase radiation sensitivity by imposing additional oxidative stress with less toxic compounds such as zerumbone, a compound derived from ginger [42]. Many of these experimental approaches appear promising but have not yet been validated in clinical trials. Conceivably, they could help improve local control and increase the rate of pCR.

Short- Versus Long-Course Radiotherapy

The efficacy of RT in the setting of high-quality surgical resection using TME principles was specifically explored in the Dutch Colorectal Cancer Group trial mentioned previously, which randomized 1861 patients with resectable disease to TME alone or to short-course RT (SCRT) followed in 2–7 days by TME. They found patients in the RT arm had a reduced rate of local recurrence compared to TME alone; however, SCRT did not affect survival [9]. This study effectively demonstrated the value of RT, however, lending early support for a short-course modality.

In SCRT, 25 Gy is usually provided in five 5 Gy fractions, compared with long-course radiation, which generally delivers 1.8 Gy across 28 fractions, along with the concurrent use of radiosensitizing 5-FU. Proponents of the SCRT highlight patient convenience and lower costs as important advantages, while those supporting long-course radiation point at decreased surgical morbidity and improved sphincter preservation, along with the benefits of chemosensitizing agents (which cannot be given safely simultaneously in the SCRT regimen). In addition, some studies have reported that the higher dose per fraction (5 Gy compared with 1.8 Gy) increases the risk of delayed toxicity and that tumor regression is lower with SCRT [9, 43]. Few trials have sought to compare these two approaches directly, though.

Bujko and colleagues are the only group to have prospectively compared the two, randomizing 316 patients to either CRT or SCRT, and found that long course was associated with a significantly decreased incidence of positive radial margins (4.4% vs. 12.9%, $p = 0.017$) and a higher rate of pCR (0.7% vs. 16.1%); however, this did not carry over into a significant difference in local recurrence or survival [44]. Moreover, they reported greater radiation toxicity in the CRT group and poorer compliance to treatment schedule. Their conclusion was that SCRT was a viable alternative to CRT with neither holding a long-term oncologic advantage, but SCRT is potentially beneficial in terms of lowering cost, and lower morbidity is associated with its use. More recently, the Trans-Tasman Radiation Oncology Group 01.04 randomized 326 patients with ERUS- or MRI-staged T3,N0–2,M0 tumors to SCRT and surgery followed by 6 months of adjuvant chemotherapy or CRT and surgery followed by 4 months of adjuvant chemotherapy [45]. Their study was powered to detect a 10% difference in local recurrence at 3 years, with a 5% level of significance. They reported a trend toward lower 5-year cumulative incidences of local recurrence for long-course CRT compared with SCRT (5.7% vs. 7.5%, $p = 0.51$). However, the differences were not statistically significant. Moreover, patient imbalances between groups have been called to attention, with fewer patients with low rectal cancers in the CRT than the SCRT arms, and varying rates of APR. The quality of surgery and accuracy of MRI staging have also been criticized [46, 47].

The CRT-course divide has, therefore, remained somewhat static across national boundaries, with a Western preference for long-course CRT and a majority of European countries favoring SCRT. Because of a current trend exploring the incorporation of therapies traditionally reserved for the adjuvant period into the neoadjuvant regimen, combinations of either short-course RT or long-course CRT with systemic therapies are being explored and gaining greater traction. As such, it may become increasingly difficult to determine whether short-course or long-course RT is more effective as independent neoadjuvant modalities.

Time Interval between CRT and Surgery

Apart from sporadic observations and reports between the 1960s and 1990s, not much attention has been placed on the interval between CRT and surgery [48]. The reasons for this are probably multifaceted, but the arbitrary 6–8-week interval between the end of CRT and surgery has spread widely and is still maintained today. Nevertheless, in the 1990s, Brierley and colleagues from the Princess Margaret Hospital used radiation alone for 229 patients whose tumors were deemed unresectable or who were medically unfit for surgery or declined to have surgery [49]. They made a key observation that out of 66 patients who had a clinical complete response (cCR) to radiation, approximately 60% had tumor involution at 4 months and the remainder at 8 months, far longer than the standard 6–8 weeks. This suggested that the extent of radiation-induced tumor necrosis would have continued beyond the time of surgery. The reluctance to extend the duration is partly due to the well-recognized increase in fibrosis following completion of RT, which increases the difficulty of the operation (although it has not been measured systematically). At least one retrospective study reported increased morbidity and worse outcomes associated with a delay in surgery [50]. However, this has yet to be verified in any prospective cohort. In fact, many retrospective studies since then have found that a prolonged interval between CRT and surgery is associated with a greater tumor response [51–54].

In the Lyon R90-01 trial—one of the only prospective trials assessing the impact of the CRT-to-surgery interval—Francois and colleagues [55] randomized patients to a long interval (6–8 weeks) and short interval (<2 weeks) and found that the longer interval was associated with a higher rate of complete response (26% vs. 10.3%, $p = 0.005$), without a significant increase in surgical morbidity. More recently, Habr-Gama and colleagues evaluated a retrospective cohort of 255 patients [56], splitting the cohort into two groups, >12-week CRT-to-surgery interval and <12-week CRT-to-surgery interval; they also found that a longer interval increased the response rate, without increasing surgical morbidity.

The Timing of Rectal Cancer Response to Chemoradiation Consortium recently completed their study [57], which consisted of a series of prospective study groups measuring the rate of pCR when increasing the CRT-to-surgery interval with the addition of cycles of mFOLFOX-6 in the neoadjuvant setting. They achieved a high pCR rate of 38% by extending the CRT-to-surgery interval of 19.3 weeks, with the incorporation of six cycles of mFOLFOX-6 following chemoradiation in the last of their study groups. While their study cannot delineate whether the increased rate of response was due to the prolonged interval or the addition of up to six cycles of mFOLFOX-6 to the regimen, it does demonstrate that the prolonged interval does not increase surgery-related morbidity or operative difficulty.

Incorporation of Traditional Postoperative Systemic Chemotherapies into the Neoadjuvant Setting

The aforementioned optimization of CRT and surgery results in excellent local control of LARC, but the proportion of patients developing distant metastasis after a seemingly curative resection remains high. Understandably, this has shifted the focus of many studies toward improved control of distant metastasis, which is now the major cause of long-term mortality from this disease. Most clinicians have based adjuvant chemotherapy for patients with LARC on the lessons learned from managing colon cancer. Another approach also extrapolates the benefits of systemic chemotherapy for colon cancer but has led to explorations on the impact of shifting traditional adjuvant chemotherapies to the neoadjuvant, preoperative setting, either before chemoradiation (induction chemotherapy) or after chemoradiation (consolidation chemotherapy). Certain groups have dubbed these efforts complete or total neoadjuvant therapy (TNT). These studies have been performed most commonly with fluoropyrimidine-/oxaliplatin-based regimens, but other targeted agents such as

those summarized in Table 18.1 have been tested as well. The rationale behind these approaches is to introduce systemic chemotherapy early, theoretically acting upon micrometastatic disease and potentially reducing eventual distant recurrence. Tumors may also be more responsive to chemotherapy delivered using their original blood supply, compared to the disrupted supply after surgery [58]. Beyond these theoretical advantages, the TNT approach is a practical response to the observation that nearly one-third of patients eligible for adjuvant chemotherapy never receive it and more than half never complete it as planned [11, 32]. Although almost all patients who receive CRT and TME should undergo adjuvant therapy, many forgo adjuvant chemotherapy due to postoperative complications, the presence of an ostomy, delays in ostomy reversal [59], or outright refusal [60]. More to the point, poor compliance to adjuvant therapy is associated with worsened survival in CRC. A systematic review of 10 studies including more than 15,000 patients demonstrated that each 4-week delay in the initiation of adjuvant chemotherapy corresponded to a 14% decrease in overall survival [61], a worrisome observation that could probably be generalized to rectal cancers. Interestingly, a recent systematic review and meta-analysis of four large phase III European trials disputed these results, showing no difference in overall survival whether adjuvant chemotherapy was given or not [62]. At this point, adjuvant chemotherapy following CRT and TME is still the standard of care. However, in light of the questions regarding its efficacy, alternative sequencing might be more accepted. Providing all or part of these therapies in the neoadjuvant setting bypasses many of these issues.

Induction Chemotherapy

Various regimens of neoadjuvant chemotherapy given prior to CRT have been tested in phase I and II trials, and most have delivered promising results, demonstrating improved tumor response rates and some suggestion of improved oncologic outcomes, with acceptable toxicity [63, 64]. Some of the earlier cohorts focused on patients thought to be at especially high risk based on imaging or clinical characteristics [65]. With encouraging response rates from these cohorts, other trials have extended these findings to regular LARC groups. One of the more tested induction regimens consists of capecitabine and oxaliplatin (CAPOX) prior to CRT.

A trial led by Maréchal and colleagues randomized patients to standard CRT and surgery or FOLFOX followed by CRT and surgery; they did not identify any improvement in tumor response, and the trial was closed due to futility. It did, however, demonstrate that the regimen was tolerable [66]. Cercek and colleagues from Memorial Sloan Kettering Cancer Center recently reviewed their experience using FOLFOX prior to CRT, demonstrating excellent treatment compliance and no signs of serious adverse effects [67]. All patients treated in their cohort underwent TME with an R0 resection, and nearly half had a tumor response greater than 90%. Even more impressive was the fact that 36% achieved either pCR or cCR, with a carefully selected group of clinical complete responders not undergoing TME at all.

Several groups have also been tested using targeted therapy as part of the induction regimen, such as VEGF inhibitor bevacizumab [68]. The EXPERT-C trial [36] tested an induction CAPOX regimen, with or without cetuximab. In the latter, Dewdney and colleagues show that KRAS/BRAF wild-type tumors (which are those expected to respond to the additional EGFR inhibitor) had greater radiologic response and overall survival, but not a higher rate of complete response after a median follow-up of close to 3 years [36].

Consolidation Chemotherapy

In the recently completed Timing of Rectal Cancer Response to Chemoradiation trial, we found that delivering two, four, or six cycles of mFOLFOX-6 after standard CRT in patients with LARC increased pCR rates progressively up to 38%, compared with a baseline 18% with CRT alone. No increase in adverse events, surgical complications, or risk of progression was observed

[36]. Along similar lines, Hong and colleagues showed that FOLFOX consolidation improves 3-year DFS compared with 5-FU+LV following CRT and TME [69]. While completely theoretical and unproven, it is possible that providing chemotherapy after CRT may result in higher rates of pCR because the additional chemotherapy extends the duration between radiation and surgery, providing added time for the tumors to respond. Habr-Gama and colleagues have also studied consolidation therapy using three cycles of bolus 5-FU over 9 weeks following CRT; they have also noted a higher rate of pCR, with no increase in postoperative complications [70].

The Rectal Cancer and Preoperative Induction Therapy Followed by Dedicated Operation (RAPIDO) trial is currently randomizing patients to preoperative short-course radiation followed by six cycles of CAPOX and TME versus traditional preoperative long-course CRT and TME, measuring 3-year disease-free survival as their primary outcome [71].

Induction vs. Consolidation

The cumulative experience leads us to ask whether one sequence (induction or consolidation) is better than the other. A new prospective trial at MSK (NCT02008656) is testing the hypothesis that TNT will improve 3-year disease-free survival compared to standard CRT. In this trial, patients are being randomized to induction or consolidation therapy with FOLFOX, which should provide data to compare these two approaches.

There is no reason to assume that one approach will prove better than the other or that an entirely new sequence might not be found. For example, a small phase II trial by Gao and colleagues recently reported one of the highest pCR rates published for LARC thus far, with 19 of 45 (42.2%) patients achieving pCR and another 40% achieving near-complete response. They described their regimen as a "sandwich," with one cycle of induction XELOX, followed by CRT and then followed by another cycle of consolidation XELOX before surgery in 6–8 weeks [72].

It can also be speculated that additional neoadjuvant therapy selects out certain aggressive and resistant tumors that are likely to progress to metastatic disease regardless of the current treatment approach. For these tumors, the administration of additional neoadjuvant therapy potentially provides the opportunity to identify distant progression, which might spare these patients radical surgery that would not benefit them and might be harmful. It is imperative to highlight the exploratory nature of these regimens, and a main concern which must be addressed and measured is whether these intensive neoadjuvant regimens increase surgical morbidity or overall toxicity. Most of these trials have collected data that is not fully mature, with no long-term oncologic and survival data. Nevertheless, given consistent improvement in tumor response and the increased proportions of pCR (which serves well as a surrogate marker), it is anticipated that we will see measurable gains in the coming years. It seems safe to say that these intensive neoadjuvant regimens will play an important role in the treatment of LARC over the coming decade.

Assessment of Response

Taking advantage of tumor response obviously requires accurate recognition of response. One of the challenges we face when trying to maximize neoadjuvant therapy is our ability to accurately assess tumor response to those therapies. When a complete or near-complete response is achieved after neoadjuvant therapy, we are increasingly inclined to consider either a local excision procedure or a "watch-and-wait" approach (Fig. 18.2). In doing so, however, we forgo the opportunity to thoroughly assess tumor response. In the case of local excision, we forgo the pathologic assessment of nodal disease, and in "watch-and-wait" approaches, we forgo the assessment of both the tumor and locoregional nodes altogether. Since the standard algorithms utilize pathological information to decide upon adjuvant therapy, our inability to fully assess the tumor may compromise our decisions regarding adjuvant treatment. What we are left with is the

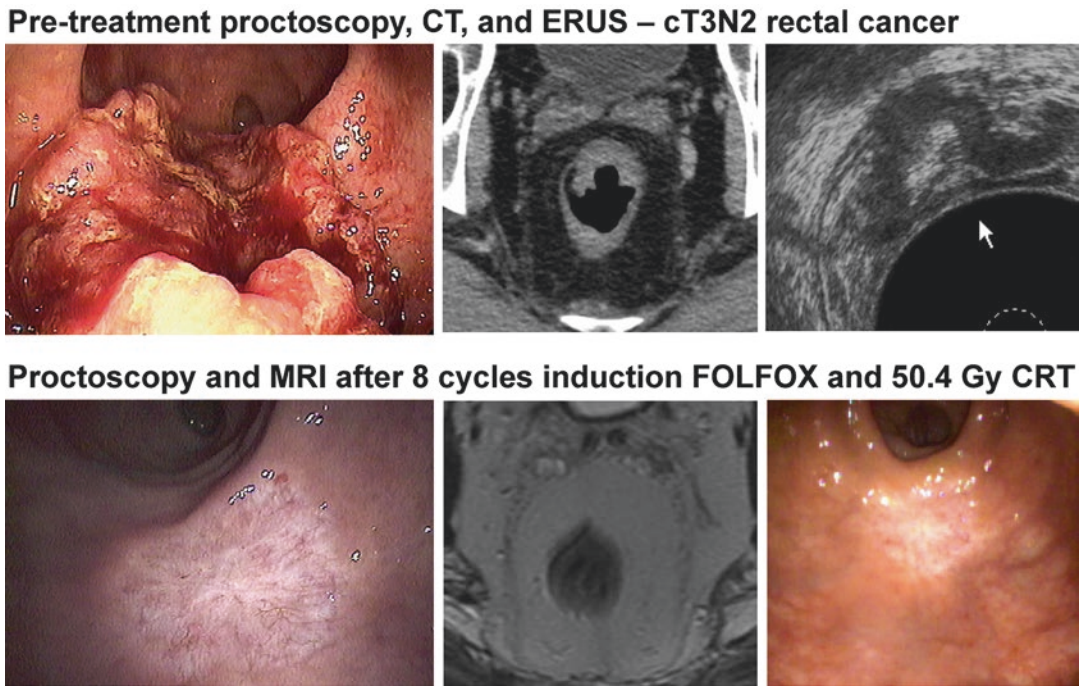

Fig. 18.2 cT3N2 rectal cancer before therapy (*top*) and after therapy consisting of eight cycles of FOLFOX and 50.4 Gy of chemoradiation (*bottom*), demonstrating a clinical complete response and currently managed with a "watch-and-wait" strategy

clinical or radiologic assessment of response. Although imperfect, these assessments are also improving. Our institution has settled upon a schema to assess tumor response in an attempt to standardize assessments that have potentially been heterogeneous (Fig. 18.3).

It has been noted that digital rectal examination after CRT, even when performed by experienced colorectal surgeons, is unreliable in determining pCR [73]. While similar studies using ERUS and ERUS/CT to assess response after CRT seemed to show reasonable correlation with subsequent pathologic staging, the accuracy still ranged from 40% to 75% [74, 75]. Across each of these studies, overstaging of the residual tumor was more common than understaging. This suggests that patients are less likely to be undertreated if we relied solely upon these measures, but more accurate measures are still needed. Part of this is because clinical assessment of tumor response has typically been performed early on after neoadjuvant treatment, when tumors have not responded completely and when the pCR rate was low upon subsequent surgical resection. If the pCR rate is increased through an intensified neoadjuvant approach, we would expect that complete response would become easier to identify in the clinical setting.

A growing body of research has found that both ^{18}FDG-PET/CT [76–79] and multiparametric MRI [80–83] can be used to distinguish between responders and nonresponders by comparing pre- and post-CRT imaging features. These have generally shown strong concordance with subsequent pathologic assessment of pCR and tumor regression [84, 85]. The goal is to improve post-CRT radiologic assessment of response to more closely approximate pathologic assessments. If pathologic response can be more accurately predicted, we will have greater confidence in offering patients with responsive tumors alternative approaches to traditional treatment algorithms.

Some small exploratory studies have assessed radiologic response to CRT very early in the

	Complete Response	Near Complete Response	No response
Endoscopy	• Flat, white scar • No ulcer • Telangiectasia • No nodularity	• Irregular mucosa • Small mucosal nodules • Superficial ulceration	• Visible tumor
DRE	• Normal	• Smooth induration	• Palpable tumor nodules
MRI-T2W	• Only dark T2 signal, no intermediate T2 signal AND • No visible lymph nodes	• Mostly dark T2 signal, some remaining intermediate signal AND/OR • Partial regression of lymph nodes	• More intermediate than dark T2 signal, no T2 scar AND/OR • No regression of lymph nodes
MRI-DW	• No visible signal on B800-B1000 AND/OR • Lack of or low signal on ADC map • Uniform, linear signal in wall above tumor is ok	• Significant regression of signal on B800-B1000 AND/OR • Minimal or low residual signal on ADC map	• Insignificant regression of signal on B800-B1000 AND/OR • Obvious low signal on ADC map

ADC – Apparent diffusion coefficient

Fig. 18.3 Schema for classifying tumor response to neoadjuvant therapy

course of CRT. Using ^{18}FDG-PET/CT, Goldberg et al. performed a small prospective study of 20 patients and found that >32% decrease in maximum SUV was predictive of pCR after 1 week of treatment [86]. Similarly, a pilot study at MSK using DWI/DCE-MRI at early time points during CRT to evaluate their potential use in predicting response is currently under way (ClinicalTrials.gov Identifier: NCT01830582).

Setting the Right Limits

Chemoradiation has clearly proved itself invaluable at controlling local recurrence of rectal cancer. The weight of evidence also demonstrates that systemic chemotherapy—when applied in the neoadjuvant setting—similarly controls tumor progression, possibly acting on micrometastatic disease to improve distant control. But while the benefits of these intensive neoadjuvant regimens are alluring, they have also sparked a heated debate about whether all patients require such intensive treatment. The oncologic success in treating LARC has been achieved at the cost of significant morbidity and compromised quality of life [43, 59, 87, 88]. The task before us is to develop treatment approaches that maximize oncologic outcome while preserving quality of life by minimizing the morbidity associated with any treatments (Fig. 18.4) [89]. Do all patients with LARC require CRT, chemotherapy, and TME? The necessity of such an intense multimodality approach should naturally be questioned.

In a number of European countries, the "right limits" have been framed around MRI-based measures of tumor aggressiveness. A risk stratification system that covers all rectal cancers and that incorporates the proximity of the primary rectal cancer to the mesorectal fascia, the depth of tumor invasion, the presence of metastatic lymph nodes, and the presence of venous invasion is used to classify LARC into "the good," "the bad," and "the ugly" [90, 91]. For their low-risk, "good" tumors, TME alone is recommended; for intermediate-risk "bad" tumors, the recommendation is short-course radiotherapy followed by TME; and for high-risk "ugly" tumors, the recommendation is CRT followed by TME. While this framework is intuitive, its utility has not yet been evaluated in prospective cohorts.

Selective Use of Chemotherapy

We can gain insight from studies that have sought to define the subgroups that benefit most from adjuvant therapy. Given the variable responses to CRT and its bearing on prognosis in LARC [2, 92], the need for adjuvant chemotherapy in patients who achieve a complete or near-complete response to CRT has been questioned [93]. A multi-institutional, retrospective analysis of 3133 patients recently revealed that the benefit of adjuvant

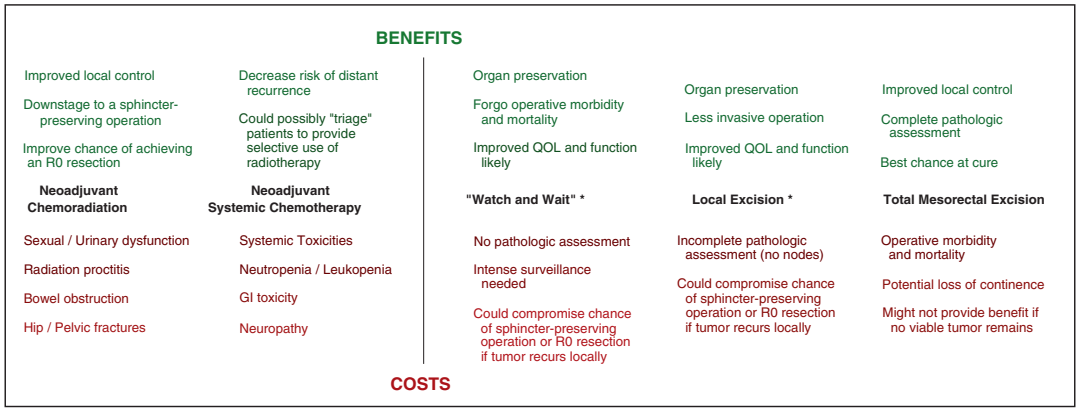

Fig. 18.4 Balancing the benefits and costs of multimodality therapy and less invasive surgical strategies

therapy differs significantly between LARC subgroups. Patients with ypT1–2 or ypT3–4 tumors appeared to benefit more from adjuvant therapy compared with ypT0N0 patients, and those who achieved a pCR did not seem to benefit from adjuvant chemotherapy [94]. Some centers now use postoperative chemotherapy selectively, based on tumor response to CRT. In the recently published ADORE phase II trial, which examined the use of selective approaches to adjuvant chemotherapy, LARC patients with ypT3–4N0 or ypTanyN1–2 rectal cancers after CRT were randomized to receive adjuvant chemotherapy with either four cycles of 5-FU and LV or eight cycles of FOLFOX. The administration of FOLFOX after surgery was associated with prolonged progression-free survival (PFS) in stage III patients, but not in stage II patients [69]. In the coming years, more carefully conducted correlative studies will hopefully delineate the clinicopathologic characteristics and molecular markers associated with response to adjuvant therapy, which will prove useful in identifying which patients do not benefit from these treatments.

Selective Use of Radiotherapy

Radiotherapy may play a more important role for some patients than others. The risk of local recurrence in LARC depends on tumor stage but also on the distance of tumor from the anal verge and its proximity to the mesorectal fascia (MRF) [9, 95]. Tumors located in the upper rectum away from the MRF have a low risk of local recurrence when treated with TME. The added benefit of radiotherapy in these patients has been questioned, as it is associated with significant toxicity including bowel obstruction, hip fractures, sexual and urinary dysfunction, and proctitis [26, 79, 80]. A growing body of evidence suggests that radiotherapy could be safely avoided in patients with intermediate-risk rectal tumors, such as those located between 5 and 12 cm from the anal verge that, on MR imaging, do not threaten the MRF [81, 82]. In a pilot phase II trial conducted at MSK, 32 patients with resectable clinically staged II–III rectal cancers were treated with neoadjuvant FOLFOX/bevacizumab and then selective CRT, based on tumor response [83]. The 30 patients who completed preoperative chemotherapy had tumor regression and underwent TME without preoperative CRT. No local recurrences were noted at 4 years, and an 84% DFS was achieved [83]. These results were used as proof of concept for the design of the "Phase II/III Trial of Neoadjuvant FOLFOX, With Selective Use of Combined Modality Chemoradiation versus Preoperative Combined Modality Chemoradiation for Locally Advanced Rectal Cancer Patients Undergoing Surgery" or the PROSPECT trial, which is now accruing worldwide. The primary

goal of this trial is to determine whether pelvic radiotherapy can be used in LARC patients selectively, rather than giving reflexive CRT, based on patients' response to neoadjuvant FOLFOX [82]. The underlying hope is that, by tailoring therapy more precisely based on clinical subgroups and tumor response to treatment, we will eliminate some of the over- or undertreatment with radiotherapy noted in previous trials.

Selective Use of Surgery

Finally, could some patients potentially forgo TME? Most studies document that 15–30% of LARC patients treated with CRT exhibit a pCR at the time of surgical resection [38, 84]. As discussed above, some of the approaches with TNT raise the pCR rate close to 40%. Keeping in mind that the response in these patients provides them with 5-year local recurrence rates of less than 1% and survival of over 95%, the natural question is whether TME is indeed necessary for these patients.

Despite the limitations in assessing tumor response by clinical and radiologic examinations described above, a number of institutions have proffered their experience with "watch-and-wait," or nonoperative management (NOM), approaches after CRT. The pioneering experience with the NOM approach—which is also the largest—comes from Habr-Gama's group in Sao Paulo, Brazil [54, 85]. In their protocol, they assessed tumor response 8 weeks after CRT using clinical, endoscopic, and radiologic tools [85]. Patients with persistent tumor proceeded to TME, while those who appeared to have a clinical complete response then underwent monthly evaluations with DRE, proctoscopy, CEA levels, and biopsy of suspicious lesions. Patients showing evidence of tumor relapse are directed to surgery, while patients with a sustained cCR after 1 year continue with surveillance every 3 months for an additional year and every 6 months thereafter. Twenty-seven percent of rectal cancer patients treated according to this protocol have a sustained cCR and are spared TME. Local relapse during follow-up developed in 10% of patients entered in the NOM protocol, but all had curative TME. The oncologic results in this NOM group were equivalent to those of patients who had a pCR after TME. A group from the Netherlands reported their experience with NOM in 21 patients with cCR as determined on clinical exam, MRI, and endoscopic biopsy, among 192 patients treated with CRT between 2004 and 2010 [86]. After a mean follow-up of 25 ± 19 months, one patient had developed local regrowth but was successfully salvaged. The other 20 patients are alive without disease. Outcomes in patients with cCR treated according to a NOM protocol were similar to outcomes of patients with a pCR after TME. At MSK, rectal cancer patients with a cCR have been managed with the NOM strategy since 2006. Of the 32 patients starting treatment before 2010 who were followed for a median of 23 months, 6 patients (21%) developed relapse, and all underwent curative salvage surgery [87]; 3 of these patients developed distant disease [87]. Survival for the entire group was no different than that of patients with pCR after TME treated during the same period, suggesting that the NOM approach results in no oncologic harm. The combined experience of these series suggests NOM as a viable approach in carefully selected patients, with the clear benefit of sparing this subgroup the morbidity associated with TME.

The safety and efficacy of the NOM approach outside of centers specializing in the treatment of rectal cancer are still unexplored. It is now clear that even with strict criteria to determine cCR, around 10–25% of patients can be expected to have a local regrowth of tumor, emphasizing the necessity of vigilant surveillance to facilitate early recognition and timely salvage. A number of prospective observational studies are under way to further evaluate the utility of NOM. Bujko and colleagues are evaluating NOM in patients 70 years or older (who understandably fare worse with TME) who initially have tumors smaller than 5 cm and less than 60% circumferential involvement and achieve a cCR with either traditional long-course CRT or short-course RT for those who cannot tolerate chemotherapy. Their hypothesis is that elderly patients with cCR will have less than 25% local recurrence and that successful salvage surgery is achievable in those cases. The planned study highlights the

importance of including patient factors (e.g., age) that may further define treatment approaches and weighing the benefits/costs of each therapy.

Tait and colleagues of the Royal Marsden Hospital, UK, have been accruing patients for their "watch-and-wait" study. They are prospectively measuring the percentage of patients who can safely avoid surgery following a cCR to CRT and are also investigating the time to maximal tumor response following CRT.

At MSK, we have begun accruing patients in a prospective, multi-institutional, randomized trial (ClinicalTrials.gov Identifier: NCT02008656) designed to test the hypothesis that patients with LARC treated with TNT (i.e., either induction or consolidation chemotherapy, with CRT) followed by TME will have improved 3-year disease-free survival, when compared to standard therapy (Fig. 18.5). After total neoadjuvant therapy has been received, patients will undergo restaging, and those who achieve a cCR will be managed with a NOM approach, while those who show progressive disease will receive TME.

A large motivation behind the exploration of NOM following cCR is the assumption (one that is likely correct) that forgoing surgery, if possible, will significantly improve quality of life. Indeed, studies on decision-making in rectal cancer suggest that both patients and their providers are willing to accept a slightly higher risk of local recurrence if a poor functional outcome or a stoma can be avoided. It is clear that CRT,

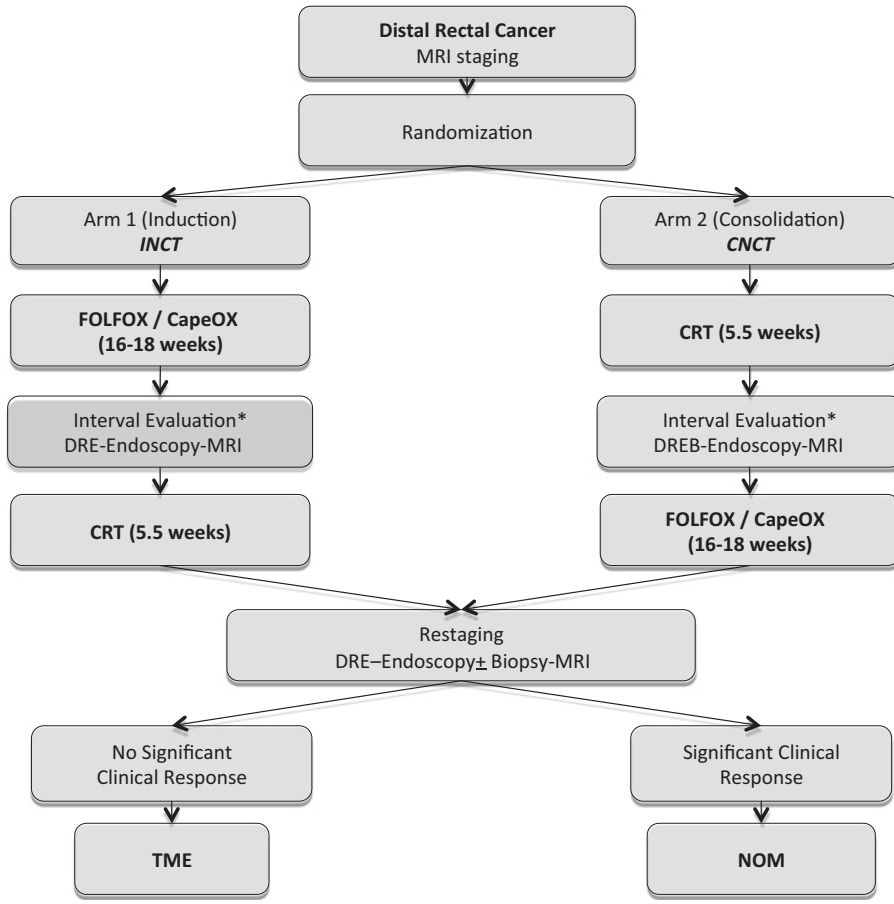

Fig. 18.5 NCT02008656 Trial Design: a prospective, multi-institutional, randomized trial measuring 3-year disease-free survival following either an induction chemotherapy or a consolidation chemotherapy approach for patients with clinical stage II/III rectal cancer

chemotherapy, and TME all affect long-term function in patients with LARC, but the individual impact of each treatment modality and the ways in which different combinations interact to affect patients' quality of life are not well understood. There have not yet been any studies evaluating quality of life and functional outcomes for patients treated with a NOM approach. As we maximize neoadjuvant therapy for patients with LARC and treat more patients with NOM, it will be especially crucial to assess quality of life measures. In doing so, we can better inform patients and frame expectations on the overall outcomes associated with our therapies.

In conclusion, major advances have been made in the optimization and maximization of neoadjuvant therapy for rectal cancer. We have reached a stage where "watch and wait" is becoming more routine. The challenges in the coming years will not be only to continue maximizing neoadjuvant therapy, but to improve our ability to predict therapeutic responses in order to tailor multimodality treatments to the individual patient.

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Molecular Markers and Mutational Analysis

19

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Introduction

Improvements in systemic therapies, surgical techniques, and efforts aimed at screening and early detection have led to a gradual decrease in colorectal cancer (CRC) incidence and mortality in the United States [1]. Nevertheless, CRC remains a leading cause of cancer death resulting in approximately 49,700 deaths annually [2]. Rectal cancer accounts for 30% of all newly diagnosed large bowel cancers with an estimated 39,610 new cases each year [2]. The Cancer Genome Atlas (TCGA) Project reported that the difference between cancers of the colon and rectum is largely based on anatomic location as comprehensive molecular characterization of these tumors has demonstrated that the two diseases share similar genomic alterations and are molecularly indistinguishable [3]. As with colon cancer, early-stage rectal cancer is cured in the majority of cases with multimodal therapy including surgery, radiation, and chemotherapy. However, approximately 25% of patients will present with metastatic disease at the time of diagnosis. Another 30–50% of patients with locoregional disease who undergo surgical resection with curative intent will develop recurrence. In these unresectable patients, systemic therapy plays a key role in their overall survival, and while the introduction of new cytotoxic drugs has improved outcomes, survival in this high-risk group is only approximately 20% at 5 years.

For this reason, efforts have been directed at identifying factors that drive tumorigenesis. The recent identification of molecular biomarkers, including RAS and BRAF, has provided predictive and prognostic information that guide the use of targeted therapeutics. Novel translational paradigms, such as gene expression analysis and proteomics, have made inroads into identifying molecular subtypes of CRC, each having unique prognostic and predictive implications. These efforts strive to provide the groundwork necessary to pursue a truly personalized approach to the management of CRC.

The mutational landscape of rectal cancer is constantly evolving. To date, by one count, 138 genes (74 tumor suppressor genes and 64 oncogenes) have been identified as driver mutations in colorectal cancer [4]. Vogelstein et al. reported that a median of 66 nonsynonymous mutations occur in sporadic colorectal cancers;

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however, only a few critical mutations are required for rectal cancer tumorigenesis with a typical tumor containing only 3–8 driver gene alterations [4, 5]. The remaining "passenger" mutations contribute to random events that do not directly drive carcinogenesis but contribute to overall tumor genomic chaos. Common driver mutations include APC, TP53, and RAS, but other less commonly mutated genes are just as critical in colorectal tumor development. Additionally, studies have shown that these tumors demonstrate significant clonal heterogeneity so that within a single cancer, groups of cells demonstrate varying mutations that drive progression and response to treatment [4, 6]. As such, every tumor has a unique genetic and epigenetic signature, a factor that makes personalized approaches to the treatment of rectal cancer both challenging and necessary. The advancement in understanding the molecular origins of CRC has led to the identification of novel prognostic biomarkers that predict patient outcomes and predictive factors that forecast response or lack thereof to specific treatments, thereby facilitating appropriate patient and therapeutic selection. Here we discuss the key genetic drivers, tumorigenic pathways, and molecular subtypes that drive CRC in both hereditary and sporadic cancers and discuss novel targeted therapies and their impact on contemporary management of the disease.

The Molecular Landscape of Rectal Cancer

Hereditary Rectal Cancer Syndromes

Approximately 30% of patients with newly diagnosed rectal cancer will have a family history of the disease in first- or second-degree relatives (Fig. 19.1). However, only a fraction of these cases can be directly attributed to known genetic syndromes, such that true hereditary colorectal cancer accounts for less than 10% of patients diagnosed with the disease [7, 8]. Hereditary nonpolyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) account for the vast majority of these cases and are highly penetrant within families. Other rare syndromes have been identified that predispose to colorectal cancer and are briefly outlined in Table 19.1. Though rare, hereditary colorectal cancer syndromes, in particular FAP and HNPCC, have contributed significantly to our understanding of the molecular genetics of colorectal cancer and are briefly discussed below.

Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

Hereditary nonpolyposis colorectal cancer (HNPCC) or Lynch syndrome is the most commonly inherited rectal cancer syndrome and accounts for 2–5% of all rectal cancers (Fig. 19.1). In contrast

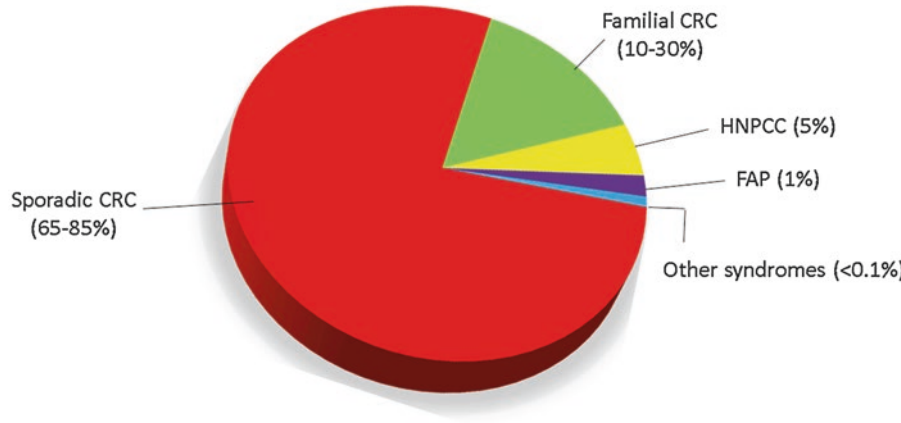


Fig. 19.1 Pie chart showing proportion of colorectal cancer cases believed to be sporadic, familial, or due to hereditary cancer syndromes. *HNPCC* hereditary nonpolyposis colon cancer, *FAP* familial adenomatous polyposis

to other CRC syndromes, these patients do not typically develop adenomatous polyps. This autosomal dominant syndrome results from germline mutations in DNA, mismatch repair (MMR) genes, and accumulation of mutations in microsatellites predisposing to colorectal and endometrial cancers [9–11]. Germline mutations in *MSH2* and *MLH1* account for 90% of all Lynch syndrome patients, with mutations in *MSH6*, *PMS2*, and *EPCAM* accounting for majority of the rest [12–14] . These patients are also at risk for development of other cancers including ovarian, gastric, and hepatobiliary malignancies. Typically, patients inherit one germline MMR gene mutation and subsequently have an acquired inactivation of remaining allele resulting in frequent mutations and development of microsatellite unstable-high (MSI-H) tumors in the fourth and fifth decade of life. The lifetime risk of colorectal cancer approaches 80%, and so preventative surgery to reduce cancer-related mortality is usually recommended around age 20 years. At the time of diagnosis, approximately 18% of patients will have synchronous tumors, so careful evaluation of the entire colon and rectum prior to surgical intervention must be performed in patients with HNPCC presenting with a cancer [15].

Familial Adenomatous Polyposis (FAP)

FAP accounts for less than 1% of all colorectal cancers. It is an autosomal dominant genetic disorder that results from germline mutations in *APC*. Phenotypically, FAP manifests as hundreds to thousands of colorectal adenomas beginning in early adolescence. Most patients will have a significant history of early colorectal cancers in first- and second-degree relatives, though about 25% of patients will present as the proband due to "de novo" APC gene mutations [16] . Lifetime incidence of colorectal cancer in patients with FAP approaches 100% with adenomas progressing to invasive cancers by the third or fourth decade of life [17, 18].

Variants of FAP from similar *APC* gene mutations have also been described and similarly predispose to development of colorectal cancer (Table 19.1).

Patients with FAP also require upper endoscopic surveillance as 90% of patients will develop polyps in the upper GI tract, particularly the duodenum. Duodenal adenocarcinoma is the second most common cause of death in these patients with 5% of duodenal polyps progressing to invasive carcinomas [19, 20]. Attenuated adenomatous polyposis coli is a less aggressive variant of FAP similarly caused by mutations in APC, with a correlation between the severity of the phenotype and the features of the APC mutation. These patients develop fewer polyps that are typically confined to the proximal colon and rarely affect the rectum [21]. Their cancer risk is also lower though the exact incidence is unknown and colon cancers develop later in the fifth decade of life.

Similar to HNPCC, prophylactic colorectal surgery is essential to decrease cancer mortality and must be balanced with quality-of-life measures. Preventative surgery is recommended at age 20 years and must be followed up by frequent surveillance of the remaining GI tract to identify other precancerous polyps.

Other Inherited Rectal Cancer Syndromes

Table 19.1 briefly describes other hereditary syndromes that predispose to the development of rectal cancer. MYH-associated polyposis is an autosomal recessive disorder that results from biallelic germline mutations in *MYH*, a base excision repair gene. For this reason, patients will not have a generational family history of cancers, but approximately 80% will develop CRC before age 60 years [22]. Other syndromes result in hamartomas of the colon and rectum with varying lifetime risk of development of CRC. *SMAD4*, *PTEN*, and *STK11* are a few genes implicated in the development of these tumors and also play a role in the development of sporadic rectal cancers as well.

Sporadic Rectal Cancer

The Cancer Genome Atlas (TCGA) Research Network in their comprehensive molecular

Table 19.1 Genetic syndromes with an inherited predisposition to development of colorectal cancers

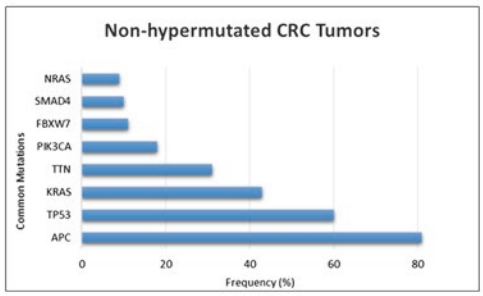
Syndrome	Gene defects	Characteristics	CRC risk	Mean age at CRC
Nonpolyposis syndromes Hereditary nonpolyposis colorectal cancer (HNPCC)/Lynch syndrome	MLH1 (30–40%) MSH2 (50%) MSH6 (7–10%) PMS2 (5%) EPCAM (1–3%)	Autosomal dominant inheritance Synchronous tumors Microsatellite unstable tumors (MSI-H) Other associated cancers : endometrial, ovarian	50–80%	40–60 years
Adenomatous polyposis syndromes Familial adenomatous polyposis (FAP)	APC	Autosomal dominant inheritance 100–1000s adenomatous polyps, duodenal and gastric poylps (fundus) Congenital hypertrophy of retinal pigment epithelium	≈100%	30–40 years
Gardner	APC	Same as FAP—simply a phenotypic variant Additionally associated with desmoid tumors (15%), osteomas of the skull and thyroid cancer	≈100%	30–40 years
Turcot's	APC (60–70%)	Same as FAP—colon polyps, CRC and CNS tumors primarily medulloblastoma	50–100%	20–40 years
	MLH1, PMS (30%)	Lynch type—no polyps, CRC and CNS tumors primarily glioblastoma multiforme		
Attenuated adenomatous polyposis coli	APC	Autosomal dominant inheritance <100 polyps Right-sided tumors and polyps with rectal sparing	Unknown	50 years
MYH-associated polyposis	MYH	Autosomal recessive inheritance 10–100s adenomatous polyps Somatic KRAS mutation (G12C) Microsatellite stable tumors (MSS)	80%	50 years
Hamartomatous polyposis syndromes Juvenile Polyposis	SMAD4/DPC4 BMPR1a	Autosomal dominant inheritance Hamartoma of colon and stomach, GI bleeding in children <10 years Associated with facial abnormalities including cleft lip or palate and macrocephaly	60–70%	60 years
Peutz–Jeghers	LKB1 STK11	Autosomal dominant inheritance hamartomatous GI polyps, hyperpigmented macules on the lips and oral mucosa, breast caner	85%	50 years
Cowden	PTEN	Autosomal dominant inheritance Hamartomas of skin, mucus membranes, thyroid, breast	16%	

analysis of colorectal cancer identified two distinct groups or CRC: non-hypermutated and hypermutated (Fig. 19.2a). In their study non-hypermutated tumors accounted for 84% of colorectal cancers and were defined as tumors having somatic mutation rates <8.2 per 10^6 bases and a median of 58 non-silent mutations [3]. These tumors demonstrated mutations classically described in the early models of colorectal cancer pathogenesis and resulted from somatic copy number alterations resulting in loss of heterozygosity in tumor suppressor genes or oncogene activations. Seventeen genes were noted to be recurrently mutated in this group with mutations in APC, TP53, KRAS, PIK3CA, FBXW7, SMAD4, TCF7L2, and NRAS being most frequent (Fig. 19.2b) [3].

a

Sporadic CRC Type	Mutation Rate	Molecular basis	Tumor Phenotype
Non-hypermutated (84%)	<8.24 per 10^6 bases Median = 58 total mutations	Chromosomal instability (CIN) - Loss of heterozygosity - Aneuploidy CIMP/non-MSI	- Microsatellite stable (MSS) - Left sided tumors
Hypermutated (16%)	>12 per 10^6 bases Median = 728 total mutations	DNA mismatch repair deficient (77)% - *MLH1* meythlated (63%) - CIMP/MSI (57%) - BRAF mutated (46%) DNA mismatch repair proficient (23%) - Other MMR gene mutations - *POLE* mutant	- Microsatellite unstable – high (MSI-H) - Proximal tumors - Mucinous - Poorly differentiated

b



c

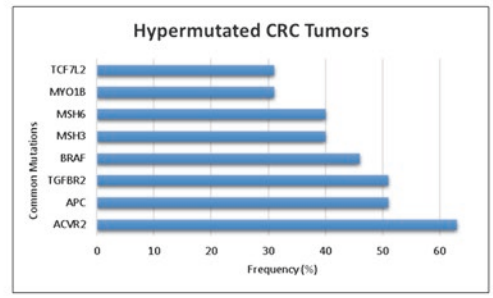


Fig. 19.2 (**a**) Molecular and clinicopathologic features associated with non-hypermutated and hypermutated colorectal cancer. (**b**) Genes significantly mutated in non-hypermutated and (**c**) hypermutated colorectal tumors [23]

Hypermutated tumors were less frequent, accounting for 16% of cases in this study. Hypermutated tumors are underrepresented in rectal cancer population by virtue of their predilection for development in the proximal colon. These tumors driven by deficiencies in DNA damage control have higher rates of mutations (>12 per 10^6 bases) with a median of 728 total mutations per tumor due to an increase in frameshift mutations [3]. Three quarters of these tumors were microsatellite unstable-high (MSI-H) due to mutations in the DNA mismatch repair pathway, in particular, due to methylation of MLH1 promoter resulting in epigenetic silencing. This commonly occurs in the context of a broader degree of global gene promoter hypermethylation and gene body hypomethylation that is termed the CpG island methylator phenotype (CIMP). Fifteen mutations were frequently mutated including ACVR2A, APC, MSH3, MSH6, and BRAF (Fig. 19.2c). Mutations at DNA polymerase ϵ (POLE) account also result in hypermutated tumors. It is notable that somatic POLE mutations accounted for the highest mutation rates in CRC, but the tumors lack MSI-high, CIMP-high, or *MLH1* hypermethylation.

CRC tumorigenesis appears to occur via deferring pathways in these two tumor types. For example, APC and TP53 mutations were common to both groups though at differing rates. These two common drivers were more frequently mutated in non-hypermutated colorectal cancer when compared to hypermutated tumors: 81% vs 51% ($p = 0.0023$) and 60% vs 20% ($p = 0.0001$), respectively. Additionally, TP53 loss and mutations in cell cycle checkpoint kinase ATM are mutually exclusive and are found at high frequency in non-hypermutated and hypermutated samples, respectively [23]. And while KRAS mutations are commonly seen across both subsets, BRAF mutations are overrepresented in hypermutated CRC. Additionally, mutations in genes such as TGFBR2 were seen exclusively in hypermutated tumors suggesting that while CRC develops from a known set of deregulated driver pathways, the sequence of genetic events leading

Table 19.2 Consensus molecular subtype (CMS) classification of colorectal cancer. Each subtype reflects unique molecular, genomic, and biological signatures [24]

Subtype	CRC incidence	Driver gene/pathway	Phenotype and prognosis
CMS1 MSI immune	14%	Hypermutation MSI-high CIMP-high *BRAF* mutated Immune activation/expression	Right-side tumors Older age at diagnosis Females Intermediate survival Worse survival after relapse
CMS2 canonical	37%	High CIN MSS WNT/MYC pathway activation *TP53* mutated *EGFR* amplification/ overexpression	Left-side tumors Better survival
CMS3 metabolic	13%	CIN-low Metabolic derangement *KRAS* mutated *PIK3CA* mutatedIGFBP2 overexpression	Intermediate survival
CMS4 mesenchymal	23%	CIN-high TGF-beta activation NOTCH3/VEGFR2 overexpression	Stromal infiltration Younger age at diagnosisWorse relapse-free and overall survival

to tumorigenesis is different for hypermutated and non-hypermutated CRC.

The CRC Subtyping Consortium (CRCSC) further characterized the genetic and epigenetic features of colorectal cancer by integrating "multi-omic" data regarding tumor mutation status, DNA copy number, methylation, microRNA, and protein expression [24]. In doing so, they identified four distinct colorectal consensus molecular subtypes (CMS), each with their own unique molecular drivers, phenotype, and tumor behavior (Table 19.2). CMS1 (MSI immune) CRC is predominantly comprised of MSI-high tumors. As such, the tumors within this subgroup tend to be hypermutated and hypermethylated and enrich for *BRAF* mutations and tumor lymphocyte infiltration.

CMS2 (canonical) and CMS3 (metabolic) are driven by chromosomal instability, typically displaying high copy number alterations in microsatellite-stable tumors. CMS2 tumors demonstrate marked upregulation of Wnt and MYC signaling, while CMS4 tumors are characterized by activation of pathways related to mesenchymal transition and stem cell phenotype (e.g., TGF-β, integrins). Additionally, CMS4 tumors have proangiogenic and stromagenic properties that result in stromal infiltration of adjacent cancer tissue [25]. This mesenchymal pathway activation results in early relapse and distant failure in patients with CMS4 mesenchymal CRC even with early-stage disease.

Finally, CMS3 (metabolic) CRC tumors are believed to be driven by metabolic reprogramming with hyperactive glutaminolysis and lipidogenesis that have been shown to contribute significantly to CRC tumorigenesis. CMS3 represents a mixed group with almost one third of tumors being MSI-high, hypermutated, or with intermediate levels of gene hypermethylation. They consistently exhibit fewer copy number alterations and enrich for activating *KRAS* mutations which have shown to contribute to metabolic adaptation in colorectal cancer and other malignancies [26–31].

While all four of the subtypes can be found in rectal cancer, there is an enrichment for CMS2 and CMS4 compared to proximal colon cancers, where CMS1 and CMS3 tend to be overrepresented.

Targeted Therapy for Rectal Cancer

As previously discussed, dramatic improvements have been seen in rectal cancer overall and disease-free survival with the introduction of cytotoxic chemotherapy agents such as fluorouracil, oxaliplatin, and irinotecan. However,

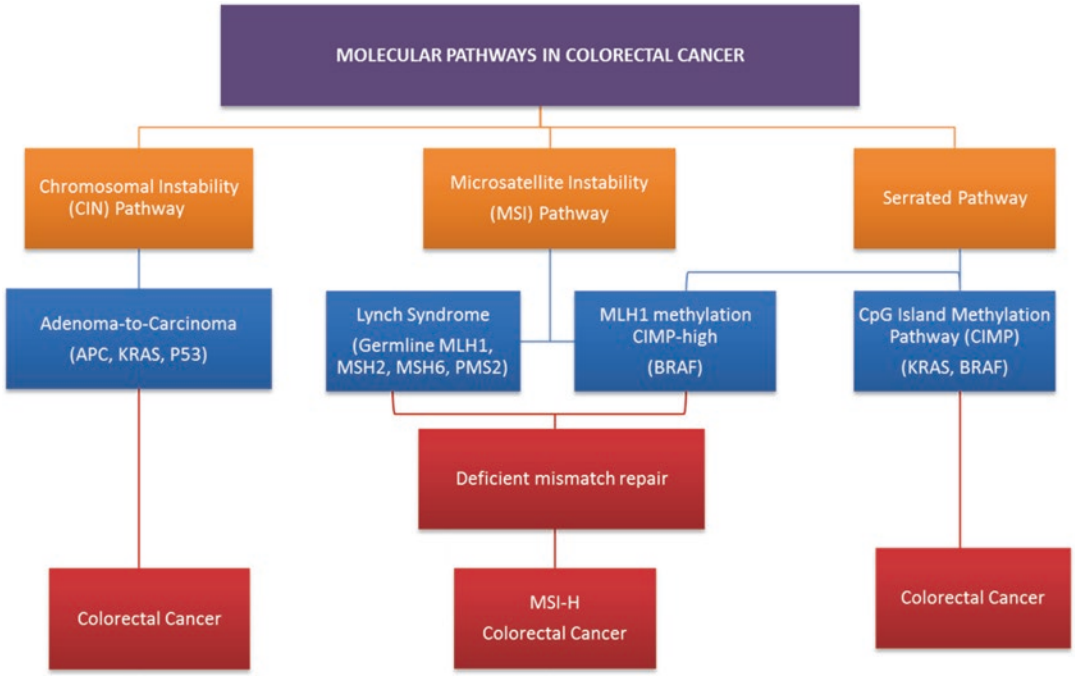


Fig. 19.3 Molecular pathways via which colorectal cancers develop. The chromosomal instability (CIN) pathway accounts for 30–70% of colorectal cancers and results in the progression from adenoma to carcinoma. Germline mismatch repair mutations lead to Lynch syndrome, which accounts for approximately one quarter of all MSI colorectal cancers. The serrated/methylated pathway occurs due to the epigenetic inactivation of *MLH1* by hypermethylation resulting in a sporadic MSI phenotype

individual responses to these agents vary significantly, and many patients unfortunately suffer the severe side effects of these therapies without deriving any significant benefit. The more precise identification of genetic driver mutations and signaling pathways in colon and rectal cancer have shifted treatment efforts from a population approach to therapy and ushered in a new era of precision medication aimed at personalized treatment regiments that offer patients maximal benefit. These therapies aim to disrupt one or more of the three widely accepted molecular pathways to colorectal tumorigenesis, each contributing to heterogeneity in tumor response and patient survival in rectal cancer (Fig. 19.3).

The classic adenoma-to-carcinoma pathway, also called the chromosomal instability (CIN) pathway, was initially described by Fearon and Vogelstein [32, 33]. They described a multistep progressive model from normal mucosa to adenoma formation and ultimately tumorigenesis characterized by acquired loss-of-function mutations in tumor suppressor genes primarily APC, TP53, and PTEN and mutational activation of oncogenes including RAS and PIK3CA, all leading to chromosomal instability and tumor formation (Fig. 19.4) [33]. Approximately 70–85% of sporadic colorectal cancers arise via this pathway. Over a prolonged period of time, chromosomal rearrangements lead to loss of heterozygosity in tumor suppressors and oncogene activation resulting in accumulation of aneuploidy and deregulated pathways that modulate cellular differentiation, proliferation, and apoptosis. Mutations in the adenomatous polyposis coli (*APC*) tumor suppressor gene located on chromosome 5q21 typically result in a truncated protein that lacks the ability to appropriately regulate β-catenin degradation [34]. Intracellular accumulation of β-catenin results in deregulation of the Wnt signaling pathway, an important event in tumorigenesis of many solid tumors [35, 36]. *APC* mutation is believed to be a key player in the adenoma–carcinoma sequence as 40–80% of all CRC

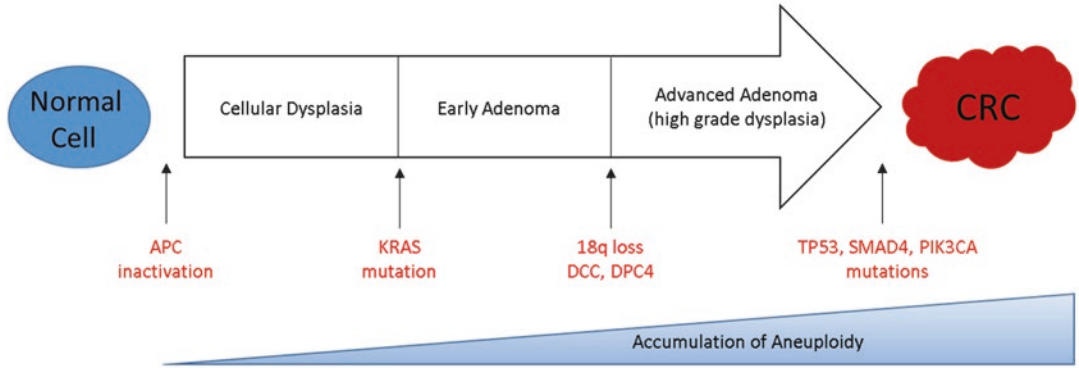


Fig. 19.4 Colorectal cancer tumorigenesis due to the accumulation of genetic alterations annotated with key driver mutations commonly seen in CIN tumors over time

tumors carry a mutation in the gene or display allelic losses of 5q [37]. *APC* mutation events appear to occur early in the adenoma–carcinoma sequence as mutations are seen at a similar frequency in early adenomas when compared to invasive colorectal carcinomas [32, 38, 39]. Genomic studies have shown that pathway alterations in Wnt/β-catenin, transforming growth factor beta (TGF-β), EGFR, and downstream mitogen-activated protein kinase (MAPK) and phosphoinositide 3-kinase (PI3K) signaling are nearly ubiquitous events in CRC [3, 40, 41]. For this reason, disruption of the Wnt/α-catenin signaling pathway was identified as a potential therapeutic target.

Alternatively, 15% of colorectal tumors can arise from alternate pathways that result in defective DNA mismatch repair due to *MLH1*, *MLH3*, *MSH2*, *MSH3*, *MSH6*, or *PMS2* inactivation. This impaired repair function results in hypermutation and microsatellite instability (MSI) [23]. This is typified by tumors arising from HNPCC with germline inactivation of mismatch repair proteins and familial MSI-H. A related but distinct pathway, termed the sessile serrated pathway, is typified by early hypermethylation and BRAF mutations with hypermethylation causing silencing of key DNA repair genes, such as MLH1, and leading to sporadic MSI tumors. While typical tubular adenomas share molecular features similar to chromosomally instable CRCs, sessile serrated adenomas arise most commonly in the background of the epigenetic CIMP pathway and MSI which appear to be the major mechanisms driving carcinogenesis [42].

Biomarkers of Prognostic and/or Therapeutic Significance

Vascular Endothelial Growth Factor (VEGF)

Angiogenesis, the recruitment of existing blood vessels and the formation of new capillaries, is vital to tumor growth and establishment. This observation leads researchers to hypothesize that targeting angiogenesis was a viable strategy in cancer therapy [43]. The VEGF family of proteins is comprised of six members, VEGF-A through VEGF-E and placenta growth factor (PIGF)-1 and PIGF-2. VEGF-A, often simply called VEGF, is a potent ligand and regulator of proliferation and angiogenesis in both normal and tumor cells [44]. The VEGF binds to its receptor VEGFR2, a tyrosine kinase, resulting in activation of multiple intracellular signaling pathways and leading to increased endothelial cell proliferation, migration, survival, and ultimately angiogenesis. Not surprisingly, VEGF overexpression has been associated with worse outcomes related to tumor progression and poor overall survival in patients with CRC [45, 46].

Bevacizumab was the first antiangiogenic targeted drug to be approved for the treatment of CRC. Bevacizumab, a recombinant monoclonal antibody against VEGF-A, was heavily anticipated to demonstrate profound antitumoral effect; however, as a single agent the drug showed limited clinical benefit [47]. However, when used in combination with cytotoxic systemic chemotherapies, bevacizumab was shown to increase

response rate in patients with mCRC leading to longer PFS and OS [48]. Bevacizumab works synergistically with 5-FU-based chemotherapy to induce apoptosis and inhibit tumor growth presumably by enhancing cytotoxic drug delivery to tumor cells [49]. Consequently, the use of bevacizumab in combination with FOLOX (5-FU, oxaliplatin, leucovorin)/FOLFIRI (5-FU, leucovorin, irinotecan) has been widely employed in the treatment of mCRC, and because of enhanced response rates in the neoadjuvant setting, a significant number of patients with potentially resectable mCRC are later able to undergo curative hepatic metastasectomy. The drug is well tolerated, but potential toxicities can be severe. GI perforation is the most feared and occurs in approximately 1.5% of patients on treatment. Other side effects include hypertension warranting medical therapy, increased risk for stoke and myocardial infarction, and impaired wound healing, though studies have shown that cessation of bevacizumab 4 weeks prior to major surgical intervention poses no increased risk of wound complications [50, 51]. The development of hypertension while on therapy has been associated with a positive treatment response [52, 53].

Epidermal Growth Factor Receptor (EGFR)

EGFR is a tyrosine kinase transmembrane receptor within the HER/ErbB family of proteins [54]. EGFR is overexpressed in tumors of epithelial origin and particularly in colon and rectal cancers. EGFR activation occurs when its primary ligands, epiregulin, amphiregulin, EGF, and TGF-α, bind to initiate activation of multiple signaling pathways. In particular, constitutive activation of the Ras/Raf/MAPK and the phosphatidylinositol 3-kinase (*PI3K)* signaling pathways lead to deregulated cellular proliferation, inhibited apoptosis, and cellular invasion (Fig. 19.5). EGFR activation therefore contributes not only to tumorigenesis, but is believed to be a key contributor to CRC metastatic progression [55].

Two classes of anti-EGFR therapies were developed to target this mechanism: tyrosine kinase inhibitors (TKIs) and monoclonal antibodies to EGFR. TKIs, such as gefitinib and erlotinib, competitively inhibit adenosine triphosphate (ATP) to block EGFR activity and preferentially suppress PI3K signaling in CRC [56]. However, efforts to utilize these agents in combination with standard chemotherapy regimens in CRC resulted in high rates of GI toxicity and were not further pursued.

Cetuximab was the first EGFR monoclonal antibody (mAb) to be FDA approved for treatment of metastatic CRC. These antibodies bind EGFR and block ligand binding, thereby inhibiting ligand-dependent autophosphorylation and inhibiting downstream MAPK and PI3K cell signaling. In their seminal paper, Cunningham et al. reported improved response, time to progression, and overall survival with single-agent cetuximab or when used in conjunction with irinotecan in mCRC patients with refractory disease [57]. Similarly, panitumumab was demonstrated to be well tolerated and improved response rates in patients with refractory mCRC and was FDA approved soon after [58]. Anti-EGFR antibody therapy is generally well tolerated. The most common side effect is an acneiform skin rash seen in 80–90% of patients on treatment [59]. Rashes tend to resolve once therapy is discontinued; however, studies have shown a positive correlation in overall survival and severity of skin rash suggesting that this side effect may serve as a forecaster of treatment response [58, 60].

Since their FDA approval in 2004, monoclonal antibodies to EGFR have been widely employed in the treatment of metastatic colon and rectal cancers. However, only few patients derive benefit to therapy with response rates only approaching 10% in most series and prompting efforts to investigate EGFR expression as a prognostic and predictive biomarker [57, 58, 60]. EGFR mutations while common in other tumors are rare in CRC [61, 62]. Early studies explored the association of increased EGFR gene copy or EGFR expression on improved overall survival (OS) and progression-free survival (PFS) in mCRC patients; however, these have not been demonstrated to be reproducibly associated with outcomes and are no longer used for patient selection [60, 63–65]. The investigation of downstream

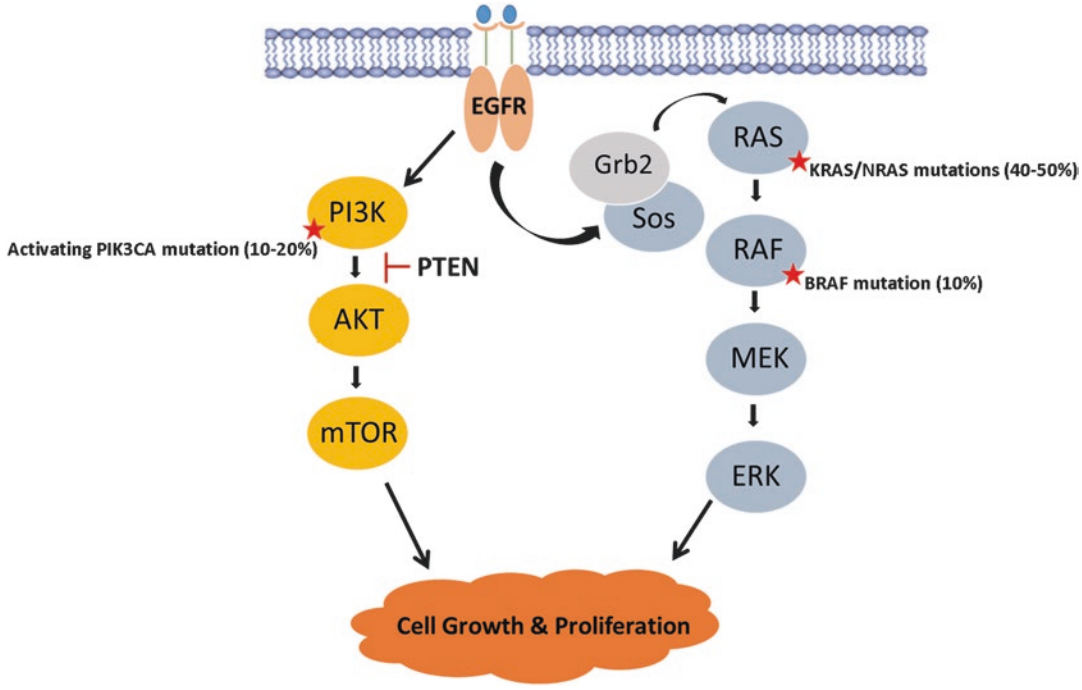


Fig. 19.5 The MAPK signaling pathway is a key player in colorectal cancer tumorigenesis. Mutations in activating RAS, RAF, and PI3K, or mutations in PTEN tumor suppressor, result in constitutive activation of the signaling cascade resulting in uninhibited cellular proliferation and tumor growth

effectors of EGFR signaling, however, has led to the identification of the RAS proto-oncogene family as critical biomarkers in CRC.

KRAS/NRAS

The RAS family of proteins is comprised of three oncogenes (KRAS, NRAS, and HRAS) that code for proteins involved in EGFR-mediated cellular signaling and regulation of proliferation (Fig. 19.5). KRAS mutations occur in 30–40% of colorectal cancers, while NRAS mutations are much less rare with NRAS occurring in 5% of tumors [66–68]. HRAS is not seen in CRC, with mutation rates <0.1%. RAS gene mutations typically occur at codon 12 and less frequently in codons 13, 59, 61, 117, and 146 altering the GTP binding domain dynamics and resulting in constitutive activation of the oncogene. Like CRC, these mutations are observed at high frequency in large adenomas, but less so in smaller adenoma suggesting that they likely contribute more to adenoma growth and CRC carcinogenesis [33, 69, 70]. KRAS and NRAS mutations in colorectal cancers carry both predictive and prognostic significance. Retrospective analysis of several clinical trials of anti-EGFR mAbs revealed that wild-type KRAS was required for anti-EGFR antibody-mediated response in patients with colorectal cancer [71–75]. KRAS/NRAS mutations result in constitutive activation of the Ras-Raf-MAPK pathway, downstream of epidermal growth factor receptor (EGFR), rendering these tumors resistant to anti-EGFR therapies [71, 76–79]. Current guidelines require testing for KRAS and NRAS at the codons above prior to initiating anti-EGFR therapy and established the Ras-Raf-MAPK pathway as a principal target for the development of novel molecular therapeutic agents for the treatment of colorectal cancer [80–82].

While RAS mutation status clearly confers predictive relevance, its prognostic implications require further investigation. While KRAS mutations may be only weakly prognostic in stage II and III colorectal cancer, they may confer poor prognosis in metastatic CRC [83, 84]. Interestingly, exon 146 mutations, though rare,

appear to confer better biology than their counterparts with codon 12, 13, or 61 mutations [85].

BRAF

The BRAF oncogene, another potent modulator of the MAPK pathway, has recently emerged as a prognostic biomarker and novel therapeutic target in CRC. $BRAF^{V600E}$ is an activating mutation that accounts for approximately 90% of all BRAF mutations seen in colorectal cancer [79, 86]. As described above, oncogenic BRAF mutations result in tumor formation typically along the serrated pathway by the methylation of CpG islands that cause the silencing of critical tumor suppressor genes and accounting for 10–15% of CRC with discrete clinical characteristics and oncologic outcomes [87–92]. BRAF mutant tumors are more prevalent in women and in patients of advanced age, typically age >70 years [93–96]. Additionally these tumors tend to be proximal in location, MSI-high, of mucinous histology, serrated and poorly differentiated [93–100]. In sporadic colorectal cancers, BRAF mutation is seen in approximately 30–60% of MSI-high tumors but only 5–10% of microsatellite-stable (MSS) tumors [79, 90, 94, 101]. $BRAF^{V600E}$ mutations cause hypermethylation of the MLH1 gene promoter, resulting in loss of the tumor suppressor function and impeding DNA mismatch repair [102–105]. Tran et al. [106] defined BRAF mutant colorectal tumors as a distinct subtype when they delineated a unique pattern of metastatic spread. In their study of a cohort of 524 patients with metastatic colorectal cancer, 11% patients were found to harbor a BRAF mutation. In these patients, metastatic spread was more common via peritoneal disease (46% vs 24%) or distant lymph node metastasis (53% vs 38%) when compared to BRAF wild-type tumors and less likely to result in lung metastasis (35% vs 49%). Not surprisingly, BRAF mutation conferred poorer overall survival with a median of 10.4 months versus 34.7 months. These patients were also less likely to undergo metastasectomy with disease present at sites not amenable to resection. These data implicated BRAF mutation as a major driver of right-sided tumor biology and a potent contributor to poor prognosis observed between right-sided and left-sided colon cancers. Interestingly, the same prognostic implications may not hold for the rare patients with BRAF mutations occurring in rectal primaries, perhaps due to the limited epigenetic alterations seen in these tumors. Further studies are needed to explore this.

Patients with this mutation stand to benefit from effective targeted therapies. The BRAF oncogene codes for a serine/threonine kinase that acts downstream of KRAS in the MAPK pathway (Fig. 19.5). BRAF mediates its effect by activating mitogen-activated protein kinase kinase (MAPKK or MEK) initiating uninhibited EGFR-independent cellular proliferation [90, 107]. BRAF and KRAS/NRAS mutations are mutually exclusive in CRC, suggesting that BRAF is the principal effector of KRAS/NRAS in the MAPK pathway with equivalent effects on tumorigenesis [79, 94, 101]. Consequently, BRAF mutant tumors are able to escape the effects of anti-EGFR therapy similar to RAS mutation and are believed to be responsible for 12%–15% of RAS wild-type patients who fail anti-EGFR therapies [90, 94, 101].

BRAF mutations have been widely studied in melanoma. In 2011, vemurafenib, a protein kinase inhibitor of $BRAF^{V600E}$, was approved by the FDA for the treatment of metastatic melanoma. The success of this and other BRAF-targeted therapies in melanoma made BRAF mutation an attractive therapeutic target in CRC. Unfortunately, in early phase studies of mCRC, the clinical response to $BRAF^{V600E}$ inhibition has not been as robust as anticipated [108–111]. Resistance to $BRAF^{V600E}$ inhibition in CRC has been attributed to increased EGFR activation due to ERK-mediated feedback leading to cellular proliferation not seen in melanomas [112, 113]. Additionally, BRAF mutant CRC demonstrated higher levels of PI3K/AKT activation when compared to BRAF mutant melanoma [114]. These findings have supported the use of combination therapy strategies in treating this subset of CRC patients.

Early-phase studies are ongoing to explore the synergistic effect of BRAF inhibition, anti-EGFR therapy, and PIK3CA inhibition. Corcoran et al. [111] reported their phase I and II experience

with dabrafenib (D) in combination with MEK inhibitor trametinib (T) in BRAF mutant metastatic colorectal cancer. Forty-three patients received combination D + T therapy with 1 patient achieving a prolonged complete response (>22 months), 5 patients (12%) with a partial response, and 22 patients (51%) with stable disease. Other trials investigating "triple combination" therapy with dabrafenib (D), trametinib (T), plus or minus panitumumab (P) anti-EGFR antibody are also ongoing. Bendell et al. [115] demonstrated that triple combination therapy was well tolerated and effective with four/six patients (67%) achieving partial tumor responses and the remaining two patients exhibiting stable disease. These early-stage trials suggest that combination therapy with two or three agents can be safely administered with early evidence of good clinical activity. Efforts are ongoing; however, the current evidence proposes that combination therapy targeting BRAF mutation in CRC may lead to better and more durable clinical responses when compared to monotherapy with $BRAF^{V600}$ inhibition.

Human Epidermal Growth Factor Receptor 2 (HER2) Gene Status

The prognostic and predictive implications of HER2 gene amplification and expression in breast and gastric cancer have been well established. In both diseases the addition of trastuzumab, a monoclonal antibody that targets the extracellular domain of the HER2 receptor, to traditional systemic therapy has led to improved outcomes in the subsets of patients with HER2-positive tumors [116–118]. More recently, HER2 gene status and its clinical implications in CRC have been investigated. HER2 gene amplification and protein overexpression occur in 5–12% of colorectal cancers and as high as 26% of rectal cancers, although the later needs to be further validated [119, 120]. Its prognostic and predictive relevance however is still not clear. Conradi et al. demonstrated improved cancer-specific survival (CSS) and a trend toward improved disease-free survival (DSF) in patients with advanced HER2-positive rectal cancers [119]. However, others have found HER2-amplified colorectal cancers confer poor prognosis. Martin et al. stratified patients by degree of HER2 amplification in mCRC. They classified patients into three categories, HER2 gene amplification in all neoplastic cells (HER-all-A), patients with HER2 gain due to gene amplification in minor clones (HER2-FISH + *), and patients with no or slight HER2 gain (HER2-FISH-). In their study these subgroups significantly predicted response rates to anti-EGFR therapy, progression-free survival (PFS), and OS [121]. Patients with HER2-all-A profile had the worst outcome of all patients, HER2-FISH- had intermediate behavior, and HER2-FISH + * conferred improved PFS and OS [121].

The most compelling data regarding HER2 status in CRC came recently from the HERCULES trial. The authors after demonstrating activity of dual HER2 blockade with trastuzumab and lapatinib in murine patient-derived xenographs designed a proof-of-concept, multicenter phase 2 trial to investigate the effect of dual anti-HER2 therapy on mCRC. Nine-hundred fourteen patients with treatment refractory KRAS wild-type mCRC were screened. HER2 status was assessed by IHC and FISH and yielded a 5% incidence of HER2-positive CRC. Twenty-seven patients were enrolled and received trastuzumab and lapatinib therapy. Of these patients 7 (26%) had rectal cancers, 16 (59%) had distal colon cancers, and 4 (15%) had proximal colon cancers again showing a correlation between HER2-positive tumors with left-sided colon and rectal cancers [122]. After a median follow-up of 94 weeks, 8 patients (30%) responded to therapy, 1 patient (4%) had a complete response, and 12 patients (44%) had stable disease [122].

These data suggest an intricate relationship between HER2 status and anti-EGFR therapy which requires further delineation. Additionally, HER2 status likely confers prognostic and predictive relevance in distal colon cancers and rectal cancers in particular.

Mismatch Repair and Tumor Immunity

Until recently, tumor immunity was not thought to play a critical role in CRC tumorigenesis. However, studies have demonstrated the relevance of immune signatures in CRC [123–125].

Tosolini et al. demonstrated that high lymphocyte infiltration in primary CRC tumors, in particular cytotoxic/T helper 1 lymphocytes (CTL/Th1) with an interferon (IFN)-γ-dominant immune profile correlated with improved RFS and OS in CRC [123]. Conversely, an immune signature driven by T helper 17 (Th17) infiltration and an interleukin (IL)-17 was associated with poor prognosis. Since then, others have attempted to incorporate these immune profiles into the traditional staging of CRC to facilitate tumor-specific interventions. "Immunoscore" outlines one such effort to include the tumor microenvironment in the risk stratification of patients with CRC. This system takes into account the presence of intratumoral clusters of lymphocytes and uses their prognostic implications to complement traditional AJCC TNM classification [126].

MSI-high tumors are especially considered to be immune driven. It is widely accepted that CRC tumors deficient in mismatch repair display high lymphocyte infiltration (particularly with CTL and Th1). Additionally, there is upregulation of immune checkpoints, which make these tumor prime candidates of targeted checkpoint inhibition [127, 128]. PD-1 and PD-L1 are overexpressed mainly in MSI tumors, making checkpoint inhibition with anti-PD-1/PD-L1 and attractive therapeutic target in these tumors [128, 129].

Nivolumab, an anti-PD-1 antibody, was investigated in phase I trials but did not demonstrate significant clinical activity in mCRC [130]. Notably, the majority of these tested tumors were negative for PD-L1 expression. There was, however, one patient from this metastatic CRC cohort, who had a PD-L1-positive, MSI-high tumor and who achieved a complete response after 6 months with no signs of disease after 3 years [131]. Similarly, Le et al. studied the efficacy of pembrolizumab, a monoclonal antibody against PD-L1 and PD-L2, in 32 patients with advanced CRC (11 deficient mismatch repair (dMMR); 21 proficient (pMMR)) [132]. There was a significantly higher rate of responders and patient with stable disease in the dMMR CRC patients (40% and 78%, respectively) than in the pMMR CRC patients (0% and 11%, respectively). Based on these data, MMR status is likely a predictive biomarker for clinical benefit from checkpoint inhibition. Larger studies are underway to evaluate the benefits of checkpoint inhibition in patients with unresectable or metastatic refractory dMMR CRC. Additionally, there is a need to investigate methods of inducing tumor immunity so that the majority of CRC patients with pMMR tumors may be able to derive benefit from these therapies.

Conclusion

The management of rectal cancer is evolving with the advent of novel targeted therapeutic driven by robust molecular investigation into CRC tumorigenesis. Novel predictive and prognostic biomarkers are increasingly important in guiding clinical decision-making and will continue to drive the development of targeted therapies in rectal cancer. Prospective randomized controlled trials are needed to further determine the validity and efficacy of these new biomarkers and will further facilitate a truly personalized approach to rectal cancer therapy based on individual tumor molecular profiles.

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Quality of Life After Multidisciplinary Management of Rectal Cancer

20

Imran Hassan and Y. Nancy You

Introduction

The goals of rectal cancer treatment include optimal local control, maximal overall survival, as well as the best preservation of pre-therapy function and well-being of the patient. As illustrated in the remainder of this textbook, significant efforts have been devoted to developing surgical and multimodality regimens to achieve these goals. Stage-specific treatments include surgery alone (local excision or radical resection) for early-stage rectal cancer (American Joint Commission on Cancer [AJCC] stage I) and multimodality therapy with radical surgery, chemotherapy, and/or pelvic radiation for locally advanced (AJCC stages II and III) and metastatic (AJCC stage IV) rectal cancer. With this current multimodality strategy, the overall 5-year survival for locally advanced rectal cancer is 65–75%, with local recurrence rates in the range of 5–10% [1–6].

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Patients and clinicians have long been aware of the profound impact of radical pelvic surgery, multimodality therapy, and their combination on patient-centered outcomes. These include short-term perioperative complications, as well as long-term morbidity, adverse functional consequences, and impaired overall health status and quality of life (QOL). Standard proctectomy for rectal cancer can involve sphincter preservation and maintenance of intestinal continuity or can result in sphincter loss and a permanent colostomy. Patients with intestinal continuity can have significant gastrointestinal dysfunction, with a collection of symptoms that has been termed the "low anterior resection syndrome" (LARS) [7], while patients with a permanent colostomy can struggle with functional problems and body image issues. Temporary or permanent injury to the pelvic nerves during pelvic dissection and/or pelvic radiation can lead to sexual and urinary dysfunction. In addition to these functional issues, patients can suffer from constitutional symptoms including decreased energy, fatigue, and psychological distress. All of these adverse functional outcomes can significantly impact the patient's physical and mental well-being and overall QOL. In the context of patient-centered research, QOL and other patient-reported outcomes (PRO) are being increasingly examined in clinical trials and comparative effectiveness studies of different treatment strategies. These data are now considered valuable and necessary in helping patients make informed treatment

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decisions while incorporating their own personal values and preferences into their treatment approach [8].

In this chapter, we will summarize available data regarding the impact of multimodality therapy on QOL, as well as discuss methodological challenges and future areas of research toward optimizing QOL after multimodality treatment.

Definitions: Quality of Life (QOL), Health-Related QOL, and Patient-Reported Outcomes (PROs)

In 1948, the World Health Organization defined health to be "a state of complete physical, mental and social well being, and not merely the absence of disease." This definition "includes psychological, physical and social functioning and incorporates positive aspects of well being as well as negative aspects of disease and infirmity" [9]. QOL has also been defined as the "the subjective evaluation of life as a whole" or, in another form, as the "patients' appraisal of and satisfaction with their current level of functioning compared to what they perceive to be possible or ideal" [10].

Despite the multitude of definitions, there is general consensus that QOL is a multi-domain construct reflecting the patient's perspective on the effect of treatment on his or her own well-being. It encompasses several key dimensions including general health, physical symptoms, functionality, treatment-related toxicity, emotional well-being, cognitive issues, role functioning, social well-being, sexual function, as well as spiritual issues [9]. While QOL includes all aspects of well-being and can even include the impact of living standards, environmental factors, and other non-health-related factors, the term health-related QOL (HRQOL) is more focused and measures aspects of QOL that are specifically affected by healthcare interventions such as surgery and other treatment modalities [10]. More broadly, "patient-reported outcomes" (PROs) include standardized measurements of the patients' subjective assessment of their health status, as well as perceptions about treatment and satisfaction with care received [11, 12]. The Food and Drug Administration (FDA) defines PROs as "any report of the status of a patients health that comes directly from the patient, without interpretation of the patients response by a clinician or anyone else" [13]. PROs can assess a number of domains including symptoms experience (e.g., pain, fatigue, and nausea), functional status (e.g., bowel, sexual or urinary function), well-being (e.g., physical, mental, social), QOL, and satisfaction with care or with treatment [13].

As the field of patient-centered outcomes has progressed during the past three decades, its related nomenclature has also evolved to become more representative of the constructs measured. For the purpose of this article, QOL, HRQOL, and PROs will be used interchangeably and synonymously. It is however important to keep in mind the distinctions between these terms as the field of patient-centered outcomes further advances in methodology and sophistication.

Why QOL Must Be a Key Endpoint Measured in the Treatment of Rectal Cancer

In defining the most relevant endpoints for phase III trials, the National Cancer Institutes (NCI) has stated that "of greatest medical importance, of course, are relative survival and quality of life" [14]. While disease control and survival outcomes have been the standard benchmarks for oncologic therapies, preserving the QOL of cancer patients, survivors, and their families has emerged as a well-defined strategic objective in recent years. Indeed, the optimal treatment of rectal cancer should allow patients to enjoy longer and better lives than they would without the treatment. Therefore, assessing statistically significant and clinically meaningful improvement in QOL represents an important measurement of therapeutic efficacy.

When applied to patients with locally advanced rectal cancer, investigations to identify the optimal multimodality treatment regimen should therefore assess not only traditional oncologic outcomes such as recurrence-free (local and distant) and overall survival but also

include the perspective of patients who eventually survive the disease and live with its treatment sequelae [14]. Pelvic surgery, radiation, and systemic chemotherapy have proven efficacy in improving oncological outcomes. Yet they also result in substantial short-term morbidity as well as adverse long-term outcomes including constitutional, gastrointestinal, sexual, and urinary dysfunction. While omission or reduction in the nature or extent of any of these modalities is likely to have a positive impact on QOL and PROs, it could potentially compromise oncologic outcomes.

As a result, the definition of the "optimal" outcome for locally advanced rectal cancer is highly dependent on whether it is evaluated from the clinicians' or patients' perspective. Most clinicians tend to consider decreased local and distant disease recurrence along with greater overall survival as the ultimate benchmarks for optimal care. On the other hand, depending on their values and belief systems, patients may accept a decreased survival in return for a better QOL. Several qualitative studies have demonstrated that patients with rectal cancer highly value functional outcomes and may be willing to accept a higher risk of local recurrence to preserve good functional outcomes [15–17]. Similarly, sphincter preservation is considered a metric of quality care in rectal cancer patients, even though a substantial proportion of patients who undergo sphincter preservation will battle with adverse gastrointestinal function. In this context, some patients may not choose sphincter perseveration to avoid the impact of gastrointestinal dysfunction on QOL. Conversely, other patients may be so mentally averse to having a permanent colostomy that they would accept substantial gastrointestinal dysfunction and a perceived diminished QOL over having a colostomy. The patient's perception of how treatment affects his or her well-being is influenced by internal standards, intrinsic values, expectations, as well as prior experiences. While this is a subjective concept, it can be objectively measured with psychometrically valid instruments.

The assessment of QOL including functional outcomes and PROs is therefore important in determining the efficacy of treatment strategies for rectal cancers. It is essential to know how each of these modalities impacts the patient's functional outcomes and QOL. Therefore, the incremental benefit of different modalities and strategies on the oncologic endpoints can be put in context for the patient in order to determine the most suitable treatment strategy. As a result, in clinical studies and trials, PRO instruments should be used to measure the impact of an intervention on one or more aspects of a patients' health status, ranging from the purely symptomatic, to more composite concepts (e.g., ability to carry out activities of daily life), and to extremely complex constructs such as QOL, which as described previously is a multidimensional concept with physical, psychological, and social components [18].

Mechanisms Through Which Multimodality Therapy Can Impact QOL

Patients undergoing treatment of locally advanced rectal cancer usually receive a combination of pelvic radiation, surgery, and systemic chemotherapy. All of these different modalities individually and in combination can have adverse effects on functional outcomes and in turn impact QOL and PROs of patients.

Surgery

Radical surgery for rectal cancer involves removal of a portion or the entire rectum in order to adequately remove the primary tumor and the surrounding lymph nodes. Depending on the relationship to the sphincter complex, patients can either undergo reestablishment of intestinal continuity (usually with temporary fecal diversion) or require a permanent colostomy. This has several consequences on gastrointestinal, sexual, and urinary function that can have a negative impact on a patients' physical, psychological, social, and emotional functioning as well the patients' overall well-being.

Patients that undergo sphincter preservation can have a constellation of gastrointestinal symptoms that has been described as the low anterior resection syndrome (LARS). The symptoms of LARS are extremely variable and range from constipation and obstructed defecation to altered bowel habits characterized by stool clustering, fecal urgency, changes in stool consistency and frequency, as well as varying degrees of incontinence [19, 20]. Clinically patients fall into two broad categories: (1) patients with urgency or fecal incontinence and (2) patients with evacuatory dysfunction (although symptoms frequently overlap) [7]. Disordered bowel function after rectal resection causing a negative influence on QOL has been considered to be the pragmatic definition of LARS [7]. The exact incidence of LARS is not known, since until recently there was no validated instrument to measure this [21], but up to 90% of patients will report altered bowel function following surgery [7].

The rectum, anal sphincters, and pelvic floor are all essential in maintaining fecal continence. All three of these can be affected by surgery resulting in patients having temporary or permanent fecal incontinence. The rectum acts as a physiologic reservoir for stool to be expelled at a socially appropriate occasion. As a result of the loss of the reservoir function, the neorectum has a lower capacity with a decrease in the maximally tolerated stool volumes. Advanced techniques for sphincter preservation include hand-sewn anastomosis with and without mucosectomy or partial resection of the internal sphincter. While these techniques allow for sphincter preservation, they can also lead to less than ideal continence due to the compromise in the integrity of the anal transition zone and the sphincter complex. During pelvic dissection, the pelvic floor muscles and/or their innervating nerves can be injured [22]. Postoperatively, if pelvic sepsis, anastomotic complications, or pelvic abscesses form, the resultant inflammation can progress to fibrosis and further impair the functioning of the pelvic floor muscles.

The majority of patients that undergo sphincter preservation require temporary fecal diversion, usually with an ileostomy. This can be associated with an increased risk of dehydration and electrolyte imbalances that may require rehospitalizations [23, 24]. On the other hand, patients with permanent stomas contend with long-term stoma-related complications such as prolapse, stenosis, hernias, and peristomal skin irritation [25, 26]. The incidence of these complications has been reported to be between 21% and 70% depending on the length of follow-up and the definition of individual complications [27]. Additional patient concerns that influence QOL include issues with body image and intimacy, depression, as well as psychological concerns of being able to maintain adequate personal hygiene.

As a result of the pelvic dissection necessary to remove the rectum, the nerves to the sexual organs and the urinary bladder can be compromised leading to sexual and urinary dysfunction. The superior hypogastric plexus comprises of sympathetic fibers from the T12, L1, and L2 nerve roots and lies anterior to the aortic bifurcation and is in close proximity to the inferior mesenteric artery (IMA). The superior hypogastric plexus divides into left and right hypogastric nerves that run parallel and medial to the ureters along the superior and posterior aspect of mesorectum. The hypogastric nerves, along with the parasympathetic pelvic splanchnic nerves or nerves erigentes, which arise from the S2 to S4 sacral nerves, form the pelvic plexus or the inferior hypogastric plexus that is located laterally at the level of the distal one-third of the rectum [28]. These nerve plexuses innervate the rectum, uterus, vagina, clitoris, urethra, penis, and prostate.

The sympathetic and parasympathetic nerves can be injured or damaged during the high ligation of the IMA, the presacral dissection at the level of the sacral promontory, laterally in the distal rectum at the level of the nervi erigentes and inferior hypogastric plexus, and anteriorly particularly in males by the periprostatic plexus. Sexual dysfunction in men can manifest as erectile dysfunction and ejaculatory disorders. Erectile dysfunction can be partial or complete and occurs due to injury to the parasympathetic nerves that supply vasodilator fibers to the erectile tissue in the penis. Absent, retrograde, or painful ejaculation can result from disruption of

the sympathetic fibers. The most common site for this to occur is at the level of the sacral promontory. Injury to the superior hypogastric plexus and hypogastric nerves results in retrograde ejaculation, while damage to the inferior hypogastric plexus and nervi erigentes causes incomplete/absent ejaculation [28]. In women the role of the sympathetic and parasympathetic system in normal sexual function is less well understood. It is known that the autonomic nervous system is responsible for vasodilatation, which is associated with increased secretions from the Bartholin's glands resulting in vaginal and vulvar lubrication [29]. Injury to these nerves during surgery can result in decreased lubrication, vaginal dryness, and dyspareunia. Denervation of the vagina can also result in a decrease in vaginal wall compliance and impaired ability to achieve orgasm [29, 30].

Urinary dysfunction following surgery can include urinary retention, bladder emptying problems, as well as urge, overflow, and/or stress incontinence. Urge incontinence results from the reduction in the bladder capacity due to injury to the sympathetic nerve supply (the hypogastric and the pelvic plexus). Injury to the parasympathetic nerve supply (pelvic splanchnic nerves) results in bladder emptying problems including overflow incontinence and urinary retention. Stress incontinence occurs due to deficiencies in the support of the urethra and bladder neck. This support normally comes from the surrounding structures particularly the pubourethral-vesical ligaments and the pelvic floor muscles. These structures are at risk of being damaged during surgery resulting in postoperative stress incontinence [22].

The perioperative course following surgery can have a significant impact on a patient's well-being. Postoperative pain, nausea, vomiting, and altered bowel habits occur commonly. These decrease the physical function and the patients' ability to work and carry out social activities [31, 32]. Additionally, perioperative complications such as anastomotic leaks, pelvic sepsis, and wound complications [33] contribute to prolonged hospitalization resulting in a delay in perioperative recovery as well as decreased physical functioning and increased mental and emotional distress.

Pelvic Radiation

Pelvic radiation is integral in decreasing the risk of local recurrence and increasing the probability of sphincter preservation. It also has several short- and long-term side effects that can be detrimental to patient QOL. The impact of pelvic radiation can differ by the duration of administration (i.e., short vs. long course), the dose administered (i.e., both fractionated and total doses), and the timing of administration (i.e., pre- vs. postoperatively).

Short-term toxicities from pelvic radiation include nausea, vomiting, diarrhea, fatigue, and perianal anal skin irritation [34]. These complications are more common and severe when radiation is administered postoperatively compared to when it is given preoperatively. In the German CAO/ARO/AIO-94 trial, 823 patients with stage II and III rectal cancers were randomized between preoperative and postoperative chemoradiation [6]. The overall rates of acute toxicity and long-term morbidity were lower in the preoperative group than in the postoperative group of patients, particularly as it related to acute and chronic diarrhea and the development of anastomotic strictures. As a result currently pelvic radiation if indicated is usually administered preoperatively.

Pelvic radiation has an unfavorable impact on the function of male and female sexual organs, urinary bladder, urinary and anal sphincter complexes, and pelvic floor musculature. The mechanisms linking radiation to sexual and urinary dysfunction are multifactorial [28]. One key mechanism of damage is progressive endarteritis in the inadequately oxygenated tissues with eventual tissue fibrosis as well as endothelial damage (arterial obliterans) resulting in chronic ischemia. Secondly, it also adversely affects the function of the pelvic nerves by causing direct damage and making them susceptible to injury during surgery. Furthermore, pelvic radiation decreases the compliance of the rectum due to fibrosis (particularly if given postoperatively), resulting

in reduced reservoir function and volume tolerance. Radiation-induced fibrosis of the myenteric plexus of the internal sphincter can result in diminished resting tone leading to incontinence. Fibrosis of the pelvic floor and the sphincter complex interferes with the coordinated movements of the pelvic muscle necessary for normal defecation and continence resulting in obstructive defecation or pelvic floor dysfunction. Varying degrees of fibrosis and small vessel injury in and around the bladder and seminal vesicles result in reduction of the bladder capacity and erectile and ejaculatory dysfunction in men. While radiation-induced impotence is mainly considered to be arteriogenic, it is likely that it is also related to direct injury and ischemic injury of the nerves involved in sexual function [29].

In females rapid cell turnover of the vagina and vulvar epithelium makes the tissue susceptible to radiation injury. The effects of radiation may manifest after a period of latency, or it could be progressive from acute edema, inflammation, and ulceration to necrosis and fibrosis [35]. Acute effects of pelvic radiation include vaginal erythema, desquamation, and mucositis. While in most patients these are self-limiting and resolve in 2–3 months following pelvic radiation, in a proportion of patients, this is progressive leading to epithelial sloughing, ulceration, and even necrosis. With a median period of 1–2 years, late effects may develop when the submucosa undergoes varying degrees of fibrosis as well as when there is ischemia from radiation-induced endarteritis. These changes are known to cause vaginal thinning, atrophy, shortening, fibrosis, stenosis, and dryness, which in turn have an adverse impact on female sexual function [36].

Chemotherapy

In the current multimodality approach, chemotherapy is administered preoperatively as a radiosensitizing agent and postoperatively in the adjuvant setting.

5-Fluorouracil (5-FU) and capecitabine (which is converted to 5-FU by intracellular thymidine phosphorylase) are the commonly used radiosensitizing agents. While in the adjuvant setting most chemotherapy regimens are either oxaliplatin [37] or irinotecan [38, 39] based. Despite the NCCN guidelines for adjuvant chemotherapy, up to one-fourth of patients do not ever receive chemotherapy following surgery, and less than 50% receive the full dose without interruptions or delays due to postoperative morbidity and delayed recovery from surgery [40]. Moreover while current multimodality therapy including TME surgery and pelvic radiation has significantly decreased the local recurrence rates, this has not resulted in better overall survival mainly due to distant metastatic disease relapse. Currently, there is growing interest in exploring different chemotherapy and/or targeted therapy regimens in the neoadjuvant setting, either as radiosensitizing agents or as systemic induction therapy. Theoretical advantages of this approach include prevention and/or eradication of micrometastatic disease early, increased rates of pathologic complete response [41, 42], and improved compliance with systemic chemotherapy [43].

Several studies have investigated the addition of oxaliplatin to 5-FU as a radiosensitizer to improve treatment outcomes. Most trials so far have demonstrated no improvement in long-term survival outcomes but more short-term toxicity and worse therapeutic ratios [44–46]. However the CAO/ARA/AIO-04 trial showed an increased proportion of pathological complete response with comparable toxicity in patients with oxaliplatin and 5-FU-based neoadjuvant chemoradiation and adjuvant chemotherapy compared to 5-FU alone [47]. In order to improve tumor regression in patients with locally advanced disease, another strategy has been to add systemic chemotherapy before chemoradiation. Results from several phase II trials have demonstrated significant tumor response in large tumors threatening the mesorectal fascia by giving systemic neoadjuvant or induction chemotherapy before chemoradiation [48–51]. The strategy of induction chemotherapy preceding chemoradiation has now therefore been added to the US National Comprehensive Cancer Network (NCCN) clinical practice guidelines as an acceptable option for the treatment of locally advanced rectal

cancer [43]. Along with chemotherapy agents, several targeted therapies have also been investigated in this context. The AVACROSS study evaluated [52] the efficacy and toxicity of bevacizumab added to induction chemotherapy (capecitabine and oxaliplatin) followed by bevacizumab-based chemoradiation. While the study achieved a pathologic complete response of 36% with acceptable toxicity, 24% of patients developed surgical complications requiring surgical intervention. The EXPERT-C was a multicenter, randomized phase II trial investigating the addition of cetuximab to neoadjuvant capecitabine and oxaliplatin (CAPOX) chemotherapy followed by chemoradiation, surgery, and adjuvant CAPOX chemotherapy [53]. QOL was assessed using the EORTC QLQ-C30 and QLQ-C29 at baseline before treatment, at 6 and 12 weeks during chemotherapy, 4–6 weeks after chemoradiation, after 1 week of adjuvant chemotherapy, and at the end of adjuvant chemotherapy. This approach was observed to improve treatment-related symptoms and did not have a significant detrimental effect on QOL and bowel function, with short- and long-term follow-up [53].

The use of systemic chemotherapy can also have an effect on the primary tumor and in case of a significant response can result in avoiding pelvic radiation and its adverse impact on short- and long-term functional outcomes. This strategy is being evaluated in the PROSPECT trial (Preoperative Radiation or Selective Preoperative Radiation and Evaluation before Chemotherapy and TME), which is a phase II/III multicenter trial [54]. Neoadjuvant FOLFOX with selective use of chemoradiation (selective arm) is being compared with the current standard of preoperative chemoradiation (standard arm). In the selective arm patients, receiving neoadjuvant FOLFOX6 will be restaged after completion of chemotherapy, and patients with a greater than 20% response will undergo surgery, while the nonresponders will receive chemoradiation. The primary endpoint for the phase II part of the trial is an equivalent R0 resection rate between the selective and standard arms. In case of equivalence, the study will proceed to a phase III trial, which will evaluate time to local recurrence and disease-free survival.

Another approach that is currently being evaluated is consolidation chemotherapy, administration of systemic chemotherapy between radiation and surgery. In a prospective phase II trial of short-course pelvic radiation, followed by four cycles mFOLFOX6 before surgery, patient-reported QOL was measured using the Functional Assessment of Cancer Therapy-Colon (FACT-C). QOL was measured before radiation, before surgery, and one-year after surgery in 80 patients [55]. There were no statistically or minimally important differences in the mean FACT-C scores from before to after treatment, although there were significant differences in QOL between patients with an ostomy compared to patients without an ostomy one year after treatment. The RAPIDO trial is a phase III study that is currently enrolling and is comparing the 3-year disease-free survival in patients randomly assigned to preoperative short-course radiation followed by six cycles of capecitabine and oxaliplatin and surgery versus long-course preoperative pelvic chemoradiation and surgery [56]. In a multicenter phase II trial, the addition of cycles of 5-FU, oxaliplatin, and leucovorin (FOLFOX6) between chemoradiation and surgery resulted in an increase in the proportion of patients achieving a complete pathological response without increasing the incidence of toxicity and perioperative complications [57]. The advantage of using this strategy to increase the incidence of complete pathologic response is that patients can become eligible for less invasive strategies with organ preservation such as local excision [58] or the "watch-and-wait" approach [59], therefore avoiding the morbidity associated with removing the rectum and its subsequent impact on functional outcomes and QOL.

All the chemotherapeutic and targeted therapies discussed above have significant toxicities and side effects. Adverse reaction associated with 5-FU and leucovorin includes gastrointestinal toxicity (diarrhea, nauseas, and stomatitis) and myelosuppression. Capecitabine has a similar profile in addition to hand-foot syndrome,

which can be dose limiting. It has also been observed that the risk of severe diarrhea is almost doubled when it is used in combination with irinotecan [60]. Oxaliplatin is associated with an acute neuropathy that is characterized by distal or perioral paresthesias. In addition, patients may develop a chronic sensory neurotoxicity that can be irreversible and adversely affect QOL [61]. Both of these regimens are also associated with dose-dependent clusters of symptoms, including fatigue, anorexia, weight loss, pain, fever, and dehydration, all of which effect functioning and QOL [62]. Therefore while the use of different chemotherapy sequences and regimens can improve oncologic outcomes, their adverse consequences will need to be balanced against their benefits.

Challenges in Evaluating QOL Outcomes

There is a substantial body of literature regarding QOL outcomes after multimodality therapy, but there are also several challenges in making meaningful conclusions from these data and using this information in decision-making [63]. The following are some of the issues that need to be considered when interpreting QOL outcomes.

Instruments to Measure QOL

Available QOL studies evaluating the effects of different treatment strategies have utilized a heterogeneous group of instruments, including both generic and disease-specific measures. This heterogeneity in measurement instruments and in outcome reporting prevents uniform and equivalent comparisons across studies and hampers comparative effectiveness research strategies. It has also been difficult to combine and contrast findings from different studies to perform meta-analysis or pooled data analyses. In order to draw valid conclusions regarding PROs, it is essential to use standardized methods and to use validated measures that demonstrate the appropriate psychometric properties [13, 64].

Delineating the Effect of Individual Modalities

Multimodality therapy for rectal cancer involves surgery, pelvic radiation, and systemic chemotherapy. Each and all of these modalities are associated with side effects that have the potential to adversely influence QOL. Since these modalities are usually utilized together or in close tandem to each other, it is challenging to discriminate which individual modality is directly responsible for an adverse effect observed at a time point that is retrospective to the treatments. It is particularly difficult to distinguish the impact from the two local treatment modalities, i.e., pelvic radiation and surgery, as both are associated with gastrointestinal, sexual, and urinary dysfunction. It is not known if their effects are cumulative or synergistic. This becomes an important consideration when it is likely that the expected additional benefit in local control from pelvic radiation is disproportional to the potential additive or synergistic detriment in functional outcomes. However, this is necessary to consider as it could influence patient decisions and choices, particularly if they value QOL over long-term survival.

The Impact of Time: Length of Follow-Up and Study Design

Functional and QOL outcomes are responsive to time. Previous studies suggest that they worsen immediately after surgery, progressively improve with time, and tend to plateau around 12–24 months postoperatively [65–68]. Confounding this natural time course is the phenomenon known as the "frame-shift response" [69, 70] or "cognitive dissonance reduction" [71]. These terms describe the ability for patients to learn to accept and/or adapt to living with poor functional outcomes and therefore do not necessarily consider the poor functional outcomes to adversely impact their QOL and well-being. For example, many patients suffer from an increased stool frequency or stool clustering where several bowel movements occur in a short period of time.

Initially, these symptoms are likely to interfere with patients' functional abilities, but over time, patients make dietary modifications and change their daily routine so as to accommodate this dysfunction. As a result, they may not report as negative an impact on QOL as they did at earlier time points. Time therefore must be considered a unique variable whose impact on outcomes of interest should be adjusted for during analysis of QOL.

When pooling data from various studies of functional outcomes and QOL, it is important to consider the study design. The two most common designs are cross-sectional or longitudinal. As a result, in comparing different cross-sectional studies, the various time points of assessment and difference in follow-up durations can make meaningful comparisons difficult. In contrast, longitudinal studies tend to have relatively short lengths of follow-up and/or suffer from attrition and missing data from later time points. With improvements in oncologic outcomes, the long-term effects of these treatment modalities in late survivors need to be reliably assessed. This is particularly applicable to pelvic radiation that is known to have adverse consequences decades after the initial treatment.

Patient- and Disease-Related Factors Affecting QOL

While the different treatment modalities used to treat locally advanced rectal cancers affect QOL outcomes, there are several patient- and disease-related factors that independently influence patient QOL. It is important to take these factors into account while making therapeutic decisions as these can interact and potentially synergistically increase the adverse impact of the various treatment modalities on QOL.

Patient-Related Factors

Patient-related factors that can independently impact QOL include age, gender, comorbid conditions, and preoperative functional status.

Age

With increasing age, sphincter tone decreases and pelvic musculature tends to relax. As a result, the incidence of fecal incontinence increases with age. This baseline trend may exacerbate the gastrointestinal dysfunction after the multimodality treatment of rectal cancer in elderly patients. In younger patients this dysfunction may not be that severe, but because of its more pronounced effect on physical and social functioning, it can lead to worse QOL.

About two-thirds of patients with rectal cancer are over 65 years of age [8]. At the same time there is a subset of patients with early onset cancers and with hereditary syndromes such as familial polyposis and Lynch syndrome that are in their third and fourth decades of life. These patients can be considered to be in the prime of their life with young families, professional careers, and personal responsibilities. Their expectations and outlook on life are likely to be different from patients who are older, and therefore the same treatment strategy in both these age groups may not be necessarily appropriate. The balance of "quantity" of life or survival versus "quality" of life needs to be considered and can lead to different decisions depending on the age groups and their priorities. Contemporary evidence suggests that healthy older patients have similar cancer-specific outcomes after multimodality treatment with minimal age-related increase in adverse effects. Yet there is a paucity of data about the short- and long-term costs of treatment with regard to QOL for the time that is gained [8]. Reliable and valid QOL assessment is essential in these patients because they may be less willing to compromise their short-term well-being for the future possibility of prolonged survival [8]. Younger patients, who are socially and physically active and likely to be in a relationship, are therefore more likely to be adversely affected by the consequences of multimodality therapy on gastrointestinal and sexual function; but for them given their priorities, this may be an acceptable trade-off if it means a significant increase in overall survival.

In a cross-sectional study of 282 long-term (>5 years) survivors who had been diagnosed and

treated for colorectal cancer (CRC) prior to age 50 and 548 survivors diagnosed after age 50, significant differences in functional outcomes persisted as assessed by the EORTC QLQ-CR29 instrument [72]. Young adult survivors were more troubled by anxiety and poor body image perception compared to older survivors. In multivariate analyses, younger age-at-disease onset was independently associated with anxiety, worse body image perception, sore skin, and embarrassment with bowel movements among long-term CRC survivors. On the other hand, later age was independently associated with male and female sexual dysfunction, micturition problems, and impotence [72].

Gender

Females who have had vaginal deliveries can have occult sphincter injuries that are well compensated but may become clinically symptomatic after surgery due to further impairment of sphincter function from surgery and pelvic radiation. Anatomically females have a wider pelvis compared to males particularly those with an android-type pelvis. It is therefore plausible to expect that females would have a lesser chance of pelvic nerve injury compared to males, but there is limited data to objectively validate this hypothesis. Comorbid conditions such as diabetes, hypertension, coronary heart disease, and chronic obstructive pulmonary disease are all considered risk factors for perioperative morbidity, which can impact postoperative well-being and functioning. Obesity per se may not have a direct effect on functional outcomes but can substantially increase the risk of preoperative morbidity [73].

Preoperative Functioning

Preoperative functioning can be affected by age and gender as discussed above. In addition, urinary symptoms such as frequency and urgency and a decline in sexual function are common with age, particularly in men. Therefore the extent of impairment caused by urinary and sexual dysfunction after treatment can be influenced by the patient's preoperative symptoms and baseline function as well as relationship status. If patients are not sexually active or already have sexual dysfunction, then treatment-related dysfunction is unlikely to influence their QOL compared to patients who were sexually active and had acceptable preoperative function.

Tumor-Related Factors

The location of the cancer within the rectum (anterior versus posterior), its distance from the anal verge, and its relationship to the sphincter/levator complex (involved versus uninvolved) impact the operative approach that can have significant consequences on functional outcomes. Patients with distal rectal cancers located less than 5 cm from the verge but without direct involvement of the sphincter/levator complex can undergo sphincter preservation but usually require a stapled or hand-sewn coloanal anastomosis. More proximal tumors in the rectum can undergo a colorectal anastomosis with tumor-specific mesorectal excision. The distance of the anastomosis from the anal verge is an independent risk factor associated with anastomotic leaks and postoperative function. The closer the anastomosis is to the anal verge, the higher is the chance of an anastomotic leak and subsequent postoperative bowel dysfunction due to pelvic sepsis [74, 75]. The height of the anastomosis is from the anal verge and also significantly impacts on the incidence in bowel dysfunction including LARS. Distal tumors, particularly those located anteriorly or those that are circumferential, are associated with an increased risk of sexual and urinary dysfunction as the anterior-based nerve complex and nerve erigentes are at risk of being damaged during the pelvic dissection to remove the rectum [36]. Tumors involving the sphincter complex usually do not undergo sphincter preservation and require an APR. Currently, there is limited patient-reported outcomes data comparing (1) the standard abdominoperineal (APR) approach and (2) the extra-levator abdominoperineal approach [76, 77].

Multimodality Treatment of Rectal Cancer and Impact on QOL

Gastrointestinal Dysfunction

Low anterior resection syndrome (LARS), characterized by irregular bowel habits, changes in frequency and consistency, and incontinence, can impact nearly two-thirds of the patients undergoing sphincter preservation surgery [7]. Many factors discussed above contribute to the patients' postoperative gastrointestinal function.

In a systematic review of 48 studies published between 1978 and 2004, the functional outcomes of 3349 patients undergoing curative resection of rectal cancer were pooled and evaluated [78]. The median follow-up for this group was 24 months (IQR 12, 57). The reported portion of patients with incontinence ranged from 3% to 79%, with a pooled incidence of 35%. Significant rates for other symptoms including urgency 35%, the routine use of pads 33%, and increased bowel movement frequency 18% were also reported. Risk factors for incontinence identified by meta-regression included preoperative pelvic radiation and in particular short-course radiation. However, there was variability and lack of consistency in reporting risk factors and outcomes, with 65% of the studies not using a validated instrument.

The meta-analysis and systemic review by Loos et al. [79] that analyzed 25 studies published between 1980 and 2012, including two randomized multicenter trials, observed similar findings. The authors noted several drawbacks of their analysis including the fact that 10 of the 25 studies included fewer than 50 patients and the group receiving pelvic radiation included 20 patients or less in 7 studies and preoperative assessment of gastrointestinal function was performed in only 4 studies. One of the two randomized trials analyzed in this meta-analysis was designed to compare surgical reconstruction techniques following low anterior resections, but found that patients that were radiated had more frequent bowel movements, increased urgency, and higher use of antidiarrheal medications [80]. The second randomized trial in the meta-analysis was the Dutch TME trial. This trial was conducted between 1996 and 1999 and randomly assigned 1530 patients with rectal cancer to preoperative short-course pelvic radiation and TME surgery versus TME surgery alone [2]. In this trial patients receiving pelvic radiation had a higher rate of fecal incontinence (62% versus 38%), more frequent bowel movements during the day (3.7 versus 3.0), and a significantly higher rate of pad wearing (56% versus 33%) compared to patients undergoing surgery alone after a follow-up of almost 5 years. After long-term follow-up, QOL was evaluated in surviving patients ($n = 606$) using the EORTC QLQ-C30 and QLQ CR-29 in 2012. Eighty-two percent ($n = 478$) of patients responded with a median follow-up of 14 years. Patients receiving pelvic radiation reported more incontinence and higher stool frequency compared to patients undergoing surgery alone.

The Medical Research Council CR07/National Cancer Institute of Canada Trial Group C016 (MRC CR07/CO16) randomized trial compared two treatment strategies directed at reducing local recurrence rates: short-course pelvic radiotherapy followed by surgery vs. surgery followed by postoperative chemoradiation only if pathological examination showed a positive circumferential radial margin [4]. Among 1350 patients, those receiving preoperative short-course radiation had a local recurrence rate of 4.4%, which was significantly less than the local recurrence rate of 10.6% among those that underwent selective postoperative chemoradiation. Patient-reported QOL was collected using the SF-36 and EORTC QLQ-CR38 questionnaires that were administered at baseline, every 3 months for one year and every 6 months for three years. Both treatment groups reported similar levels of decreased physical function at 3 months, which subsequently returned to baseline levels. While there were no differences in general health and bowel function between the groups, the exploratory analysis observed a significant increase in fecal incontinence at 2 years associated with preoperative short-course pelvic radiation [81].

The Trans-Tasman Radiation Oncology Group Trial 01.04 was a randomized trial comparing preoperative short-course vs. long-course pelvic

chemoradiation. Among 326 randomized patients (163 in each arm), three-year local recurrence, overall survival, and late toxicity rates were not statistically different [82]. QOL was evaluated using the EORTC QLQ-CR38 preoperatively and 1, 2, 3, 6, 9, and 12 months postoperatively. The overall health-related QOL was similar between the two groups, with surgery having the most adverse effect on QOL [83]. These findings were in concordance with the Polish randomized trial that compared preoperative short-course vs. long-course pelvic chemoradiation among 312 patients [84]. Early toxicity was higher in the chemoradiation group, but the overall survival, local recurrence, and late toxicity rates were not different between the two groups. QOL was measured using the EORTC QLQ-C30 instrument, and anorectal and sexual function was assessed using a study-specific questionnaire after a median follow-up of 12 and 13 months, respectively, from surgery. There were no differences in QOL and anorectal and sexual function between the two groups [85].

Battersby et al. conducted a multicenter cross-sectional study of 578 patients with rectal cancer undergoing curative anterior resections between 2001 and 2012 from 12 centers in the United Kingdom, using validated instruments to assess bowel function (LARS, low anterior resection syndrome score, and Wexner fecal incontinence score) and QOL (EORTC-30) [86]. The mean follow-up for this group was 5 years. Patients were also asked a single anchor question: "overall how much does your bowel function affect your quality of life?". Responses were used to stratify patients into three categories of bowel function-related QOL (BQOL): "not at all" represents no impairment; "very little" represents minor impairment; and "somewhat" and "a lot" were combined to represent major impairment. Eighty-five percent of patients reported some BQOL impairment and more than 40% considered bowel dysfunction to have a significant effect on their QOL at a median of 5 years from surgery. The two independent factors for BQOL impairment were preoperative radiation and a low tumor height. When both these risk factors were present, 93% of the patients were likely to have BQOL impairment, with almost two-thirds reporting major impairment. However 50% of the study participants did not have either risk factor but still had an 81% likelihood of BQOL impairment, suggesting that there remains unaccounted factors that contribute gastrointestinal dysfunction after surgery.

In a prospective analysis of QOL and bowel function, 260 patients with rectal cancer were evaluated at the time of diagnosis and 3 and 12 months after surgery using the EORTC QLQ-C30, a study-specific bowel function questionnaire, and the recently developed LARS score [67]. All patients in this cohort had gastrointestinal continuity reestablished with approximately 17% receiving neoadjuvant chemoradiation. A significant proportion of patients had symptoms of LARS, and in turn poor QOL. The risk of LARS was also significantly increased after neoadjuvant therapy and TME.

Collectively taken together, these data from randomized trials and cohort studies suggest that regardless of the regimen and timing, decisions regarding pelvic radiation and surgical resection must be made in the context of informing patients about the negative impact on gastrointestinal function and QOL.

Sexual Dysfunction

Sexuality remains an important aspect of most patients' well-being. Multimodality therapy has been associated with an increased prevalence of male and female dysfunction. Sexual dysfunction after treatment of rectal cancer is a multidimensional problem that can occur for a number of reasons including physical, psychological, emotional, and social factors. There can be causes unrelated to treatment such as failing health in a partner or loss of a partner, as well as side effects of treatment such as diminished body image particularly if they have a colostomy, organic dysfunction from nerve damage/injury, treatment- or disease-related fatigue, as well as depression. Based on reported data the incidence of sexual dysfunction is 23% to 69% in males and 19% to 62% in women [87]. The wide ranges are due to

differences in case mix, how sexual dysfunction is defined and measured, indications and technique of surgery, as well as variations in study sample sizes, use of non-validated questionnaires, and timing of assessment in relation to the different treatment modalities.

Sexual dysfunction is common in males after treatment for rectal cancer. Erectile dysfunction ranges from 17 to 100% after APR and 0 to 50% after anterior resection. Studies that have used non-standardized instruments and definitions have reported a lower incidence of sexual dysfunction in the range of 23%–35% compared to studies that have used validated instruments [87]. Majority of the studies that have evaluated sexual function in men have used the EORTC CR38 questionnaire that evaluates the extent of sexual dysfunction (instead of the incidence). These studies have observed a 30–40% decrease in sexual activity among sexual active men after treatment for rectal cancer [87].

Surgery and pelvic radiation have an adverse impact on male sexual function [88]. In the Dutch TME trial, after a 24-month follow-up, sexual function deteriorated following surgery and was worse for patients receiving pelvic radiation. In the functional scales, both erection and ejaculatory problems were more severe in patients receiving pelvic radiation [89]. This effect persisted long term, and after a median follow-up of 14 years, irradiated patients reported more erection problems. Males in both groups reported less sexual activity, interest, and enjoyment and more erection difficulties compared to the normative Dutch population [90].

The impact of minimally invasive techniques on sexual function has been controversial. While cohort studies suggest better outcomes, majority of the controlled studies has not appreciated a significant difference [87]. In the conventional versus laparoscopic-assisted surgery in colorectal cancer (CLASICC) trial, sexual functioning score and erectile function were worse in men after laparoscopic surgery than after open surgery, but this was not statistically significant [91]. The COLOR II (colorectal cancer laparoscopic or open resection) trial was a multicenter international randomized trial in which patients with rectal cancer within 15 cm of the anal verge were randomized to open or laparoscopic surgery between 2004 and 2010 [92]. Among the 617 randomized patients, 365 completed the EORTC QLQ-CR38 questionnaire preoperatively and 1, 6, 12, and 24 months after surgery. The mean age was 67 years and there were 146 females. Fifty-six percent received preoperative pelvic radiation and 36% underwent an abdominoperineal resection. There were no differences in sexual dysfunction between the two groups at any time point. After adjusting for available confounders including pelvic radiation, no differences were seen. Prior to surgery 65% of male patients undergoing laparoscopic surgery and 56% patients undergoing open surgery reported some degree of erectile dysfunction, which increased to 76% and 75%, respectively, at 12 months following surgery [92].

Most studies evaluating sexual function do not include age- and sex-matched normative controls; as a result it is unclear if the observed sexual dysfunction is treatment related or due to underlying factors such as age and comorbidities [93]. In a cross-sectional population-based analysis, 1359 colorectal cancer survivors between 1998 and 2007 from the Eindhoven Cancer Registry were compared to 400 normative control participants. Male rectal cancer survivors (51%) were less sexually active and had more problems with erectile functioning (54%) than men from the normative population (64% and 27%, respectively) [93]. On the EORTC sexual functioning scale, rectal cancer survivors (26 ± 25) had lower score (indicating poorer function) than men from the normative population (38 ± 24), but sexual enjoyment scores were similar between the two groups.

The duration of adverse impact on sexual function has been evaluated in two longitudinal studies. In the Trans-Tasman trial [83], low scores for sexual function (indicating decreased interest and activity) were reported among males prior to treatment. Following treatment, a further significant decline in male sexual functioning, enjoyment and worsening of male sexual problems were reported, and these scores did not return to pretreatment levels even after 12 months. In the

QOL and functional outcomes analysis of the CR-07 trial, male sexual function was the main outcome adversely effected, and surgery was the main contributor, but short-course pelvic radiation additionally increased this dysfunction. These deficits persisted to at least 3 years after surgery, suggesting the long-lasting and irreversible nature of the impact [81].

Organic factors for female dysfunction include damage to the autonomic pelvic nerves involved in sexual function during surgery, radiation-induced damage to the vagina, and ovarian failure in premenopausal women. As a result of this female patients can develop change in vaginal dimensions, vaginal dryness, dyspareunia, and difficulty achieving orgasms, all factors that contribute to decreased sexual function that in turn can adversely affect QOL. The prevalence of female sexual dysfunction after multimodality treatment of rectal cancer, like in men, varies widely across the literature due to many of the same reasons. Furthermore, most instruments such as the EORTC assess sexual function in the context of sexual intercourse and exclude patients if they are not sexually active. Another unique issue related to measuring the prevalence of sexual dysfunction in women has been the low response rates due to the personal nature of the questions.

Female patients in the Dutch TME trial [94] receiving preoperative short-course radiation were significantly less sexually active following multimodality treatment compared to before treatment and had worse sexual functioning compared to patients undergoing surgery alone after 24 months of surgery. In the long-term follow-up of this cohort, QOL was evaluated in 197 women who had survived and responded after a median follow-up of 14 years. Female patients that had received preoperative pelvic radiation reported significant vaginal dryness, decrease in sexual enjoyment, and dyspareunia compared to patients undergoing surgery alone as well as the general Dutch population [90]. In a population-based cross-sectional study of female patients who had undergone surgery for rectal cancer between 2001 and 2007 in Denmark [95], sexual and urinary function was evaluated using validated instruments. The Sexual Function-Vaginal Changes Questionnaire (SVQ) was used to assess sexual function in 607 eligible patients of which 505 (83%) agreed to participate. Patient underwent either a low anterior resection or an APR and had undergone preoperative short- or long-course pelvic radiation if indicated. The median age of this cohort was 64 years (range 26–87 years), and the median duration from surgery was 55 months (range 26–98 months). Approximately 40% of females were not sexually active after treatment. The main reasons reported were lack of desire, vaginal dryness and dyspareunia, failing health, or lack of a partner. Among patients who were sexually active, vaginal dryness, dyspareunia, and reduced vaginal dimensions were reported by 72%, 53%, and 29%, respectively. Preoperative pelvic radiation and a permanent colostomy were independent risk factors for sexual dysfunction. These observations are similar to the findings from the population-based study of female rectal cancer survivors from the Eindhoven Cancer registry [93]. Among female survivors prevalence of vaginal dryness (35%) and dyspareunia (30%) was significantly higher than those reported by the normative population (5% and 0%, respectively). Female patients also reported lower score for sexual functioning (15 vs. 22) and for sexual enjoyment (51 vs. 66) compared to the normative population [93].

In a cross-sectional study of patients that underwent rectal cancer surgery at a single institution between 1980 and 2003, sexual function was measured in women using the Female Sexual Function Index (FSFI) and the EORTC QLQ-C30/CR38 [96]. Out of the 100 patients mailed the questionnaires, 81 (81%) women responded. Despite high global QOL scores, 29% of the women reported that "surgery made their sexual lives worse." Undergoing an APR and receiving preoperative pelvic radiation were independently associated with the outcome "surgery made their sexual lives worse." In another institutional study in which sexual function among females undergoing rectal cancer surgery was prospectively assessed using study-specific questions, patients undergoing APR were less sexually active (25% vs. 50%) and had a lower frequency of intercourse at one year after surgery [97].

Approximately one-third of the participants in the Trans-Tasman trial [83] were women, but only a small proportion completed questions regarding sexual activity. This is partly due to the fact that the EORTC questions only apply to females who are sexually active. The issue of non-responsiveness to questions of this nature among women was also seen in the CLASSIC, CR-07, and COLOR II trials, as well as other studies also [81, 98, 91, 92, 99]. As a result our understanding of the extent and nature of sexual dysfunction and its impact on QOL among women after multimodality treatment is substantially deficient and an important area for future research.

Urinary Dysfunction

The incidence of urinary dysfunction after rectal cancer surgery ranges from 30% to 70% [22]. This wide variation, like for sexual dysfunction, is related to how it is defined and objectively measured. Confounding the issue is the impact of preoperative function, patient comorbidities, and the natural decline in urinary function with age. Long-term urinary incontinence after multimodal therapy has been reported to develop in one-third of the patients, and combined fecal and urinary incontinence occurs in 14% of patients with normal preoperative function [66].

Despite the prevalence, the contribution of individual treatment modalities (surgery and radiotherapy) to the development of urinary dysfunction is imprecisely known. In an analysis of urinary dysfunction among patients from the Dutch TME trial [22], long-term incontinence was reported by 38% of patients, of whom 72% had normal preoperative function, while long-term difficulty in emptying the bladder was reported by 31% of patients, of whom 65% had normal preoperative function. After adjusting for various patient-, disease-, and treatment-related factors, pelvic radiation was not associated with urinary dysfunction, leading the authors to conclude that while urinary dysfunction is a significant problem after rectal cancer treatment, it is not due to pelvic radiation but from surgery. In the COLOR II trial in which urinary dysfunction was measured using the EORTC QLQ-CR38, there were no differences between the laparoscopic and open groups for micturition problems at any time point. After adjusting for confounders including pelvic radiation, no difference was seen [92]. In the population-based cross-sectional study by Bregendahl et al. [95] using the International Consultation on Incontinence Modular Questionnaire-Female Lower Urinary Tract Symptoms (ICIQ-FLUTS), the presence of urgency and urge or stress-related incontinence was reported in 60% to 80% of the women leading to distress in a quarter to one-third of the affected patients. Voiding difficulties were less frequent ranging from 20% to 35% but were associated with preoperative radiotherapy.

Body Image and Permanent Ostomy

There has been a widely held assumption that patients with intestinal continuity have a better QOL than those with a permanent colostomy as the latter is considered a major psychological burden that adversely impacts patient QOL. The basis for this arises from historical experiences when ostomy care may have been suboptimal and not considered an actual patient need. Currently, ostomy care is an organized specialty and vital service line that responds to a wide range of patient needs. Also these historical data were collected without rigorous methodology nor measurements with validated psychometric properties.

The National Surgical Adjuvant Breast and Bowel Project (NSABP) R-04 stage II and III rectal cancer patients to four different neoadjuvant chemoradiotherapy regimens in patients undergoing curative surgery [100]. A secondary aim of the NABP R-04 was to evaluate the impact of the type of surgical management of rectal cancer on QOL at one year after surgery. The QOL instruments used in this study included the Functional Assessment of Cancer Therapy for patients with colorectal cancer (FACT-C) and the EORTC QLQ-CR38. Among 1608 randomized patients, 1502 patients were available for evaluation. QOL data at one year was available for 615 patients

with sphincter preservation and 372 patients with an APR. There were no statistically significant differences in gender, TNM stage, receipt of adjuvant chemotherapy, or tumor size between the two groups. The FACT-C scores were not statistically significantly different between types of surgery for the FACT-C total score or for any of the subscales at one year after surgery. On the EORTC QLQ-CR38, patients undergoing an APR reported worse body image, male sexual enjoyment, and micturition symptom scores compared to patients undergoing sphincter preservation. Patients undergoing sphincter preservation reported worse symptoms in the GI tract and weight loss compared to patients undergoing an APR.

In a Danish population-based cross-sectional study, QOL of patients with a permanent stoma after rectal cancer treatment between 2001 and 2007 was evaluated using a study-specific questionnaire [101]. Among the 732 eligible patients, 644 responded (response rate of 88%) with a median follow-up of 4.5 years (range 2–8 years). Although 68% of patients reported that having an ostomy impacted their QOL, the magnitude of the impact was rated as minor in 50%. Leakage from the appliance (59%), disturbances from the odor (58%), parastomal hernia (57%), and pain at the stoma site (30%) were the most common reported concerns. There was no association between QOL and gender, use of pelvic radiation, and follow-up duration. These findings were similar to the QOL data collected from Swedish patients that underwent an APR between 2007 and 2009 and were alive 3 years following surgery (n = 852). The response rate was 58% (495 patients) and almost 90% of patients did not feel limited by their colostomy [102].

In 2005 Pachler and Wille-Jorgensen performed an analysis of 11 non-randomized studies in which QOL was measured either after an APR or a low anterior resection using a validated QOL instrument. After analysis that included 1412 patients, the authors concluded, "included studies challenge the assumption that anterior resection patients fare better". The same authors updated their analysis in 2012, when they analyzed 35 non-randomized with 5127 patients. However their conclusions were exactly the same in that they did not feel that the evidence allowed firm conclusions to the question of whether the QOL of patients after sphincter preservation is better to that of patients with a permanent colostomy. On the other hand, a more recent systematic review of 14 descriptive cross-sectional studies did demonstrate that a colostomy negatively influenced overall QOL [27]. Importantly, only three studies in this analysis had more than 100 patients with a colostomy, and the follow-up duration varied between 1 and 12 years between studies [27].

Taken together, patients with a permanent ostomy face practical difficulties related to the daily care of the ostomy, as well as other problems related to body image, sexual function, social activities, and depression. However, whether an ostomy negatively impacts QOL likely evades a simple positive or negative answer but requires a multifactorial consideration.

Areas for Intervention and Future Directions

Optimizing the Benefit vs. Risk Ratio for Multimodality Intervention

The increased recognition of the functional sequelae and the detrimental impact on QOL that occur in association with multimodality therapy of rectal cancer has continued to drive a more tailored and judicious approach to the use of these treatment modalities. With improved identification and selection of patients whose disease might be expected to benefit the most from each modality, we could potentially spare others from unwarranted toxicities. Recent efforts to improve the benefit vs. toxicity ratio of multimodality therapy for rectal cancer have included (1) consideration for rectal sparing approaches including the "watch-and-wait" approach or local excisional procedures, (2) more selective use of pelvic radiation, and (3) questioning which rectal cancer patients really benefit from adjuvant chemotherapy. With these continued efforts to risk-stratify subpopulations of rectal cancer patients, more tailored and precise use of treatment modalities can help spare the potential detrimental effects in some patients.

Targeting Proactive Interventions for Patients at High Risk for Poor Quality of Life

Evidence-based interventions that directly improve functional outcomes and QOL have been limited. However, clinicians still have a wide armamentarium of interventions that can ameliorate many symptoms. Most commonly, dietary modifications, stool softeners, laxatives, medicinal fiber, and bulking agents can manipulate stool consistency and bowel flora to help manage stool frequency and clustering associated with LARS. Anal manometry studies, biofeedback, and pelvic floor physical therapy help address any underlying pelvic floor dysfunction that may be contributing to postoperative bowel function problems including LARS. Sacral nerve stimulation (SNS) has been shown to result in >50% improvement of symptoms in 80% of patients with fecal incontinence not responsive to conservative treatment results. In a recent review of 34 patients with LARS that underwent definitive implantation with SNS, 94% (32 patients) experienced improvement of symptoms with a median follow-up of 15 months [103]. Given the incidence of LARS and its negative impact on QOL, this represents a promising avenue of future investigation. Additionally, referral to a gastroenterologist can be beneficial for expanding the differential diagnosis and for considering other medications for symptomatic management. Currently, many options exist for sexual dysfunction, ranging from cognitive therapy, pharmaceutical medications, implantable devices, and psychosocial support. Therefore, proactive inquiry of sexual symptoms followed by referral to specialists in sexual medicine is beneficial [104]. In a prospective trial of 70 female colorectal and anal cancer patients, active intervention in the form of telephone-based, four-session Cancer Survivorship Intervention-Sexual Health (CSI-SH) was more effective than sexual function assessment alone for improving PROs [104]. Additionally proactive referral of patients to other health professionals including urologists, nutritionists, social workers, and psychologists, to provide support for social and mental well-being may help improve functional outcome and QOL.

Incorporating the Patient's Priorities and Preferences in Treatment Decision-Making

Treatment decisions for rectal cancer are complex and involve balancing of benefits and risks. Shared decision-making (SDM) is a proven process to incorporate the patient's preferences and voice in healthcare decisions and thus has been shown to be effective in making health decisions toward outcomes that matter most to the patient. Through a collaborative process, it takes into account the best clinical evidence available, as well as the patient's values and preferences. The practical implementation of the shared decision-making model into daily practice has been hampered by three main barriers which are (1) time constraints, (2) lack of applicability due to patient characteristics, and (3) lack of applicability due to the clinical situation [105]. Because physicians may misjudge patients' desire for active involvement in decision-making, it is important to proactively invite all patients to express their voice. Several models exist that link shared decision-making approaches to improved QOL outcomes in cancer patients. Empowered patients use their self-knowledge to select treatment options that can maximize their well-being. In a biopsychosocial model, patients who perceive that they played an active role in decision-making may have better coping and QOL outcomes. Finally, in a behavioral model, patient's participation in SDM may improve engagement in the overall treatment process and thereby improve QOL outcomes [106]. A systematic review of 17 studies found suggestive albeit weak evidence positively associating SDM and improved QOL outcomes, and there was no evidence for a negative association [106]. More research comprehensively examining different aspects of SDM was recommended.

Conclusion

The management of patients with rectal cancer represents a challenge to clinicians in achieving the ideal balance between subjective measures (such as QOL and functional outcomes) and

objective outcomes (like survival and local recurrence). Current multimodality treatment strategies including surgery, pelvic radiation, and adjuvant chemotherapy are associated with substantial compromises in gastrointestinal, sexual, and urinary dysfunction, and with an adverse influence of patients' QOL. As precision medicine assists with development of more risk-tailored treatment strategies, it is essential to outcomes and QOL. The ideal treatment strategies should consider not only tumor biology and patient biology but also the needs and expectations of each patient. Further sophistication and refinement of instruments for measuring patient-reported outcomes are imperative to make meaningful comparisons and conclusions. Among patients who have adverse functional outcomes, appropriate therapies should be promptly initiated to offset their adverse influence on patient QOL.

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Complications After Rectal Cancer Surgery

21

Cindy Kin, Amy Lightner, and Mark Welton

Introduction

Rectal cancer presents a uniquely complex challenge for surgeons. The close anatomic association of the rectum to genitourinary and neurovascular structures makes operating in the close confines of the pelvis particularly unforgiving. The addition of cancer-related factors such as locally advanced tumors and preoperative pelvic radiation further increases the risk of complications. Patient factors such as a narrow male pelvis and obesity further compound these risks. Thus, the surgical treatment of rectal cancer can be fraught with complications.

While the safety of rectal cancer surgery has improved greatly due to advances in standardized quality measures, anesthetic management, surgical technique, and postoperative care, there is still a significant risk of complications that may be infectious, hemorrhagic, genitourinary, obstructive, or functional. This chapter provides surgeons who perform rectal cancer operations with a practical guide to the diagnosis, evaluation, management, and subsequent outcomes of intraoperative and postoperative complications.

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Infectious Complications

Patients undergoing rectal cancer operations are particularly vulnerable to infectious complications due to the high-risk nature of low pelvic anastomoses, the high concentration of bacteria in the large bowel, and the immunosuppression caused by chemotherapy and radiation. Surgical site infections (SSIs) include superficial incisional, deep incisional, and organ space infections and represent the most common postoperative complications in rectal cancer surgery. SSIs are associated with worse quality of life, increased hospital length of stay, increased mortality, and increased cost [1].

The diagnosis of rectal cancer itself is a risk factor for the development of an infectious complication, as patients undergoing operations for rectal cancer compared to other colorectal surgical indications have the greatest odds for developing an SSI. Rectal cancer patients have the highest odds ratio (OR) for superficial incisional SSI compared to patients undergoing colorectal

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operations for other indications and twice the odds for developing deep incisional and organ space SSI compared to surgical patients with benign colorectal disease [2].

Risk factors for SSI in rectal cancer surgery include male gender, advanced age, anemia, high body mass index (BMI), higher ASA class, alcohol abuse, smoking, neoadjuvant pelvic radiation therapy, intraoperative hypotension, creation of an ostomy, and open approach [3–5]. The Surgical Care Improvement Project put forth a set of preventive measures intended to decrease SSIs, which includes: administration of prophylactic antibiotics within 1 h prior to incision, appropriate selection of prophylactic antibiotics, appropriate hair removal, and prevention of perioperative hypothermia. Implementation of this group of interventions was successful in decreasing the incidence of SSI in patients undergoing colorectal surgery in several centers, which also resulted in significant cost savings [6, 7]. Choice of prophylactic antibiotics appears to be particularly important in preventing SSI, as patients undergoing colorectal surgery who receive cefazolin/metronidazole, quinolone/metronidazole, or ertapenem before incision are less likely to have SSI and those who receive oral antibiotics also have reduced SSI rates [8–10].

Wound Infections (Superficial Incisional and Deep Incisional SSIs)

Superficial and deep incisional SSIs are more common in patients undergoing proctectomy than in patients undergoing colectomy [11] (Fig. 21.1). Quality improvement initiatives that bundled interventions to prevent SSI in colorectal surgery were effective in reducing superficial SSI rates, along with significant reductions in cost and length of stay [7, 12]. Newer interventions to prevent wound infections include the use of incisional negative pressure wound therapy which resulted in a wound complication rate of 12.5% compared with 29% of patients who had standard wound dressings [13]. Another intervention is the use of supplemental perioperative oxygen with 80% fraction of inspired oxygen (FiO_2) vs the control of 30% FiO_2, which also resulted in a significant reduction in wound infections [14, 15].

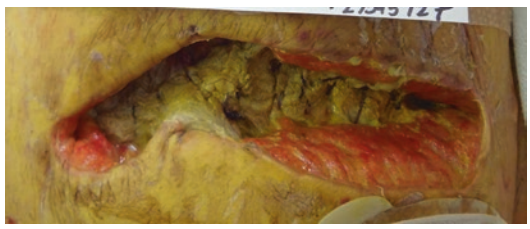

Fig. 21.1 Wound infection in a patient who underwent open low anterior resection with loop ileostomy for rectal cancer after pelvic radiation therapy. She had a long history of smoking as well. This wound healed by secondary intention over a period of 3 weeks

The perineal wound resulting from abdominoperineal resection (APR) poses a particular challenge, with a significant proportion of patients suffering from wound complications [16]. The risk is especially high in patients who undergo extralevator abdominoperineal excision (ELAPE), with a 44% risk of wound complication and 26% risk of perineal hernia [17]. Patients who underwent neoadjuvant pelvic radiation are also at higher risk for perineal wound complications, especially if the perineal wound is closed primarily [18–21]. In addition to the morbidity caused by perineal wound complications, a recent study found that perineal wound dehiscence was also associated with decreased survival after APR, with a difference of 10 months [22].

Primary closure of perineal wounds has been questioned due to the high morbidity of these wounds, especially with the larger defects resulting from ELAPE. A prospective randomized controlled trial of primary perineal wound closure vs closure with a pedicled vertical rectus abdominis myocutaneous (VRAM) flap demonstrated a lower rate of wound complications in the latter group [23] (Fig. 21.2). Other retrospective studies have supported this finding [24, 25]. The gluteus maximus and gracilis are other options for reconstruction of the perineal wound. More recently, pelvic floor reconstruction with the use of biologic mesh has been introduced as an alternative for tissue flaps—preliminary studies suggest that they have equivalent outcomes [26]. Perineal wounds that have been closed primarily had improved healing with the use of an omental flap to fill the pelvis [27–29].

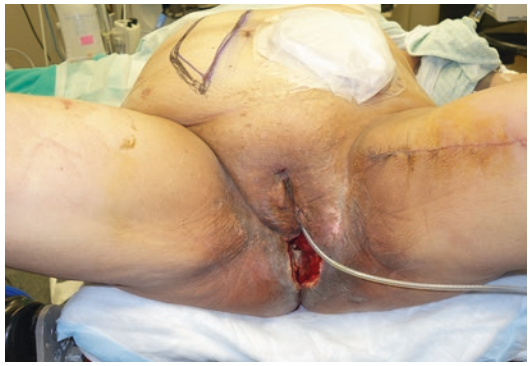

Fig. 21.2 Perineal wound dehiscence in a patient who underwent laparoscopic abdominoperineal resection with posterior vaginectomy and reconstruction of the perineal defect with a gracilis flap for a locally advanced anal squamous cell carcinoma that persisted after chemoradiation therapy

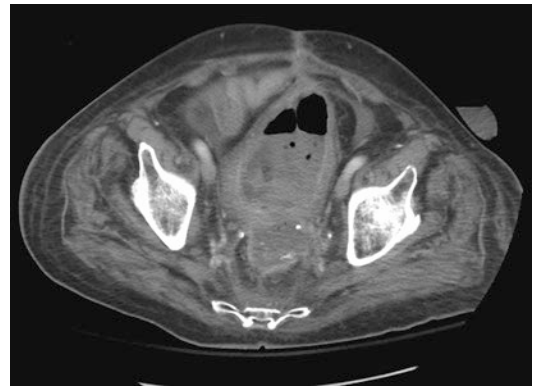

Fig. 21.3 Pelvic abscess in a patient who underwent low anterior resection with end colostomy after neoadjuvant pelvic radiation for rectal cancer. His course was complicated by massive bleeding from the rectum several weeks after his initial operation, for which he was transferred to our institution. Angiography demonstrated extravasation from a branch of the internal iliac artery; embolization successfully controlled the bleeding. He developed this pelvic abscess, which was due to a pelvic hematoma and dehiscence of the rectal stump staple line. Ultimately, he underwent completion proctectomy

Pelvic Abscess

While incisional SSI rates have improved, organ space SSIs often manifesting as pelvic abscesses remain a significant cause of morbidity. Postoperative pelvic abscesses occur in 10–30% of rectal cancer patients and are more common in patients undergoing surgery for that indication than for ulcerative colitis or diverticular disease [30, 31]. Pelvic abscesses may be due to anastomotic leak, but may also be due to infected hematomas in the pelvis in the absence of anastomotic leak. The risk of pelvic abscess without an anastomotic leak is higher in patients who had neoadjuvant pelvic radiation therapy [32] (Fig. 21.3).

Clinical signs and symptoms of postoperative pelvic abscess include: fever, leukocytosis, prolonged ileus, urinary retention, diarrhea, and pain. Patients with a perineal wound infection that fails to heal with local wound care may have a deeper pelvic abscess that is necessitating through the perineal wound. Computed tomography (CT) scanning will confirm the diagnosis with the appearance of a fluid collection with rim enhancement. Abscesses smaller than 3 cm can be managed medically with broad-spectrum antibiotics. Larger collections can usually be drained percutaneously under image guidance. Patients with perineal wounds who have pelvic abscesses may undergo image-guided or surgical drainage through the perineal wound. Patients with large abscesses that are not amenable to percutaneous drainage may require operative washout and drain placement; reoperation greater than a week after the initial operation is ill-advised unless there is a pressing clinical need and no other treatment options.

Anastomotic Leak

Anastomotic leak is one of the most dreaded complications of colorectal surgery. The incidence of clinically significant leakage after colorectal anastomosis ranges from 3% to 21% and is associated with a 6% to 30% mortality rate [31–33]. Risk factors for anastomotic leak include: more distal anastomoses [34, 35], neoadjuvant pelvic radiation therapy, male gender [36], prolonged operative time, intraoperative spillage, advanced tumor stage, perioperative transfusion requirement, and multiple firings of the linear stapler across the rectal stump [37–39].

Intraoperative placement of pelvic drains is a common practice for rectal resections involving a

low colorectal anastomosis but prevents neither the formation of pelvic abscesses nor the development of anastomotic leak [40]. It is unclear whether a protective stoma affects the risk of anastomotic leak, with some studies suggesting that it decreases the leak rate and others arguing that the presence of a stoma does not decrease the leak rate but rather mitigates the septic complications of an anastomotic leak [41, 42]. Thus, the need to reoperate is lower, as is the mortality rate from the complication [39, 43, 44]. A well-accepted rule of thumb is to proximally divert colorectal anastomoses at 6 cm or less from the anal verge with a covering loop ileostomy. A loop ileostomy is preferred to loop colostomy for its ease of care for the patient and simpler operation at closure. While the effect of mechanical bowel prep on SSI in colorectal surgery is controversial, it should be considered in the case of total mesorectal excision (TME) with a low pelvic anastomosis and loop ileostomy [10]. Finally, perioperative supplemental oxygen administration with 80% FiO_2 compared to 30% FiO_2 appeared to decrease the risk of low colorectal anastomotic leak in a randomized controlled trial [45].

Diagnosis of Anastomotic Leak

While leaks classically present between 5 and 7 days after the operation, up to half of all leaks may present after the patient has been discharged, with over 12% occurring over a month after surgery [46]. While early leaks present with varying levels of severity from an ileus or fever to peritonitis and sepsis, late leaks tend to present insidiously with pelvic pain, failure to thrive, and other nonspecific symptoms that can be attributable to other postoperative complications.

When there is clinical suspicion of a leak, radiologic examination can aid in confirming the diagnosis. CT scanning, with or without enteric or rectal contrast, is a valuable tool to evaluate for the presence of free air, fluid collections, and gas-containing collections suggestive of an anastomotic leak. The size and location of a fluid collection will help direct subsequent management. Another imaging option is a water-soluble contrast enema to determine whether there is extravasation of intraluminal contents.

Management of Anastomotic Leak

The management of an anastomotic leak depends on whether the leak is contained or not. Uncontained leaks in which feculent or purulent fluid spreads throughout the abdominal cavity may cause peritonitis and septic shock and is a clear indication for an emergent laparotomy with abdominal washout and either takedown of the anastomosis with creation of an end colostomy or pelvic drainage and proximal fecal diversion. These intraoperative decisions depend on many factors including the condition of the patient, accessibility and visibility of the anastomosis, and location and size of the anastomotic defect. In the situation of an anastomotic leak requiring operative washout, resection of the anastomosis with creation of a new anastomosis is not advisable. If the decision is made to take down the leaking anastomosis to create an end colostomy, one must pay particular attention to the management of the rectal stump to reduce the risk of a rectal stump dehiscence, which can cause chronic pelvic sepsis. Oversewing of the rectal stump staple line, drain placement over the rectal stump, and rectal tube placement may all help in reducing the risk of rectal stump dehiscence.

Contained leaks result in limited extravasation of intraluminal contents. Small abscesses (<3 cm) can be successfully treated nonoperatively with broad-spectrum antibiotics. Larger abscesses (>3 cm) may require percutaneous drainage in addition to broad-spectrum antibiotics. Contained leaks managed in this manner usually heal without surgical intervention (Fig. 21.4). A colorectal anastomotic leak that fails to heal may develop into a colocutaneous fistula or a sinus tract that causes recurrent pelvic abscesses (Fig. 21.5a, b). Reoperation to address a chronic anastomotic fistula should be deferred for at least six months if possible to allow for spontaneous closure of the leak and fistula tract and resolution of inflammatory adhesions in the pelvis. Resection of the anastomosis and redo colorectal or coloanal anastomosis is sometimes possible, although often completion proctectomy with permanent end colostomy is necessary or preferable.

Outcomes After Anastomotic Leak

Anastomotic leak after rectal resection is associated with poorer quality of life and functional outcomes [47, 48]. Patients who experienced anastomotic leak after proctectomy with colorectal anastomosis had more frequent bowel movements during the day and night, worse control of solid stool, and increased pad use [49]. One explanation of the reason for poor function after anastomotic leak is that the chronic inflammation induces pelvic fibrosis, which in turn reduces the compliance of the rectum and colon.

Anastomotic leaks are also associated with an increased risk of mortality compared with patients without a leak, with decreased overall 5-year survival (44–53% versus 64%) and cancer-specific 5-year survival (42% vs 67%) [50, 51]. Patients with anastomotic leaks were also found to have increased local recurrence and systemic recurrence rates [51–55].

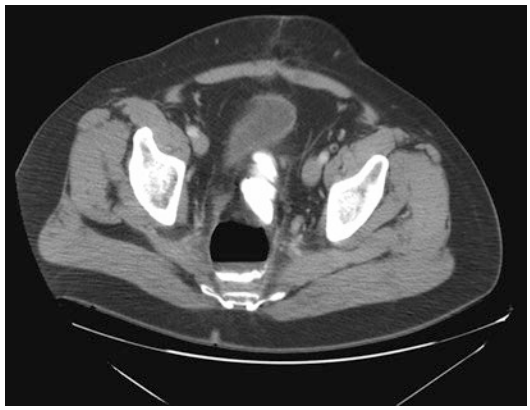

Fig. 21.4 Presacral collection containing gas and fluid, including rectal contrast, in a patient who underwent low anterior resection for a mid-rectal tumor after neoadjuvant pelvic radiation therapy. This patient was managed with percutaneous drainage of the presacral abscess and ultimate resolution of the anastomotic leak without reoperation

Hemorrhagic Complications

Anastomotic Bleed

Minor anastomotic bleeding that does not require transfusion or intervention is common and is typically self-limited, resolving within 24–48 h. Major anastomotic bleeding which requires transfusion and intervention is relatively uncommon, with rates under 1% reported [56, 57]. Due to the small numbers of reported cases, risk factors for anastomotic bleeds have not been identified. Common intraoperative techniques to reduce the risk for anastomotic bleeding include inspection of the staple line, suture ligation of bleeding points along the transverse staple line

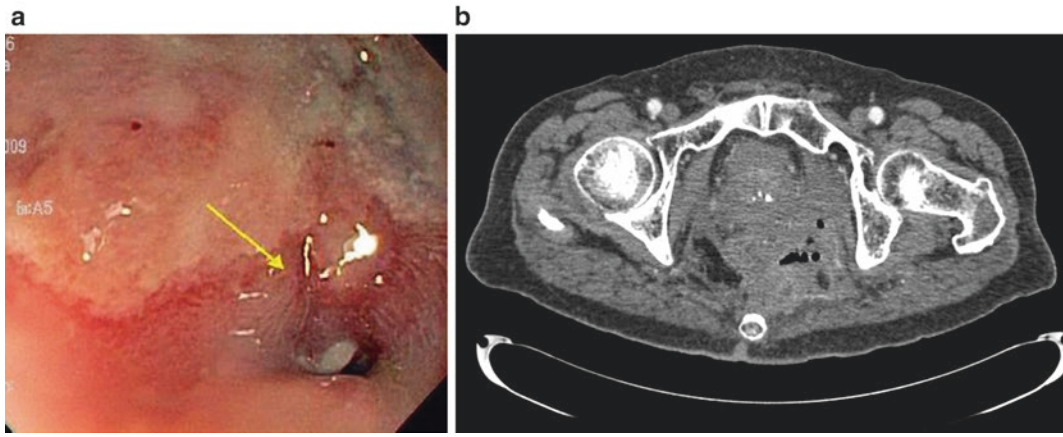

Fig. 21.5 (**a**) Fistula opening at a colorectal anastomosis in a patient with a chronic anastomotic leak after low anterior resection for rectal cancer. (**b**) The chronic anastomotic leak led to recurrent pelvic abscesses requiring percutaneous drainage. The patient finally underwent completion proctectomy with end colostomy to address this problem

prior to creating the anastomosis, and suture reinforcement of the anastomosis. Endoscopic evaluation of the anastomosis is also commonly performed not only to confirm that the anastomosis is intact but also to check for major intraluminal bleeding. If there is intraoperative evidence of significant intraluminal bleeding from the anastomosis, oversewing of the anastomosis is usually successful in establishing hemostasis.

Major anastomotic hemorrhage in the postoperative period requires resuscitation and correction of coagulopathy to establish hemodynamic stability. For ongoing bleeding, endoscopic management and angiographic embolization are options to consider prior to operative intervention. Most patients can be successfully treated with endoscopic electrocautery, epinephrine injection, or placement of hemostatic clips. If the bleeding anastomosis is not successfully controlled by endoscopic means, angiography and embolization or surgical control of the anastomosis can be considered. Angiography and embolization increases the risk of ischemia to the anastomosis, and thus the risk for anastomotic leak or stricture [58].

Intraoperative Presacral Venous Plexus Hemorrhage

Presacral venous bleeding can be a dangerous intraoperative complication of rectal surgery. The posterior rectal dissection should remain in the avascular plane between the fascia propria of the rectum and the presacral fascia. Dissection inside this plane may cause bleeding from the mesorectum and compromise the oncologic integrity of the resection. Dissection outside this plane can cause lacerations of the lower presacral venous plexus or the sacral basivertebral veins, leading to massive venous hemorrhage that can be quite difficult to control. It is imperative to stay in the 1–2 mm just outside the fascia propria of the rectum. To do this one must understand the rectum moves cranially away from the sacrum/coccyx as it passes ventrally to exit the pelvic floor. Proper retraction and direct visualization decrease the chance of entering the wrong plane.

The first steps in management of presacral venous hemorrhage should be application of direct pressure, resuscitation, and consideration of calling for experienced assistance. Blood products should be brought to the operating room. The pressure should be maintained continuously for 30 min. Implementation of this strategy not only gives the anesthesiologist time to resuscitate the patient but also may lead to resolution of venous bleeding or at least significantly decrease the rate of bleeding to allow for definitive surgical hemostasis. Adequate exposure is critical, underscoring the importance of an experienced assistant. Conventional hemostatic techniques such as suture ligation are often ineffective and may even worsen the hemorrhage, as the veins are thin walled and are likely to retract [59]. Direct electrocautery is best applied slightly cephalad to the points of bleeding. If this is ineffective, then the use of a muscle flap to apply indirect high-energy electrocoagulation can be quite effective in controlling presacral venous hemorrhage. A 1 to 2-cm square piece of rectus abdominis muscle is harvested and placed over the area of bleeding in the pelvis, and high-energy electrocautery applied to the muscle flap, which will coagulate the retracted bleeding veins by welding the muscle tissue into the sacrum [60, 61]. Another well-established technique for control of presacral venous hemorrhage is the use of sterile thumbtacks or occluder pins pushed directly into the presacral plexus to tamponade the bleeding [62, 63]. These techniques are particularly effective when the veins have retracted into the venous plexus within the sacrum.

Hemostatic agents may also be useful in control of pelvic venous bleeding. Topical hemostatic products such as FloSeal (Baxter, USA) and Surgicel (Ethicon, USA) in combination with pelvic packing were shown to be successful, as was the use of medical glue in combination with a hemostatic gauze applied to the presacral plexus [64–66]. Another hybrid approach using a hemostatic sponge affixed to the presacral fascia with a laparoscopic helical tacker was also shown to be effective [67].

Finally, in the most extreme circumstances, intractable bleeding may require a “damage

control" strategy with pelvic packing and temporary abdominal closure followed by resuscitation, stabilization, and correction of coagulopathy. Return to the operating room for removal of packs should be performed in 24–48 h, at which time the vast majority of patients will have stopped bleeding. Variations on this strategy include the use of a saline bag or tissue expander to achieve the same effect.

Postoperative Pelvic Bleeding

Pelvic hemorrhage can occur after rectal resection but rarely requires reoperation or other intervention. Most cases result in pelvic hematomas, which have a high risk of developing into the pelvic abscesses that may require percutaneous drainage. However, patients with ongoing active bleeding require resuscitation and correction of coagulopathy and may require angiographic embolization or reoperation for control of bleeding.

Pseudoaneurysms of the internal iliac artery or its branches are a rare cause of bleeding after resection for locally advanced rectal cancer [68, 69]. Pelvic radiation therapy is thought to increase the risk of pseudoaneurysm development. Chronic anastomotic leaks or pelvic recurrences may also erode into these vessels and cause pelvic bleeding. Most of these cases can be treated with angiography and embolization, although failure of these methods may require operative intervention for surgical ligation.

Genitourinary Complications

Ureteral Injury

Urologic and gynecologic operations are the most common cause of iatrogenic ureteral injury, followed by colorectal operations with an incidence of about 0.2% [70, 71]. Ureteral injuries were independently associated with higher morbidity and mortality, longer lengths of stay, and greater hospital charges. Risk factors for this complication include diagnosis of rectal cancer or metastatic cancer, adhesions, weight loss or malnutrition, and teaching hospitals [71].

There are several locations where ureteral injuries can occur in the course of an operation for rectal cancer (Fig. 21.6a). An injury to the middle third of the left ureter may occur during ligation of the inferior mesenteric artery; this can be avoided by identifying the ureter prior to vessel ligation and ensuring that the dissection plane is between the retroperitoneum and the colon mesentery. Another potential spot for ureteral injury is during mobilization of the upper mesorectum at the level of the sacral promontory; this risk can be minimized by ensuring that the dissection is proceeding within the proper planes and identifying the course of the ureter. It may be difficult to identify the ureter at this location due to obesity, radiation, or other associated conditions such as diverticulitis. In these instances it is helpful to identify the more proximal ureter behind the descending colon and follow it distally to the pelvis. Injury to the distal ureter as it enters the bladder can occur in the deep pelvis during proctectomy as well as the perineal dissection of an abdominoperineal resection. Patients with locally advanced tumors, prior radiation therapy, and prior operations in the area have a higher risk of injury due to the obliteration of the normal planes, allowing the ureter and other retroperitoneal structures to be pulled up during retraction of the colon and rectum during dissection. Again, identification of the more proximal ureter in healthy tissue and tracing it down to the point of concern is helpful.

While the use of ureteral stents has not been shown to reduce the risk of ureteral injury, they may be helpful in immediate identification of the complication and thus prevent missed ureteral injuries [71, 72]. Intraoperative recognition of ureteral injuries allows for immediate reconstruction and avoids the potential morbidities such as renal failure due to ureteral obstruction, urinomas, and the need for additional interventions and operations to manage the injury [73]. For these reasons, preoperative ureteral stent placement should be considered in cases of particularly extensive or complicated pelvic surgery, such as locally advanced or recurrent rectal cancers. However, as ureteral stents can also cause iatrogenic ureteral injury, albeit rarely, it is not advisable to routinely place stents for uncomplicated cases [74].

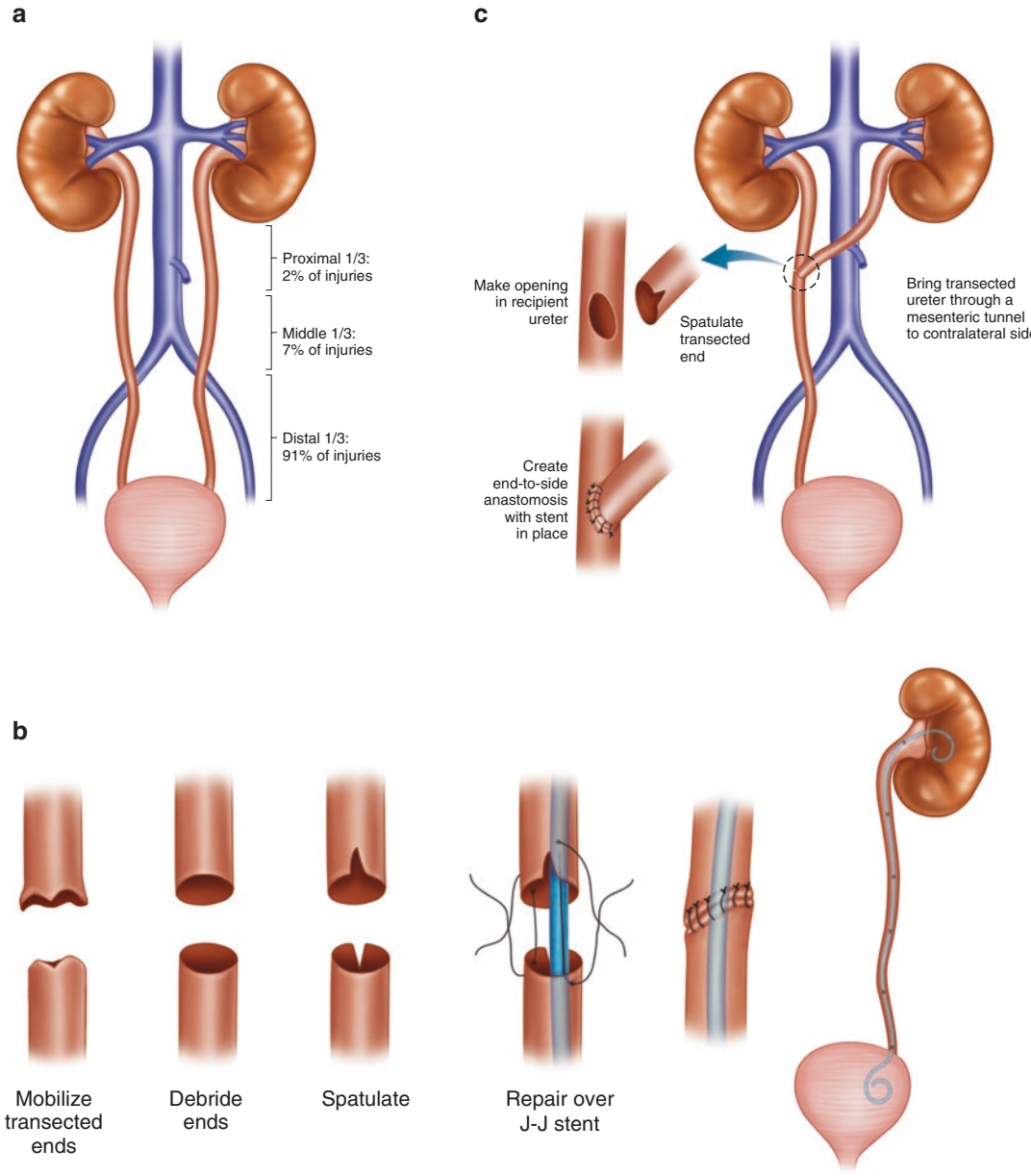

Fig. 21.6 (**a**) The majority of ureteral injuries occur in the distal third. (**b**) Injuries in the proximal and middle third of the ureter are generally treated with ureteroureterostomy. (**c**) Injuries in the middle or distal third of the ureter are occasionally managed with transperitoneal ureteroureterostomy, if the ureter cannot be reconstructed primarily or brought to the bladder. Primary ureteroureterostomy and neoureterocystostomy are preferable to this strategy. (**d**) Injuries to the middle or distal third of the ureter may best be managed with anastomosis of the ureter to the bladder, often with the help of a Boari flap or psoas hitch to decrease tension on the anastomosis

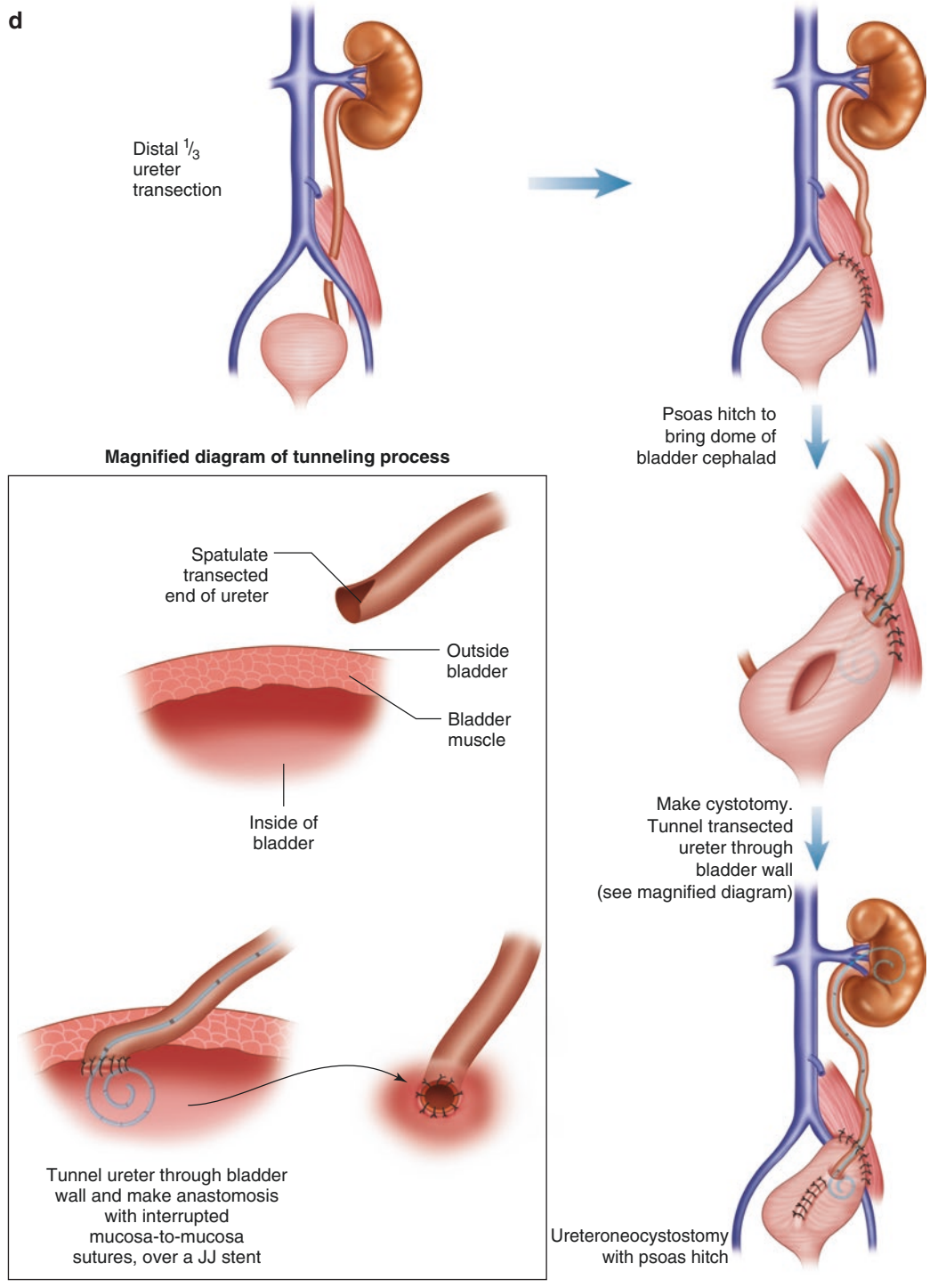

Fig. 21.6 (continued)

General principles for ureteral repair include the use of absorbable suture to prevent stone formation, spatulation to prevent anastomotic stricture, repair over a stent, adequate mobilization to ensure a tension-free anastomosis, and placement of a closed suction drain in the area of the repair. The type of repair depends on the anatomic location of the ureteral injury. Only 2% of iatrogenic ureteral injuries occur in the proximal third of the ureter [75]. These are typically repaired with a simple spatulated ureteroureterostomy over a stent with excellent outcomes (Fig. 21.6b). Injuries to the middle third of the ureter are also infrequent, accounting for only 7% of ureteral injuries. Short segment injuries can be repaired with a ureteroureterostomy, while injuries involving longer segments may require ureteroneocystostomy often with the aid of a psoas hitch or Boari flap to decrease tension on the anastomosis (Fig. 21.6d). Injuries to the distal third of the ureter are the most common, accounting for 91% of the injuries, and may be repaired by primary ureteroureterostomy for short segment injuries or ureteroneocystostomy with or without a psoas hitch or Boari flap depending on the mobility of the ureter and the bladder [76] (Fig. 21.6d). Injuries to the middle or distal ureter are occasionally managed with transperitoneal ureteroureterostomy if the ureter cannot be primarily reconstructed or if an anastomosis to the bladder is not possible (Fig. 21.6c). This technique is less preferable than the other methods of reconstruction because it places the contralateral kidney and ureter at risk for stricture.

Postoperatively, an indwelling catheter is left in place to decompress the bladder for at least 2 weeks. Increased output from the surgical drain may be an indicator of ongoing urine leak; this can be confirmed by checking a creatinine level on the drain fluid. Anastomotic leaks from ureteral repairs usually heal with continued drainage and stenting; very rarely do they require reoperation. A contrast study may be obtained at a week after the repair to rule out a leak, prior to removal of the urinary catheter. The double-J ureteral stent typically remains in place for several more weeks. There is no indication for prophylactic antibiotics while the stent is in place.

Patients who have unrecognized ureteral injuries may present with increased pelvic drain output, elevated creatinine due to either obstruction if the ureter was ligated or due to systemic absorption of a urinoma, or hydronephrosis noted on imaging studies. Delayed diagnosis of ureteral injuries typically requires percutaneous nephrostomy placement and possible percutaneous drainage of a urinoma. Retrograde stenting of an injured ureter is occasionally successful; antegrade stenting can also be attempted through the nephrostomy. Reoperation for definitive repair at a later date is usually necessary. Delayed ureteral strictures can occur due to thermal injury and may be managed with stenting and/or nephrostomy depending on the degree of stricture.

Overall long-term outcomes are much better if the ureteral injury is identified and repaired at the time of the initial operation [77]. Complications specific to the type of repair performed include ureteral strictures in 10% of ureteroureterostomy repairs, which can be managed with endoscopic balloon dilation. Reflux or stricture occurs in 5% of ureteroneocystostomy repairs and can be managed with drainage and dilation, respectively. Finally, fistulas form in 1% of patients and may require drainage and operative repair.

Urethral Injuries

Injuries to the urethra can occur during the perineal phase of abdominoperineal resections and most commonly involve the membranous or prostatic portions. If the injury is recognized at the time of the operation, the defect can be closed primarily in layers and a urethral catheter left in place for at least 2 weeks. Most iatrogenic urethral injuries are identified immediately due to the appearance of the indwelling urethral catheter, but delayed injuries may present with urinary leakage into the pelvis or through the perineal wound. Replacement of a urethral catheter, preferably under direct vision with cystoscopy, should be the first step in management. The injury may heal over several weeks with the catheter, but if it does not, then delayed repair with the use of muscle flaps may be necessary [76, 78].

Bladder Injuries

Factors that increase the risk for iatrogenic bladder injuries during rectal cancer surgery include a history of pelvic radiation, locally advanced tumors, and prior pelvic surgery. Rectal cancers that invade directly into the bladder should be managed with en bloc resection of the involved portion of the bladder. If there is a concern for bladder injury during the operation, the bladder can be distended with saline or a dilute methylene blue solution instilled through the indwelling urinary catheter to test for leaks. Bladder injuries that are identified at the time of the operation should be repaired [76]. Small extraperitoneal injuries can be managed with indwelling urinary catheter drainage for 1 to 2 weeks, followed by cystogram to exclude an ongoing urine leak prior to removal. Injuries to the dome of the bladder can be repaired in two layers with absorbable suture. Injuries to the trigone or near the ureteral orifices are more difficult to manage, requiring an anterior cystotomy and closure of injury from the inside of the bladder. If possible, an omental flap should be placed between bladder and the colorectal anastomosis to decrease the risk of fistulization.

Delayed diagnosis of bladder injuries may present with urinoma formation or increased pelvic drain output, which can be sent for a creatinine level. Cystogram will confirm the diagnosis and help quantify the size of the injury. Small injuries require at least urinary drainage for 2 weeks, during which they may heal; larger injuries in patients who have had prior pelvic radiation therapy may require more prolonged bladder decompression or even operative repair.

Urinary Dysfunction

The incidence of urinary dysfunction after rectal cancer surgery ranges from 30% to 70% [79, 80]. At 5 years after rectal cancer resection, 33% of patients had urinary incontinence and 31% had difficulty with bladder emptying [80]. The majority of these patients had normal urinary function prior to surgery. Risk factors for urinary dysfunction include: preoperative urinary dysfunction, T stage, inability to identify the pelvic autonomic nerves during the operation, and possibly neoadjuvant pelvic radiation therapy [81, 82]. Damage to the superior hypogastric plexus and hypogastric nerves causes reduced bladder capacity and may result in urge incontinence. Damage to the sacral splanchnic nerves may lead to difficulty in bladder emptying, urinary retention, and overflow incontinence [83].

Intraoperative identification and preservation of the pelvic autonomic nerves reduces the risk of urinary dysfunction [84, 85]. Anatomic studies have identified a prehypogastric nerve fascial layer between the fascia propria of the rectum and the parietal presacral fascia; sharp dissection anterior to this prehypogastric nerve fascia would spare the pelvic autonomic nerves and improve function [86]. Since the nerves can be challenging to identify, a nerve stimulator may improve identification, prevent injury, and improve rates of urinary dysfunction [87].

Sexual Dysfunction

Sexual dysfunction is common after proctectomy for rectal cancer due to dissection near the pelvic nerves. While postoperative sexual dysfunction in men is well studied with complication rates of 15–60%, the data for women is sparse but appears to be in that same range [83, 88, 89]. Damage to the sympathetic nerves during high ligation of the IMA or posterior dissection at the level of the sacral promontory can lead to retrograde ejaculation, which is the most commonly diagnosed type of sexual dysfunction in men and also the most likely to resolve with time. Damage to the parasympathetic plexus (nervi erigentes and cavernous nerves) during the anterior dissection or the pelvic plexus during the lateral dissection can lead to erectile dysfunction. The greatest risk likely occurs during the process of separating the anterior wall of the rectum from the prostate and seminal vesicles. Thus, preservation of Denonvilliers' fascia if oncologically feasible may reduce the rate risk of injury to these nerves and preserve erectile function [90].

In addition to surgical dissection, the risk of sexual dysfunction following proctectomy is worsened by advanced patient age, abdominoperineal resection, diminished preoperative libido, and neoadjuvant radiation therapy [89, 91, 92]. Surgical approach may also be a risk factor as several studies have found increased rates of sexual dysfunction after laparoscopic total mesorectal excision as compared to an open approach [93, 94]. Intraoperative nerve stimulation of the parasympathetic nerves during total mesorectal excision has been shown to correlate with long-term sexual function [95, 96].

Infertility

Infertility is defined as 1 year of unprotected intercourse without conception in women of childbearing age. Much of the research regarding infertility after proctectomy comes from women undergoing proctocolectomy for ulcerative colitis or familial adenomatous polyposis since these diseases often result in proctectomy for patients during their reproductive years. Preoperative infertility rates are around 20% and increase to 63% after total proctocolectomy [97]. Women of childbearing age who undergo pelvic radiation prior to surgery or systemic chemotherapy afterward are likely to experience premature ovarian failure. Options for fertility preservation, such as oocyte cryopreservation, should be discussed [98].

Trapped Ovary Syndrome

Trapped ovary syndrome can occur in young women who have undergone any type of pelvic surgery and is due to adhesions that create septations in the pelvis. When the patient ovulates, fluid released into the pelvic cavity collects in these spaces, and as the trapped fluid expands, patients may develop pelvic pain. The diagnosis may be confirmed with an ultrasound or CT scan demonstrating a cystic lesion without air or surrounding inflammation. In severe cases, operative intervention can be undertaken to lyse the adhesions, release the fluid, and suspend the ovaries to the pelvic brim to prevent it from recurring. One may consider suspending the ovaries at the time of proctectomy in young women to prevent this syndrome from occurring. Placement of an adhesion barrier film in the pelvis may also aid in decreased adhesive formation.

Obstructive Complications

Small Bowel Obstruction

Small bowel obstruction (SBO) is a common complication in the postoperative period, occurring in up to 9.5% of patients within the first 30 days, and usually can be attributed to inflammatory adhesions [99]. Reoperation for early postoperative SBO should be avoided if at all possible due to the high risk of enterotomy in the first 6 weeks after surgery and the high rate of resolution with nasogastric tube decompression and supportive management. Indications to operate include failure of decompression and bowel rest or clinical signs of small bowel ischemia. If strangulated bowel is found during an operation for SBO, the risk of death is increased fourfold, underscoring the importance of ruling out ischemia when evaluating a patient with postoperative bowel obstruction [100]. Water-soluble contrast studies of the small bowel in a nontoxic patient should be considered for both prognostic and potentially therapeutic purposes [101, 102].

Anastomotic Stricture

The reported incidence of colorectal anastomotic stricture or stenosis ranges widely, due in part to an inconsistent definition of stricture [103]. While some define an anastomotic stricture as the inability to pass a proctoscope of a particular diameter, others use a clinical definition of obstructive symptoms. The causes of anastomotic stricture include tissue ischemia, inflammation, radiation, anastomotic leak, or recurrent disease.

Management of anastomotic strictures depends upon the etiology and anatomic location. As recurrent cancer is responsible for approximately 10% of anastomotic strictures, it is imperative to rule out malignancy with endoscopic biopsy before determining appropriate management [104]. In the case of malignant stricture, full workup with CT of the chest, abdomen, and pelvis is required to determine distant metastases and possible MRI to determine the local extent of disease. Management of malignant strictures is primarily surgical if the disease is resectable. In the presence of distant metastatic disease or unresectable local disease, proximal fecal diversion or stent placement should be considered for palliation.

Benign low colorectal or coloanal strictures can be effectively treated with repeated dilatation using an examining finger or dilators. More proximal colorectal strictures can be managed endoscopically with balloon dilation and stent placement [104–106] (Fig. 21.7a). Endoscopic dilatation is more effective with benign strictures compared with malignant strictures. Complications of endoscopic dilatation include benign restenosis in 11% of patients, perforation in 5%, and abscess formation in 2%.

Strictures refractory to endoscopic management may require surgical intervention—either resection of the anastomosis with colorectal or coloanal anastomosis or conversion to an end colostomy [103].

Functional Bowel Complications

Low Anterior Resection Syndrome

LAR syndrome is a collection of symptoms experienced after partial or complete rectal resection with colorectal or coloanal anastomosis. These symptoms include stool frequency, urgency, clustering of bowel movements, fecal incontinence, and increased flatulence. Approximately 50–90% of patients after low anterior resection experience one or more of the symptoms, which adversely affects quality of life [107, 108]. While symptoms tend to improve over the course of a year, many patients have prolonged or permanent changes to their bowel function.

LAR syndrome results from a combination of factors including reduced length of the rectum, decreased rectal compliance, irregular and increased colonic motility, loss of rectoanal coordination, and a reduction in anal resting and squeeze pressures [109, 110].

Dietary changes are the first-line therapy to manage the symptoms of LAR syndrome and include small frequent meals, increased fluid intake, increasing fiber intake to improve stool bulk, and improve emptying. Avoidance of caffeine, alcohol, and dairy products may be beneficial. If these strategies fail to improve the symptoms, more intensive interventions may be necessary, such as sphincter muscle strengthening exercises or biofeedback therapy, regular

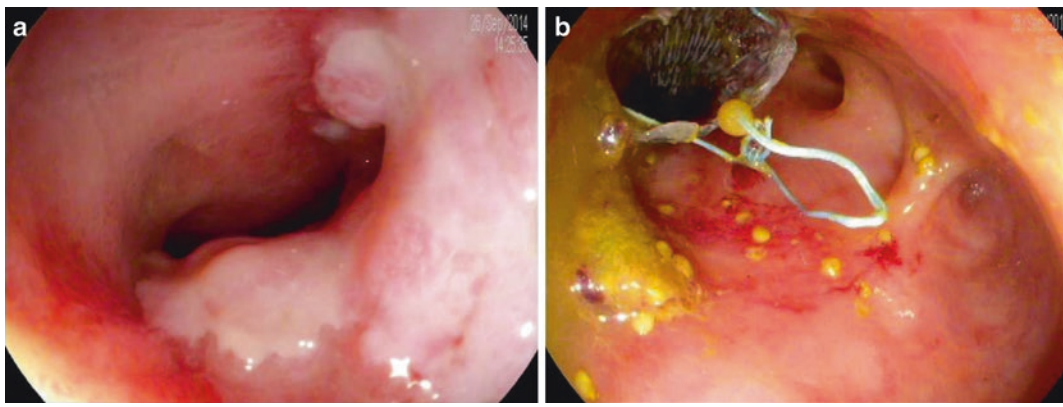

Fig. 21.7 (**a**) A symptomatic colorectal anastomotic stricture developed after low anterior resection and was proven to be benign. (**b**) A self-expanding metal stent was deployed across the stricture with resolution of symptoms

enemas to improve emptying, and sacral nerve stimulation [111, 112].

Fecal Incontinence

Postoperative fecal incontinence after restorative proctectomy occurs in at least 20% of patients and may be as high as 80% depending on the parameters used to define it [113]. Risk factors include advanced age, more distal tumor and anastomotic height, intersphincteric proctectomy, anastomotic leakage, neoadjuvant pelvic radiation therapy, and preoperative fecal incontinence [48, 114–119]. In low pelvic anastomoses, a colonic J-pouch may decrease incontinence with superior functional reserve compared to a straight coloanal anastomosis in the first year after surgery, but it does not have a long-term advantage [109, 115].

Intersphincteric resection for low rectal cancer has a particularly high rate of poor functional outcome due to the associated fecal incontinence. A meta-analysis demonstrated that 51% had perfect continence, while 29% had some level of fecal soiling and 24% were incontinent to flatus. Urgency and frequency were also common [120].

Anal sphincter rehabilitation has been shown to reduce stool frequency and difficulty in defecation compared to patients who did not undergo rehabilitation. Quality of life was improved as well, with regard to depression, self-perception, vitality, and mental functioning [121].

Stoma Complications

Stoma-related complications can lead to frustration and poor quality of life, so much so that reoperation may be required [122]. Especially in cases of permanent end colostomies, great care must be taken to create a stoma that will offer the best functional result, as a well-functioning and easily pouched stoma can offer patients a much higher quality of life.

Stoma Prolapse and Parastomal Hernia

Stoma prolapse is full-thickness protrusion of the intestine through the stoma skin defect and occurs in 7 to 26% of patients, with loop stomas having a higher rate of prolapse than end stomas [123]. Half of patients with a prolapsed colostomy also have an associated parastomal hernia. Risk factors for both these complications include obesity, use of the tranverse or sigmoid colon rather than the descending colon, chronic obstructive pulmonary disease, bowel redundancy, weak fascia, stoma site lateral to the rectus muscle, oversized aperture, and creation of a stoma during an emergency operation [124]. Operations to address stoma prolapse include resecting the redundant segment of colon that is prolapsed. Operations to address parastomal hernia may involve resiting the stoma or performing a primary or mesh repair of the hernia to decrease the size of the stoma defect, although any repair is prone to a high rate of hernia recurrence.

Stomal Retraction

Stomal retraction defined as a stoma that is at least 0.5 cm below the skin surface within 6 weeks of construction and is the most common reason for reoperation [122]. Retraction is due to excessive tension on the bowel, a thick abdominal wall, poorly located stoma, or ischemia of the bowel at the stoma site. A local stoma revision is the preferred initial approach, although a laparotomy may be required if the bowel cannot be adequately mobilized or if resiting of the stoma is required.

Pouching Difficulties

Creation of a temporary diverting loop ileostomy in the setting of a low rectal anastomosis is common in rectal cancer surgical treatment, and these stomas have higher complication rates compared to end colostomies [124]. Education on proper pouching techniques is imperative to prevent local skin complications. A poorly placed stoma has a high risk for pouching difficulties as well, and for this reason it is advisable to have the patient meet with an enterostomal therapist prior

to surgery for stoma site selection, as well as preliminary education to help them prepare for this change.

Dehydration

The most common indication for readmission for patients with new ileostomies is dehydration. Maintenance of a proper diet and hydration regimen is just as important as proper stoma creation, as the average daily output of an ileostomy is 500 to 1300 mL. Preoperative and postoperative education on diet, hydration, use of fiber supplements, and bowel stoppers is critical for the prevention of such complications.

Special Considerations for Stoma Creation

Construction of a well-vascularized, protruding, tension-free stoma is particularly challenging in the obese patient with a thick mesentery and a thick abdominal wall. Technical maneuvers to maximize mobility and length of the colon to be used for an end colostomy include taking down the lateral attachments of the left colon, dividing the medial peritoneal attachments at the base of the mesentery, mobilizing the splenic flexure, and ligating the IMA proximal to the left colic artery. Other maneuvers to bring a thick colon through the abdominal wall successfully include trimming the mesentery to allow easier passage of the colon through the stoma defect, using a stoma site above the umbilicus where the abdominal wall is thinner, and making sure that the stoma defect matches the size of a thick colon and mesentery. The risk of postoperative stoma complications is significantly higher in obese patients due to these technical difficulties [125].

Conclusions

Rectal cancer operations present a host of challenges and potential complications. Short-term consequences of these postoperative complications include increased length of stay, need for additional procedures or operations, and increased cost of care. These complications can also have significant long-term consequences, from poor bowel, bladder, and sexual function to chronic pain to increased risk for recurrence and death. To maximize oncologic and functional outcome, we advocate that rectal cancer operations be performed in a multidisciplinary setting by surgeons who have experienced operating in the pelvis.

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Palliative and End-of-Life Treatment

22

Robert S. Krouse and Felipe A. Maegawa

Introduction

The evolution of rectal cancer treatments has led to survival advantages for many patients. Nonetheless, clinicians must be prepared for the specialized care for rectal cancer survivors living with progressive cancer whose problems may be unique and quite complex. Recognition of the needs of patients has propelled the development of programs to provide concomitant palliative and supportive care with cancer treatment, which can help address the myriad concerns for both patients and their family and caregivers. The Institute of Medicine calls for reimbursement for practitioners for time spent with patients related to end-of-life planning [1], further displaying the added focus on patients with advanced disease. Patients who present with advanced stage rectal cancers and those experiencing progressive disease despite treatment should have access to concomitant palliative care early in their treatment course. This can facilitate the transition from a focus on disease modifying treatment to more symptom focused care. It is important to recognize that the complex issues of suffering will intensify in the setting of advanced disease. Practical expertise in the care of the dying is recognized as one of several important themes of care in order to achieve a "good death" [2].

All teams caring for rectal cancer patients with advanced disease must engage in new types of conversations with patients and their families and among themselves and broaden their assessments to be able to ensure physical comfort, address psychological needs, and identify goals of care and social and spiritual sources of distress. Communication skills are key for all providers to have successful interactions with patients and families. Patient and family perception of quality and satisfaction with medical care are closely linked to the ability to effectively communicate the clinical situations, treatment options, and empathic support for all involved. The misperception of palliative therapies with life-extending treatments must be carefully addressed [3]. When providers can communicate effectively with patients and families their clinical situation, they are better equipped to make decisions that focus on achievable goals of care in the terminally ill rectal cancer patient.

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Specific Problems in the Setting of Advanced Rectal Cancer

There are multiple specific issues that require attention in the advanced rectal cancer patient. When patients present with these issues, evaluation of the extent of disease, overall performance status, and treatment options may take some time to ascertain.

Aggressive palliative treatment of symptoms should be undertaken. At this point discussions with the patient, their family or caregivers, and the medical team should review the patient's goals of care and align them with available treatment options. Patients must be informed in that treatments are not always successful to relieve symptoms, and the problem may recur. The risks and benefits of interventions may be difficult to ascertain. Regardless of the outcome of any intervention, the patient is likely to have a limited survival such that ongoing palliative/hospice support will be necessary in the hospital or after discharge.

Treatment options may include typical tumor-specific therapies, including surgery, chemotherapy, and radiotherapy. Other options include symptom-specific medications or interventions via gastroenterology or interventional radiology. Again, teams must be wary of patients or families misinterpreting goals of treatments and clearly understand that symptom management is of primary concern.

Tumor resection in the setting for palliative intent is controversial in the setting of rectal cancer. Reasons to consider resection may be related to pain, obstruction, or bleeding. Delays in further chemotherapy need to be carefully considered. Evidence regarding its impact on survival is controversial [4, 5]; multiple factors must be considered prior to advocating a major resection in the palliative setting. In some cases, a transanal approach may be warranted [6, 7].

Malignant Bowel Obstruction

Malignant bowel obstruction (MBO) is defined as: (1) clinical evidence of a bowel obstruction by history, physical exam, or radiographic examination, (2) bowel obstruction beyond the ligament of Treitz, (3) intra-abdominal primary cancer with incurable disease, or (4) non-intra-abdominal primary cancer with clear intraperitoneal disease [8]. It occurs in approximately 10–28% of colorectal cancers [9]. MBO in the setting of rectal cancer can be considered based on if it is small bowel obstruction (SBO), often due to carcinomatosis, or primary or recurrent rectal obstructions. The goals of treatment include relieving nausea and vomiting, allowing oral intake, alleviating pain, and permitting the patient to leave the acute care setting. No matter what the etiology of the MBO, when patients are admitted to the hospital, conservative measures (nasogastric tube, decompression, intravenous hydration, NPO) are typically initiated.

Small Bowel Obstruction

There are multiple approaches to treating rectal cancer patients with an SBO and thus have variable outcomes based on the service (surgical or medical) that they are admitted [10]. Regardless, palliative pharmacologic therapies have the goals of reducing intestinal inflammation and edema and/or controlling pain, nausea, vomiting, and dehydration. Pain medications, most likely opioids, act both directly to relieve pain related to intestinal obstruction and to reduce painful bowel contractions against the obstruction. Antiemetics can be given through a variety of non-oral routes to control vomiting [11], although complete relief of emesis is achieved in a minority of patients through antiemetics alone. Hormonal manipulation of gut activity has substantially aided MBO management. Anti-secretory agents include somatostatin analogs, steroids, and scopolamine. Octreotide, a synthetic analog of the gut hormone somatostatin, dramatically decreases gastrointestinal secretions and reduces bowel motility, often markedly reducing or resolving MBO symptoms [12]. Duration of treatment may be short-lived (median 9.4 to 17.5 days) [12], although symptoms are frequently relieved for the life of the patients. Anticholinergic medications, such as scopolamine, can decrease peristalsis and secretions and lead to improved control of vomiting

and intestinal colic for malignant GI obstruction. While direct comparisons of these agents have not yielded clear recommendations [13, 14], a combination of these medications may offer synergistic benefits. Finally, corticosteroids are commonly used as adjunctive agents or alone in MBO management, with the goals of decreasing tumor-associated bowel edema and of providing antiemetic benefits. Although meta-analysis has suggested no statistical benefit of corticosteroid use, a subset of patients may benefit from them and medication-related morbidity is low [15], particularly in patients in the terminal stages of their disease. If surgery is being considered, it has been shown that somatostatin or its analogs are likely not a risk to an operation. Steroids may carry operative risks and should be initiated with caution.

Persistent SBOs in the face of palliative treatments or evidence of complete obstructions are indications that a surgical procedure should be considered unless actively dying. Many patients are deemed inoperable (6.2–50%) [16]. This may be due to poor operative risk or other contraindications to surgery such as advanced tumor that precludes the ability to achieve meaningful recovery from surgery. Operative risk may be precluded based on the presence of significant comorbidities (e.g., cardiac and pulmonary function) or poor functional status (e.g., Karnofsky <50%). Other considerations include burden of metastatic disease (e.g., overwhelming metastasis to the liver malfunction) or the presence of other manifestations of end-stage rectal cancer including ascites (greater than 3 L), particularly ascites that rapidly recurs after drainage, extensive carcinomatosis, multiple obstructions, or presence of a palpable intra-abdominal mass [11, 17].

The optimal procedure is that which is the quickest, safest, and most efficacious in alleviating the obstruction and preserving quality of life. While bowel resection may lead to the best outcome [18, 19], bypass may be a safer option that still achieves the goal of resumption of oral intake, and the placement of a gastrostomy tube for intermittent venting might be optimal in some settings. In addition, an intestinal stoma may be necessary after resection or to adequately bypass the blockage. Cytoreductive procedures (resection of intraperitoneal tumor) frequently carry a high morbidity and have limited applicability during palliative surgery.

Although it is recognized that improvement in health-related quality of life (HRQOL) after surgery is variable (42–85%) [16, 20], there is no consistent parameter used to determine this clinical outcome; operations *may* offer an advantage of an increased survival. Surgical risks must be carefully considered prior to an operation, as morbidity (42%) [21] and mortality (5–32%) [16, 19, 21] are common, and the re-obstruction rate is high (10–50%) [16].

Rectal Obstruction

There are a myriad of options for patients who present with an obstruction due to recurrent or primary rectal tumors in the palliative setting. Most patients with a large bowel obstruction are treated by a diverting stoma ostomy, although some may benefit from endoscopic, interventional radiologic, or other nonsurgical therapies [22]. Major resection should be considered only if patients have "reasonable" long-term survival and is typically not the primary alternative.

Endoscopic procedures may be utilized to relieve a tumor-related obstruction. Laser recanalization can be performed in this setting, subsequently allowing other treatments [23–25]. The potential for endoluminal stents may be considered but may not be appropriate for mid or low rectal cancers as there may be insufficient bowel for distal stent positioning. Low lying stents for rectal cancer can be associated with significant pain due to pressure on the pelvic floor or sphincter. For higher lesions, stents may be potentially effective for symptom control to stenting; stenting is likely to lead to a shorter hospital stay [26] and improve HRQOL [27].

While endoscopic techniques, such as laser or balloon dilatation, may be used to initially canalize the lumen, it is usual that if a lumen cannot be clearly located, this procedure will be aborted. For institutions who do offer rectal endoluminal wall stents, there has been reported a high success

rate for relief of symptoms (64–100%) in complete and incomplete colorectal obstructions [28, 29]. However patients should be carefully selected for endoluminal stents as there are risks for stent-related complications such as perforation, erosion, or migration [28]. In addition, these patients should be followed closely as it has been reported that 18% will ultimately need a surgical procedure [30]. Furthermore, as tumor ingrowth may occur, the endoluminal monitoring with potential for re-intervention will be required [30]. Finally, many patients with obstructing rectal cancers may not be eligible for stenting due to tumor factors or fibrosis from prior radiation and diverting loop colostomies may be the best alternative.

Another nonsurgical option for patients with primary tumors in place may include radiation therapy. In a palliative setting, a subjective response rate for rectal tumors of 63% (objective response of 82%) has been reported, although results were combined with several different tumor-related symptoms [31]. Along with continuous infusion 5-fluorouracil, radiation therapy has been shown to prevent the need for initial diverting colostomy from colorectal tumor-related bowel obstruction in 89% of patients with unresectable pelvic or metastatic disease [32]. Responses are slow and complications increase with dose, so radiation therapy can be used with endoscopic techniques, such as lasers [33], to treat malignant rectal obstructions. Because many of the complications occur long after the radiation therapy, they might never manifest for the end-of-life patient [34].

Malignant Ascites

Ascites in the terminally ill rectal cancer patient may be due to overwhelming liver metastasis, cirrhotic liver disease, or carcinomatosis. Colorectal cancer is the underlying malignancy associated with 3.7–9.7% of patients with malignant ascites, and it is estimated that approximately 4% of patients with colorectal cancer will eventually develop malignant ascites [35, 36]. There are six mechanisms to explain the development of ascites in the setting of malignant disease (Table 22.1) [36]. It can be a difficult management problem, and treatment may be determined by the extent of ascites, condition of patient, or etiology. If ascites is minimal, no therapy is indicated. Larger volumes of ascites can lead to discomfort, fullness, or respiratory problems. Diuretics and paracentesis are typically the primary treatment options. The success of diuretics in the management of malignant ascites is only about 43%, which is mostly seen in patients with massive hepatic metastasis and a serum-ascites albumin gradient >1.1 g/dL [37]. In a survey study on management of malignant ascites among Canadian physicians, Lee et al. demonstrated that paracentesis was most often utilized (98%), and it was perceived to be most effective [38]. Temporary relief of symptoms is achieved in approximately 90% of the patients treated with paracentesis [37]. However, paracentesis requires repeated treatments which leads to depletion of protein and electrolytes, frequent hospitalizations, and exposure to the risk of peritonitis [39]. In patients in whom frequent large-volume paracentesis is required, placement of peritoneovenous shunt (PVS) can be considered. The two most common are the LeVeen or Denver® shunts. The only one commercially available today is the Denver® shunt [40]. Ascitic fluid travels from the peritoneal cavity into the venous circulation due to higher peritoneal pressures. Complications include sepsis, disseminated intravascular coagulation (DIC), heart failure, and pulmonary embolism leading to a rapid death. Although malignant cells is drained from the

Table 22.1 Causes of malignant ascites

Cause	Frequency among patients with malignant ascites
Peritoneal carcinomatosis (%)	53.3
Extensive liver metastasis causing portal hypertension (%)	13.3
Peritoneal carcinomatosis and extensive liver metastasis (%)	13.3
Hepatocellular carcinoma and cirrhosis (%)	13.3
Chylous ascites (%)	6.7
Budd-Chiari syndrome	Rare

Adapted from Runyon et al. [36]

peritoneal cavity into the venous system, studies have shown that PVS do not establish clinically important hematogenous metastasis [41]. While the incidence of major complications may be less common than previously reported for peritoneovenous shunts, the overall complication rate can be quite high (14–51%) [42–45]. DIC is the major complication that most frequently will lead to patient death. It has been reported from 5 to 10% of these procedures. Congestive heart failure is another major complication. The more common complication is shunt occlusion. The advantage of the Denver® shunt over the LeVeen shunt is that the Denver® shunt has a pump to help the shunt remain patent (26% Denver® vs. 50% LeVeen shunt occlusion rates) [44]. Denver® shunts have been shown to have quite high function of these shunts until death (96%) [43]. The risk of infection is variable (0–18%) [43], and this may lead to shunt removal if not relieved with antibiotics. Importantly, relief of symptoms can be as high as 87.5% [43]. In a reviewed study of 341 patient who underwent placement of Denver® shunt for malignant ascites, 75% of the patients achieved relief of symptoms, none died of shunt-related complications, and the tumor systemic disseminations was less than 1.5% [40]. Therefore, a peritoneovenous shunt may be an excellent option in properly selected patients.

Another invasive treatment for malignant ascites besides PVS includes placement of percutaneous catheters to allow intermittent paracentesis. These catheters can be placed surgically or by the interventional radiology team via computed tomography [46] or ultrasound guidance [47]. Multiple types of catheters have been used, including a pigtail catheter, peritoneal dialysis catheters (e.g., Tenckhoff catheter), pleural cavity catheters (e.g., Pleurx® catheter), fenestrated port-a-catheters, and even a Foley catheter [48–52]. The patient and/or caregiver can be trained to drain excess peritoneal fluid when the patient is symptomatic. The success rates for permanent intraperitoneal catheters functioning until death are quite high (90%) [47, 48]. There is low procedural morbidity. The major complications are obstruction and infection and are around 17% [47, 48], although catheter sepsis has been reported to be 35% [53].

Hyperthermic intraperitoneal chemotherapy (HIPEC) with cytoreductive surgery has been associated with increased survival for patients with carcinomatosis from different types of cancers; however, it has limited application and significant morbidity risk in the palliative setting. HIPEC, without cytoreduction, is an accepted approach for palliation of malignant ascites with good early data. In addition, this procedure can be performed laparoscopically in an attempt to minimize complications [54]. Laparoscopic HIPEC appears to be safe and highly effective for the treatment of malignant ascites. The morbidity, although low, suggests this procedure is best utilized in settings of ascites refractory to less aggressive treatments [55, 56]. The improvement in ascites and lack of a need for catheters or follow-up procedures are encouraging, but it should be noted that none of the studies of palliative laparoscopic HIPEC have included symptom assessment or HRQOL outcome measures. HIPEC has also been shown to be accomplished via ultrasound guidance, further making this technique possible for patients with advanced disease [57].

Bleeding

Tumor-related bleeding or radiation proctitis bleeding may be a difficult problem for the rectal cancer patient. In addition, patients may have a coagulopathy related to illness or treatments. Interventions are infrequently required, as there is likely a high morbidity, and intestinal stomas would likely be necessary. If surgery is deemed necessary, the optimal approach will depend mainly on the location of the tumor, along with the least morbid and most efficacious procedure possible. If tumor is amenable, transanal resection can be accomplished. This can be via transanal microsurgery [6, 7]. These procedures may be technically difficult or not possible in this setting.

Nonsurgical options include radiation therapy, arterial embolization, and endoscopic procedures. Endoscopic laser technologies are efficacious [27]. Other endoscopic treatment for bleeding includes argon plasma coagulation,

photodynamic therapy, electrocoagulation, and injection therapy (e.g., 3% polidocanol) [58–60]. While most complications are minor, all of these techniques carry small risks of perforation, but for low to mid rectal tumors, this risk is limited.

Targeted radiation therapy is a reasonable option for slow, unremittent bleeding from rectal tumors [61, 62]. External beam radiation has an efficacy of approximately 75% [63]. Endocavitary radiation therapy can treat bleeding 35–45% [64]. Of course, multiple sessions may be required. While these techniques may have varying degrees of success, they may be utilized in attempts to avoid more invasive and morbid procedures.

Pain

Pain related with malignant disease is a complex symptom, which interferes significantly with most aspects of patients' lives, including performance of daily activities, social interaction, psychological and emotional status, and ultimately quality of life. Pain is also associated with poor prognosis among patients with advanced rectal cancer [65]. It is estimated that the prevalence of chronic pain in patients with advanced cancer is over 70% [66]. Therefore, all patients with advanced rectal cancer should be screened for pain, so that they can receive a comprehensive assessment and treatment plan. Many patients with advanced rectal cancer experience pain, which can be acute, following invasive procedures or complications (bowel obstruction, pathological fractures), or chronic, usually related to local tissue injury, when the neoplasm invades pain-sensitive structures [67]. Being a subjective experience, pain evaluation involves a thorough history of the pain characteristics, extent of the underlying malignancy, and treatment received. Moreover, a detailed physical examination should be performed to identify the physical findings relevant to the patient's condition. These findings, in addition with objective data from laboratory and imaging studies, are helpful tools to determine the pain etiology. The constellation of symptoms and signs of cancer pain can in most instances suggest a cancer pain syndrome [68].

Pain management in patients with advanced cancer is considered a domain of palliative care [69]. In the context of palliative care, pain management is a major component of the interdisciplinary care that focuses on preserving function, helping in adaptation to changes in disease course, and in maintaining quality of life. In general, the first-line approach of management of pain is the use of analgesics. The World Health Organization (WHO) published a stepwise and systematic approach for cancer pain management called "analgesic ladder," which has influenced clinical practice worldwide [70] (Fig. 22.1). The basic principal behind the analgesic ladder is a

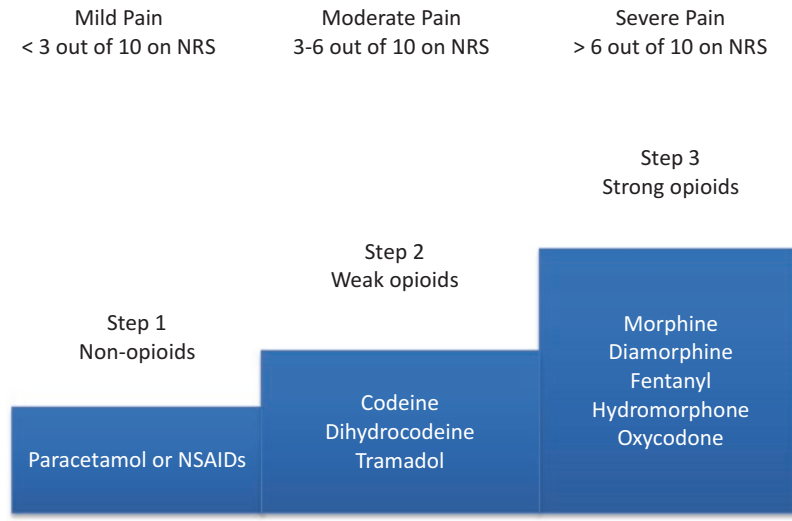

Fig. 22.1 Analgesic ladder. *NRS* numerical rating scales, *NSAIDs* nonsteroidal anti-inflammatory drugs. Adapted from: World Health Organization (WHO) Cancer pain ladder for adults. Available from http://www.who.int/cancer/palliative/painladder/en/. Accessed December 1, 2014

stepwise approach to pain control based on the patient's severity of pain. Several clinical guidelines were developed based on the premises of the analgesic ladder [71–73].

Besides the use of analgesics, specific treatments that focus on the etiology of pain are important and fundamental adjuvants for pain management. Therefore, identifying a specific pain syndrome or pain etiology should be an integral part of the assessment of the patient with advanced cancer. Regarding patients with advanced rectal cancer, possible pain syndromes and etiologies include pain caused by bowel obstruction, bone pain, and pathologic fractures due to skeletal metastases, chemotherapy-induced neuropathy, radiation proctitis, and plexopathies.

The prevalence of bone metastasis in patients with colorectal cancer ranges between 5.5% and 10.4% [74, 75]. A recent analysis of the natural history of bone metastasis secondary to colorectal cancer suggests that there is a very aggressive disease course in the bone metastasis, which can result in debilitating symptoms within a short period of time [76]. The complications related to bone metastasis include pain, pathological fractures, and spinal cord compression. Bone pain that failed the use of analgesics and is limited to a single or limited number of sites, external beam radiation therapy can provide pain relief in 60–85% of the cases [77]. The American Society for Radiation Oncology (ASTRO) recommends a single fraction of radiation using a dose of 8Gy to palliate pain from bone metastases. Patients with one or more bone lesions should be given bisphosphonates, in order to prevent pathological fractures, which can cause significant pain, morbidity, and decrease overall survival [78]. More recently, zoledronic acid was shown to be effective for prevention of skeletal-related events (SREs) in patients with bone metastasis from colorectal cancer [76]. Another agent approved for treatment of bone metastases from solid tumors which delays development of SREs is the monoclonal antibody Denosumab [79].

The goals of therapy for bone metastasis include pain relief, preservation of function, as well as skeletal integrity. Therefore, on impending or complete fractures of long bones surgical fixation is warranted [80]. Vertebral metastatic lesions which cause instability of the spine or cord compression should be fixated by surgery or percutaneous repair [81]. It is important to remember that pain caused by an unstable spine will not respond to radiation therapy or spinal bracing [82].

Radiation proctitis which is characterized by bleeding, rectal pain, and tenesmus occurs in 15–32% of the patients who undergo radiation for rectal cancer [83, 84]. Patients with severe tenesmus or pain can be treated with sucralfate (2 g twice daily) or glucocorticoid enemas (hydrocortisone 100 mg twice daily or prednisolone 20 mg twice daily) [85, 86]. Advanced rectal cancer patients can develop lumbosacral plexopathy due to direct tumor invasion or due to the effects from radiation therapy. Lumbosacral plexopathy causes severe, progressive, and debilitating pain. Patients typically present with pain, followed by numbness, paresthesias, and weakness [87]. The plexopathy caused by tumor invasion is more rapidly progressive and debilitating than the one caused by radiation [88]. An earlier diagnosis is associated with better response to treatment and less neurologic deficits. Treatment should be individualized based on patients' general condition, wishes, comorbidities, and life expectancy. Therapeutic options include: surgical resection in selected cases, radiotherapy, interventional pain management procedures, and systemic therapy including chemotherapy and biologic therapy [88, 89]. Cameron et al., in a systematic review, demonstrated that palliative radiotherapy was effective in improving advanced rectal cancer symptoms, pain being the more prevalent symptom, in 71–81% of the cases [61]. However, the same study reported they encountered a great inter-study variability, making it impossible to perform a meta-analysis, highlighting the need for prospective studies including patient-defined target symptoms.

Conclusions

Specialized care for the terminally ill requires careful consideration of the complex issues they face. As treatments evolve, so will care issues.

This includes the long-term effects of cancer care, as well as the effects of living with metastatic disease. Clearly this will mean that early palliative care is indicated, interdisciplinary team approach should be utilized, and each issue must take individuated attention. It is imperative that palliative care providers are familiar with the approaches to the issues that affect rectal cancer patients in the palliative setting and involve appropriate specialists when indicated, and the benefits outweigh the risks of proposed interventions. The patient, family, and treating teams should establish realistic goals and understanding of the likelihood of success, impact on HRQOL, and potential for harm. Continued team follow-up with early referral to palliative services is an essential element for the specialized care of the terminally ill cancer patient.

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Index

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