Published in final edited form as:

Ann Surg Oncol. 2015 July ; 22(7): 2168–2178. doi:10.1245/s10434-014-4271-8.

Long-Term Survival After High-Dose-Rate Brachytherapy for Locally Advanced or Recurrent Colorectal Adenocarcinoma

Stephanie Terezakis, MD¹, Lisa Morikawa, MD², Abraham Wu, MD³, Zhigang Zhang, PhD⁴, Weiji Shi, MS⁴, Martin R. Weiser, MD⁵, Philip B. Paty, MD⁵, Jose Guillem, MD⁵, Larissa Temple, MD⁵, Garrett M. Nash, MD⁵, Michael J. Zelefsky, MD³, and Karyn A. Goodman, MD³

¹Department of Radiation Oncology and Molecular Radiation Sciences, Johns Hopkins School of Medicine, Baltimore, MD

²Department of Radiation Oncology, Clínicas Oncológicas Integradas (COI), Rio de Janeiro, Brazil

³Department of Radiation Oncology, Memorial Sloan-Kettering Cancer Center, New York, NY

⁴Department of Biostatistics, Memorial Sloan-Kettering Cancer Center, New York, NY

⁵Department of Surgery, Memorial Sloan-Kettering Cancer Center, New York, NY

Abstract

Background—We evaluated outcomes of intraoperative radiotherapy delivered with focal high-dose-rate (HDR) brachytherapy [intraoperative radiotherapy (IORT)] in the management of locally recurrent (LR) and locally advanced (LA) primary T4 colorectal carcinoma (CRC). LR CRC or LA primary disease is a clinical challenge due to the difficulty in obtaining negative margins after radical surgery and the high risk of subsequent recurrence. Few data exist on long-term outcomes of patients treated with surgery and HDR-IORT for LR or LA primary CRC.

Methods—Three hundred CRC patients underwent HDR-IORT to the pelvis with gross surgical resection during November 1992–December 2007. Median follow-up for surviving patients was 53 (range 5–216) months. Eighty-eight patients (29 %) were treated for LA primary and 212 (71 %) LR disease. HDR-IORT was delivered using an iridium-192 remote afterloader and a Harrison–Anderson–Mick applicator. Median IORT dose was 1,500 (range 1,000–2,000) cGy.

Results—Five-year overall survival probability was 49 %. Positive margin status was associated with inferior overall survival and disease-free survival. Competing-risks analysis for time to local failure and distant metastases identified a 5-year cumulative incidence of local failure and distant metastases of 33 and 47 %, respectively. Five-year cumulative incidence of local failure was 22 % for the LA group and 38 % in the LR group. Five-year probability of disease-free survival was 48 and 31 % for LA and LR patients, respectively, and 5-year probability of overall survival was 56 and 45 % for LA and LR patients, respectively.

Conclusions—HDR-IORT combined with resection results in encouraging local control rates with acceptable toxicity for patients with locally aggressive CRC.

Patients with locally advanced (LA) primary T4 and locally recurrent (LR) colorectal cancer (CRC) are at high risk for local failure due to the potential for residual disease despite aggressive surgical resection. These tumors have a propensity to invade adjacent structures and adhere to the pelvic sidewall and sacrum, making complete surgical resection difficult.¹ Multiple studies have demonstrated that local control and survival is worse in patients with gross or microscopic residual disease after pelvic surgery.¹⁻⁷ The prescribed dose with external-beam radiotherapy (EBRT) is limited by the tolerance of surrounding normal tissues. Intraoperative radiation treatment (IORT) is a method used to escalate radiation dose to the tumor bed to address potential sites of residual disease while still respecting normal tissue tolerance. Delivering radiation at the time of surgery also allows intraoperative assessment by the surgeon and radiation oncologist to precisely delineate the tumor bed. Single-institution studies suggest the addition of IORT to multimodal therapy improves outcomes compared with historical controls in patients with LA or LR colorectal tumors.^{1,6, 8-13} Therefore, IORT has been integrated into the treatment paradigm for managing these difficult pelvic tumors.

We have previously reported the experience at Memorial Sloan-Kettering Cancer Center (MSKCC) with high-dose-rate (HDR) brachytherapy, and demonstrated encouraging results with a combined treatment strategy using EBRT, chemotherapy, surgical resection, and IORT.^{12,13} This study aims to report clinical outcomes for the populations of LA and LR CRC patients and to identify clinical characteristics associated with local control and survival with this multimodal approach to improve patient selection for this aggressive local therapy.

METHODS AND MATERIALS

Patient Characteristics

Between November 1992 and December 2007, 300 patients underwent gross surgical resection and HDR-IORT to the pelvis at MSKCC for either primary LA ($n = 88$) or LR ($n = 212$) CRC. After approval by the institutional review board, clinical information was obtained from the electronic medical record system and from an existing IORT database. The median follow-up for surviving patients was 53 (range 5–216) months. Two hundred sixty-four patients were followed for >1 year and 192 patients were followed for >2 years. Table 1 lists patient and treatment characteristics. Of the 212 LR cases of CRC, the majority of patients ($n = 129$) presented with disease in the rectum at initial diagnosis; the remaining patients had recurrent disease in the pelvis with an initial primary lesion in the colon ($n = 46$), rectosigmoid colon ($n = 36$), or cecum ($n = 1$). Thirty patients (10 %) had extrapelvic metastatic disease at diagnosis or before IORT. Patients with anal squamous cell carcinoma or who were administered IORT to treat extrapelvic recurrent disease were excluded from this analysis.

Treatment Characteristics

At the time of the operation with IORT, 234 patients (78 %) had undergone prior pelvic surgery. The surgical procedure at the time of IORT was an abdominoperineal resection in 101 patients, while 100 had low anterior resection, 60 had a pelvic exenteration, and 37 had

wide local excision (Table 1). Fourteen patients also underwent sacrectomy. Pathologic assessment was performed on all specimens after surgical resection by an MSKCC pathologist for delineation of nodal and margin status. Surgeon and operative assessments were reviewed in conjunction with pathology reports for identification of R0, R1, or R2 resection. R1 resection was further subdivided into close (≤ 2 mm) margins or positive margins.

HDR-IORT was delivered using the Harrison–Anderson–Mick applicator. The MSKCC HDR-IORT technique has been previously published.^{12,13} The median IORT dose was 1,500 (range 1,000–2,000) cGy to a median target area of 30 (range 4–225) cm². The dose was prescribed to 0.5 cm from the applicator surface (1 cm from the source). The median maximal tumor dimension was 5 (range 0.2–15) cm, and 44 patients (15 %) had multifocal satellite nodules. The median total treatment time for the IORT was 22 (range 5–83) min, and the median source insertion to removal time was 29 (range 7–91) min. The median total surgical procedure time was 480 (range 130–870) min, and the median hospital stay was 9 (range 4–45) days.

The paradigm for treatment of LA T4 patients involved delivery of preoperative chemoradiotherapy followed by surgical resection and IORT, and adjuvant chemotherapy. LR patients had predominantly received EBRT at initial diagnosis; those who had not received EBRT previously were treated with preoperative radiation at the time of local recurrence followed by surgical resection and IORT in addition to neoadjuvant and adjuvant chemotherapy (Table 1). Nearly all of the patients (96 %) had EBRT during their treatment course. Two hundred seventy-eight patients (92 %) underwent prior EBRT either at initial diagnosis or preoperatively with IORT; 11 (4 %) received EBRT after surgery and IORT. Median EBRT dose before IORT was 5,040 (range 3,060–7,020) cGy. Median postoperative EBRT dose was 4,500 (range 4,500–5,040) cGy. EBRT was generally delivered using 15 MV photons with a three- or four-field technique.

Two hundred eighty-one patients (94 %) received chemotherapy. All but six received 5-fluorouracil-based chemotherapy before surgery, and 132 (88 %) of 150 received it postoperatively. After 2003, oxaliplatin was routinely introduced into the chemotherapy regimens both pre- and post-operatively. Forty-seven patients received oxaliplatin either pre- or post-operatively, and 20 received oxaliplatin preoperatively.

Outcome Assessment

Follow-up clinical visits were conducted at intervals of 3–6 months by at least one physician from the surgical, radiation, or medical oncology departments. Computed tomographic scan of the abdomen and pelvis or magnetic resonance imaging of the pelvis was obtained at each 3- and 6-month interval. Follow-up was calculated from the date of HDR-IORT. Toxicity was assessed from clinical visit documentation and graded using the National Cancer Institute Common Toxicity Criteria for Adverse Events (CTCAE, v.3.0). The highest grade given at any time was used in the analysis.

Statistical Analysis

For the end points of overall survival (OS) and disease-free survival (DFS), a univariate analysis was first performed by the Cox proportional hazards model. A multivariate analysis (MVA) was performed by constructing a Cox model using a stepwise selection procedure. Variables with $p < 0.1$ in the univariate analysis were used to build the multivariate model with a stepwise selection procedure. Variables were entered into the model if the score Chi-square statistic achieved a p value of ≤ 0.05 and were removed from the model if the Wald Chi-square statistic achieved a p value of ≤ 0.05 .

A competing-risks analysis using R package *cmprsk* was performed for the end points of local control and time to distant metastasis. p values and 95 % confidence intervals were two-sided. $p < 0.05$ was considered statistically significant. SAS 9.2 (SAS Institute, Cary, NC, USA) and R 2.9.2 were used for statistical analysis.

RESULTS

Local Control

A local pelvic recurrence developed in 94 (31 %) of all 300 patients; of these, 76 occurred in the 212 LR patients and 17 among the 88 LA patients. Of patients who experienced a local failure, 62 were not alive at last follow-up (69 %). One hundred (49 %) of 206 patients had locally controlled disease at time of death. The 5-year cumulative incidence of local failure was 22 % for the LA group and 38 % in the LR group. Positive margin status was associated with local failure on MVA for the LR group (hazard ratio, 2.28 [95 % confidence interval 1.39–3.37]) (Table 2); however, there were no factors significantly associated with local recurrence for the LA group (Table 3). The 5-year cumulative incidence of local failure in the LR group was 29 % for patients with negative margins, 35 % for close (≤ 2 mm) margins, and 51 % for positive margins ($p = 0.002$ by Gray's method) (Table 4).

Distant Metastasis

Among 270 nonmetastatic patients with LA or LR disease, 122 developed distant metastases after IORT. The most common sites of distant failure were lung (53 %) and liver (22 %). The 5-year cumulative incidence of distant metastasis was 39 % for the LA group and 51 % for the LR group. Among the LR patients, a positive surgical margin and receipt of oxaliplatin was associated with a higher risk of developing distant metastasis on MVA. Only pathologically involved lymph node status was associated with an increased risk of distant metastases among the LA patients with a 5-year cumulative incidence of distant metastases of 63 and 32 % for node-positive and node-negative disease, respectively.

DFS and OS

The 5-year probability of DFS and the 5-year probability of OS for the overall population was 37 and 49 %, respectively. The 5-year probability of DFS was 48 and 31 % for LA and LR patients, respectively (Fig 1). A positive surgical margin (vs. negative margin) was associated with inferior DFS ($p < 0.0001$) and OS ($p < 0.0001$) on MVA for LR patients (Table 2). The 5-year probability of DFS in patients with LR disease with a negative, close, or positive margin was 48, 35, and 7 %, respectively (Table 4; Fig. 2). The 5-year probability

of DFS in patients with LA disease with a negative, close, or positive margin was 50, 44, and 45 %, respectively (Table 5).

The 5-year probability of OS was 56 and 45 % for LA and LR patients, respectively (Fig. 3). The 5-year probability of OS in patients with LR disease with a negative, close, or positive margin was 57, 49, and 25 %, respectively (Table 4; Fig. 4). The 5-year probability of OS in patients with LA disease with a negative, close, or positive margin was 57, 45, and 60 %, respectively. Lymph node involvement and type of surgery were associated with OS for LA patients on MVA (Table 3). The 5-year OS for LA patients with involved lymph nodes was 38 versus 62 % with node-negative disease ($p = 0.02$). In addition, LA patients undergoing low anterior resection had an improved OS compared with abdominoperineal resection ($p = 0.03$), likely representing the greater extent of disease in the abdominoperineal resection group.

Toxicity

Complications that could be related to the aggressive multimodal treatment regimen (surgery, IORT, EBRT, or concurrent chemoradiotherapy) were identified by any description in the medical record of signs or symptoms that could specifically be related to the surgical procedure during which IORT was performed. Toxicity data are reported in Table 6. One patient in the series had a grade 5 toxicity associated with fistula formation. The incidence of toxicity was not significantly associated with radiation dose level.

DISCUSSION

LA and LR CRCs are challenging clinical entities and have a dismal prognosis when treated with surgery or radiation alone.^{1,14–18} Local recurrence rates, even after combined EBRT and extensive pelvic surgery, are approximately 50 %.^{19,20} The morbidity of uncontrolled pelvic disease is frequently significant. As a result, a multimodal approach has evolved to aggressively treat these problematic tumors.

Isolating the magnitude of the benefit of IORT is extremely difficult, given the number of therapies these patients receive during their management course. Nonetheless, this management paradigm of radical resection with IORT resulted in excellent overall local control relative to historical data, particularly for patients with negative surgical margins.^{4,8–11,21–24} In this study, the 5-year cumulative incidence of local failure was 22 % for patients with LA disease at presentation and 38 % for patients with LR disease at presentation. This is comparable to the results of the largest study of intraoperative electron radiotherapy published by Haddock et al. at the Mayo Clinic, in which 607 patients were evaluated with a median follow-up of 44 months for surviving patients and the 5-year local failure rate was 28 % for all patients.²⁵ However, a positive surgical margin remained a significant predictor for DFS and OS in patients with recurrent disease at presentation, which is consistent with multiple prior reports.^{2–7} More striking was the fact that the 5-year probability of DFS in patients with LR disease with a positive margin was 7 % and the 5-year probability of OS in patients LR disease with a positive margin was 25 %. The potential use of radiosensitizers could improve the therapeutic ratio in this setting, particularly in patients in whom a gross total resection may be difficult to achieve. The findings in this

study suggest that further improvement in local therapy for treatment of these LA tumors is warranted and that aggressive local treatment may affect survival.

Despite the relatively poor prognosis of patients presenting with recurrent or LA CRC, the overall 5-year OS was 49 and 53 % of patients were free of distant metastases at 5 years. However, outcomes were improved in patients with positive prognostic factors, such as negative surgical margins, in whom the 5-year OS was higher at 57 % for patients with recurrent disease at presentation. Patients with LR disease at presentation also fared worse than those with LA T4 disease at presentation with 5-year OS rates of 45 and 56 %, respectively. Therefore, there is incentive to approach these patients with definitive therapy. Effective local therapy may also improve quality of life for patients who may otherwise have significant morbidity as a result of local disease progression.

However, systemic failure still remains problematic for these patients, with a 5-year cumulative incidence of distant metastases of 47 % in this series; patients with LA disease had a 5-year cumulative incidence of distant metastases of 39 % compared to 51 % for patients with recurrent disease at presentation. This rate was similar to other studies despite aggressive use of chemotherapy in nearly all patients and the incorporation of oxaliplatin delivered either before or after surgery.^{6,23} Positive margin status was also significantly associated with systemic failure, suggesting that residual disease after local therapy may affect the development of distant metastases. To address the possible effect of systemic therapy, we examined the use of chemotherapy, era of treatment, and oxaliplatin use before chemotherapy, but these variables were not significant on univariate or multivariate analysis. Despite the important advances made to widen the options for systemic therapy and the encouraging results of oxaliplatin use, systemic failure remains problematic regardless of the effectiveness of local therapy.

Progressive tumors in the pelvis have the potential to cause significant morbidity; given that a considerable number of patients had locally controlled disease at the time of last follow-up, the rates of late toxicity in this report were quite reasonable. Evaluating toxicity resulting from IORT is extremely difficult, given the multiple therapies that these patients undergo, including EBRT, chemotherapy, and extensive surgical resection. The toxicities reported in this series are likely multifactorial, and in some patients, adverse effects from IORT may not be distinguished from toxicity resulting from surgery alone or from tumor progression. The rate of toxicities thought to be the result of IORT, including peripheral neuropathy and ureteral stenosis, were comparable in this study to other series in the literature.^{2,6,22,26–28} In an initial report from our institution, the overall rate of gastrointestinal, wound, and neurologic toxicities were similar to this updated series after the addition of over 200 patients and longer follow-up.¹² There was no association between IORT dose level and incidence of toxicity, which is consistent with the findings from prior reports from our institution.^{12,13,29}

Ideally, a randomized controlled trial would elucidate the impact of IORT on local control and survival of patients with LA and LR CRC. However, given the heterogeneity of this patient population and the limited availability of IORT, it is unlikely that large patient numbers will ever be accrued to complete such a study. There has been one phase 3

randomized trial of IORT performed in the setting of primary LA (T3–4 or node positive) disease, which showed no difference in local control rates with the addition of IORT at the time of surgical resection after preoperative chemoradiotherapy; however, the local failure rate for the control arm was only 7 %, so this study of 142 patients was underpowered to show a benefit in this low-risk population.³⁰ In addition, there was a large percentage of T3 patients included in this study, which are not typically the ideal candidates for an IORT boost. There was no difference in surgical complications between the arms. The authors concluded that the technique should be reserved for cases at a higher risk of local recurrence. Multiple studies have demonstrated excellent local control in a patient population with LA disease using a management strategy incorporating IORT.^{6,8–13,31} Moreover, the majority of patients in our study had recurrent disease, which is associated with even greater surgical challenges as a result of the disrupted fascial planes and postoperative fibrosis and adhesions. As shown in our study, these patients have a higher risk of local recurrence and may benefit more from the IORT. Therefore, in the absence of a large, well-powered, randomized study including patients with recurrent CRC, we continue to recommend an aggressive treatment approach using IORT as a definitive strategy in these potentially curable patients. We continue to evaluate novel techniques to deliver HDR-IORT more focally and have previously reported on a dose-painting HDR-IORT technique.³² With the Harrison–Anderson–Mick applicator, dose can be sculpted inside of the target area, permitting dose escalation or de-escalation, allowing for planned non-homogenous dose distributions or dose painting. This technique allows for sites suspicious for residual microscopic disease to be treated to higher doses while minimizing dose to normal organs, which may improve outcomes for patients with positive margins who remain at highest risk of recurrence.

Aggressive local therapy combining EBRT, chemotherapy, surgery, and IORT in this challenging patient population results in excellent local control and acceptable toxicity rates. Given the potential for morbidity in the setting of local progression in the pelvis in patients with LA T4 lesions or recurrent colorectal tumors, these patients should be referred for evaluation for definitive multimodal therapy.

REFERENCES

1. 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; 75:939–952. [PubMed: 7531113]
2. Lindel K, Willett CG, Shellito PC, Ott MJ, Clark J, Grossbard M, et al. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. *Radiother Oncol*. 2001; 58:83–87. [PubMed: 11165686]
3. Pelton J, Lanciano R, Hoffman J, Hanks G, Eisenberg B. The influence of surgical margins on advanced cancer treated with intraoperative radiation therapy (IORT) and surgical resection. *J Surg Oncol*. 1993; 53:30–35. [PubMed: 8479194]
4. 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; 15:1937–1947. [PubMed: 18389321]

5. Eble MJ, Lehnert T, Treiber M, Latz D, Herfarth C, Wannenmacher M. Moderate dose intraoperative and external beam radiotherapy for locally recurrent rectal carcinoma. *Radiother Oncol.* 1998; 49:169–174. [PubMed: 10052883]
6. Mathis KL, Nelson H, Pemberton JH, Haddock MG, Gunderson LL. Unresectable colorectal cancer can be cured with multimodality therapy. *Ann Surg.* 2008; 248:592–598. [PubMed: 18936572]
7. Wiig JN, Tveit KM, Poulsen JP, Olsen DR, Giercksky KE. Preoperative irradiation and surgery for recurrent rectal cancer. Will intraoperative radiotherapy (IORT) be of additional benefit? A prospective study. *Radiother Oncol.* 2002; 62:207–213. [PubMed: 11937248]
8. Gunderson LL, Nelson H, Martenson JA, Cha S, Haddock M, Devine R, et al. Locally advanced primary colorectal cancer: intraoperative electron and external beam irradiation +/- 5-FU. *Int J Radiat Oncol Biol Phys.* 1997; 37:601–614. [PubMed: 9112459]
9. Lanciano RM, Calkins AR, Wolkov HB, Buzydlowski J, Noyes RD, Sause W, et al. A phase I/II study of intraoperative radiotherapy in advanced unresectable or recurrent carcinoma of the rectum: a Radiation Therapy Oncology Group (RTOG) study. *J Surg Oncol.* 1993; 53:20–29. [PubMed: 8479193]
10. Bussieres E, Gilly FN, Rouanet P, Mahe MA, Roussel A, Delannes M, et al. Recurrences of rectal cancers: results of a multimodal approach with intraoperative radiation therapy. French Group of IORT. Intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* 1996; 34:49–56. [PubMed: 12125680]
11. Kim HK, Jessup JM, Beard CJ, Bornstein B, Cady B, Stone MD, et al. Locally advanced rectal carcinoma: pelvic control and morbidity following preoperative radiation therapy, resection, and intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* 1997; 38:777–783. [PubMed: 9240646]
12. Alektiar KM, Zelefsky MJ, Paty PB, Guillem J, Saltz LB, Cohen AM, et al. High-dose-rate intraoperative brachytherapy for recurrent colorectal cancer. *Int J Radiat Oncol Biol Phys.* 2000; 48:219–226. [PubMed: 10924992]
13. Harrison LB, Minsky BD, Enker WE, Mychalczak B, Guillem J, Paty PB, et al. High dose rate intraoperative radiation therapy (HDR-IORT) as part of the management strategy for locally advanced primary and recurrent rectal cancer. *Int J Radiat Oncol Biol Phys.* 1998; 42:325–330. [PubMed: 9788411]
14. Wanebo HJ, Gaker DL, Whitehill R, Morgan RF, Constable WC. Pelvic recurrence of rectal cancer. Options for curative resection. *Ann Surg.* 1987; 205:482–495. [PubMed: 2437869]
15. Wanebo HJ, Marcove RC. Abdominal sacral resection of locally recurrent rectal cancer. *Ann Surg.* 1981; 194:458–471. [PubMed: 7283507]
16. Cummings BJ, Rider WD, Harwood AR, Keane TJ, Thomas GM. Radical external beam radiation therapy for adenocarcinoma of the rectum. *Dis Colon Rectum.* 1983; 26:30–36. [PubMed: 6822158]
17. Sadahiro S, Suzuki T, Ishikawa K, Fukasawa M, Saguchi T, Yasuda S, et al. Preoperative radio/chemo-radiotherapy in combination with intraoperative radiotherapy for T3–4Nx rectal cancer. *Eur J Surg Oncol.* 2004; 30:750–758. [PubMed: 15296989]
18. Rhomberg W, Eiter H, Hergan K, Schneider B. Inoperable recurrent rectal cancer: results of a prospective trial with radiation therapy and razoxane. *Int J Radiat Oncol Biol Phys.* 1994; 30:419–425. [PubMed: 7523346]
19. Dosoretz DE, Gunderson LL, Hedberg S, Hoskins B, Blitzer PH, Shipley W, et al. Preoperative irradiation for unresectable rectal and rectosigmoid carcinomas. *Cancer.* 1983; 52:814–818. [PubMed: 6871823]
20. Mendenhall WM, Million RR, Bland KI, Pfaff WW, Copeland EM 3rd. Initially unresectable rectal adenocarcinoma treated with preoperative irradiation and surgery. *Ann Surg.* 1987; 205:41–44. [PubMed: 3800461]
21. Schild SE, Wong W. The role of retrograde urethrography in the planning of prostate cancer radiotherapy. *Med Dosim.* 1997; 22:83–86. [PubMed: 9243458]
22. Wallace HJ 3rd, Willett CG, Shellito PC, Coen JJ, Hoover HC Jr. Intraoperative radiation therapy for locally advanced recurrent rectal or rectosigmoid cancer. *J Surg Oncol.* 1995; 60:122–127. [PubMed: 7564378]

23. Nuyttens JJ, Kolkman-Deurloo IK, Vermaas M, Ferenschild FT, Graveland WJ, De Wilt JH, 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; 58:106–112. [PubMed: 14697427]
24. Nag S, Martinez-Monge R, Martin EW. Intraoperative electron beam radiotherapy in recurrent colorectal carcinoma. *J Surg Oncol.* 1999; 72:66–71. [PubMed: 10518101]
25. 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; 79:143–150. [PubMed: 20395067]
26. Calvo FA, Gomez-Espi M, Diaz-Gonzalez JA, Alvarado A, Cantalapiedra R, Marcos P, et al. Intraoperative presacral electron boost following preoperative chemoradiation in T3–4Nx rectal cancer: initial local effects and clinical outcome analysis. *Radiother Oncol.* 2002; 62:201–206. [PubMed: 11937247]
27. Nakfoor BM, Willett CG, Shellito PC, Kaufman DS, Daly WJ. The impact of 5-fluorouracil and intraoperative electron beam radiation therapy on the outcome of patients with locally advanced primary rectal and rectosigmoid cancer. *Ann Surg.* 1998; 228:194–200. [PubMed: 9712564]
28. Tepper JE, Gunderson LL, Orlow E, Cohen AM, Hedberg SE, Shipley WU, et al. Complications of intraoperative radiation therapy. *Int J Radiat Oncol Biol Phys.* 1984; 10:1831–1839. [PubMed: 6436198]
29. Idrees K, Minsky B, Alektiar K, Guillem J, Weiser M, Temple L, et al. Surgical resection and high dose rate intraoperative radiation therapy for locally recurrent rectal cancer. *Acta Chir Iugosl.* 2004; 51:11–18.
30. Dubois JB, Bussieres E, Richaud P, Rouanet P, Becouarn Y, Mathoulin-Pelissier S, et al. Intraoperative radiotherapy of rectal cancer: results of the French multi-institutional randomized study. *Radiother Oncol.* 2011; 98:298–303. [PubMed: 21339010]
31. Gunderson LL, Nelson H, Martenson JA, Cha S, Haddock M, Devine R, et al. Intraoperative electron and external beam irradiation with or without 5-fluorouracil and maximum surgical resection for previously unirradiated, locally recurrent colorectal cancer. *Dis Colon Rectum.* 1996; 39:1379–1395. [PubMed: 8969664]
32. Morikawa LK, Zelefsky MJ, Cohen GN, Zaider M, Chiu J, Mathur N, et al. Intraoperative high-dose-rate brachytherapy using dose painting technique: evaluation of safety and preliminary clinical outcomes. *Brachytherapy.* 2013; 12:1–7. [PubMed: 23167979]

FIG. 1.
Kaplan-Meier estimates of disease-free survival for patients with locally advanced primary T4 and locally recurrent colorectal cancer

FIG. 2.
Kaplan-Meier estimates of disease-free survival for patients with locally recurrent colorectal cancer stratified by margin status

FIG. 3.
Kaplan-Meier estimates of overall survival for patients with locally advanced primary T4 and locally recurrent colorectal cancer

FIG. 4.
Kaplan-Meier estimates of overall survival after local recurrence stratified by margin status

TABLE 1

Patient and treatment characteristics

Characteristic	Locally recurrent <i>n</i> (%) (<i>n</i> = 212)	Locally advanced <i>n</i> (%) (<i>n</i> = 88)	Total <i>n</i> (%) (<i>n</i> = 300)
Gender			
Male	114 (54 %)	54 (61 %)	168 (56 %)
Female	98 (46 %)	34 (39 %)	132 (44 %)
Presentation			
Primary		88 (100 %)	88 (29 %)
Recurrence	212 (100 %)		212 (71 %)
Surgical margins			
R0: negative	96 (45 %)	58 (66 %)	154 (51 %)
R1: close (≤ 2 mm)	41 (20 %)	16 (18 %)	57 (19 %)
R1: positive	72 (34 %)	13 (15 %)	85 (28 %)
NA	3 (1 %)	1 (1 %)	4 (1 %)
Lymph node pathology			
Negative	131 (62 %)	63 (72 %)	194 (65 %)
Positive	26 (12 %)	21 (23 %)	47 (16 %)
NA	55 (26 %)	4 (5 %)	59 (20 %)
Pathologic T stage of primary tumors			
T0		4 (5 %)	
T1		1 (1 %)	
T2		10 (11 %)	
T3		44 (50 %)	
T4		22 (25 %)	
NA		7 (8 %)	
Site of recurrence			
Suture line	18 (8 %)		
Anastomotic	57 (27 %)		
Pelvic sidewall	67 (32 %)		
Other	54 (25 %)		
Unknown	16 (8 %)		
Surgery at time of IORT			
Wide local excision	35 (17 %)	2 (2 %)	37 (12 %)
Low anterior resection	63 (30 %)	37 (43 %)	100 (33 %)
Abdominoperineal resection	68 (32 %)	33 (38 %)	101 (34 %)
Pelvic exenteration ^a	45 (21 %)	15 (17 %)	60 (20 %)
NA	1 (0 %)	1 (1 %)	2 (1 %)
External-beam radiotherapy ^a			
Initial diagnosis	114 (54 %)	4 (5 %)	118 (39 %)
Before IORT	81 (38 %)	79 (90 %)	160 (53 %)

Characteristic	Locally recurrent <i>n</i> (%) (<i>n</i> = 212)	Locally advanced <i>n</i> (%) (<i>n</i> = 88)	Total <i>n</i> (%) (<i>n</i> = 300)
After IORT	7 (3 %)	4 (5 %)	11 (4 %)
Chemotherapy ^a			
Initial diagnosis	149 (70 %)	2 (5 %)	151 (50 %)
Before IORT	99 (47 %)	80 (91 %)	179 (60 %)
After IORT	91 (43 %)	59 (67 %)	150 (50 %)

NA pathologic assessment unavailable, *IORT* intraoperative radiotherapy

^aSome patients received more than one treatment at initial diagnosis, before IORT, and/or after IORT. Data are presented as *n* (%) for number and proportion of total patients/subgroup at each of the treatment periods

TABLE 2

Stepwise multivariate analyses final model for patients with locally recurrent disease at presentation

Variable	HR (95 % CI) for:		
	Local failure	Disease-free survival	Overall survival
Site of recurrence			
Suture line		1.00	1.00
Anastomosis		1.76 (0.73–4.24)	2.11 (0.81–5.48)
Pelvic sidewall		1.70 (0.70–4.15)	2.37 (0.96–6.10)
Distant in pelvis		2.55 (1.05–6.16)	2.81 (1.08–7.28)
Other		1.56 (0.50–4.88)	1.59 (0.50–5.03)
Surgical margins			
Negative	1.00	1.00	1.00
Positive	2.28 (1.39–3.72)	3.42 (2.19–5.32)	2.27 (1.50–3.43)
Close	1.22 (0.63–2.34)	1.59 (0.91–2.76)	1.19 (0.69–2.06)

HR hazard ratio, *CI* confidence interval

TABLE 3

Stepwise multivariate analysis final model for patients with locally advanced T4 disease at presentation

Variable	Overall survival, HR (95 % CI)
Type of surgery	
APR	1.00
LAR	0.49 (0.25–0.93)
Pelvic exenteration	0.72 (0.32–1.63)
Pathologic lymph nodes	
No	1.00
Yes	2.22 (1.17–4.24)

HR hazard ratio, *CI* confidence interval, *APR* abdominoperineal resection, *LAR* low anterior resection

TABLE 4

Univariate analysis of 5-year LF, DFS, and OS for patients with LR disease at presentation ($N = 212$ for LF and OS, $N = 188$ for DFS)

Variable	No. of patients LF, OS/DFS	LF		DFS		OS	
		HR (95 % CI)	5 years	HR (95 % CI)	5 years	HR (95 % CI)	5 years
Use of oxaliplatin							
No	200/177	1.00	37.2 % (30.0–44.4)	1.00	32.3 % (24.6–40.2)	1.00	44.6 % (36.8–52.1)
Yes	12/11	1.29 (0.47–3.57)	45.7 % (7.8–83.5)	1.38 (0.64–2.98)	14.0 % (0.7–45.6)	0.72 (0.23–2.28)	71.4 % (25.8–92.0)
Site of recurrence							
Suture line	18/16	1.00	28.6 % (3.7–53.5)	1.00	58.0 % (29.2–78.6)	1.00	70.0 % (38.2–87.6)
Anastomosis	57/50	1.30 (0.45–3.74)	29.6 % (17.2–42.1)	2.42 (1.01–5.77)	35.4 % (22.0–49.0)	2.76 (1.08–7.07)	46.3 % (31.3–60.1)
Pelvic sidewall	67/59	1.65 (0.60–4.55)	40.1 % (26.7–53.4)	2.48 (1.03–5.95)	21.6 % (9.8–36.3)	3.08 (1.22–7.81)	40.0 % (27.2–52.6)
Distant in pelvis	54/48	2.39 (0.87–6.60)	43.4 % (29.2–57.6)	3.48 (1.46–8.28)	24.2 % (12.2–38.4)	3.48 (1.36–8.92)	40.5 % (25.8–54.7)
Other	16/15	1.99 (0.60–6.64)	48.9 % (18.5–79.3)	1.40 (0.45–4.34)	42.3 % (13.5–69.1)	1.53 (0.49–4.82)	56.1 % (22.8–79.8)
Type of surgery							
APR	68/62	1.00	40.1 % (26.9–53.3)	1.00	37.6 % (24.2–50.9)	1.00	50.7 % (36.1–63.5)
LAR	63/57	0.67 (0.38–1.19)	33.7 % (21.1–46.3)	0.86 (0.54–1.38)	35.1 % (21.9–48.6)	1.32 (0.80–2.16)	50.8 % (36.2–63.7)
Local excision	35/28	1.47 (0.80–2.69)	55.0 % (34.9–75.2)	1.52 (0.85–2.71)	14.8 % (2.8–36.1)	1.08 (0.62–1.90)	36.6 % (18.4–55.1)
Pelvic exenteration	45/40	0.69 (0.36–1.32)	29.1 % (15.5–42.7)	1.32 (0.80–2.16)	22.8 % (10.1–38.4)	1.56 (0.98–2.46)	34.3 % (20.0–49.0)
Dose level							
<1,200 cGy	38/37	1.00	35.9 % (19.8–52.0)	1.00	43.9 % (26.859.8)	1.00	55.4 % (37.6–70.0)
>1,200–1,500 cGy	99/83	0.81 (0.44–1.48)	28.3 % (18.7–37.8)	1.36 (0.82–2.26)	35.6 % (24.1–47.3)	1.22 (0.76–1.95)	44.6 % (33.2–55.4)
>1,500 cGy	74/67	1.56 (0.86–2.80)	51.2 % (38.2–64.2)	2.15 (1.28–3.61)	18.6 % (9.0–30.9)	1.41 (0.85–2.34)	41.3 % (28.0–54.1)
Pathologic lymph nodes							
No	131/119	1.00	35.0 % (26.1–44.0)	1.00	35.3 % (25.8–44.9)	1.00	47.7 % (37.7–57.1)
Yes	26/22	1.19 (0.60–2.39)	43.9 % (21.6–66.1)	1.31 (0.75–2.29)	15.2 % (2.7–37.2)	1.26 (0.72–2.20)	36.1 % (15.5–57.3)
NA	55/47	1.21 (0.74–1.97)	40.7 % (26.6–54.9)	1.03 (0.67–1.59)	27.5 % (13.8–43.1)	1.17 (0.78–1.74)	44.3 % (29.7–57.9)
Surgical margins							
Negative	96/87	1.00	28.9 % (18.9–38.8)	1.00	48.4 % (36.2–59.6)	1.00	57.2 % (45.5–67.2)
Positive	72/63	2.28 (1.39–3.72)	51.4 % (39.1–63.7)	3.74 (2.44–5.73)	7.0 % (1.9–16.7)	2.58 (1.74–3.84)	24.6 % (14.2–36.6)
Close	41/36	1.22 (0.63–2.34)	35.3 % (17.7–52.9)	1.65 (0.97–2.83)	34.9 % (17.7–52.7)	1.30 (0.76–2.20)	49.1 % (29.5–66.0)
Pelvic sidewall dissection							

Variable	No. of patients LF, OS/DFS	LF		DFS		OS	
		HR (95 % CI)	5 years	HR (95 % CI)	5 years	HR (95 % CI)	5 years
No	57/42	1.00	33.6 % (20.2–47.0)	1.00	30.5 % (16.4–45.9)	1.00	53.0 % (37.0–66.7)
Yes	155/146	1.20 (0.68–2.11)	39.1 % (30.7–47.4)	1.08 (0.69–1.67)	31.4 % (22.9–40.2)	1.36 (0.88–2.10)	42.9 % (34.1–51.4)

Excludes 24 patients who had metastasis at initial diagnosis of rectal cancer or before surgery where they had IORT

LF local failure, OS overall survival, DFS disease-free survival, HR hazard ratio, CI confidence interval, APR abdominoperineal resection, LAR low anterior resection, NA not available, IORT intraoperative radiotherapy

TABLE 5

Univariate analysis of 5-year LF, DFS, and OS rates for patients with locally advanced T4 disease ($N = 88$ for LF, OS and $N = 82$ for DFS)

Variable	No. of patients LF, OS/DFS	LF		DFS		OS	
		HR (95 % CI)	5 years	HR (95 % CI)	5 years	HR (95 % CI)	5 years
Use of oxaliplatin							
No	79/75	1.00	21.0 % (11.4–30.7)	1.00	49.5 % (36.6–61.2)	1.00	56.5 % (44.3–67.0)
Yes	9/7	2.50 (0.57–10.90)	NA	1.99 (0.60–6.64)	NA	1.01 (0.24–4.27)	40.0 % (1.1–82.9)
Type of surgery							
APR	33/32	1.00	22.4 % (5.8–38.9)	1.00	43.5 % (22.8–62.6)	1.00	50.4 % (30.6–67.2)
LAR	37/33	0.94 (0.36–2.43)	24.8 % (9.4–40.1)	0.73 (0.36–1.50)	52.2 % (32.7–68.5)	0.58 (0.31–1.08)	60.5 % (41.7–75.0)
Pelvic exenteration	15/14	0.52 (0.11–2.50)	13.3 % (0–31.4)	0.74 (0.29–1.90)	51.6 % (22.1–74.8)	0.72 (0.32–1.61)	58.7 % (30.0–79.0)
Dose level							
<1,200 cGy	42/38	1.00	15.3 % (3.8–26.9)	1.00	53.2 % (35.8–67.9)	1.00	58.9 % (42.4–72.1)
>1,200–1,500 cGy	33/33	2.03 (0.76–5.41)	29.7 % (11.5–48.0)	1.46 (0.73–2.90)	41.3 % (21.4–60.2)	1.65 (0.90–3.05)	54.6 % (33.6–71.4)
>1,500 cGy	12/10	1.44 (0.30–6.90)	20.2 % (0–47.7)	0.93 (0.28–3.16)	61.7 % (20.7–86.3)	1.73 (0.65–4.62)	48.2 % (14.1–76.2)
Pathologic lymph nodes							
No	63/58	1.00	22.1 % (11.2–33.0)	1.00	51.7 % (36.6–64.8)	1.00	61.6 % (47.1–73.2)
Yes	21/20	0.94 (0.31–2.80)	22.4 % (1.8–42.9)	1.68 (0.85–3.36)	33.5 % (12.5–56.2)	1.94 (1.03–3.63)	37.6 % (17.0–58.3)
Surgical margins							
Negative	58/54	1.00	23.3 % (10.8–35.7)	1.00	50.3 % (34.5–64.2)	1.00	56.7 % (41.4–69.5)
Positive	13/12	0.68 (0.16–2.96)	16.9 % (0–40.3)	1.41 (0.60–3.28)	44.0 % (14.9–70.2)	1.71 (0.84–3.51)	44.9 % (17.7–69.0)
Close	16/16	1.33 (0.41–4.32)	26.3 % (3.0–49.5)	1.50 (0.67–3.38)	44.9 % (19.2–67.8)	1.19 (0.56–2.52)	60.2 % (31.6–80.0)
Pelvic sidewall dissection							
No	20/18	1.00	20.7 % (2.0–39.4)	1.00	54.5 % (29.2–74.2)	1.00	60.5 % (33.9–79.1)
Yes	68/64	0.81 (0.30–2.20)	22.9 % (11.6–34.1)	1.10 (0.52–2.33)	45.7 % (31.3–59.1)	1.00 (0.51–1.96)	55.1 % (41.5–66.7)

Eighty-eight patients for LF and OS, and 82 for DFS; the latter value excludes 6 patients who had metastasis at initial diagnosis of rectal cancer or before surgery where they had IORT

LF local failure, DFS disease-free survival, OS overall survival, HR hazard ratio, CI confidence interval, NA not available, APR abdominoperineal resection, LAR low anterior resection, IORT intraoperative radiotherapy

TABLE 6

Toxicity

	Grade of Toxicity No. (%)					
	1	2	3	4	5	Total
Gastrointestina						
Fistula	0 (0 %)	8 (3 %)	12 (4 %)	8 (3 %)	1 (0.03 %)	29 (10 %)
Obstruction	0 (0 %)	11 (4 %)	34 (11 %)	13 (4 %)	0 (0 %)	58 (19 %)
Infection						
Abscess	0 (0 %)	7 (2 %)	21 (7 %)	10 (3 %)	0 (0 %)	38 (13 %)
Wound complication	4 (1 %)	36 (12 %)	23 (8 %)	14 (5 %)	0 (0 %)	77 (26 %)
Genitourinary						
Bladder	3 (1 %)	27 (9 %)	17 (6 %)	1 (0.03 %)	0 (0 %)	48 (16 %)
Ureter	3 (1 %)	8 (3 %)	35 (12 %)	6 (2 %)	0 (0 %)	52 (17 %)
Neurologic						
Peripheral neuropathy	10 (3 %)	25 (8 %)	5 (2 %)	1 (0.03 %)	0 (0 %)	41 (14 %)