Patterns of Recurrence in Anal Canal Carcinoma

Moshe Faynsod, MD; Hernan I. Vargas, MD; Jorge Tolmos, MD; Vikram M. Udani; Sunil Dave; Tracey Arnell, MD; Bruce E. Stabile, MD; Michael J. Stamos, MD

Hypothesis: The initial modality of treatment of anal canal carcinoma (ACC) influences the pattern of recurrence of disease.

Design: A retrospective analysis comparing patterns of recurrence in patients with ACC undergoing either surgery or chemoradiotherapy as their initial therapeutic intervention. Anal margin cancers and adenocarcinomas were excluded.

Setting: A university-affiliated urban medical center.

Patients: Eighty-one patients were given a diagnosis of ACC between February 1, 1952, and December 31, 1998. Fifty-one (63%) of the patients initially underwent surgery: abdominoperineal resection in 38 patients (75%) and local excision in 13 patients (25%). Chemoradiotherapy was the initial therapeutic intervention in 30 patients (37%).

Main Outcome Measures: The patterns of recurrence (local vs distant disease) and survival were compared between the group that underwent palliative surgery (hereafter referred to as the surgical group) and the group that received chemoradiotherapy (hereafter referred to as the chemoradiotherapy group).

Results: The mean follow-up was 40 months. Local recurrence occurred in 7 patients (14%) in the surgical group vs 7 patients (23%) in the chemoradiotherapy group (P = .46). Using Kaplan-Meier actuarial analysis, local recurrence rates for the surgical and chemoradiotherapy groups at 1 year were 0% and 6%, respectively (P = .32), and at 5 years were 17% and 36%, respectively (P = .02). The average (±SD) time to local recurrence in the surgical group was 23±0.7 months and for the chemoradiotherapy group 16±2.9 months (P = .27). Five (71%) of the 7 patients with local recurrences in the chemoradiotherapy group underwent salvage abdominoperineal resection with 100% disease-free survival at a mean follow-up of 35 months. When patients presenting with metastatic disease were excluded, distant recurrences developed in 7 patients (16%) in the surgical group and 2 (7%) in the chemoradiotherapy group (P = .31). Actuarial 5-year distant recurrence rates for the surgical and chemoradiotherapy groups were 26% and 19%, respectively (P = .65). Five-year survival was 42% in the surgical group and 74% in the chemoradiotherapy group (P = .01).

Conclusion: There was a higher rate of local recurrence in patients with ACC treated with chemoradiotherapy vs surgical resection as the initial therapeutic intervention. However, when this occurred, abdominoperineal resection was effective salvage therapy and was associated with a 100% disease-free survival at 3 years. Therefore, chemoradiotherapy is justified as the initial treatment for ACC and has an overall 5-year survival that is significantly higher than that attained with initial surgical treatment.

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METHODS

The University of California, Los Angeles Medical Center Tumor Registry was used to identify all patients who received a diagnosis of ACC between February 1, 1952, and December 31, 1998. All patients with anal margin tumors and those with pathologic features identifying adenocarcinoma were excluded from the study. Data were collected retrospectively by medical chart review including age, sex, date of diagnosis, tumor histologic features, tumor stage, type of primary therapy, subsequent therapy, date and site of recurrence, date of last follow-up, and date of death. Staging was determined using the TNM classification published by the American Joint Committee on Cancer Staging.9 Tumor size was determined by physical examination for patients undergoing chemoradiotherapy (hereafter referred to as the chemoradiotherapy group) and by pathologic examination of the excised specimens for patients treated Surgically (hereafter referred to as the surgical group). Local recurrence was defined as a biopsy specimen positive for carcinoma subsequent to a negative biopsy specimen following chemoradiotherapy or as a positive biopsy specimen of the anal canal or perineal region following surgical excision. All patients with initially positive biopsy specimens following completion of primary therapy were considered primary treatment failures rather than recurrences. Distant recurrence was defined as identification of metastatic tumor recurrence at a site not in direct continuity with the primary tumor site, including the internal iliac or inguinal lymph nodes.

Statistical analysis was performed by one of us (J.T.) using the t test for continuous variables. Categorical variables were compared using 2-sided χ² test with Yates correction for small numbers. P < .05 was considered statistically significant. Five-year recurrence and overall 5-year survival were determined using Kaplan-Meier survival analysis.10 Differences in actuarial results were determined using the log-rank test. All values are expressed as mean ± SD.

Nigro6 published data in 1984 for 104 patients that suggested that treatment with chemoradiotherapy alone yielded clinical outcomes similar to those of radical surgical excision. Surgery was reserved for residual disease after the primary nonsurgical treatment. Since this article, other investigators have assessed the efficacy and safety of primary chemoradiotherapy and have demonstrated good to excellent results relating to disease-free survival, sphincter preservation, and morbidity.2 As a result, there has been a move toward nonsurgical therapy for ACC with most cases treated with combination chemoradiotherapy as the primary intervention; the 5-year survival rates have ranged from 23% to 71%, depending on the cancer stage.8 We have previously reported a 40-year experience with ACC and noted a similar shift toward chemoradiotherapy as the primary treatment. Our goal in this study was to elucidate whether the primary treatment modality affected the pattern of recurrence in this disease.

RESULTS

There were 81 patients treated for ACC over the 46-year period. The mean follow-up was 40 months (follow-up range, 8-184 months). Of the 81 patients, the primary therapy was chemoradiotherapy in 30 (37%) and surgical resection in 51 (63%), including APR in 38 (75%) and wide local excision in 13 (25%). Patient demographics are given in Table 1.

Two primary treatment failures were identified in the chemoradiotherapy group. While one of these patients was lost to follow-up, the second underwent salvage chemotherapy with a complete response and was disease free at 11 months' follow-up.

Local recurrence occurred in 7 (23%) of the 30 patients who were primarily treated with chemoradiation at a mean time to recurrence of 16 ± 2.9 months. Seven (14%) of the 51 patients who underwent primary surgery developed local recurrences with a mean time to recurrence of 23 ± 5.6 months (P = .46). The time to local recurrence between the 2 groups was also not significantly different (P = .26). Using actuarial analysis, the 1-year local recurrence rate was 6% for the chemoradiotherapy group vs no recurrences in the surgical group (P = .32). The 5-year actuarial recurrence rates were significantly different at 36% and 17%, respectively (P = .02) (Figure 1). Five (71%) of the 7 patients who experienced local recurrences in the chemoradiotherapy group underwent salvage APR with a 100% disease-free survival at a mean follow-up of 33 months. Of the remaining 2, one was lost to follow-up while the other underwent salvage chemotherapy. When the primary surgical group was subdivided by operative procedure, 2 (15%) of 13 patients treated with wide local excision and 5 (13%) of 38 patients treated by APR had local recurrences (P = .77). Both patients with local recurrence after local excision had originally presented with stage II disease, while all 5 patients with local recurrence after APR had presented with stage III disease.

Four patients who initially underwent local excision were found to have positive margins and underwent a subsequent APR within 6 weeks of their initial procedure. These patients were categorized in the surg-
surgical group as having undergone initial APR. None of these patients experienced local recurrence following APR.

Of the 34 patients who underwent initial APR, 2 had positive lateral margins. These were further treated with adjuvant chemotherapy consisting of fluorouracil and mitomycin. Of these patients, one developed carcinomatosis within 1 year while the other developed lung metastasis at 16 months postoperatively.

Seven (14%) of the 51 surgical patients had distant recurrences, while 2 (7%) of 30 patients who received primary chemoradiotherapy had distant recurrences ($P = .49$). The actuarial 5-year distant recurrence rates were 26% for the surgical group vs 19% for the chemoradiotherapy group ($P = .65$). No statistically significant differences were found when specific sites of distant recurrence were compared between the groups. 

Table 2 lists the sites of distant recurrence for each group. Table 2 gives the distribution of patients in each primary treatment group by stage of disease at presentation together with their incidences of local and distant recurrences. There were no significant differences. The actuarial 5-year survival rate was 42% for patients who underwent primary surgery vs 74% for those who received primary chemoradiotherapy ($P = .01$) (Figure 2).

In 1973, Nigro et al11 first reported a series of 3 cases of epidermoid carcinoma of the anal canal treated with external beam radiation (30 Gy) and chemotherapy consisting of a combination of mitomycin and fluorouracil. This was followed by surgical excision after 6 weeks in 2 patients, neither of whom had tumor found in the pathology specimen. Since then, several investigators have demonstrated the success of sphincter preservation by using primary chemoradiotherapy for the treatment of ACC.12 We have studied the pattern of recurrence of ACC after either palliative surgery or chemoradiotherapy in a population treated over a 46-year span. Our study represents a historical analysis. Prior to the early 1980s, our primary approach to ACC was surgical, reflecting the standard of care at the time. With the introduction of the Nigro et al protocol,12 our institution altered its paradigm for the treatment of ACC. Since then, we have been treating ACC with primary chemoradiotherapy. In our series, 28 (93%) of 30 patients treated with primary chemoradiotherapy received between 43 and 55 Gy in combination with mitomycin and fluorouracil. Most (63%) of the patients were treated in the years prior to the widespread adoption of the Nigro et al protocol. The last surgical resection performed as primary therapy for ACC was an APR in 1988. In recent years, surgical resection has been reserved for recurrence or primary failure after initial chemoradiotherapy.

Using actuarial data analysis, a higher rate of local tumor recurrence at 5 years was found in patients who underwent initial chemoradiotherapy compared with patients who underwent primary surgical excision. Longo et al13 reviewed 159 patients with ACC and found tumor stage and method of initial treatment affected the likelihood of disease recurrence. They found an 11% local recurrence rate among patients with stage I disease treated with multimodality therapy vs 41% in patients with stage II disease. They also found that APR afforded better local control when compared with chemoradiotherapy. These results mirror our findings. Our data also suggest that surgery is a more effective means of providing local control. Additionally, substantial differences in the stage distributions were noted between the treatment groups at initial presentation, making the local control advantage even more impressive. The surgical group contained most (53%) of stage III and IV tumors while the chemoradiotherapy group had a smaller proportion (33%) of these advanced tumors. However, the patients who underwent chemoradiotherapy were very likely understaged owing to the lack of surgical specimens for pathologic staging. This may account for the higher local recurrence rates observed among patients with stage I and II disease initially treated with chemoradiotherapy.

### Table 2. Site of Distant Recurrence by Primary Therapy and by Stage of Disease

<table>
<thead>
<tr>
<th>Site</th>
<th>Patients Who Underwent Primary Chemoradiotherapy (n = 2)</th>
<th>Patients Who Underwent Primary Surgery (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of Patients Presenting Cancer Stage</td>
<td>No. of Patients Presenting Cancer Stage</td>
</tr>
<tr>
<td>Brain</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Liver</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Lung</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Carcinomatosis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Unknown</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

*Based on Reming et al. NA indicates not applicable.*

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moradiotherapy. Use of salvage APR after local recurrence following che-

terapy. This is in part because of our success with the


Longo et al15 confirmed the salvage potential of APR after failure of initial chemo-

to of local recurrence, after treatment with primary chemoradi-

therapy. In such instances of local recurrence, APR pro-

vided effective salvage treatment with excellent disease-

free survival after medium-length follow-up. We are

vestigating the utility of salvage chemotherapy in cases

of local recurrence after primary chemoradiotherapy based

On the encouraging results of reported preliminary clinical

experience.15

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Table 3. Recurrences by Stages of Disease*

<table>
<thead>
<tr>
<th>Stage</th>
<th>All Patients</th>
<th>Local Recurrence</th>
<th>Distant Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>7 (24)</td>
<td>1 (14)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>II</td>
<td>11 (37)</td>
<td>4 (36)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>III</td>
<td>8 (27)</td>
<td>2 (25)</td>
<td>2 (25)</td>
</tr>
<tr>
<td>IV</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Unknown</td>
<td>2 (6)</td>
<td>0 (0)</td>
<td>NA</td>
</tr>
<tr>
<td>Total, No. (%)</td>
<td>30 (100)</td>
<td>7 (23)</td>
<td>2 (7)</td>
</tr>
</tbody>
</table>

*NA indicates not applicable.

In summary, our findings emphasize the need for care-

ful surveillance for recurrence, particularly local rec-

urrence, after treatment with primary chemoradio-

therapy. Despite the increased incidence of local recur-

rence, a significant improvement in overall 5-year sur-

vival was observed with the use of primary chemoradio-

therapy. This is in part because of our success with the

use of salvage APR after local recurrence following che-

moradiotherapy.

No significant difference was noted in the rates of metas-

tatic disease between the 2 groups. Furthermore, metas-

tatic disease did not exhibit any predictable pattern or

predilection that might allow for a rational fol-

low-up protocol. The observation of 2 cases of carci-

nomatosis after APR introduces the possibility of viola-

tion and contamination of the peritoneal cavity with viable

tumor cells.

Our experience confirms that the aggressive use of

radical surgical resection (APR) in cases of local recur-

rence after chemoradiotherapy provides excellent sal-

vage therapy for local control. Hughes et al14 reported on

the use of salvage APR in 6 patients with persistent dis-

case and 2 with recurrent disease with an overall 92% success in local control. Longo et al15 confirmed the sal-

vage potential of APR after failure of initial chemoradio-

therapy with a 57% 18-month mean survival time. All

reported studies using salvage APR contain too few pa-

tients to draw firm conclusions.

Despite the increased incidence of local recur-

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moradiotherapy.
DISCUSSION

Theodore E. Schrock, MD, San Francisco, Calif: The authors are to be congratulated on this retrospective review of an uncommon disease that is difficult to study prospectively at any single institution or even in multi-institutional cooperative trials. Good records, proper categorization, and statistical analysis make for an excellent contribution. The authors appropriately limited their study population to patients with ACC since carcinoma of the anal margin and any histological pattern other than epidermoid are different biologically and surgically.

The combination of chemotherapy and radiotherapy for ACC was revolutionary when introduced by Nigro in the early 1970s. Prior to that time radical extirpative surgery was the treatment of choice. Patients treated by APR not only had permanent colostomies, but also attempts to obtain wide local margins around bulky tumors sometimes led to large, slowly healing wounds or long-term disability from perineal hernias or vaginal stenosis. Further, the surgical approach sometimes was extended to include radical ilioinguinal lymphadenectomy and its attendant morbidity consequences for the lower extremities. In the 1960s many surgeons joined with their radiation oncology colleagues to treat this disease by radiotherapy, initially intended to be followed by surgical extirpation, but eventually as an alternative to excision. Nigro demonstrated that chemoradiotherapy effectively enhanced the treatment locally, regionally, and systemically, and within a short time this approach was adopted by surgeons worldwide.

The authors pose the question whether the patterns of recurrence are different if the primary treatment is surgical excision or chemoradiotherapy. In their population of 81 patients between 1952 and 1998, 51 (66%) underwent primary surgical treatment. The presenter, Dr Faysnold, dealt with my first question which is simply: why such a large proportion of these patients were treated surgically. The answer he gave us is that those were largely patients earlier in the experience.

The authors found a greater rate of local recurrence in the chemoradiation group, although it was statistically insignificant except by actuarial analysis at the 5-year point. We should recognize as a point of terminology that particularly when the initial treatment was chemoradiotherapy, we were talking about persistence of tumor here more than recurrence. Local recurrence after chemoradiotherapy was defined as a positive biopsy specimen subsequent to a negative biopsy specimen. That implies routine biopsies are performed for these patients. Since some surgeons do not obtain biopsy specimens routinely, I am curious about the authors’ recommendation.

Salvage abdominoperineal for local recurrence after chemoradiation had uniformly good outcomes over the short-term. Some groups give another course of chemoradiotherapy instead of operating on patients with local persistence or recurrence, even boosting the radiation dose quite high. Have the authors taken that approach, and what is their current protocol to treat local persistence or recurrence after chemoradiotherapy? Importantly, long-term survival was greater in patients treated by primary chemoradiation, although this comparison is weakened by the stage differences pointed out in these 2 populations.

With a small risk of overinterpreting the data, one may conclude that the authors have successfully treated patients with ACC by primary chemoradiation, followed them closely, intervened surgically for local recurrence, and thereby limited the morbidity of radical operation to a few patients without sacrifice of long-term survival in most.

One final question to the authors. Are there any patients today in whom you would choose abdominoperineal resection primarily.

Karen Deveney, MD, Portland, Ore: I too enjoyed this paper, possibly because it also agrees with the treatment that we have used over the last 20 years, primary chemoradiotherapy. It has been my experience, however, that delayed healing occurs when APR is done long after chemoradiotherapy. Can one potentially identify any subgroup, either with histological characteristics or gross characteristics such as the local extent of invasiveness, poor differentiation, cytologic subgrouping, or rapid growth rate, which might predict that they will do worse and perhaps employ APR first with postoperative chemoradiotherapy in this?

It has also been our experience that the chemotherapy can have quite toxic effects in some of these patients, especially if they are aged. Was there a standard chemotherapy regimen, and were there any significant morbidities or mortality from the chemoradiotherapy itself?

I also agree with the possible understaging in the chemoradiotherapy group and would like to ask if you are employing endorectal ultrasound better to stage these patients preoperatively at the present.

William P. Schecter, MD, San Francisco: I also enjoyed this study very much. I noticed that the period spanned 1952 to 1998, but the epidemiology of squamous cell carcinoma of the anus has changed dramatically with the AIDS [acquired immunodeficiency syndrome] epidemic and the changing demographics of the gay population. Although it is true that the biology of anal cancer is probably different than anal margin cancers noted by Dr Schrock, I believe that most cases of squamous cell carcinoma of the anus are due to sexually transmitted infection, part of the spectrum of human papillomavirus infection ranging from dysplasia to invasive cancer. I am rising to remind surgeons that gay patients who present with warts are at high risk for the development of invasive squamous cell carcinoma of the anus and should be carefully followed up and screened. I also noticed that your male-to-female ratio across this entire period was almost 1:1 whereas in the [San Francisco] Bay Area the previous sex ratio was 3:1 in favor of women, but in the last 15 years it has changed to 2:1 in favor of men. Did you notice a change in sex ratios over the period of your study?

Finally I would also like to comment about a group of patients in which I think it is not a good idea to give up front chemoradiotherapy—patients with a big Buschke-Lowenstein tumor greater than 7 or 8 cm. The Nigro protocol was really designed for tumors less than 4 cm, and I think if you have a bulky infected tumor, you do the patient a disservice by giving chemoradiotherapy first because it is much more difficult to salvage the patient without a lot of postoperative morbidity when operating in an irradiated field.

Albert D. Hall, MD, Greenbrae, Calif: Do you have patients who presented with advanced anal squamous carcinoma and bilateral groin lymph node metastases whom you treated with primary APR and groin dissections? Is it rational to consider a primary surgical approach when the anal cancer is bulky and the workup shows only groin lymph node metastases?

Dr Stabile: As you have heard, ACC is a rare disease and constitutes only a small percentage of gastrointestinal tract tumors. As Dr Schecter and others have noted, there seems to be an increasing incidence of the disease in our population that may be related to sexual transmission of human papillomavirus-16 and other viruses that might have causative roles.

We have learned over the years that there are several outcome determinants that we need to pay particular attention to. Most importantly is the stage of the disease. This is utmost in terms of planning therapy and establishing prognostic estimates. The use of endorectal ultrasound has augmented our ability to stage these patients accurately at the time of
Another outcome determinant has been sex. Historically, the female group has been much the larger and has fared better stage for stage. Males, seem to be disadvantaged, given a particular stage and a particular therapy. The treatment used is the other important determinant of outcome.

Dr Schrock gave a nice encapsulation of the history of the treatment of ACC. The early surgical results were not only deforming because the patients lost their anorectums, but they were also not particularly satisfactory for long-term outcomes. Dr Schrock mentioned the issue of whether there was persistence of disease rather than recurrence in the group treated with chemoradiotherapy. We routinely obtained biopsy specimens of all patients 6 to 8 weeks following completion of their therapeutic course, and only 2 patients were discovered by that method to actually have persistent disease. All of the other patients had initially negative biopsy specimens and were subsequently found on later follow-up to have recurrent tumors. This is not to say that there were not sampling errors, and Dr Schrock's point is well taken. Certainly some proportion of these patients who are termed recurrences may, in fact, have had persistent disease that was missed by the biopsy technique.

Dr Schrock asked about our experience with salvage chemoradiotherapy. Thus far, we have only had 2 such patients and they have been treated with salvage chemotherapy using a cisplatin-based regimen. One patient died of persistent disease 2 years later, and the other patient was lost to follow-up after completion of the salvage chemotherapy regimen.

We have not used resective therapy as the primary treatment for 12 years now. Our last patient treated primarily by surgical resection received an APR in 1988. We have since converted entirely to the chemoradiotherapy as primary therapy.

Dr Deveney wondered whether there were predictors that might help stratify patients as to risk of recurrence and we and others have found that only stage of disease seems to predict this with any statistical power. We have looked at histological and other features of the tumor, but only pathologic stage has been an accurate predictor of recurrence.

Dr Deveney questioned the morbidity of chemoradiation treatment. We have had some serious consequence of the use of the chemoradiotherapy protocol, and that was in a patient who developed renal failure and subsequently died of the complication.

Dr Schecter well enunciated the issue of sexually transmitted disease, and we routinely perform HIV [human immunodeficiency virus] testing in these patients. There seems to be a changing sex incidence in the disease. It is interesting that in our series, which differs from most in the literature, there has been a slight preponderance of male patients from the outset and throughout the series.

In terms of the bulky Buschke-Lowenstein tumors, we have not seen one recently, but I would agree with Dr Schecter that it is probably inappropriate to embark initially on a chemoradiotherapy protocol. We would do a debulking operation or a local excision prior to beginning chemoradiotherapy.

Dr Hall inquired about our use of radical lymph node dissection. We have not performed radical lymph node dissection on any of the patients in our series. I think the literature would strongly support that it is not a highly beneficial procedure in this disease, although there probably are anecdotal cases where it has provided good palliation.