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ACR Appropriateness Criteria®

RECURRENT RECTAL CANCER

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Summary of Literature Review

Introduction/Background

Local or regional failure in rectal cancer presents a major dilemma. Therapy strategies for patients with local pelvic recurrences are individualized, depending on the site of local recurrence as well as the type of therapy previously received.

For new patients with recurrences at the anastomoses from a previous low anterior resection who had not received adjuvant radiation therapy (RT) previously, appropriate treatment would include either reresection followed by postoperative combined-modality therapy (CMT) or a preoperative CMT approach followed by surgical intervention with or without intraoperative radiation if technically and medically feasible. For those patients having previously received pelvic radiation, limited reirradiation with or without chemotherapy and intraoperative radiotherapy (IORT) is an option.

Radiation Versus Chemoradiation

In the setting of a patient presenting with a local pelvic or perineal scar recurrence after abdominal-perineal resection (APR), surgery remains an option, followed by CMT if the patient had not previously been treated. Type of primary surgery, symptoms, location of the recurrence, and whether the tumor is fixed to adjacent structures affect overall prognosis, with a median survival time of 28 months with a R0 resection compared to 12 months with an R1 or R2 resection [1]. A high postoperative morbidity rate can occur in patients undergoing radical resection, including sacrectomy [2]. Alternatively, preoperative RT with curative intent could also be given for local recurrences in the setting of a previous APR. Patients with poor performance status could be treated with palliative CMT alone. The chemotherapy agent 5-fluorouracil (5-FU) is generally incorporated with RT in an effort to increase radio responsiveness; however, the effectiveness of chemoradiation compared to radiation alone in this setting or in patients with other sites of pelvic recurrence is debatable.

Importance of Preoperative or Definitive Radiation (With or Without chemotherapy) in Patients With Locally Recurrent Rectal Cancer

Vermaas et al [3] compared the results of preoperative RT and surgery to surgery alone in patients with recurrent rectal cancer. Local control after preoperative treatment was statistically significantly higher at 3 and 5 years compared to the surgery-alone group. There was, however, no difference in overall or metastases-free survival between the groups. Larsen et al [4] evaluated preoperative and perioperative risk factors for morbidity and mortality after irradiation and surgery in patients >75 years of age with locally advanced or recurrent rectal cancer. They reported a 46% R0 resection rate in patients with recurrent cancers. Margin status was found to be predictive of disease-free survival rates in patients undergoing aggressive surgery including sacrectomy for recurrent rectal cancer [5]. They did, however, report a 42% significant complication rate with patients

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undergoing sacrectomy having a higher complication rate. Surgery also provided a longer median survival time—21 months, compared to 12 months for patients receiving combined RT and chemotherapy alone—in a population-based study of 141 patients with recurrent rectal cancers [6]. A 57% 5-year survival rate was reported in 25 patients undergoing a curative resection. Chemoradiotherapy with or without surgery was found to be beneficial in a trial of 67 patients treated with locally recurrent rectal cancer not receiving previous therapy with a 5-year overall survival rate of 48.9%. Interestingly, no statistically significant difference was found when comparing clinical outcomes between the patients receiving chemoradiotherapy with and without surgery [7].

Hu et al [8] investigated the use of 3-D conformal RT combined with FOLFOX4 chemotherapy in 48 patients with unresectable recurrent rectal cancer. They reported a >90% relief in pain with a 56.5% overall response rate in the study group. They did report, however, more peripheral neuropathy in the study group compared to the control group. You et al [9] also reported on the use of an oxaliplatin-containing regimen in patients with recurrent rectal cancer without prior RT. Complete clinical response was documented in 14% with a partial remission in 61% with an overall and disease-free survival of 45% and 14%, respectively (see Variant 1 and Variant 2).

Reirradiation

For patients with locally recurrent rectal cancer following high-dose pelvic radiation, management decisions have generally been directed toward palliative care, employing diverting colostomies and chemotherapy. Although historically considered unsafe, reirradiation in the pelvis has been investigated in selected patients with locally recurrent rectal cancer and found to be reasonably well tolerated and can provide symptomatic relief in most patients. Additionally, a significant percentage of patients were able to undergo radical surgical salvage, with a 2-year survival rate of 66% in this group [10]. An update from the same institution included 52 patients with recurrent rectal cancer who underwent reirradiation [11]. A 15% bowel obstruction rate and a 7% fistula rate were reported when reirradiation was combined with surgery [12]. The median reirradiation dose was 30.6 Gy. Twenty-two patients were treated in a hyperfractionated approach (1.2 Gy twice daily [BID]). Total cumulative doses ranged from 66.6 Gy to 104.9 Gy with a median total dose of 84.4 Gy. The whole pelvis was not treated, and small bowel and bladder were excluded from the reirradiation field. The actuarial survival at 2 years was 25%, decreasing to 14% at 3 years. Bleeding was stopped in 100% of patients, with palliation of pain seen in 65%. The incidences of RTOG® grade 3 and 4 late toxicity were 23% and 10%, respectively. The use of hyperfractionated RT resulted in reduced late toxicity in comparison to conventionally treated patients receiving once-daily irradiation. Pacelli et al [13] treated 58 patients who had rectal cancer recur after previous RT, delivering either 23.4 Gy in 1.8 Gy fractions or 1.2 Gy BID to 40.8 Gy. Intraoperative electron beam radiotherapy (IOERT) was delivered in 20 cases. They reported a 40% 5-year overall survival rate, with 5-year overall survival greater in patients who also underwent an R0 resection. A 60% overall response rate and 93% clinical response rate was found in 72 patients receiving 3-D conformal accelerated hyperfractionated RT, 1.2 Gy BID to 36 Gy, with unresectable patients receiving 51.6 to 56.4 Gy, combined with capecitabine. Grade 3–4 diarrhea was noted in 9.7%, with late small-bowel obstruction seen in 1.4%.

Valentini et al [14] evaluated the response rate, resectability rate, local control, and treatment-related toxicity of preoperative hyperfractionated chemoradiation for patients with locally recurrent rectal cancer who had received previous radiation. They found that 86.4% of patients had treatment completed without any interruption, with only a 5.1% rate of acute lower gastrointestinal toxicity. They also reported a 39% 5-year survival rate. Juffermans et al [15] reported a 72% good or complete palliative effect for a median of 6 months in patients receiving reirradiation and hyperthermia. Henry et al [16] reported a median overall survival time of 38 months with an estimated 40% 5-year survival rate in patients having resection of isolated pelvic recurrences. In this study, 56 of 88 patients had additional radiation, including 24 treated with brachytherapy, 8 treated with IORT, and 24 treated with external beam radiation. Preoperative carcinoembryonic antigen and final margin status were statistically significant predictors of outcome.

Hansen et al [17] reported on a cohort of 577 patients with local recurrence of rectal cancer, with 35.2% receiving palliative RT and 71.4% having RT prior to additional resection with a 1.6% 30-day mortality rate. Only 17% of patients had RT prior to the recurrence, either preoperative (8%) or postoperative (9%), at the time of the treatment of the primary tumor. Patients received 50 Gy if they received definitive RT and 30 Gy if they received palliative RT. Patients undergoing an R0 resection had a 55% survival rate as compared to 20% if undergoing an R1 resection.

Every effort should be made to obtain an R0 resection. Most studies have found completeness of resection to be an independent prognostic variable for survival [6,13,17-24].

Patients selected for this experimental approach might include those with locally recurrent disease alone or in combination with metastatic cancer, when suffering from intractable pain and/or bleeding. They should have a Karnofsky performance status (KPS) of ≥70% and have no prior history of bowel obstruction within the pelvis. The optimal reirradiation dose has yet to be determined; however, final cumulative dose decisions should be determined based on the initial radiation dose given, the amount of small bowel in the radiation treatment field, the distance in time to recurrence, and the volume previously treated, as well as the intended volume to be retreated with irradiation. Reirradiation doses exceeding 50 Gy were found to significantly increase the infield progression-free survival [25]. When reirradiating the pelvis, every effort should be made to limit the dose to the bowel or bladder (see Variant 3).

Review of Intraoperative Radiotherapy

IORT provides an additional therapy option in patients with locally recurrent rectal cancer, including those who have received prior external beam pelvic radiation. IORT involves radiation treatment delivered during a surgical procedure to the tumor bed, with the advantage of sparing surrounding normal tissues. Radiation is delivered either by a linear accelerator, resulting in the production of electron beams (IOERT), or in the form of either low-dose-rate (LDR) or high-dose-rate (HDR) brachytherapy. LDR brachytherapy involves permanent placement of radioactive I-125 or Pd-103 seeds in the tumor bed.

HDR brachytherapy uses a machine housing a high-activity Ir-192 source that can be connected to a multichannel applicator that can conform to the tumor bed [26-28]. With HDR-IORT, the dose distribution (depth and location) can be individualized by altering source dwell positions. A dose of 10–20 Gy can be delivered over several minutes, compared to hours with LDR brachytherapy. IOERT has been used in an effort to improve local control and quality of life. It requires less planning and setup time when compared to HDR-IORT; however, it is more challenging for treating larger areas, and dosimetry planning is not as reliable. Ideally, each department could benefit from the flexibility of having both HDR-IORT and IOERT in order to accommodate diverse cases [29].

Intraoperative Radiotherapy

Abuchaibe et al [30] reported that the extent of surgical resection was the most important factor for improving local control in patients undergoing IORT, with a local control rate of 50% and a 2-year actuarial local relapse-free survival rate of 56% reported in this group of patients. Overall, including patients unable to undergo a complete resection, the 2-year actuarial local relapse-free survival rate was only 14%. Use of IOERT with close or positive resection margins has historically resulted in inferior outcomes in patients with locally recurrent rectal cancer [13]. Dresen et al [18] reported on 57 patients receiving reirradiation of 30.6 Gy with IOERT. The IOERT dose was dependent upon the completeness of resection, with patients having an R0 resection receiving 10 Gy, patients with an R1 resection receiving 12.5 Gy, patients with an R2 resection and <2 cm residual receiving 15 Gy, and those with ≥2 cm receiving 17.5 Gy. The 5-year overall survival rate was 48.4% in those patients undergoing a R0 resection.

Patients undergoing a radical resection and the stage of the primary tumor were the only factors predicting overall survival in multivariate analysis.

Ferenschild et al [19] reported 3-year and 5-year rates of local control to be 49% and 34%, respectively, in patients receiving 10 Gy IOERT and 50 Gy external beam radiotherapy (EBRT). Once again, those patients undergoing complete resection fared better than those with an incomplete resection.

In one of the largest studies to date, Haddock et al [31] reported on a series of 607 patients with recurrent colorectal cancer who received IOERT (median: 15, range: 7.5 to 30 Gy), as a component of their treatment. As a component of their treatment, 96% had EBRT, with a median 45.5 Gy, and 37% had an R0 resection. Survival rates at 5 years and 10 years were 30% and 16%, respectively. Central and local relapse was more common in patients with previous RT and with subtotal resection. Grade 3 and higher toxicity was attributable to IOERT in 11% of patients. Neuropathy was seen in 15% of patients and increased with IOERT doses >12.5 Gy.

Recurrence was found to be higher in a series of patients undergoing retreatment for recurrent rectal cancer if they had an R1 or R2 resection as compared to an R0 resection [22]. Reirradiation was incorporated with regional hyperthermia in 24 patients with recurrent rectal cancer. Patients received a median dose of 39.6 Gy (range: 30–45) combined with 5-FU [32]. The local progression-free survival time was 15 months with a 1-year overall

survival rate of 87% and a 1-year local progression-free survival rate of 61%, and 12.5% of patients had a grade 5 acute toxicity.

Although Vermaas et al reported a 27% local control rate in 11 patients treated with IORT, having received earlier EBRT, they also reported a high morbidity rate. In addition, Dresen et al reported a 4.8% mortality rate, Ferenschild et al had 17 of 25 patients with postoperative morbidity, and Kanemitsu et al had an 81% surgical morbidity rate, emphasizing that this procedure needs to be performed in highly selected patients with good performance status [18-20,33]. Multiple single-institution studies have now demonstrated improved local control and, in some cases, improved survival when IORT is combined with preoperative chemoradiation and aggressive surgery [29,34,35].

Roeder et al [36] found that neoadjuvant EBRT given either prior to or after IOERT resulted in significantly increased rates of free margins (52% versus 24%) in a series of 97 patients treated with locally recurrent rectal cancer. Resection margin status was the strongest prognostic factor for overall survival. The 90-day postoperative mortality was 3.1%.

A number of photon intraoperative systems have been introduced recently. Guo et al [37] treated patients with recurrent rectal cancer with 5 Gy postoperatively to a depth of 1 cm with a commercially available photon radiosurgery system. The surface dose ranged from 13.4 to 23.1 Gy. A 43% 3-year overall survival rate was noted for patients with recurrent disease. The authors reported no intraoperative complications but did report that hydronephrosis after IORT occurred in 24% of patients, but 7 of 10 of these patients also had concomitant disease recurrence.

Additional studies are needed to determine how to optimally combine EBRT and IORT with modern systemic chemotherapy to improve quality of life, limit toxicity, and improve survival in patients with recurrent rectal cancer.

High-Dose-Rate Intraoperative Radiation Therapy

Nuyttens et al [26] reported a 14% local failure rate within the HDR-IORT field in 37 patients with close or positive margins following resection. Therefore, controversy exists as to the importance of final margin status in patients undergoing HDR-IORT [16,26]. Heriot et al [38] had 12 of 160 patients with recurrent rectal cancer receive 10 Gy of HDR-IORT. The presence of involved lymph nodes, the use of HDR-IORT, and an R1 resection resulted in impaired survival. The poor survival is most likely a result of use of HDR-IORT in patients not obtaining a R0 resection.

Permanent Seed Implants

Another method of IORT is the use of permanent I-125 seeds. Wang et al [39] treated 13 patients with a median minimal peripheral dose of 140 Gy (range: 120–160) with a median pain-free interval of 7 (range: 0–14) months. All but 1 of the patients in the study received previous radiation, with 4 patients receiving radiation twice with doses ranging from 80 Gy to 120 Gy. The 1-year and 2-year local control rates were 14.4% and 0%, respectively. Grade 4 complications were noted in 2 patients (15.4%), with 1 developing a cutaneous fistula and the other a fistula after developing recurrent disease. Five patients developed fibrosis, and one developed perineal edema. All side effects were observed within the first 12 months.

Stereotactic Body Radiotherapy

Stereotactic body radiotherapy (SBRT) has been used to treat well-demarcated lesions in the brain, lung, and liver. It is being used to treat tumors in additional anatomic areas as experience grows in the use of this technique. Kim et al [21] used SBRT to treat 23 patients with nodal recurrence of rectal cancer. They delivered a median dose of 39 Gy (range: 30–51) in 3 fractions. They reported an overall survival rate of 25% and a local control rate of 74%. One patient was reported to have severe radiation-related toxicity (see Variant 4). Defoe et al [40] treated 14 patients with recurrent rectal cancer who had previously received RT, median 50.4 Gy, with SBRT with either 36 Gy in 3 fractions or a single fraction of 12, 16, or 18 Gy. The 1-year and 2-year local control rates were 90.9% and 68.2%, respectively, with 90% and 79% 1-year and 2-year overall survival rates. None of the patients experienced grade 3 or 4 toxicity and 57% of patients had no pain after the treatment.

Patient selection is crucial and should be determined in a multidisciplinary setting prior to offering treatment for recurrent rectal cancer. Patients with central recurrence have been demonstrated to have the best outcome,

whereas palliative RT is beneficial for patients with side-wall recurrence. Demonstrated expertise in the use of each modality is essential, given the high morbidity rates with IORT.

Particle Therapy

The use of particle therapy, both proton and carbon ion, has been investigated in the treatment of recurrent rectal cancer with the advent of new particle facilities worldwide. Particle therapy has the potential advantage of treating the tumor while depositing less radiation around the surrounding tissue, a benefit in previously irradiated tissue. A phase I/II study is planned with increasing doses in the phase I part of the study ranging from 12 x 3 GyE to 18 x 3 GyE. The primary endpoint in this portion of the study will be toxicity as in any phase I study with progression-free survival the primary endpoint in the phase II portion of the study [41]. A comparison of multimodality therapy including 3-D conformal RT, chemotherapy and hyperthermia was performed to carbon ion treatment of patients with locally recurrent rectal cancer who hadn't received previous RT in Japan between two institutions. An 85% 2-year overall survival rate was noted in patients treated with carbon ion therapy. There were no reported acute or late gastrointestinal toxicities but 13 and 10 acute and late skin toxicities, respectively [42]. Yamada et al [43] treated 112 patients with 117 sites of locally recurrent primarily resected rectal cancer. None of the patients experienced any grade 3–5 acute reactions with a reported local control rate of 70%, 89%, and 97% for patients treated with 67.2 GyE, 70.4 GyE, and 73.6 GyE, respectively. Overall survival rates were 72% and 40% at 3 years and 5 years, respectively, for patients treated with 73.6 GyE. Recently, Berman et al [44] reported on the use of proton beam therapy in the treatment of 7 patients with locally recurrent rectal cancer who previously had been treated with a median of 50.4 Gy. Mean proton therapy dose was 61.2 Gy (RBE) for a total combined dose of 95.4–151.2 Gy. A total of 3 acute grade 3 and 3 late grade 4 toxicities were reported. Two of 6 patients with a complete metabolic response had recurred locally, but 3 of 6 had complete pain relief, and 3 had partial pain relief. Further studies are needed to fully define the role of particle therapy in this group of patients.

Summary of Recommendations

- The treatment of patients with recurrent rectal cancer is complex and dependent upon many factors, including but not limited to previous RT to the pelvis.
- Newer systemic treatments have improved response rates and given physicians more options in the treatment of patients with this difficult situation.
- The use of induction chemotherapy prior to RT is an evolving treatment option.
- Specialized treatment modalities such as IORT and focused treatments, including SBRT, should be used at institutions with experience in these techniques and preferably in patients enrolled in clinical trials.
- Preoperative chemotherapy with a 5-FU-based regimen with surgical reevaluation is the most appropriate treatment option in patients with recurrent disease who have not received prior RT.
- Patients with good performance status presenting with liver metastasis and who have not had prior RT to the pelvic area may benefit from preoperative chemoradiotherapy followed by re-evaluation for surgery and resection of the liver metastasis.
- Reduced-dose RT, either given daily or hyperfractionated, combined with chemotherapy and re-evaluation for resection, is the preferred choice of treatment in patients with recurrent rectal cancer who have received prior RT to the pelvis.
- The use of induction chemotherapy prior to RT may be appropriate for selected patients presenting asymptomatically.
- IORT, either with electron beam or with HDR afterloading catheters, could be used in selected centers with the appropriate experience in patients with unresectable recurrent rectal cancer.
- Particle therapy may be an option as additional particle therapy facilities are opened, especially in patients who received previous RT.

Summary of Evidence

Of the 44 references cited in the *ACR Appropriateness Criteria® Recurrent Rectal Cancer* document, all of them are categorized as therapeutic references including 15 well-designed studies, 23 good quality studies, and 1 quality study that may have design limitations. There are 5 references that may not be useful as primary evidence.

The 44 references cited in the *ACR Appropriateness Criteria® Recurrent Rectal Cancer* document were published between 1993–2014.

Most of the references are well-designed or good quality studies and provide good evidence.

Supporting Documents

For additional information on the Appropriateness Criteria methodology and other supporting documents go to www.acr.org/ac.

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Clinical Condition: **Recurrent Rectal Cancer**

Variant 1: **56-year-old patient with recurrent rectal bleeding and pain with defecation. Two years ago patient underwent a low anterior resection (pT3N0) and 6 months of adjuvant chemotherapy. Endoscopic ultrasound (EUS) now shows an anastomotic recurrence 6 cm above the anal verge. Biopsy positive for adenocarcinoma. No sites of metastatic disease. Tumor currently unresectable and nonobstructing. KPS 90.**

Treatment	Rating	Comments
Initial Radiation Therapy Treatment		
30 Gy/3.0 Gy to pelvis	1	
30 Gy/3.0 Gy to pelvis with 5-FU-based chemotherapy	2	
30.6 Gy in 1.8 Gy to pelvis with 5-FU based chemotherapy	2	
40.8 Gy in 1.2 Gy BID with 5-FU based chemotherapy	2	
50.4 Gy/1.8 Gy to pelvis	2	
50.4 Gy/1.8 Gy to pelvis with 5-FU-based chemotherapy	9	
50.4 Gy/1.8 Gy to pelvis with FOLFOX chemotherapy	4	This treatment is preferred only on clinical trial.
59.4–64.8 Gy/1.8 Gy to pelvis	3	
59.4–64.8 Gy/1.8 Gy to pelvis with 5-FU-based chemotherapy	4	
SBRT to rectal lesion	2	
External beam RT +/- concurrent chemotherapy with IORT	4	The need for IORT is based on the response to neoadjuvant therapy.
Surgery		
Preoperative RT +/- 5-FU-based chemotherapy and reevaluate operability	9	
Tumor excision and abdominal-perineal resection (APR) before external beam RT	2	
No surgery	1	
5-FU-based Chemotherapy Timing		
4–6 months after therapy to primary	8	
12 months after therapy to primary	3	
Induction chemotherapy prior to RT	2	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Recurrent Rectal Cancer**

Variant 2: **56-year-old patient with recurrent rectal bleeding and pain with defecation. Two years ago the patient underwent a low anterior resection (pT3N0) and 6 months of adjuvant chemotherapy. EUS now shows an anastomotic recurrence 6 cm above anal verge. Biopsy positive for adenocarcinoma. Lesion not fixed to the pelvic sidewall on physical examination and CT. Patient now has a biopsy-proven resectable liver metastasis involving the right lobe (5 cm). KPS 90.**

Treatment	Rating	Comments
Radiation Therapy		
30 Gy/3.0 Gy to pelvis	1	
30 Gy/3.0 Gy to pelvis with 5-FU-based chemotherapy	2	
30.6 Gy in 1.8 Gy to pelvis with 5-FU based chemotherapy	2	
40.8 Gy in 1.2 Gy BID with 5-FU based chemotherapy	2	
50.4 Gy/1.8 Gy to pelvis with 5-FU-based chemotherapy	8	
50.4 Gy/1.8 Gy to pelvis with FOLFOX chemotherapy	4	This treatment is preferred only on clinical trial.
50.4 Gy/1.8 Gy to pelvis	2	
SBRT to rectal lesion	2	
External beam RT +/- concurrent chemotherapy with IORT	4	The need for IORT is based on the response to neoadjuvant therapy.
Treatment of Rectal Primary		
Preoperative RT +/- 5-FU-based chemotherapy and reevaluate operability	8	
Resection of primary rectal tumor +/- IORT boost followed by adjuvant chemoradiation (5-FU based)	3	
No surgery	2	
Treatment of Liver Metastasis		
After resection of primary rectal tumor	5	
At the same time as the resection of the primary rectal tumor	7	
After 3–6 months postsurgical chemotherapy	6	
Before resection of primary site, after preoperative RT	2	
Before resection of primary site, before preoperative RT	2	
5-FU-based Chemotherapy Timing		
4–6 months after therapy to primary	8	
12 months after therapy to primary	3	
Induction chemotherapy prior to RT/surgery	4	

Rating Scale: **1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate**

Clinical Condition: **Recurrent Rectal Cancer**

Variant 3: **56-year-old patient with recurrent rectal bleeding and pain with defecation. Two years ago the patient underwent a low anterior resection after preoperative chemotherapy and radiotherapy for a (pT3N1) rectal cancer and 6 months of adjuvant chemotherapy. Endoscopic ultrasound (EUS) now shows an anastomotic recurrence 6 cm above the anal verge. Biopsy positive for adenocarcinoma. No sites of metastatic disease. KPS 90.**

Treatment	Rating	Comments
Initial Radiation Therapy Treatment		
30 Gy/3.0 Gy to pelvis	1	
30 Gy/3.0 Gy to pelvis with 5-FU-based chemotherapy	2	
30.6 Gy in 1.8 Gy to pelvis with 5-FU based chemotherapy	4	
40.8 Gy in 1.2 Gy BID with 5-FU based chemotherapy	4	
50.4 Gy/1.8 Gy to pelvis	1	
50.4 Gy/1.8 Gy to pelvis with 5-FU-based chemotherapy	1	
50.4 Gy/1.8 Gy to pelvis with FOLFOX chemotherapy	1	This treatment is preferred only on clinical trial.
59.4–64.8 Gy/1.8 Gy to pelvis	1	
59.4–64.8 Gy/1.8 Gy to pelvis with 5-FU-based chemotherapy	1	
SBRT to rectal lesion	1	
External beam RT +/- concurrent chemotherapy with IORT	3	Consider this treatment only at experienced centers.
Surgery		
Preoperative RT +/- 5-FU-based chemotherapy and reevaluate operability	8	
Tumor excision and abdominoperineal resection (APR) before external beam RT	2	
No surgery	1	
5-FU-based Chemotherapy Timing		
4–6 months after therapy to primary	8	
12 months after therapy to primary	3	
Induction chemotherapy prior to RT	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		

Clinical Condition: **Recurrent Rectal Cancer**

Variant 4: **56-year-old male with severe pain that radiates to perineal region. Two years ago the patient was diagnosed with T3N1 rectal cancer 6 cm from anal verge. Underwent an abdominal-perineal resection, pelvic RT totaling 50.4 Gy plus 5-FU, followed by 6 months of adjuvant chemotherapy. CT of abdomen and pelvis reveal rectal mass (4 cm) invading bony pelvis at sciatic notch. No sites of metastatic disease. KPS 90.**

Treatment	Rating	Comments
Radiation Therapy		
10–30 Gy/2.0 Gy to pelvis	2	
10–30 Gy/2.0 Gy to pelvis with 5-FU-based chemotherapy	3	
10–30 Gy/2.0 Gy to pelvis with 5-FU-based chemotherapy + IORT boost to pelvic sidewall	3	
Permanent radioactive implant of symptomatic lesion	2	
Hyper-or standard dose radiation fractionated to 30–40 Gy with 5-FU based chemotherapy followed by reevaluation for surgical resection +/- IORT	7	
SBRT to rectal lesion	2	
Surgery		
Reevaluate operability after external beam RT +/- 5-FU	8	
Surgery post external beam RT +/- 5-FU + IORT boost	7	
Attempt tumor removal + IORT	2	
Reevaluate operability after permanent implant	2	
Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate		