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Recurrent Squamous Cell Carcinoma of the Anal Canal

Predictors of Initial Treatment Failure and Results of Salvage Therapy

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Objective
The outcomes of patients with squamous cell carcinoma of the anal canal treated by either sphincter-preserving procedures or radical surgery were evaluated, with the goals of identifying factors predicting treatment failure and quantifying results of salvage therapy in patients with recurrent disease.

Basic Procedures
A population-based study on all patients in all 159 hospitals of the Department of Veterans Affairs (VA) from 1987 to 1991 was carried out. Data were compiled from several national computerized VA data sets. Supplementary information from local tumor registrars also was obtained, including demographic information, discharge summaries, operative reports, pathology reports, and medical oncology and radiation oncology summaries. From these sources, information on tumor histology, tumor stage, tumor grade, presence of regional or distant metastases, surgical procedures, use of chemotherapy and radiation therapy (RT), toxicity of chemotherapy and RT, development of recurrent disease, treatment of recurrence, survival, and cause of death were obtained.

Main Findings
Four hundred five patients with anal cancer were identified by computer search, and 204 (51%) were evaluable; 164 of 204 (80%) had squamous cell carcinoma, 137 of whom (84%) were treated with sphincter-preserving procedures, and 27 of whom (16%) were treated by by radical surgery. One hundred fourteen of 138 (83%) were treated by multimodality therapy, which we defined as local excision followed by chemotherapy and RT. The mean dose of RT among patients treated by multimodality therapy was 4200 ± 540 cGy and 82% of those treated with multimodality therapy received 5-FU/mitomycin C. Recurrent disease was diagnosed in 43 of all 149 patients (29%) with potentially curable disease. (stages I–III) Multivariate analysis revealed that stage at diagnosis ($p = 0.04$) and method of treatment ($p = 0.03$) were the sole predictors of recurrence. Fifty-three percent of patients who underwent salvage abdominoperineal resection (APR) are alive, whereas only 19% who underwent salvage chemotherapy with or without RT are alive.

Principal Conclusions
These data indicate that multimodality therapy currently is being employed in the majority of patients with squamous cell carcinoma of the anal canal in the VA system. Tumor stage and

method of treatment appear to affect the likelihood of development of recurrent disease. Salvage APR has curative potential. Results with salvage chemotherapy and RT are disappointing.

Squamous cell carcinoma of the anal canal is an uncommon tumor that comprises 2% to 4% of malignant neoplasms of the anorectum.[1-2] Anal margin cancers, although often erroneously believed to behave like anal canal carcinomas, have a clinical course much like skin cancers in other areas and thus, carry a better prognosis than those of the anal canal. This is reflected in American Joint Committee on Cancer (AJCC) staging rules, in which anal canal lesions are considered separately from anal margin tumors.[3] For many years, the treatment of choice for anal canal carcinoma was abdominoperineal resection (APR).[4] Treatment employing APR has yielded 5-year survival rates ranging from 40% to 70%.[5-6] More recently, radical surgery as primary treatment has been superseded largely by combined chemotherapy and radiation therapy (RT), with 5-year survival rates between 60% and 80%.[7-16] Currently, radical surgery that sacrifices anorectal function usually is reserved for patients with residual or recurrent cancer after chemotherapy and RT and for patients who develop toxic side effects that result in discontinuation of treatment.

Because squamous cell carcinoma of the anal canal is relatively uncommon, and current treatment is likely to result in permanent locoregional control, few surgeons will accumulate enough experience with salvage therapy to determine which characteristics of primary therapy predispose to locoregional failure and how well patients fare after various strategies for salvage. The results achieved at Veterans Administration Medical Centers in the management of recurrent squamous cell carcinoma of the anal canal are given in this report. We evaluated TNM stage, tumor grade, and other parameters as predictors of failure, and separately assessed outcomes after various forms of treatment.

MATERIAL AND METHODS

Previously, we have described in detail the methods used to compile data on this series of patients with anal canal cancer.[17] In brief, computer-based data sets encompassing all patients in all 159 hospitals of the Department of Veterans Affairs (DVA) for the 5-year period 1987 to 1991 were the primary sources of data for this work. The Patient Treatment Files data set was abstracted for patients with International Classification of Diseases, Ninth Revision, Clinical Modification, Third Edition (ICD-9-CM)[18] diagnostic code 154.2 for anal cancer. This data allowed us to identify all 104 VA Hospitals with ≥1 patient with anal canal cancer for the period of analysis.

Next, additional data from local tumor registrars was sought from these 104 hospitals. This search was conducted by mail. We requested data that were not obtainable in computer-based data files, including demographic information, discharge summaries, operative reports, pathology reports, and medical oncology and radiation oncology summaries. Data obtained included age, sex, date of admission, diagnostic procedures, operative procedures, use of chemotherapy and radiation therapy, tumor histology, tumor size, presence of regional or distant metastases at diagnosis, toxicity from chemotherapy and radiation, development and location of recurrent disease, treatment of recurrence, additional surgical procedures, date of discharge, survival, and cause of death.

Current AJCC (Table 1) staging rules were employed to stage tumors of the anal canal.[3] Operative reports and pathology reports were scrutinized meticulously to exclude other tumors of the anal canal, such as basaloid carcinoma, adenocarcinoma, and melanoma, as well as anal margin or perianal skin cancers. Tumor grade was judged from pathology reports and reported as Grade I (well differentiated), Grade II (moderately differentiated), Grade III (poorly differentiated), or Grade IV (undifferentiated).

Some patients died in VA hospitals, and data on these individuals is available using Patient Treatment Files, a comprehensive VA data set. Another computer-based

Table 1. AJCC STAGING RULES USED FOR ANAL CANAL CANCERS

T_1 = tumor < 2 cm	
T_2 = tumor 2–5 cm	
T_3 = tumor > 5 cm	
N_0 = tumor not involved in regional lymph nodes	
N_1 = tumor involvement of regional lymph nodes	
M_0 = no distant metastases	
M_1 = distant metastases	
Stage Grouping	
Stage I	$T_1N_0M_0$
Stage II	$T_2N_0M_0$
	$T_3N_0M_0$
Stage III	$T_{any}N_1M_0$
Stage IV	$T_{any}N_{any}M_1$

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national VA data set, the Beneficiary Identification and Records Location System (BIRLS) was used to obtain further information on those who died after discharge, whether in another hospital, at home, or during a subsequent admission to a VA hospital. The BIRLS contains records of all veterans whose beneficiaries applied for death benefits at the time of death. The date of death is recorded for each veteran in whose name benefits are requested, and it is estimated that 80% to 89% of all veterans' deaths are recorded by BIRLS. The U.S. Social Security Administration death records were searched for data on those patients without a BIRLS death record, and those without a record of death in any of these three systems were assumed to be alive.

We entered all data into a computerized database. Statistical analysis of the entered data was done using the chi square test to evaluate categorical variables and analysis of variance to compare continuous variables. Statistical significance for each test was set at a probability of $p < 0.05$. To determine predictors of recurrence, logistic regression analysis was performed on all variables.

RESULTS

During the 5 years from January 1, 1987, through December 31, 1991, there were 405 patients in the DVA system with anal cancer identified from the Patient Treatment Files. Questionnaires were mailed to the 104 hospitals at which these patients received initial care. Sixty-six of the tumor registrars responded, submitting information on 221 patients. Analysis of the primary data sources on these patients was done by one of us (WEL) and yielded sufficiently complete information on 164 patients for them to be judged evaluable. These patients form the basis of this report. In all 164 patients, the histology was squamous cell carcinoma, the tumor location was anal canal, and data on tumor stage, treatment, and survival was suitable for analysis. The mean age of all patients was 59 ± 11 years. There were 162 men (99%) and 2 (1%) women. One hundred forty-eight (90%) patients were white and 16 (10%) were black. At the time of diagnosis, 69 patients (42%) were married, 39 (24%) were divorced, 12 (7%) were separated, 15 (9%) were widowed, and 29 (18%) had never been married. Patients were treated initially by one of the following seven regimens: 1) local excision only; 2) local excision and postoperative RT; 3) local excision and postoperative chemotherapy; 4) local excision followed by postoperative chemotherapy plus RT, which we refer to as multimodality therapy in this report; 5) APR only; 6) APR and postoperative RT; 7) APR followed by postoperative chemotherapy plus RT. (Table 2)

Sphincter Preservation

Stage I

There were 73 patients with stage I disease initially treated by sphincter-preserving procedures. Fifty-nine of the 73 (81%) were treated by local excision followed by chemotherapy plus RT, 9 (12%) were treated by local excision only, and 5 (7%) were treated by local excision plus RT.

Of the 59 patients with stage I disease treated by local excision followed by chemotherapy plus RT, 19 (32%) had grade I tumors, 17 (29%) had grade II tumors, and 11 (19%) had grade III tumors; in 12 of the 59 (20%), initial tumor grade was unavailable. These 59 patients receiving local excision followed by chemotherapy plus RT were treated as follows: The mean dose of radiation was 4130 ± 1300 cGy. Eleven (19%) developed major toxicity from RT, and 9 (15%) had RT interrupted; however, 51 of the 59 (86%) eventually completed RT. Fifty-one received 5-FU/mitomycin C, whereas eight received other chemotherapy regimens. Fifty-three (90%) completed chemotherapy. Eleven (19%) developed recurrent anal cancer. Six of these 11 recurrences were local, 2 were in the groin lymph nodes, and 3 were in distant organs. Three of the 11 patients with recurrences did not complete therapy (one failed to complete chemotherapy and two failed to complete RT). Five of the 11 patients with recurrences had tumors that were initially grade I, three had tumors that were initially grade II, two had tumors that were grade III, and in one, the initial grade was unknown. Four of the patients with locally recurrent cancer underwent salvage APR for failed chemotherapy and RT, and two died of metastatic anal cancer. The mean survival of these four patients after proctectomy was 16 months. Two of 11 patients underwent a diverting stoma without therapy directed at tumor recurrence, and both died. Five of the 11 were treated for recurrent disease with further chemotherapy and RT without any additional surgery. Currently, one is alive. The mean survival in this group was 10 months. Eleven of the 59 patients (19%) treated initially with local excision followed by chemotherapy and RT died; in 8, death was uniformly due to cancer. The mean survival of these 59 patients was 39 months.

Five of the 73 patients with stage I cancer receiving sphincter-preserving therapy were treated by local excision followed by RT alone. Two of these five patients had grade I tumors, two had grade II lesions, and in one, the grade was unknown. The mean dose of RT in these five patients was 5100 ± 200 cGy. One patient developed significant perianal dermatitis, but all patients completed RT. One (initial grade II) developed a recurrence. He was treated by local excision of his recurrence and further chemotherapy. All five patients currently are alive. The

Table 2. RESULTS OF PRIMARY TREATMENT IN 164 EVALUABLE PATIENTS WITH POTENTIALLY CURABLE (149/164) SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL STRATIFIED BY STAGE

Stage	Treatment	No. of Patients	Location of Failure		
			Local	Groin	Distant
Stage I (N = 78)	LE	9 (12%)	4/9 (44%)	0/9 (0%)	0/9 (0%)
	LE + RT	5 (6%)	1/5 (20%)	0/5 (0%)	0/5 (0%)
	LE + CH	0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
	MM	59 (76%)	6/59 (11%)	2/59 (3%)	3/59 (5%)
	APR	1 (1%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
	APR + RT	4 (5%)	1/4 (25%)	0/4 (0%)	0/4 (0%)
	APR + CH + RT	0 (0%)	0 (0%)	0/0 (0%)	0/0 (0%)
Stage II (N = 59)	LE	3 (5%)	3/3 (100%)	0/3 (0%)	0/3 (0%)
	LE + CH	2 (3%)	0/2 (0%)	0/2 (0%)	1/2 (50%)
	LE + RT	1 (2%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
	MM	37 (63%)	15/37 (41%)	0/15 (0%)	0/15 (0%)
	APR	5 (8%)	0/5 (0%)	0/5 (0%)	0/5 (0%)
	APR + RT	4 (7%)	1/4 (25%)	1/4 (25%)	1/4 (25%)
	APR + CH + RT	7 (12%)	2/7 (29%)	0/7 (0%)	2/7 (29%)
Stage III (N = 12)	LE	1 (8%)	1/1 (100%)	0/1 (0%)	0/1 (0%)
	LE + RT	0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
	LE + CH	0 (0%)	0/0 (0%)	0/0 (0%)	0/0 (0%)
	MM	6 (50%)	0/6 (0%)	1/6 (17%)	2/6 (33%)
	APR	1 (8%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
	APR + RT	1 (8%)	0/1 (0%)	0/1 (0%)	0/1 (0%)
	APR + CH + RT	3 (25%)	1/3 (33%)	0/3 (0%)	0/3 (0%)

LE = local excision; RT = radiation therapy; CH = chemotherapy; MM = LE + RT + CH; APR = abdominal resection.

mean survival time for patients in this subgroup was 37 months.

Nine of the 73 patients were treated by local excision only. Two had grade I cancer, four had grade II lesions, one had grade III, and the tumor in two patients was of unknown grade. Four (44%) patients developed a local recurrence; in one of these four, the tumor was originally grade I, two had a tumor of initial grade II, and in one, the original grade was unknown. One of the four was treated with fecal diversion and died 6 months after surgery. One was treated by salvage APR and currently is alive 11 months after proctectomy. Two were treated by RT and chemotherapy after further local excision and are both dead; one death was secondary to anal cancer. Overall, six of the 9 patients currently are alive. The mean survival time for patients in this subset was 33 months.

Stage II

There were 43 patients with stage II disease treated by sphincter-preserving procedures. Patients were treated as follows: 37 of 43 (86%) were treated by local excision followed by chemotherapy plus RT; two (5%) were treated by local excision followed by chemotherapy; three (7%) were treated by local excision alone and one (2%) received local excision followed by RT only.

The grade of the tumors in 37 patients treated by local excision followed by RT and chemotherapy was grade I in 9 of 37 (24%), grade II in 18 (49%), grade III in 3 (8%), and unknown in 7 (19%). The mean RT dose was 4160 ± 1300 cGy. Fourteen (13%) developed major toxicity from RT and 5 (36%) had RT interrupted; however, 31 (84%) eventually completed RT. One patient died from causes other than anal canal cancer before completing RT. Thirty patients received 5-FU/mitomycin C, whereas seven received other chemotherapy regimens. Thirty-three (89%) completed chemotherapy. Fifteen of the 37 patients receiving local excision plus RT and chemotherapy (41%) developed recurrence. Three of the 15 patients had not completed initial therapy. Ten of the 15 patients underwent salvage APR and six currently are alive. The mean survival after proctectomy of all ten patients was 20 months. Two of the 15 patients (one with an initial grade II tumor and one with a tumor of unknown grade) underwent fecal diversion; both died. Three of the 15 patients (two with initial grade II lesions and one with a tumor of unknown grade) were treated by further local excision and additional RT and chemother-

apy; one of the three currently is alive. Overall, 11 of the 37 patients in this subset died; all but three of the deaths were secondary to anal canal cancer. The mean survival time for patients in this subset was 31 months.

Two of 43 patients (5%) were treated by local excision followed by 5-FU/mitomycin C without RT. Both completed chemotherapy and no additional surgery was required. One of the two with an initial grade III tumor developed liver metastases, received no further therapy, and died. The one patient with a grade II cancer currently is free of disease.

Three of 43 patients were treated by local excision alone, and all three developed a recurrence. One of these three initially had a grade II carcinoma; he was treated with salvage APR and died of anal canal cancer 7 months after proctectomy. The second of three (grade II) was treated by local excision and chemotherapy plus RT, but died before completing RT. The third patient (unknown grade) died of other causes with metastatic anal cancer.

One of 43 patients (grade II) was treated by local excision followed by RT. He received 4200 cGy without toxicity, developed a recurrence, which was treated by APR, and died of anal cancer 20 months after proctectomy.

Stage III

There were seven patients with stage III disease treated with sphincter-preserving procedures. One of the seven (unknown grade) underwent local excision only. He developed a local recurrence, was treated with further RT and chemotherapy, and currently is alive.

The remaining six patients were treated by local excision followed by chemotherapy and RT. The initial tumor grade in these six patients was grade I in one (17%), grade II in four (66%) and grade III in one (17%). The mean dose of RT was 3980 ± 460 cGy. Three patients developed RT toxicity; one had RT interrupted, but all completed RT. Four were treated by 5-FU/mitomycin C; two were treated with other chemotherapy combinations. Three of the patients, all with initial tumor grade II, developed recurrent disease, one in the groin and two in distant sites. All three patients were treated with further chemotherapy only, and all three patients died of anal canal cancer.

Radical Surgery

Stage I

There were five patients with stage I disease treated initially by radical surgery after tissue diagnosis.

One patient with a grade II carcinoma was treated by APR followed by 4440 cGy of RT. He currently is alive without evidence of disease.

Four patients were treated by APR, followed by chemotherapy plus RT. The mean dose of RT was 4730 ± 850 cGy. There was no radiation toxicity, and all completed RT. All four patients received and completed 5-FU/mitomycin C. One patient whose tumor was initially grade II developed a recurrence. He received no further treatment and died of widely metastatic disease. The remaining three, all with grade I neoplasms, currently are alive without evidence of disease.

Stage II

There were 16 patients with stage II disease who were treated primarily by radical surgery. Seven of the 16 in this subset were treated by APR followed by chemotherapy plus RT. The mean dose of RT was 4080 ± 950 cGy. Three patients developed toxicity from RT, three had RT interrupted, and five completed RT. Six patients received 5-FU/mitomycin C; one received 5-FU only. One patient developed toxicity from chemotherapy and did not complete his planned regimen. Four of the seven patients (two with initial grade II tumors and two with grade III) developed recurrences. All four received further chemotherapy. Three of the four died. The mean survival time for all seven patients in this group was 32 months.

Five of the 16 patients were treated by APR only. One had a grade I cancer and four had grade II lesions. Among all five patients, there was no recurrent anal canal cancer and no further surgery, and all five are alive. The mean survival time for these 16 patients was 29 months.

Four of the 16 patients were treated by APR plus RT. The mean dose of RT in these four was 4470 ± 1500 cGy. All four patients tolerated and completed RT. Three (one with a grade II lesion initially and two with grade III) developed recurrences, were treated by further RT and chemotherapy, and died. One of the four with a grade II tumor currently is alive without recurrence.

Stage III

There were five patients with stage III disease treated with radical surgery. Three of the five were treated by APR followed by RT and chemotherapy. The mean dose of RT was 4880 ± 600 cGy. There was no toxicity, and all completed RT. All patients received 5-FU/mitomycin C. One with an initial grade III tumor developed a recurrence, was treated with further chemotherapy, and died. Two (one with grade I and one with grade II cancers) currently are alive.

One patient (unknown grade) was treated by APR only and currently is free of disease. One patient (grade II) was treated by APR and 4980 cGy of postoperative RT, but died of other causes without evidence of metastatic disease.

Patients with Distant Metastatic Disease at time of Diagnosis

Fifteen patients had distant metastases at the time of initial diagnosis of anal canal cancer (stage IV disease). Fourteen were treated by sphincter-preserving procedures. Three patients (21%) had grade I tumors, nine (64%) had grade II lesions, and in two (14%), the grade was unknown. Two of the 14 patients were treated by local excision only. Twelve were treated by local excision followed by chemotherapy plus RT. The mean dose of RT was 4230 ± 540 cGy. Four patients developed RT toxicity, six had RT interrupted and eight completed RT. Two had RT interrupted for reasons not related to toxicity. Nine patients received 5-FU/mitomycin C, and three had other regimens. Four patients completed chemotherapy. No patient was ever tumor-free in this group, and 11 patients died of metastatic anal canal cancer. One of the 15 patients with stage IV disease (grade II) was treated by APR, 5-FU, and 4870 cGy of RT. He died of metastatic cancer.

Results of Salvage Therapy for Recurrent Anal Canal Carcinoma

Salvage APR

Seventeen patients underwent salvage APR to treat recurrence after initial sphincter-preserving procedures. Two patients underwent APR after initial local excision only; one (50%) is alive at 15 months, and the other died. One of the 17 patients underwent APR after failure of local excision and RT and died of anal canal cancer 20 months after surgery. Fourteen patients underwent APR after failure of initial chemotherapy and RT. Eight patients (57%) currently are alive with a mean survival time of 18 months.

Salvage Chemotherapy Plus RT

Fifteen patients underwent salvage chemotherapy and RT. Twelve patients underwent salvage chemotherapy and RT after initial sphincter-preserving procedures. Eight patients developed recurrences after failed primary chemotherapy and RT. Five patients underwent further chemotherapy plus RT for local recurrences in the anal canal. Three underwent groin dissection followed by further chemotherapy plus RT for recurrence in the groin. Two currently are alive, and the mean survival time of all eight patients was 16 months. Four of the 15 patients developed local recurrences after initial local excision only and were treated with subsequent chemotherapy plus RT. One of these four (25%) is alive at 27 months. Three of the 15 patients underwent salvage chemotherapy and RT after radical surgery. One is alive 15 months after groin dissection and salvage chemotherapy and RT after initial APR and chemotherapy plus RT. Two patients died after salvage chemotherapy and RT after local failure of initial APR and chemotherapy plus RT.

Salvage Chemotherapy

Four patients who developed liver metastases after initial sphincter-preserving procedures were treated with further chemotherapy. Three died, with a mean survival time of 9 months. Five patients developed liver metastases after radical surgery. One patient currently is alive with persistent liver metastases after salvage chemotherapy. The mean survival time of these four patients was 12 months.

Others

Five patients (four of five after primary chemotherapy plus RT and one of five after local excision) underwent a diverting stoma only for large anal recurrences without therapy, addressing the primary tumor. One patient who developed a groin recurrence after primary chemotherapy without RT and received no further treatment. One patient who developed liver metastases after sphincter-preserving procedures received no further treatment. One patient who developed liver metastases after APR, chemotherapy, and RT received no further treatment. All of these patients have died or have persistent cancer.

Logistic Regression Analysis

In an attempt to identify significant predictors of recurrence, a multivariate logistic regression analysis was performed. The purpose was to construct a parsimonious model with the ability to predict the dichotomous dependent variable recurrence while minimizing the data required to do so. A backward, stepwise method was used with the initial model consisting of age, tumor grade, tumor stage, type of treatment, dose of RT, specific type of chemotherapy, whether treatment had been completed, and whether the VA had a university affiliation. Stepwise analysis reduced the model to only stage and type of treatment, of which both stage ($p = 0.04$) and method of treatment ($p = 0.03$) were significant predictors of recurrence. Age, tumor grade, dose and duration of RT, whether therapy was completed and university affiliation were not predictors of recurrence. Overall, the percent predicted correctly by the reduced model was 68%. Ten patients were predicted incorrectly to develop recurrence and 28 patients were predicted incorrectly not to develop recurrence. The goodness-of-fit was not significant, indicating that the reduced model did not differ significantly from the perfect model. Other variations of the model were constructed, but no other variation predicted as well with as few variables as the one reported here.

DISCUSSION

Surgery, usually APR, was the earliest effective treatment for anal cancer. Beahrs[4] reported in 1976 on 47 patients who underwent APR for anal cancer, with 57% and 40% 5-year and 10-year survival rates, respectively. Among 103 patients reported from Memorial Sloan-Kettering Cancer Center,[19] the overall absolute 5-year survival rate was 55%. Patients with low-stage lesions fared much better than those with high-stage tumors. Boey[20] reported an encouraging 69% 5-year survival rate among patients who underwent APR, of whom 40% were patients with metastases to inguinal or mesenteric nodes. Salmon,[21] combining both initial RT and APR, reported that 50% of patients were alive with no evidence of disease after 5+-year follow-up. Pinna-Pintor[22] reported a 62% 5-year survival rate among 94 cases treated by radical surgery. Tumor stage predicted outcome in the current study. These studies demonstrated that tumor stage affects the probability of survival after APR, and that one can expect a 50+% survival rate after APR in suitable patients.

Radiation therapy, as a definitive treatment, was the next form of effective therapy developed and has been popular since the 1920s.[23] Dalby[24] reported a 5-year survival rate of 44% in a series of 106 patients treated with interstitial radium needles. Cummings[25] et al. reported on a series of 51 patients treated with primary RT, with surgery reserved for those who had residual carcinoma. The 5-year survival rate was 59%; RT alone controlled disease in 29 of 51 patients. Papillon,[26] in a report of 64 patients treated with external beam and interstitial RT, found a 68% 5-year disease-free survival rate. His large experience with this modality led him to recommend brachytherapy for T_1 and T_2 lesions and 3000 cGy of external beam therapy with or without APR for T_3 and T_4 lesions.

Concomitant chemotherapy plus RT is used widely to treat epidermoid cancers of the anal canal. The drugs combined most frequently with radiotherapy are 5-FU and mitomycin, but cisplatin and bleomycin also are active agents and have been incorporated into other protocols. Although randomized trials comparing RT plus chemotherapy with radical RT alone have not been completed, nonrandomized studies have suggested that some drug and RT combinations appear to be superior to RT alone.[12,14] Combined modality therapy protocols without initial APR have resulted in 5-year survival rates of 65% to 80%; approximately 85% of patients retain anorectal function when the primary tumor is controlled by a combination of chemotherapy and RT.

Multimodality therapy (chemotherapy and RT) has become the most common primary treatment of squamous cell carcinoma of the anal canal since Nigro's initial report.[7] His subsequent studies[8] on 28 patients demonstrated that 3000 cGy and 5-FU infusion plus bolus mitomycin C gave encouraging results. These findings have been confirmed largely by others.[27-32] A recent randomized multicenter trial demonstrated that if mitomycin C is omitted, the recurrence rate increases.[33]

Table 3. STAGE AND TUMOR GRADE* OF 164 EVALUABLE PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL

Stage	Tumor Grade	No. of Patients
Stage I (N = 78)	Grade I	24/78 (31%)
	Grade II	26/78 (33%)
	Grade III	12/78 (15%)
	Grade unavailable	16/78 (21%)
Stage II (N = 59)	Grade I	11/59 (19%)
	Grade II	28/59 (47%)
	Grade III	7/59 (12%)
	Grade unavailable	13/59 (22%)
Stage III (N = 12)	Grade I	2/12 (17%)
	Grade II	6/12 (50%)
	Grade III	2/12 (17%)
	Grade unavailable	2/12 (17%)
Stage IV (N = 15)	Grade I	4/15 (27%)
	Grade II	9/15 (60%)
	Grade III	0/15 (0%)
	Grade unavailable	2/15 (13%)
All stages (N = 164)	Grade I	41/164 (25%)
	Grade II	69/164 (42%)
	Grade III	21/164 (13%)
	Grade unavailable	33/164 (20%)

* A grade I–IV staging system was used in this analysis; no patients with fully anaplastic tumors were encountered in this series.

The demographics in our study were not surprising. The majority of patients were older white men who currently are or had been married. Eighteen percent had never been married. The 164 patients with squamous cell carcinoma represents 80% of the 204 patients with all histological types of anal cancer from the evaluable patient population during the time frame of this analysis.

The majority of patients had stage I lesions (Table 3). Nine percent had stage IV tumors, which are incurable with current therapy. The majority of patients (N = 114, 70%) were treated by primary chemotherapy and RT (Table 2). The combination of chemotherapy and RT appeared to improve survival when compared with local excision, radiotherapy, or chemotherapy as single modalities. The number of patients receiving chemotherapy alone were too small to allow for any statistical analysis. Twenty-six patients with potentially curable disease underwent APR as primary therapy; 20 of 26 also received postoperative adjuvant RT with or without chemotherapy. The addition of both chemotherapy and RT to rad-

Table 4. OUTCOME IN 84 PATIENTS TREATED INITIALLY BY LOCAL EXCISION FOLLOWED BY RADIATION THERAPY AND CHEMOTHERAPY IN WHOM BOTH TUMOR STAGE AND TUMOR GRADE WERE AVAILABLE

	Percent Alive			
Stage	Grade I	Grade II	Grade III	p*
I	13/17 (76%)	15/19 (79%)	9/12 (75%)	NS
II	9/9 (100%)	15/18 (83%)	2/3 (67%)	NS
III	0/1 (0%)	2/4 (50%)	0/1 (0%)	NS

* Paired student's t-test; NS = not significant.
Patients with Stage IV disease were considered incurable and not included in this analysis.

ical surgery did not appear to reduce the probability of death when compared with APR without postoperative adjuvant therapy or radical surgery plus RT alone.

Among the 114 patients treated by primary chemotherapy and RT, nearly 50% had stage I lesions. More than 90% of patients with stage I and stage II lesions completed therapy. Not surprisingly, the highest recurrence rate was found among stage II lesions. Multiple regression analysis indicates that the percentage of patients who remained alive was predicted by the stage of the primary lesion, reconfirming the importance of correct tumor staging in patient management. The mean dose of radiation received was comparable among all clinical stages, suggesting that treatment intensity does not account for the difference in outcomes among stages. Radiation-related toxicity ranged between 21% and 56%, but 88% of patients completed RT. Although tumor stage at diagnosis predicted survival, tumor grade did not. (Table 4).

The overall outcomes of all forms of treatment are depicted in Table 5. Currently, 75% of patients with potentially curable disease who underwent local excision followed by chemotherapy and RT are alive, whereas 57% of those who underwent APR alone or with postoperative adjuvant therapy (chemotherapy and/or RT) are living. Among those 108 patients currently alive, 13% have residual disease. In those patients who underwent an additional surgical procedure (APR) for salvage after developing recurrence, 53% are alive.

A similar study examining multiple modalities of treating anal cancer was reported by Hughes.[34] Among 70 patients with epidermoid carcinoma of the anus over a 9-year period, five treatment groups were analyzed. The groups consisted of either wide local excision with postoperative RT, APR with either preoperative or postoperative RT, RT alone, RT with continuous 5-FU infusion, and patients treated for recurrent disease. Abdominoperineal resection and RT resulted in an overall 5-year survival rate of 77% (median follow-up = 48 months). All patients treated by wide local excision and RT and 75% of patients in a protocol using chemotherapy and RT enjoyed a complete clinical response. The colostomy-free local control rate with chemotherapy and RT was $^{16}/_{24}$ (67%). local control across all stages was 50% for those patients receiving 4500 to 4900 cGy and 90% for patients receiving ≥ 5500 cGy, but was not correlated with total 5-FU dose in Hughes series. Abdominoperineal resection was performed to salvage six patients with persistent disease and two with recurrent disease, resulting in an overall local control rate of 92% ($^{22}/_{24}$). The actuarial survival was 96% at a follow-up time of 14

Table 5. OUTCOME OF PRIMARY TREATMENT OF 164 EVALUABLE PATIENTS WITH SQUAMOUS CELL CARCINOMA OF THE ANAL CANAL, BY STAGE

Stage	Treatment	Percent Alive
Stage I (N = 78)	Local excision only (N = 9)	6/9 (67%)
	Local excision plus RT (N = 5)	5/5 (100%)
	Multimodality therapy (N = 59)	48/59 (81%)
	APR plus RT (N = 1)	1/1 (100%)
	APR plus chemotherapy and RT (N = 4)	3/4 (75%)
Stage II (N = 59)	Local excision only (N = 3)	0/3 (0%)
	Local excision plus chemotherapy (n = 2)	1/2 (50%)
	Local excision plus RT (N = 1)	0/1 (100%)
	Multimodality therapy (N = 37)	26/37 (70%)
	APR only (N = 5)	5/5 (100%)
	APR plus RT (N = 4)	1/4 (25%)
	APR plus chemotherapy and RT (N = 7)	4/7 (57%)
Stage III (N = 12)	Local excision only (N = 1)	1/1 (100%)
	Multimodality therapy (N = 6)	3/6 (50%)
	APR only (N = 1)	1/1 (100%)
	APR plus RT (N = 1)	0/1 (0%)
	APR plus chemotherapy and RT (N = 3)	2/3 (6%)
Stage IV (N = 15)	Local excision only (N = 2)	0/2 (0%)
	Multimodality therapy (N = 12)	1/12 (8%)
	APR plus RT and chemotherapy (N = 1)	0/1 (0%)

Multimodality = local excision followed by chemotherapy and RT.

months. For the entire patient group, minor late complications occurred in 23%, and major complications occurred in 9%.

A number of prognostic factors have been examined to determine outcome after potentially curative therapy for anal canal cancer. Clinical T stage has been correlated with prognosis. Metastases to locoregional lymph nodes (N stage) is an indicator of a poor prognosis. Histologic features, such as tumor grade, have prognostic value in some tumor types, although our logistic regression analysis suggests that it is not important in anal cancer. Goldman[35,36] found that tumor differentiation had independent prognostic value, although Shepherd[37] found grade to have only marginal prognostic significance. In other epidermoid cancers, such as head and neck carcinomas, histological grade is of much less prognostic value than TNM stage.[38] Surprisingly, our analysis suggests that failure to complete RT or chemotherapy was not a predictor of recurrence.

One of the current controversies in this disease is the way to manage patients who fail multimodality therapy; we devoted considerable effort in this study to evaluating outcomes in this patient subset. Abdominoperineal resection often can be offered, but it does not salvage most individuals. Additional treatment with the chemotherapy with RT offers considerable promise, as demonstrated in a recent large controlled trial[33]; however, results were quite disappointing in the current analysis. Other investigators have suggested that drugs known to be active in squamous cell carcinoma in salvage therapy, such as cisplatin, bleomycin, vincristine, and methotrexate, may be beneficial regimens.[39–45] Brachytherapy combined with further external radiation also has been used successfully for recurrent disease.[46] Our series, like others,[47] demonstrates that salvage APR has curative potential (Table 6).

This national study from the DVA reflects the current trends in the treatment of squamous cell carcinoma of the anal canal. The majority of patients (70%) were treated by primary chemotherapy and RT. Eighty-eight percent of patients completed primary chemotherapy and RT. Most patients tolerated this therapy well, with an acceptable rate and severity of toxicity. The variation in regimens used within various institutions presumably reflects individual physician bias or protocols under evaluation.

Thirty percent of patients did not receive primary chemotherapy and RT as definitive treatment. Fifteen patients (10%) were treated by local excision alone. Our analysis suggests that this form of treatment has no role as potentially-curative therapy for squamous cell carcinoma of the anal canal, although it may be acceptable for squamous cell carcinoma of the anal margin. Local excision with radiotherapy also is touted as potentially curative therapy for squamous cell carcinoma, although the addition of chemotherapy to this regimen seems to yield results that are superior to those of RT alone. It appears from our analysis, and others, that APR with or without adjuvant therapy is suitable as definitive treatment in noncompliant patients and those patients not anticipated to tolerate chemotherapy and RT. Local control and survival rates similar to or better than those achieved with chemotherapy and RT may be anticipated with APR.

Table 6. OUTCOME IN 14 PATIENTS INITIALLY TREATED WITH EXCISION PLUS CHEMOTHERAPY PLUS RT WITH CURATIVE INTENT WHO UNDERWENT SALVAGE ABDOMINOPERINEAL RESECTION FOLLOWING TUMOR RECURRENCE, STRATIFIED BY INITIAL TUMOR STAGE

Initial TNM Stage	No. of Patients	No. Alive	Survival (Duration)*
I	4	2/4	16 months
II	10	6/10	20 months
III	0	N/A	N/A

* Mean survival duration following APR.

Multimodality therapy in the form of local excision with chemotherapy and RT appears to offer the greatest chance of successful therapy while avoiding a colostomy. Abdominoperineal resection offers a similar likelihood of disease-free outcome, with sacrifice of sphincter function and resultant colostomy. Local excision alone does not have curative potential as single-modality treatment of squamous cell carcinoma of the anal canal. Recurrence of disease after adequate primary therapy is related significantly to tumor stage. For those patients who suffer recurrence after adequate sphincter-sparing therapy, salvage APR offers a chance for cure.

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