Combined Preoperative Radiation and Chemotherapy for Squamous Cell Carcinoma of the Anal Canal

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Twenty-eight patients with squamous cell carcinoma of the anal canal were treated by preoperative radiation therapy and chemotherapy. The radiation therapy was given for 3000 rad (30 Gy) at 200 rad per day, 5 days a week, to the primary tumor with margin and to the pelvic and inguinal lymph nodes. Chemotherapy was given in the form of 5-fluorouracil infusion 1000 mg/m² on days 1–4 of the radiation therapy and repeated on days 29–32 of the treatment regimen. Mitomycin C was given in the form of intravenous bolus for 15 mg/m² on day 1. Surgery was done 4–6 weeks following the last day of radiation treatment. Twelve patients underwent anteroposterior resection, and seven of the 12 had no residual tumor in the surgical specimen, while one patient had microscopic tumor only. An additional 14 patients had complete clinical disappearance of their tumor, and, on excision of the scar, it was found free of microscopic cancer. Two other patients are clinically free of tumor but had no biopsy after therapy. While transient proctitis leukopenia and thrombocytopenia were moderate to severe, no serious complications were observed in these patients. Twenty-two patients are free of tumor and alive one to eight years after treatment. One patient died a cardiac death without tumor four years after surgery. Four patients, all with residual tumor in the specimen, have died of cancer. Their primary lesions were more than 7 cm in maximum diameter at initial examination. One patient died of disseminated disease with no local recurrence after abdominal perineal resection.


Cancer of the anus is a rare lesion comprising less than 5% of all rectal cancers. These cancers are best divided into two groups according to site or origin: (1) those that arise in the tissues at or immediately above the dentate line, referred to as anal canal cancer; and (2) those that begin in the epithelium distal to the dentate line and extending into the perianal skin. This latter group is called anal margin cancer. The division is useful because lesions arising in these two locations differ in histological appearance, method of treatment, and in prognosis.  

This report deals only with squamous cell cancer of the anal canal which is both more common and more lethal than anal margin cancer. The five year survival rate after abdominoperineal resection for anal cancer ranges from about 20% to 78% depending upon the criteria used in the selection of patients.  

Squamous cell cancer of the anal canal arising at or immediately above the dentate line is generally ulcerative and anaplastic. Here the epithelium is cloacogenic in origin, and the cells which are transitional in character are unstable. Neoplasms arising from it are generally a mixture of cell types, and pathologists usually refer to such cancers as cloacogenic, transitional, epidermoid, and basaloid according to the predominant cell configuration. Nevertheless, they are all variants of squamous cell cancer. Of more importance in determining therapy is the size of the lesion and its degree of anaplasia. Most of these cancers are ulcerative, more than 2 cm in diameter, and moderately to poorly differentiated. Consequently, the conventional therapy has been abdominal perineal resection of the rectum with a wide excision of the perineal tissues.

Surgery is curative only in patients whose lesion is confined to tissues that can be excised. It appears from reported survival rates that this is not possible in about 50% of these patients. This is due in part to the anatomic features of the anal region which make it difficult if not impossible to adequately remove the lateral and distal zones of lymphatic spread. In addition, only a limited amount of tissue around the primary lesion can be removed. These facts suggest the need for additional therapy to deal more effectively with the regional extensions of cancer in this area.
A combination of radiotherapy and chemotherapy given preoperatively would appear to have potential value because squamous cell cancer is generally radiosensitive and chemotherapy has been shown to potentiate the effect of radiation.\textsuperscript{11-13}

In 1974, Nigro \textit{et al.}\textsuperscript{14} published a report on the use of preoperative radiation and chemotherapy followed by operation in three patients with cancer of the anal canal.\textsuperscript{14} This brief experience was successful enough to warrant further investigation by others\textsuperscript{7,15,16} and our series was updated by Buroker \textit{et al.}\textsuperscript{17,18} and again by Nigro \textit{et al.}\textsuperscript{19} The current report deals with our experience using this therapy in a larger number of patients.

\textbf{Method}

Seventeen women and 11 men, ranging in age from 42 to 79 years, with biopsy proven squamous cell cancer of the anal canal involving the dentate line, are included in this review. All lesions were ulcerated, moderately to poorly differentiated, and all but nine were 5 cm or less in greatest diameter (Table 1 and 2). Two patients had inguinal node metastases, one unilateral and one bilateral. There was no evidence of disease in distant organs in any patient, as determined by physical examination, chest x-ray, laboratory studies, radioisotope scans of the liver and bones and of CT scans of the head and pelvis and abdomen. All were judged to be candidates for abdominal perineal resection of the rectum.

Preoperative combined chemoradiation therapy was administered to all patients. Chemotherapy and radiation therapy were begun jointly on day one of the therapy. 5-Fluorouracil (Roche Laboratories, Division of Hoffmann-La Roche, Nutley, New Jersey) was given via a central venous catheter in a dosage of 1000 mg/m\textsuperscript{2}/24 hr for 4 days as a continuous infusion. This 96-hour infusion was repeated in one month even in the presence of mild bone marrow depression since 5-FU infusions have been shown to be nonmyelosuppressive.\textsuperscript{19,20} Mitomycin C (Bristol Myers, Syracuse, NY; manufactured by Ben Venue Laboratories, Incorporated, Bedford, OH) was given as a bolus intravenous injection at a dosage of 15 mg/m\textsuperscript{2}.\textsuperscript{§} Radiation therapy was given to 3000 rad (30 Gy), calculated at the central axis mid-plane of the pelvis, at 200 rad (2 Gy) per day, 5 days a week starting on day 1. The parallel-opposing anteroposterior portals included the primary lesion with margin, the true pelvis, and the inguinal lymphatics (Fig. 1). Surgery was performed 4 to 6 weeks following completion of the radiation therapy. Leukocyte and platelet counts were obtained weekly until the time of surgery.

\begin{table}
\centering
\caption{Size of Lesion}
\begin{tabular}{|c|c|}
\hline
Maximum diameter & No. patients \\
\hline
3 & 6* \\
4 & 11* \\
5 & 2 \\
6 & 4 \\
7 & 2 \\
8 & 3 \\
\hline
Total & 28 \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\caption{Degree of Differentiation (diff)}
\begin{tabular}{|c|c|}
\hline
Well diff & 7 \\
Moderately well diff & 9* \\
Poorly diff & 12* \\
\hline
Total & 28 \\
\hline
\end{tabular}
\end{table}

\textsuperscript{*} One patient had inguinal node metastases.

\textsuperscript{§} The first five patients had the higher doses of 5-FU and Mitomycin C suggested in the initial report.\textsuperscript{14}

\textbf{Results}

All 28 patients were evaluable for the effect of the preoperative therapy. Following radiation and chemotherapy, there was no gross tumor in the anal canal in 24 patients while in four, gross tumor remained though reduced in size (Table 3). Twelve of the 28 patients had

\textbf{FIG. 1. Anteroposterior treatment portal film.}
TABLE 3. Effect of Preoperative Therapy

<table>
<thead>
<tr>
<th>Anal canal lesion</th>
<th>No gross tumor</th>
<th>Gross tumor present</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>4*</td>
<td></td>
</tr>
</tbody>
</table>

* Original lesions: 1–7 cm (well differentiated), 3–8 cm (1: moderately differentiated; 2: poorly differentiated).

TABLE 4. Results after Operation

<table>
<thead>
<tr>
<th>Wayne of scar biopsy</th>
<th>No tumor found</th>
<th>Microscopic tumor only</th>
<th>Gross tumor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abdominoperineal resection</td>
<td>7</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Excision of scar</td>
<td>14</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>12</td>
<td>14</td>
<td>2*</td>
</tr>
</tbody>
</table>

* No tumor on clinical examination.

Table 5. Survival (28 Patients)

<table>
<thead>
<tr>
<th>Abdominoperineal resection (NED 6/12 patients)</th>
<th>Excision of scar (14/14 patients)</th>
<th>Biopsy only (2/2 patients)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 yrs 1/1</td>
<td>6 yrs 1/1</td>
<td>2 yrs 1/1</td>
</tr>
<tr>
<td>8 yrs 1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 yrs 2/2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>5 yrs 1/1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4 yrs 1/2*</td>
<td>4 yrs 3/3</td>
<td>2 yrs 1/1</td>
</tr>
<tr>
<td></td>
<td>3 yrs 2/2</td>
<td>1 yr 5/5</td>
</tr>
<tr>
<td></td>
<td>1 yr 5/5</td>
<td>1 yr 1/1</td>
</tr>
<tr>
<td>Younger than 2 yrs 0/5*</td>
<td>Younger than 1 yr 3/3</td>
<td></td>
</tr>
</tbody>
</table>

* Cardiac death no tumor on autopsy.
† All lesions 6 cm or larger in diameter: one well differentiated (7 cm), one moderately well differentiated (8 cm), three poorly differentiated (1–7 cm and 2–8 cm).

The other patient with unilateral involvement of the inguinal nodes had a negative scar excision and had no disease in the superficial groin dissection. He is currently doing well.

The current status of the 28 patients is shown in Table 5. There were six deaths in the series. Four deaths occurred in patients whose initial lesion was over 6 cm in greatest diameter, and all these lesions were present, although smaller after preoperative therapy. One patient who had no cancer in the operative specimen after radical operation died of disseminated disease two years after operation. One patient died of cardiovascular disease over four years after radical surgery; there was no evidence of cancer at autopsy.

While the first five patients had higher doses of the chemotherapeutic drugs, with severe leukopenia and thrombocytopenia in two, none of the latter patients experienced leukocyte or platelet counts less than 1500/mm$^3$ or 50,000/mm$^3$, respectively. Radiation therapy did not have to be discontinued in any patient. Other toxic effects included diarrhea, perianal discomfort and erythema, dysuria, and nausea. These were all reversible and easily controlled, as was the hematopoetic toxicity.

**Discussion**

Our experience with combined chemoradiation therapy for anal canal cancer has convinced us that it is effective enough not to require abdominal perineal resection if the lesion disappears, as proved by adequate examination and local excision of scar. If residual cancer is present, and if there is no evidence of disseminated disease, we proceed with radical abdominoperineal resection. On the other hand, if disseminated disease is present, we deal with the residual local lesion, if present, in as conservative a manner as possible to control symptoms.

We prefer combined therapy because the chemotherapy potentiates the radiation effect for satisfactory management of the local lesion, and because it provides systemic therapy which may be of value for the manage-
ment of subclinical tumor implants outside the pelvis. The results of this sphincter-saving method of treatment lead to excellent local control, disease-free survival, and quality of life.

Our experience with the favorable therapeutic effects of this combined therapeutic approach to the management of squamous cell cancer of the anal canal, we believe, justifies its routine use. The preoperative arm of the therapy appears to be sufficient to control the disease in most patients whose primary lesion is 5 cm or less in greatest diameter. Even in those who continue to have residual disease, radical operation may be performed under generally more favorable circumstances. Finally, radiation and chemotherapy alone may control local symptoms in patients with inguinal lymph node involvement.

Our failure to control local disease in five of nine patients with lesions 6 cm in diameter or larger with subsequent cancer death indicates the need for additional treatment by combined radiation chemotherapy following surgical staging after abdominal perineal resection. We are now pursuing such a program. The rationale for the second course of radiation therapy is to strengthen the effect of the systemic part of the treatment. It is at present the weaker aspect of this therapeutic approach. Theoretically it is possible that with less tumor burden the additional chemotherapy might reduce micrometastases.

REFERENCES