Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
1. Asoglu O, Karanlik H, Muslumanoglu M, et al. Prognostic and predictive factors after surgical treatment for locally recurrent rectal cancer: a single institute experience. *Eur J Surg Oncol.* 2007;33(10):1199-1206.	Observational-Tx	50 patients	To retrospectively evaluate the results of resecting the local recurrence of rectal cancer and to analyze factors that might predict curative resection and those that affect survival.	Median time from original surgery to recurrence was 24 (4–113) months. 48% R0 resection with median survival of 28 months compared to 12 months in R1 or R2 resections. Type of primary surgery, symptoms, location, and fixity of recurrent tumor associated with increased possibility of curative resection. Previous surgery and curative surgery are significant predictors of disease-specific and OS.	2
2. Melton GB, Paty PB, Boland PJ, et al. Sacral resection for recurrent rectal cancer: analysis of morbidity and treatment results. *Dis Colon Rectum.* 2006;49(8):1099-1107.	Observational-Tx	29 patients	To evaluate case selection, morbidity, and outcome for patients undergoing composite sacropelvic resection for locally advanced recurrent rectal cancer.	93% received previous RT with original surgery or prior to sacrectomy or intraoperatively 59% complications with perineal wound breakdown and pelvic abscess the most common. 62% R0 and 34% R1 resection. 47% and 85% 2 and 5 year recurrence rates. 63% and 20% 2 and 5 year disease-specific survival. Sacrectomy for rectal cancer is a high-risk procedure that can achieve clear resection margins with low mortality in select patients. This procedure has a low cure rate but may provide local disease control with acceptable morbidity.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
3. Vermaas M, Ferenschild FT, Nuyttens JJ, et al. Preoperative radiotherapy improves outcome in recurrent rectal cancer. *Dis Colon Rectum.* 2005;48(5):918-928.	Observational-Tx	117 total patients: 92 patients suitable; 59 preoperative RT with a median dose of 50 Gy; 33 did not receive preoperative RT	To compare the results of preoperative RT followed by surgery with surgery only.	The median follow-up of patients alive for the total group was 16 (range, 4–156) months. Tumor characteristics were comparable between the 2 groups. Complete resections were performed in 64% of the patients who received preoperative RT and 45% of the nonirradiated patients. A CR after RT was found in 10% of the preoperative RT patients (n = 6). There were no differences in morbidity and reintervention rate between the 2 groups. Local control after preoperative RT was statistically significantly higher after 3 and 5 years (P=0.036). OS and metastases-free survival were not different in both groups. CR to preoperative RT was predictive for an improved survival. Preoperative RT for recurrent rectal cancer results in a higher number of complete resections and an improved local control compared with patients treated without RT. Preoperative RT should be standard treatment for patients with recurrent rectal cancer.	1
4. Larsen SG, Wiig JN, Tretli S, Giercksky KE. Surgery and pre-operative irradiation for locally advanced or recurrent rectal cancer in patients over 75 years of age. *Colorectal Dis.* 2006;8(3):177-185.	Observational-Tx	86 consecutive patients: 51 primary locally advanced rectal cancer; 35 recurrent rectal cancer	To identify and evaluate preoperative and perioperative risk factors for morbidity and mortality and outcome after irradiation/surgery in patients over 75 years of age.	70% R0 in locally advanced and 46% R0 in recurrent cancers. 5-year survival 29% in locally advanced and 32% in recurrent cancers. 5-year local recurrence rate 24% in R0 and 54% in R1 in locally advanced. 5-year local recurrence rate 24% and 45% in recurrent cancer. Thorough preoperative evaluation and preparation and judicious surgery are important for achieving potentially curative treatment with acceptable morbidity in locally advanced and recurrent rectal cancer in patients over 75 years of age. We suggest that these patients should be evaluated and considered for treatment by multidisciplinary teams as younger patients.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
5. Wells BJ, Stotland P, Ko MA, et al. Results of an aggressive approach to resection of locally recurrent rectal cancer. *Ann Surg Oncol.* 2007;14(2):390-395.	Observational-Tx	52 consecutive patients	To retrospectively analyze outcomes of an aggressive approach to resection of LRRC.	Median follow-up time was 29 months (range 3–72). 46/52 patients resected with curative intent 41/52 R0 resection. 28/52 had en bloc sacrectomy. 42% significant complications with higher complications for patients undergoing sacrectomy. Median OS and DFS were 40 and 24 months. OS predicted by presence of metastasis and margin status and DFS predicted for by margin status.	2
6. 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(2):447-454.	Observational-Tx	141 patients with LRRC	To assess current management and outcomes in patients with LRRC.	40% treated with surgery with curative intent (of which 30% received additional RT), 34% with RT and/or chemotherapy, and 26% with symptomatic palliation only. Total 5-year survival was 9%. 57% 5-year survival in 25 patients undergoing curative resection. No patient not treated with curative surgery or having palliative treatments only survived 5-years. Median survival was 21 months after surgery, 12 with RT/chemotherapy and 3 months with symptomatic palliation. Although outcome for patients with local recurrence of rectal cancer is dismal, the prognosis has improved slightly over time. A radical resection is a prerequisite for cure and the proportion having a potentially curative resection has increased. Multidisciplinary management, including optimized preoperative staging and patient selection for surgery, radical surgical approach and more effective adjuvant treatments are necessary to further improve the prognosis.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
7. Lee JH, Kim DY, Kim SY, et al. Clinical outcomes of chemoradiotherapy for locally recurrent rectal cancer. *Radiat Oncol.* 2011;6:51.	Observational-Tx	67 LRRC patients	To assess the clinical outcome of chemoradiotherapy with or without surgery for LRRC and to find useful and significant prognostic factors for a clinical situation.	The median survival duration of all patients was 59 months. 5-year OS, relapse-free survival, locoregional relapse-free survival, and distant MFS were 48.9%, 31.6%, 66.4%, and 40.6%, respectively. A multivariate analysis demonstrated that the presence of symptoms was an independent prognostic factor influencing OS, relapse-free survival, locoregional relapse-free survival, and distant MFS. No statistically significant difference was found in OS (P=0.181), relapse-free survival (P=0.113), locoregional relapse-free survival (P=0.379), or distant MFS (P=0.335) when comparing clinical outcomes between the chemoradiotherapy with and without surgery groups.	2
8. Hu JB, Sun XN, Yang QC, Xu J, Wang Q, He C. Three-dimensional conformal radiotherapy combined with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer. *World J Gastroenterol.* 2006;12(16):2610-2614.	Experimental-Tx	48 patients	To investigate the effect of 3D-CRT in combination with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer.	For the study group and the control group, the pain-alleviation rates were 95.2% and 91.3% (P>0.05); the overall response rates were 56.5% and 40.0% (P>0.05); the 1-year and 2-year survival rates were 86.9%, 50.2% and 80.0%, 23.9%, with median survival time of 25 months and 16 months (P<0.05); the 2-year distant metastasis rates were 39.1% and 56.0% (P=0.054), respectively. The side effects, except peripheral neuropathy which was relatively severer in the study group, were similar in the 2 groups and well tolerated. 3D-CRT combined with FOLFOX4 chemotherapy for unresectable recurrent rectal cancer is a feasible and effective therapeutic approach, and can reduce distant metastasis rate and improve the survival rate.	1
9. You YT, Chen JS, Wang JY, et al. Concurrent chemoradiotherapy in the treatment of locally recurrent rectal cancer. *Hepatogastroenterology.* 2013;60(121):94-98.	Observational-Tx	96 patients	To assess the outcome of concurrent chemoradiotherapy in treating isolated local recurrent rectal cancer.	A total of 96 patients completed planned concurrent chemoradiation. Complete clinical responses were found in 13/96 patients (14%), partial responses in 59 (61%), stable disease in 21 (22%) and disease progression in 3 (3%). The OS and DFS rates in all the 96 patients were 45% and 14%, respectively.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
10. Mohiuddin M, Lingareddy V, Rakinic J, Marks G. Reirradiation for rectal cancer and surgical resection after ultra high doses. *Int J Radiat Oncol Biol Phys.* 1993;27(5):1159-1163.	Observational-Tx	32 patients	To evaluate toxicity/response of reirradiation in patients with recurrent rectal cancer.	Treatment was well tolerated. Follow-up ranges from 6 to 36 months. 17 patients underwent surgical exploration 6–8 weeks following reirradiation. 11/15 resected patients are alive from 6 to 36 months with a 2-year survival of 66%. Of the patients treated palliatively, symptomatic relief was observed in 13/15 patients. Median survival in this group was 14 months. Based on this experience, it is believed that in selected patients radical surgical resection after cumulative ultra-high doses (70–90 Gy) of radiation can be performed safely. A viable anastomosis is also possible in spite of these high doses. Planned reirradiation for palliative relief of symptoms can be effective without unusual risks of complication. Long-term effects of such ultra-high dose radiation and surgery continue to be monitored.	2
11. Lingareddy V, Ahmad NR, Mohiuddin M. Palliative reirradiation for recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 1997;38(4):785-790.	Observational-Tx	52 patients	To analyze the efficacy and acute and late toxicity of reirradiation for recurrent rectal cancer.	The RTOG Grade 3 acute toxicity rate was 31%. The RTOG Grade 3 and 4 late toxicity rates were 23% and 10%, respectively. On multivariate analysis, the only factor associated with reduced late toxicity was hyperfractionated delivery of reirradiation. Bleeding, pain, and mass effect were palliated completely in 100%, 65%, and 24% of instances, respectively, and the majority of responding patients were palliated until death. The overall median survival time from retreatment was 12 months. The 2- and 3-year overall actuarial survival rates were 25% and 14%, respectively. This unique institutional approach to recurrent rectal cancers resulted in excellent palliation of symptoms. Late complications appeared reduced by hyperfractionated treatment delivery.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
12. Mohiuddin M, Marks GM, Lingareddy V, Marks J. Curative surgical resection following reirradiation for recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 1997;39(3):643-649.	Observational-Tx	39 patients	To evaluate the potential for curative surgical resection of residual disease following reirradiation for recurrent rectal cancer.	Patients have been followed for 24 months to 75 months after reirradiation for recurrent rectal cancer with a median follow-up of 3 years. Reirradiation was well tolerated, with 7 patients requiring a significant treatment break. Early termination of reirradiation occurred in 5 patients because of diarrhea, moist desquamation, or mucositis. Postoperatively, 2 patients developed delayed wound healing. Late complications included 6 patients who developed small bowel obstruction with 3 patients developing a bowel fistula. The median survival of patients is 45 months, with a 5-year actuarial survival of 24%. Actuarial local control at 5 years was 45%. The rate of distant metastases was 17%.	3

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EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
13. Pacelli F, Tortorelli AP, Rosa F, et al. Locally recurrent rectal cancer: prognostic factors and long-term outcomes of multimodal therapy. *Ann Surg Oncol.* 2010;17(1):152-162.	Observational-Tx	58 patients	To retrospectively analyze demographic, pathologic, and therapeutic factors were evaluated to assess long-term prognosis and local control.	44 (75.9%) of 58 patients underwent surgical resection. The overall 5-year survival rate for patients who underwent surgical resection was 54.2%, whereas none of the unresected patients lived 5 years ($P<0.001$). Patients with R0 resection showed a statistically higher 5-year OS and local control rate (72.4% and 70.2%, respectively) compared to R1 patients (37.5% and 31.2%, respectively). At multivariate survival analysis, feasibility of a surgical resection and radicality of excision proved to be independent positive prognostic factors. In contrast, increased presalvage carcinoembryonic antigen serum levels, back pain at diagnosis, and an increasing degree of fixation of recurrent disease to the pelvic wall at preoperative CT scan were statistically significantly linked to decreased OS. Preoperative chemoradiation and radicality of the surgical excision independently influenced the local control among surgically resected patients. Surgical resection still remains the most important therapeutic and prognostic factor for patients with LRRC. Multimodal treatments can be safely performed by an experienced team in referral tertiary centers and can result in a safer outcome, better local disease control, and even long-term survival in carefully selected patients.	2
14. 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(4):1129-1139.	Observational-Tx	59 patients	Phase II study to evaluate the response rate, resectability rate, local control, and treatment-related toxicity of preoperative hyperfractionated chemoradiation for LRRC in patients previously irradiated to the pelvis.	Use of hyperfractionated chemoradiation was associated with a low rate of acute toxicity and an acceptable incidence of late complications. Pain control was excellent. The overall 5-year survival was 39%. Despite 87.4% of patients having F1-3 stage disease, approximately one-third (35%) achieved R0 resection and two-thirds of patients in this cohort of patients were alive at the 5-year mark. However, further studies using innovative treatment algorithms are warranted to hopefully, improve the local tumor response and control.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
15. Juffermans JH, Hanssens PE, van Putten WL, van Rhoon GC, van Der Zee J. Reirradiation and hyperthermia in rectal carcinoma: a retrospective study on palliative effect. *Cancer*. 2003;98(8):1759-1766.	Observational-Tx	47 patients	To evaluate the palliative effect of reirradiation and hyperthermia in patients with unresectable, recurrent colorectal carcinoma.	72% of patients had a good or complete palliative effect for a median duration of 6 months. Patients with smaller tumors, better WHO performance, and a longer interval between first RT and reirradiation had slightly better but nonstatistically significant difference. The described combined treatment was feasible and well tolerated. Comparison of results from RT plus hyperthermia with results after RT alone suggested that additional hyperthermia prolonged the duration of palliation. Firm proof of the contribution of hyperthermia will require performing a phase III study.	2
16. Henry LR, Sigurdson E, Ross EA, et al. Resection of isolated pelvic recurrences after colorectal surgery: long-term results and predictors of improved clinical outcome. *Ann Surg Oncol.* 2007;14(3):1081-1091.	Observational-Tx	90 patients	To assess the predictors of improved clinical outcome in patients treated for isolated pelvic recurrences after colorectal surgery.	56/88 patients had additional RT (24 brachytherapy and 8 IORT). 53% of patients had complications and 4.4% operative mortality. Median OS was 38 months with 40% estimated 5-year survival. 51/86 patients had recurrence (15 local, 16 distant and 20 both).	2
17. Hansen MH, Balteskard L, Dorum LM, Eriksen MT, Vonen B. Locally recurrent rectal cancer in Norway. *Br J Surg.* 2009;96(10):1176-1182.	Observational-Tx	577 patients	To describe management and outcome in patients with LRRC based on data from the Norwegian Colorectal Cancer Registry.	185 patients (32.1%) had curative resections (R0/R1), 203 (35.2%) had palliative RT with or without palliative surgery and chemotherapy, and 189 (32.8%) received no treatment at all or only palliative surgery or chemotherapy. The 5-year OS rate was 14.9%. 97 patients had an R0 resection, and 88 had an R1 resection, with 5-year OS of 55% and 20% respectively. This outcome reflected surgical treatment in 33 different hospitals. Some 274 patients (47.5%) had metastases. The 5-year survival rate after R0 resection was 62% in patients without metastases. Obtaining an R0 resection is the most important prognostic factor in treating recurrent rectal cancer.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
18. Dresen RC, Gosens MJ, Martijn H, 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(7):1937-1947.	Observational-Tx	147 consecutive patients	To assess the outcome of LRRC patients treated with multimodality treatment, consisting of neoadjuvant radio (chemo-) therapy, extended resection, and IORT.	Median OS was 28 months (range 0–146 months). 5-year OS, DFS, MFS, and local control were 31.5%, 34.1%, 49.5% and 54.1% respectively. Radical resection (R0) was obtained in 84 patients (57.2%), microscopically irradical resection (R1) in 34 patients (23.1%), and macroscopically irradical resection (R2) in 29 patients (19.7%). For patients with a radical resection median OS was 59 months and the 5-year OS, DFS, MFS, and local control were 48.4%, 52.3%, 65.5% and 68.9%, respectively. Radical resection was significantly correlated with improved OS, DFS, and local control ($P<0.001$). Patients who received reirradiation or full-course RT survived significantly longer ($P=0.043$) and longer without local recurrence ($P=0.038$) or metastasis ($P<0.001$) compared to patients who were not reirradiated. Radical resection is the most significant predictor of improved survival in patients with LRRC. Neoadjuvant radio (chemo-) therapy is the best option in order to realize a radical resection. Reirradiation is feasible in patients who already received irradiation as part of the primary rectal cancer treatment.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
19. Ferenschild FT, Vermaas M, Verhoef C, Dwarkasing RS, Eggermont AM, de Wilt JH. Abdominosacral resection for locally advanced and recurrent rectal cancer. *Br J Surg.* 2009;96(11):1341-1347.	Observational-Tx	353 patients	To analyze the results of resection of locally advanced and recurrent rectal cancers, including sacral resection.	A mid-sacral resection was carried out in 12 patients (level S3) and a low sacral resection in 13 (level S4/S5). 19 patients had an R0, 4 had an R1 and 2 had an R2 resection. There was no postoperative mortality. Median follow-up was 32 months. Incomplete resection had an independent negative influence on local control (5-year local recurrence rate 42% vs 0% in those with and without incomplete resection; $P<0.001$). The 5-year OS rate was 30%. 5 patients with recurrent tumor had pathological invasion into the sacral bone and none survived beyond 1 year. Abdominosacral resection can be performed in patients with locally advanced and recurrent rectal cancer. Patients who cannot undergo a complete resection or have clear evidence of cortical invasion have a poor prognosis.	1
20. Kanemitsu Y, Hirai T, Komori K, Kato T. Prediction of residual disease or distant metastasis after resection of locally recurrent rectal cancer. *Dis Colon Rectum.* 2010;53(5):779-789.	Observational-Tx	101 consecutive patients	To preoperatively identify patients at high risk of relapse at extrapelvic sites or residual disease after salvage surgery for LRRC to maximize the survival benefit by indicating whether a surgical approach might be successful.	The 5-year disease-specific survival rates of R0, R1, and R2 resection were 43.3%, 19.5%, and 10.0%, respectively ($P<.001$). In a logistic regression analysis, upper sacral (above the inferior margin of the second sacrum)/lateral invasive type and high-grade lymphatic invasion of the primary tumor were associated with palliative surgery. A Cox regression analysis revealed that upper sacral/lateral invasive type, extrapelvic disease, hydronephrosis at recurrence, and high-grade lymphatic or venous invasion of the primary tumor were associated with a lower distant DFS rate. Patients with 1 or more of these risk factors had a 3-year distant DFS rate of 6.2% compared with 54.1% for those with none of these risk factors. It was possible to preoperatively identify patients at high risk of relapse or residual disease. This system might be used on an individual basis to select patients with LRRC for chemotherapy or RT before surgical intervention with curative intent.	1

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
21. Kim MS, Choi C, Yoo S, et al. Stereotactic body radiation therapy in patients with pelvic recurrence from rectal carcinoma. *Jpn J Clin Oncol.* 2008;38(10):695-700.	Observational-Tx	23 patients	To investigate the clinical applications of SBRT using the CyberKnife system for pelvic recurrence from rectal cancer with a focus on survival and toxicity.	The median follow-up was 31 months. 4-year OS and local control rates were 24.9% and 74.3%, respectively. No prognostic factor was found to affect patient survival or local progression. One patient developed a severe radiation-related toxicity, but recovered completely after treatment. SBRT for pelvic recurrence was found to be comparable with other modalities with respect to OS and complication rates. Further studies are needed to confirm these preliminary results.	2
22. Kusters M, Dresen RC, Martijn H, 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(5):1444-1449.	Observational-Tx	170 patients	To analyze results of multimodality treatment in relation to subsite of LRRC.	R0 resections were achieved in 54% of the patients, and 5-year cancer-specific survival was 40.5%. The worst outcomes were seen in presacral LRRC, with only 28% complete resections and 19% 5-year survival (P=0.03 vs other subsites). Anastomotic LRRC resulted in the most favorable outcomes, with 77% R0 resections and 60% 5-year survival (P=0.04). Generally, if a complete resection was achieved, survival improved, except in posterolateral LRRC. Local re-recurrence and metastasis rate were lowest in anastomotic LRRC. Classification of the subsite of LRRC is a predictor of potentially resectable and consequently curable disease. Treatment of posterior LRRC imposes poor results, whereas anastomotic LRRC location shows superior results.	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
23. Rades D, Kuhn H, Schultze J, et al. Prognostic factors affecting locally recurrent rectal cancer and clinical significance of hemoglobin. *Int J Radiat Oncol Biol Phys.* 2008;70(4):1087-1093.	Observational-Tx	94 patients	To investigate potential prognostic factors, including hemoglobin levels before and during RT, for associations with survival and local control in patients with unirradiated LRRC.	Improved survival was associated with better performance status ($P<0.001$), lower AJCC stage ($P=0.023$), surgery ($P=0.011$), chemotherapy ($P=0.003$), and hemoglobin levels ≥12 g/dL both before ($P=0.031$) and during ($P<0.001$) RT. On multivariate analyses, performance status, AJCC stage, and hemoglobin levels during RT maintained significance. Improved local control was associated with better performance status ($P=0.040$), lower AJCC stage ($P=0.010$), lower grading ($P=0.012$), surgery ($P<0.001$), chemotherapy ($P<0.001$), and hemoglobin levels ≥12 g/dL before ($P<0.001$) and during ($P<0.001$) RT. On multivariate analyses, chemotherapy, grading, and hemoglobin levels before and during RT remained significant. Subgroup analyses of the patients having surgery demonstrated the extent of resection to be significantly associated with local control ($P=0.011$) but not with survival ($P=0.45$). Predictors for outcome in patients who received RT for LRRC were performance status, AJCC stage, chemotherapy, surgery, extent of resection, histologic grading, and hemoglobin levels both before and during RT.	2
24. Das P, Delclos ME, Skibber JM, et al. Hyperfractionated accelerated radiotherapy for rectal cancer in patients with prior pelvic irradiation. *Int J Radiat Oncol Biol Phys.* 2010;77(1):60-65.	Observational-Tx	50 patients	To retrospectively determine rates of toxicity, freedom from local progression, and survival in rectal cancer patients treated with reirradiation.	2 patients had grade 3 acute toxicity and 13 patients had grade 3 to 4 late toxicity. The 3-year rate of grade 3 to 4 late toxicity was 35%. The 3-year rate of freedom from local progression was 33%. The 3-year freedom from local progression rate was 47% in patients undergoing surgery and 21% in those not undergoing surgery ($P=0.057$). The 3-year OS rate was 39%. The 3-year OS rate was 66% in patients undergoing surgery and 27% in those not undergoing surgery ($P=0.003$). The 3-year OS rate was 53% in patients with a retreatment interval of >2 years and 21% in those with a retreatment interval of ≤2 years ($P=0.001$).	2

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Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
25. Koom WS, Choi Y, Shim SJ, et al. Reirradiation to the pelvis for recurrent rectal cancer. *J Surg Oncol.* 2012;105(7):637-642.	Observational-Tx	22 patients	To investigate late toxicity and infield progression-free survival in patients with LRRC who had previously received irradiation to the pelvis.	2 patients (9%) had grade-3 acute toxicity and 8 patients (36%) had grade-3 to -4 late toxicity. The incidence of grade-3 to -4 late toxicity in the gastrointestinal and urinary system was 18% and 27%, respectively. Recurrent tumor location (axial or anterior) and surgical resection after reirradiation significantly influenced severe late toxicity (P=0.024 and P=0.039, respectively). In the 17 patients not undergoing surgery after reirradiation, median infield progression-free survival was 16 months. Reirradiation doses exceeding 50 Gy (alphabeta10) (equivalent dose in 2 Gy fractions) significantly increased the infield progression-free survival (P=0.005).	1
26. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, et al. High-dose-rate intraoperative radiotherapy for close or positive margins in patients with locally advanced or recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 2004;58(1):106-112.	Observational-Tx	37 patients	To analyze local failure and survival in patients treated with HDR-IORT.	Overall, 12 patients (32%) had local recurrence, 5 (14%) of which were in the HDR-IORT field. The 3-year local failure rate for primary tumors and recurrent tumors was 19% and 52%, respectively (P=0.0042). The 3-year local failure rate was 37% for negative margins and 26% for positive margins (P=0.51). A high mean dose at the clip (17.3 Gy) was found. The OS was significantly different for primary vs recurrent tumors, stage, and grade. Because of the HDR technique, a high dose at the clips was found, with good local control. More out-of-field than in-field failures were seen. The local failure rate was significantly different for primary vs recurrent disease.	2

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27. Kolotas C, Roddiger S, Strassmann G, et al. Palliative interstitial HDR brachytherapy for recurrent rectal cancer. Implantation techniques and results. *Strahlenther Onkol.* 2003;179(7):458-463.	Observational-Tx	44 implants in 38 patients	To report the methods and clinical results of CT-based interstitial HDR brachytherapy procedures for the palliative treatment of recurrent rectal cancer.	After a median follow-up of 23.4 months, a total of 13/38 patients were alive. The median postbrachytherapy survival was 15 months with 18/25 deaths due to distant metastases. Tumor response was as follows: 6/38 PR, 28/38 stable disease, and 4/38 local progression. A planning target volume coverage >85% was achieved in 42/44 implants. The treatment was well tolerated, and no acute complications were observed. One patient developed a fistula after 8 months. Pain relief was recorded in 34 patients (89.5%), and the median duration of this palliative effect was 5 months with a range of 1–13 months. Interstitial HDR brachytherapy is a valuable tool for the delivery of high doses and achieves effective palliation in recurrent rectal carcinoma.	1
28. Kuehne J, Kleisli T, Biernacki P, et al. Use of high-dose-rate brachytherapy in the management of locally recurrent rectal cancer. *Dis Colon Rectum.* 2003;46(7):895-899.	Observational-Tx	27 patients	To evaluate the use of fractionated perioperative HDR brachytherapy in association with wide surgical excision (debulking) in the treatment of LRRC.	Follow-up ranged from 18 to 93 (mean, 50) months and was available in 27 patients. 10 patients (37%) were alive at the time of this report. 9 patients are without evidence of disease. 5 patients (18%) died of non-cancer-related causes without evidence of recurrent disease. 5 complications potentially related to treatment (3 abscesses, 2 fistulas) occurred in 5 patients. High-dose radiation brachytherapy delivers high-dose, highly controlled, focused radiation to specific sites of disease, thereby minimizing injury to normal tissues. The results in this series suggest increased local control, better palliation, and increased salvage of patients.	2

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29. Mannaerts GH, Rutten HJ, Martijn H, Hanssens PE, Wiggers T. Comparison of intraoperative radiation therapy-containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer. *Dis Colon Rectum.* 2001;44(12):1749-1758.	Observational-Tx	146 patients	To explore the treatment variables that may have contributed to the improvement in outcome by comparing 3 treatment modalities from 2 collaborating institutions in patients with similar tumor characteristics.	The 3-year survival, DFS, and local control rates were 14%, 8%, and 10%, respectively, in the electron-beam RT-only group and 11%, 0%, and 14%, respectively, in the combined electron-beam RT-surgery group. The overall IORT-multimodality treatment group showed significantly better 3-year survival, DFS, and local control rates of 60%, 43%, and 73%, respectively, compared with the historical control groups ($P<0.001$). The outcome of patients with LRRC was improved after the introduction of IORT-multimodality treatment.	2
30. Abuchaibe O, Calvo FA, Azinovic I, Aristu J, Pardo F, Alvarez-Cienfuegos J. Intraoperative radiotherapy in locally advanced recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys.* 1993;26(5):859-867.	Observational-Tx	27 patients	To promote local control and improve quality of life in patients with recurrent colorectal cancer with use of IORT.	2 year DFS and local relapse-free survival for entire group: 14% and 26%. 2 year DFS and local relapse-free survival for patients undergoing complete resection: 34% and 56%. Complete resection rates were higher with tumors <5 cm and in patients not previously treated with RT. Currently, the policy is to recommend IORT in patients with "favorable factors" such as: absence of previous pelvic RT, single previous surgical procedure, and complete resections.	2
31. Haddock MG, Miller RC, Nelson H, et al. Combined modality therapy including intraoperative electron irradiation for locally recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys.* 2011;79(1):143-150.	Observational-Tx	607 patients	To evaluate survival, relapse patterns, and prognostic factors in patients with colorectal cancer relapse treated with curative-intent therapy, including IOERT.	Median OS was 36 months. 5- and 10-year survival rates were 30% and 16%, respectively. Survival estimates at 5 years were 46%, 27%, and 16% for R0, R1, and R2 resection, respectively. Multivariate analysis revealed that R0 resection, no prior chemotherapy, and more recent treatment (in the second half of the series) were associated with improved survival. The 3-year cumulative incidence of central, local, and distant relapse was 12%, 23%, and 49%, respectively. Central and local relapse were more common in previously irradiated patients and in those with subtotal resection. Toxicity Grade 3 or higher partially attributable to IOERT was observed in 66 patients (11%). Neuropathy was observed in 94 patients (15%) and was more common with IOERT doses exceeding 12.5 Gy.	1

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
32. Milani V, Pazos M, Issels RD, et al. Radiochemotherapy in combination with regional hyperthermia in preirradiated patients with recurrent rectal cancer. *Strahlenther Onkol.* 2008;184(3):163-168.	Observational-Tx	24 patients	To report the results of a multimodal salvage therapy including radiochemotherapy and regional hyperthermia in preirradiated patients with recurrent rectal cancer.	The median local progression-free survival was 15 months (95% CI, 12–18 months] with a median follow-up of 27 months (16–37 months). The overall 1-year and 3-year survival rates were 87% and 30%, respectively. Pain was the main symptom in 17 patients. Release of pain was achieved in 12/17 patients (70%). No grade 3 or 4 hematologic or skin toxicity occurred. Grade 3 gastrointestinal acute toxicity was observed in 12.5% of the patients. Paratumoral thermometry revealed a homogeneous distribution of temperatures. Radiochemotherapy combined with regional hyperthermia is an efficient salvage therapy showing high efficacy with acceptable toxicity and can be recommended as treatment option for this unfavorable group of preirradiated patients with local recurrence of rectal cancer.	1
33. Vermaas M, Nuyttens JJ, Ferenschild FT, Verhoef C, Eggermont AM, de Wilt JH. Reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients. *Radiother Oncol.* 2008;87(3):357-360.	Observational-Tx	11 patients	To evaluate reirradiation, surgery and IORT for recurrent rectal cancer in previously irradiated patients.	This treatment was related with high morbidity, a short pain-free survival (5 months) and poor local control (27% after 3 years), although some patients have long-term distant control and survival.	2

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
34. Calvo FA, Meirino RM, Orecchia R. intraoperative radiation therapy part 2. Clinical results. *Crit Rev Oncol Hematol.* 2006;59(2):116-127.	Review/Other-Tx	N/A	A review on the clinical results of IORT.	Retrospective analysis of clinical experiences in cancer sites such as operable pancreatic tumor, locally advanced/recurrent rectal cancer, head and neck carcinomas, sarcomas and cervical cancer are consistent with local tumor control promotion compared to similar clinical experiences without IORT. New emerging indications such as the treatment of breast cancer are presented. The IORT component of the therapeutical approach allows intensification of the total radiation dose without additional exposure of healthy tissues and improves dose-deposit homogeneity and precision. Results of the application of IORT on selected disease sites are presented with an analysis on future possibilities. To improve the methodology, clinical trials are required with multivariate analysis including patient, tumor and treatment characteristics, prospective evaluation of early and late toxicity, patterns of tumor recurrence and overall patient outcome.	4
35. Willett CG, Czito BG, Tyler DS. Intraoperative radiation therapy. *J Clin Oncol.* 2007;25(8):971-977.	Review/Other-Tx	N/A	To review IORT.	The addition of IORT to conventional treatment methods has improved local control as well as survival in many disease sites in both the primary and locally recurrent disease settings. More recently, there has been interest in the use of IORT as a technique of partial breast irradiation for women with early breast cancer. Given newer and lower cost treatment devices, the use of IORT in clinical practice will likely grow, with increasing integration into the treatment of nonconventional malignancies. Optimally, phase III randomized trials will be carried out to prove its efficacy in these disease sites.	4

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
36. Roeder F, Goetz JM, Habl G, et al. Intraoperative Electron Radiation Therapy (IOERT) in the management of locally recurrent rectal cancer. *BMC Cancer*. 2012;12:592.	Observational-Tx	113 patients	To evaluate disease control, OS and prognostic factors in patients with LRRC after IOERT-containing multimodal therapy.	Margin status was R0 in 37%, R1 in 33% and R2 in 30% of the patients. Neoadjuvant EBRT resulted in significantly increased rates of free margins (52% vs 24%). Median OS was 39 months. Estimated 5-year rates for central control (inside the IOERT area), local control (inside the pelvis), distant control and OS were 54%, 41%, 40% and 30%. Resection margin was the strongest prognostic factor for OS (3-year OS of 80% (R0), 37% (R1), 35% (R2)) and LC (3-year LC 82% (R0), 41% (R1), 18% (R2)) in the multivariate model. OS was further significantly affected by clinical stage at first diagnosis and achievement of local control after treatment in the univariate model. Distant failures were found in 46 patients, predominantly in the lung. 90-day postoperative mortality was 3.1%.	2
37. Guo S, Reddy CA, Kolar M, 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;7:110.	Observational-Tx	42 patients	To review patients treated with IORT following definitive resection of a locally advanced or recurrent rectal cancer from 2000-2009.	Of 42 patients, 32 had recurrent disease (76%) while 10 had locally advanced disease (24%). 18 patients (43%) had tumors fixed to the sidewall. Margins were positive in 19 patients (45%). Median follow-up after IORT was 22 months (range 0.2–101). Median survival time after IORT was 34 months. The 3-year OS rate was 49% (43% for recurrent and 65% for locally advanced patients). Local recurrence was evaluable in 34 patients, of whom 32% failed. The 1-year local recurrence rate was 16%. Distant metastasis was evaluable in 30 patients, of whom 60% failed. The 1-year distant metastasis rate was 32%. No intraoperative complications were attributed to IORT. Median duration of IORT was 35 minutes (range: 14–39). Median discharge time after surgery was 7 days (range: 2–59). Hydronephrosis after IORT occurred in 10 patients (24%), 7 of whom had documented concomitant disease recurrence.	2

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
38. Heriot AG, Byrne CM, Lee P, et al. Extended radical resection: the choice for locally recurrent rectal cancer. *Dis Colon Rectum.* 2008;51(3):284-291.	Observational-Tx	160 total patients: 95 received neoadjuvant therapy; 63 radical resection; 90 extended radical resection	To prospectively assess factors that affect survival after surgery for LRRC.	Median cancer-specific and OS was 48 months (41.5% 5-year survival) and 43 months (36.6% 5-year survival), respectively. Margin involvement was a significant predictor of cancer-specific ($P<0.001$) and OS ($P<0.02$). Resection for recurrent rectal cancer results in good survival with acceptable morbidity, unaffected by the extent of resection. Extended radical resection to obtain clear resection margins is the appropriate management of LRRC.	1
39. Wang JJ, Yuan HS, Li JN, Jiang WJ, Jiang YL, Tian SQ. Interstitial permanent implantation of 125I seeds as salvage therapy for re-recurrent rectal carcinoma. *Int J Colorectal Dis.* 2009;24(4):391-399.	Observational-Tx	13 patients	To assess the feasibility, efficacy, and morbidity of (125)I seeds interstitial permanent implant as salvage therapy for re-recurrent rectal cancer.	After a median follow-up of 10 months (range 3–45), the pain-free interval was 0–14 months with a median of 7 months (95% CI: 3–11 months). The response rate of pain relief was 46.2% (6/13). Local control was 3–14 months with a median of 7 months (95% CI: 3.5–10.5 months). The 1- and 2-year local control rates were 14.4% and 0%, respectively. 3 (23.1%) patients died of local recurrence; 7 (53.8%) patients died of local recurrence and metastases; 1 (7.7%) patient died of metastases. 2 (15.4%) patients survived to follow-up. At the time of analysis, the median survival was 10 months (95% CI: 3.9–16.1 months). The 1- and 2-year actuarial OS rates were 46.2% and 11.5%, respectively. 2 (15.4%) patients experienced a grade 4 toxic event. Seed migration to the pelvic wall was observed in 1 (7.7%) patient. There was no associated neuropathy. (125)I seed implantation is feasible, effective, and safe as a salvage or palliative treatment for patients with re-recurrent rectal cancer.	2

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
40. Defoe SG, Bernard ME, Rwigema JC, Heron DE, Ozhasoglu C, Burton S. Stereotactic body radiotherapy for the treatment of presacral recurrences from rectal cancers. *J Cancer Res Ther*. 2011;7(4):408-411.	Observational-Tx	14 patients	To evaluate the safety and efficacy of cyberknife SBRT in the management of presacral recurrences.	One patient (6.7%) received SBRT as boost therapy. All patients had prior RT [median 50.4 Gy (20–81 Gy)]. Median tumor volume was 52.5 cc (19–110 cc). At initial follow-up of a median 4.9 months (1–16.3 months), treatment responses were CR (n=3) and stable disease (n=8). With a median follow-up of 16.5 months (6–69 months), the 1- and 2-year LC rates were 90.9% and 68.2%, respectively, and the 1- and 2-year OS rates were 90% and 78.8%, respectively. No factors were significantly predictive of LC and OS. There were no grade 3 or 4 toxicities. 50% (n=7) of our patients experienced pain with recurrence before treatment and 4 (57.1%) of them reported no pain after completion of their SBRT.	1
41. Combs SE, Kieser M, Habermehl D, et al. Phase I/II trial evaluating carbon ion radiotherapy for the treatment of recurrent rectal cancer: the PANDORA-01 trial. *BMC Cancer*. 2012;12:137.	Review/Other-Tx	N/A	To determine the MTD for carbon ion RT for the treatment of recurrent rectal cancer and to determine feasibility of this treatment in patients with recurrent rectal cancer.	With conventional photon irradiation treatment of recurrent rectal cancer is limited, and the clinical effect is only moderate. With carbon ions, an improved outcome can be expected due to the physical and biological characteristics of the carbon ion beam. However, the optimal dose applicable in this clinical situation as re-irradiation still has to be determined. This, as well as efficacy, is to be evaluated in the present Phase I/II trial.	4

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
42. Mobaraki A, Ohno T, Yamada S, Sakurai H, Nakano T. Cost-effectiveness of carbon ion radiation therapy for locally recurrent rectal cancer. *Cancer Sci.* 2010;101(8):1834-1839.	Review/Other-Tx	25 patients	To evaluate the cost-effectiveness of carbon ion RT compared with conventional multimodality therapy in the treatment of patients with LRRC.	14 and 11 patients receiving treatment for the local recurrence between 2003 and 2005 were followed retrospectively at NIRS and GUH, respectively. Treatment was carried out with carbon ion RT alone at NIRS, while multimodality therapy including 3D-CRT, chemotherapy, and hyperthermia was performed at GUH. The 2-year OS rate was 85% and 55% for carbon ion RT and multimodality treatment, respectively. The mean cost was yen4 803 946 for the carbon ion RT group and yen4 611 100 for the multimodality treatment group. The incremental cost-effectiveness ratio for carbon ion RT was yen6428 per 1% increase in survival. The median duration of total hospitalization was 37 days for carbon ion RT and 66 days for the multimodality treatment group.	4
43. Yamada S, Shinoto M, Shigeo Y, et al. [Current status and perspective of heavy ion beam therapy for patients with pelvic recurrence after primarily resected rectal cancer]. *Gan To Kagaku Ryoho.* 2009;36(8):1263-1266.	Observational-Tx	112 patients	To evaluate the tolerance for and effectiveness of carbon ion radiotherapy in patients with LRRC.	None of 112 patients experienced National Cancer Institute-Common Toxicity Criteria grade 3 to 5 acute reactions. The local control rate in patients treated with 67.2 GyE, 70.4 GyE and 73.6 GyE in the present study was 70%, 89% and 97% at 5 years, respectively. The OS rates in patients treated with 73.6 GyE were 72% at 3 years and 40% at 5 years.	2

Recurrent Rectal Cancer
EVIDENCE TABLE

Reference	Study Type	Patients/ Events	Study Objective (Purpose of Study)	Study Results	Study Quality
44. Berman AT, Both S, Sharkoski T, et al. Proton Reirradiation of Recurrent Rectal Cancer: Dosimetric Comparison, Toxicities, and Preliminary Outcomes. *Int J Part Ther*. 2014;1(1):2-13.	Observational-Tx	7 patients	To present a dosimetric comparison of proton RT vs intensity-modulated RT in LRRC and the preliminary toxicities and outcomes of these patients.	Median follow-up was 14 months (4.9–22.6). Median dose of prior RT was 5040 cGy. Mean proton RT dose was 6120 cGy (RBE) (range, 4500–6480 cGy). The total dose sum of prior RT treatment and proton RT was 109.8 Gy (RBE) (range, 95.4–151.2). One patient had surgery prior to and 1 after proton RT. 6 patients received concurrent 5-fluorouracil-based chemotherapy. Bowel volume receiving 10 and 20 Gy, and the dose to 200 and 150 cm3 of bowel were significantly reduced. There were 3 acute grade 3 and 3 late grade 4 toxicities. 4 patients were alive at time of follow-up. 6 had a metabolic complete response, of whom 2 subsequently locally recurred. One had initial progressive disease. Of 6 symptomatic patients, 3 had complete pain resolution and 3 partial.	1

Evidence Table Key

Study Quality Category Definitions

- *Category 1* The study is well-designed and accounts for common biases.
- *Category 2* The study is moderately well-designed and accounts for most common biases.
- *Category 3* There are important study design limitations.
- *Category 4* The study is not useful as primary evidence. The article may not be a clinical study or the study design is invalid, or conclusions are based on expert consensus. For example:
  a) the study does not meet the criteria for or is not a hypothesis-based clinical study (e.g., a book chapter or case report or case series description);
  b) the study may synthesize and draw conclusions about several studies such as a literature review article or book chapter but is not primary evidence;
  c) the study is an expert opinion or consensus document.

Dx = Diagnostic

Tx = Treatment

Abbreviations Key

3D-CRT = 3D-confromal radiation therapy

CI = Confidence interval

CR = Complete response

CT = Computed tomography

DFS = Disease-free survival

HDR = High-dose-rate

HDR-IORT = High-dose-rate intraoperative radiation therapy

IOERT = Intraoperative electron radiation therapy

IORT = Intraoperative radiation therapy

LRRC = Locally recurrent rectal cancer

MFS = Metastasis-free survival

OS = Overall survival

PR = Partial remission

RT = Radiation therapy

SBRT = Stereotactic body radiotherapy