Definitive Treatment of Anal-canal Carcinoma by Means of Radiation Therapy and Chemotherapy*

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In the light of the relatively poor response of squamous-cell carcinoma of the anus to surgery, an alternative method of treatment has been sought. During the past five years, in a series of 19 patients, the first four were treated by a combination of preoperative irradiation, 5-fluorouracil (5-FU) and mitomycin C as radiosensitizers plus surgery. As a result of complete responses at the time of surgery of all these patients, 15 additional patients have been treated by definitive radiotherapy combined with 5-FU and mitomycin C, thereby avoiding abdominoperineal resection. Eighteen patients had local control, and the one treatment failure is discussed. The method of treatment is described, and recommendations are made concerning techniques to be used or to be avoided. [Key words: Radiation, anus; Carcinoma, squamous-cell; Chemotherapy; Radiosensitization]

SQUAMOUS-CELL carcinoma of the anus is a comparatively rare disease. It comprises only between 1 and 3 per cent of all carcinomas of the lower rectum. There will be an anticipated 1400 new cases during 1981 in the United States; it is more prevalent in women; and the mean age of patients is 60 years. Historically, the vast majority of patients with lesions of the anal region have been treated by a purely surgical approach, either abdominoperineal resection or local excision. This has been based on the premise that, because adenocarcinomas of the rectum and squamous-cell carcinomas of the anus are close together physically, they must behave alike biologically. They are, in fact, two quite different tumors, carcinoma of the anus appearing to be more radiosensitive than originally thought and probably more so than epidermoid carcinoma at other sites.

The results of surgery are disappointing: the anatomic features are such as to be favorable to the early spread of malignant cells. The area has a profuse blood supply and an excellent lymphatic drainage system which leads in various directions. This naturally predisposes to early lymphatic involvement of the deep pelvic nodes which are often impossible to remove surgically. This tendency has an influence on the management of this disease.

Beahrs, in his Janeway Lecture to the American Radium Society in 1979, states, "The overall 5 year survival rate for 82 patients with anorectal and anal canal squamous cell carcinoma was 57.8%." Other noteworthy surgeons report survival figures lower than this. For example, in a recent review by Quan, a five-year survival rate of 40 per cent was reported. In spite of these results, radiation therapy has often been disfavored in the past for this fairly radiosensitive disease, both from the point of view of local morbidity and poor survival rates.

In an effort to improve the results from surgery alone for squamous-cell carcinoma of the anus, a combination of radiotherapy and chemotherapy has been utilized at Highland Hospital since 1976. Over the past decade or so, several papers of great interest stimulated the consideration of using these modalities in the treatment of carcinoma of the anus.

In 1968, Carter and Moertel et al. described response rates in treating various malignancies with 5-fluorouracil (5-FU) and mitomycin C, and for several decades there had been reports on the use of 5-FU as an effective chemotherapeutic agent.

Soon after, reports appeared demonstrating the synergistic effect of 5-FU when combined with radiation therapy and also the advantages of administering 5-FU intravenously over a long period.

Byfield et al. states that preclinical studies suggested that, with prolonged exposures in excess of
the cell cycle time, low concentrations of 5-FU are required to obtain genuine radiosensitization: "... 5-FU induced unbalanced growth and interacted somehow with x-ray damage leading to enhanced cell killing." The time dependence of 5-FU radiosensitization appeared greater than the concentration dependence. Clinical response to 5-FU per se may not be required to obtain radiosensitization.

In 1974, Nigro et al.11-12 reported the use of preoperative chemotherapy (5-FU and mitomycin C) and radiation therapy for squamous-cell carcinoma of the anus and later for adenocarcinoma of the rectum. These data, as well as a report by Newman and Quan,13 supported the benefit of a more aggressive multimodality approach to the management of carcinoma of the anus.

Results: Anal Canal Carcinomas

Nineteen patients with lesions involving the anal canal have been treated. Perianal lesions were excluded from this series. The first four patients who were treated in this manner had radical surgery in the form of an abdominoperineal resection four weeks after having received 4000 rads midline; no tumor was found in the resected specimens. Because of the success in these four patients and because of the ease of follow-up, the following 15 patients were treated definitively by means of radiation therapy with the chemotherapy. Eighteen patients had local control. The one patient who died of distant metastases had a lung metastasis and positive inguinal nodes at the time of presentation. At post-mortem examination, there was no evidence of any cancer in the anus or inguinal area. Three patients died from other causes, and one patient who, in the past, had uterine and vaginal carcinoma and then presented with carcinoma of the anus, has had a recurrence; she was one of the patients who did not receive an interstitial implant. Because of her multifocal disease, it was planned to carry out an abdominoperineal resection. In retrospect, it is questionable whether the results might not have been better with cobalt therapy, which