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CLINICAL INVESTIGATION

COMBINED MODALITY THERAPY INCLUDING INTRAOPERATIVE ELECTRON IRRADIATION FOR LOCALLY RECURRENT COLORECTAL CANCER

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Purpose: To evaluate survival, relapse patterns, and prognostic factors in patients with colorectal cancer relapse treated with curative-intent therapy, including intraoperative electron radiation therapy (IOERT).
Methods and Materials: From April 1981 through January 2008, 607 patients with recurrent colorectal cancer received IOERT as a component of treatment. IOERT was preceded or followed by external radiation (median dose, 45.5 Gy) in 583 patients (96%). Resection was classified as R0 in 227 (37%), R1 in 224 (37%), and R2 in 156 (26%). The median IOERT dose was 15 Gy (range, 7.5–30 Gy).
Results: Median overall survival was 36 months. Five- 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.
Conclusions: Long-term survival and disease control was achievable in patients with locally recurrent colorectal cancer. Continued evaluation of curative-intent, combined-modality therapy that includes IOERT is warranted in this high-risk population. ©2010 Mayo Foundation for Medical Education and Research © 2010 Elsevier Inc.

Colorectal cancer, Intraoperative radiation therapy, Local disease relapse, Radiation tolerance.

INTRODUCTION

In 2008, nearly 149,000 patients in the United States were diagnosed with colorectal cancer (1). Although adjuvant therapy has decreased the risk of pelvic relapse (2, 3), the consequences of local relapse are devastating (4, 5). Locoregional relapse of colon cancer occurs relatively frequently with tumor penetration through the bowel wall and regional lymph node involvement (6–10). Relapse in presacral or para-aortic lymph nodes is observed in patients with node-positive disease.

Locoregional relapse after resection of colorectal cancer is associated with a poor prognosis; median survival is 11 to 15 months (5, 11–13), and generally fewer than 5% of patients survive for 5 years (5, 11, 14, 15). Palliative therapies for pelvic recurrence are of limited effectiveness, especially for patients surviving longer than a few months. Additional radiation therapy often is not recommended for patients with relapse in previously irradiated fields.

Since 1981, curative-intent therapy at our institution has included intraoperative electron radiation therapy (IOERT) for patients with locally advanced malignancies. We have previously reported preliminary results of IOERT-containing regimens for patients with recurrent rectal cancer (16, 17) or locally advanced relapse of colorectal cancer (18, 19). The current study evaluated survival, patterns of relapse, and prognostic factors of patients with recurrent colorectal cancer.

METHODS AND MATERIALS

The Mayo Clinic institutional review board approved this study. From April 1981 through January 2008, 607 patients with recurrent colorectal cancer underwent surgical resection and concurrent

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IOERT. All had locally advanced recurrence in the primary tumor bed or in regional pelvic or para-aortic lymph nodes. Patient characteristics are shown in Table 1. The median time from primary diagnosis to diagnosis of recurrence was 27 months.

External-beam radiation therapy (EBRT) was included in the treatment for recurrence in 583 (96%). The median dose was 45.5 Gy (delivered in 1.8- to 2.0-Gy fractions). Twenty previously irradiated patients and 4 unirradiated patients received only IOERT (no EBRT). The timing of EBRT was preoperative in 529 (91%; median, 45 Gy; range, 5.0–65.0 Gy), postoperative in 43 (7%; median, 50.0 Gy; range, 5.4–55.8 Gy), and both preoperative and postoperative in 11 (2%; median, 39.6 Gy; range, 22.0–60.8 Gy). Previously unirradiated patients received a median EBRT dose of 50.4 Gy (range, 8.4–65.0 Gy), whereas those with prior EBRT in the field of relapse had a lower dose of EBRT (median, 27.5 Gy; range, 5.0–39.6 Gy). To evaluate changes over time (advances in diagnostic imaging, radiation treatment planning, and systemic chemotherapy), the series was divided into two equal groups, using the midpoint of March 1997. Specific changes in EBRT technique were not evaluated, but in the second half of the cohort, 99% of previously irradiated patients received additional EBRT, with a median dose of 30 Gy.

Radiosensitizing chemotherapy was delivered concomitantly with EBRT in 492 (81%) patients and consisted of bolus 5-fluorouracil (5-FU), with or without leucovorin, protracted venous infusion 5-FU, or oral capecitabine. Additional adjuvant chemotherapy was used in 107 (18%) patients.

All patients underwent surgical exploration and maximal resection of tumor before administration of IOERT. Margins of resection were negative but close (R0) in 227 (37%) and microscopically positive (R1) in 224 (37%). In 156 (26%) patients, IOERT was delivered to gross residual disease (R2).

A single IOERT field was treated in 586 (97%) patients and multiple fields in 21 (3%). Two patients received intraoperative high–dose-rate brachytherapy with ^{192}iridium. The IOERT was delivered through circular (flat, 15°, or 30° bevel) or elliptical (flat or 20° bevel) acrylic applicators. Electron energies used ranged from 6 to 20 MeV, with doses calculated at the 90% isodose depth. The most common electron energies were 9 MeV (53%) and 12 MeV (22%). Five hundred sixty-five circular fields were treated (diameter, 4.0–9.5 cm). Sixty-three elliptical fields were treated (width, 6–12 cm; length, 11–20 cm).

The median IOERT dose was 15 Gy (range, 7.5–30 Gy; 98% of patients received ≤20 Gy). Previously unirradiated patients received a median IOERT dose of 12.5 Gy. Those who had been previously irradiated received a median dose of 17.5 Gy. The IOERT dose also depended on resection margins, with median IOERT doses of 12.5, 15, and 20 Gy for R0, R1, and R2 resections, respectively.

Survival and disease relapse data were collected prospectively; this information was supplemented with a chart review. All patients were followed up until death or for a median of 44 months for 194 surviving patients. Kaplan-Meier survival curves were constructed (20). Endpoints included survival, central relapse (within the IOERT field), local relapse, and distant relapse. Because of the competing risks of death and disease relapse, risks of central, local, and distant relapse were estimated using the cumulative incidence method (21, 22). Prognostic factors for survival and disease relapse were evaluated using the log-rank test. Any p values less than 0.05 were considered statistically significant. Complications were scored using a four-grade system with criteria developed by the National Cancer Institute intraoperative radiation therapy contract group (23).

Table 1. Patient characteristics (N = 607)

Characteristic	Value
Age, median (range), y	62 (21–87)
Gender, *n* (%)	
M	369 (61)
F	238 (39)
Location of primary tumor, *n* (%)	
Rectum	427 (70)
Colon	180 (30)
Pathology, *n* (%)	
Adenocarcinoma	602 (99)
Carcinoid tumor	1 (<1)
Neuroendocrine carcinoma	1 (<1)
Squamous cell carcinoma	2 (<1)
Transitional cell carcinoma	1 (<1)
Histologic grade of recurrent tumor	
1	1 (<1)
2	189 (31)
3	360 (59)
4	34 (6)
Unknown	23 (4)
Prior treatment, *n* (%)	
Surgery	
No resection or bypass	8 (1)
Subtotal resection	71 (12)
Complete resection	515 (85)
Unknown	13 (2)
Chemotherapy	364 (60)
Radiotherapy	
None	336 (55)
In field of relapse	248 (41)
Outside of field of relapse	23 (4)

RESULTS

Survival

Survival estimates for the 607 patients are shown in Fig. 1. Median survival was 36 months. The 5- and 10-year survival estimates were 30% and 16%, respectively. Univariate analysis of potential prognostic factors for survival (Table 2) showed that longer length of time to relapse from diagnosis of primary disease, EBRT dose, IOERT dose, biologically equivalent dose, tumor volume, sex, and tumor histology were not associated with greater survival.

Prognostic factors with p values less than 0.10 were entered into a multivariate proportional hazards model (Table 3). Only treatment era (better survival for more recently treated patients), no prior chemotherapy, and tumor resection margins (R0 better than R1 better than R2) at time of IOERT were statistically significant. Survival estimates, stratified by volume of residual disease, are shown in Fig. 2. Survival estimates, stratified by prognostic factor, are summarized in Table 4.

Disease relapse

The cumulative incidence of central, local, and distant disease relapse is shown in Fig. 3 and Table 5. Most relapses were observed within 3 years of treatment.

Central relapse was uncommon and occurred in only 14% of patients at 5 years. Relapse was more common in

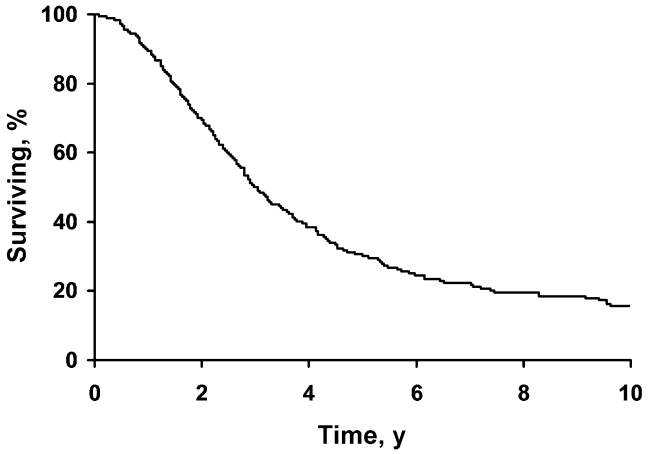

Fig. 1. Kaplan-Meier survival curve (N = 607).

previously irradiated patients than in those without prior EBRT (16% vs. 9% at 3 years) and in patients with subtotal resection (R1 and R2) compared with R0 resection (13% vs. 8% at 3 years).

Local relapse was observed in 28% of patients at 5 years. Local relapse was more common in patients with subtotal resection (R1 and R2) than in those with R0 resection (26% vs. 16% at 3 years). Local relapse was also more common in previously irradiated patients (31% vs. 17% at 3 years).

The cumulative incidence of distant relapse was 53% at 5 years. Distant relapse was more common in patients with subtotal resection (R1 and R2) than in patients with R0 resection (53% vs. 40% at 3 years). The cumulative incidence of distant relapse was lower in the 304 patients treated after March 1997 than in those treated earlier (44% vs. 52% at 3 years).

Table 2. Potential prognostic factors for survival (univariate analysis)

Factor	5-y survival, %	p
Location of primary tumor		0.07
Colon	34	
Rectum	28	
Prior EBRT		0.07
No	34	
Yes	26	
Prior chemotherapy		0.08
No	34	
Yes	27	
Age (y)*		0.09
<61.5	31	
>61.5	29	
Tumor margin		<0.001
R0	46	
R1	27	
R2	16	
Systemic chemotherapy		0.03
No	28	
Yes	40	
Treatment era†		<0.001
Before March 1997	25	
March 1997 and later	36	
Chemotherapy with EBRT		0.02
No	22	
Yes	32	

Abbreviation: EBRT = external beam radiation therapy.

* Patients were divided into two groups by age at recurrence. Median age was used as the cutoff value.

† Patients were divided by treatment era. The cutoff date was selected to form two groups of equal size.

Table 3. Potential prognostic factors for survival (multivariate analysis)

Factor	p value
R0 vs. R1 vs. R2 margin	<0.001
No prior chemotherapy	<0.001
Treatment after March 1997	0.01
Colon vs. rectum (primary tumor)	0.07
Systemic chemotherapy	0.08
Age <61.5 y	0.12
Chemotherapy with EBRT	0.40
Prior EBRT	0.90

Abbreviation: EBRT = external beam radiation therapy.

Complications and toxic events

We identified 621 treatment-related complications that affected 302 patients. Of those, 302 complications were considered severe or greater; the most common complications are summarized in Table 6. Both the incidence and severity of neuropathy were related to IOERT dose (Table 7). Six patients (<1%) died without relapse of treatment-related complications, and none had been previously irradiated. One patient died of uncontrolled bleeding from the colostomy, 6 weeks after IOERT. Five additional patients died 3 to 22 months after surgery for small-bowel obstruction, small-bowel perforation, or complications arising after surgical correction of the bowel complication.

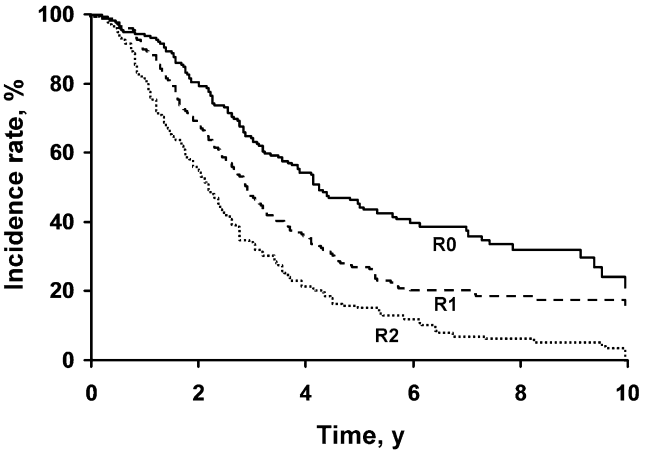

Fig. 2. Kaplan-Meier survival curves (N = 607). Patients were stratified by volume of residual disease. R0 denotes negative margins; R1, microscopically positive margins; R2, gross residual disease.

Table 4. Survival estimates by prognostic factor

Factor	Overall survival, mo, median	Years of survival, % of patients				Multivariate *p* value
		1	2	5	10	
Tumor margin						<0.001
R0	52	94	80	46	25	
R1	35	90	69	27	18	
R2	27	82	56	16	4	
IOERT						0.01
Before March 1997	32	84	63	25	12	
March 1997 and later	43	95	78	36	ND	
Prior chemotherapy						<0.001
No	42	91	73	34	18	
Yes	35	89	67	27	14	

Abbreviations: IOERT = intraoperative electron beam irradiation; ND = no data.

DISCUSSION

The medical literature offers little guidance for curative-intent therapy for patients with locoregional relapse of colorectal cancer. Most reports are single-institution retrospective analyses with inherent selection biases. Since 1981, a curative-intent approach, including the use of intraoperative electrons as a component of therapy, has been used relatively uniformly at our institution. Although retrospective in nature, the current analysis was accomplished using a prospectively defined database designed at the outset of the IOERT program. This report, which describes one of the largest single-institution experiences treating patients with recurrent colorectal cancer, shows that a considerable number of patients with locoregional relapse may have long-term survival with disease control after receiving combined aggressive locoregional therapy and systemic therapy.

Treatment approaches that exclude intraoperative radiation therapy

Locally recurrent colorectal cancer is often associated with symptoms of pain, bleeding, and intestinal obstruction (3, 4, 12, 24, 25). External-beam radiation effectively palliates pain in 60% to 80% of patients (4, 14, 24). Doses exceeding 50 Gy have been associated with better symptomatic response (11, 14). Symptom relief is often temporary, lasting less than 6 months in most patients (24). Most patients are symptomatic at death, the most common site of subsequent relapse is local, and nearly one-fourth of patients with local relapse die without distant disease (4, 5). Median survival ranges from 11 to 15 months (5, 11–13), and 5-year survival is generally reported in fewer than 5% of patients (5, 11, 14, 15).

Selected patients with recurrent colorectal cancer may be cured with surgical resection alone, and 5-year survivals ranging from 25% to greater than 70% have been reported when the disease is confined to the anastomosis (26–28). However, fewer than 15% have anastomosis-limited disease (28, 29). Several investigators have reported the likelihood of

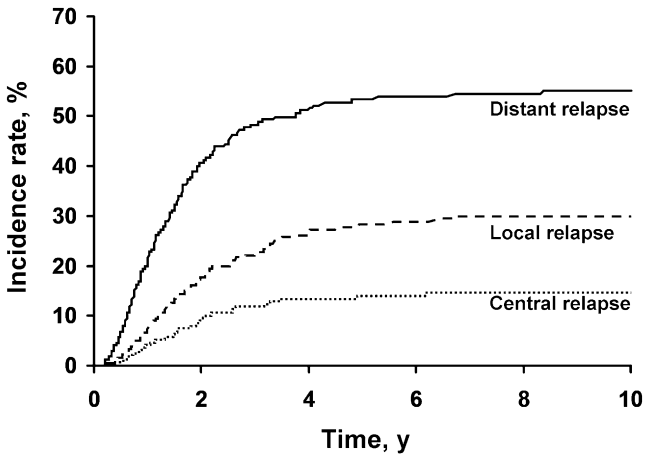

Fig. 3. Cumulative incidence of relapse within the intraoperative irradiation field ($N = 607$).

Table 5. Kaplan-Meier survival and cumulative incidence of disease relapse

Endpoint	Time in years, % of patients			
	2	3	5	10
Survival*	70	50	30	16
Cumulative incidence of relapse				
Central	9	12	14	15
Prior EBRT	12	16	18	18
No prior EBRT	7	9	11	12
R0 margin	7	8	9	12
R1-R2 margin	10	13	16	16
Local	18	23	28	30
Prior EBRT	24	31	37	37
No prior EBRT	14	17	22	25
R0 margin	14	16	21	23
R1-R2 margin	20	26	32	33
Distant	41	49	53	55
R0 margin	29	40	48	48
R1-R2 margin	47	53	56	58
Before March 1997	45	52	56	58
After March 1997	35	44	49	ND

Abbreviations: EBRT = external beam radiation therapy; ND = no data.

* Median overall survival was 36 months.

Table 6. Severe, life–threatening, or fatal treatment-related complications

Complication	Treatment-related complication, *n* (%)	IOERT-related complication, *n* (%)
Wound infection, abscess, fistula	81 (13)	42 (7)
Gastrointestinal tract fistula or obstruction	82 (13)	7 (1)
Ureteral obstruction	44 (7)	18 (3)
Neuropathy	23 (4)	18 (3)

Abbreviation: IOERT = intraoperative electron radiation therapy.

Table 7. Neuropathy as a function of IOERT dose

IOERT dose	Neuropathy, *n* (%)*			
	Grade 1	Grade 2	Grade 3	Any grade†
≤12.5 Gy	9 (3)	11 (4)	3 (1)	23 (9)
>12.5 Gy	23 (7)	32 (10)	15 (4)	70 (21)
All patients	32 (5)	43 (7)	18 (3)	93 (15)

Abbreviation: IOERT = intraoperative electron radiation therapy.
* Grade 1, pain not requiring narcotics; Grade 2, moderate weakness or pain requiring narcotics; Grade 3, severe weakness or intractable pain (or both).
† Pearson χ^2 $P<.001$.

R0 resection to be in the range of 5% to 15% (14, 15, 26, 30). When an R0 resection can be performed, 5-year survival in the range of 20% to 40% has generally been reported (13, 25, 26, 30).

The prognostic importance of surgical margin status has been well established in non-IOERT series (14, 26, 31, 32). The likelihood of R0 resection may be improved with the performance of sacrectomy, with additional risks of morbidity and death. Survival at 5 years has been reported in 31% of patients after abdominosacral resection, with a 7% surgical mortality rate (33). If the sacrectomy does not result in negative margins, long-term survival is rare, and median survival is roughly half of that observed with R0 patients (34, 35). Less than 5% of patients who undergo palliative resection without sacrectomy have long-term survival (12, 13, 36).

Intraoperative radiation therapy as a component of treatment

Given the lack of a control group in the current series, we cannot draw definitive conclusions regarding the impact of IOERT on disease control and survival. Our observed 5-year survival rate of 46% in R0 patients compares favorably to our prior published experience of 34% achieving 5-year survival (65 patients, only 3 of whom received IOERT) (25). In addition, the 35-month median survival and 27% 5-year survival observed in 224 R1 patients and the 27-month median survival and 16% 5-year survival in 156 R2 patients compares favorably to our prior experience (36), in which palliative resection alone did not produce long-term survivors and palliative resection with EBRT resulted in a 5-year survival rate of 7%. The survival of R1 and R2 patients in the current series is similar to that reported after R0 resection in several other series (14, 26, 31, 34).

Results of curative-intent salvage therapy with IOERT or intraoperative, high–dose-rate brachytherapy are summarized in Tables 8 and 9. Clearly, when comparing 5-year survival and local control rates, intraoperative radiation therapy (IORT) is not a substitute for R0 resection, with 5-year survival rates in the range of 30% to 60% and local control in excess of 50% for R0 resection with IORT. In contrast, 5-year survival is in the range of 0% to 25% for R1 or R2 resection with IORT (37, 38, 40, 42, 43). The results of IORT series compare favorably with those of series reporting surgical resection alone for locally advanced disease or surgical resection with EBRT. Lybeert *et al.* (5) reported improved survival with the addition of EBRT (doses >50 Gy), but local relapse occurred in 57% of patients and was the predominant pattern of relapse.

For local relapse, the dose of radiation required for control exceeds small-bowel tolerance when delivered with EBRT alone. Local control of microscopic volumes of colorectal cancer requires doses of 60 Gy or higher when conventionally fractionated (45). An external-beam dose of 50.4 Gy in 28 fractions, followed in 4 weeks by 12.5-Gy IOERT, is equivalent to a 66-Gy dose delivered in 2-Gy fractions. Doses exceeding 12.5 Gy in a single fraction are associated with increased incidence and severity of neuropathy. Because of dose limitations for single-fraction, high-dose radiation, IOERT without additional EBRT is not expected to be effective.

Uniformly poor survival and local control can occur after IOERT without additional EBRT (38, 39, 44, 46). Many investigators have excluded previously irradiated patients when evaluating curative-intent therapy. Frykholm *et al.* (4) described a non-IOERT series of patients treated with curative intent: patients without prior EBRT had a survival rate of 9% at 5 years, whereas previously irradiated patients had a 0% survival rate. Concern about toxicity with reirradiation has led many investigators to omit EBRT in previously irradiated patients, but reirradiation with doses of 30 to 50 Gy has been associated with acceptable toxicity in multiple series (47, 48). The current study describes one of the largest cohorts of reirradiated patients (n = 228). An EBRT dose of 30 Gy, followed immediately by resection and 12.5-Gy IOERT, is calculated by linear quadratic modeling to be equivalent to 62 Gy in 31 fractions. Despite higher local relapse rates in patients with prior EBRT, multivariate analysis showed that it was not associated with inferior survival; thus, prior radiation should not be an absolute contraindication to this approach.

Systemic therapy as a component of IORT approaches

The observation that survival improved for more recently treated patients is of interest. The reasons for this improvement are unknown but may relate to changes in selection based on improved imaging techniques or improved survival as a result of an increase in the use of systemic therapy.

Table 8. Results after IORT in R0 patients

Study	No. of patients	IORT dose, Gy	EBRT dose, Gy*	5-y survival rate, %†	5-y local control rate, %†
Vermaas *et al*., 2005 (31)	17	10	50	45 (3-y)	35 (3-y)
Alektiar *et al*., 2000 (37)	53	10–18	45–50.4	36	43
Abuchaibe *et al*., 1993 (38)	8	15	40–50	29	50
Dresen *et al*., 2008 (39)	84	10	50.4 or 30.6‡	59 (3-y)	75 (3-y)
Lindel *et al*., 2001 (40)	25	10–15	50.4	40	56
Eble *et al*., 1998 (41)	14	12–20	41.4	71 (4-y)	79 (4-y)
Wiig *et al*., 2002 (42)	18	15	46–50	60	70
Valentini *et al*., 1999 (43)	11	10–15	45–47	41	80
Current study	226	12.5 (median)	30.0-0.4‡	46	72

Abbreviations: EBRT = external beam radiation therapy; IORT = intraoperative radiation therapy.
* EBRT generally was delivered only to patients not previously treated with radiation, except for patients in Dresen *et al*., 2008 (39) and the current series.
† Five-year rates are shown unless otherwise indicated.
‡ Lower doses were administered in previously irradiated patients.

Before 1996, maintenance systemic therapy was rarely used as a component of IOERT in our institution. As noted in a prior Mayo publication (16), only 2 of 123 IOERT patients with recurrent colorectal cancer, treated from April 1981 through August 1995, received maintenance systemic therapy. In a Japanese IORT series (49), 5-year survival after resection and IOERT was 35% when patients received postoperative 5-FU–based chemotherapy, whereas it was 0% for those not treated with chemotherapy. Survival of patients with metastatic disease has increased from a median of 10 to 12 months with fluoropyrimidine therapy alone (50) to a median exceeding 20 months with modern systemic and targeted therapy (51–53). Inasmuch as the effective systemic armamentarium has expanded considerably in recent years and survival of patients with metastatic disease has been prolonged, the importance of sustained local control of disease has been magnified.

CONCLUSION

Long-term survival was observed for many patients with recurrent colorectal cancer treated with chemoradiation, resection, and IOERT. Prior EBRT was not a contraindication to this approach. Survival was higher for patients with R0 resection, patients with no prior chemotherapy, and patients treated more recently. Long-term survival was observed even for patients with R1 or R2 resection. For patients without prior EBRT, 50.4 Gy in 28 fractions with concomitant fluoropyrimidine, followed by resection and IOERT 1 month later, is recommended. For patients with prior EBRT, 30 Gy in 15 to 17 fractions, followed immediately by resection and IOERT, is recommended. Limiting the IOERT dose to 12.5 Gy may result in decreased peripheral nerve toxicity. This aggressive locoregional approach should continue to be investigated.

Table 9. Results after IORT in R1 and R2 patients

Study	No. of patients	Surgical margins	IORT dose, Gy	5-y survival rate, %*	5-y local control rate, %
Vermaas *et al*., 2005 (31)	10	R1–R2	10	21 (3-y)	21 (3-y)
Alektiar *et al*., 2000 (37)	21	R1	10–18	11	26
Abuchaibe *et al*., 1993 (38)	19	R1–R2	15	7	16
Dresen *et al*., 2008 (39)	34	R1	12.5	27 (3-y)	29 (3-y)
	29	R2	15–17.5	24 (3-y)	29 (3-y)
Lindel *et al*., 2001 (40)	9	R1	10–15	11	33
	15	R2	15-20	13	12
Eble *et al*., 1998 (41)	9	R1	10–20	33 (4-y RFS)	67
	8	R2	10–20	25 (4-y RFS)	63
Martinez-Monge *et al*., 1999 (44)	39	R1	10–15	6	26
	41	R2	15–20	7	29
Wiig *et al*., 2002 (42)	29	R1	15	20	50
	12	R2	17.5–20	0	…
Current study	224	R1	15 (median)	27	68
	156	R2	20 (median)	16	68

Abbreviations: IORT = intraoperative radiation therapy; RFS = relapse-free survival.
* Five-year rates are shown unless otherwise indicated.

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