Multidisciplinary Management of Cancer of the Anus

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Anal margin cancers are treated by local excision, with radical surgery reserved only for invasive cancers or those associated with fistula or condylomata. Squamous cell cancers of the anal canal have been treated by abdominoperineal resection regardless of cell type. Radiation therapy alone has been advocated by some, and we initiated a study using a combination of radiation, chemotherapy, and surgery. This study includes 104 patients treated from December, 1971, to July, 1983. Routine abdominoperineal resection was discontinued by us in 1975 because chemoradiation therapy eliminated the primary lesion in 5 of the first 6 patients. In the series, gross tumor disappeared in 97 patients after chemoradiation therapy. Radical operation was done routinely in 24 patients, for residual disease in 7, and for recurrent disease in 7 others. There were 21 deaths of which 13 were due to cancer of the anal canal. Large primary lesions and recurrent local disease account for the majority of deaths due to cancer. The 5-year survival rate is projected to be 83%, with 65 patients followed for at least 5 years. Under our current regimen only 16 of the 38 patients would have had radical surgery. Chemoradiation therapy is advocated for all patients with squamous cell cancer of the anal canal and for invasive cancers of the anal margin. Patients with large (6-8 cm) primary cancers and those with recurrent disease should have additional chemoradiation therapy and/or abdominoperineal resection of the rectum.

In 1941, Gabriel suggested that cancer of the anal region be divided into 2 groups according to the site of origin [1]. He called the first anal margin cancer because it develops in the perianal skin. Since these lesions are external, they are identified by direct inspection and biopsy. The second he called anal canal cancer because it originates in the area of the dentate line in the tissue immediately proximal to it, referred to as the cloacogenic zone. These lesions are identified by internal examination since, generally, they are not visible outside the anus. This division is useful because the cancers in the 2 areas differ in histological appearance, degree of anaplasia, method of treatment, and prognosis. The surface covering the anal margin area is normal skin except that it is slightly more pigmented, and it contains an excess of sweat glands and hair. Cancers that arise in this tissue are generally the same as those in the skin elsewhere. On the other hand, the epithelium in the area above the dentate line contains cells that vary in size and shape. They include transitional cells resembling urinary tract epithelium, and a mixture of cuboidal, columnar, and squamous cells. This variation accounts for different histologic patterns of cancers which arise from this varied and unstable tissue [2]. Although pathologists use terms such as cloacogenic, transitional, basaloid, epidermoid, and squamous to describe these cancers, we use the single term, squamous cell cancer of the anal canal, for all of them. This simplifies the discussion of therapy which is the same for all these cancers regardless of cell type.

Anal margin cancers which make up only about a third of all cancers of the anal region reflect the characteristics of the skin from which they develop. They are squamous cell carcinoma, basal cell cancer, Bowen’s disease, and Paget’s disease. Most of these lesions are localized and are effectively treated by wide local excision [3]. Occasionally, however, anal margin tumors become truly invasive cancers which must be treated with radical surgery [4] or with combined therapy (described below) for anal canal cancer. There is a group of miscellaneous lesions, all rare, that occur outside the anus which also must be treated aggressively. Anorectal fistula that contain malignant tissue is an example. Abdominoperineal resection with wide excision of the affected area is standard treatment [5], but we suggest that radiation and chemotherapy should precede the operation. On rare occasions, condylomata acuminata of the perianal area is associated with squamous cell cancer. Radical surgery has been advocated for this lesion [6]. We have, however, successfully treated 2 patients with the chemoradiation therapy alone with no recurrence, one for 6 years and the other for 3 years. Consequently, we suggest combined therapy for patients with this lesion. If the primary lesion disappears, abdominoperineal resection may not be required.

The vast majority of tumors of the anal region occur in the anal canal as described above. The lesion is generally ulcerative, and it may, on occasion, extend proximally into the rectum or distally to the anal verge and even outside the anus. Some lesions are elongated, elliptical, and fissure-like while others are circular surrounding the anal canal to various degrees. It is important to emphasize that these lesions, whatever their size, involve the area of the dentate line. The diagnosis is made by biopsy which is best done under anesthesia, usually caudal or spinal. Staging of anal canal cancer is difficult because of the peculiar anatomical features of the area. The lining of the canal is not clearly delineated into separate layers as it is in the colon. In addition, the canal is surrounded by a thick ring of muscle consisting of the internal and external sphincter mus-
Table 1. Size of primary tumor.

<table>
<thead>
<tr>
<th>Maximum diameter (cm)</th>
<th>No. of patients</th>
</tr>
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<tbody>
<tr>
<td>Small (2–3)</td>
<td>39</td>
</tr>
<tr>
<td>Medium (4–5)</td>
<td>46</td>
</tr>
<tr>
<td>Large (6–8)</td>
<td>19</td>
</tr>
<tr>
<td>Total</td>
<td>104</td>
</tr>
</tbody>
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Table 2. Chemoradiation therapy.

- **External irradiation**
  - 3,000 rad (30 GY) to the primary tumor, pelvic and inguinal nodes; start: day 1 (200 rad/day).

- **Systemic chemotherapy**
  - A. 5-FU 1,000 mg/m² per 24 hours as a continuous infusion for 4 days; start: day 1.
  - B. Mitomycin C: 15 mg/m² intravenous bolus; start: day 1 only.
  - C. 5-FU: Repeat 4-day infusion; start: day 28.

Material and Methods

This series consists of 76 women and 28 men ranging in age from 32 to 80 years with biopsy-proven squamous cell cancer of the anal canal treated from December, 1971, to July, 1983. All lesions involved the area of the dentate line, and they included the variety of cell types commonly described as arising in the tissue immediately above the dentate line. This, naturally, excludes adenocarcinoma which can develop in the anal glands. There were no patients with perianal cancers or in situ anal canal cancers in this series. Forty-four patients were treated by us at Wayne State University while 60 were managed by individual surgeons around the country. The latter information was obtained by questionnaire. Patients who had demonstrable metastases to distant organs on initial examination were excluded. We included, however, all patients with inguinal metastases, even one who had extensive bilateral involvement. The lesions were ulcerative, and all but 6 were moderately to poorly differentiated. Thirty-nine patients had small lesions (2–3 cm), 46 had moderate-sized growths (4–5 cm), and 19 had large lesions (6–8 cm) (Table 1). Four patients had inguinal node metastases, 1 bilateral, at the time of diagnosis. All patients but 1 were judged to be candidates for abdominoperineal resection of the rectum.

Preoperative radiation and chemotherapy as outlined in Table 2 was administered to all patients. Radiation and drug therapy were begun jointly on day one. The drug, 5-fluorouracil (5-FU), was given via a central venous catheter in a dosage of 1,000 mg/m² per 24 hours for 4 days as a continuous infusion. This 96-hour infusion was repeated in 1 month. Mitomycin C was given as a single bolus intravenous injection at a dosage of 15 mg/m². Radiation therapy was given to 3,000 rad (30 GY), calculated at the central axis midplane of the pelvis, at 200 rad (2 GY) per day, 5 days per week starting on day one. The parallel-opposing anteroposterior portals included the primary lesion with margin, the true pelvis, and the inguinal lymphatics. Abdominoperineal resection was performed 4–6 weeks following completion of radiation therapy. Leukocyte and platelet counts were obtained until the time of operation.

The first 5 patients in our series received the higher doses of 5-FU and mitomycin C suggested in our initial report [13]; however, toxicity was excessive in 3 patients so the amounts of the drugs were reduced to those described here. Ninety-nine patients, therefore, received the reduced drug regimen. The protocol was changed again in 1975 when we found that 5 of the 6 patients had no cancer in the operative specimen after abdominoperineal resection of the rectum. Subsequently, radical operation was not done by us unless cancer remained following chemoradiation therapy. Some surgeons who submit-