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RADIATION THERAPY AND RADIATION THERAPY INNOVATIONS IN COLORECTAL CANCER (PP LEE AND AC RALDOW, SECTION EDITORS)

Local Therapy Options for Recurrent Rectal and Anal Cancer: Current Strategies and New Directions

Edward Christopher Dee[1] · Christine E. Eyler[2] · Nina N. Sanford[3] · Jennifer Y. Wo[2]

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Abstract

Purpose of Review Although uncommon, locally recurrent rectal cancer (LRRC) and locally recurrent anal cancer (LRAC) after definitive chemoradiation can confer high morbidity and mortality. Although surgery is critical for management, recent studies show promising results with other locally directed and/or systemic treatment approaches. Here we review the literature to examine recent advances in management of this patient population.

Recent Findings For LRRC, studies demonstrate success with newer surgical approaches and redefine contraindications for surgery. The roles of brachytherapy, repeat external beam irradiation, and induction chemotherapy are under investigation. Advances in LRAC show that surgery remains a core element of treatment after primary chemoradiation failure. Recent reports of overall survival are promising.

Summary Surgery remains the mainstay of treatment for LRRC and LRAC, and overall survival is improving. Benefits of newer surgical, radiotherapeutic, and other treatment approaches are being elucidated. These findings pave the way for further improvements in cancer-specific outcomes and quality of life.

Keywords Locally recurrent rectal cancer · Locally recurrent anal cancer · Oncologic outcomes · Rectal cancer · Oncologic outcomes · Intraoperative radiotherapy

Introduction to Recurrent Anorectal Malignancies

Anorectal malignancies including rectal and anal cancer, respectively, accounted for 44,180 and 8300 new cancer diagnoses (13% and 3% of gastrointestinal malignancies [1, 2]) in the USA in 2019 [1]. Rectal cancer is primarily of adenocarcinoma histology [3]. Cancer of the anal canal is primarily of squamous cell carcinoma (SCC) histology [4] and is frequently associated with human papillomavirus (HPV) infection [5]. Primary rectal cancers are usually treated with surgical resection with the addition of pre- or postoperative chemoradiation and chemotherapy for more advanced disease [6], while primary anal SCCs are generally treated with definitive chemoradiation [5].

Due in large part to the anatomy of the pelvis—with many key genitourinary and gastrointestinal organs in close proximity confined within a small bony space—pelvic recurrences

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✉ Jennifer Y. Wo
jwo@mgh.harvard.edu

Edward Christopher Dee
Edward_Dee@hms.harvard.edu

Christine E. Eyler
ceyler@partners.org

Nina N. Sanford
Nina.Sanford@UTSouthwestern.edu

[1] Harvard Medical School, Boston, MA, USA

[2] Department of Radiation Oncology, Massachusetts General Hospital, Boston, MA, USA

[3] Department of Radiation Oncology, University of Texas Southwestern, Dallas, TX, USA

can be associated with significant morbidity including sacral and perineal discomfort, pelvic tumor abscesses, sacral nerve dysfunction, sexual dysfunction, and fistula formation. In addition to worse disease outcomes, local recurrences also worsen quality of life [7–11], warranting continued efforts to decrease the likelihood of recurrent disease and optimize disease outcomes in the setting of recurrence. Given the trend towards watch-and-wait [12, 13, 14••] and radiation dose de-escalation [15–17] strategies, with rectal cancer series showing a local recurrence risk of approximately 20% in those achieving a clinical complete response to neoadjuvant treatment [14••], there may be an increasing absolute number of local recurrences in the future. An understanding of the consequences of recurrent disease and salvage options is critical as patients make decisions regarding primary cancer treatment.

Introduction to Locally Recurrent Rectal Cancer (LRRC)

In the 1990s, locoregional relapse in rectal cancer occurred in approximately 3 to 30% of patients [18–20]. With the widespread adoption of neoadjuvant chemoradiation and total mesorectal excision (TME), the rates of local recurrence have decreased [21, 22••, 23], possibly due to removal of tumor cells that otherwise would have been left in the mesorectal fat [21]. Additionally, newer surgical techniques may further decrease the recurrence rate. For example, several studies have compared abdominoperineal excision (APE) to extralevator abdominoperineal excision (ELAPE) [24], with some [25•, 26] but not all [27–29] demonstrating lower rates of local recurrence after ELAPE. Despite improvements in therapeutic approaches, pelvic recurrences occur at a rate of 5–15% [30–32]. LRRC portends poor outcomes; without treatment, only 5% of patients are alive at 5 years, and median survival is approximately 6 months [30, 33–35]. The addition of radiotherapy and chemotherapy improves outcomes with median survival of about 15 months [30, 36]; however, only complete oncologic resection (R0 resection) offers a chance for cure [37, 38]. Interestingly, a longer time interval between initial rectal cancer surgery and salvage surgery was not found to confer a survival advantage in one study [9].

Anatomical Classifications of LRRC

Several classification systems exist for LRRC. The Memorial Sloan Kettering group defines the following four locations: (1) axial (i.e., no involvement of pelvic walls or neighboring organs, including anastomotic recurrence after low anterior resection, local recurrence after transanal or transsphincteric excision, and perineal recurrence after abdominoperineal resection [APR]); (2) anterior (involving the seminal vesicles, prostate, bladder, vagina, or uterus); (3) posterior (involving the coccyx and sacrum); and (4) lateral (involving the bony pelvic sidewall or sidewall structures including the pelvic ureters, iliac vessels, lateral lymph nodes, pelvic autonomic nerves, and sidewall musculature) [39, 40]. In a series of 119 patients, axial LRRC was more likely to have R0 resection than lateral LRRC [39]. Another group demonstrated similar results, with anastomotic LRRC maintaining the best outcomes (5-year overall survival [5yrOS] 60%, $p = 0.04$ vs. other subsites), and presacral LRRC maintaining the worst outcomes (5yrOS 19%, $p = 0.03$) [41].

Another anatomic classification of LRRC is the Leeds classification, which defines recurrences as central, sacral, sidewall, or composite [42]. Central LRRC has the most favorable prognosis due to the highest likelihood of R0 resection [39, 43]. In contrast, sidewall LRRC has the worst prognosis and the lowest likelihood of R0 [39]. A recent study showed a significant reduction of the proportion of patients with central LRRC over the period from 1995 to 2002 during which time TME started to become widely implemented, suggesting full implementation of TME may explain lower rates of central LRRC and higher proportions of non-central recurrences [22••].

Klose et al. [44•] report another anatomical distinction: they showed improved outcomes for intraluminal LRRC compared to extraluminal LRRC (5yrOS 50% compared to 27%, $p = 0.0279$). Curative resection was associated with prolonged survival and was more likely with intraluminal recurrence [44•].

Introduction to Clinical Evaluation and Management of LRRC

Suspected LRRC should be evaluated with CT chest, abdomen, and pelvis (Fig. 1a, b) to confirm the mass and exclude metastases, MRI pelvis to assess the anatomical location of the tumor, and FDG-PET scan to assess for occult metastases [37]. Confirmatory biopsy at time of recurrence is recommended. In biopsy-negative cases, repeat biopsy, upfront resection if feasible, or active surveillance with close interval follow-up may be considered [37]. The NCCN Guidelines [45] recommend preoperative chemoradiation or upfront resection for potentially resectable pelvic/anastomotic recurrences, with consideration of intraoperative radiotherapy (IORT). Treatment of unresectable LRRC involves chemotherapy with fluorouracil (5-FU) or capecitabine, with or without radiotherapy. Though surgical resection is the primary curative treatment for LRRC, the Beyond TME Collaborative's 2013 consensus statement incorporated multiple modalities in the treatment of LRRC beyond surgery [46]. These recommendations included chemoradiation/radiotherapy for radiation-naïve regions, consideration of neoadjuvant re-irradiation for previously irradiated regions,

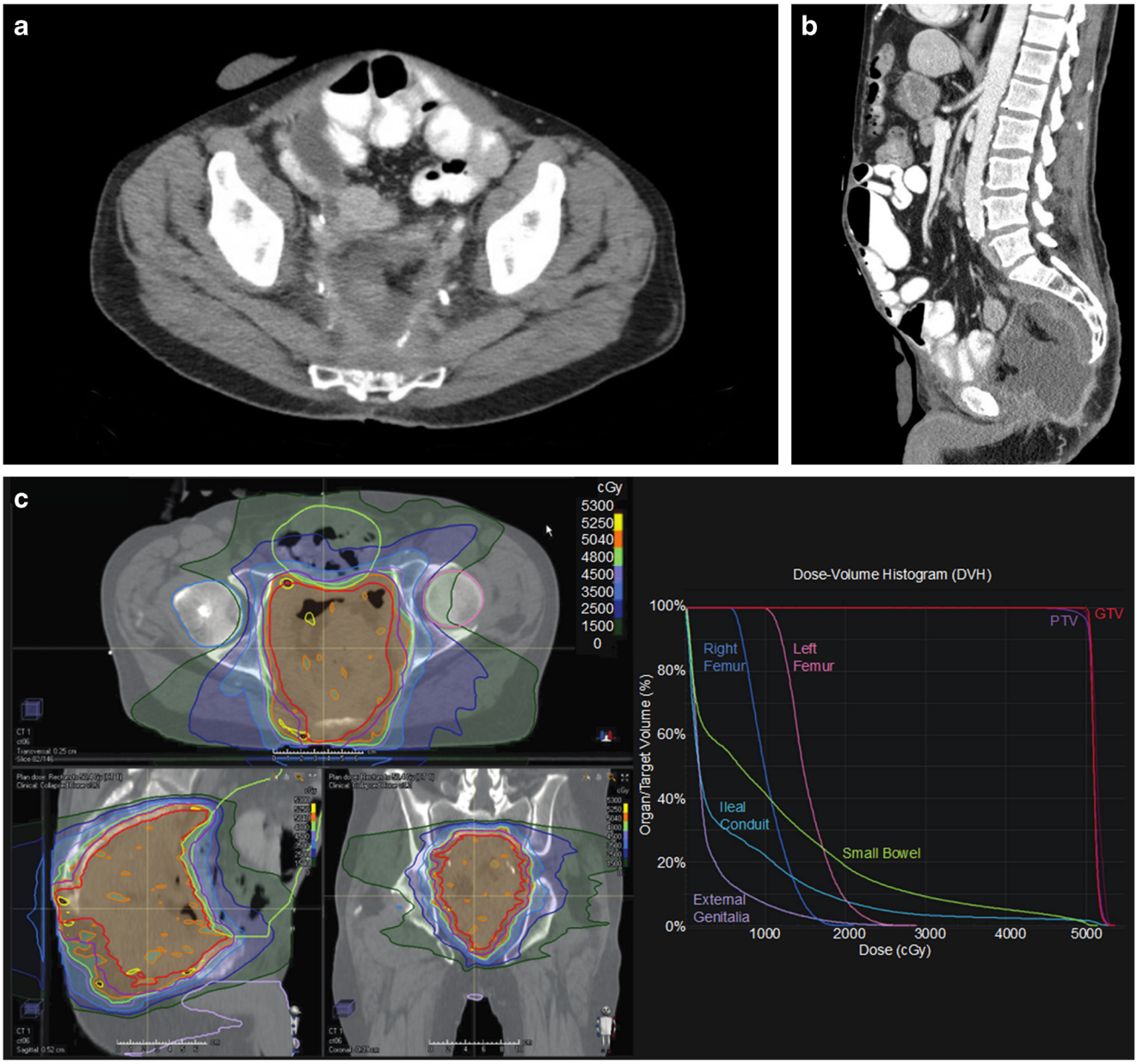

Fig. 1 Axial (**a**) and sagittal (**b**) imaging of a 70-year-old patient with pelvic recurrence diagnosed 5 years after prior neoadjuvant chemo-RT, APE, and adjuvant chemotherapy. His pelvic recurrence was complicated by small bowel obstruction, bilateral hydronephrosis requiring percutaneous nephrostomy tubes, and persistent pelvic tumor abscess with perirectal fistulous tract formation. **c** Representative radiation treatment plan for the patient. Given localized recurrence, he was treated with pelvic re-irradiation with intensity-modulated radiation therapy (IMRT) to 50.4 Gy in 28 fractions with concurrent capecitabine

consideration of 5FU-based chemotherapy, and further study of brachytherapy and IORT options. New developments in the different modalities are discussed below.

Role of Resection Margins on Surgical Outcomes

Resection with negative surgical margins (i.e., R0 resection) is key to curative treatment in LRRC [21, 22••]. Unlike primary rectal cancer, however, LRRC may not be confined to a well-defined surgical compartment, and multicompartment exenterative procedures are often required to achieve R0 resection [47••, 48]. A review of 19 studies [21] found that 40–50% of LRRC patients could be expected to undergo surgery with curative intent, and of those, 30–45% would have R0 resections, resulting in only 20–30% of patients receiving potentially curative operations (some of the reviewed studies included patients who underwent chemoradiation as well [49, 50]).

Although studies from the early 2000s demonstrate poor prognosis for LRRC (5yrOS < 10% [7, 11]), other

more recent studies report better outcomes, perhaps due to incorporation of multiple modalities. A 2015 study demonstrated 5yrOS of 40% for R0 resection [51]. In 2016, Harris et al. [9] found that among patients who had undergone resection, R0 was achieved in 59%; among R0 patients, the 5-year cancer-specific survival was 44%. In their cohort, the subgroup that received perioperative chemoradiation experienced improved 5-year cancer-specific survival for R0 resection, but not for microscopic residual tumor (R1) and macroscopic residual tumor (R2) resections.

A 2018 study [22••] found that among 121 LRRC patients who had surgical resection, R0 was achieved in 64 patients (80% of whom had central LRRC), and was the single most important factor for potential cure. 5yrOS was 43% after R0, 14% after R1, and 4% after R2 resections [22••]. Patients with R1 resections were more likely to develop local re-recurrences and distant metastases as first failure compared to those undergoing R0 resections [22••]. Notably, an increased likelihood of re-recurrence and poorer overall survival was found among patients with close margins of < 2 mm compared to those with tumor-free margins of > 2 mm [48]. Table 1 summarizes the published literature regarding LRRC outcomes.

Improvements in Surgical Technique

Improvements in surgical technique facilitating improved disease resection and survival gain [8, 9] have more commonly justified the high morbidity of what often amounts to extensive salvage surgery [55]. Newer techniques such as abdominolithotomy sacrectomies for lesions at or below S3 and isolated anterior vertebral body excisions are reported [56, 57]. Although sacral invasion at S2 or higher was previously a surgical contraindication, several groups are actively exploring more extensive resections involving the bony pelvis [52, 58–60].

The envelope is similarly being pushed for more aggressive resections in the case of tumor involvement of the lateral pelvic sidewall [61, 62]. Although many suggest that extensive lateral involvement remains a relative contraindication to surgery [46, 63], some have described techniques that allow for R0 resection in over half of these patients [64, 65]. A recent study reported pelvic exenteration with lateral pelvic wall excision for LRRC and achieved R0 resection in 62% of patients (3yrOS 45%) [53••], which stands in stark contrast to another study that showed only 19% R0 resection if there was pelvic side wall recurrence [39]. Other surgical developments including an abdominal-only approach for exenteration with sacrectomy [56] and laparoscopic approaches to central

Table 1 Outcomes in different studies of LRRC after salvage surgery

Author	Year	Institution	Number of patients	5-year overall survival	Treatment before LRRC resection
Guyot [11]	2005	Cancer Registry of Côte d'Or, France	338	15.6% (LRRC)	NR
Palmer [7]	2007	Stockholm Colorectal Cancer Study Group, Sweden	141	9% overall LRRC 57% if potentially curative resection	30% irradiated, 2% chemotherapy before LRRC resection
Dozois [52]	2011	Mayo Clinic, Minnesota	9	30%	78% chemo-RT, 11% chemotherapy only
Klose [44•]	2015	University of Heidelberg, Germany	90	40%	47.8% neoadjuvant radio/chemotherapy
Solomon [53••]	2015	Australia	200	35%	38.5% RT either as neoadjuvant or during treatment of primary tumor
Nielsen [51]	2015	Denmark	213	Intended curative surgery: 30% R0: 40% R1: 16%	52% (110) pre-op RT, 69% of whom with 5-FU-based chemotherapy
Harris [9]	2016	New Zealand, Australia, UK	533	All-cause: 28% CSM: 37% R0: 44% R1: 26% R2: 10%	NR
Kishan [88]	2017	Massachusetts General Hospital, Boston	25	28.2% overall	92% with concurrent chemotherapy, 100% RT
Westberg [22••]	2018	Swedish Colorectal Cancer Registry	426	R0: 43% R1: 14% R2: 4%	38% pre-op RT
Detering [145]	2019	Dutch Colorectal Audit, Netherlands	107	30% 2yrOS for 20 who underwent resection	82% pre-op RT

NR not reported

LRRC [8, 66–68] have also been recently reported. Notably, quality-of-life metrics are encouraging for patients undergoing these extensive resections [59, 69].

Induction Chemotherapy in LRRC

Given that R0 resection is not always achievable on initial identification of LRRC [22••], improvements in chemotherapy may permit downstaging of recurrent lesions. Van Zoggel et al. [70•] evaluated the influence of neoadjuvant induction chemotherapy (ICT, with CAPOX or FOLFOX) in patients with LRRC who had preoperative chemoradiation for the primary cancer or an earlier local recurrence. These patients were compared with patients who received chemoradiation alone without ICT. Of patients with ICT, 55% had surgery with clear resection margins, of whom 17% exhibited a pathological complete response (pCR). In patients who received chemoradiation alone, a rate of R0 and R1 resection similar to those with ICT was found, but only 4% had pCR ($p = 0.015$). High pCR in patients treated with ICT before chemoradiation is comparable to pCR rates after chemoradiation in locally advanced primary rectal cancer [71]. pCR was associated with improved overall survival, local recurrence-free survival, and metastasis-free survival [70•], suggesting benefit from ICT. Further investigations are warranted to select more effective regimens or target subgroups that would benefit most from ICT.

Re-irradiation for LRRC

Re-irradiation of LRRC from previously irradiated primary tumors has been reported using generally lower dose per fraction, sometimes with twice daily external beam radiotherapy (EBRT) hyperfractionation (e.g., 1.2 Gy twice daily to 30 Gy) [72]. Re-irradiation with a limited dose of 30–39 Gy and concomitant chemotherapy has been generally shown to be safe in control of LRRC, after primary treatment doses ranging from 25 to over 54 Gy (Fig. 1c) [73–76]. Others report safe use of preoperative EBRT to 20–30 Gy in patients with LRRC and re-recurrences who had a prior cumulative dose of less than 64 Gy [59]. In 2002, Mohiuddin et al. [76] reported that in patients with LRRC who had received radiation for the primary tumor with subsequent re-irradiation for the recurrent tumor, resection was associated with increased median survival and 5yrOS. In their study, re-irradiation doses ranged from 15 to 49.2 Gy, and total cumulative doses ranged from 70.6 to 108 Gy (median total dose of 85.8 Gy); they recommended an interval time to re-irradiation of at least 24 months if cumulative dose exceeded 100 Gy, although they recommended further research validating this threshold [76]. In a 2003 study, patients who had already had pre- or postoperative radiotherapy to 25–50 Gy were found to tolerate LRRC re-irradiation up to at least 30 Gy [74]. In 2006, a phase II study provided further evidence for the acceptability of complications and downstaging due to re-irradiation [72]. In terms of treatment fields, Bosman et al. describe a Dutch experience: three-dimensional conformal technique (3DCRT) delivered dose to planning target volumes (PTV) defined by gross target volumes with 2 cm margins; no areas outside tumor volume received RT dose [73]. At our institution, while 3DCRT is employed standardly for neoadjuvant chemoradiation for primary rectal tumors, in the setting of re-irradiation, we would recommend intensity-modulated radiation therapy (IMRT) or proton radiotherapy to minimize risk of long-term toxicity. Additionally, in the setting of re-irradiation, we recommend only coverage of gross disease alone without planned elective nodal coverage or clinical target volume expansion. PTV expansion should be performed per institutional standards. Though many of the previous studies indicated re-irradiation as a safe and effective approach, data from Yu et al. [77] remind us that the intrinsic radiosensitivity of LRRC may be decreased and the overall response magnitude of LRRC to re-irradiation may be limited in extent especially if compared to primary rectal cancers.

A review [75] of LRRC treatment in previously irradiated patients, which included nine studies and 474 patients, found that various treatment regimens were used, mostly with curative intent. Re-irradiation regimens included neoadjuvant and/or adjuvant EBRT, IORT added to EBRT, or IORT only, generally with acceptable radiation toxicity [75]. Furthermore, re-irradiation was found to be associated with increased R0 rates, which improved local control and overall survival [75]. Patients who received re-irradiation and R0 resection had 3-year local control rates ranging from 50 to over 70% [50, 73, 75]. Data from locally advanced rectal cancer suggest that IMRT can reduce dose delivered to small bowel, although clinical improvement over 3DCRT has not yet been demonstrated [78]. A large database study shows no improvement when IMRT is used over 3DCRT for rectal cancer, though further studies in LRRC are merited [79]. Encouragingly, recent advances in radiotherapy are seen in the employment of other radiotherapy techniques, such as IORT and proton radiotherapy.

Intraoperative Radiotherapy

The role of IORT in LRRC is still being elucidated. IORT is a mechanism of administering electron radiotherapy to a surgical bed, concentrating on high-risk regions identified intraoperatively [80]. One advantage of this modality is that electrons deliver dose at a relatively shallow depth such that dose to normal structures may be minimized. Among earlier studies, some advocate the value of IORT [81–83], whereas others

report no difference in survival with and without IORT [80]. Although no phase III trials examine the value of IORT in LRRC, IORT may be beneficial in the setting of R1 resections and has generally been shown to be associated with acceptable toxicity rates [9]. Some advocate IORT in the setting of exenteration with risk of close or positive margins [59] and highlight that when disease recurrence occurred following IORT, the least likely site of recurrence was in the IORT treatment zone [84].

In 2011, Haddock et al. reported 607 patients with recurrent colorectal cancer who received IORT with electrons, and found that 5yrOS was 46%, 27%, and 16% for R0, R1, and R2 resections respectively [84]. Although there was no comparator arm without IORT [84], the authors highlight that their IORT cohort's R0 5yrOS (46%) was improved compared to that of their older cohort in whom only three of 65 received IORT (5yrOS 34%) [85]. Their IORT cohort R1 and R2 patients also did better than those without IORT treated by the same group [88]. They further note that IORT without EBRT is not sufficient [84]. As microscopic local control requires 60 Gy or more in conventional fractionation [86], EBRT with 50.4 Gy in 28 fractions followed by 12.5 Gy IORT, which is equivalent to 66 Gy given in 2 Gy fractions, suffices; however, IORT doses exceeding 12.5 Gy are poorly tolerated, and therefore, IORT may not provide optimal local control without EBRT [84].

More recently, Bosman et al. sought to assess the toxicity and outcomes of re-irradiation with EBRT (approximately 30 Gy) and IORT electron boost (10 Gy, 12.5 Gy, and 15 Gy for R0, R1, and R2 resections, respectively) in 135 LRRC patients [73]. The re-irradiated patients were compared to a full-course group that did not receive radiotherapy for the primary tumor (but received a full course of treatment for LRRC including EBRT and IORT) and to a historical control group that did not receive preoperative irradiation. R0 resection was achieved in 55.6% of re-irradiated patients, which was similar to the full-course group. Among re-irradiated patients, rates of grade III and IV complications (~35%) and 30-day mortality (4.6%) were attributed to more advanced disease necessitating more extensive surgery [73]. Although there was no overall survival difference between the re-irradiated patients and full-course patients, both irradiated groups had better survival than the non-irradiated historical control group [73]. A 2017 study of 25 LRRC patients treated with standard fractionation RT found that the eight patients also treated with IORT experienced improved OS, although this was only significant when surgical resection was removed from the multivariate model [87]. Although these more recent studies suggest benefit of IORT, with new delivery systems being developed [89], a direct comparison is needed to assess the value and safety of IORT in LRRC compared to standard radiation regimens.

Proton Therapy for LRRC

Literature for the use of proton therapy in LRRC is sparse. Several studies have demonstrated the dosimetric advantage of protons compared to three-dimensional conformal photon radiation therapy and intensity-modulated radiation therapy in the treatment of rectal cancer with respect to normal tissue dose; however, no clear decreases in toxicity or improvements in quality of life were definitively reported [90–92]. A 2014 Japanese case report describes LRRC treated with protons alone that resulted in complete clinical response, without recurrence 7 years after treatment [93]. Another group reported seven patients with LRRC in or near prior radiation fields (median prior total dose 50.4 Gy) who were treated with protons, of whom six had a complete response by PET-CT, and four were alive at a median follow-up of 19 months; in this group, dosimetric improvements to bowel were achieved resulting in low toxicity rates [94]. Further investigations are warranted to better evaluate the potential benefits of proton radiotherapy in this setting.

Brachytherapy for LRRC

In contrast to EBRT and IORT, brachytherapy delivers a continuous, locally administered radiation dose that induces sufficient damage to cancer cells yet allows repair of sublethal DNA damage in normal tissue; brachytherapy also often restricts the volume of normal tissues exposed to radiation and thus widens the therapeutic index [95]. Bishop et al. studied the role of interstitial brachytherapy in the treatment of LRRC in 2015, with a cohort of 20 patients (17 with LRAC, three with locally recurrent anal cancer) [96•]. Reported 3yrOS was 48%; 3-year local control rate was 60%; median survival was 31 months; and 5yrOS was 38% [96•]. Given that 65% of patients had multiple pelvic recurrences and 30% had distant metastases at the time of implant, their outcomes support interstitial brachytherapy as an effective therapeutic option for LRRC that compares favorably with other approaches [61, 96•]. In terms of symptom palliation, brachytherapy for LRRC has been encouraging. In the series of Bishop et al., 69% of patients reported less pain after the implant, and over 50% experienced permanent relief [96•], consistent with earlier studies [97, 98]. These data support further investigation of the role of brachytherapy in treating and palliating LRRC.

Hyperthermia for Rectal Cancer

Hyperthermia, added as an adjunct to other treatment modalities, involves raising the temperature of tumor tissue to 40–43 °C and exerts its effects through direct cytotoxicity, augmentation of the effects of radiation and cytotoxic

medications, alteration of the tumor microenvironment, generation of a proinflammatory state, and recruitment of natural killer cells [99]. The use of intra- or postoperative hyperthermia for primary rectal cancer, in combination with radiotherapy and chemotherapy, was associated with improved treatment response rates [100] and lower rates of local recurrence [101], with evolving data about prognosticating biomarkers such as CA9 [102]. Hyperthermia as an adjunct to radiotherapy also improved response rates in inoperable recurrent rectal cancer [103]. Although data are scarce for hyperthermia in LRRC, one study treated 24 patients with previously irradiated LRRC, with overall 1yrOS and 3yrOS of 87% and 30%, respectively, suggesting good efficacy and acceptable toxicity [104]. A 2016 study in normal porcine muscle and human volunteer imaging-only studies (magnetic resonance thermometry without heating) suggest the feasibility of magnetic resonance-guided high-intensity focused ultrasound as a delivery system for hyperthermia [105]. Further studies are needed to quantify the benefit for hyperthermia for this challenging condition.

Introduction to Anal Cancer and Treatment Paradigm

Although increasing in frequency in recent years due to HPV-associated disease, anal squamous cell carcinoma (SCC) remains an uncommon malignancy, accounting for less than 3% of gastrointestinal cancers with annual incidence of 1–3 cases per 100,000 in the USA [2, 5]. Definitive radiotherapy with concurrent 5-FU and mitomycin C is the standard treatment for anal SCC, with 5yrOS of 60–80% [106], although current trials like the PersonaLising Anal cancer radioTherapy dOse (PLATO) trial are assessing ways to optimize radiotherapy based on tumor location and stage [107].

Introduction to Locally Recurrent Anal Cancer (LRAC)

Despite generally excellent outcomes after primary chemoradiation and the ability to avoid surgery in the majority of patients, studies show persistent disease in 10–15% [108–110] of patients and recurrent disease in 10–30% of patients [111]. Harris et al. [112] sought factors related to treatment failure following chemoradiation and found that only T4 disease at presentation was associated with the eventual need for salvage surgery. Gunderson et al. [113] found increasing risk of locoregional failure at 5 years in patients with T2N0 disease (17% chance of locoregional failure at 5 years), T3N0 (18%), T2N1–3 (26%), T4N0 (37%), T3N1–3 (44%), and finally patients with T4N1–3 disease (60%) [113]. They suggest consideration of intensified radiotherapy in patients who fall in the latter three categories as a means to mitigate risk of LRAC [113, 114]. Efforts to identify patients upfront with high risk for refractory or relapsed disease after definitive chemoradiation may also contribute to decisions regarding up front treatment intensification; for example, metabolic tumor volume during treatment of anal canal SCC as determined by interim PET-CT may be associated with likelihood of locoregional control, but this strategy requires further validation as predictive of response to chemoradiation [115].

Surgery in LRAC

In the setting of partial response or locoregional failure resulting in LRAC, upfront salvage APR is potentially curative [116] with 5yrOS from approximately 40 to 60% [117–119]. Studies have demonstrated resectable disease in approximately three-quarters of LRAC patients [116]. However, morbidity is high, with wound complication rates reaching 80% [120, 121]. Despite the extent of these resections, recent surgical advances are promising with regard to improvements in morbidity and mortality.

Earlier studies have suggested 5yrOS for LRAC after APR ranging from 30 to 60% [122–124]. In 2007, Mullen et al. [125] showed that long-term survival following salvage surgery could be achieved in the majority of patients with a 5yrOS of 64%, but node-positive disease and patients with previous radiation doses of less than 55 Gy had worse prognoses. Later reports showed further survival improvements to over 80% [126] and are summarized in Table 2 [112, 116, 118, 119, 122–129, 130, 131•, 132], though improvements in postresection LRAC survival in newer studies compared to older ones may be due to stage migration [133].

Investigators also sought to identify differences in outcome between persistent versus recurrent anal cancer. While some studies found no survival difference in patients who underwent surgical salvage therapy for persistent versus recurrent disease [125, 127, 131•], others found that patients with persistent disease or early recurrence fared worse than those with late recurrence [119, 123, 129, 134], possibly due to more aggressive inherent tumor biology in patients with persistent disease or early recurrence [134]. The exact mechanisms that mediate these potential differences are yet to be elucidated [119], although given the role of HPV infection as a positive prognostic factor in primary anal SCC [135], HPV may play a role in the potential difference between recurrent and persistent disease.

In 2018, Bignell et al. showed that APE with reconstruction of the perineal defect using vertical rectus abdominis myocutaneous flap is feasible with excellent oncologic outcomes and represents an advance from typical APE afforded by flap that allows both extensive resection and reduction in wound complications [118]. Although their 29-patient cohort

Table 2 Outcomes in different studies of LRAC after salvage surgery

Author	Year	Number of patients	5-year overall survival	Median survival (months)	Difference between persistent and recurrent disease
Ellenhorn [127]	1994	38	44%	41	No
Van der Wal [128]	2001	17	47%	33	No
Nilsson [129]	2002	35	52%	NR	Yes, persistent worse
Akbari [123]	2004	57	33% (all), 40% (potentially curative resection)	34.1	Yes, persistent worse
Renehan [116]	2005	73	40%	NR	Yes, persistent worse
Mullen [125]	2007	31	64%	NR	No
Schiller [124]	2007	40	39%	41	Yes, persistent worse, although not statistically significant
Harris [112]	2013	11	64%	28	NR
Hannes [126]	2016	14	86%	NR	NR
Alamri [130]	2016	27	78%	NR	NR
Pesi [119]	2017	20	37.4%	47.4	Yes, persistent worse, although not statistically significant
Bignell [118]	2018	29	67%	16	NR
Hagemans [131]	2018	47	41.6%	47	No

NR not reported

demonstrated 5yrOS of 67%, consistent with other recent reports [112, 126, 130], they demonstrated a low local re-recurrence rate of 7%, with only one with positive margins (3%) (rate of re-recurrence including regional and distant re-recurrences was 31%) [118]. The authors suggest the benefit of myocutaneous reconstruction, which allows for a wide perineal excision without concern for closure. They also argue that as mortality is high following regional or distant re-recurrence after salvage surgery, aggressive resection to achieve R0 resection is warranted [118]. This low rate of local re-recurrence is reassuring compared to the rates in other studies [131•], as local re-recurrence has significant implications for quality of life in addition to having a poor median survival of less than 1 year, even after salvage re-operation [131•].

Systemic Therapies for Metastatic or Unresectable Anal SCC

Per NCCN guidelines, cisplatin-fluorouracil, carboplatin-paclitaxel, and perhaps less commonly FOLFOX chemotherapy combinations are currently recommended options for patients with unresectable or metastatic LRAC [136]. Published prospective data regarding treatment regimens are lacking, while retrospective data support cisplatin-fluorouracil as front-line therapy [54, 137]. However, only half achieves objective responses, and none achieves complete responses; long-term survival is limited to patients treated with complementary surgery [54, 137]. Emerging but as yet unpublished data from the phase II InterAACT trial suggests that carboplatin-paclitaxel may have improved secondary endpoints of survival and serious adverse events, though the primary outcome of response rate appeared non-significant [138]. Another recent study is elucidating improved chemotherapy regimens that afford both good toleration and long-lasting response [139••]. Given the changing epidemiology of anal SCC to include more HPV-associated tumors that may be responsive to immunotherapy [5, 140], there is excitement about evaluating immunotherapies in the treatment of locally recurrent or metastatic anal cancer. The KEYNOTE-028 trial assessed the safety and efficacy of pembrolizumab, a humanized PD-1 antibody, in patients with PD-L1-positive locally advanced or metastatic anal carcinoma that had failed prior standard therapy, with 17% of patients exhibiting partial response and 42% maintaining stable disease [141].

EBRT and IORT for LRAC

The role of EBRT re-irradiation and IORT in LRAC is being clarified. Osborne et al. reported a cohort of ten LRAC patients who had received at least 30 Gy to the primary tumor and received 27 to 45 Gy re-irradiation in twice daily fractions of 1.5 Gy [142]. In this study, they used dose volumes that included gross tumor with 2–3 cm block margins or 1.5–2 cm PTV margins, with elective nodal dose for some patients; 3DCRT was used for half of the patients, and IMRT was used for the other half, although the authors did not comment on differences in toxicities given the sample size [142]. All three patients treated with definitive re-irradiation with no surgery were disease-free at a median of 84 months follow-up, and of five who received preoperative re-irradiation with subsequent

surgery, three were disease-free at a median of 43 months [142]. Similar to our discussion of LRRC, in the setting of re-irradiation, at our institution, we would consider IMRT and/or proton radiotherapy to minimize risk of late toxicity and treat gross disease alone with an institutionally established PTV margin. Hallemeier et al. reported treatment of LRAC that included IORT in some patients [143]. In their IORT cohort, although 50% had positive resection margins, only 21% developed recurrence within the IORT field, suggesting benefit from IORT [143]. In contrast, Wright et al. analyzed 14 patients with LRAC who underwent salvage surgery and IORT and found that IORT was not associated with locoregional control or survival benefit and did not compensate for lack of R0 resection [144]. Further work is required to understand the role of IORT in LRAC.

Conclusions

LRRC and LRAC are important, often functionality- and life-limiting sequelae of primary rectal and anal malignancies. However, recent advances as outlined in this review are continuing to push the boundaries of treatment, with promising improvements in surgical, radiotherapeutic, and chemotherapeutic options. Further work is needed to identify which subgroups of LRRC and LRAC can benefit most from these therapeutic advances.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019;69:7–34.

2 Siegel RL, Miller, et al. Cancer statistics, 2018. CA Cancer J Clin. 2018;68:7–30.

3 Tawadros PS, Paquette IM, Hanly AM, Mellgren AF, Rothenberger DA, Madoff RD. Adenocarcinoma of the rectum in patients under age 40 is increasing. Dis Colon Rectum. 2015;58:474–8.

4 Valvo F, Ciurlia E, Avuzzi B, Doci R, Ducreux M, Roelofsen F, et al. Cancer of the anal region. Crit Rev Oncol Hematol. 2019;135:115–27.

5 Morton M, Melnitchouk N, Bleday R. Squamous cell carcinoma of the anal canal. Curr Probl Cancer. 2018;42:486–92.

6 Gaertner WB, Kwaan MR, Madoff RD, Melton GB. Rectal cancer: an evidence-based update for primary care providers. World J Gastroenterol. 2015;21:7659–71.

7 Palmer G, Martling A, Cedermark B, Holm T. A population-based study on the management and outcome in patients with locally recurrent rectal cancer. Ann Surg Oncol. 2007;14:447–54.

8 Lee DJK, Sagar PM, Sadadcharam G, Tan KY. Advances in surgical management for locally recurrent rectal cancer: how far have we come? World J Gastroenterol. 2017;23:4170–80.

9 Harris CA, Solomon MJ, Heriot AG, Sagar PM, Tekkis PP, Dixon L, et al. The outcomes and patterns of treatment failure after surgery for locally recurrent rectal cancer. Ann Surg. 2016;264:323–9.

10 Camilleri-Brennan J, Steele RJC. The impact of recurrent rectal cancer on quality of life. Eur J Surg Oncol. 2001;27:349–53.

11 Guyot F, Faivre J, Manfredi S, Meny B, Bonithon-Kopp C, Bouvier AM. Time trends in the treatment and survival of recurrences from colorectal cancer. Ann Oncol. 2005;16:756–61.

12 Smith JJ, Strombom P, Chow OS, et al. Assessment of a watch-and-wait strategy for rectal cancer in patients with a complete response after neoadjuvant therapy. JAMA Oncol. 2019. https://doi.org/10.1001/jamaoncol.2018.5896.

13 Habr-Gama A, Sabbaga J, Gama-Rodrigues J, Julião GPS, Proscurshim I, Aguilar PB, et al. Watch and wait approach following extended neoadjuvant chemoradiation for distal rectal cancer: are we getting closer to anal cancer management? Dis Colon Rectum. 2013;56:1109–17.

14•• van der Valk MJM, Hilling DE, Bastiaannet E, et al. Long-term outcomes of clinical complete responders after neoadjuvant treatment for rectal cancer in the International Watch & Wait Database (IWWD): an international multicentre registry study. Lancet. 2018;391:2537–45 **An analysis of over 1000 watch-and-wait patients with rectal cancer, in whom TME was omitted after neoadjuvant therapy, reporting 2-year cumulative incidence of local regrowth of 25.2%.**

15. Leichman L, Nigro N, Vaitkevicius VK, et al. Cancer of the anal canal. Model for preoperative adjuvant combined modality therapy. Am J Med. 1985;78:211–5.

16. Hatfield P, Cooper R, Sebag-Montefiore D. Involved-field, low-dose chemoradiotherapy for early-stage anal carcinoma. Int J Radiat Oncol Biol Phys. 2008;70:419–24.

17. Glynne-Jones R, Tan D, Hughes R, Hoskin P. Squamous-cell carcinoma of the anus: progress in radiotherapy treatment. Nat Rev Clin Oncol. 2016;13:447–59.

18. Abulafi AM, Williams NS. Local recurrence of colorectal cancer: the problem, mechanisms, management and adjuvant therapy. Br J Surg. 1994;81:7–19.

19. McCall JL, Cox MR, Wattchow DA. Analysis of local recurrence rates after surgery alone for rectal cancer. Int J Color Dis. 1995;10:126–32.

20. Karanjia ND, Schache DJ, North WRS, Heald RJ. "Close shave" in anterior resection. Br J Surg. 1990;77:510–2.

21. Nielsen M, Laurberg S, Holm T. Current management of locally recurrent rectal cancer. Color Dis. 2011;13:732–43.

22•• Westberg K, Palmer G, Hjern F, Johansson H, Holm T, Martling A. Management and prognosis of locally recurrent rectal cancer—a national population-based study. Eur J Surg Oncol. 2018;44:100–7 **A large national Swedish study assessing changes over time of LRRC epidemiology and treatment outcomes.**

23. De Chaisemartin C, Penna C, Goere D, Benoist S, Beauchet A, Julie C, et al. Presentation and prognosis of local recurrence after total mesorectal excision. Color Dis. 2009;11:60–6.
24. Carpelan A, Karvonen J, Varpe P, Rantala A, Kaljonen A, Grönroos J, et al. Extralevator versus standard abdominoperineal excision in locally advanced rectal cancer: a retrospective study with long-term follow-up. Int J Color Dis. 2018;33:375–81.
25• Bianco F, Romano G, Tsarkov P, Stanojevic G, Shroyer K, Giuratrabocchetta S, et al. Extralevator with vertical rectus abdominis myocutaneous flap vs. non-extralevator abdominoperineal excision for rectal cancer: the RELAPe randomized controlled trial. Color Dis. 2016. https://doi.org/10.1111/codi.13436 **A RCT that assesses the value of extralevator abdominoperineal excision (ELAPE) in achieving improved circumferential resection margin in LRRC.**
26. Han JG, Wang ZJ, Wei GH, Gao ZG, Yang Y, Zhao BC. Randomized clinical trial of conventional versus cylindrical abdominoperineal resection for locally advanced lower rectal cancer. Am J Surg. 2012;204:274–82.
27. Ortiz H, Ciga MA, Armendariz P, Kreisler E, Codina-Cazador A, Gomez-Barbadillo J, et al. Multicentre propensity score-matched analysis of conventional versus extended abdominoperineal excision for low rectal cancer. Br J Surg. 2014;101:874–82.
28. Prytz M, Angenete E, Ekelund J, Haglind E. Extralevator abdominoperineal excision (ELAPE) for rectal cancer—short-term results from the Swedish Colorectal Cancer Registry. Selective use of ELAPE warranted. Int J Color Dis. 2014;29:981–7.
29. Klein M, Fischer A, Rosenberg J, Gögenur I. ExtraLevatory AbdominoPerineal Excision (ELAPE) does not result in reduced rate of tumor perforation or rate of positive circumferential resection margin: a nationwide database study. Ann Surg. 2015;261:933–8.
30. Bakx R, Visser O, Josso J, Meijer S, Slors JFM, van Lanschot JB. Management of recurrent rectal cancer: a population based study in greater Amsterdam. World J Gastroenterol. 2008;14:6018–23.
31. Sebag-Montefiore D, Stephens RJ, Steele R, Monson J, Grieve R, Khanna S, et al. Preoperative radiotherapy versus selective postoperative chemoradiotherapy in patients with rectal cancer (MRC CR07 and NCIC-CTG C016): a multicentre, randomised trial. Lancet. 2009;373:811–20.
32. Tanis PJ, Doeksen A, Van Lanschot JJB. Intentionally curative treatment of locally recurrent rectal cancer: a systematic review. Can J Surg. 2013;56:135–44.
33. Gunderson LL, Sosin H. Areas of failure found at reoperation (second or symptomatic look) following "curative surgery" for adenocarcinoma of the rectum: clinicopathologic correlation and implications for adjuvant therapy. Cancer. 1974;34:1278–92.
34. Wanebo HJ, Koness RJ, Vezeridis MP, Cohen SI, Wrobleski DE. Pelvic resection of recurrent rectal cancer. Ann Surg. 1994:586–97. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1234440/, https://doi.org/10.1097/00000658-199410000-00017
35. Caricato M, Borzomati D, Ausania F, Valeri S, Rosignoli A, Coppola R. Prognostic factors after surgery for locally recurrent rectal cancer: an overview. Eur J Surg Oncol. 2006;32:126–32.
36. Wong CS, Cummings BJ, Brierley JD, Catton CN, McLean M, Catton P, et al. Treatment of locally recurrent rectal carcinoma—results and prognostic factors. Int J Radiat Oncol Biol Phys. 1998;40:427–35.
37. Mirnezami AH, Sagar PM, Kavanagh D, Witherspoon P, Lee P, Winter D. Clinical algorithms for the surgical management of locally recurrent rectal cancer. Dis Colon Rectum. 2010;53:1248–57.
38. Harji DP, Griffiths B, Mcarthur DR, Sagar PM. Current UK management of locally recurrent rectal cancer. Color Dis. 2012;14:1479–82.
39. Moore HG, Shoup M, Riedel E, Minsky BD, Alektiar KM, Ercolani M, et al. Colorectal cancer pelvic recurrences: determinants of resectability. Dis Colon Rectum. 2004;47:1599–606.
40. Guillem JG, Ruo L (1998) Strategies in operative therapy for locally recurrent rectal cancer. Semin Colon Rectal Surg 9:259–268.
41. Kusters M, Dresen RC, Martijn H, Nieuwenhuijzen GA, van de Velde CJH, van den Berg HA, et al. Radicality of resection and survival after multimodality treatment is influenced by subsite of locally recurrent rectal Cancer. Int J Radiat Oncol Biol Phys. 2009;75:1444–9.
42. Boyle KM, Sagar PM, Chalmers AG, Sebag-Montefiore D, Cairns A, Eardley I. Surgery for locally recurrent rectal cancer. Dis Colon Rectum. 2005;48:929–37.
43. Yamada K, Ishizawa T, Niwa K, Chuman Y, Akiba S, Aikou T. Patterns of pelvic invasion are prognostic in the treatment of locally recurrent rectal cancer. Br J Surg. 2001;88:988–93.
44• Klose J, Tarantino I, Schmidt T, Bruckner T, Kulu Y, Wagner T, et al. Impact of anatomic location on locally recurrent rectal cancer: superior outcome for intraluminal tumour recurrence. J Gastrointest Surg. 2015;19:1123–31 **A description of outcomes based on novel anatomic considerations with key impact on tumor prognosis.**
45. Benson AB, Venook AP, Al-Hawary MM, et al. Rectal cancer, version 2.2018 clinical practice guidelines in oncology. JNCCN J Natl Compr Cancer Netw. 2018;16:874–901.
46. Beyond TME Collaborative. Consensus statement on the multidisciplinary management of patients with recurrent and primary rectal cancer beyond total mesorectal excision planes. Br J Surg. 2013:100(8)1009–14. https://www.ncbi.nlm.nih.gov/pubmed/23754654
47•• Sasikumar A, Bhan C, Jenkins JT, Antoniou A, Murphy J. Systematic review of pelvic exenteration with en bloc sacrectomy for recurrent rectal adenocarcinoma: R0 resection predicts disease-free survival. Dis Colon Rectum. 2017;60:346–52 **A thorough review of 220 patients with LRRC that demonstrates feasibility of rectal excision with en bloc sacrectomy in select patients.**
48. Alberda WJ, Verhoef C, Schipper MEI, Nuyttens JJ, Rothbarth J, De Wilt JHW, et al. The importance of a minimal tumor-free resection margin in locally recurrent rectal cancer. Dis Colon Rectum. 2015;58:677–85.
49. Heriot AG, Byrne CM, Lee P, Dobbs B, Tilney H, Solomon MJ, et al. Extended radical resection: the choice for locally recurrent rectal cancer. Dis Colon Rectum. 2008;51:284–91.
50. Dresen RC, Gosens MJ, Martijn H, Nieuwenhuijzen GA, Creemers GJ, Daniels-Gooszen AW, et al. Radical resection after IORT-containing multimodality treatment is the most important determinant for outcome in patients treated for locally recurrent rectal cancer. Ann Surg Oncol. 2008;15:1937–47.
51. Nielsen M, Rasmussen P, Pedersen B, Hagemann-Madsen R, Lindegaard J, Laurberg S. Early and late outcomes of surgery for locally recurrent rectal cancer: a prospective 10-year study in the total mesorectal excision era. Ann Surg Oncol. 2015;22:2677–84.
52. Dozois EJ, Privitera A, Holubar SD, Aldrete JF, Sim FH, Rose PS, et al. High sacrectomy for locally recurrent rectal cancer: can long-term survival be achieved? J Surg Oncol. 2011;103:105–9.
53•• Solomon MJ, Brown KGM, Koh CE, Lee P, Austin KKS, Masya L. Lateral pelvic compartment excision during pelvic exenteration. Br J Surg. 2015;102:1710–7 **Important description of the evolution of radical pelvic exenteration techniques for LRRC involving the lateral pelvic compartment.**
54. Eng C, Chang GJ, You YN, et al. The role of systemic chemotherapy and multidisciplinary management in improving the overall survival of patients with metastatic squamous cell carcinoma of

the anal canal. Oncotarget. 2015. https://doi.org/10.18632/oncotarget.2563.
55. Yang TX, Morris DL, Chua TC. Pelvic exenteration for rectal cancer: a systematic review. Dis Colon Rectum. 2013;56:519–31.
56. Solomon MJ, Tan KK, Bromilow RG, Al-Mozany N, Lee PJ. Sacrectomy via the abdominal approach during pelvic exenteration. Dis Colon Rectum. 2014;57:272–7.
57. Evans MD, Harji DP, Sagar PM, Wilson J, Koshy A, Timothy J, et al. Partial anterior sacrectomy with nerve preservation to treat locally advanced rectal cancer. Color Dis. 2013. https://doi.org/10.1111/codi.12215.
58. Milne T, Solomon MJ, Lee P, Young JM, Stalley P, Harrison JD. Assessing the impact of a sacral resection on morbidity and survival after extended radical surgery for locally recurrent rectal cancer. Ann Surg. 2013;258:1007–13.
59. Colibaseanu DT, Mathis KL, Abdelsatter ZM, Larson DW, Haddock MG, Dozois EJ. Is curative resection and long-term survival possible for locally re-recurrent colorectal cancer in the pelvis? Dis Colon Rectum. 2013;56:14–9.
60. Lau YC, Jongerius K, Wakeman C, Heriot AG, Solomon MJ, Sagar PM, et al. Influence of the level of sacrectomy on survival in patients with locally advanced and recurrent rectal cancer. Br J Surg. 2019;106:484–90.
61. Hahnioser D, Nelson H, Gunderson LL, Hassan I, Haddock MG, O'Connell MJ, et al. Curative potential of multimodality therapy for locally recurrent rectal cancer. Ann Surg. 2003;237:502–8.
62. Sagar PM. Ultraradical resection for locally recurrent rectal cancer. Dis Colon Rectum. 2014;57:1–2.
63. Chew MH, Brown WE, Masya L, Harrison JD, Myers E, Solomon MJ. Clinical, MRI, and PET-CT criteria used by surgeons to determine suitability for pelvic exenteration surgery for recurrent rectal cancers: a Delphi study. Dis Colon Rectum. 2013;56:717–25.
64. Senchenkov A, Moran SL, Petty PM, Knoetgen J, Clay RP, Bite U, et al. Predictors of complications and outcomes of external hemipelvectomy wounds: account of 160 consecutive cases. Ann Surg Oncol. 2008;15:355–63.
65. Austin KKS, Solomon MJ. Pelvic exenteration with en bloc iliac vessel resection for lateral pelvic wall involvement. Dis Colon Rectum. 2009;52:1223–33.
66. Akiyoshi T, Nagata J, Nagasaki T, Konishi T, Fujimoto Y, Nagayama S, et al. Laparoscopic salvage lateral pelvic lymph node dissection for locally recurrent rectal cancer. Color Dis. 2015;17:O213–6.
67. Nagasaki T, Akiyoshi T, Ueno M, Fukunaga Y, Nagayama S, Fujimoto Y, et al. Laparoscopic salvage surgery for locally recurrent rectal cancer. J Gastrointest Surg. 2014;18:1319–26.
68. Park SY, Choi GS, Jun SH, Park JS, Kim HJ. Laparoscopic salvage surgery for recurrent and metachronous colorectal cancer: 15 years' experience in a single center. Surg Endosc. 2011;25:3551–8.
69. Austin KKS, Young JM, Solomon MJ. Quality of life of survivors after pelvic exenteration for rectal cancer. Dis Colon Rectum. 2010;53:1121–6.
70. van Zoggel DMGI, Bosman SJ, Kusters M, Nieuwenhuijzen GAP, Cnossen JS, Creemers GJ, et al. Preliminary results of a cohort study of induction chemotherapy-based treatment for locally recurrent rectal cancer. Br J Surg. 2018;105:447–52 **Initial results of study assessing the value of induction chemotherapy as a neoadjuvant option for patients who have already undergone preoperative (chemo)radiotherapy for the primary tumor.**
71. De Campos-Lobato LF, Stocchi L, Da Luz MA, Geisler D, Dietz DW, Lavery IC, et al. Pathologic complete response after neoadjuvant treatment for rectal cancer decreases distant recurrence and could eradicate local recurrence. Ann Surg Oncol. 2011;18:1590–8.
72. Valentini V, Morganti AG, Gambacorta MA, et al. Preoperative hyperfractionated chemoradiation for locally recurrent rectal cancer in patients previously irradiated to the pelvis: a multicentric phase II study. Int J Radiat Oncol Biol Phys. 2006;64:1129–39.
73. Bosman SJ, Holman FA, Nieuwenhuijzen GAP, Martijn H, Creemers GJ, Rutten HJT. Feasibility of reirradiation in the treatment of locally recurrent rectal cancer. Br J Surg. 2014;101:1280–9.
74. Glimelius B. Recurrent rectal cancer. The pre-irradiated primary tumour: can more radiotherapy be given? Color Dis. 2003;5:501–3.
75. Van Der Meij W, Rombouts AJM, Rutten H, Bremers AJA, De Wilt JHW. Treatment of locally recurrent rectal carcinoma in previously (chemo)irradiated patients: a review. Dis Colon Rectum. 2016;59:148–56.
76. Mohiuddin M, Marks G, Marks J. Long-term results of reirradiation for patients with recurrent rectal carcinoma. Cancer. 2002;95:1144–50.
77. Yu SKT, Bhangu A, Tait DM, Tekkis P, Wotherspoon A, Brown G. Chemoradiotherapy response in recurrent rectal cancer. Cancer Med. 2014;3:111–7.
78. Hathout L, Williams T, Jabbour SK. The impact of novel radiation treatment techniques on toxicity and clinical outcomes in rectal Cancer. Curr Colorectal Cancer Rep. 2017;13:61–72.
79. Sun Z, Adam MA, Kim J, Czito B, Mantyh C, Migaly J. Intensity-modulated radiation therapy is not associated with perioperative or survival benefit over 3D-conformal radiotherapy for rectal Cancer. J Gastrointest Surg. 2017;21:106–11.
80. Wiig JN, Poulsen JP, Tveit KM, Olsen DR, Gierckskiy KE. Intraoperative irradiation (IORT) for primary advanced and recurrent rectal cancera need for randomised studies. Eur J Cancer. 2000;36:868–74.
81. Valentini V, Morganti AG, De Franco A, Coco C, Ratto C, Doglietto GB, et al. Chemoradiation with or without intraoperative radiation therapy in patients with locally recurrent rectal carcinoma: prognostic factors and long term outcome. Cancer. 1999;86:2612–24.
82. Hashiguchi Y, Sekine T, Sakamoto H, Tanaka Y, Kazumoto T, Kato S, et al. Intraoperative irradiation after surgery for locally recurrent rectal cancer. Dis Colon Rectum. 2005;42:886–93.
83. Haddock MG, Gunderson LL, Nelson H, Cha SS, Devine RM, Dozois RR, et al. Intraoperative irradiation for locally recurrent colorectal cancer in previously irradiated patients. Int J Radiat Oncol Biol Phys. 2001:1;49(5):1267–74. https://www.ncbi.nlm.nih.gov/pubmed/11286833
84. Haddock MG, Miller RC, Nelson H, Pemberton JH, Dozois EJ, Alberts SR, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. Int J Radiat Oncol Biol Phys. 2011;79:143–50.
85. Suzuki K, Dozois RR, Devine RM, Nelson H, Weaver AL, Gunderson LL, et al. Curative reoperations for locally recurrent rectal cancer. Dis Colon Rectum. 1996:39(7):730–6. https://www.ncbi.nlm.nih.gov/pubmed/8674362
86. Allee PE, Tepper JE, Gunderson LL, Munzenrider JE. Postoperative radiation therapy for incompletely resected colorectal carcinoma. Int J Radiat Oncol Biol Phys. 1989;17:1171–6.
87. Kishan AU, Voog JC, Wiseman J, et al. Standard fractionation external beam radiotherapy with and without intraoperative radiotherapy for locally recurrent rectal cancer: the role of local therapy in patients with a high competing risk of death from distant disease. Br J Radiol. 2017. https://doi.org/10.1259/bjr.20170134.
88. Suzuki K, Gunderson LL, Devine RM, Weaver AL, Dozois RR, Ilstrup DM, et al. Intraoperative irradiation after palliative surgery for locally recurrent rectal cancer. Cancer. 1995;75:939–52.
89. Guo S, Reddy CA, Kolar M, Woody N, Mahadevan A, Deibel FC, et al. Intraoperative radiation therapy with the photon radiosurgery

system in locally advanced and recurrent rectal cancer: retrospective review of the Cleveland clinic experience. Radiat Oncol. 2012;7:1–8. https://doi.org/10.1186/1748-717X-7-110.
90. Colaco RJ, Nichols RC, Huh S, Getman N, Ho MW, Li Z, et al. Protons offer reduced bone marrow, small bowel, and urinary bladder exposure for patients receiving neoadjuvant radiotherapy for resectable rectal cancer. J Gastrointest Oncol. 2014;5:3–8.
91. Palmer M, Mok H, Ciura K, Georges R, Nguyen B, Crawford C, et al. Dose reduction to small bowel and other relevant structures in rectal carcinoma with proton therapy. Int J Radiat Oncol. 2012;84:S846.
92. Wolff HA, Wagner DM, Conradi LC, Hennies S, Ghadimi M, Hess CF, et al. Irradiation with protons for the individualized treatment of patients with locally advanced rectal cancer: a planning study with clinical implications. Radiother Oncol. 2012;102:30–7.
93. Ie M, Yamaguchi T, Kinugasa Y, Sato S, Yamakawa Y, Kagawa H, et al. Complete response of locally recurrent anorectal cancer to proton beam therapy alone—a case report. Gan To Kagaku Ryoho. 2014;41:2623–5.
94. Berman AT, Both S, Sharkoski T, Goldrath K, Tochner Z, Apisarnthanarax S, et al. Proton reirradiation of recurrent rectal cancer: dosimetric comparison, toxicities, and preliminary outcomes. Int J Part Ther. 2014;1:2–13.
95. Goes RN, Beart RW, Simons AJ, Gunderson LL, Grado G, Streeter O. Use of brachytherapy in management of locally recurrent rectal cancer. Dis Colon Rectum. 1997;40:1177–9.
96. Bishop AJ, Gupta S, Cunningham MG, Tao R, Berner PA, Korpela SG, et al. Interstitial brachytherapy for the treatment of locally recurrent anorectal cancer. Ann Surg Oncol. 2015;22:596–602 **A key study exploring the benefit of brachytherapy in LRRC and LRAC.**
97. Wang JJ, Yuan HS, Li JN, Jiang YL, Tian SQ, Yang RJ. CT-guided radioactive seed implantation for recurrent rectal carcinoma after multiple therapy. Med Oncol. 2010;27:421–9.
98. Wang ZM, Huang G, Chen KM, Lu J, Gong J, Zheng YF, et al. Clinical application of CT-guided 125 I seed interstitial implantation for recurrent rectum carcinoma. J Interv Radiol. 2009;18:681–4.
99. Hildebrandt B, Wust P, Gellermann J, Nicolaou A, Trappe RU, Felix R, et al. Treatment of locally recurrent rectal cancer with special focus on regional pelvic hyperthermia. Onkologie. 2004;27:506–11.
100. De Haas-Kock DFM, Buijsen J, Pijls-Johannesma M, Lutgens L, Lammering G, Van Mastrigt GAPG, et al. Concomitant hyperthermia and radiation therapy for treating locally advanced rectal cancer. Cochrane Database Syst Rev. 2009. https://doi.org/10.1002/14651858.CD006269.pub2.
101. Ohno S, Sumiyoshi Y, Mori M, Sugimachi K. Hyperthermia for rectal cancer. Surgery. 2002;131:S121–7.
102. Kim SW, Yea JW, Kim JH, Gu MJ, Kang MK. Selecting patients for hyperthermia combined with preoperative chemoradiotherapy for locally advanced rectal cancer. Int J Clin Oncol. 2018;23:287–97.
103. González DG (1996) Thermoradiotherapy for Tumors of the Lower Gastrointestinal Tract. In: Thermoradiotherapy and Thermochemotherapy. Medical Radiology (Diagnostic Imaging and Radiation Oncology). Springer, Berlin, Heidelberg. https://doi.org/10.1007/978-3-642-60938-1_8
104. Milani V, Pazos M, Issels RD, Buecklein V, Rahman S, Tschoep K, et al. Radiochemotherapy in combination with regional hyperthermia in preirradiated patients with recurrent rectal cancer. Strahlenther Onkol. 2008;184:163–8.
105. Chu W, Staruch RM, Pichardo S, Tillander M, Köhler MO, Huang Y, et al. Magnetic resonance-guided high-intensity focused ultrasound hyperthermia for recurrent rectal cancer: MR thermometry evaluation and preclinical validation. Int J Radiat Oncol Biol Phys. 2016;95:1259–67.
106. Fraunholz I, Rabeneck D, Weiß C, Rödel C. Combined-modality treatment for anal cancer: current strategies and future directions. Strahlenther Onkol. 2010;186:361–6.
107. Sebag-Montefiore D, Adams R, Bell S, et al. The development of an umbrella trial (PLATO) to address radiation therapy dose questions in the locoregional management of squamous cell carcinoma of the anus. Int J Radiat Oncol. 2016;96:E164–5.
108. Nigro ND. Multidisciplinary management of cancer of the anus. World J Surg. 1987;11:446–51.
109. Cummings BJ. Concomitant radiotherapy and chemotherapy for anal cancer. SeminOncol. 1992;19:102–8.
110. Mackowski A, Levitt M, Makin G, Salama P, Tan P, Penter C, et al. Anal squamous cell carcinoma: are we improving outcomes? ANZ J Surg. 2018;88:1013–6.
111. Ajani JA, Winter KA, Gunderson LL, Pedersen J, Benson AB, Thomas CR, et al. Prognostic factors derived from a prospective database dictate clinical biology of anal cancer: the intergroup trial (RTOG 98-11). Cancer. 2010;116:4007–13.
112. Harris DA, Williamson J, Davies M, Evans MD, Drew P, Beynon J. Outcome of salvage surgery for anal squamous cell carcinoma. Color Dis. 2013;15:968–73.
113. Gunderson LL, Moughan J, Ajani JA, et al. Anal carcinoma: impact of TN category of disease on survival, disease relapse, and colostomy failure in US gastrointestinal intergroup RTOG 98-11 phase 3 trial. Int J Radiat Oncol Biol Phys. 2013;87:638–45.
114. Kachnic LA, Winter K, Myerson RJ, et al. RTOG 0529: a phase 2 evaluation of dose-painted intensity modulated radiation therapy in combination with 5-fluorouracil and mitomycin-C for the reduction of acute morbidity in carcinoma of the anal canal. Int J Radiat Oncol Biol Phys. 2013;86:27–33.
115. Hong JC, Cui Y, Patel BN, et al. Association of interim FDG-PET imaging during chemoradiation for squamous anal canal carcinoma with recurrence. Int J Radiat Oncol Biol Phys. 2018;102:1046–51.
116. Renehan AG, Saunders MP, Schofield PF, O'Dwyer ST. Patterns of local disease failure and outcome after salvage surgery in patients with anal cancer. Br J Surg. 2005;92:605–14.
117. Renehan AG, O'Dwyer ST. Management of local disease relapse. Color Dis. 2011;13:44–52.
118. Bignell M, Chave H, Branagan G. Outcome of surgery for recurrent anal cancer: results from a tertiary referral centre. Color Dis. 2018;20:771–7.
119. Pesi B, Scaringi S, Di Martino C, Batignani G, Giudici F, Bisogni D, et al. Results of surgical salvage treatment for anal canal cancer: a retrospective analysis with overview of the literature. Dig Surg. 2017;34:380–6.
120. Singh M, Kinsley S, Huang A, Ricci JA, Clancy TE, Irani J, et al. Gracilis flap reconstruction of the perineum: an outcomes analysis. J Am Coll Surg. 2016;223:602–10.
121. Chessin DB, Hartley J, Cohen AM, et al. Rectus flap reconstruction decreases perineal wound complications after pelvic chemoradiation and surgery: a cohort study. Ann Surg Oncol. 2005;12:104–10.
122. Longo WE, Vernava AM, Wade TP, Coplin MA, Virgo KS, Johnson FE. Recurrent squamous cell carcinoma of the anal canal: predictors of initial treatment failure and results of salvage therapy. Ann Surg. 1994;220:40–9.
123. Akbari RP, Paty PB, Guillem JG, Weiser MR, Temple LK, Minsky BD, et al. Oncologic outcomes of salvage surgery for epidermoid carcinoma of the anus initially managed with combined modality therapy. Dis Colon Rectum. 2004;47:1136–44.
124. Schiller DE, Cummings BJ, Rai S, Le LW, Last L, Davey P, et al. Outcomes of salvage surgery for squamous cell carcinoma of the anal canal. Ann Surg Oncol. 2007;14:2780–9.

125. Mullen JT, Rodriguez-Bigas MA, Chang GJ, Barcenas CH, Crane CH, Skibber JM, et al. Results of surgical salvage after failed chemoradiation therapy for epidermoid carcinoma of the anal canal. Ann Surg Oncol. 2007;14:478–83.
126. Hannes S, Reinisch A, Bechstein WO, Habbe N. Salvage abdominoperineal excisions in recurrent anal cancer—impact of different reconstruction techniques on outcome, morbidity, and complication rates. Int J Color Dis. 2016;31:653–9.
127. Ellenhorn JDI, Enker WE, Quan SHQ. Salvage abdominoperineal resection following combined chemotherapy and radiotherapy for epidermoid carcinoma of the anus. Ann Surg Oncol. 1994;1:105–10.
128. Van Der Wal BCH, Cleffken BI, Gulec B, Kaufman HS, Choti MA. Results of salvage abdominoperineal resection for recurrent anal carcinoma following combined chemoradiation therapy. J Gastrointest Surg. 2001;5:383–7.
129. Nilsson PJ, Svensson C, Goldman S, Glimelius B. Salvage abdominoperineal resection in anal epidermoid cancer. Br J Surg. 2002;89:1425–9.
130. Alamri Y, Buchwald P, Dixon L, Dobbs B, Eglinton T, McCormick J, et al. Salvage surgery in patients with recurrent or residual squamous cell carcinoma of the anus. Eur J Surg Oncol. 2016;42:1687–92.
131. Hagemans JAW, Blinde SE, Nuyttens JJ, Morshuis WG, Mureau MAM, Rothbarth J, et al. Salvage abdominoperineal resection for squamous cell anal cancer: a 30-year single-institution experience. Ann Surg Oncol. 2018;25:1970–9 **A recent single-center report of APR for LRAC, updating our data on outcomes for this relatively rare condition**.
132. Shridhar R, Shibata D, Chan E, Thomas CR. Anal cancer: current standards in care and recent changes in practice. CA Cancer J Clin. 2015;65:139–62.
133. Pia Sormani M. The Will Rogers phenomenon: the effect of different diagnostic criteria. J Neurol Sci. 2009. https://doi.org/10.1016/S0022-510X(09)71300-0.
134. Severino NP, Chadi SA, Rosen L, Coiro S, Choman E, Berho M, et al. Survival following salvage abdominoperineal resection for persistent and recurrent squamous cell carcinoma of the anus: do these disease categories affect survival? Color Dis. 2016;18:959–66.
135. Yao J-N, Zhang X-X, Zhou H-N, Li Y-L, Xu H-R, Wang C-F, et al. Human papillomavirus related anal squamous cell carcinoma survival: a systematic review and meta-analysis. Transl Cancer Res. 2017;6:463–73.
136. NCCN. Anal carcinoma (version.2018).
137. Sclafani F, Morano F, Cunningham D, Baratelli C, Kalaitzaki E, Watkins D, et al. Platinum-fluoropyrimidine and paclitaxel-based chemotherapy in the treatment of advanced anal cancer patients. Oncologist. 2017;22:402–8.
138. Rao S, Sclafani F, Eng C, et al. InterAACT: a multicentre open label randomised phase II advanced anal cancer trial of cisplatin (CDDP) plus 5-fluorouracil (5-FU) vs carboplatin (C) plus weekly paclitaxel (P) in patients (pts) with inoperable locally recurrent (ILR) or metastatic treatments. Ann Oncol. 2018;29:viii715–6.
139•• Kim S, François E, André T, et al. Docetaxel, cisplatin, and fluorouracil chemotherapy for metastatic or unresectable locally recurrent anal squamous cell carcinoma (Epitopes-HPV02): a multicentre, single-arm, phase 2 study. Lancet Oncol. 2018;19:1094–106 **A phase II study attempting to establish a new standard of chemotherapeutic care for LRAC.**
140. Strauss J, Gatti-Mays ME, Redman J, et al. Safety and activity of M7824, a bifunctional fusion protein targeting PD-L1 and TGF-β, in patients with HPV associated cancers. J Clin Oncol. 2018;36:3007.
141. Ott PA, Piha-Paul SA, Munster P, et al. Safety and antitumor activity of the anti-PD-1 antibody pembrolizumab in patients with recurrent carcinoma of the anal canal. Ann Oncol Off J Eur Soc Med Oncol. 2017;28:1036–41.
142. Osborne EM, Eng C, Skibber JM, et al. Hyperfractionated accelerated reirradiation for patients with recurrent anal cancer previously treated with definitive chemoradiation. Am J Clin Oncol Cancer Clin Trials. 2018;41:632–7.
143. Hallemeier CL, You YN, Larson DW, Dozois EJ, Nelson H, Klein KA, et al. Multimodality therapy including salvage surgical resection and intraoperative radiotherapy for patients with squamous-cell carcinoma of the anus with residual or recurrent disease after primary chemoradiotherapy. Dis Colon Rectum. 2014:57(4):442–8. https://doi.org/10.1097/DCR.0000000000000071
144. Wright JL, Gollub MJ, Weiser MR, Saltz LB, Wong WD, Paty PB, et al. Surgery and high-dose-rate intraoperative radiation therapy for recurrent squamous-cell carcinoma of the anal canal. Dis Colon Rectum. 2011;54:1090–7.
145. Detering R, Karthaus E, Borstlap W, Marijnen C, van de Velde C, Bemelman W, et al. Treatment and survival of locally recurrent rectal cancer: a cross-sectional population study 15 years after the Dutch TME trial. Eur J Surg Oncol. 2019. https://doi.org/10.1016/j.ejso.2019.06.016.

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