Curr Colorectal Cancer Rep (2017) 13:402–409
DOI 10.1007/s11888-017-0387-0

Intraoperative Radiation Therapy for Locally Advanced or Locally Recurrent Rectal Cancer

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Published online: 29 August 2017

Abstract Colorectal cancer is a major cause of morbidity and mortality across the world. Although surgery alone is very effective for patients with early stage disease, patients with more advanced disease required a combined modality approach. Standard doses of radiation therapy are usually ineffective in controlling localized disease that cannot be widely resected. Radiation dose escalation with intraoperative radiation therapy (IORT) has been investigated for many years as a component of a trimodality strategy in patients at high risk for local recurrence. This paper reviews the evidence supporting inclusion of IORT in addition to external beam radiation, surgery, and chemotherapy in patients with very locally advanced primary rectal cancer and patients with locally advanced recurrent rectal cancer.

Keywords IORT · IOERT · IOHDR · Locally advanced rectal cancer · Recurrent rectal cancer · Dose escalation

Introduction

Although the incidence of colorectal cancer and the death rate in the USA is declining in both men and women, it remains the second most common cause of cancer death in men and third most common cause in women [1]. Worldwide, the number of new colorectal cancers in 2012 was 1.4 million with more than 690,000 deaths [2]. Among the approximately 40% of colorectal cancer patients with rectal cancer, local recurrence is a contributing factor to both morbidity and mortality in a significant number of patients. As surgical techniques have improved and total mesorectal excision (TME) has been adopted as the standard for rectal cancer resections, local recurrence rates have decreased significantly. However, even with a standardized TME, local recurrence rates may exceed 20% for stage III patients treated with surgery alone. Radiation therapy plays a critical role in decreasing the risk of local recurrence in locally advanced rectal cancer patients and in the curative intent management of patients with local recurrence of rectal cancer.

Within a decade of the discovery of X-rays, reports of intraoperative applications of radiation appeared in Europe. In the 1930s, Stanford investigators reported on the use of intraoperative orthovoltage radiotherapy in patients with rectal cancer [3]. Although initially investigated as a stand-alone modality, intraoperative radiation therapy (IORT) is best applied as a dose escalation tool for patients in whom normal tissue constraints preclude tolerable delivery of radiation doses associated with acceptable rate of local control. This paper will review the rationale for and the modern results of the application of an IORT boost in patients with very locally advanced primary rectal cancer or locally recurrent rectal cancer.

Locally Advanced Rectal Cancer

In the classic Gastrointestinal Study Group randomized trial that demonstrated both a survival and local control benefit in R0 patients with adjuvant radiation with 5-flourouracil (5-

This article is part of the Topical Collection on *Radiation Therapy and Radiation Therapy Innovations in Colorectal Cancer*

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FU), the radiation dose in the combined modality arm was 40 or 44 Gy in 1.8–2.0-Gy fractions [4]. Pelvic relapse was reduced from 24% in the surgery alone control arm to 11% in the combined modality arm. Because the dose of 40–44 Gy was thought to potentially be suboptimal, in the subsequent North Central Cancer Treatment Group (NCCTG) trial, the dose was modestly increased to 45 Gy with a 5.4-Gy boost exclusive of small bowel [5]. This dose was based more on normal tissue tolerance rather than evidence of ideal radiation dose in the adjuvant setting. The TD 5/5 (1–5% risk of injury at 5 years) for 100-cm^3 small bowel is considered to be 4500 cGy and the TD 50/5 (25–50% risk of injury at 5 years) is 5000 cGy [6]. Despite this dose increase, local relapse was 13.5% in the combined modality arm [5].

The most common dose employed in modern randomized studies involving chemoradiation therapy for rectal cancer has been 45–50.4 Gy. In resectable patients, this dose has been associated with low rates of local recurrence in both the preoperative and postoperative settings. In the German trial comparing preoperative versus postoperative chemoradiation for rectal cancer, the local relapse rate in the preoperative arm was only 5% at 5 years and 7% at 10 years [7]. For the past 30 years, research in rectal cancer has been mostly focused on dose modifiers, whereas radiation dose has only been studied in limited fashion. Given the low local relapse rates observed with modern preoperative chemoradiation, dose escalation in resectable T3 patients is unlikely to be of benefit. Current efforts are focused on reducing the use of neoadjuvant chemoradiation therapy in selected T3 patients.

Radiation alone in the preoperative setting has been shown to be effective in preventing local relapse using a dose of 25 Gy in five fractions. In the Dutch study evaluating total mesorectal excision alone or in combination with 25 Gy in five fractions preoperatively, the local recurrence rate in the preoperative radiation arm was 5.6% at 5 years [8]. Using the linear quadratic model without time corrections, a dose of 45 Gy in 25 fractions has a biologically equivalent dose (BED) of 53 Gy_{10} while 25 Gy in 5 fractions has a BED value of 37.5 Gy_{10}. However, after correcting for time differences between the two regimens assuming initiation of repopulation after 7 days, an alpha value of 0.25 and a potential doubling time of 5 days, the BED of both regimens is equivalent at 41 Gy_{10}. Not surprisingly, two randomized trials comparing long-course chemoradiation to short-course radiation without chemotherapy found no difference in local control between the two regimens [9, 10].

IORT is not indicated in patients with T3 rectal cancer who are resectable with negative margins at initial presentation. In one of the few prospective trials to evaluate IORT in rectal cancer, French investigators randomized patients with T3 or T4 or node-positive rectal cancer to 40 Gy in 4-week preoperative radiation therapy followed by surgery alone or surgery with an 18-Gy IORT boost. Only 7% of patients on the trial had T4 disease, and there was no difference in local control or survival. The local relapse rate without IORT was only 7%, suggesting that the population was not at high risk for local relapse with standard dose radiation therapy [11].

A subset of patients present with very locally advanced disease which may be defined as disease extension to surrounding structures resulting in a high likelihood of microscopic or gross residual disease after surgery. This group of patients may potentially benefit from dose escalation with an IORT boost. When high-resolution MRI demonstrates tumor extension to the circumferential resection margin, the MERCURY group reported a local relapse rate of 20% even after long-course preoperative radiation [12]. When the resection margin was pathologically involved at the time of surgery (R1 resection), the local relapse rate was 32% at 5 years and 5-year survival was observed in only 22% of patients. Positive resection margins are relatively common even in the modern era with a reported rate of 17% in both a National Cancer Database report and in the Dutch TME trial [13•, 14].

There is ample evidence to suggest that standard doses of radiation therapy are inadequate to control residual disease after an R1 resection. An older small Mayo Clinic series of postoperative radiation therapy to a dose of 50 Gy following R1 resection reported a 70% local relapse rate [15]. Another small series from Massachusetts General Hospital reported 40% local relapse after 50–60-Gy postoperative radiation following R1 resection [16]. In the randomized Dutch TME trial, patients randomized to surgery alone who had positive resection margins were mandated to receive 50.4 Gy in 28 fractions postoperatively but only 47% actually received radiation [14]. There was no difference in local relapse rates between the patients who received the protocol prescribed radiation versus those who did not (17.3 versus 15.7% local relapse at 2 years, respectively). Furthermore, among the patients who were randomized to preoperative radiation with 25 Gy in five fractions and had positive resection margins, there was no significant improvement in local relapse associated with preoperative radiation therapy, and on multivariate analysis, the addition of postoperative radiation was not associated with local control. Finally, in the MRC CR07 trial rectal, relatively high rates of local relapse were observed in patients with positive margins [17]. In this trial, patients with operable rectal cancer were randomized to short-course preoperative radiation (25 Gy in 5 fractions) versus surgery followed by selective long-course radiation (45 Gy in 25 fractions) only in patients with positive circumferential resection margins. Among the patients with positive margins, local relapse was observed at 3 years in 14% of patients with preoperative radiation and 21% with postoperative radiation.

Given the suggestion that doses of 60 Gy or higher are required for control of microscopic rectal cancer, a number of institutions have investigated IORT as a tool to escalate dose in patients with very locally advanced rectal cancer.

IORT has been delivered with two main techniques with similar results. Intraoperative electron beam radiation (IOERT) is delivered via mobile electron linear accelerators or via standard fixed linear accelerators through specially designed collimating cones in shielded operating rooms or in radiation departments. Electron energies typically vary from 6 to 15 MeV and are chosen according to desired depth of treatment. Dose is typically prescribed to the 90% isodose line. Alternatively, intraoperative high-dose rate brachytherapy using Iridium 192 can be delivered using a single plane applicator such as the Freiburg flap or Harrison-Anderson-Mick (HAM) applicator. Dose is typically prescribed at 1-cm depth from the surface of the applicator and is higher at the surface of the applicator compared to IOERT surface doses. Both techniques have the advantage of being able to avoid dose to mobile critical structures such as bowel in contrast to other external beam radiotherapy techniques of dose escalation such as stereotactic body radiation or dose-painted intensity modulated radiation therapy (IMRT).

Results of selected series using IORT for very locally advanced disease are shown in Table 1. The range of IORT doses used is fairly narrow with most patients treated with 10–15 Gy. Choice of IORT dose has been highly influenced by the early Mayo Clinic series in primary locally advanced colorectal cancer in which incidence and severity of neuropathy were associated with IORT dose [29]. IOERT doses of 15 Gy or higher were associated with a 21% risk of grade 2–3 neuropathy. No grade 3 neuropathies were observed with doses less than 15 Gy versus 5% for 15–17.5 Gy and 22% for 20 Gy or more. IORT doses of 15 Gy or higher are largely reserved for patients with incomplete resection or patients with previous pelvic radiation limiting the preoperative external beam radiation (EBRT) dose. Other investigators have not corroborated these findings.

Many IORT series have local control rates at 5 years of 90% or higher. Although randomized controlled comparisons have not been done in very locally advanced patients, several series have included a non-randomized contemporary control group. In the Tokai University series, patients were allowed to choose to have IORT after being informed that there was no proven benefit [19]. Five-year local control was observed in 98% of the 99 IORT patients versus 84% in 68 non-IORT patients ($p = 0.002$). Overall survival at 5 years was 79% in the IORT group versus 58% in the non-IORT group ($p = 0.02$) In the Rome Catholic University series, IORT was given to patients referred to participating IORT surgeons [22]. Among the 29 patients who received IORT, the 5-year local control rate was 100% versus 81% in 49 non-IORT patients ($p = 0.014$). On multivariate analysis, IORT was the only significant variable predicting for local control. In the Rotterdam IOHDR series, local control at 5 years was observed in 84% of 31 IORT patients versus 41% of 17 non-IORT patients ($p = 0.01$) [25••]. On multivariate analysis, IORT use and poor tumor differentiation were associated with local recurrence-free survival. Overall survival was also higher in IORT patients at 5 years (41 versus 13%,

Table 1 Disease control and survival with IORT for primary very locally advanced rectal cancer

Study	No. of patients	Publication year	EBRT dose (Gy)	IORT technique	IORT dose (Gy)	5-year LC	5-year OS	5-year DFS	5-year DM
Willett, MGH [18]	42	1991	50.4	IOERT	10–20	88%	–	43%	–
Sadahiro, Tokai University [19]	99	2004	20	IOERT	15–25	98%	79%	71%	20%
Krempien, Heidelberg [20]	210	2006	41.4	IOERT	10–15	93%	69%	66%	33%
Mathis, Mayo Clinic [21]	146[b]	2008	50.4	IOERT	7.5–25	86%[b]	52%[b]	43%[b]	49%[b]
Valentini, Rome [22]	29	2009	45–55	IOERT	10–15	100%	–	–	–
Kusters, European pooled [23]	605	2010	45–50.4	IOERT	10–12.5	88%	67%	–	29%
Hyngstrom, MDACC [24••]	30	2014	50.4	IOHDR	10–15	94%	61%	–	–
Alberda, Rotterdam [25••]	31	2014	45–50[a]	IOHDR	10	84%	41%	–	–
Sole, Madrid [26••]	335	2014	45–50.4	IOERT	10–15	92%	75%	72%	29%[c]
Zhang, Shanghai [27••]	71	2015	45–50.4	IOERT	10–20	90%	75%	69%	54%[c]
Holman, Mayo Clinic-Catharina Hospital pooled [28••]	417	2016	45–54	IOERT	10–20	81%	56%	55%	36%

Results of selected series

IORT intraoperative radiation therapy, *IOERT* intraoperative electron radiation therapy, *IOHDR* intraoperative high-dose rate brachytherapy, *LC* local control, *DMs* distant metastases, *OS* overall survival, *DFS* disease-free survival, *EBRT* external beam radiation therapy, *MGH* Massachusetts General Hospital, *MDACC* MD Anderson Cancer Center

[a] Some patients treated with 25 Gy in five fractions

[b] Includes 40 colon primary patients

[c] Crude

$p = 0.008$) and IORT use was the only variable predictive of survival on multivariate analysis. No difference in perioperative morbidity and mortality was observed between the two groups. Finally, in a series from Jiao Tong University in Shanghai, IORT use was based on patient preference and facility availability [27••]. Among the 71 IORT patients, the 5-year survival was 75 versus 66% for the 77 non-IORT patients ($p = 0.189$). Locoregional control at 5 years was observed in 90% of IORT patients versus 79% of non-IORT patients ($p = 0.049$). There was no observed difference in acute or late toxicities between the two groups.

A number of prognostic factors for disease control and survival have been identified. Although both the MDACC IOHDR series and the Shanghai series found no difference in local control or survival was observed in R0 versus R1 patients, most investigators have found completeness of resection to be highly associated with disease control and survival [18, 23, 24••, 26••, 27••, 28••]. In the European pooled analysis of 605 patients, a multivariate analysis was performed examining prognostic factors for local recurrence, distant metastases, and overall survival [23]. Lack of downstaging after preoperative EBRT, node-positive disease, margin involvement, and lack of postoperative chemotherapy were all associated with local relapse. Male sex, clinical T4 disease, lack of downstaging after preoperative EBRT, node-positive disease, and margin involvement were all associated with distant metastasis. Age, male sex, lack of downstaging, node-positive disease, margin involvement, and lack of postoperative chemotherapy were all associated with increased risk of death. In the large series of 335 patients from Madrid, multivariate analysis identified distal margins <10 mm, R1 resection, poorly differentiated tumor, and tumor regression grade 1–2 to be associated with locoregional relapse risk [26••]. Factors associated with relapse of disease within the IORT field were R1 resection, ypN+ stage, and abdominoperineal resection (versus sphincter sparing resection). The only factor associated with recurrence of disease outside of the IORT fields was lack of adjuvant chemotherapy.

In a combined Mayo Clinic-Catharina Hospital series, margin status was the only factor found on multivariate analysis to be predictive of cancer-specific survival [28••]. Overall survival at 5 years was observed in 64% of R0 patients versus 35% of R1 patients and 14% of R2 patients ($p < 0.0001$). Cancer-specific survival at 5 years was 73% in R0 patients, 44% in R1 patients, and 20% in R2 patients. The only risk factor for distant relapse was incomplete resection (R1 or R2). In an analysis unique to this series, the time from the last day of preoperative EBRT to the date of surgery was evaluated as a potential prognostic factor. Although an interval greater than 8 weeks was associated with a higher likelihood of R0 resection (80 versus 69%, $p = 0.014$), both R0 resection and an interval less than 8 weeks to surgery were associated with improved local control. Local control at 5 years was observed in 87% of R0 patients versus 60% for R1 patients and 57% for R2 patients. On multivariate analysis, interval to surgery of 8 weeks or less and R0 resection (versus R1 or R2) were associated with a 40% reduction in risk of local relapse. An interval to surgery greater than 8 weeks was especially associated with local relapse risk in R1/2 patients with a 3-year local relapse rate of 43% in R1/2 patients versus 18% in R0 patients ($p = 0.018$). This analysis suggests that although a longer interval to surgery is associated with R0 resection, surgery should not be delayed more than 8 weeks after completion of preoperative EBRT due to potential loss of additive effects of the preoperative EBRT and IORT doses leading to a higher risk of subsequent local relapse.

Locally Recurrent Rectal Cancer

Historically, local recurrence of rectal cancer was incurable with the exception of the uncommon patients with early anastomic recurrence without extension into surrounding tissues. Although advances in modern systemic therapy have significantly prolonged life in patients with recurrent or metastatic rectal cancer, curative therapy of local recurrence typically requires an aggressive multimodality approach including radiation, surgery, and systemic therapy. Surgery for most pelvic recurrences of rectal cancer requires an experienced team of surgeons and may require in addition to colorectal surgeon the assistance of urologists, gynecologic surgeons, vascular surgeons, plastic surgeons, orthopedic surgeons, and others. The expertise needed to offer curative intent treatment for local relapse is only available in specialized tertiary centers. Because of the complex nature of the management of locally recurrent disease and the lack of alternative curative options, randomized controlled trials have not been performed. IORT has been utilized as a component of therapy for management of local recurrence both as a dose escalation tool and to allow adequate radiation dose for local control in patients who have been previously irradiated whose option for additional EBRT may be limited. The risk of at least microscopic residual disease after surgery is high, and as discussed above, high doses of radiation are required for local control.

Early experience with IORT containing multimodality regimens for recurrent rectal cancer at Mayo Clinic did include a contemporaneous control group not treated with IORT [30]. Among a group of 106 patients who underwent R1 or R2 resection, 3- and 5-year survival following surgery alone were 8 and 0%. The 5-year survival was 19% for patients who received IORT versus 7% for patients treated with EBRT and/or brachytherapy but without IORT ($p = 0.0006$). Local control among IORT patients was achieved in 60 versus 7% at 3 years. For patients with gross residual disease (R2), survival at 3 years was 44% for IORT patients versus 15% for non-IORT patients; local relapse was observed in 40% of IORT

patients versus 93% of non-IORT patients. Patients presenting with pain and patients with more than one site of fixation seemed to derived greater improvements in local control and survival with the addition of IORT. In a recent small series of 25 patients treated with radiation for recurrent rectal cancer, 16 of whom underwent surgery and 8 of whom received IORT; IORT and surgery were associated with improved overall survival [31]. In a systematic review of 29 reports in the literature from 1965 to 2011, inclusion of IORT for close or positive margins had a significant positive effect on local control, disease-free survival, and overall survival without impact on overall complications [32•].

The results of selected series which included IORT as a component of treatment in patients with locally recurrent rectal cancer are shown in Table 2. The use of EBRT in addition to IORT has been variable and related to prior radiation history among the cohorts. Some series have routinely included EBRT even in previously irradiated patients. The IORT dose applied is consistently between 10 and 20 Gy. About a third of patients overall are 5-year survivors. Local control is variable, but generally achieved in over 50% of patients in modern series. The risk of distant metastatic relapse is higher than that observed in primary very locally advanced rectal cancer, emphasizing the need for more effective systemic therapy.

The most consistently identified prognostic factor for both survival and disease control is completeness of resection which is related both to the aggressiveness of the treatment as well as the biology of the recurrent disease [33, 35, 36, 39,40, 41••]. In the combined 565 patient Mayo Clinic-Catharina Hospital analysis, overall survival at 5 years was observed in 33% of patients overall, and in R0, R1, and R2 patients, the 5-year survival was 48, 25, and 17%, respectively [41••]. Local control at 5 years was observed in 55% overall, and in R0, R1, and R2 patients, the local control rates were 72, 36, and 39%, respectively. In this series, the use of neoadjuvant EBRT increased the likelihood of R0 resection which increased from 26% with no preoperative therapy to 43% with moderate dose re-irradiation in previously irradiated patients and 50% in patients who received full dose preoperative EBRT. Local control at 5 years was observed in 62% after full-course neoadjuvant EBRT, 48% after moderate dose re-irradiation, and 41% with no preoperative EBRT. A longer time from completion of preoperative EBRT to surgery up to 11–12 weeks was also associated with an increased likelihood of R0 resection and local control. This finding is confounded by the fact that at Mayo Clinic, previously irradiated patients were treated with 30-Gy preoperative re-irradiation and chemotherapy and immediate surgery and patients without prior radiation treated to full-dose EBRT did not undergo surgery

Table 2 Disease control and survival following combined modality therapy including IORT in patients with recurrent rectal cancer

Study	No. of patients	Publication year	EBRT percent	EBRT dose (Gy)	IORT technique	Margins	IORT dose (Gy)	5-year LC	5-year OS	5-year DFS	5-year DM
Eble, Heidelberg [33]	31	1998	100%	41.4	IOERT	R0–2	10–20	71%[a]	19%[d]	71%[d]	33%[a]
Martinez-Monge, OSU [34]	28	1999	21%	20–50.4	IOERT	R1–2	10–20	40%	8%	–	–
Martinez-Monge, OSU [34]	23	1999	26%	20–50.4	IOHDR	R1–2	10–20	21%	13%	–	–
Alektiar, MSKCC [35]	74	2000	39%	36–59.4	IOHDR	R0–1	10–18	39%	23%	23%	61%
Lindel, MGH [36]	49	2001	94%	19.8–50.4	IOERT	R0–2	10–20	35%	27%	20%	–
Hashiguchi, Saitama [37]	17	2003	69%	40–60	IOERT	R0–1	15–30	24%	35%	24%	–
Nuyttens, Rotterdam [38]	19	2004	100%	25/5 or 50/25	IOHDR	R0–1	10	48%[b]	34%[b]	–	53%
Dresen, Eindhoven [39]	147	2008	84%	30.6–50.4	IOERT	R0–2	10–17.5	54%	32%	34%	50%
Haddock, Mayo Clinic [40]	607[c]	2011	96%	50.4[e]	IOERT	R0–2	12.5–20	72%	30%	–	53%
Hyngstrom, MDACC [24••]	70	2014	74%	30–50.4	IOHDR	R0–1	10–15	56%	56%	–	–
Holman, Mayo Clinic-Catharina Hospital pooled [41••]	565	2017	95%	45–54[e]	IOERT	R0–2	10–20	55%	33%	–	57%

Results of selected series

R0 pathologically negative margins, *EBRT* external beam radiation therapy, *IORT* intraoperative radiation therapy, *LC* local control, *DMs* distant metastases, *OS* overall survival, *OSU* Ohio State University, *MSKCC* Memorial Sloan Kettering Cancer Center, *MGH* Massachusetts General Hospital, *MDACC* MD Anderson Cancer Center, *IOHDR* intraoperative high-dose rate brachytherapy

[a] Crude

[b] 3-year results

[c] Includes 180 colon primary patients

[d] 4-year results

[e] 5–39.6 Gy in previously irradiated patients

for at least a month. In an earlier Catharina Hospital analysis, patients who underwent anterior resection as opposed to abdominoperineal resection for treatment of disease at primary presentation and patients who did not have pain at the time of diagnosis of recurrent disease were more likely to undergo R0 resection [39].

IORT alone without EBRT has not been a successful strategy [34, 35]. Given that a cumulative equivalent dose in 2-Gy fractions (EQD2) of 60 Gy or higher is required for control of microscopic disease and 70 Gy or higher for gross disease, it is not surprising that a single dose of 10–20 Gy is associated with inferior local control and survival compared to the combination of EBRT and IORT. Most patients with a prior history of pelvic radiation with local relapse can be safely re-irradiated with moderate dose EBRT [42, 43]. Bowel is typically the dose-limiting structure and elective volumes are not treated in the re-irradiation setting. Peripheral nerves are dose limiting for IORT and doses greater than 20 Gy are not generally advised. In the Mayo Clinic series, IORT doses of 15 Gy or higher were associated with a 14% incidence of grade 2 (moderate weakness or pain requiring narcotics) or grade 3 (severe weakness or intractable pain) versus only 5% with lower doses. However, the combination of 30 Gy in 15 fractions over 3 weeks preoperative EBRT followed immediately by surgery + IORT 12.5-Gy IORT is equivalent in the linear quadratic model with time corrections to an EQD2 of 60 Gy, a dose which has been associated with local control of microscopic rectal cancer [16]. Therefore, preoperative chemoradiation to a dose of at least 30 EQD2 with capecitabine or infusion 5-FU is the preferred strategy in patients with prior pelvic radiation.

A number of other potential prognostic factors have been identified. In the Japanese series from Saitama, better survival was associated with lack of unresectable distant metastases, a CA 19–9 level <37 U/mL, lack of pain at presentation, and use of adjuvant chemotherapy [37]. Although in most series distant metastatic disease at the time of local relapse has been an inclusion factor, patients with resectable or ablatable limited distant metastases may be considered for aggressive local therapy including IORT. In the Catharina Hospital series of 147 patients from the Netherlands, factors associated with increased survival on multivariate analysis included R0 resection, initial stage I rectal cancer versus stage II or III, and anterior resection versus more extensive surgery for the recurrent disease [39]. Factors in this series which were associated with improved metastasis-free survival on multivariate analysis included R0 resection, initial stage I rectal cancer, use of EBRT for treatment of recurrence, and anterior resection versus abdominoperineal resection for treatment of the primary rectal cancer. In the Mayo Clinic series, prior pelvic radiation was associated with decreased local control and central control within the IORT field [40]. In the MDACC IOHDR series, patients with body mass index (BMI) ≥30 kg/m^2 and patients with postdischarge complications had a higher likelihood of local relapse [24••].

Conclusion

A large and growing body of evidence suggests that high-dose radiation with the combination of EBRT and IORT is effective in improving local control in unresectable or subtotally resected primary or recurrent rectal cancer. Level 1 evidence supporting the inclusion of IORT is lacking and could be developed in the primary locally advanced setting. Patients with locally recurrent disease require an experienced multidisciplinary team and are best managed in tertiary centers. R0 resection is the most important survival-related factor, and preoperative therapies to increase the likelihood of R0 resection should be used. Previously irradiated patients can be safely treated with moderate dose EBRT with concomitant chemotherapy and IORT. Distant metastatic relapse is the predominant pattern of relapse, especially in the recurrent disease setting, and effective systemic therapy will be a key component of improving survival in the future.

DMs Distant metastases, *EBRT* External beam radiation therapy, *IOERT* Intraoperative electron radiation therapy, *IOHDR* Intraoperative high-dose rate brachytherapy, *IORT* Intraoperative radiation therapy, *LC* Local control, *MDACC* MD Anderson Cancer Center, *MGH* Massachusetts General Hospital, *MSKCC* Memorial Sloan Kettering Cancer Center, *OS* Overall survival,

Compliance with Ethical Standards

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

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

Disclaimers The views expressed are those of the authors.

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- •• Of major importance

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