Resection With External Beam and Intraoperative Radiotherapy for Recurrent Colon Cancer

Richard D. Pezner, MD; David Z. J. Chu, MD; Lawrence D. Wagman, MD; Nayana Vora, MD; Jeffrey Y. C. Wong, MD; Stephen I. Shibata, MD

Objective: To review treatment outcomes for patients with locoregional recurrent colon cancer who underwent resection, intraoperative radiotherapy (IORT), and external beam radiotherapy (EBRT).


Setting: Tertiary care cancer center.

Patients: Eleven patients with bulky recurrent colon cancer extending to adjacent organs or structures signed informed consent forms to receive IORT.

Intervention: Of 10 patients who underwent exploratory laparotomy, 5 had no metastatic disease and underwent resection, IORT, and EBRT. Complete resection was accomplished in 4 patients. Doses of IORT ranged from 13 to 20 Gy depending on residual tumor burden; EBRT was typically delivered postoperatively to a dose of 45 Gy.

Main Outcome Measures: Survival and locoregional tumor control.

Results: All 4 patients who underwent complete resection, IORT, and EBRT are alive without locoregional recurrence 53 to 77 months after treatment. Of these, only 1 patient developed distant metastases. The fifth patient, who had gross residual tumor, developed local recurrence 5 months after IORT. One patient developed an IORT complication—ureteral fibrosis leading to ipsilateral nephrectomy.

Conclusion: Long-term disease-free survival can be achieved in selected patients with bulky regional recurrence of colon cancer with complete tumor resection, IORT, and EBRT.


Few patients with colon cancer that arises outside the pelvis (ie, not in the rectum or rectosigmoid junction) develop locoregional tumor recurrence after definitive surgical resection. Only 6% to 9% of patients who undergo complete surgical resection develop cancer regrowth in the tumor bed as the first site of recurrence.1-4 In patients with primary tumors that extend to adjacent organs or structures, 11% to 29% may develop isolated locoregional recurrences.2,3 Such recurrences are difficult to control. Although some recurrences are limited to the anastomotic site, such that complete resection is possible, most will be bulky tumors that involve adjacent vital structures and produce devastating problems such as bowel obstruction, bleeding, ureteral obstruction, and severe pain from nerve or bone invasion. Selected patients have undergone radical surgical resection, with some having long-term survival benefit.3,4,6-8 More recently, intraoperative radiotherapy (IORT), usually in combination with external beam radiotherapy (EBRT), has been used at the time of resection.9,10 The rationale for this approach is that the total radiation dose delivered by the combination of IORT and EBRT would be greater than could be safely delivered by either modality alone, thus offering the possibility of a greater chance of long-term locoregional tumor control.

RESULTS

Of 4 patients who underwent complete tumor resection, IORT, and EBRT, 3 are alive with no evidence of disease 53, 64, and 66 months after treatment.

See Invited Critique at end of article

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PATIENTS AND METHODS

Between January 1990—when City of Hope National Medical Center, Duarte, Calif, inaugurated an IORT program—and June 1994, 11 patients with recurrent colon adenocarcinoma signed informed consent forms to receive IORT if indicated at exploratory laparotomy. There were 5 men and 6 women who ranged in age from 31 to 77 years (mean, 60 years). The primary site was the cecum in 2 patients, ascending colon in 1 patient, hepatic flexure in 2 patients, descending colon in 2 patients, and sigmoid in 4 patients. Stage at initial diagnosis was I in 1 patient, II in 4 patients, III in 5 patients, and IV (liver metastases) in 1 patient. Ten patients underwent complete resection on the primary tumor, whereas 1 patient with a T4 primary tumor was left with gross residual tumor. Five patients also received adjuvant 5-fluorouracil chemotherapy with either leucovorin calcium or levamisole hydrochloride.

Recurrent disease, as evaluated by computed tomographic scan, presented as a solitary retroperitoneal, presacral, or psosas mass in 8 patients, liver metastases in 1 patient, tumor bed recurrence and liver metastases in 1 patient, and para-aortic adenopathy in 1 patient. Only 1 of 11 patients had a previous recurrence (ovarian metastasis) before consideration for IORT. Preoperative computed tomographic scan showed ureteral obstruction in 2 patients. Results of cystoscopy showed bladder invasion in another patient. Computed tomographic scan showed tumor sizes ranging from 3 to 8 cm (≥5 cm in 7 patients). Intraoperative radiotherapy was considered for selected patients known to have distant metastases in the event that all sites of disease could be grossly resected.

Six of 11 patients did not receive IORT. One patient did not undergo laparotomy because results of his preoperative radiolabeled anti–carcinoembryonic antigen monoclonal antibody scan led to the discovery of a biopsy-proven nonpalpable supraclavicular nodal metastasis. Five patients underwent laparotomy but did not receive IORT because of the discovery of widespread disease, including peritoneal metastases in 2 patients, liver and peritoneal metastases in 1 patient, porta hepatis nodal and liver metastases in 1 patient, and multiple unresectable para-aortic nodal metastases in 1 patient. Among 6 patients who did not receive IORT, 5 had a history of disease outside the tumor bed before laparotomy (ie, liver metastases in 2 patients and supraclavicular nodal, para-aortic nodal, and previous ovarian metastases in 1 patient each). After documentation of widespread metastases, these 6 patients survived for 6 to 21 months (mean, 11 months).

The other 3 patients had no evidence of metastases found at laparotomy and underwent resection and IORT (Table 1). For these 3 men and 2 women, the disease-free interval from initial diagnosis of colon cancer to the date of diagnosis of recurrent cancer ranged from 5 to 31 months (<12 months in 4 patients). All had tumor bed recurrences that extended to adjacent organs or structures (Table 1). Tumors ranged in size from 3 to 8 cm. Complete resection of all gross disease was accomplished in 4 patients. Pathologic margins were clear in 3 patients and were involved by tumor in 1 patient. One patient had gross tumor left on the sacrum despite preoperative EBRT and low anterior resection.

Intraoperative radiotherapy was delivered after resection and before reconstruction. On completion of resection, the surgeon and radiation oncologist evaluated the feasibility of safely and effectively delivering IORT to the tumor bed defined by the surgeon. The patient’s wound was closed and covered in sterile drapes. While under anesthesia, the patient was transported to the linear accelerator suite in the radiation oncology department for delivery of IORT. Critical organs such as the bowel, bladder, stomach, and liver were retracted away from the IORT cone applicator placed on the tumor bed. In 1 patient, a ureter that had been encased by tumor was in the IORT field (Figure 1). In the other 4 patients, ureters either were not near the tumor bed or were uninvolved and able to be retracted out of the IORT field (Figure 2). Fixed critical structures within the IORT field, such as kidney and sciatic nerve, were protected by placement of small sterile lead shields or by limiting dose penetration by selection of appropriate electron beam energy. The cone end protruding out of the wound was then carefully docked to the IORT cone holder, which was attached to the collimator head of the linear accelerator (Clinac 1800; Varian Associates, Palo Alto, Calif). Doses prescribed to the 90% isodose were 13 to 14 Gy for negative margins, 17 Gy for positive margins, and 20 Gy for gross residual tumor (Table 1). Electron beam energies ranged from 9 to 20 MeV, depending on the thickness of the tumor bed. Applicator cone sizes ranged from 5.7 to 9.5 cm. On completion of IORT, the cone was undocked and removed, the wound was closed, and the patient was returned to the operating room to complete the procedure.

External beam radiotherapy was delivered after surgery in 4 patients and before surgery in 1 patient (Table 1). The interval from date of surgery to start of postoperative EBRT ranged from 2 to 11 weeks. The time from the end of preoperative EBRT to surgery was 2 weeks. The EBRT dose was 45 Gy, given in 25 fractions for 5 to 8 weeks. Field sizes were determined so that they encompassed the tumor bed and adjacent nodal sites with generous margins. Survival was estimated from the date of IORT administration.
tomy 15 months after tumor resection and IORT. The patient recuperated well from nephrectomy and never developed pyelonephritis or renal insufficiency.

**COMMENT**

Complete surgical resection has been the single most effective treatment modality for patients with isolated locoregional recurrence of extrapelvic colon cancer.\(^3,4,6,7,12,13\) Success depends on tumor presentation not involving unresectable structures such as the sciatic nerve and the lumbosacral spine and the ability of the surgeon to perform a procedure that may be as extensive as an exenteration.\(^7,12-14\) A urinary diversion procedure may be performed if a ureter or the bladder must be resected because of tumor involvement.\(^14\) Results of retrospective studies report that up to 40% of selected patients with isolated locoregional tumor bed recurrences, including small-bowel anastomotic site recurrences, may survive at least 5 years after complete surgical resection.\(^3,9,6,6,12,15\)

The value of preoperative or postoperative EBRT combined with resection for patients with locoregional recurrent colon cancer has not been well defined.\(^7\) External beam radiotherapy is of palliative value for many patients who have unresect-

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**Table 1. Treatment Details of Patients With Recurrent Colon Cancer Who Received IORT***

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Recurrent Tumor Findings</th>
<th>Extent of Resection and IORT</th>
<th>Pathologic Margin Status</th>
<th>EBRT Timing, Dose, Interval Delay†</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>5-cm Mass involving psoas, small bowel, femoral nerve, and abdominal wall</td>
<td>Mass and involved organs; 14-Gy IORT; 9.5-cm cone</td>
<td>Negative</td>
<td>Postoperative, 45 Gy, 15 d</td>
</tr>
<tr>
<td>2</td>
<td>3-cm Mass involving psoas</td>
<td>Mass and psoas; 14-Gy IORT; 7.6-cm cone</td>
<td>Negative by 0.7 cm</td>
<td>Postoperative, 45 Gy, 11 wk</td>
</tr>
<tr>
<td>3</td>
<td>8-cm Anastomotic mass involving multiple small-bowel loops</td>
<td>Mass with 126-cm small bowel; 13-Gy IORT; 7.6-cm cone</td>
<td>Negative</td>
<td>Postoperative, 45 Gy, 5 wk</td>
</tr>
<tr>
<td>4</td>
<td>6-cm Psoas mass encasing ureter</td>
<td>Mass and psoas; 17-Gy IORT; 8.3-cm cone</td>
<td>Microscopic positive</td>
<td>Postoperative, 45 Gy, 21 d</td>
</tr>
<tr>
<td>5</td>
<td>6-cm Anastomotic mass fixed to sacrum</td>
<td>Low anterior resection, diverting colostomy; 20-Gy IORT; 5.7-cm cone</td>
<td>Gross residual tumor</td>
<td>Preoperative, 45.3 Gy, 2 wk</td>
</tr>
</tbody>
</table>

* IORT indicates intraoperative radiotherapy; EBRT, external beam radiotherapy.
† Timing indicates preoperative vs postoperative; dose, 1 Gy = 100 rad; and interval delay, time from date of IORT to first-day postoperative EBRT or time from end preoperative EBRT to date of IORT.

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**Table 2. Outcome for Patients With Locoregional Recurrent Colon Cancer Who Underwent Resection, Intraoperative Radiotherapy, and External Beam Radiotherapy (EBRT)**

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Complications</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>None</td>
<td>No evidence of disease, 66 mo; lost to follow-up</td>
</tr>
<tr>
<td>2</td>
<td>Postoperative anastomotic leak delaying start of EBRT</td>
<td>Lung metastases, 30 mo; alive without locoregional recurrence, 77 mo</td>
</tr>
<tr>
<td>3</td>
<td>Severe short bowel syndrome requiring total parenteral nutrition</td>
<td>No evidence of disease, 64 mo</td>
</tr>
<tr>
<td>4</td>
<td>Ureteral stenosis leading to nephrectomy at 15 mo</td>
<td>No evidence of disease, 53 mo</td>
</tr>
<tr>
<td>5</td>
<td>None</td>
<td>Local recurrence, 5 mo; died of cancer, 6 mo</td>
</tr>
</tbody>
</table>

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**Figure 1.** Computed tomographic scan of patient 4 showing bulky recurrent sigmoid colon cancer encasing the ureter and invading psoas muscle (arrow).

**Figure 2.** Ureter retracted out of the resected tumor bed in patient 1 before placement of the intraoperative radiotherapy cone applicator (arrow).
able disease, although long-term disease-free survival is rare with EBRT alone.6,6,8

Intraoperative radiotherapy is a technique to deliver a large single dose of radiation directly to the tumor bed defined by the surgeon at the time of resection.9,10 Critical organs such as the small bowel, bladder, and ureters can be moved out of the path of the IORT beam to significantly reduce the risk of late radiation complications. Radiation dose to structures that cannot be easily moved such as the sciatic nerve or kidneys can be limited by placement of small shields at the time of IORT or by choice of electron beam energy to limit the dose of radiation delivered deep to the tumor bed. External beam radiotherapy can be kept to a dose range that is sufficient for microscopic disease beyond the IORT field but below the level of a high risk of bowel complications.16 Results of retrospective studies17-22 suggest that IORT may significantly improve control of locoregional recurrent rectal cancer provided that tumor fixation does not prevent resection of all gross disease and previous EBRT does not limit the dose of IORT or EBRT that may be safely delivered.

Locoregional recurrence of cancer originating in the colon outside of the pelvis is not as likely to have limitations such as tumor extension to unresectable structures or a history of previous EBRT. Several institutions have reported use of IORT in some patients with recurrent colon cancers, but the relative benefit of the addition of IORT to surgery has not been analyzed in detail.12,14,19,21 The largest experience was reported by Gunderson et al.22 They delivered 10- to 20-Gy IORT to 43 patients with recurrent colon cancer who had no previous history of EBRT. Preoperative EBRT was used in most patients. They reported an actuarial 5-year tumor control rate within the IORT and EBRT region of 80%, with a 5-year disease-free survival of 21%.

In our small series, 4 of 11 evaluable patients, and more important, 4 of 5 patients who received IORT, were long-term survivors. Selection of appropriate candidates may be a factor in our favorable results. Intraoperative radiotherapy was used only in patients who did not have disseminated disease to the liver, peritoneum, or other sites. Resection of all gross disease was accomplished in all of our long-term survivors. None of the patients in our series who underwent IORT had small anastomotic recurrences; all had bulky tumors that extended to adjacent organs or structures. We were also able to deliver both IORT and EBRT, which may yield a higher local control rate than with either radiation modality alone.17,19,20 A long disease-free interval between initial diagnosis of cancer and diagnosis of recurrence was considered a favorable prognostic factor by others21 but was not noted in our study.

External beam radiotherapy can be delivered either before or after surgery. Preoperative EBRT may reduce the size of a tumor to make it more likely to be resectable. However, there may be an increased risk of postoperative wound-healing complications. Patients with metastatic disease at laparotomy would not likely have a survival benefit from EBRT. In comparison, EBRT delivered after surgery can be reserved for patients without metastatic disease. The main disadvantage of postoperative EBRT is that a significant delay in treatment start may compromise its effectiveness because of intervening tumor regrowth.

Sciatic neuropathy and ureteral stenosis are the most common complications related to IORT delivered to abdominal and pelvic sites.9,10,17,22 Although none of our patients had neuropathy, others17-22 report symptomatic neuropathy in 0% to 17% of patients with recurrent colorectal cancer who received IORT. Intraoperative radiotherapy can produce ureteral stenosis leading to hydroureteronephrosis and possible loss of kidney function.23 Uretal stenosis was noted by Gunderson et al.22 in 12 (36%) of 33 patients with recurrent colorectal cancer who received IORT to a ureter. In our patients, the only IORT complication was in the only patient who received treatment to a ureter. Ureters without cancer should be excluded from the IORT field (Figure 2). If the ureter must be in the IORT field, a stent can be placed.19,22 Alternatively, a urinary diversion procedure can be performed.

Our results demonstrate that selected patients with bulky tumor bed recurrence of colon cancer can be long-term disease-free survivors when treated with a combination of complete surgical resection, IORT, and wide-field postoperative EBRT. Our series is too small to estimate what proportion of treated patients will have a survival benefit. More effective treatment is necessary for patients whose disease cannot be completely resected or who cannot safely receive full-dose IORT and EBRT. We24 are studying whether the delivery of chemotherapy at the time of IORT will improve locoregional tumor control and reduce the subsequent appearance of distant metastases.

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REFERENCES

The role of adjuvant therapy for recurrent colorectal cancer is still evolving. Radical surgical resection alone or combined with external radiotherapy and often with chemotherapy have been commonly used in treating isolated locoregional recurrence of colon cancer. In the past 2 decades, a major advance in this field has been the addition of intraoperative radiotherapy (IORT) to external beam radiotherapy (EBRT).

Using this combination, Pezner and colleagues successfully treated a few patients with bulky recurrent colon tumors and achieved long-term local control and survival. Although small in number, this study has further illustrated important points. Intraoperative radiotherapy has the advantage of delivering a high-energy electron beam in a single dose to a clearly defined residual tumor bed without exposure and damage to adjacent organs and tissues. However, IORT and EBRT cannot eliminate local failures if complete tumor excision is not achieved, as observed in this study and others. Curative resections are often not possible in locally recurrent colon lesions because most recurrent tumors manifest with fixity to adjacent structures. Intraoperative radiotherapy is not without complications. Radiation injury to nerves, ureter, and bowel may occur when not adequately shielded from the IORT field. This could become an important consideration as more countries embark on this technique.

In recurrent colon cancer, the risk of systemic disease is high. The addition of chemotherapy and radiation modifiers in conjunction with IORT and EBRT seems justifiable. It would be of interest to await the results of controlled studies that are currently in progress of the use of systemic therapy with IORT and EBRT to improve locoregional control and the risk of disseminated disease.

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