

# Locally advanced rectal cancer: management challenges

RF Kokelaar  
MD Evans  
M Davies  
DA Harris  
J Beynon

Department of Colorectal Surgery,  
Singleton Hospital, Swansea, UK

**Abstract:** Between 5% and 10% of patients with rectal cancer present with locally advanced rectal cancer (LARC), and 10% of rectal cancers recur after surgery, of which half are limited to locoregional disease only (locally recurrent rectal cancer). Exenterative surgery offers the best long-term outcomes for patients with LARC and locally recurrent rectal cancer so long as a complete (R0) resection is achieved. Accurate preoperative multimodal staging is crucial in assessing the potential operability of advanced rectal tumors, and resectability may be enhanced with neoadjuvant therapies. Unfortunately, surgical options are limited when the tumor involves the lateral pelvic sidewall or high sacrum due to the technical challenges of achieving histological clearance, and must be balanced against the high morbidity associated with resection of the bony pelvis and significant lymphovascular structures. This group of patients is usually treated palliatively and subsequently survival is poor, which has led surgeons to seek innovative new solutions, as well as revisit previously discarded radical approaches. A small number of centers are pioneering new techniques for resection of beyond-total mesorectal excision tumors, including en bloc resections of the sciatic notch and composite resections of the first two sacral vertebrae. Despite limited experience, these new techniques offer the potential for radical treatment of previously inoperable tumors. This narrative review sets out the challenges facing the management of LARCs and discusses evolving management options.

**Keywords:** rectal cancer, exenteration, pelvic sidewall, sacrectomy

## Introduction

In the UK, 14,000 new cases of rectal cancer are diagnosed every year, and 40,000 in the US, of which between 5% and 10% are locally invasive (T4) at presentation.<sup>1,2</sup> Tumors extending beyond the total mesorectal excision (TME) plane may be suitable for a multivisceral approach if a complete (R0) resection is achievable.<sup>3-5</sup> An R0 resection is the single greatest predictor of outcome after surgery for rectal cancer, and any surgery must be undertaken with the intention of achieving histologically clear resection margins.<sup>4-7</sup> Unfortunately, despite optimal surgery and adjuvant therapies, 10% of patients experience a local recurrence, of which approximately half will have a locoregional disease only.<sup>8</sup>

The surgical management of locally advanced (LARC) and locally recurrent rectal cancers (LRRC) has developed since Brunschwig first described pelvic exenteration for cervical cancer in 1948.<sup>9</sup> Currently, the 5-year survival rate for LARC is between 52% and 65%,<sup>10,11</sup> but is significantly lower in LRRC where 5-year survival is between 35% and 50%.<sup>12,13</sup> Survival for both LARC and LRRC is still worse if the tumor is not centrally located in the pelvis, especially if it extends to the pelvic sidewall or high sacrum where it is usually deemed inoperable.<sup>14</sup>

Correspondence: RF Kokelaar  
Department of Colorectal Surgery,  
Singleton Hospital, Sketty Lane, Sketty,  
Swansea SA2 8QA, UK  
Tel +44 1792 285030  
Email rory.kokelaar@wales.nhs.uk

These poor outcomes have led surgeons to seek novel approaches to anatomically unfavorable tumors and revisit previously discounted operations for highly selected patients.<sup>15–18</sup> Currently, a number of pioneering procedures are being developed in specialist centers around the world, although their utilization is limited to a very small number of highly specialized units.

## Aim

The aim of this review was to consider the current surgical approaches to anatomically unfavorable primary and recurrent rectal tumors beyond-TME margins, with a particular emphasis on emerging surgical techniques in this field.

## The current approach to beyond-TME tumors

### The MDT

The management of cancer has developed significantly since the Calman-Hine Framework was established in 1995, advocating a site-specific multidisciplinary team (MDT) organization of care involving a broad range of clinical specialties and support services.<sup>19</sup> This principle has been further extended in the management of advanced pelvic malignancies to include specialists across an even wider spectrum where individual expertise may be required on a case-by-case basis for multivisceral or radical resections. The recent international consensus statement on the management of rectal cancers beyond-TME recommends that all LARC and LRRC should be managed in a super-specialized MDT.<sup>1</sup> In the spirit of this extended framework, our own unit established the Swansea Pelvic Oncology Group in 1999, bringing together colorectal surgeons and oncologists with colleagues in urology, gynaecology, plastic-reconstructive, and orthopedic surgery, a practice now well established in most centers dealing with complex cases.<sup>20</sup> The foundation of super-specialist centers allows for the development of expertise in managing what are, within the normal practices of an MDT, uncommon cases, with the aim of developing a high-volume and high-quality service.

### Staging

The ultimate goal of exenterative surgery is to achieve a R0 resection. In node-negative patients with locally advanced disease in whom clear margins are achieved we have reported a 53% 5-year survival rate.<sup>20</sup> This surgery should only routinely be undertaken where the intent is to achieve a histologically clear resection, as there is no survival advantage following an R1 resection (microscopic margin involvement) or palliative

“debulking” procedures compared to no surgery.<sup>21,22</sup> It is, however, appreciated that there will always be a small number of patients who are better palliated with resection. To this end, accurate multimodal preoperative staging (magnetic resonance imaging [MRI]/computed tomography [CT]/endorectal ultrasound scan [ERUS]) is imperative, combined with experienced clinical assessment of the tumor under anesthetic or in the clinic.<sup>23–25</sup> The detection of LRRC by radiology alone may be challenging in the postsurgical postradiotherapy pelvis, and thus serial imaging and judicious use of [<sup>18</sup>F] fluorodeoxyglucose positron-emission tomography-CT may be advantageous, although further evidence is required for routine implementation.<sup>26</sup> Histologically confirmed recurrence should be sought as the gold standard of diagnosis in LRRC, particularly as the patients may be subjected to extensive ablative procedures, which carry significant morbidity if not potential mortality.

### Chemoradiotherapy

In order to achieve a R0 resection, neoadjuvant therapy may be employed where margins are threatened. Neoadjuvant long-course chemoradiotherapy (CRT) (45–50.4 Gy plus augmented 5-fluorouracil regimens according to local guidelines) has been demonstrated to improve the operability of previously inoperable LARC and reduce local recurrence rates.<sup>27–29</sup> A number of additional techniques in boosting pre-operative radiotherapy dose have been trialed, including high-dose-rate endorectal brachytherapy (HDREBT) and intraoperative radiotherapy (IORT).<sup>30,31</sup> Despite HDREBT showing promising results in down-staging T2/3 rectal tumors prior to surgery, there is a paucity of evidence to support its implementation in beyond-TME tumors.<sup>32,33</sup> A recent review indicates that local disease control, disease-free, and overall survival may be improved with IORT in LARC and LRRC, although wound complications were higher.<sup>34</sup> This review does, however, acknowledge the heterogeneity of the studies included and does not assert recommendations for the implementation of IORT nor does it address the specific challenges of beyond-TME tumors. The role of neoadjuvant radiotherapy in the context of new chemotherapy regimens has however been challenged and is being examined further in the ongoing PROSPECT trial, which is investigating the efficacy of neoadjuvant chemotherapy alone in patients with cT2N1 or cT3N0-1 tumors who are eligible for sphincter sparing TME.<sup>35,36</sup> The benefits of preserving oncological outcomes while avoiding radiotherapy-related local toxicity and the associated side effects would be significant both to the patient and surgeon

operating in a radiation-naïve field; however, the outcomes from this study will offer little evidence to support the management of beyond-TME tumors as this group is excluded from the study. Radiotherapy for LRRC in the radiation-naïve pelvis is, however, recommended prior to surgery, although its implementation in a previously irradiated field remains controversial and lacking in evidence.<sup>37</sup> Adjuvant CRT may be indicated where circumferential margins are involved, in node-positive disease, or where extramural vascular invasion is demonstrated.

### Exenteration and reconstruction

The choice of surgery depends on the site of the tumor and structures into which it is invading. There is currently no consensus in terminology for pelvic multivisceral surgery for primary tumors as most classification systems were developed for recurrent tumors, although the principles are broadly transferrable. In our unit, we advocate the classification of locally advanced tumor extension as anterior, posterior, lateral sidewall, or composite, in keeping with previous systems and the practice of other UK units.<sup>4</sup> Standard multivisceral resections for LARC and LRRC may be considered as either total pelvic exenteration or posterior pelvic clearance, depending on the patient's gender, previous surgery, and extent of invasion into the pelvic organs and sacrum.<sup>38,39</sup> To ensure an R0 resection, significant reconstruction of viscera and soft tissues may be required following radical resection, including bladder reconstruction/formation of ileal conduit and reconstruction of the perineal defect. Local rotational and pedicled myocutaneous flaps are particularly useful in reconstructing the perineum and filling the dead-space in the exenterated pelvis, but should only be undertaken by experienced teams.<sup>40-42</sup> Currently, there is limited experience of vaginal/external genital reconstruction in the context of rectal cancers, but where indicated should be performed using myocutaneous flaps as these offer reduced morbidity.<sup>43</sup>

### Patient selection

The technical feasibility of operating on LARC and LRRC must be tempered against the physiological burden of lengthy (often up to 12 hours if extensive reconstruction is necessary) and challenging operations.<sup>4</sup> Patients with inoperable metastatic disease or who are physiologically unfit (American Society of Anesthesiologists [ASA] score IV/V) are clearly not suitable for this arduous surgery. Assessing a patient's fitness for surgery is best undertaken by an anesthetist who has experience of working within the pelvic oncology MDT and who is able to assess the relevance of preexisting

cardiopulmonary disease. The role of objective physiological testing in managing patients with advanced pelvic malignancies is under review, but cardio-pulmonary exercise testing may be valuable where judgments are equivocal, especially in the elderly patient.<sup>44,45</sup> The attitude of the patients prior to their disease process and the ablative surgery that they will be subjected to cannot be ignored. It is imperative that they have a positive mental attitude and the will to survive.

### Current limitations

Despite the advances in multivisceral surgery for LARC and LRRC, there are some anatomical considerations that are either relative or absolute contraindications to surgery and a curative approach to management.<sup>1</sup> The relative factors that determine potential operability are: extension of the tumor through the sciatic notch, involvement of the iliac vessels that would necessitate vascular reconstruction, and involvement of the sacrum above the S2/3 junction. When involved by tumor, it is deemed that these anatomical challenges either make an R0 resection technically unachievable or carry so much morbidity that surgery would not be in the patient's best interests. Bilateral sciatic nerve involvement and circumferential bone involvement remain absolute contraindications to surgery.

Survival in this group of patients is abysmal and most patients are best managed palliatively, and so developing novel techniques to improve the potential operability of these anatomically unfavorable tumors beyond-TME, or revisiting previously discarded operations, may be the only other options. Undertaking operations on such cases require careful consideration on a patient-by-patient basis, and surgery should only be attempted where an R0 resection can reasonably be expected. Currently, there are only a handful of MDTs worldwide with the expertise to attempt such surgery, although there is growing evidence that solutions may be forthcoming.

### New avenues

Considering the prerequisite of an R0 resection, the surgical approach to excision of pelvic sidewall tumors may involve the iliac vessels, sciatic nerve, and bony pelvis, or combinations thereof. Patients with LRRC invading the lateral sidewall have significantly poorer survival compared to local recurrence at other sites, reported at 5%–7% at 5 years with palliative or no treatment.<sup>46,47</sup> This poor prognosis has led to a growing interest in revisiting more radical surgical options for sidewall tumors as well as novel techniques being sought.

### Previously discarded operations

Outside of the practice of colorectal surgery, pelvic sarcoma surgery (bony and soft tissue), where there is involvement of the sciatic nerve or iliac vessels, has traditionally employed external hemipelvectomy (EHP) or hindquarter amputation.<sup>48,49</sup> These mutilating operations have traditionally had a high level of associated morbidity, although rehabilitation and reconstructive advances have improved outcomes considerably.<sup>50</sup> Oncological outcomes are mixed due to the diversity of tumors these procedures are employed to treat, but some series have yielded mobilization rates of 85% following EHP in highly selected patients.<sup>51</sup> One small series of eight female patients undergoing EHP for LRRC or primary rectal cancer involving the lumbosacral nerves demonstrated a 75% R0 resection rate and 62% 5-year survival, with acceptable morbidity and 50% mobilization with prosthesis.<sup>52</sup> The patients in this series, however, were highly selected, with a median ASA score of 2 and median body mass index of 21.5 kg/m<sup>2</sup>.

An alternative to EHP in pelvic sarcoma where there is no neurovascular involvement is internal hemipelvectomy (IHP).<sup>53,54</sup> This procedure, and its variants, allows the lower limb to be spared and has demonstrated good oncological outcomes in appropriately selected sarcoma patients and carries less morbidity than EHP.<sup>55,56</sup> There is no published experience of IHP in rectal cancer and only a single case report in its utilization for a locally invasive recurrent right-colon cancer involving the iliac crest.<sup>57</sup>

### En bloc sciatic notch procedures

Given the limitations of extensive bony pelvic resection for rectal tumors, the focus of sidewall surgery has moved to more limited but highly targeted resections of tumor and adjacent structures en bloc, but without the necessity to fully dissect a whole field or mutilate the patient, although this may entail a higher R1/2 rate. A retrospective study of multivisceral resections for rectal cancer, including limited sidewall excisions (vascular only), has demonstrated an R0 resection rate of 53%, with 46% overall remaining disease-free at an average of 30 months.<sup>17</sup> In this series, a bespoke approach was taken to lateral sidewall excisions depending on the exact extent of the tumor, preserving as much tissue as possible, and 25 patients (69%) were alive at a mean follow-up of 19 months. These results are broadly comparable to the experience in sarcoma surgery, where good long-term graft patency has also been reported utilizing the superficial femoral vein.<sup>58-60</sup> Although a classification system exists for vascular involvement in lower limb and

pelvic sarcoma patients, it is not intended as a guide to judging operability; instead, high-quality vascular imaging and support from specialist vascular team are important in managing such patients.<sup>61</sup>

There is limited previous experience with composite sciatic excision in rectal cancer surgery as it has previously been regarded as a contraindication to a radical approach. Kameyama et al reported a series of three patients who underwent sciatic excision due to intolerable pain as a result of LRRC involving the sciatic nerve.<sup>62</sup> Each patient reported an improvement of symptoms and was able to ambulate when discharged from hospital, but two died within 16 months of surgery due to recurrence or metastasis. The third patient was only followed-up for 7 months. Shaikh et al recently reported a case series of six highly selected patients undergoing a novel extended lateral pelvic sidewall excision procedure for either primary or recurrent rectal or anal cancer, each achieving an R0 resection.<sup>63,64</sup> This standardized technique comprises an extra-pelvic phase and an abdominal phase that converge on the sciatic notch from either side, allowing en bloc resection of tumor. Half of the patients required excision of the sciatic nerve due to tumor involvement, and all patients had the internal iliac vessels ligated either above or below the level of the superior gluteal artery. In this small series, there was no immediate mortality and only minor morbidity, with the range of hospital length of stay 14 to 33 days. All patients were able to mobilize on discharge, those having had sciatic nerve excision requiring additional physiotherapy and an orthosis. Despite the promising results, it is important, however, to note that this initial small series was conducted by an MDT with extensive experience of operating on and rehabilitating patients who had undergone extensive soft-tissue excisions for bony and soft-tissue sarcomas. A good functional result can, however, be expected in a majority of well-selected patients following sciatic excision provided sufficient support is provided, in keeping with the experience in sarcoma surgery.<sup>65,66</sup>

### High sacral resection

Resection of the sacrum below or at the level of S3 has been shown to be oncologically beneficial and functionally/morbidity acceptable.<sup>10,65,67,68</sup> Sacral resection is normally performed in the prone position and the amputation should be one segment above the one involved. However, primary or recurrent tumor involvement at or above the S2 level has been considered a contraindication for resection due to the high prevalence of unacceptable autonomic and somatic neurological deficit,<sup>69</sup> although bowel and bladder function,

as well as mobility with minimal aid, has been shown to be recoverable in a large proportion of patients with appropriate rehabilitation.<sup>70,71</sup> Additionally, sacral resection involving the cranial half of the S1 vertebral body renders the pelvis unstable and thus requires extensive pelvic reconstruction with internal fixation and grafting that is generally considered unacceptable.<sup>72</sup>

High sacral resection does, however, offer a significant survival advantage if R0 resection can be achieved. In initial investigations, Wanebo et al reported a 5-year survival rate of 25% of patients following sacrectomy compared to 3% receiving palliative therapy alone (although the palliative therapy employed in this study has now been superseded by superior treatments).<sup>73</sup> In another series, the same author reported an 85% R0 rate among high sacrectomy cases with 31% of 5-year survival.<sup>74</sup> In a limited series of nine patients who received a high sacral resection, including one at L5 level, Dozois et al reported a 100% R0 rate and median survival of 31 months.<sup>75</sup> More recently, Milne et al demonstrated an R0 resection rate of 72% in 100 patients undergoing pelvic exenteration with sacrectomy (61 rectal, 17 anal, and four other cancers) with 38% and 30% overall and disease-free survival, respectively.<sup>76</sup> R0 rate was not affected by the extent of sacral resection, although high sacrectomy did increase the rate of neurological deficit ( $P=0.04$ ). The complication rates of such operations are, however, high (74%), especially for wound healing and pelvic infection in a post-radiotherapy field, although there was no in-hospital mortality in this series.

The clear survival benefit of R0 sacral resection has prompted innovation in limited sacral resection. Shaikh et al described a novel high subcortical sacrectomy (HiSS) procedure for primary and recurrent tumors invading the anterior

cortex of S1 and/or S2 in a series of five patients. In this procedure, the anterior central sacral column (limited by the lateral aspect of the sacral foramina) is lifted from the wider sacrum to a depth not exceeding 10 mm of cancellous bone, delivering the anterior sacrum en bloc with invading tumor and anterior structures, preserving the posterior portion and alar of the sacrum and thus biomechanical integrity, avoiding the need for reconstruction.<sup>77,78</sup> Each of the five patients in this small study achieved an R0 resection and all had no evidence of local recurrence at between 12 and 20 months follow-up. Due to the position of tumors, some patients required excision of the sacral nerve roots at the foramina, and thus neurological compromise could not be completely avoided. Concerns regarding bleeding during this procedure due to the high vascularity of the pre-sacral fascia and cancellous bone were managed by the liberal use of high-powered diathermy and bone wax. Blood loss was reported as ranging between 500 and 1,500 mL, but no details were provided regarding need for intraoperative blood transfusion, which has previously been shown to increase the incidence of tumor recurrence.<sup>79</sup> One patient had a Clavien–Dindo postoperative complication of IIIb (anastomotic leak), but there was no in-hospital mortality.

Figure 1 illustrates the anatomical principles of the HiSS procedure in a male patient with a primary high-rectal carcinoma treated in our unit by abdominoperineal resection with HiSS and vertical rectus abdominis myocutaneous flap. The tumor can be observed on the MRI extending to and involving the anterior sacral fascia at the S1–S2 level, beyond the planes of TME, with the illustration demonstrating the subcortical resection. In this case, an R0 resection was achieved; the procedure lasted 7 hours and 13 minutes, the patient required no blood product transfusion, and was discharged fully ambulatory on day 9 without immediate complication.



**Figure 1** T2 sagittal magnetic resonance imaging demonstrating a high-rectal carcinoma extending to the pre-sacral fascia S1–S2 level (arrow).  
**Note:** Illustration of the high subcortical sacrectomy resection (dashed line) in the same patient.

Brown et al reported a further composite procedure for LIRC following high anterior resection involving the left sacrum from mid-S1 to S2/3 levels, S1 and S2 nerve roots, piriformis, and internal iliac vessels.<sup>80</sup> In this single case, a posterior approach to the sacrum was performed by medial detachment and lateral reflection of the glutei. Radiologically guided osteotomies were then created just distal to the superior endplate of S1 and at the middle of the body of S3 on the affected side only. These osteotomies were then connected vertically in the midline and laterally to free the block of sacrum, completing a limited unilateral sacral disconnection prior to abdominal exenteration. The benefit of this technique is that it avoids complete high sacrectomy, thus maintaining the stability of the pelvis and structural integrity of the sacrum, allowing for full weight bearing without reconstruction. The authors acknowledge that this approach was potentially hazardous, as it requires an approach onto the internal iliac vessels without proximal control.

### Smaller resections of the bony pelvis

There is limited published experience of minor bony resections of the pelvis in the colorectal literature. Wanebo et al reported eight limited resections of the bony pelvis (five involving ileum or ischium, and three involving pubic rami or symphysis) as part of a larger mixed cohort of LARC and LIRC, of which four patients survived a minimum of 3 years.<sup>81</sup> Lopez and Luna-Pérez reported a mixed cohort of 34 pelvic tumors (including rectal, gynecological, urological, and sarcoma) involving the bony pelvis, achieving an R0 resection rate of 88% and a cancer-specific 5-year survival of 52%.<sup>82</sup> Despite the heterogeneity of patients and procedures in these two studies, the overriding principle that an R0 resection is the most significant factor in predicting survival is maintained and that composite pelvic resections are feasible for a limited number of patients.

### Conclusion

Despite recent advances in exenterative surgery for LARC and LIRC, there are aspects of disease management that need further development and assessment of efficiency. Of particular interest are tumors affecting the pelvic sidewall and high sacrum, which have generally been regarded as inoperable and therefore with an associated poor prognosis. Of particular concern are the anatomical challenges associated with extended pelvic resections and the consequent morbidity resulting from sacrificing important neuronal, vascular, and skeletal structures in search of an R0 resection. Any decision to operate in such circumstances must be

weighed carefully against the risks of disability and morbidity. To this end, novel approaches to en bloc resections are being developed in highly specialized centers with appropriate expertise, although the number of patients suitable and centers able to provide such services are currently too small to determine whether long-term outcomes and wider implementation of these techniques will be recommended. What is undoubtedly clear, however, is that patients with complex LARC or LIRC should be managed in super-specialized centers if radical surgery is to be pursued in order to give the patients the best chance of cure.

### Disclosure

The authors report no conflicts of interest in this work.

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