The surgeon and the radiation therapist share the primary responsibility for the maintenance of local control in the management of carcinoma of the rectum. Usually, radiation therapy is used to control microscopic disease, while surgery is employed to control macroscopic disease. For ionizing radiation to be effective, targeted tissues must be well oxygenated. Likewise, the risk of local recurrence must be great enough to justify the potential risk of the complications secondary to radiation therapy.

Acceptance of the above-stated axioms dictates that the combination of radiation therapy and surgery be used to treat carcinoma of the rectum that has penetrated through the bowel wall into the pericolic fat and/or when positive lymph nodes are present. Local recurrence rates are as high as 50% in these circumstances. Quirke and associates noted that 27% of patients with cancer of the rectum and rectosigmoid had metastatic cancer extending to the resected lateral mesenteric margin, and 85% of these patients had a local recurrence. A positive margin correlated with advanced Dukes' stage and histologic grade, not with type of operation. Other correlates with local recurrence are perineural invasion, venous invasion, and bowel perforation (either prior to operation or iatrogenically at the time of surgery).

To be most effective, radiation therapy should be given preoperatively rather than postoperatively since cancer cells trapped in the scar of the healing wound are poorly oxygenated. Likewise, fewer enteric complications from radiation occur with preoperative radiation therapy. The small bowel is not trapped in the pelvis by postoperative adhesions, thereby assuring with postoperative radiation that the same portion of bowel will receive the radiation dose. In the preoperative situation, in the absence of pelvic adhesions from a prior operative event, the small bowel is free to move around in the pelvis so that a different bowel axis exists from day to day during radiation therapy. In a Swedish multicenter randomized trial, only 12% of patients in the preoperative radiation therapy group had a local recurrence vs 21% (P<0.02) in the postoperative radiation therapy group. Morbidity, mortality, and survival at a mean of six years were the same for both groups.

Reduction in local recurrence from either preoperative or postoperative radiation therapy is well documented. Three randomized trials have demonstrated a survival advantage with the use of preoperative radiation therapy in the treatment of carcinoma of the rectum. Reis-Neto et al administered 40 Gy in four weeks preoperatively and compared these patients to those undergoing only surgery. The five-year determinant survival for the radiation group was 76.7% compared with 31.1% for the surgery-alone group. Isolated local recurrence was 2.9% and 23.5%, respectively. In the radiation therapy group, three quarters of the patients had tumor regression greater than 70% of original size. The report of the Northwest Region Rectal Cancer Group in the United Kingdom demonstrated that patients who received preoperative radiation therapy and a curative surgical resection had a significantly better survival than the surgery-alone group. The recently reported randomized trial from the Stockholm Colorectal Cancer Study Group also demonstrated a survival advantage for the patients who received preoperative radiation therapy when compared with surgery alone.

At the University of Florida, we have used preoperative radiation therapy for 207 patients with a minimal follow-up of five years. Each of these patients had either Dukes' stage BII or C lesions prior to radiation therapy. Downstaging resulted in 29% of the patients being BI, 6% being A, and 8% being 0 (no tumor identified in the resected specimen). The 10-year determinant survival by stage was 87% for stages 0 to A, 64% for stage B, and 42% for stage C.

More recently, neoadjuvant chemotherapy combined with radiation therapy has been used preoperatively. It would appear from published series that the addition of chemotherapy to radiation therapy has resulted in a higher complete response rate when the surgical specimens are examined (Table). Whether this complete response rate will result in a better survival with the addition of chemotherapy is yet to be determined. Currently, the regimen used at the University of Florida is 5-fluorouracil (275 mg/m² per day) as a continuous infusion with the peak dose at midnight and the nadir at noon to take advantage of the circadian rhythm. This therapy is combined with at least 45 Gy in four and one-half weeks. To date, no patient has required admission to the hospital for complications secondary to the radiation therapy, theoretically because of circadian rhythm dosing.

### Effects of the Addition of Chemotherapy to Preoperative Radiation on Complete Response Rate

<table>
<thead>
<tr>
<th>Study Site</th>
<th>Chemotherapy</th>
<th>Complete Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>University of Florida</td>
<td>None</td>
<td>8%</td>
</tr>
<tr>
<td>Washington School of Medicine</td>
<td>None</td>
<td>6%</td>
</tr>
<tr>
<td>University of Texas M. D. Anderson Cancer Center</td>
<td>5-FU</td>
<td>29%</td>
</tr>
<tr>
<td>Duke University Medical Center</td>
<td>5-FU, cisplatin</td>
<td>27%</td>
</tr>
<tr>
<td>Memorial Sloan-Kettering Cancer Center</td>
<td>5-FU, leucovorin</td>
<td>20%</td>
</tr>
<tr>
<td>University of Florida</td>
<td>5-FU</td>
<td>22%</td>
</tr>
</tbody>
</table>

* All patients received 40 to 50 Gy of radiation therapy.

With the advent of both transrectal ultrasound and magnetic resonance imaging, the depth of penetration into the rectal wall both before and after radiation therapy can be determined. In patients who have a clinical complete response to radiation therapy, the possibility of transanal full-thickness excision exists. The group from Jefferson Medical School reported a 6% recurrence rate and an overall 89% five-year survival rate for downstaged, locally excised lesions that have not invaded through the full thickness of the rectal wall. Likewise, 14 patients who initially had T3 lesions and were downstaged underwent local excision with no recurrences at five
In conclusion, radiation therapy as an adjunct to the treatment of rectal cancer has evolved from its use postoperatively as an agent primarily to reduce local recurrence rate to preoperative radiation therapy in combination with chemotherapy both to provide possible systemic control of disease and to serve as a local radiation therapy sensitizer. Recent evidence suggests that the use of neoadjuvant therapy not only decreases local recurrence rate, but also significantly prolongs survival.

References


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