INVITED REVIEW

Pelvic Exenteration in Rectal Cancer

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▏▎▎▍ **ABSTRACT**

Primary rectal cancer can recur loco-regionally in the pelvic compartment despite multidisciplinary treatment being given and oncological principles of total mesorectal excision being instituted. Recurrent disease in the tumor bed exhibits special characteristics in terms of pelvic location, tumoral extent, and extra-pelvic metastatic status. The effective treatment of this heterogeneous tumor family depends on adequate staging, skillset for doing multi-organ resection, logical usage of adjuvant chemoradiotherapy, and crucial decision-making by the tumor board. For many years, the surgical community was reluctant to perform these radical, aggressive exenterative surgical interventions due to high morbity/mortality and technical difficulties. However, in solid tumor surgery, because of the proven independent and robust prognostic association between complete tumor resection and overall survival, the number of centers doing radical pelvic exenteration in properly selected patients has gradually increased in the last 10 years. With the aid of modern technology, advances in pelvic oncologic surgery and anesthesiology, and optimum patient care, the morbity and mortality rate has decreased and overall survival has increased. Advanced age, uncontrollable co-morbidities, refractory to medical treatment, multi-organ resection, septic complications, and a lack of surgical experience are powerful prognosticators. Research into this complex surgical field in terms of colorectal cancer is still ongoing.

Keywords: Rectum cancer, pelvic exenteration, oncologic outcomes

Introduction

Oncological outcomes with curative surgery for rectal cancer have improved considerably in recent years. These positive oncological results are a result of both developments in surgical technique for total mesorectal excision and the clinical application of neoadjuvant treatments.[1-5] However, local recurrence (4-11%) remains a challenging problem.[6-12] Locally recurrent rectal cancer (LRRC) is traditionally considered to be an "unrecoverable condition" and a 3-year survival rate is reported to be less than 4% in untreated patients.[13-16] When palliative chemotherapy (CT) and/or radiotherapy (RT) is applied, this survival rate can reach 8.5%. Infiltrative and/or destructive tumors can frequently destroy intrapelvic organs and structures, leading to malignant fistulas, severe pain, intestinal obstruction, incontinence and rapid collapse of the patient. Even palliative supportive treatments may render them inapplicable due to

tumor-related toxic effects. Although palliative treatments are beneficial in the first stage, even in the best conditions, long-term benefit cannot be expected and they should be reserved for end-stage disease. Radical exenterative surgery is a potentially curative treatment modality for pelvic oncologic colorectal surgery. Today, potentially curative (R0 resection) pelvic exenteration (PE) is performed in specialized centers with low morbidity and mortality rates in properly selected patients. Five-year overall survival is reported to be 40-50%.[1-16] In light of the mounting evidence and with the development of pelvic surgery, yesterday's concerns (high morbidity and mortality rates) are reduced, the number of trained centers that can apply the surgical technique has increased, oncological patient outcomes have improved, and the quality of life of patients has reached reasonable levels within six months. In order to understand PE, it is necessary to first understand radical pelvic oncology and causes of local recurrence.

86

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

Radical Pelvic Surgery

The pelvis is a three-dimensional, compartmental and complex anatomical space.[17-20] Gastrointestinal, gynecological, vascular, neurological and urological systems are all in close proximity. These systems are supported by a wide variety of bones, muscles and ligaments. There is a dense lymphatic, vascular and neurologic network that is intertwined between these units and that tumor cells can also use to spread.[17-20] Knowing the relationships between these different embryological developmental compartments is essential for successful surgery. The surgery of pelvic organs and structures, known as a "no go" area for many years, has been divided into sub-branches. Although the sub-branches describe their specific specialty, none can provide a holistic overview of the whole of pelvic surgery.[21-23] In standard surgical training, however, it is not possible to train for the pelvis and retroperitoneum. Moreover, there are not enough experienced trainers specialized in these subjects and three-dimensional pelvic anatomical dissection experience cannot be taught while tumors are, of course, three dimensional entities. The curious surgeon can learn as much as he/she can see and understand during surgeries simply by looking at cloned or poorly copied drawings in books. In both of these cases, the "burglar" tumor that has reached the vital-risk organs of the retroperitoneum and pelvis, which is generally withdrawn, cannot be "chased home" by the surgeon, and tumor cells that have traveled with intercompartmental transgression cannot be completely excised (resection resulting in R1-R2 margins!). The lack of experience of cadaver surgery makes the situation even more difficult. Thus, without an accurate anatomical road map, the surgical team will make mistakes, which will result in complications and/or oncological failure. Retrospective follow-up traces of many unwanted complications and local recurrences lead to technically limited and insufficient surgery.[24-26] *The authors draw attention to the importance of adding retroperitoneal and pelvic surgery training to the standard surgical training for effective radical resection of LRRC.*

Local Recurrence Problem

Local recurrence in solid organ cancers is a serious and under-emphasized problem. This also applies to rectal cancer. There are few publications about the question of why it can recur despite *potentially curative radical resection* in primary or recurrent rectal cancer.[27-30] It is surprising that research has focused on primary carcinogenesis, but that despite the application of all oncological principles, no study has investigated recurrent tumorigenesis. The clinical recurrence of specific tumor cells in the primary surgical site (tumor bed) or at the adjacent-surrounding tissue border is called local recurrence (LR) - although this could actually be considered a cellular persistence. LR often refers to the incomplete removal of cancer cells in the periphery of the initial/index cancer. The location and extent of these LRs, whether they are together with lymph nodes or not, extend beyond the compartment (anatomical borders are tumor suppressors), and how many organs they involve, are the subjects that the oncological colorectal surgeon most wants to know. If the surgical team has not developed an expanded multi-organ resection technique, cells from the tumor that have escaped the compartment, or made anatomical border violations will lead to tumor recurrence and dissemination, and then recurrences in the early period and/or metastatic disease will be inevitable because of a loss of tumor control.

Recurrent tumor cells are cells that are genetically unstable, grow rapidly, have a short *sojourn time* in the tissue, and show cellular de-differentiation.[28] They have increased metastatic ability. According to the "spectrum model", proposed by Samuel Helman in 1994, 65% of recurrent tumor cells are present for a long time, and if they are recognized early, the final result will be positively affected. Ten percent are systemic from the start and cannot be controlled by scanning. Twenty five percent do not have clinical metastatic potential and do not benefit from follow-up and systemic therapy.[28-30]

When we categorize the biological basis of pelvic recurrence, the following factors emerge:[30,31]

A) Intrapelvic and perineal tumor cell implants;

B) Tumor cell implants in anastomosis;

C) Ovarian tumor metastases;

D) Distal and radial (lateral) positive margins;

E) Lymph node metastasis in residual mesorectum;

F) Lateral pelvic lymph node metastasis;

G) and presence of tumor cells in the lymphatic leakage flowing into the area as a result of surgical trauma.

Complicating Risk Factors

Prognostic and predictive risk factors include large tumors, irradiated bowel, disrupted/unionized anatomical planes, technical difficulties due to tumor compartment disruption, fibrosclerotic ceramicized tissues, complex anatomy, inflexible and non-retractable deep and narrow pelvis, short and schinesic rectal stump, chronic abdominopelvic inflammation or persistent low-grade infection, "medically high-risk patient" who will not have a second chance, previously incomplete (inadequate) surgical attempts, inexperienced surgical team, long-term (more than 15 sessions) CT, poor performance, presence of malnutrition/cachexia/sarcopenia/frailty, and the presence of poorly managed multiple co-morbidities in the patient.[32-34] When we delve further into these critical issues, it emerges that the important factors are the anatomically anterior angulation of the pelvis, non-retractable bone margins, very narrow male pelvis structure (android), the close course of valuable

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

87

vascular, neural and urological structures, their complex relationships and the rich vascular anatomy of the sacrum. Physiopathological factors include the difficulty of reaching the tumor, which is the main target, as a result of the small intestine ridges turning/bending to attach to the pelvic entrance or being fixed by embedding, the ureters to take an ectopic position in the postoperative pelvis, and the union of the the previous intestinal anastomosis or rectal/vaginal stump to the surrounding organs/structures and surfaces without serosa. *En bloc multicompartmental "outline" radical resection* should be performed in order to fully resect this tumor burden and the multiple organs that it has involved, by carefully studying the intrapelvic position and extent of the tumor with a very comprehensive preoperative radiological evaluation.[28-34] Naturally, this oncological technical sensitivity brings with it reconstructive difficulties: difficulties in providing anatomical "fresh" living tissue and the complete lack of available artificial organs. In principle, pelvic cancer surgery has reached a stage that requires complex cancer surgery due to the often advanced disease, instead of a blind surgical technique that goes directly into the tumor from top to bottom.[1-8] *The patient does not need the so-called standard surgeries (because it is not enough!). The patient needs an extended radical surgery suitable for the extraordinary needs of his/her disease, that is an attempt at PE.*[1-7]

Oncological Significance of Pelvic Intracompartmental and Supracompartmental Resection

Visceral morphogenetic units and endopelvic parietal compartments are shown in Figure 1. Radical pelvic surgery is a compartment surgery. Most recurrent rectal tumors involve more than one compartment and often require en-bloc resection of multiple organs in the multiple compartments.[30-36] When we say radically
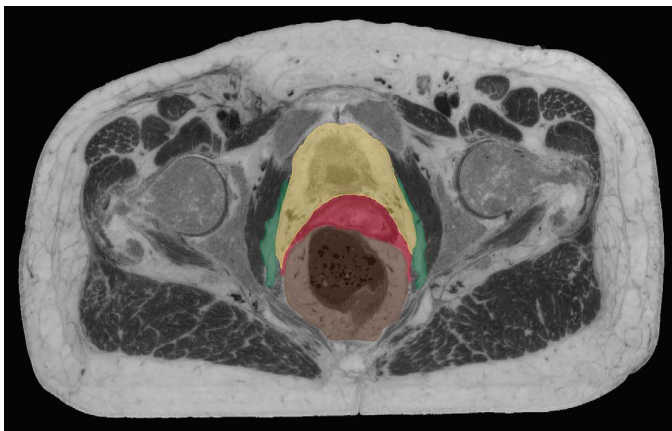

Figure 1. Visceral morphogenetic units (MGU) and endopelvic parietal compartments
Yellow: Urogenital MGU. Red: Mullerian MGU. Brown: rectal MGU, Green: Paravisceral endopelvic compartments

compartmentalized surgery, we must understand that a morphogenetic unit or a segment of it is resected. Pelvic examples of this are TME for rectal cancer and total mesometrial resection for cervical cancer.[30-36] When we say ultra-radical (Extended) compartmentalized surgery, two or three morphogenetic units are resected en bloc. According to this oncological principle, exenterative surgery is performed by multi-mesovisceral excision and dissection along the rectum, genital tract, bladder, hind intestine, and Müllerian and urogenital morphogenetic sections. The resection of the visceral morphogenetic sections can be extended laterally to include the *lateral endopelvic parietal compartments (LEER)*[37], endopelvic fascia and pelvic floor muscles. These definitions have been developed using the concept of the embryological compartment. It is well known that the compartment containing the tumor, whether it is rectal or gynecological, can hide residual tumor cells thus allowing local spread of cancer. In there, tumor cells spread by "following the embryological developmental steps of the tumor as if in a hereditary memory fraternity" (Höckel[37]) and by benefiting from trauma and inflammation. Detection of unusual spread to different pelvic lymph nodes is also due to inadequate resection of the tumor in the presence of advanced tumor progression of these pelvic visceroparietal compartments. *Therefore, in locally advanced or locally very advanced primary and recurrent rectal cancers or other pelvic cancers, the oncological colorectal surgeon should always predict and plan the surgery accordingly, taking account of radial progressive tumor permeation (involvement of the extra-radial margin) that threatens the functional anatomy.*

Local Recurrence Classification

Many different centers have proposed classification systems for LRRC according to the anatomical location of the recurrence in the pelvis.[4-12] Most of these classifications bring together important technical points in exenterative surgery. Classification first identifies the anatomical connection between the tumor and the adjacent organ, then expresses the relationship of the tumor with neurovascular and bone structures in the periphery of the pelvis. These factors determine the technical difficulty of performing R0 resection and the complexity of the surgery. These classifications also determine the functional outcomes for the patient and the required reconstructions (urinary, vascular, orthopedic and plastic repair of the perineal defect). Posterior and lateral compartment resections, which were associated with poor oncologic outcomes in the past, could now be performed with better results in prominent experienced centers. Posterior recurrences can infiltrate the presacral fascia, sacrum and its nerve roots, and require radical sacrectomy for oncologic clearance. Lateral compartment recurrences

88

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

appear as isolated iliac nodal recurrences or as infiltrative tumor recurrences, that start from the center and attack neurovascular structures in the pelvic side-wall. Anteriorly located recurrences may even erode the urological organs, leading to malignant fistulas and encavitation. Especially after abdominoperineal resection (APR), it can lead to devastating catastrophic fistulizations for the patient from the closed perineal space, tumor shedding with tumor necrosis, and deep pelvic sepsis (Figure 2). Since different types of recurrences require different exenterations, there is no universally accepted terminology yet. In general, upper pelvic recurrences that are centrally located, involve at most two organs, are fixed to a single point and do not show lateral wall infiltration are more suitable for complete resection. On the other hand, recurrences that are fixed in many areas, obliterate the natural spaces, infiltrate the side-walls, or have vascular/neural invasion have a poor prognosis. *In summary, it determines the pelvic tumor burden and location. However, no classification truly reflects the possible diversity of exenteration processes because the magnitude of the surgical procedure for each patient is different.*

Terms to Describe PE

At our center we use the "Magrina Classification" for total PE (TPE).[38,39] TPE is an en-bloc resection of the internal reproductive organs, bladder, and rectosigmoid. In superiorly located tumoral lesions, adequate tumor resection can be performed by resecting the viscera above or at the level of the levator muscles (supralevatoric TPE). In this procedure, the levator muscle, anus and urogenital diagram are preserved. In very low-lying malignant lesions, we perform "Infralevatoric" TPE, in which the levator muscles, urogenital diagram, anus and perineal soft tissues are carefully resected. Additional tissues (small intestine, vein, bone) are resected in "Extended" TPE procedure.

Figure 2. Malignant entero-vesico-perineal fistulization caused by recurrent disease after abdominoperineal resection
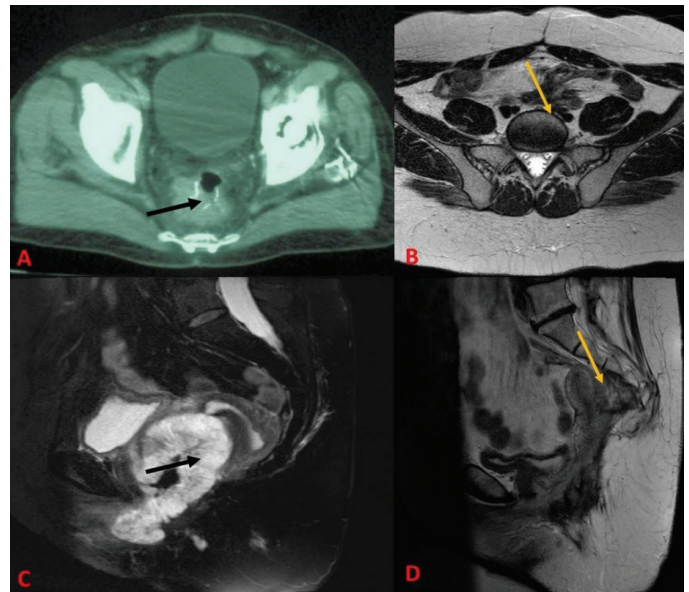

Figure 3. (A) Peri-anastomotic recurrence, (B) Recurrence around the iliac vessels and ureter, (C) Large vaginal recurrence (D) Recurrent mass invading the distal sacrum and uterus

Apart from the definition of LEER[37] and ElSiE[40], we also make use of the classification used by the team of Georgiou et al.[36,41]. In other words, TPE can be expanded to the posterior compartment, with the addition of the coccyx, presacral fascia, partial or total sacrectomy, or to the lateral compartment by expanding to include the external and/or internal iliac vessels. Wide resection can be performed by including the lateral pelvic lymph nodes, sciatic nerve, S1-S2 nerve roots, priformis, and obturator internus muscle[42-46].

The Management of the Patient with Recurrent Rectal Cancer

PE in all its forms are applied at a rate of 70-80% for pelvic cancer other than colorectal cancer (most commonly cervical cancer). It can be performed in approximately 20% of cases of recurrent rectosigmoid cancer and patient management can be examined in three stages. These are: stage 1, diagnosis, evaluation and preoperative staging of the disease (studies of diameter, location, extent and metastatic burden of the disease); stage 2, preoperative chemoradiotherapy (CRT) in suitable candidates; and stage 3, surgical approach to local pelvic recurrence (Table 1-3).

Stage 1

Overall Assessment and Staging[36,41,42,46]

The surgical point to be reached is a complete resection with a negative margin, if technically possible. Patients who are too physically or psychologically debilitated to undergo curative radical resection, or patients with ASA IV-V are not suitable candidates. We can only recommend combined treatments for candidates whose motivation, realistic expectations and

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

89

Table 1. Stage 1 in the management of LRRC

General assessment and risk identification
Healthy, good performance (ASA I-III)
Nutritional prognostic index
Glasgow prognostic index
Charlston co-morbidity index
Initial staging: exclusion of contraindications
Prove local disease (Bx > tissue evidence)
Determine resectability (advanced radiological examination)
- Clinical rectal and vaginal touch
- Systemic and abdominal examination
- Imaging
Conventional CT (spiral CT when necessary)
MRI
ERUS
PET-CT

LRRC: Locally recurrent rectal cancer, ASA: American Society of Anaesthesiologists, CT: Chemotherapy, MRI: Magnetic resonance imaging, PET/CT: Positron emission tomography/computed tomography

Table 2. Stage 2 in the management of LRRC

Preoperative treatment
If the patient has not received RT before > CT-RT should be given
If limited RT has been given before > modified regimen is given
If the patient has previously received a full dose of RT > no additional RT is given, CT can probably be given
Restaging is required to exclude distant metastases in the interval period.

LRRC: Locally recurrent rectal cancer, CT: Chemotherapy, RT: Radiotherapy

emotional status are suitable and who receive family support. Patients should have an open mind to understand short- and long-term risks and functional limitations. Despite all efforts, they should display a compatible mental structure that accepts the possibility of postoperative complications or disease recurrence. Table 1 lists the imaging methods we use to understand the location, extent and extrapelvic extension of the local disease. In addition to these, a full body examination, rectal and bimanual recto-vaginal palpation are required. In addition to the evaluation of extraluminal recurrence, of course, intraluminal recurrence should be investigated by using colonoscopy. Since pelvic recurrence is often extraluminal, magnetic resonance imaging [magnetic resonance imaging (MRI); Figure 3A-D] provides

the most important information to reveal the relationship of the main tumor mass with vessels, bones, nerves, muscles and soft tissue at in terms of adhesion, abutment, invasion and infiltration. Positron emission tomography/computed tomography (PET/CT; Figure 4), on the other hand, provides an understanding of the extrapelvic disease at different levels (pluri-metastatic disease) together with conventional CT. The task of distinguishing between benign fibrosis and recurrent rectal cancer remains a challenging one. The distinction between post-RT inflammation and recurrent disease can be attempted by multiple biopsies. Endo-anal ultrasonography (USG) and/or transvaginal USG guided biopsies may be helpful. A comprehensive radiological discussion is beyond the scope of this section.

Multidisciplinary Tumor Board for Colorectal and Pelvic Malignancy

Patient selection and treatment planning should be performed by a multidisciplinary team, dedicated to colorectal and pelvic surgical oncology. Over the years, it has been shown that multidisciplinary meetings, consisting of special units that include different disciplines and offer different oncological views, improve patient outcomes. The role of these councils is to make the correct patient selection. It is always the duty of this council to reduce the number of non-curative (R2) resections and "open-close" laparotomies, thus protecting the patient from unnecessary morbidity and preventing the implementation of palliative treatments from being delayed. Interdisciplinary communication is maintained in the perioperative period, and the problems that may arise should be tackled. In the busy working environment, patients who have been reviewed and discussed in the council are not left unattended at critical decision stages and responsibility is shared. The council determines the selection and succession of the right treatment method with the most up-to-date information.

To Determine Resectability

Resectability varies depending on the anatomical structures in which the recurrent tumor mass is attached/fixed to the intrapelvic location. What is resectable in LRRC varies widely between surgeons and centers, and the technical skill process is still evolving. Due to anatomical and technical limitations, many units have reported absolute and relative contraindications for curative surgery. With the development of lateral neurovascular surgical techniques and composite bone resection techniques in the last decade, more radical "high and wide" (Sagar[3]) pelvic resections can be performed. In our center, TPE is applied if possible R0 resection is foreseen in selected patients who are medically fit, whose co-morbidities are under control, who understand the treatment process, are willing, and
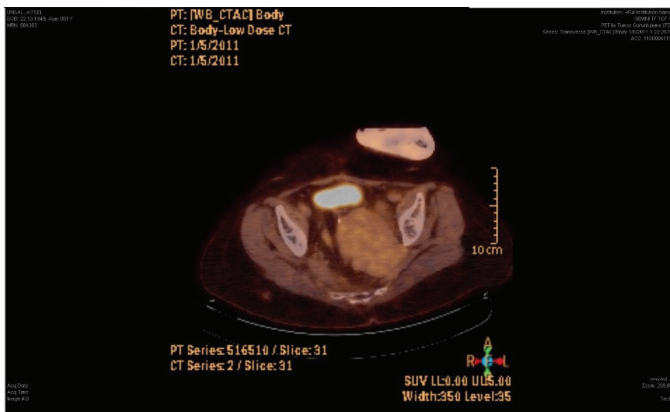
90

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

Figure 4. PET/CT shows left lateral wall invasion of LRRC
PET/CT: Positron emission tomography/computed tomography, LRRC: Locally recurrent rectal cancer

have sufficient performance. Bias-withdrawal towards pelvic sidewall involvement, which is traditionally considered a contraindication, is due to potential catastrophic bleeding and neurological damage. Since 2009 this has been used in certain centers (Mayo, MSCCC, St. Mark's, Sydney and Tokyo) with successful results (R0: 21-53%, final 69%). A small number of specialized centers have accumulated en-bloc resection experience in tumors that go beyond the iliac vessels and surround the sciatic nerve.[40,47] Radical resection of the sciatic notch includes en-bloc resection of the internal iliac vein, pyriformis and obturator internus muscles, along with the sacrospinous ligament, and the ischial spine. This may or may not be accompanied by sacrectomy. Partial or complete sciatic nerve resection can be performed with R0 rates comparable to central recurrences (65%).[47-53] In a recent study involving 64 patients with sciatic nerve resection, 96% of patients were able to walk with ankle-foot orthoses and an assisted mobility device despite complete nerve excision. Physical quality of life returned to preoperative levels after 12 months. When we look at the results of these leading centers, it can be seen that sciatic nerve involvement does not prevent the patient from being a candidate for curative surgery.[52,53] In LRRC in which recurrence extends directly to the posterior compartment, composite sacrectomy is performed to achieve R0 resection. Lower (partial) sacral amputation can be performed without major morbidity. However, the hope of curative surgery is controversial when there is high sacrum involvement above the S2/3 junction. Often this situation is considered inoperable in many centers. Again, in the last ten years, it has been proven in centers that have accumulated experience that high sacrectomy is possible and safe.[54-58] Based on PelvEx data from exenteration units with international cooperation, en-bloc sacrectomy can be performed with an R0 resection, similar to partial sacrectomy.[51-58] However, high sacrectomy is naturally associated with higher blood loss, more complications, and neurological loss. According to these latest data, high sacrectomy is not an absolute contraindication for curative surgery. However, additional morbidity should always be considered and included in the consent. A complete R0 resection with microscopic negative margins is the strongest predictor of survival, as has been shown on numerous occasions in specific studies. It has been reported that many factors affect the possibility of radical resection. Factors assocaited invariably with low success rates include: advanced age; male gender; advanced stage of the primary tumor; high carcinoembryonic antigen concentration; previous APR; extensive pelvic sidewall involvement; sciatic nerve involvement; high sacral involvement; and presence of bilateral hydronephrosis. We have stated that there are classifications for tumor location and extent that guide the patient selection and help guide the surgical technique. *However, at the end of the day, all these classifications cannot fully predict resectability in the preoperative period, not least because new findings detected intraoperatively can change earlier decisions.* Another important issue is the contraindications for surgical resection. It is evident that many issues that were accepted as absolute contraindications previously are now seen as indications for surgery, for example in some studies carried out in recent years such as those from Sydney and St Mark's teams. Therefore, we would like the reader to make an in-depth effort about this complex cancer surgery.

Contraindications Include:

1) Unresectable metastatic-extrapelvic disease or metastatic disease that does not respond to preoperative CT;

2) Sacral root involvement (a relative contraindication);

3) Pelvic sidewall involvement;

4) S1-S2 neural involvement (a relative contraindication as this was performed in Dokuz Eylül University Faculty of Medicine;

5) Patient with high surgical risk (ASA IV-V);

6) The patient who does not have the ability to "recognize and be responsible" for the outcomes that the treatment process may result in. The patient should be able to think clearly and be in control of and responsible for their own actions - "compos mentis").

Stage 2

Preoperative Multimodal Treatment

Curative radical surgery is the mainstay of treatment in locally recurrent cancer. However, on the basis of past surgeries, radical resection is not always possible due to the opportunistic and invasive nature of the tumor throughout the compartments. In order to improve oncological

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

91

outcomes, RT and CT should be used whenever possible (Table 2).

Metastatic Disease

When LRRC is diagnosed, 36-41% of patients have synchronous distant metastases.[51] In patients with unresectable metastatic deposits, local recurrence resection with curative intent is no longer possible. However, if patients with resectable visceral metastases are motivated and good candidates for exhaustive surgery, radical pelvic surgery and metastasectomy are performed. Although each patient is decided on a patient-disease basis, synchronous metastasectomy is generally avoided because radical resection of pelvic recurrence is associated with increased morbidity rates, involves prolonged surgery time and requires a durable team. Of course, naive patients will receive primary RT in the presence of recurrent disease. However, the more common situation is that the role of re-irradiation is controversial in patients who have received high-dose pelvic RT previously.[52,53] There are centers that do not prefer re-irradiation due to increased radiation toxicity concerns and the relative radioresistance of the recurrent tumor. In some centers and also in Dokuz Eylül University Faculty of Medicine, RT can be applied again using hyperfractionated regimens. More studies and evidence are needed concerning this subject.

Stage 3

Surgical Technique and Intraoperative Radiotherapy[6-10]

TPE is a complex set of surgical interventions consisting of heterogeneous surgical procedures. The extent of resection and reconstruction is determined by the anatomical location of the recurrence and the degree of local invasion. While there can never be a uniform, well-defined TPE suitable for every tumor burden/distribution, in general, all types of surgery can be considered in three basic phases:

1. Investigation of the abdomino-pelvic region for metastatic disease;
2. Dissection and resection phase in which the tumor is constantly removed together with the organs it has seized;
3. Reconstruction phase.

Teamwork should be performed with at least two exenteration-trained colorectal surgeons in patient preparation. Furthermore, the patient should be seen by onco-orthopedic, onco-plastic and vascular surgeons. Surgery should be scheduled as the first patient and no other difficult case should be put on the list. The patient is placed in the modified Lloyd-Davis position, supported by gel pads. The lumbar curve is supported by tilting the pelvis forward-upward from the operating table. Positioning

legs, Thompson abdominal wall retraction system and fume extractor aspirator equipment are essential. The right or left arm is closed according to the surgeon's preference. Three illuminated pelvic retractors should be available. A ureteric stent can be placed in selected patients.[59] Adequate erythrocyte suspension (ES) and fresh frozen plasma (FFP) should be provided. If any, the stoma site should be covered with occlusive pad and drape. Planned stoma locations must be marked. If potentially required, the myocutaneous flap donor site (vertical, oblique and transverse rectus abdominus muscles [RAM]) should be carefully marked.[60] If vascular reconstruction is considered, the lower extremity is covered up to the knee to obtain an autologous vein graft. In all other cases, the leg is painted up to the root and covered. Exploration is started with a midline laparotomy, all adhesions are removed and the small intestine is confined to the upper abdomen in the Trendelenburg position. The presence of paraaortic, paracaval, or peritoneal metastatic LAP/deposit is investigated (Figure 5). Presence of metastatic disease (radiologically occult in the preoperative period) and/or cytopositive peritoneal tumor with evidence of frozen section will eliminate the chance of curative intervention, and the team should be aware that TPE will transform into a palliative intervention. However, resectable oligo-metastatic, hepatic and/or peritoneal involvement does not change the chance of curative TPE. The small intestine coil, which is fixed to the pelvic inlet, especially adheres to the tumor, is divided on both sides with a stapler and left on the specimen (Figure 6). The ureters are dissected and suspended at the beginning of the surgery. In the next stage, the ureters are divided from the distal part approaching the tumor, the tip is sent for frozen section examination and it is proven to be tumor-free. Then, a thin oxygen catheter is placed and the urine output is collected. If intestinal continuity is planned, the left colon is mobilized and divided proximal to the recurrent tumor, confined to the upper abdomen for the neorectum. Knowing the fixed pelvic anatomical landmarks, the surgeon creates and maintains pelvic "situational awareness" (Nelson H.) for themselves throughout the surgery. The iliac vascular compartment elements are suspended. Without ligating and dividing the internal iliac artery, the external iliac artery does not relax (floating), and the internal and external iliac veins cannot be reached. The internal iliac artery is ligated after giving the superior gluteal artery if the gluteal flap is to be used for perineal defect reconstruction. The anterior branch of the internal iliac artery is followed. Pararectal and paravesical spaces are revealed. The ureter is followed in the Okabayashi space, and each organ anterior to the ureter is easily dissected. At this point, the surgical team should remember the "Catch-22 phenomenon": this concept
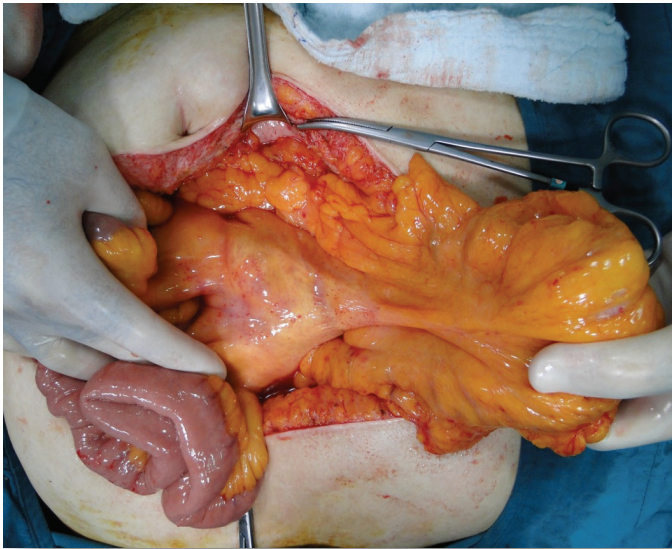
92

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

Figure 5. Clustered mesenteric metastatic lymph nodes

should be paid attention to in order not to pass the "point of no return" and not harm the patient. A Catch 22 is a situation in which you cannot do a second thing until you have done a first thing, but you cannot do the first thing until the second thing has been performed - a Catch 22. This concept can be very difficult for the surgeon because of anatomical limitations in complex, multi-visceral, multi-compartmental, intrapelvic resections, encountering huge tumors, fibrosclerotic brazed plans, and party time of bacteria (opening the organ cavity). After these stages are completed, the course of the intervention is divided into complex technical pathways, including central recurrence, posterior recurrence, anterior-dominant recurrence or vascular-sacral-neurovascular resection originating from lateral dominant recurrence (Figure 7A-D).[2-12] In other words, the location of the recurrence naturally guides the surgical techniques to be performed, for example, sacrectomy, pubic bone resection,[61] lateral extended pelvic wall resection, and lateral iliac vessel or nerve resection. At this point, the authors recommend that the reader examine the relevant specific sources in depth.[2-14,52,53]

Reconstruction

The reconstruction elements will also vary, depending on how much dissection and which structures are to be resected in order to achieve a complete oncological clearance. If a portion of the vessel is removed from the iliac vein, vascular repair is performed with a veil, or if a complete vessel resection is performed, vessel reconstruction is performed with an interposition graft.[62] Vascular reconstruction should be done immediately. Distal ureterectomy or partial cystectomy often requires uretero-neocystomy with the Boari flap technique.[2-11] Total cystectomy, on the other hand, often requires ileal or urinary reconstruction with
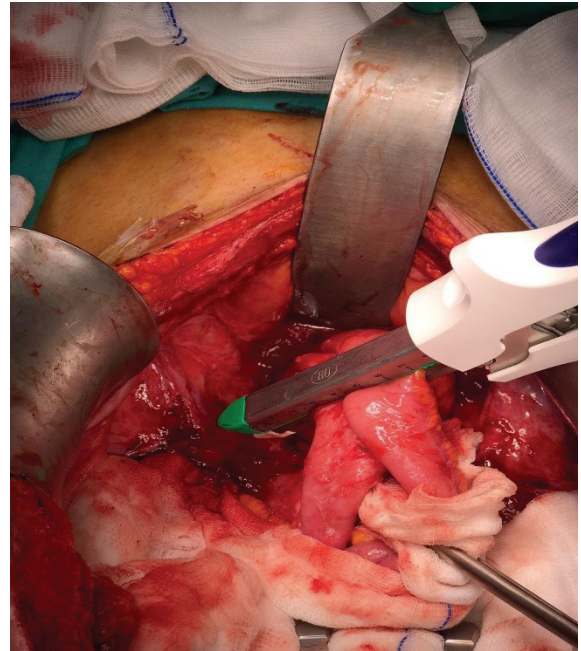

Figure 6. Small intestinal loop fixed to LRRC and obscuring the pelvic inlet, recurrent mass is left on by following the oncological principle of an block resection
LRRC: Locally recurrent rectal cancer

colonic conduit, especially if the patient has a short life expectancy.[63] We perform uretero-enteric anastomoses over a thin feeding catheter. If we have performed abdomino-sacral resection, we complete the urinary reconstruction in the supine position. Small bowel anastomosis is performed after ileal conduit. Urostomy and colostomy are matured. If the abdominal wall is not depleted of stomata, we perform perineal defect closure with a type of RAM flap or, if it is depleted, with a gluteus maximus flap, in the prone position (flip-flap).[64,65]

Intraoperative Radiotherapy

After the recurrent tumor mass is resected, frozen section samples are sent from the suspected surgical margins. At this point, if the center is able, the patient is transferred to the intraoperative radiotherapy (IORT) unit and treated for selective margin involvement (R1), as the tumor is almost invariably locally extensive beyond physical and radiological examination. On the other hand, the major limitation of pelvic external RT is that the dose required to achieve local tumor control exceeds the tolerance of the surrounding healthy tissue. The most promising approach to overcome this limitation is IORT. Although the oncological benefit obtained in various studies has been reported to tend towards the positive, the dearth of effective prospective randomized studies and the high-cost infrastructure setup have affected the widespread use of IORT. Moreover, IORT carries risks of complications; the most common are peripheral neuropathy, ureteral stenosis, and osteonecrosis.[6-12]

Sökmen et al.
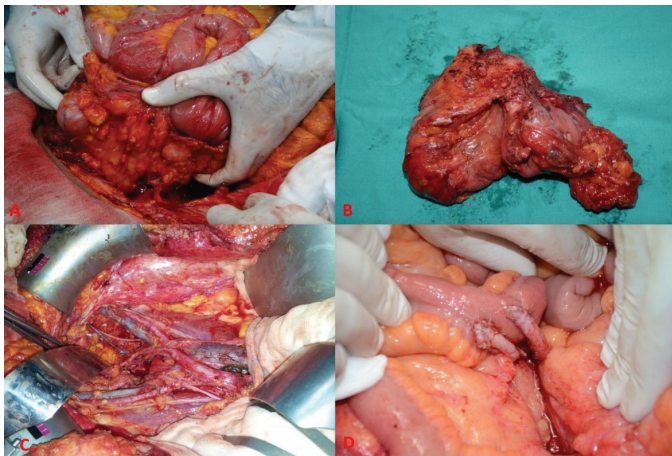Surgical Nuances of Pelvic Exenteration

93

Figure 7. (A) Giant tumoral mass, (B) TPE resection material, (C) Intrapelvic multiorgan resection (D) Ureteric reimplantation to ileal conduit
TPE: Total pelvic exenteration

Palliative TPE: to Whom and When?

We would like to highlight three important points:

1. Surgeons learn to operate over time. This is even more valid when considering difficult and complex surgeries;

2. We physicians make decisions based on the best available evidence, knowledge and experience, and patients experience the results;

3. It has been shown repeatedly that there is a primary T4 advanced or recurrent colorectal cancer type that does not metastasize but remains locally invasive for a long time, which, despite its expansile and infiltrative growth, surprisingly cannot metastasize.

However, tumor necrosis as a result of CRT, causes serious symptoms which seriously impair patient quality of life, including severe pain, tumor fragmentation, malignant fistulas, urine-stool coming from the vagina, tumor shedding with foul-smelling discharge, and loss of soft tissue that is digested with intestinal contents and infected. In the evaluation of the patient, there is no obvious distant organ metastasis or it has a low volume and responds to CT. Although palliative TPE is a major, complicated and risky intervention in such candidate patients, it has been increasingly recommended by experienced centers in recent years, since it is an intervention that controls symptoms, improves quality of life, and ensures the continuation of systemic CT.[66-68] Although it is very controversial, palliative TPE can be applied if these issues are handled very carefully and the patient is selected and comprehensive consent is obtained. *However, it should not be forgotten that the oncological gain of palliative surgery cannot be measured, and the expectations of the patient's relatives will almost always exceed what the surgical team can give.* A major complicated operation should never be offered as a salvage or curative
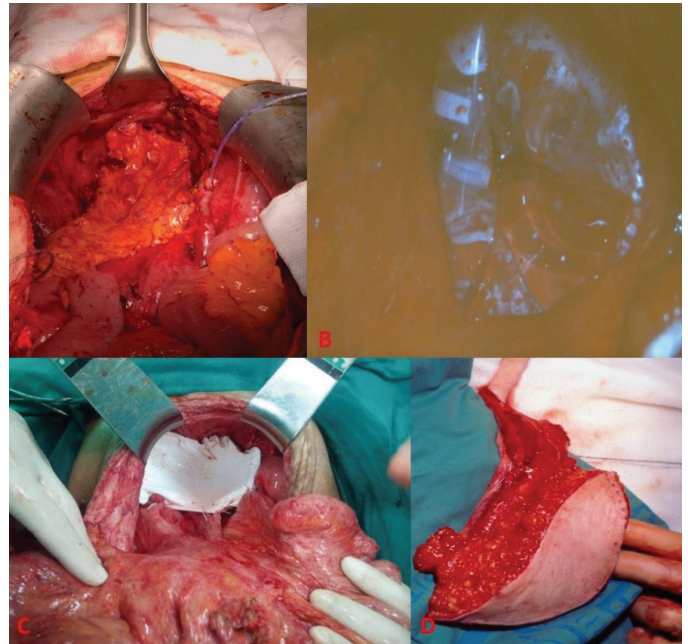

Figure 8. (A) Omental J-flap with pelvic partition (hammock), (B) Hammock with breast prosthesis, (C) Hammock with synthetic biomaterial (D) Rectus abdominus flap
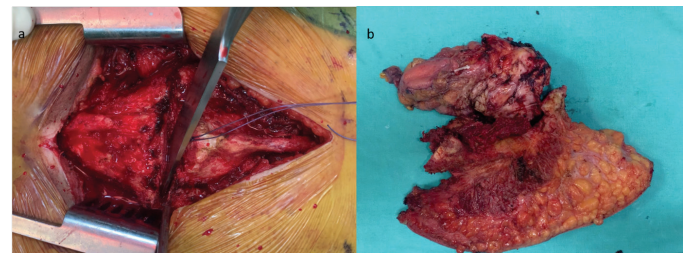

Figure 9. In a patient with irradiated LRRC for the second time invading the sacrum bone, (a) the sacrum is divided by an osteotome between the sacral 3 and 4 foramen, (b) the distal sacrum 4-5 and the coccyx are resected en-block together with the bladder and recurrent rectal mass.
LRRC: Locally recurrent rectal cancer

method to an exhausted, debilitated, cachectic, sarcopenic and terminally ill patient. Palliative support care should be given to patients with medical problems and low performance who cannot tolerate the risks of surgery, while the effort of the surgical team and hospital resources should be used in a way that does not harm the patient.[66-68]

Morbidity-Mortality and Oncological Outcomes[6-12]

One third of the patients who have undergone an exenterative intervention live for 5 years. Recurrence is observed in one third (re-resection is performed if possible in selected patients) and a third die from disseminated metastatic disease. In a study conducted by the PelvEx colloborative group including 1,184 patients, the rate of major postoperative complications was reported to be 32%, the mean hospital stay was 15 days, and the surgical re-exploration rate was 10%. Complications are mainly

94

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

related to four areas: cardiopulmonary; infectious (pelvic sepsis); intestinal obstruction; and fistula development. The most common systemic complications are SIRS/sepsis, disseminated intravascular coaggulation, pulmonary embolism and acute respiratory distress syndrome. Re-operation of these complications has a high mortality. All efforts should therefore be made to prevent them during exenteration. The R0 resection rate was reported to be 55% in the PelvEx study and 58% in the current analysis by Platt et al.[57]. We must repeat: the most important predictor for survival is R0 resection. In a recent study involving 210 patients, it was shown that even the millimetric width of the margin positivity negatively affected local recurrence and survival rates.[51] Recurrent disease develops in 55% of patients after salvage surgery for LRRC. Of these 14-21% are isolated local recurrences. Rescue surgery can be attempted a second time in appropriate patients,[69] but often patients fail systemically and die from distant metastasis.[51] In very experienced centers, the mortality rate is 0.6-4% (the rate reported in the past was 7-22%).[52,53]

Combined Application of TPE, Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Cytoreductive surgery (SRC) and Hyperthermic Intraperitoneal Chemotherapy (HIPEC) are curative treatments for selected patients with peritoneal carcinomatosis. PE is a treatment option for locally advanced pelvic cancers. Due to the high-risk of complications arising from each oncological procedure, most researchers do not recommend applying SRC + HIPEC together with TPE. However, TPE + SRC + HIPEC, which has been tried in selected patients in highly experienced centers, is an ultra-radical intervention, and it is known that there are centers that attempt this marathon.[70,71] The presence of pelvic peritoneal/multiorgan involvement in a suitable-indicated patient for SRC and HIPEC should not be considered as a definitive contraindication if an R0 resection is targeted.[71] Of course, there is a need to evaluate the oncological benefit and increased morbidity-mortality rates with a longer follow-up and to investigate how the quality of life is affected.[71]

The Experience of the Medical Faculty of Dokuz Eylül University

As the Dokuz Eylül University Faculty of Medicine Colorectal Team, we would like to describe our total PE experience. We performed TPE in 29 patients with clear indications for various pathologies, 17 (58.6%) had rectal cancer, 6 (20.7%) had cervical cancer and 6 (20.7%) had other different diagnoses. Of the 17 rectal cancer patients in whom we performed TPE, 5 (29.4%) had locally advanced rectal cancer and the remaining 12 (70.6%) had recurrent rectal cancer. Of these patients, 14 (82.35%) received neoadjuvant chemo-RT, and 5 (29.4%) underwent TPE after

Table 3. Stage 3 in the management of LRRC

Surgical resection
Abdominopelvic introspection
Rule out severe-metastatic disease (preop. undetected)
Identify anatomical fixed points (promontory, sacrum, iliac bifurcation, bladder)
Surgical margins: Plural? Nearest border?
What about adjacent structures: iliac vascular structures, ureter, obturator nerve, sciatic notch, sacrum, bladder, and vagina?
Disection, mobilization, resection, stoma or anastomosis
Extended radical resection when needed (interdisciplinary teamwork)
Exenteration (anterior, posterior, total)
Extended TPE (for example, sacrectomy and/or lateral sidewall resection)
Frozen section sampling from borders
IORT if needed/possible
Reconstruction[72-75]
Vascular repair
Ileal conduit
Omental J-flap (Figure 8A) or if the omentum has been depleted, right colon pelvic hammock, breast prosthesis (Figure 8B), or hammock (pelvic partition) with synthetic biomaterial (Figure 8C)
A type of rectus abdominus flap (Figure 8D)
Gluteal muscle flap if the anterior abdominal wall is depleted by stomata

LRRC: Locally recurrent rectal cancer

receiving RT for the second time after recurrence. Again, 5 (29.4%) of these 17 patients had peritoneal carcinomatosis, and we performed a pelvic exenterative procedure. Eleven (64.7%) of our patients were male and 6 were female. The mean age was 49.7 years (22-76 years). The mean ± standard deviation operative time was 521.7±250.6 minutes. Sacrum resection (Figure 9A, B) was performed in 4 of 17 patients, 4 of them underwent sacrum 4-5 resection (partial) and 1 patient underwent total sacrectomy. Postoperative perineal reconstruction was achieved with primary closure in 11 (64.7%), gluteal rotation flap in 4 (23.5%), vertical rectus abdominus myocutaneous flap in one (5.9%), and a prosthetic patch in one (5.9%). Morbidity/mortality developed in 10 (58.8%) patients in the postoperative period; Clavien-Dindo (C/D) grade I-II morbidity in 1 (5.9%) patient, C/D grade III-IV morbidity in 8 (47.1%) patients, and perioperative mortality in 1 (5.9%) patient. In the postoperative period, 8 (47.1%) developed infection. Local recurrence in 3 (17.6%) of our patients who underwent TPE for rectal cancer, extensive intra-abdominal disease in 4 (23.5%), and distant

Sökmen et al.
Surgical Nuances of Pelvic Exenteration

95

metastasis in 1 (5.9%) patient developed. The mean follow-up period of our patients was 12.4 months (27 days-34.5 months). One- and two-year overall survival times were 53.2% and 21.5%, respectively.

Horizon

The treatment of LRRC has changed radically in the last two decades. With a multidisciplinary approach, each patient management strategy is discussed and extended radical resection becomes the standard treatment. The surgical philosophy of PE can be summarized as follows:

- It is the most radical surgical option against pelvic cancer. Basically, all pelvic organs are removed.

- The goal of exenterative surgery is always tumor resection with negative surgical margins.

- Applying PE in limited forms may protect the organs that are not involved, but the cost is an increased risk of recurrence.

- The more advanced the primary rectal cancer is, the more likely it is to fail central therapy.

- The patient and his/her relatives should be informed about all the risks, losses and gains of this complex and intensive surgery.

- The patient should confirm that he/she understands and accepts all possible consequences.

- An equally curative form of treatment for intrapelvic destructive recurrent disease is not yet available.

- TPE can provide a significant recovery rate in patients with LRRC.

- In patients with limited response rates and limited duration of action and in whom CT resistance develops, PE should be considered in every case in order to clear the recurrent malignancy.

- TPE and extended TPE are very stressful operations for both the patient and the surgeon. Both need to be very resilient and selfless.

- A stereotypical, template-like and smooth exenterative surgical technique is not possible.

- Unanswered issues include whether to perform concomitant PE-metastasectomy, repeat pelvic RT, high rates of systemic failure despite adjuvant CT, and whether better functional outcomes can be achieved.

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Surgical and Medical Practices: S.S., B.M., T.B., Concept: S.S., B.M., T.B., Design: S.S., B.M., T.B., Data Collection or Processing: S.S., B.M., T.B., Analysis or Interpretation: S.S., B.M., T.B., Literature Search: S.S., B.M., T.B., Writing: S.S., B.M., T.B.

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96

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97

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