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Intraoperative radiotherapy in the multimodality approach to colorectal cancer

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In 2002, an estimated 107,300 Americans are expected to develop colon cancer and an estimated 41,000 rectal cancers will be diagnosed [1]. Although 70% to 90% of all patients who have colorectal cancer undergo surgical resection with curative intent, 5% to 19% of patients who have colon cancer and 7% to 33% of patients who have rectal cancer will experience locoregional relapse [2–7]. Local failure is especially high in 5% to 12% of colorectal cancers, with contiguous involvement of adjacent organs (T4 tumors), or locally advanced disease [8–12]. Despite full-dose preoperative radiation, chemotherapy, and complete resection of the cancer (T4), local recurrence occurs in 30% to 55% of patients [13].

In the presence of local recurrence, either isolated in the pelvis as seen in rectal cancers or isolated outside the pelvis but intra-abdominally, as can occur in colon cancers, an aggressive multimodality approach is required to accomplish negative margins and a chance of cure. Without treatment, the mean survival time for patients with recurrent colorectal cancer is approximately 8 months [14] and is associated with severe symptomatic disease, especially pain. Radiotherapy alone, or in combination with chemotherapy, achieves temporary symptomatic improvement in most patients, but the 5-year survival rate is usually less than 5% [15–18]. Complete surgical removal of the disease remains the patients' best chance of

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cure. Palliative surgery alone only prolongs survival to a mean of 11 months [14]. Administration of intraoperative radiotherapy (IORT) can achieve the biologic equivalent of 2 to 3 times that of the same dose of fractionated external beam radiotherapy (EBRT) [19]. In addition, IORT has the advantage of accurate delivery to the area of maximum concern, whereas adjacent normal structures are displaced from the irradiation field. The combination of preoperative chemoradiotherapy, radical surgery, and IORT has been performed in selected patients and has been suggested to improve local control and survival [18–23]. Although the benefits of such treatment also must be weighed against the potential for significant morbidity associated with multimodality therapy, the morbidity of treatment must be weighed against the morbidity of uncontrolled cancer [24,25].

The goal of a multimodality approach including IORT is better local control and improved survival. Such aggressive treatment can be applied not only in patients who have recurrent rectal cancer or in patient who have isolated extrapelvic intra-abdominal recurrent colon cancer but also in patients who have locally advanced colorectal cancers where the risk of local failure is high. Each of these disease presentations is discussed later; however, they share common principles in management approaches.

Locally recurrent rectal cancer

Patient selection and evaluation

The aim of any postoperative follow-up strategy should be detection of resectable disease. Any abnormality discovered during follow-up of a patients who has rectal cancer warrants further investigation to rule out metastatic disease, confirm the presence of recurrent disease, and determine resectability.

Once it is determined that the patient is suitable for surgery, the next step is to exclude extrapelvic disease by obtaining a CT scan of the abdomen and pelvis and a chest radiograph. Evaluation of the liver can be further supplemented by hepatic ultrasound, where indicated. With an equivocal chest film, a chest CT scan also should be obtained. MRI and fluoro-desoxyglucose positron emission tomography (FDG-PET) also can be helpful in detecting extrapelvic disease and may help distinguish between recurrent disease and scar tissue [26]. Patients with documented distant metastases are not usually candidates for an aggressive multimodality approach, because the potential of cure is low and their life span is not adequate to evaluate treatment-related effectiveness or tolerance. For patients with limited liver or lung metastases amenable to surgical resection, however, combined-modality therapy directed at recurrent local disease may be warranted.

Next, the extent of local disease must be evaluated. If the rectum is still present, the local evaluation includes digital examination, proctoscopy, or colonoscopy. Once histologic evidence of recurrent disease is obtained from CT-guided, transrectal or transvaginal biopsies, resectability must be

determined. The combination of fixation and anatomic location of the recurrence determines resectability. Fixation of the recurrence in the pelvis can be categorized as follows: the tumor is not fixed (F0), the tumor is fixed but resectable (FR), and the tumor is fixed and not resectable (FNR; Fig. 1). FR is further subdivided by noting the anatomic extent of fixation (anterior, posterior, and lateral). This classification allows the determination of the extent of resection that is required. Thus, anteriorly fixed lesions may require a hysterectomy or a partial cystectomy, or both, and in lesions with posterior fixation, a sacrectomy may be necessary.

Despite this classification, it is not always possible to predict resectability before surgery. Some indicators predict that curative surgery with negative-resection margins is not likely (Box 1). Circumferential tumors that extend to the pelvic sidewall should be considered unresectable, especially when bilateral ureteral obstruction exists. Sacrectomy proximal to S2 results in sacroiliac joint instability. In a recent study of 304 patients with recurrent rectal cancer from the Mayo Clinic, initial surgery with end-colostomy, symptomatic pain (both univariate analyses), and an increasing number of sites of the recurrent tumor fixation in the pelvis (multivariate analysis) were associated with subtotal resection [27]. In other studies, factors associated with higher likelihood of complete resection were as follows: female gender [28,29], younger age at diagnosis of recurrence [30], the first operation performed at an outside institution [28], a sphincter-saving procedure [30], and transanal local excision [28]. Most studies indicate that 24% to 64% of patients who have locally recurrent rectal cancer can be resected with negative margins [20,22,27,28,31–38]. The appropriateness of a multimodality approach including IORT should be determined by the surgeon and radiation oncologists in the setting of a joint-preoperative consultation, whenever feasible.

Multimodality therapy

Preoperative radiotherapy and chemotherapy

The cornerstone of treatment for locally recurrent rectal cancer with a curative intent is surgery. It has been reported, however, that surgery alone results in high local and systemic failure rates [14]. In addition, although it provides symptomatic relief, irradiation alone does not result in any significant chance of cure. Delivery of EBRT plus concomitant chemotherapy preoperatively institutes simultaneously effective local and systemic treatment [39,40]. The danger of starting chemotherapy before EBRT is that the local component of disease may continue to progress and subsequent resection may never be feasible. Because the risk of subsequent distant metastases exceeds 60% in patients who present for IORT at the time of local recurrence [18,41,42], effective systemic therapy is needed as a component of an aggressive multimodality approach aimed at improving survival. Furthermore, preoperative chemoradiation can lead to down-staging,

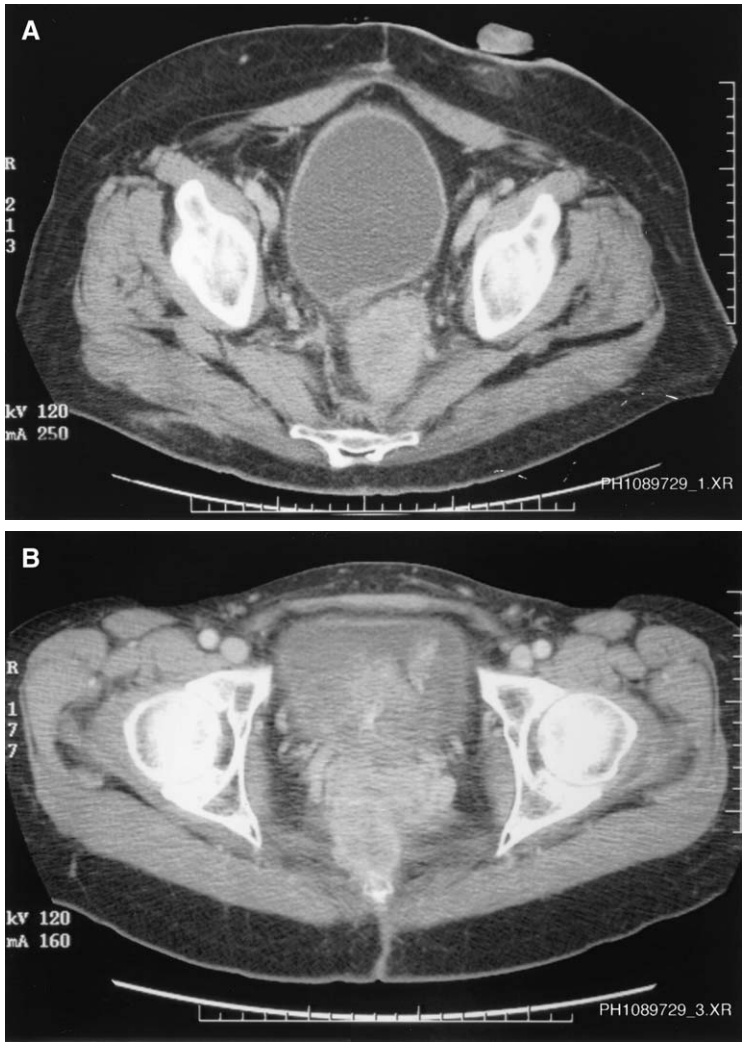

Fig. 1. Classification of locally recurrent rectal cancers according to fixation in the pelvis. (*A*) F0, no fixation. No evidence of fixation to local organs or structures. Anteriorly, there is a clear separation between the bladder and the recurrence. Complete resection with negative margins would be anticipated. (*B*) FR, fixed, but resectable. The recurrence involves the bladder anteriorly and the coccyx posteriorly, making a resection of the bladder with ileal-conduit reconstruction and a resection of the coccyx necessary to achieve negative margins. (*C*) FNR, fixed and nonresectable. Anterior, posterior, and lateral sidewall involvement, rendering this recurrence unresectable.

which has been shown to be a significant prognostic factor [43,44]. At the Mayo Clinic, a full course of EBRT (5040 cGy), with protracted venous infusion of 5-fluorouracil (5-FU) chemotherapy (225 mg/m^2/24 h), is administered preoperatively to patients who have not had previous pelvic

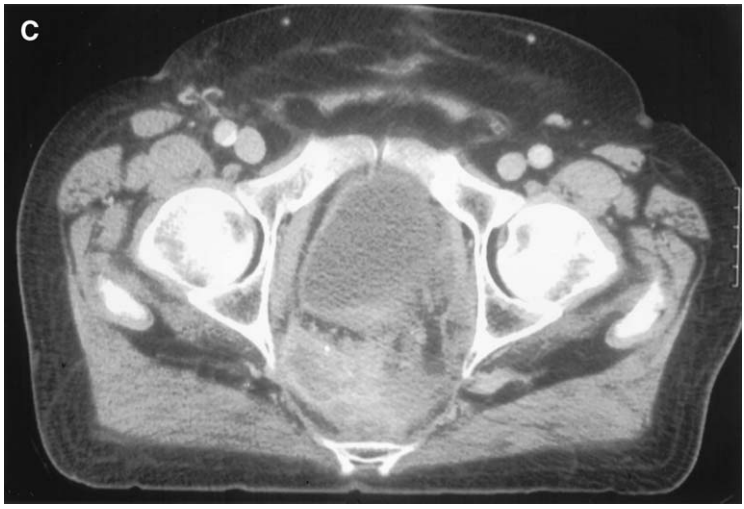

Fig. 1 (*continued*)

irradiation [19]. Patients who had received previous adjuvant radiotherapy in the treatment of their primary tumor are treated with 1000 to 3000 cGy preoperatively, depending on the dose and distribution of the previous radiation therapy and the relative location of critical normal structures, such as the small bowel [45].

Operative procedures

For patients receiving 1000 to 3000 cGy, there is no planned delay from the completion of EBRT to the surgical procedure. Following a full course of preoperative chemoradiation (5040 cGy), however, surgical exploration is undertaken 4 to 6 weeks after the completion of treatment. The planned delay following the full course of EBRT allows ongoing tumor shrinkage and resolution of treatment-induced acute inflammation. The aim of surgery

Box 1. Contraindications for resection of locally recurrent rectal cancer

Extrapelvic disease
Sciatic pain
Bilateral ureteral obstruction
Circumferential or extensive pelvic sidewall involvement
S1 or S2 involvement (bony or neural)
Poor general condition and surgical risk (ASA IV)

Abbreviation: ASA IV, class IV according to the American Society of Anesthesiologists (ASA).

is to achieve en bloc removal of all gross and microscopic residual disease, with disease-free margins (R0 resection). Pelvic recurrences are typically amenable to re-resection if they are strictly posterior or anterior. Evidence of lateral pelvic sidewall involvement diminishes the chance of complete resection. There are several options for radical surgery, depending on the pattern of pelvic recurrence. The recurrence of nonfixed, F0 lesions after local excision or low anterior resection requires complete abdominal perineal resection. The distinction between fibrosis and tumor infiltration is difficult at best and a frozen section should be obtained. Anterior lesions demonstrate the greatest diversity between men and women. In women, the uterus and the vagina are often infiltrated and posterior exenteration, including the uterus and vagina, is adequate. Surgical reconstruction of the perineum and the posterior vaginal wall may call for a myocutaneous rectus abdominis flap or an omental flap and gracilis procedure. Lesions invading the trigone or the prostate are often circumferential, and a total cystectomy and ileal conduit might be necessary to achieve negative margins [46]. The ideal procedure for FR posterior lesions is a distal sacrectomy, with the proximal limit around S2-3. The preservation of one S3 root is generally possible and is usually sufficient to preserve bladder function [47,48]. Distal sacrectomy and laminectomy require prone repositioning of the patient. Preoperative planning is essential to have all the resources and specialists available to have the best chances of achieving negative-resection margins.

Intraoperative radiotherapy

EBRT is supplemented by IORT at the joint discretion of the surgeon and the radiation oncologists. IORT is generally applied if suspected or confirmed microscopic residual tumor is present and in cases of gross residual disease. IORT should be delivered to initial sites of fixation, even if fixation is no longer evident at the time of surgery because of down-staging.

IORT can be delivered by one of two techniques: accelerator-generated electron beam (IORT) or high-dose-rate brachytherapy (IOHDR). The potential advantage of IOHDR is the flexibility of the applicators, which allow maximal conformity to most tumor beds. IOHDR treatment times may be prolonged, however, and IORT is the most commonly used approach. Since April 1989, both the operative procedure and the delivery of IORT at the Mayo Clinic are performed in a dedicated IORT suite with a linear accelerator. When IORT is required, a Lucite applicator is positioned in the pelvis to target the tissues at risk. The applicator is selected for size (usually 5–9 cm in diameter) and shape (typically circular and 30° beveled). The applicator is immobilized with a modified Bookwalter retractor (Codman Co., Raynham, Massachusetts). The patient is positioned under the linear accelerator and the applicator is docked to the accelerator head. Tumor adherence to anterior pelvic structures, including the prostate or base of bladder, can produce a technical challenge for IORT and a perineal approach for IORT is usually necessary if IOHDR is not

available. Patients can be treated in either the prone or supine position. The IORT dose is calculated at the 90% isodose line and is dependent on the amount of residual disease remaining after maximal resection and the amount of EBRT that has or can be delivered as a component of treatment. Guidelines for IORT dose in patients who receive full-dose EBRT are as follows: close but histologically negative margins, 750 to 1250 cGy; microscopic margin involvement, 1000 to 1250 cGy; gross residual disease of 2 cm or less in largest dimension, 1500 cGy; gross residual tumor of 2 cm or greater, 1750 to 2000 cGy [19]. When EBRT doses are limited because of prior treatment, higher doses of IORT are used with a goal of achieving equivalent doses of 50 Gy for negative-margin resections and 60 Gy or greater for patients with residual disease.

Results

Historical comparisons

Without treatment, survival rates for patients with recurrent rectal cancer are low (Table 1) [14]. With radiotherapy alone or in combination with chemotherapy, relief of pain or bleeding can be achieved in 80% to 90% of patients, but the median duration of symptom relief is only 6 to 9 months, and long-term survival is infrequent ($\leq$5% of patients) [15–17,49,50]. Wong et al [51] Reported on 519 patients with recurrent rectal cancer, who were treated with definitive EBRT and achieved a 5-year survival rate of 5% and a local control rate of only 7% [51]. Because 40% to 50% of the recurrences appear without simultaneous distant metastases [2,3,19,52], local resection of recurrences can have a curative goal. The results after surgery alone, however, mainly have been disappointing [18,52]. Radiotherapy following radical surgery has been shown to improve local and distant control, and 5-year survival rates of 5% to 9% can be achieved [53,54].

The response to irradiation correlates with dose, and doses in excess of 60 to 70 Gy are required to achieve sterilization of residual disease [54,55]. These doses significantly exceed the normal tissue tolerance of the small bowel, which is generally the dose-limiting normal structure for EBRT in the pelvis [19,55]. The addition of IORT, applied as a boost to the area at risk for residual tumor or recurrence, can overcome the problem of dose limitation and potentially improve the therapeutic ratio. The small bowel can virtually always be displaced from the IORT boost field and, when not involved by tumor, other sensitive structures, such as the ureter and bladder, also can be displaced or shielded. A recent comparison of IORT therapy containing multimodality treatment with historical treatment modalities for locally recurrent rectal cancer achieved significantly better 3-year survival, disease-free survival, and local control rates of 60%, 43%, and 73%, respectively, with the combination of EBRT, surgery, and IORT (see Table 1) [20]. Many studies have compared retrospectively the results of IORT versus no IORT [18,20,21,32,56,57], the combination of EBRT plus IORT

Table 1
Selected historical studies for treatment of locally recurrent rectal cancer

First author	Publication year	Treatment modality	No. patients	Median survival	Survival	Local relapse	Distant relapse (%)	DFS (%)
Wong [51]	1998	EBRT[a]	519	14	5 y, 5%	93%	—	2
Lybeert [54]	1992	Surgery + EBRT	76	14	5 y, 5%	68%	41	—
Guiney [53]	1997	Surgery + EBRT	39	18	5 y, 9%	82%	49	—
Mannaerts [20]	2001	EBRT only	94	18	3 y, 14%	3 y, 90	—	8
		EBRT + surgery	19	19	3 y, 11%	3 y, 86	—	0
		EBRT + surgery + IORT	33	—	3 y, 60%	3 y, 27	—	43

Abbreviation: DFS, disease-free survival.
[a] Plus surgery in 49 patients (20 with curative, negative margins).

versus IORT only [21,33,34], or IORT plus EBRT, with or without chemotherapy [32,37], and reported 5-year survival rates of 21% to 41% and local control rates of 31% to 89% (Tables 2 and 3). The comparability of such analyses and the comparability of historical studies can be questioned for the following reasons: the lack of prospective data; the dramatic change of time in surgical care [52]; the inclusion of patients with local and distant recurrence [19,58,59]; possible selection bias of patients with less aggressive tumor variants; the difference in treatment protocols; and the difference in adjuvant treatment, both for the primary tumor and for the locally recurrent cancer. These issues make it difficult to draw definitive conclusions. Available data suggest, however, that an aggressive approach with preoperative radiochemotherapy followed by maximal surgical resection and IORT in selected patients can significantly improve long-term survival and local control rates (see Tables 2 and 3). Several factors influencing survival and local control have been identified from such studies. The most consistently reported factors with independent prognostic impact are the number of fixations of the recurrent cancer in the pelvis [27,32], the presence of symptomatic pain [21,27,32,60], and the amount of residual disease after surgical resection.

Residual disease

A curative or R0 resection is defined as a circumstance when no residual cancer remains following surgery. Resections are considered palliative if either microscopic (R1) or gross (R2) cancer remains at the end of the procedure. In a recent series from the Mayo Clinic, 304 patients with locally recurrent rectal cancers were treated with the multimodality approach between 1981 to 1996 [27]. The actuarial overall 5-year survival rate was 25%. Curative R0 resections were obtained in 138 patients (45%) in whom a 5-year survival rate of 37% was achieved, compared with 22% and 14% in patients with either microscopic ($n = 27$) or gross residual disease ($n = 139$), respectively. The amount of residual disease was the most important predictive factor of survival. This finding is in agreement with most studies: that the ability to perform a curative-intent R0 resection is the main determinant of patient survival [22,28,29,33,36,37,45,56,61–63]. Factors associated with a higher chance of receiving curative surgery were discussed earlier.

Wiig et al [56] recently reported an estimated 5-year survival rate of 60% in R0-resected patients, regardless of IORT treatment, and questioned the need for IORT in R0 resections. The finding that survival was equivalent between R0 patients in whom IORT was deemed unnecessary and R0 patients who were believed to require IORT could be interpreted as evidence of IORT benefit in selected R0 patients, however. Most series with R0 resections only applied IORT in a few patients [56] and reported 5-year survival rates of 25% to 60% [27,35,37,38,56,64]. The possibility of selection bias precludes the ability to draw definitive conclusions about the independent contribution of IORT treatment after an R0 surgery. It might

Table 2
Survival and disease relapse in selected series using multimodality therapy with intraoperative radiotherapy for locally advanced and recurrent colorectal cancers

First author	Study year	No. patients	R resection (%)	Follow-up median (mo)	No. IORT	Overall survival	Local relapse	Distant relapse	DFS
Recurrent rectal cancer									
Hashiguchi [21]	1975–97	51	24	30 (mean)	27	5 y, 21%	11%[a]	65%	—
Valentini [32]	1989–97	47	45	80	11	5 y, 41%	21%	—	20%
Alektiar [33]	1992–98	74	72	22	All	5 y, 23%	61%	62%	—
Rutten [38]	1994–00	62	48	—	All	5 y, 33%	37%	—	—
Lindel [37]	1987–97	69	49	—	46	5 y, 27%	65%	—	20%
Wiig [56]	1990–99	107	41	—	59	5 y, 30%	50%	—	—
Shoup [22]	1990–00	100	64	23.2	All	—	67%	60%	39%
Bussieres [34]	—	73	57	30	All	3 y, 31%	69%	—	—
Mannaerts [20]	1994–99	33	64	—	All	3 y, 60%	27%	—	43%
Harrison [35]	1992–96	46	57	18	All	2 y, 47%	37%	—	47%
Recurrent colon cancer									
Taylor [76]	1981–00	73	52	71	All	5 y, 25%	5 y, 18%	5 y, 48%	—
Locally advanced cancer									
Rectal cancer									
MGH, in [84]	—	64	63	—	All	5 y, 63%[b]	5 y, 9%[b]	—	—
Calvo [82]	1995–00	100	NA	23	94	4 y, 65%	4 y, 6%	—	4 y, 75%
Mannerts [60]	1994–99	44	82	21 (mean)	38	3 y, 72%	3 y, 18%	3 y, 32%	3 y, 65%
Harrison [35]	1992–96	22	82	18	All	2 y, 69%	2 y, 19%	—	2 y, 69%
Colon cancer									
Taylor [76]	1981–00	25	60	71	All	5 y, 49%	5 y, 12%	5 y, 24%	
Colon + rectal cancer									
Gunderson [42]	1981–95	—	36	18 (min)	All	5 y, 46%	5 y, 16%	5 y, 59%	

Abbreviation: DFS, disease-free survival.
[a] R0 and R1 resection only.
[b] R resection only.

Table 3
Survival and disease relapse with palliative surgery with or without intraoperative radiotherapy in selected series of locally recurrent rectal cancer

First author	Publication year	Treatment modality (R1 or R2 resection)	No. patients	Median survival (mo)	5-y survival (%)	Local relapse (%)	Distant relapse (%)	DFS (%)
Nag [67]	1999	+ IORT (R1)	15	—	15[a]	57[a]	—	—
		+ IORT (R2)	13	—	9	67[a]	—	—
Lindel [37]	2001	+ IORT (R1 and R2)	24	—	14	83	—	32
Shoup [22]	2002	+ IORT (R1)	29	—	9	—	—	9
Wiig [56]	2002	no IORT (R1)	10	—	~20	70	—	—
		+ IORT (R1)	29	—	~20	50	—	—
Suzuki [18]	1995	no IORT (R1 and R2)	64	17	7	93	54	—
		+ IORT (R1 and R2)	42	30	19	40	60	—
Gunderson [19]	1996	no prior EBRT (R1 and R2)	123	28	20	25	64	—
Haddock [45]	2001	+ prior EBRT (R1 and R2)	51	23	12	55	71	—

Abbreviation: DFS, disease-free survival.
[a] 3-y result.

be argued that, in a true R0 resection, there are no cancer cells remaining to be eradicated by IORT. In clinical practice, however, because of the complexity of differentiating fibrosis and recurrent cancer, some patients who undergo R0 resection may have residual disease and should therefore have a potential benefit from IORT. This situation is especially true for patients with initial fixation of disease who have responded to preoperative therapy, because significant residual tumor burdens (up to 10^5 cells) may be pathologically impossible to detect.

Palliative surgery

Another group of patients who seem to benefit from IORT are the patients who have undergone palliative (R1 and R2) resection. In the Mayo Clinic analysis by Suzuki et al [18], 106 patients underwent palliative resection of locally recurrent rectal cancer. The addition of IORT in 42 patients was associated with an improvement in survival rates from 7% to 19% ($P < 0.001$) and a reduction in the 3-year local failure rate from 93% to 40%. This finding was confirmed in an updated analysis of 85 patients who underwent palliative resection and IORT and achieved an actuarial median survival of 30 months and a 5-year survival rate of 21% [27]. Improved local control rates from 30% to 50% with the addition of IORT was documented in another study of 29 R1-resected patients [56]. The estimated 5-year survival rate did not improve, however (20% in both the IORT and the non-IORT group). Although differences seen from series to series may reflect the selection bias in nonrandomized trials instead of treatment effect, it is possible that improvements in local control with the addition of IORT may translate into improvements in survival.

The prognosis for patients with locally recurrent rectal cancer has been shown to be worse in previously irradiated patients than in those who have not received irradiation previously. In a randomized Swedish study [65] comparing preoperative radiation to surgical resection alone, 15% of ir-radiated patients suffered local recurrence, and treatment (combination of surgery, radiation, and chemotherapy) resulted in a median survival time of 11 months compared with 15 months for patients with locally recurrent cancer treated initially with surgery alone. The addition of IORT after palliative resection has demonstrated better local control and longer survival rates, but results in previously irradiated patients with recurrent disease remain inferior to results in patients with no prior EBRT [38]. Five-year actuarial local relapse rates of 66% in previously irradiated patients versus 37% in patients who did not previously undergo radiation therapy, and 5-year survival rates of 12% versus 20%, respectively, were documented in two Mayo Clinic studies [19,45].

Palliative resection plus IORT without additional EBRT is associated with unacceptably high rates of local relapse. Twelve of 37 previously irradiated patients received IORT without additional EBRT and developed local recurrences, with no 5-year survivors [66]. Similar results have been

reported by others [34]. Patients treated with high-dose EBRT are often not considered candidates for reirradiation because of the potential for severe late radiation toxicity [24]. Mohiuddin et al [49], however, reirradiated 32 patients who had recurrent rectal cancer to a median dose of 34.2 Gy and reported acceptable late toxicity (6% small bowel obstruction, 6% pelvic abscess, and 12% wound healing).

Morbidity and intraoperative radiotherapy tolerance

Multimodality therapy for locally recurrent rectal cancer has a high tumor- or treatment-related morbidity of 25% to 71% and a mortality of 0% to 7% [27,30,36,45,47,56,62,67]. The most commonly occurring complications include pelvic abscess, small bowel obstruction, fistula formation, and perineal wound problems [21,27,33,35]. The major IORT-related toxicities are ureteral stenosis [68] and peripheral neuropathy [25,37]. In a Mayo Clinic analysis of 123 patients who underwent recurrent colorectal IORT, 6% developed partial ureteral obstruction and 10% developed an obstruction requiring stents [19]. The ureter is not dose-limiting for IORT because stents can be placed to overcome obstruction and preserve renal function as indicated. Therefore, when tumor is adherent to ureter, it should be included in the IORT boost field. Peripheral nerve is the main dose-limiting structure for IORT as judged from data generated from clinical and animal studies [55]. Peripheral neuropathy of any degree, reported in 16% to 34% of patients, may consist of motor and sensorial impairment and sacral and pelvic pain [25,33,37,45]. Gunderson et al [19] reported a relationship between IORT dose and the incidence of grade 2 and 3 neuropathy ($\leq$12.5 Gy [7%] versus $\geq$15 Gy [19%]). More recent studies, however, have failed to correlate the risk of neuropathy with EBRT or IORT dose [37,45].

Two recent studies on quality of life after multimodality therapy reported that many patients have to deal with long-term physical morbidity, need help with daily care, and might experience considerable social impairment [69,70]. Another study [48], however, observed 16 patients after sacrectomy for recurrent rectal cancer and found that 8 of 9 patients remaining alive reported a reduction in pain and an improved quality of life, with 67% of patients returning to gainful employment postoperatively. Without surgery, this group of patients faces a grim future, with sacral or trigone invasion. The consequences of a multimodality approach to recurrent rectal cancer must be weighed against the chance of cure if the patient is treated and the disability eventually caused by uncontrolled tumor progression if the patient is not treated. These potential drawbacks should be discussed with the patient preoperatively and taken into account when designing a treatment strategy.

Summary

Significant long-term survival and local control can be achieved with a multimodality approach, including IORT in selected patients with locally

recurrent rectal cancer. The most important predictive factor for survival is the amount of residual disease after surgery. Preoperative chemoradiation improves resectability, the addition of IORT correlates with improved local control and survival, and reirradiation in previously irradiated patients is feasible. Patient selection for such an aggressive multimodality approach is essential to minimizing treatment-related morbidities.

Locally recurrent colon cancer

Local, nonhepatic, intra-abdominal recurrences of colon cancers are rare (5%–19%) [7,71–74], and only a few studies have specifically evaluated the treatment of patients who have these recurrences [31,73–76]. Recurrences often occur at the site of the anastomosis and, without adjacent invasion, surgical resection and adjuvant chemotherapy is a sufficient treatment in most patients. If the recurrence is locally invasive, as in the pelvis, or involves the peritoneum or lymph nodes, treatment is more challenging and a more aggressive approach is warranted.

Patients who receive nonsurgical therapy or undergo only palliative resection for such recurrences historically have a 5-year survival rate of less than 5% [9,71,77]. In a recent analysis of 73 patients with isolated, nonhepatic, intra-abdominal recurrent colon cancer at Mayo Clinic, a median survival time of 33 months and a 25% 5-year survival rate were achieved with a multimodality approach combining preoperative chemoradiation, surgical resection, and IORT [76]. Local control of recurrent colon cancer was 82%; however, 48% of patients developed distant metastasis, emphasizing the need for effective systemic adjuvant therapy. Fifteen patients presented with isolated nodal recurrences (para-aortic, celiac, iliac, and other areas) and responded well to a multimodality approach, including IORT, with a 5-year survival rate of 45%. Therefore, the authors concluded that limited intra-abdominal nodal recurrences should be considered for aggressive surgical treatment, and IORT and EBRT to the remaining lymphatic basin. As in recurrent rectal cancers, the amount of residual disease after surgery significantly influenced outcome, with 5-year survival rates of 37%, 25%, and 0% for patients with R0, R1, and R2 resections, respectively. Similar results were achieved in two other studies with smaller patient numbers [67,78].

Patients who have localized recurrent colon cancer that seems amenable to complete gross resection should be evaluated and considered for multimodality therapy. Although the prognosis is poorer for patients who cannot undergo gross total resection, long-term survival is observed even in this group of patients when IORT is a component of therapy. Abdominal CT scan and FDG-PET [77] are useful in defining local versus multifocal recurrence, but operative exploration remains the only definitive way to fully assess potential resectability. The best sequence and type of

multimodality therapy have yet to be determined, but preoperative chemoradiation, followed by surgical resection and IORT, seems to demonstrate long-term survival in selected patients.

Locally advanced colon and rectal cancer

Locally advanced tumors are often characterized as tumors that cannot be resected without leaving microscopic or gross residual disease at the resection site because of tumor adherence or fixation to that site. Approximately 5% to 12% of all patients who have colorectal cancers will present with contiguous involvement of adjacent organs [8–11]. These patients do poorly with surgery alone, and irradiation and chemotherapy have been added to improve the outcome.

Preoperative EBRT has a downsizing and down-staging effect, which improves the probability of a complete resection. The addition of preoperative chemotherapy to EBRT increases the resectability rate from 64% to 90%, compared with patients receiving radiation therapy alone [44,79], and may also address the problem of systemic failure that has an incidence higher than 50% [80]. Clinical response and tumor/nodal pathologic down-staging after preoperative chemoradiation showed a close correlation, with improved survival and local control rates, in a recent analysis of 165 patients [44]. Despite full-dose preoperative radiation, chemotherapy, and complete resection of the cancer, local failure rates remain in the range of 30% to 55% [13]. Several studies have shown that local control is dose-dependent and should exceed 60 Gy for patients with microscopically positive margins [81]. An additional boost delivered during the operation can overcome dose limitations [54,55], and radiation can be applied specifically to the area at risk. Preoperative patient evaluation, indications and contraindications for a multimodality approach, dosage and application of IORT are similar to that for recurrent rectal cancer and have been described earlier. The decision to treat with IORT is, again, an intraoperative collaborative judgment made by the surgeon and the radiation oncologist.

Most studies report their results of multimodality therapy together with recurrent cancers and only a few studies have focused on locally advanced colorectal cancers alone [42,60,82,83]. In those studies, an R0, R1, and R2 resection for locally advanced rectal cancer could be achieved in 36% to 82%, 10% to 34%, and 8% to 29% of patients, respectively; the achievement rates for locally advanced colon cancer were 49%, 17%, and 34% for R0, R1, and R2 resections, respectively. Massachusetts General Hospital reported 5-year actuarial local control and disease-free specific survival rates of 91% and 63%, respectively for 40 patients undergoing R0 resection with IORT [84]. For 24 patients undergoing partial resection, local control and disease-specific survival correlated with the extent of residual cancer: 65% and 47% for microscopic residual disease and 57% and 14% for gross residual disease.

The impact of degree of resection and amount of residual disease on disease control and survival were similar in a Mayo Clinic series of 61 patients [42]. Other factors with a trend to improved local control in this study were grades 1 to 2 versus grades 3 to 4 disease (local failure rates, 7% versus 17%) and nodal status of negative versus positive (local failure rates, 4% versus 19%). Additional factors with statistical impact on distant relapse included use of EBRT and 5-FU versus EBRT alone ($P = 0.013$) and primary colon versus rectal cancer ($P = 0.03$). Because distant relapse was observed in 48% of these patients, more routine use of systemic chemotherapy was recommended. As in recurrent rectal cancer, the amount of residual disease after surgical resection remains the most important predictor of survival in all studies. Local control rates of 70% to 85%, disease-free survival rates of 45% to 48%, and overall survival rates of 51% to 60% are reported in most studies using a multimodality approach with IORT for locally advanced rectal cancers [24,42,45,60,82].

For 25 patients who had locally advanced colon cancers treated with a multimodality approach, a recent analysis reported a median survival time of 38 months and a 5-year survival rate of 49% [76]. Local failure was uncommon (12% of patients) with such treatment regimens. Treatment-related morbidity was high (4 patients [16%] died of sepsis), and the heterogeneous nature of patients with locally advanced colon cancers and the small sample size limit the ability to make definitive conclusions. Selected patients, however, seem to benefit from such an aggressive approach.

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