Combined Therapy for Cancer of the Anal Canal:
A Preliminary Report*

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IN COMPARISON with adenocarcinoma of the rectum, anal cancer is uncommon.[2] According to Morson,[3] one squamous-cell cancer is seen for every 28 rectal adenocarcinomas, an incidence of about 3.5 per cent. As a consequence, individual experience with anal cancer is limited. Fortunately, several recent collective reviews provide guidelines for treatment.[4, 5]

Surgery has largely supplanted radiation therapy as the primary treatment modality for anal cancer, especially when there is a chance for cure. Local excision is usually done for cancer of the anal margin, while resection of the rectum is the preferred treatment for cancer of the anal canal. Results of surgical treatment of cancer of the anal margin are good, since the lesions are usually well differentiated, but this is not the case with cancer of the anal canal. These lesions, which lie in close relationship to the dentate line, are neoplasms with rapid growth characteristics. They are highly anaplastic squamous cancers with various cell types sometimes described in terms such as "transitional," "basaloid," or "cloacogenic." These tumors generally have a poor prognosis.[3]

There are causes for the low cure rates even beyond the biologic characteristics of the neoplasm itself. The anatomic features of the anal canal are such as to promote early spread of malignant cells. The area has both a profuse blood supply and an abundant lymphatic drainage system which leads in all directions. At the same time, there is a serious limitation in the amount of tissue around the anal canal which can be removed. Lymphatic involvement occurs early to areas like the deep pelvic nodes, which are always difficult and sometimes impossible to remove.[3]

It appears to us that surgical excision is not likely to be adequate treatment for many patients with cancer of the anal canal. Consequently, we believe the therapeutic approach should be changed to include other treatment modalities. Squamous-cell cancers are known to be sensitive to irradiation. Furthermore, there is evidence that chemotherapy, given simultaneously with irradiation, tends to potentiate its effect.[1] It would seem logical to use these methods in combination with surgical excision. Accordingly, we have begun to use radiation therapy and chemotherapy before operation.

Radiation treatment is begun first and is given as follows: 3,000 rads full-pelvis dose calculated to the midplane of the pelvis is delivered in 15 treatments of 200 rads each in a three-week period. The day after the

* Read at the meeting of the American Proctologic Society, Detroit, Michigan, June 10 to 14, 1973.

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start of radiation therapy, the patient is given 25 mg/kg body weight of 5-fluorouracil daily in 5 per cent glucose in the form of a continuous 24-hour infusion. The infusion is continued for five days. Also, on the first day, the patient is given Mitomycin C, 0.5 mg/kg body weight. This is given as a single bolus injection. It is important that the 5-fluorouracil be infused at a constant rate since changes in the infusion rate markedly affect toxicity. The five-day regimen of chemotherapy and radiation therapy is administered in the hospital. After the five days, radiation therapy may be concluded on an outpatient basis.

Abdominoperineal resection of the rectum is done about six weeks later. The Miles operation is modified to include a wide perineal phase with excision of the rectovaginal septum. Prophylactic groin dissection is not done. When the inguinal nodes are involved, a block dissection is done on the affected side as soon as convenient after recovery from the primary operation.

We have treated three patients in this manner; two completed the program while one refused the surgical part.

Report of Three Cases

Patient 1: A 69-year-old woman had had rectal pain and bleeding for two months. There was a 4 cm, elongated ulcer on the anterior wall of the anal canal astride the dentate line. Biopsy showed a poorly differentiated squamous-cell cancer.

Radiation therapy was started on December 10, 1971. The patient received 2 MEV radiations over a 20-day elapsed period to the midplane of the pelvis through anterior and posterior portals measuring 16×16 cm. A 2,130-rad midplane dose was delivered, but treatment had to be interrupted for a week because of a severe respiratory infection. On resumption of treatment, 250 KV radiations were directed transperineally through a 6×4 cm portal. In an eight-day period 1,340 rads were delivered. The tumor bulk received a total dose of 3,500 rads in a five-week period because of the delay.

On December 11, 1971, the day after the start of radiation therapy, the patient received 1,500 mg 5-fluorouracil in 5 per cent glucose in the form of a continuous 24-hour infusion. This was given for a total of five days. On the first day of chemotherapy, she was also given 50 mg Poriferomycin intravenously as a single bolus injection (Poriferomycin became unavailable, so we are now using Mitomycin C).

After eight weeks, the lesion had disappeared and, on March 20, 1972, abdominoperineal resection of the rectum was done, along with excision of the rectovaginal septum. There was no tumor in the operative specimen. The patient is apparently well 14 months later.

Patient 2: A 51-year-old woman was seen because of rectal soreness and bleeding of three months' duration. There was a 5-cm elongated ulcer on the left lateral wall of the anal canal. Biopsy showed basaloid carcinoma.

Radiation therapy was started on March 29, 1972, and completed on April 25, 1972. The patient received cobalt-60 teletherapy, 3,060 rads to the midplane of the lower pelvis through anterior and posterior portals each measuring 14×16 cm. The total number of treatments was 17.

Chemotherapy was started on the day following the beginning of radiation therapy. The patient received 1,500 mg of 5-fluorouracil in 5 per cent glucose in the form of a continuous 24-hour infusion for five days. On the first day she was also given 30 mg of Mitomycin C intravenously as a single bolus infusion.

After six weeks, the symptoms and the lesion had disappeared, and the patient refused operation. There was no evidence of recurrence on June 1, 1973.

Patient 3: A 56-year-old woman complained of rectal pain, bleeding, and a 20-pound weight loss over a three-month period. There was a 5-cm linear ulcer in the anal canal astride the dentate line just to the right of the midline. In addition, there was an associated mass (4 cm) in the rectovaginal septum. Biopsy showed cloacogenic carcinoma.

Radiation therapy was begun on October 27, 1972. The patient received 2 MEV radiations, directed to anterior and posterior (16×16 cm) pelvic portals. In 15 treatments, from October 27, 1972, to November 15, 1972, 3,000 rads were delivered.

On December 11, 1972, symptoms were relieved and the lesion had completely healed. The mass in the rectovaginal septum had disappeared.

Abdominoperineal resection of the rectum with excision of the rectovaginal septum was performed on January 11, 1973. There was no tumor in the operative specimen, and the patient is apparently well six months later.

Discussion

The lesions in all three patients reported here disappeared following the preoperative therapy outlined above. No cancer was found in the operative specimens of the two

patients who were operated upon. In the patient who refused operation, there is no sign of recurrence after 14 months.

We have also treated another woman who had a very large liver due to metastatic disease from a cloacogenic cancer of the anal canal which had been resected two years before. (She had not received preoperative therapy before the original operation.) We gave her 2,000 rads over the liver, and the same chemotherapeutic agents given the three patients reported here for cancer of the anal canal. In a few weeks the liver had shrunk to less than normal size, and there is no evidence of residual disease either by biopsy or by laparoscopy. We do not, of course, consider this curative, but we have not seen such a dramatic response to any therapy for this condition before.

Certainly, three patients are too small a series to permit a meaningful conclusion. However, we believe this experience is significant enough to warrant further trial. These tumors are known to be sensitive to radiation therapy, but the cure rate for cancer of the anal canal using either irradiation or operative treatment is low.

A number of investigators report five-year survival rates for anal cancer of 50 per cent or more, but these series have included cancer of the anal margin, which usually has a very good prognosis. When only cancer of the anal canal is considered, the cure rate is much less. Perhaps the combination of radiation therapy and chemotherapy given simultaneously as suggested here, followed by operation, will improve survival rates of patients who have cancer of the anal canal.

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Memoir

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Dr. Carroll was elected to Affiliate Membership in the American Society of Colon and Rectal Surgeons in 1957. He was certified by the American Board of Colon and Rectal Surgery; was a Fellow, American College of Surgeons, member of American Medical Association, Ohio State Medical Association, Columbus Academy of Medicine, and Ohio Valley Proctologic Society. Dr. Carroll was on the staff of Grant and Mount Carmel Hospitals. He died July 24, 1973.