35
Colorectal Cancer: Management of Local Recurrence

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Key Concepts

- Patients with colorectal cancer at the highest risk for local recurrence are those who present with obstruction or perforation, higher-stage disease, and adverse pathologic features, or undergo an operation that does not adhere to standard oncologic principles.
- The most significant predictor of survival following surgery for local recurrence is the ability to achieve a negative-margin (R0) resection.
- The probability of achieving an R0 resection is much greater in patients with recurrences involving an anastomosis or urogynecologic structures compared with those involving para-aortic tissue, sacrum, or lateral pelvic sidewall.
- A dedicated multidisciplinary team at an institution experienced in the management of patients with local colorectal cancer recurrence can facilitate complex surgical decision-making and greatly enhance patient outcomes.
- A multimodality approach that includes chemotherapy and radiotherapy improves local control and improves 5-year survival in patients with local recurrence.

Introduction

The medical and surgical management of colorectal cancer has a rich history, and treatment paradigms have evolved significantly over the last 100 years [1–6]. Major advances have been made in our understanding of tumor biology, the role of chemoradiotherapy, and most importantly, the significance of precise surgical technique. These advances have dramatically decreased local recurrence and increased 5-year survival in patients with primary colorectal cancer [1, 6–9]. Despite these advances, local recurrence following surgery remains a significant problem [4, 10–18]. In addition to its impact on survival, major morbidity from local recurrence can have a dramatic detrimental impact on quality of life [19–21].

In the United States, approximately 90,000 patients are diagnosed with colon cancer each year, and in those that undergo surgery, somewhere between 8 and 12 % will develop a local recurrence [22, 23]. Of the 40,000 patients diagnosed with rectal cancer each year, approximately 5–30 % will develop a local recurrence [24–28]. Patients with colorectal cancer at the highest risk for local recurrence are those that have higher-stage disease, high-grade tumors, and lymphovascular involvement or present with obstruction, perforation, or a locally advanced tumor at the time of presentation [29–34]. Operations done by noncolorectal-trained surgeons, or by surgeons who perform less than 20 rectal cancer resections per year, have been reported to have higher local recurrence rates [30]. Recently, the importance of a threatened or violated circumferential margin as an independent predictor of future recurrence has reinforced the importance of meticulous surgical technique [15, 35, 36]. All efforts to reduce the risk of local recurrence should be made when managing primary colorectal cancer, and the best results are achieved when patients are managed by experienced teams [37, 38].

When patients with colorectal cancer develop local recurrence, surgery offers the best opportunity for cure [15, 24, 39]. In the last 20 years, surgery for local recurrence has become safer, indications have expanded, and better results are being achieved leading to meaningful survival for many patients [17, 18, 40–42]. This chapter will review all aspects of management in patients with local recurrence as well as outcomes of surgery. Due to the complexity of medical and surgical decision-making, in addition to the surgical expertise required to perform these technically challenging operations, the treatment of patients with local recurrence should preferentially occur at centers that have a dedicated and experienced multidisciplinary team.

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Preoperative Evaluation and Patient Selection

The majority of colorectal cancer relapses following surgery occur within 3 years of resection [7, 16, 26, 28, 43]. Most but not all patients will have symptoms from recurrent disease, and these will include pain, malaise, bleeding, and symptoms of partial obstruction [21]. In some patients, carcinoembryonic antigen (CEA) levels will be elevated, and this finding in the asymptomatic patient should trigger a workup for recurrence.

In patients with suspected local recurrence, every attempt should be made to obtain tissue for confirmation. Patients with luminal local recurrences can undergo endoscopy to obtain tissue. In patients with suspicious radiographic findings, obtaining tissue confirmation may be more challenging. Most patients with recurrent colon cancer will have obvious findings on imaging to confidently diagnose them with recurrence, and a transabdominal biopsy should be avoided. In contrast, every attempt should be made to obtain tissue confirmation in patients with suspected pelvic recurrence. One should be hesitant to undertake a major pelvic resection without tissue confirmation of recurrence. In our experience, computed tomography (CT)-guided percutaneous biopsy has been very useful to confirm or refute the presence of recurrence. In some cases, it may be very difficult to differentiate postoperative changes from recurrent tumor based on imaging alone. CT-guided percutaneous biopsy can confirm recurrence, but a negative result does not rule it out. In the absence of a tissue diagnosis, a rising CEA, with a notable change in the size of the lesion on serial imaging, and lesions that are positron emission tomography (PET) avid can be considered consistent with recurrent disease.

Patients with recurrent colorectal cancer being considered for curative-intent resection undergo imaging studies to assess the local-regional characteristics of the recurrence and to exclude metastatic disease [17, 18, 40]. Our protocol includes fusion PET-CT imaging of the chest, abdomen, and pelvis and magnetic resonance imaging (MRI) of the pelvis for recurrent rectal cancers. Several studies have confirmed that 18-fluorodeoxyglucose PET imaging has a high sensitivity for the detection of locoregional and distant recurrences in patients with colorectal cancer [44–46]. In the evaluation of 58 patients for advanced or recurrent colorectal cancer, Ogunbiyi et al. found that PET imaging had a sensitivity and specificity of 91 % and 100 %, respectively [47]. Chessin et al. showed that fusion imaging that combines CT and PET imaging has an enhanced sensitivity of 98 % as compared to 64 % with standard CT for the detection of rectal recurrence; in other studies, fusion imaging led to altered management in 58 % of patients [48, 49]. Moreover, PET retains its diagnostic ability even after irradiation, and because of this, we believe that all patients being considered for resection should undergo this study.

When seeing patients with local recurrence, it is important to obtain a complete history and physical examination. All records of previous treatments (surgical and chemoradiotherapy) should be reviewed. Pain and neurologic dysfunction may be a sign of advanced pelvic disease [15]. Bilateral lower extremity edema is an indicator of venous or lymphatic obstruction. A full colonoscopy should be done to rule out any synchronous lesions. If the rectum is intact, a digital rectal exam can assess the relationship of the recurrent cancer to the sphincter complex, prostate, or posterior vaginal wall. Cystoscopy may be useful to assess transmural invasion of the bladder.

Laboratory tests should be obtained by looking particularly for anemia and the nutritional state of the patient. The patient's albumin, prealbumin, and transferrin levels will give an idea of the protein reserves of the patient. If required, nutritional supplementation should be instituted to strengthen the immune system and optimize wound healing. A significantly elevated CEA should raise concern for occult metastatic disease [50].

Operations for local recurrence are often long and can be associated with significant blood loss, systemic inflammation, and tissue trauma, and the overall stress response associated with these big operations can pose significant risk to patients [51, 52]. Despite this, recent series have demonstrated a very low mortality following these major resections [17, 18, 40]. Patients with significant chronic obstructive pulmonary disease and cardiovascular conditions should be carefully evaluated and optimized preoperatively. Patients with ASA classifications of IV or V will be at the highest surgical risk and are generally not candidates for a major resection.

The decision to go ahead with a major, potentially morbid operation for local recurrence requires that the patient is fully informed regarding the risks and life-changing impact on quality of life. Ultimately, it should be the well-informed patient who decides what disability that might arise from surgery they are willing to live with. The likelihood of a stoma is high, and patients should be counseled by a stoma therapist preoperatively [53–55]. Patients undergoing multivisceral and musculoskeletal resections will require the most intense counseling regarding their postoperative recovery, limitations, and potential morbidity and mortality [14, 27, 42, 56].

The inclusion criteria for surgery in patients with recurrence have expanded significantly in the last 10 years [57]. In determining who should be offered surgery, one must consider the goals of the operation. If palliation is the goal, surgery must have a high probability of symptomatic relief and not be significantly morbid. If oncologic cure is the goal, the ability to confidently achieve a margin-negative (R0) resection must be highly probable. Based on multiple studies in patients with recurrent colorectal cancer, the number one determinant of oncologic benefit is the ability to achieve an

R0 resection. Multiple points of tumor fixation may limit the surgeon's ability to achieve an R0 resection, and this finding on evaluation has been associated with poor outcomes [15]. Patients operated for central recurrences that extend anteriorly (urogenital, gynecologic organs) have the best opportunity for an R0 resection and, therefore, good outcomes following surgery [15, 16, 58]. When a recurrence in the pelvis extends posteriorly to the sacrum or lateral to the pelvic sidewall, the ability to achieve an R0 resection becomes much less certain. In cases where there is significant lateral extension of the tumor, specifically through the sciatic notch, a positive margin is almost certain unless an extended resection such as a hemipelvectomy is done [41].

Contraindications to surgery will vary from institution to institution and from surgeon to surgeon. Local recurrences that involve major vascular structures, the high sacrum, or extensive pelvic sidewall disease were frequently listed in publications as contraindications to surgery in the past [16, 59, 60]. In the modern era, several well-recognized and respected centers have expanded their indications in light of increasing data demonstrating meaningful survival in patients undergoing extended resections [17, 18, 40, 42, 57]. In the author's view, contraindications to surgery should be based primarily on the inability to completely clear the tumor with the understanding that limited survival benefit is achieved if gross residual tumor remains.

Classification of Local Recurrence and Determining Resectability

Classification schemes for both recurrent colon cancer and rectal cancer have been proposed and are used not only to characterize patterns of recurrence but also to predict R0 resectability and oncologic outcomes [61].

Locoregional recurrence in patients with colon cancer can be classified as four distinct groups and include peri-anastomotic (mural disease), mesenteric (regional nodal disease), retroperitoneal or pelvic (drop metastases, distant nodal disease, or residual disease transmural disease), and peritoneal. In a study from the Memorial Sloan Kettering Cancer Center, Bowne et al. demonstrated that the most common site of recurrence was peri-anastomotic (36 %), followed by peritoneal (16 %), mesenteric (15 %), and retroperitoneal (12 %) [62]. In our experience, some cases of recurrence were directly attributed to inadequate mesenteric resections at the time of original surgery. However, most nodal-based relapses were found at nodal sites (iliac, para-aortic) not typically removed during standard oncologic resection [63].

Pelvic recurrences can be broadly categorized in terms of what resection would be necessary for complete tumor removal. With this in mind, the authors have generally classified recurrences as those requiring an anterior, posterior, lateral, or combined resection (Figure 35-1). In anterior resections, the rectum and urogynecologic structures are removed. A posterior resection involves removing the rectum and a portion of the sacrum. A lateral resection involves removal of the rectum and iliac vessels and/or components of the lumbosacral plexus. The term "combined resection" or "composite resection" includes any combination of anterior, posterior, or lateral structures.

For recurrent colon cancer, CT imaging is our study of choice to make decisions regarding resectability. For recurrent rectal cancer, MRI of the pelvis is our study of choice to assess neuromuscular and bony involvement and for surgical planning. We use a musculoskeletal protocol that is done with and without gadolinium and includes sagittal, axial, and coronal oblique views (Figure 35-2). MRI has highly detailed soft-tissue resolution, which is helpful in planning lines of resection as it pertains to adjacent structures. Specifically, for tumors with posterior and lateral extension, MRI can determine proximal sacral extent, involvement of lumbosacral nerves, and whether or not a margin can be obtained on the lateral pelvic sidewall. Computerized tomography or MR angiogram or venogram may add additional information regarding vascular involvement and indicate the need for a vascular surgeon to be a member of the multidisciplinary surgical team.

A major challenge from a surgical planning perspective in many cases of local recurrence is the fact that the borders of recurrences can be indiscrete and ill defined on imaging. Recurrences may be infiltrative and sheetlike and sometimes have islands of intervening normal tissue. This makes it difficult to preoperatively determine where the "true margins" are. Because of this, one must be prepared to alter the surgical plan intraoperatively as findings may differ significantly from what the preoperative imaging suggested. Intraoperative frozen section pathologic analysis can be very useful to ensure that further resection can be done if there is a persistent microscopic margin discovered at the time of surgery.

Another challenge in management of local recurrence is differentiating both postoperative and radiation-induced fibrosis from actual tumor. MRI with T2-weighted imaging can assist because fibrosis and tumor demonstrate different signal intensities [64]. Gadolinium-enhanced MRI is reported to have an 88 % and 95 % sensitivity and specificity, for the detection of pelvic recurrences in the setting of previous surgery and radiation [65].

Multimodal Therapy Including Intraoperative Radiation

Multimodal therapy in the management of locally recurrent colorectal cancer refers to a treatment approach that includes pre- and postoperative systemic chemotherapy, preoperative external beam radiotherapy (EBRT), and, in some protocols, intraoperative radiation therapy (IORT). The authors have used this approach very selectively in patients with recurrent

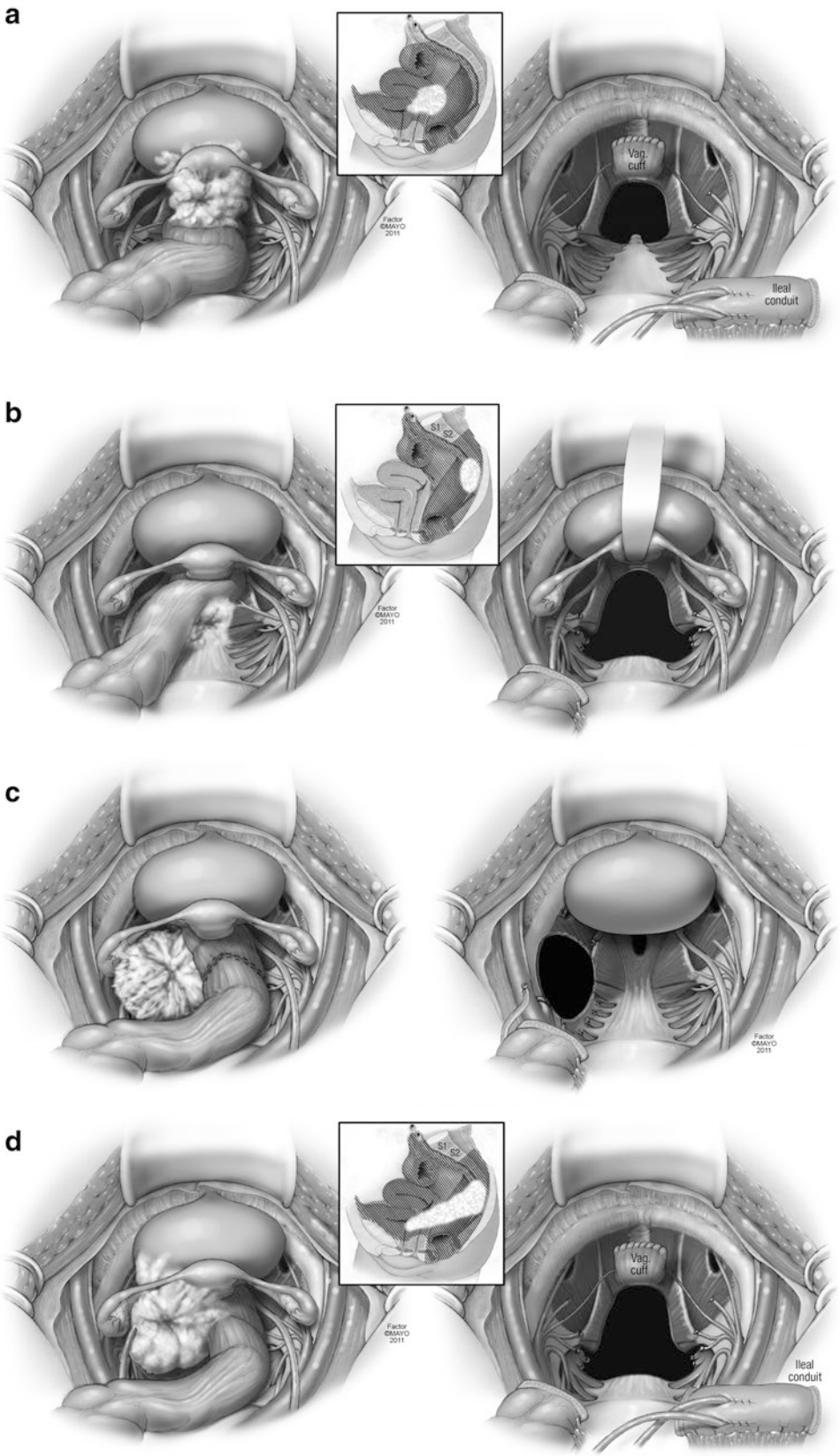

FIGURE 35-1. Classification of recurrence. (**a**) *Anterior*: involves structures anterior to the neorectum. (**b**) *Posterior*: involves structures posterior to the neorectum. (**c**) *Lateral*: involves pelvic sidewall and associated structures. (**d**) *Combined anterior-posterior*: tumor includes anterior and posterior structures. ©By permission of Mayo Clinic Foundation for Medical Education and Research. All rights reserved.

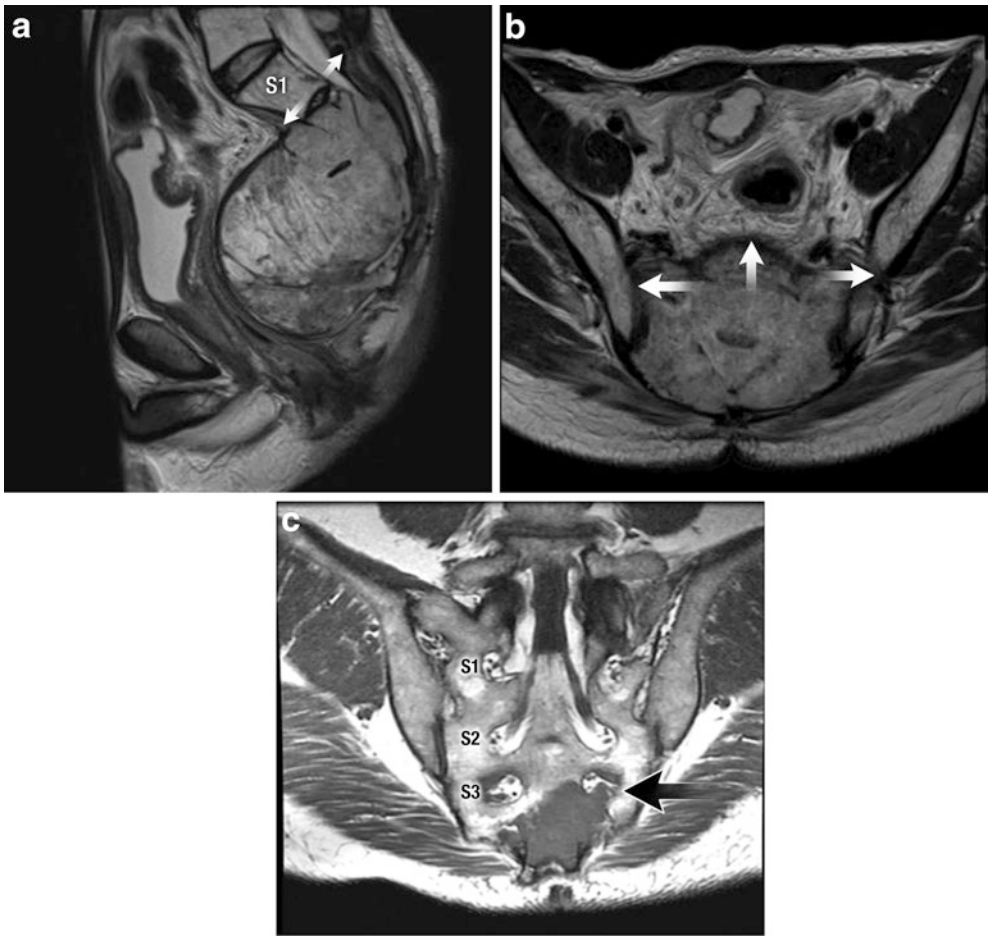

FIGURE 35-2. MRI assessing neuromuscular and bony involvement for surgical planning in recurrent rectal cancer. (**a**) Sagittal section showing cephalad and posterior extension of the recurrence to the first sacral body (S1). *White arrows* demonstrating lines of resection necessary for R0 resection; (**b**) coronal section demonstrating soft-tissue extension anteriorly and laterally, with viscera and bilateral iliac involvement (*white arrows*); (**c**) coronal/oblique view showing left nerve root involvement (*black arrow*).

colon cancer and in almost all cases of recurrent rectal cancer. In patients with locally recurrent colon cancer, there is usually less concern about the ability to get a wide surgical resection unless tumor abuts fixed critical structures (e.g., lumbar spine, aorta, vena cava). In these cases, we will employ a full multimodality approach that included IORT [63]. Since 1981, curative-intent therapy at our institution has included IORT for locally advanced and locally recurrent rectal cancer. Our protocol includes neoadjuvant chemotherapy and EBRT, IORT, and postoperative chemotherapy [13, 21, 66]. Patients who are radiation naïve receive 50.4 Gy of EBRT with concurrent five FU-based chemotherapies over 5 weeks followed by a 6–8-week recovery period before surgery. In patients who have received previous irradiation, we give 20–30 Gy with concurrent five FU-based chemotherapies, over a 3-week period followed by surgery within 7 days of the last dose of radiation. The amount of radiation given intraoperatively to the tumor resection bed depends on the margin status at the time of resection. For wide margins (500–750 cGy), R1 (1000–1250 cGy), <2 cm of gross residual (1500 cGy) and for >2 cm gross residual (1750–2000 cGy) [66]. Given that distant relapse of disease is the most common cause of death following surgery for local recurrence, systemic chemotherapy is part of our multimodality protocol. In a series of 607 patients with locally recurrent colorectal cancer treated at our institution with a multimodality approach that included IORT, the cumulative incidence of distant relapse was 53 % at 5 years. Distant relapse was less common in patients who had R0 vs. R1 or R2 resections and in those treated with postoperative chemotherapy [66]. Significant advances in chemotherapeutic regimens over the last 20 years have likely decreased the incidence of distant failures following surgery for local recurrence, but the optimal regimen and length of treatment are still debated.

Though there is a paucity of randomized data, many authors agree that a multimodality approach can significantly decrease local relapse and improve 5-year survival in

TABLE 35-1. Survival and local recurrence after intraoperative radiation therapy in patients undergoing R0 resection (adapted with permission from Ref [66])

Study	Patients (no.)	IORT dose (Gy)	EBRT dose (Gy)	5-year survival rate (%)	5-year local control rate (%)
Vermaas et al. 2005	17	10	50	45 (3 years)	35 (3 years)
Alektiar et al. 2000	53	10–18	45–50.4	36	43
Abuchaibe et al. 1993	8	15	40–50	29	50
Dresen et al. 2008	84	10–15	50.4 or 30.6	59 (3 years)	75 (3 years)
Lindel et al. 2001	25	10–20	50.4	40	56
Eble et al. 1998	14	12	41.4	71 (4 years)	79 (4 years)
Wiig et al. 2002	18	15	46–50	60	70
Valentini et al. 1999	11	10–15	45–47	41	80
Haddock et al. 2011	226	12.5 (median)	30.0–0.4	46	72

EBRT external beam radiation therapy, *IORT* intraoperative radiation therapy. EBRT generally was delivered only to patients not previously treated with radiation, except for patients in Dresen et al. (2008) [39] and the current series. Five-year rates are shown unless otherwise indicated. Lower doses were administered in previously irradiated patients

TABLE 35-2. Survival and local control after intraoperative radiation therapy in patients undergoing R1 and R2 resection (adapted with permission from Ref [66])

Study	Patients (no.)	Surgical margins	IORT dose (Gy)	5-year survival rate (%[a])	5-year local control rate (%)
Vermaas et al. 2005	10	R1–R2	10	21 (3 years)	21 (3 years)
Alektiar et al. 2000	21	R1	10–18	11	26
Abuchaibe et al. 1993	19	R1–R2	15	7	16
Dresen et al. 2008	34	R1	12.5	27 (3 years)	29 (3 years)
	29	R2	15–17.5	24 (3 years)	29 (3 years)
Lindel et al. 2001	9	R1	10–15	11	33
	15	R2	15–20	13	12
Eble et al. 1998	9	R1	10–20	33 (4-year RFS)	67
	8	R2	10–20	25 (4-year RFS)	63
Martinez-Mong et al. 1999	39	R1	10–15	6	26
	41	R2	15–20	7	29
Wiig et al. 2002	29	R1	15	20	50
	12	R2	17.5–20	0	–
Haddock et al. 2011	224	R1	15 (median)	27	68
	156	R2	20 (median)	16	68

IORT intraoperative radiation therapy, *RFS* relapse-free survival

Five-year rates are shown unless otherwise indicated

colorectal cancer patients with local recurrence [15, 67, 68]. Several centers have shown good results with the use of IORT in patients with recurrent colorectal cancer, and 5-year survival rates range from 29 to 60 % in patients undergoing R0 resection (Table 35-1). Five-year survival rates after IORT in patients having R1 or R2 resection can be as high as 16 % and 27 %, respectively (Table 35-2). In most series where IORT is not included in the management of patients who had an R2 resection, no long-term survival is seen [66].

Radiation-induced toxicity is a significant concern in patients receiving multimodality therapy that includes IORT. In many cases, it may be hard to separate IORT-related complications from surgical ones. In a published series of 607 patients from our institution with recurrent colorectal cancer treated with EBRT and IORT, we attributed radiation specifically as the cause for some septic complications (wound related, enterocutaneous fistulas), small bowel and ureteral obstructions, as well as neuropathy [66]. Both the incidence and severity of neuropathy were related to IORT dose. Doses that exceeded 12.5 Gy were associated with a higher rate and severity. In total, 15 % of patients experienced some grade of neuropathy, with only 3 % of patients suffering from grade 3 neuropathy defined as severe weakness or intractable pain.

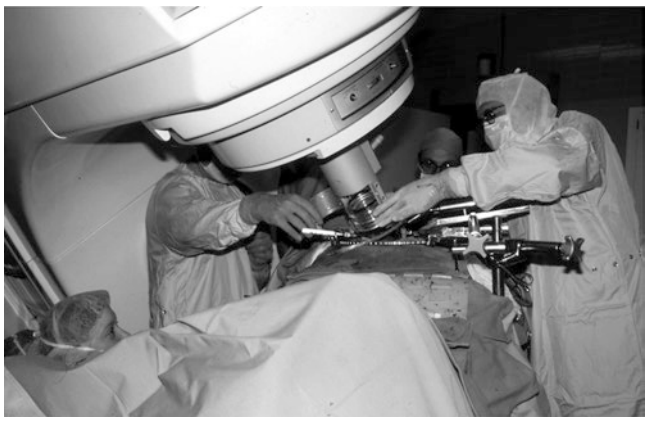

FIGURE 35-3. The IORT suite; the operating table is positioned under the linear accelerator by the radiation oncologist and the appropriate Lucite cone is affixed to direct the beam.

Technical Aspects of Surgical Resection

General Considerations

We use ureteral stents for all operations in patients with local recurrence in the pelvis. The Lloyd-Davies position is used to allow access to the perineum. Care is taken to protect the extremities from nerve injury with adequate padding of both the tucked arms and lateral lower extremities in the stirrups. An exploratory laparotomy is carried out through a midline incision to confirm absence of extra-pelvic disease and determine local resectability. Any lesions suspicious for metastatic disease are biopsied and sent for frozen section analysis. The presence of metastatic disease typically precludes resection for cure, and proceeding on to resection of the local recurrence has to be weighed carefully. All adherent tissue to the recurrence tumor should be resected en bloc. In general, the technical approach to local recurrence in the abdomen or in the pelvis is carried out by widely mobilizing normal surrounding tissues and organs in preserved embryologic planes when feasible and working toward the distorted anatomy and malignant pathology. This allows exposure of structures that are close to the recurrence but will be preserved if not invaded. In addition, vascular pedicles and collateral vasculature should be well delineated prior to ultimate mobilization of the recurrence and surrounding adherent tissue or organs, so that when significant bleeding is encountered, proximal and distal vascular control can be achieved safely.

Most cases for recurrence at our institution are done in a dedicated IORT operating room. This suite houses our linear accelerator and mobile anesthesia equipment that allows the patient to move into the optimal position for IORT (Figure 35-3). The radiation dose and field are selected based on tumor margin status. At our institution, Lucite cones are used to focus the beam of radiation delivered by the linear accelerator and protect the small bowel and other organs from radiation injury (Figure 35-4). The radiation oncologist and surgeon position the cone together for optimal radiation delivery.

Recurrent Colon Cancer

As previously stated, local recurrence in patients with colon cancer typically occurs in one of three patterns, luminal, locoregional, or para-aortic lymphatics, and in the resection bed of the previous index colectomy. Luminal and locoregional nodal recurrences are generally straightforward technically, and surgery involves resection of additional colon and adjacent mesentery. During operations in patients with retained mesentery from incomplete previous surgery, it is the author's experience that isolation and ligation of the vascular pedicles of the original tumor (that should have been removed during the index operation) is a good initial step to allow safe mobilization of the recurrence that lies within the retained mesentery. In cases where para-aortic or para-iliac nodes are involved, major vascular reconstruction may be necessary in addition to en bloc resection of surrounding structures (Figure 35-5) [69].

In cases where recurrence occurs in the previous resection bed, locoregional structures associated with the course of the colon are often involved (kidney, ureters, psoas muscle, stomach, spleen, duodenum, and pancreas). The most complex resections done for local recurrence after right colon resection are those that involve the duodenum and the head of the pancreas. When a Whipple operation is required, we involve a hepatobiliary surgeon to assist with resection and reconstruction. In cases where IORT will be used, radiation is delivered to the at-risk tumor bed just prior to closure.

Recurrent Rectal Cancer

Recurrences That Extend Anteriorly

After ruling out metastatic disease, the left colon is fully mobilized and transected at the appropriate level for subsequent end colostomy (in patients who have intestinal continuity). The entrance to the pelvis is cleared of loops of small bowel for optimal pelvic exposure. Dissection begins in the lower abdomen before entering the presacral space along the lower aorta and continues distally over the iliac vessels and ureters. Vasiloops are used to retract the ureters and vascular structures. In the re-operative pelvis, dense fibrosis and distorted anatomy require careful, meticulous dissection to avoid inadvertent injuries and major bleeding complications. In the author's experience, the most at-risk region for significant bleeding occurs during mobilization of the left common iliac vein, and this dissection should proceed with caution. Posterior lumbar branches, if not identified and injured, can lead to significant blood loss if avulsed.

The anterior and lateral lines of resection (decided upon during preoperative review of imaging) are delineated and confirmed, and the involved structures and organs are mobilized widely for subsequent en bloc resection. The presacral space is further developed, and the dissection is

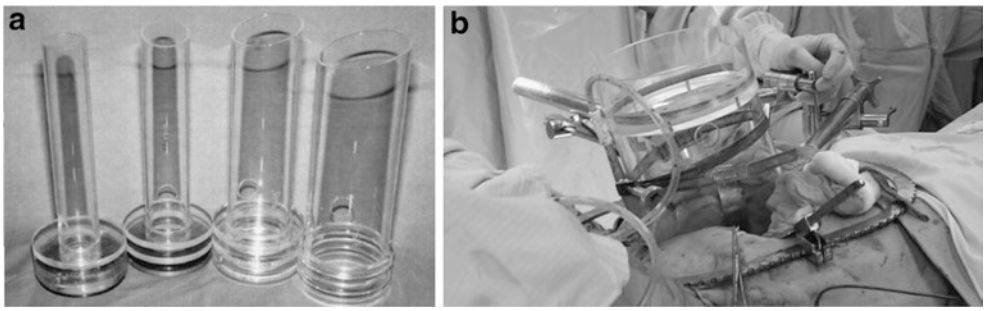

FIGURE 35-4. (**a**) Assortment of Lucite cones of different size used to direct the IORT field, (**b**) in situ placement of the Lucite tube.

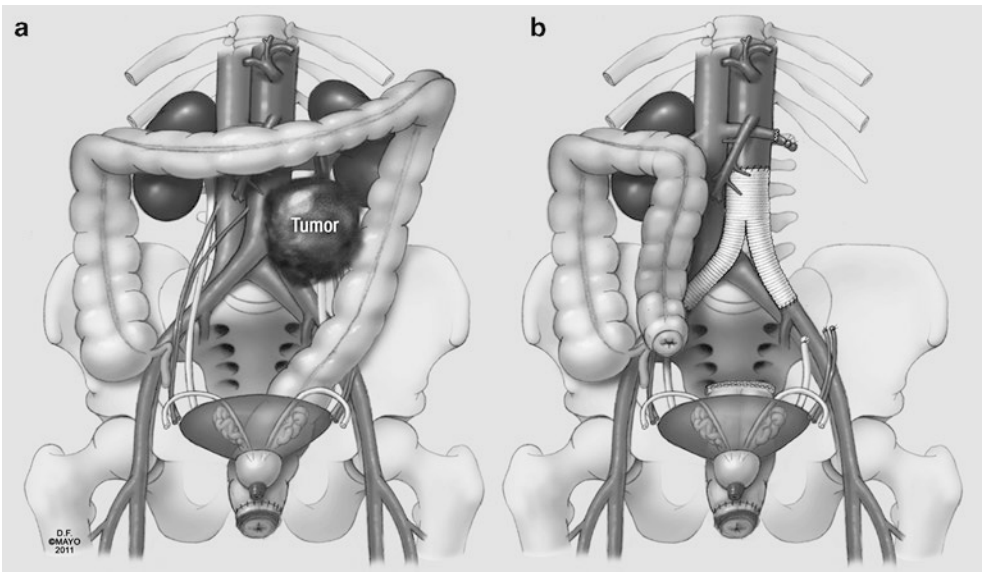

FIGURE 35-5. (**a**) Illustration of a local recurrence involving the aortic bifurcation, colon, kidney, and ureter, (**b**) en bloc resection with aortoiliac reconstruction.

carried down along the anterior sacrum being careful to stay anterior to Waldeyer's fascia to avoid the presacral venous plexus. The dissection is then carried laterally along the pelvic sidewall on each side with careful protection of the lumbosacral plexus and internal iliac vessels. The deepest part of the pelvic dissection will be the pelvic floor musculature, which can be incised during the abdominal portion of the procedure. When the transabdominal portion reaches this point, a combined transperineal approach facilitates final tumor removal. The transperineal portion begins with purse-string closure of the anus (if present), and then a wide, elliptical incision is made to include the sphincter complex and as much pelvic floor musculature as possible. With a surgeon working above, the two dissection planes can be joined safely and with careful attention to the tumor margins.

In women, anterior involvement may require resection of the posterior wall of vagina, and this portion of the operation is approached transvaginally and transabdominally simultaneously. In men, anterior fixation often requires cystoprostatectomy due to invasion of the trigone and prostate. Partial cystectomy may be sufficient in rare cases. When a urinary conduit is necessary, the ureters are mobilized as close to the bladder as possible to provide adequate length to reach the conduit. To mobilize the bladder, the space of Retzius is entered to fully mobilize the anterior portion of the bladder. The blood supply to the bladder (superior and inferior pedicles) is taken serially along the pelvic sidewall off the internal iliac vessels. The wings of peritoneum to the bladder are then taken down until the bilateral vasa are identified and clipped. The endopelvic fascia is opened bilaterally. The dorsal venous complex is subsequently ligated. The urethra is then delivered into the wound and transected.

Once the tumor is out, the surgeon orients the specimen for the pathologist and frozen section margins are assessed. If margins are not clear, further resection is undertaken when safe to achieve an R0 resection. At this point, IORT is given to the at-risk resection bed. Creation of end colostomy and urinary conduit completes the procedure. In women in whom a large portion of the posterior vaginal wall is removed, a vertical rectus abdominis flap (VRAM) is used for vaginal reconstruction.

Resection That Includes Sacrectomy

Stage I: Anterior Component

This dissection begins as outlined above for anterior recurrences. Once the deep pelvic portion of the operation begins, the anterior, lateral, and superior (along the spine) lines of resection are delineated, and the involved neuromuscular structures and organs are mobilized widely for subsequent en bloc resection. Frozen section biopsies are taken as needed to establish that final margins will be negative.

Vascular exposure often requires mobilization of the lower aorta and vena cava, in addition to the iliac arteries and veins. If vascular structures need to be resected en bloc with the tumor, the decision to do so is made here. If the resection does not require aortoiliac reconstruction, circumferential mobilization of the common and external iliac arteries will facilitate exposure of the veins. The internal iliac artery branches are ligated and divided first, distal to the takeoff of the posterior division superior gluteal artery branch, to preserve blood flow to the gluteal muscles and soft tissue of the perineum. Multiple internal iliac vein branches are then ligated after control of the main trunk(s) of the internal iliac vein has been achieved. The branches are ligated and divided before ligation of the main trunk to avoid venous distention of the branches, which can lead to troublesome bleeding (Figure 35-6). Lateral and middle sacral vein branches, which drain into the posterior aspect of the left common iliac vein and caval confluence, are ligated and divided. Suture ligature is preferable for short, broad-based internal iliac vein branches. The vascular dissection is carried along both sides of the sacrum onto the pelvic floor. In general, the internal iliac vessels are taken at their confluence as part of any sacrectomy above the third sacral body. For sacrectomy at or below the third sacral body, we generally preserve the internal iliac vessels.

Once the most proximal lumbosacral level of transection is determined, unicortical anterior osteotomies are performed at the bony level of resection (Figure 35-7). Prior to closing the abdomen, a thick Silastic mesh is placed anterior to the sacrum and posterior to the ureters, aorta, iliac vessels, and soft-tissue structures to protect against injury when blind osteotomies are performed during the second stage of the procedure, at which point the patient is in prone position. A titanium screw is also placed at the level of the osteotomy site to facilitate performing the posterior osteotomies by using intraoperative fluoroscopy (Figure 35-8).

During the anterior stage of the operation, IORT may be delivered prior to final tumor resection if orientation of the Lucite cone in the prone position will not be feasible to radiate the at-risk tumor bed. A colostomy and ileal or colonic urinary conduit are fashioned as needed, and a VRAM flap is then elevated for subsequent perineal reconstruction.

Stage II: Posterior Component

The second stage of the procedure is typically carried out 2 days after the anterior portion. With the patient in the prone position, a posterior midline incision is made along the middle

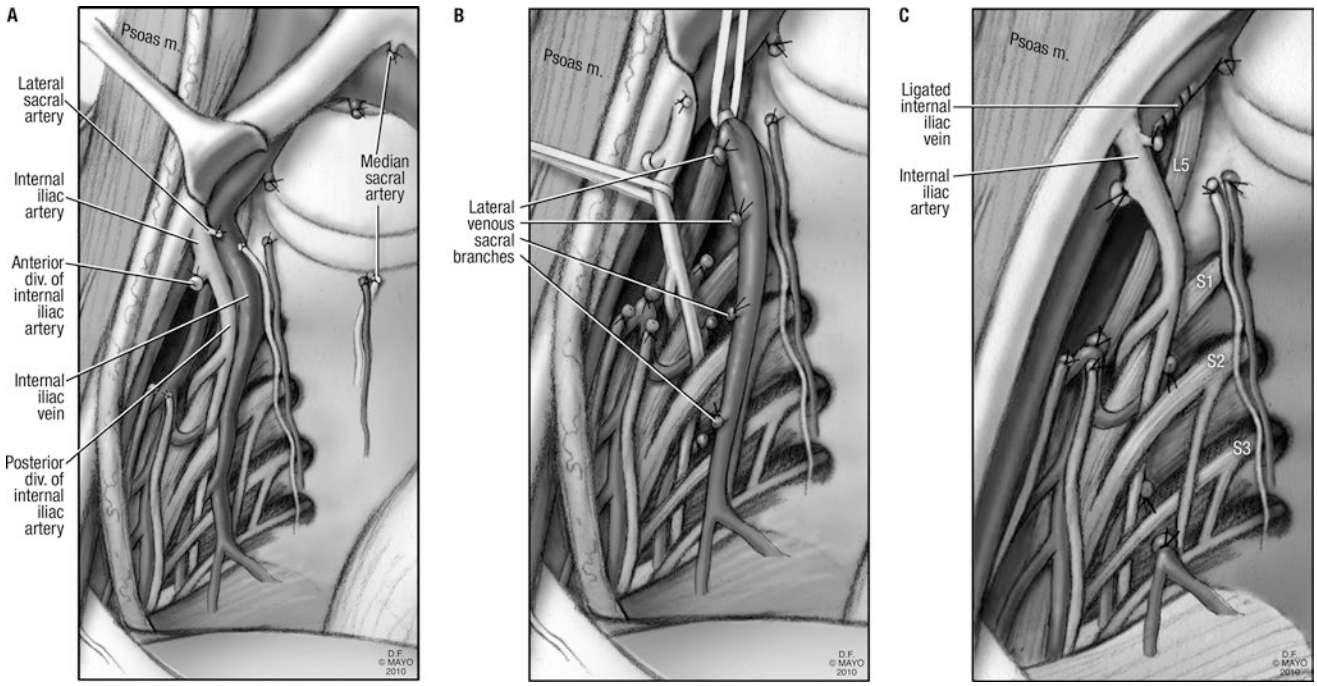

FIGURE 35-6. (**a**) Pelvic vascular anatomy. Ligation of anterior division of internal iliac artery, lateral sacral arteries and veins, and sacral artery and vein. (**b**) Ligation of lateral venous sacral branches. (**c**) Ligation of internal iliac vein.

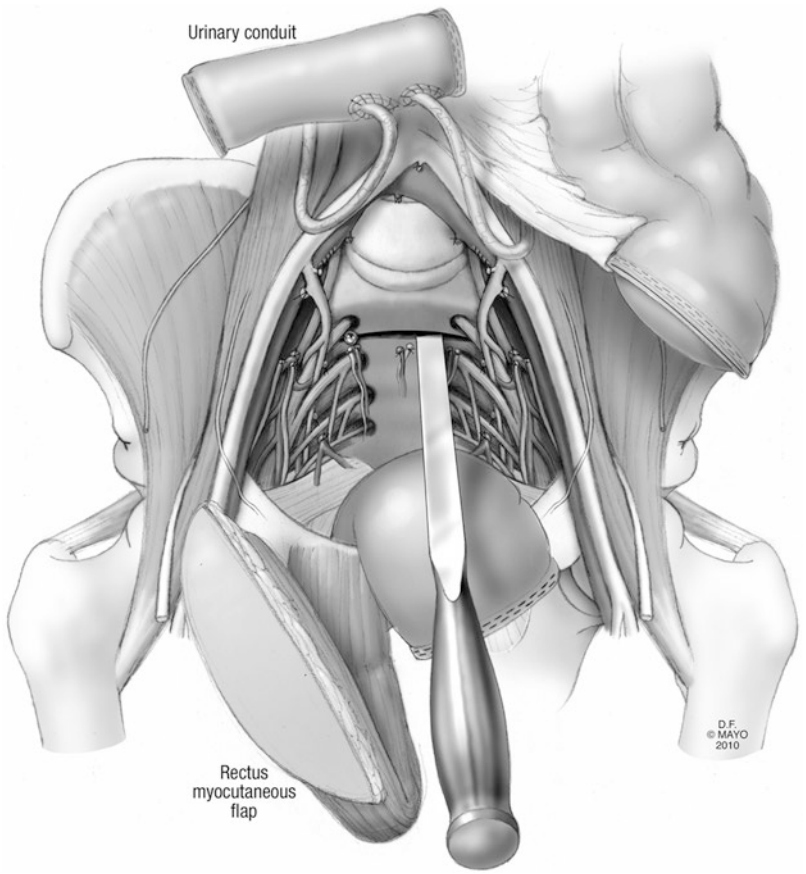

FIGURE 35-7. Unicortical anterior transverse osteotomy.

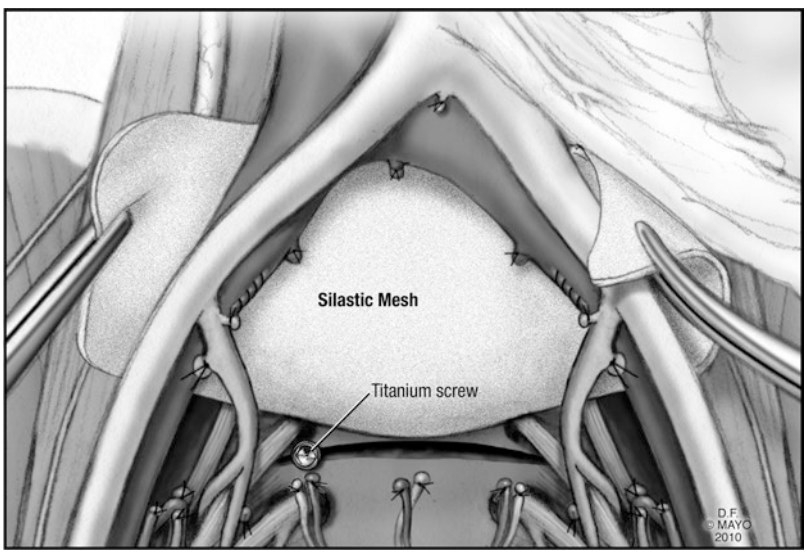

FIGURE 35-8. Placement of Silastic mesh to protect pelvic vasculature during the posterior osteotomies. Titanium screw marks the level of the anterior osteotomy to guide fluoroscopic identification of anterior osteotomy level when performing posterior osteotomy.

portion of the sacrum, and the gluteus maximus muscles are dissected away from the sacral attachments. The sacrospinous and sacrotuberous ligaments are divided to access the pelvic cavity posteriorly. The piriformis muscles are divided while protecting the sciatic and pudendal nerves. Laminectomy, dural sac ligation, and posterior sacral osteotomies are then carried out (Figure 35-9). Final osteotomies are performed based on the preoperative MRI imaging studies and intraoperative fluoroscopy to identify the anterior positioned titanium screw. After resection, the surgical team meets with the pathologist to accurately orient the specimen, and together they assess the completeness of resection. If frozen section analysis demonstrates an R1 or R2 margin, wider resection is undertaken as it can be done safely. Before soft-tissue wound reconstruction is done, IORT is given (if not given during stage I) and the dose is based on tumor margin status, as discussed above.

Stage III: Spinal Reconstructive Component

In cases where the lumbosacral line is transected, spinopelvic stability is compromised and patients will require instrumented reconstruction. For resections above the level of the S1 neuroforamen but below the lumbosacral junction, clinical experience and biomechanical studies have shown that in situ spinopelvic stabilization is beneficial to avoid collapse of the residual sacrum [70]. In these cases, an instrumented posterior spinopelvic fusion is made from the lower lumbar spine to the remaining pelvis.

Resections done through the lumbosacral junction, or higher, disrupt spinopelvic continuity. These patients undergo reconstruction using a combination of dual fibula grafts and instrumented stabilization from the lower lumbar spine to the remaining pelvis (Figure 35-10) [71]. The decision to use fibula allo- or autografts is individualized.

A concurrent hemipelvectomy is considered if the local extent of disease leads to sacrifice of both the femoral nerve and the lumbosacral plexus/sciatic nerve or the hip joint and the femoral or sciatic nerves. Resections of this magnitude would otherwise leave a nonfunctional limb. In addition, patients will have such a large soft-tissue defect that a pedicled quadriceps apron flap is necessary for closure. In these cases, the fibula from the amputated limb can be preserved on a pedicle at the end of the quadriceps flap for reconstruction. This is then used to restore spinopelvic continuity.

Soft-Tissue Reconstruction

Nonhealing perineal wounds following an abdominal perineal approach to complex pelvic tumors are reported to occur in 7–66 % of patients [72]. We, as well as others, have found that the use of a VRAM flap is associated with fewer perineal wound complications [72, 73]. The VRAM provides a well-vascularized, bulky tissue paddle that not only fills dead space but also can be used to reconstruct the perineal skin defect. Our technique is described elsewhere, but in essence, the VRAM is mobilized en bloc with the overlying fat and

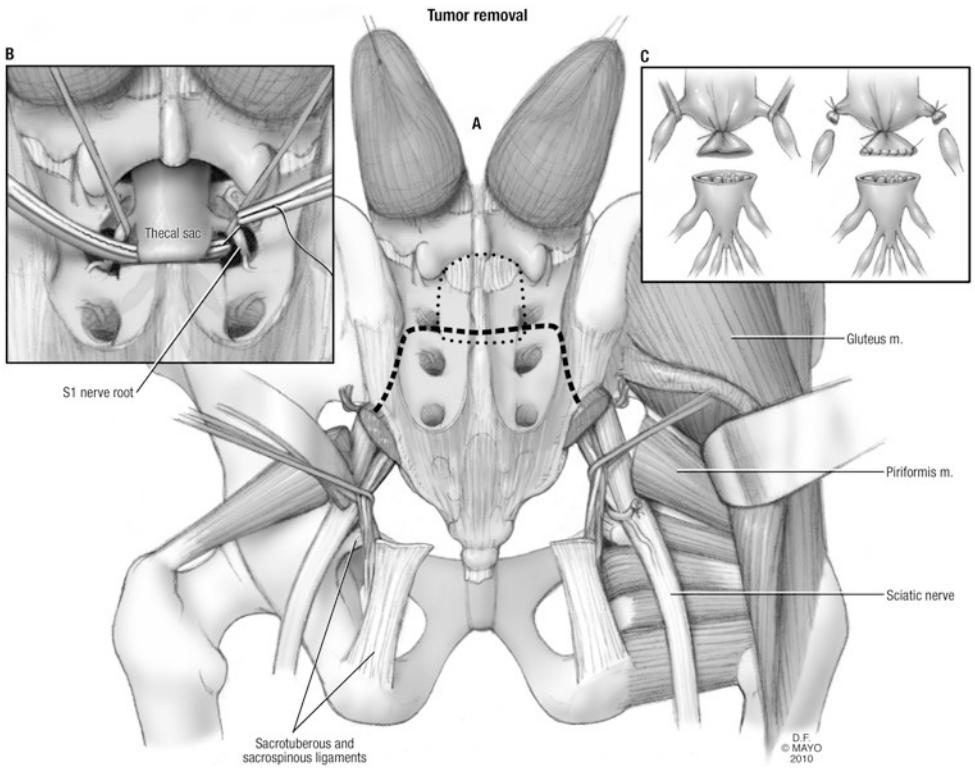

FIGURE 35-9. (**a**) Posterior transverse osteotomy (*thick dotted black line*). Sacrospinous and sacrotuberous ligament transection. The gluteus maximus muscle is reflected laterally to expose obturator vessels and the sciatic nerve. (**b**) Laminectomy to identify thecal sac, (**c**) dural sac, and sacral root ligation.

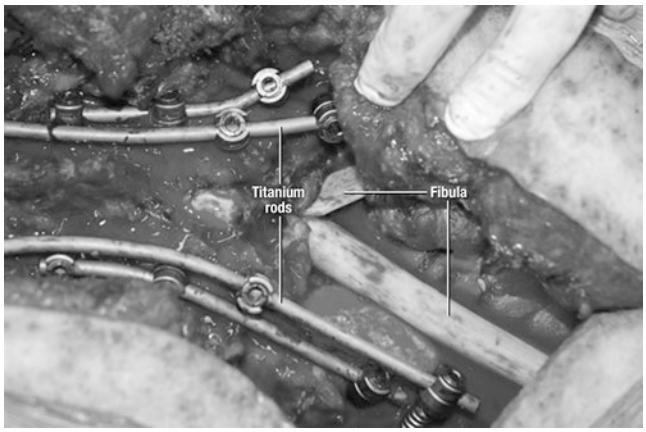

FIGURE 35-10. Intraoperative photograph of fibula grafts and instrumented spinopelvic reconstruction following total sacrectomy.

skin [74]. Particular attention is paid to the blood supply, especially the deep inferior epigastric artery and vein. Once mobilized, it is rotated transabdominally in the perineum keeping the overlying skin and fat intact, which helps bridge the significant defects that these resections leave behind. In cases where the rectus is not available, a pedicled omental flap can be a good second choice if it is robust. It can fill the pelvic dead space providing vascularized tissue and has been shown to decrease risk of pelvic sepsis following surgery [75]. Moreover, the omentum can line the raw surfaces of the pelvis, preventing the small bowel from getting trapped in the deep pelvis, which is a common cause of small bowel obstruction following exenteration.

Thigh fillet flaps are used after hindquarter amputation and are based on the superior and inferior gluteal vessels. This flap allows one to take advantage of the bulky gluteal muscle, which can cover large defects after the ipsilateral pelvis has been resected. Long anterior hemipelvectomy flaps are based on the vascular muscle distribution supplied by the superficial femoral artery. This flap includes the bulk of the quadriceps femoris and—like the posterior hemipelvectomy flap—can provide significant coverage of very large pelvic and soft-tissue defects.

Results of Surgery

Recurrent Colon Cancer

Limited data exists on surgical and oncologic outcomes in patients with locally advanced recurrent colon cancer. Few centers have published their experience, and patient groups are small and heterogeneous, making definitive conclusions regarding management difficult. In a series from the Mayo Clinic, 73 patients underwent a multimodality approach that included IORT for recurrent colon cancer [63]. In this cohort, an R0 resection was achieved in 52 % and led to a 5-year survival of 37 %. In a series from Leeds, Harji et al. reported on 42 patients with recurrent colon cancer [76]. An R0 resection was achieved in 64 %, and mean survival did not differ between R0 vs. R1 resected patients (29 months vs. 26 months). Survival outcomes were dependent on location of recurrence, and median survival after resection was 33 months for anastomotic, 26 months for pelvic, and 19 months for abdominal recurrences. In the largest series published, Bowne et al. from the Memorial Sloan Kettering Cancer Center reported on 100 patients operated on for curative-intent resection for locally recurrent colon cancer [62]. Fourteen patients were found to have unresectable disease at the time of surgery and 65 % had an R0 resection. Multivisceral resection was common, and the best oncologic outcomes were achieved in patients undergoing R0 resection. Actuarial 5-year survival was 35 % for their entire cohort but was 58 % in those undergoing R0 resection.

In all three of these series, surgery could be performed safely, but multivisceral en bloc resection was required in many patients in attempts to reach a negative-margin resection. Margin status and location of recurrence appear to be the most important predictors of outcome in patients with recurrent colon cancer.

Recurrent Rectal Cancer

In the past, published series of surgery for locally recurrent rectal cancer were limited by small numbers and heterogeneous patient groups. In 2015, we now have robust data that confirms that an R0 resection, the ultimate goal for these operations, is achievable in 70–93 % [17, 18, 42] and overall 5-year survival can be as high as 40 %. Moreover, in series published where IORT is a component of multimodality therapy, meaningful survival can also be achieved in patients who have R1 or R2 resections [40]. Aggressive surgery that includes more lateral pelvic resections (pelvic sidewall tumors) and higher sacral resection (above the third sacral body) is increasingly reported by experienced centers with good results [17, 18, 56, 57].

In a Mayo Clinic series, Hahnloser et al. reported outcomes in 394 patients that underwent a curative-intent resection for locally recurrent cancer [15]. Operative mortality was 0.3 % (1 patient with uncontrolled hemorrhage), and significant morbidities were seen in 26 % of patients (most common was pelvic sepsis). Margin status for this cohort was R0 (45 %), R1 (9 %), and R2 (46 %). Survival was clearly impacted by margin status, 37 % for R0 and 16 % for R1/R2 patients. Other significant findings in this study were that symptomatic pain at presentation and >1 fixation point of the recurrence was associated with margin-positive resection and therefore a poor outcome. Patient demographics, factors related to the initial rectal cancer, and extended vs. limited resection did not impact overall oncologic outcomes. In a series from the Leeds General Infirmary, Boyle et al. reviewed outcomes in 64 patients with locally recurrent rec-

tal cancer, 57 of which underwent curative-intent resection [39]. Pelvic exenteration or sacrectomy was required in 32 %. An R0 resection was achieved in 37 %, perioperative mortality was 1.6 %, and morbidity was 40 %. Overall median survival was 34 months, and R0 resected patients had a significantly longer survival compared to R1 or R2 patients (median survival for R2 was 8 months). In a recent report from Denmark, Nielsen et al. published results on early and late outcomes of surgery for locally recurrent rectal cancer [77]. In their series, 115 patients underwent curative-intent resection. 30-day mortality was 0.8 % and an R0 resection was achieved in 61 %. The 3- and 5-year survival rates for R0 resections were 55 % and 42 %, respectively. No patients with R2 resection lived past 3 years.

Local excision for early rectal cancers has gained wider acceptance in the last 10 years [78]. The risk of local recurrence following local excision remains elevated, especially for high-risk T1 and T2 cancers. When local recurrence occurs following local excision, surgical salvage is the only treatment that has the potential to achieve meaningful survival. In a recent report, Bikhchandani et al. found that R0 resection was possible in 93 % and 5-year survival rate and DFS were 50 % and 47 %, respectively [79]. Metastatic disease following salvage surgery was the most common cause of death in this cohort. You et al. from the MD Anderson Cancer Center reported on 40 patients undergoing surgical salvage following local excision for rectal cancer [80]. A multimodality approach was used and R0 resection was achieved in 80 %. Multivisceral resection was required in 33 % and perioperative morbidity was 50 %. The 5-year overall and 3-year recurrence-free survival was 63 % and 43 %. Pathological stage at initial local excision, receipt of neoadjuvant chemoradiotherapy before local excision, pathological stage at salvage, and R0 resection at salvage significantly influenced re-recurrence-free survival.

The importance of an R0 resection in patients undergoing surgery for recurrent rectal cancer cannot be overstated. A recent meta-analysis of survival based on resection margin status following surgery for recurrent rectal cancer was published by Bhangu and colleagues [81]. In their analysis, they reviewed 22 studies that included 1460 patients and found that 57 % underwent R0 resection, 25 % R1, and 11 % R2. The range of median survival was 28–92 months for R0 resections, 12–50 months for R1, and 6–17 months for R2. Patients undergoing an R0 resection survived on average for 28 months longer than those undergoing R1 resection and 53 months longer than those undergoing R2 resection.

Surgery for Re-recurrent Disease

In the author's view, a second colorectal cancer recurrence is not a contraindication to curative resection as long as the principles of determining resectability for primary recurrence are followed. In a study by Colibaseanu et al., 47 patients underwent surgery for locally re-recurrent colorectal cancer [40]. An R0 resection was achieved in 60 % and 30-day mortality was nil. Overall 2- and 5-year survival was 83 and 33 %. Disease-free survival at 2 and 5 years was 55 and 27 %. In another study by Harji et al., 30 patients underwent resection for a second-time locally recurrent rectal cancer [82]. In their series, an R0 resection was achieved in 30 %, and they achieved a 1- and 3-year survival rate of 77 % and 27 %, respectively. It was the conclusion of both studies that in patients where R0 resection was possible, surgical resection for re-recurrent colorectal cancer had comparable oncologic outcomes than those patients undergoing surgery for first-time recurrences.

Resection That Includes the Aortoiliac Axis

The safety and feasibility of aortoiliac axis reconstruction in the course of complex tumor resections has been well described [83]. Small series have been published that specifically evaluate outcomes following resection in patients with locally recurrent colorectal cancers that involve the aortoiliac axis. In a study by Abdelsattar et al., 12 patients underwent major vessel resection that included the internal and external iliac arteries and veins and in some cases the aorta [69]. An R0 resection was achieved in 7 patients and R1 in 5. No graft complications were seen in long-term follow-up and 30-day mortality was nil. Overall survival and DFS at 4 years were 55 and 45 %. In another study by Austin et al., en bloc vascular resection was done as part of pelvic exenteration for pelvic malignancies in 36 patients (69 % were rectal cancers) [84]. An R0 resection was achieved in 60 % of the locally advanced primary and recurrent rectal cancer cases. For the overall cohort, 46 % of patients were disease-free with the average disease-free interval being 30 months. Both studies concluded that despite the complexity of the technique, the surgery can be performed safely when done by expert multidisciplinary teams, and overall survival and DFS are comparable to outcomes seen with locally advanced disease to nonvascular structures.

Sacropelvic Resections

Owing to the complex anatomical relationships of the pelvic structures, some local recurrences involve multiple fixation points and will require both multivisceral and neuromusculoskeletal resection to achieve a negative-margin resection. Operations for recurrences involving the lateral pelvic sidewall or high lumbosacral skeletal components are among the most technically challenging to perform. In the past, limited data existed regarding both the safety and the oncologic benefits of surgery in these patients. Once thought to be a common contraindication to surgery for recurrent colorectal cancer, high sacral and other complex sacropelvic resections are being done by an increasing number of centers around the world [57]. In most recent series from

specialized centers, authors have shown that surgery in these complex patients can be done safely and with meaningful oncologic outcomes.

In a small series of 9 patients who had sacral resection at the level of the second sacral body or higher (up to fifth lumbar space), Dozois et al. reported an R0 rate of 100 %, no 30-day mortality, and an overall median survival of 31 months [41]. Three patients were long-term survivors at 40, 76, and 101 months. In another study from the same institution, Colibaseanu et al. reviewed 30 patients that had undergone curative-intent extended sacropelvic resections [17]. Four patients in this series underwent hindquarter amputations and over 50 % had sacral resections above the third sacral body. There were no 30-day mortalities and R0 resection was achieved in 93 %. Overall survival and DFS at 2 and 5 years were 79 and 43 %. Overall survival in this series was not different in patients undergoing high (>3rd sacral body) vs. low sacral resection.

In a study from the Royal Prince Alfred Hospital in Sydney, Australia, Milne et al. reported on 100 patients undergoing sacropelvic resection for advanced pelvic malignancies, of which 18 were primary rectal cancers and 61 were recurrent rectal cancers [18]. In the entire cohort, an R0 resection was achieved in 72 %, no 30-day mortality was seen, and overall survival and DFS were 38 % and 30 %, respectively. In a study by Sagar et al. from the Leeds General Infirmary, 40 patients underwent composite sacropelvic resection [56]. An R0 resection was achieved in 50 %, and the mean disease-free interval was 55.6 months for R0 and 32 months for R2 patients.

Postoperative Complications and Quality of Life

Despite the complex nature and magnitude of surgery for local recurrence, several recent series have demonstrated that these cases can be done with an operative mortality rate that ranges from 0 to 3 % [17, 18, 40, 42]. When it does occur, 30-day mortality is usually a result of uncontrolled sepsis. This is a dramatic improvement compared to series published 20 years ago, where operative mortality could be as high as 8.5 % [14]. Several factors are responsible for the significant decrease in operative mortality, better patient selection, improved surgical technique by experienced specialists, better anesthesia, and better postoperative ICU management.

Early and late complications following surgery for local recurrence remain a significant challenge. Most series report intra-abdominal/pelvic sepsis and wound-related complications as the most significant causes of morbidity [17, 18, 56, 60, 67, 85]. Other common complications are postoperative bleeding requiring transfusion, voiding dysfunction, prolonged ileus, delayed small bowel perforation, and late fistulas. Universally, higher complications are associated with extended resections such a sacrectomy and exenteration [15, 17]. Urologic complications both early (ureteral obstruction, leak) and late (ureteral stricture) are reported in many series. In a study by Rahbari et al., risk factors associated with postoperative complications were analyzed [86]. In their series, 92 patients underwent curative-intent surgery for recurrent rectal cancer. To identify predictors of complications after resection, univariate and multivariate analysis was done. On univariate analysis, partial sacrectomy ($p=0.0001$), intraoperative blood loss ($p=0.005$), amount of transfusion ($p=0.02$), and operating time ($p=0.006$) were associated significantly with surgical complications. Multivariate logistic regression analysis of ASA score, BMI, partial sacrectomy (yes or no), blood loss, operating time, and the use of IORT (yes or no) revealed that partial sacrectomy is the only independent predictor of surgical morbidity. It is the author's perspective that careful surgical planning, reducing blood loss, reducing operating time, and the judicious use of soft-tissue flaps can significantly decrease postoperative morbidity.

Little information exists about the impact of major surgical intervention on quality of life in patients with recurrent colorectal cancer. While oncologic outcomes remain the most important outcome measure for patients and physicians deciding on an aggressive surgical approach, quality of life after surgery must be considered and discussed with patients so that they are well informed. In the modern era, advances in surgical technique and expertise allow surgeons to perform increasingly more complex operations, and how these operations impact quality of life is a relevant and growing area of interest to both patients and surgeons.

In a study by Austin and colleagues at the Royal Prince Alfred Hospital in Sydney, Australia, quality of life in 75 patients undergoing pelvic exenteration for advanced rectal cancer was assessed using the Short Form 36 version 2 (SF-36v2) and Functional Assessment of Cancer Therapy-Colorectal (FACT-C) instruments [87]. They found that FACT-C scores in survivors were good and comparable to those of patients who had low anterior resections or abdominal perineal resections. Though the summary scale of the SF-36v2 form was lower in exenteration patients than the general Australian population, the mental component summary scale was high and comparable. In a systematic review of health-related quality of life (HRQoL) in patients with locally recurrent rectal cancer, Harji et al. reviewed a total of 14 studies compromising 501 patients [88]. This study (the first published study to focus exclusively on HRQoL in patients with locally recurrent rectal cancer) identified several consistent themes. There are few studies of variable quality, reporting on a large number of HRQoL domains. Moreover, the heterogeneous treatment approach and patient population make study comparisons difficult. Harji and colleagues conclude that a disease-specific, validated, and reliable outcome measures are both lacking and required to provide meaningful data in patients who undergo surgery for locally recurrent rectal cancer. This tool, once developed,

could then be used to prospectively measure HRQoL. This data would be very useful in assisting in surgical decision-making for both the physician and the patient.

Palliative Approach

Patients with an asymptomatic recurrence which is unresectable, either due to the presence of concurrent metastases or because of local factors, do not warrant surgical intervention [89]. In symptomatic patients, EBRT can sometimes relieve obstruction, decrease bleeding, and reduce pain [90]. Endoscopic stenting is especially helpful with malignant obstructions and can in some cases be used to palliate malignant fistulas that are inoperable [91, 92]. Patients not candidates for stents may need a colostomy for symptomatic relief.

Chemotherapy has been shown to prolong survival and palliate symptoms in patients with primary metastatic colorectal cancer, and in large, the treatment of unresectable recurrent colorectal cancer is based on extrapolations from this data. FOLFOX and FOLFIRI are the most commonly used chemotherapy protocols in patients with unresectable metastatic disease. The three most prominent trials comparing the two regimens did not distinguish which is superior, though both regimens prolong survival [93–95]. Newer agents such as bevacizumab, cetuximab, and panitumumab have and continue to be studied as monotherapy or as part of multidrug regimens [96–98].

Patients in whom a palliative approach is taken will benefit greatly by meeting with a palliative medicine team to discuss treatment goals and assist with end-of-life decisions. In addition, a cancer pain specialist can assist in reducing suffering through optimal pain management, and this should be the goal in patients undergoing a palliative approach.

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