Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal

A Randomized Controlled Trial

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Context Chemoradiation as definitive therapy is the preferred primary therapy for patients with anal canal carcinoma; however, the 5-year disease-free survival rate from concurrent fluorouracil/mitomycin and radiation is only approximately 65%.

Objective To compare the efficacy of cisplatin-based (experimental) therapy vs mitomycin-based (standard) therapy in treatment of anal canal carcinoma.

Design, Setting, and Participants US Gastrointestinal Intergroup trial RTOG 98-11, a multicenter, phase 3, randomized controlled trial comparing treatment with fluorouracil plus mitomycin and radiotherapy vs treatment with fluorouracil plus cisplatin and radiotherapy in 682 patients with anal canal carcinoma enrolled between October 31, 1998, and June 27, 2005. Stratifications included sex, clinical nodal status, and tumor diameter.

Intervention Participants were randomly assigned to 1 of 2 intervention groups: (1) the mitomycin-based group (n=341), who received fluorouracil (1000 mg/m^2 on days 1-4 and 29-32) plus mitomycin (10 mg/m^2 on days 1 and 29) and radiotherapy (45-59 Gy) or (2) the cisplatin-based group (n=341), who received fluorouracil (1000 mg/m^2 on days 1-4, 29-32, 57-60, and 85-88) plus cisplatin (75 mg/m^2 on days 1, 29, 57, and 85) and radiotherapy (45-59 Gy; start day=day 57).

Main Outcome Measures The primary end point was 5-year disease-free survival; secondary end points were overall survival and time to relapse.

Results A total of 644 patients were assessable. The median follow-up for all patients was 2.51 years. Median age was 55 years, 69% were women, 27% had a tumor diameter greater than 5 cm, and 26% had clinically positive nodes. The 5-year disease-free survival rate was 60% (95% confidence interval [CI], 53%-67%) in the mitomycin-based group and 54% (95% CI, 46%-60%) in the cisplatin-based group (P=.17). The 5-year overall survival rate was 75% (95% CI, 67%-81%) in the mitomycin-based group and 70% (95% CI, 63%-76%) in the cisplatin-based group (P=.10). The 5-year local-regional recurrence and distant metastasis rates were 25% (95% CI, 20%-30%) and 15% (95% CI, 10%-20%), respectively, for mitomycin-based treatment and 33% (95% CI, 27%-40%) and 19% (95% CI, 14%-24%), respectively, for cisplatin-based treatment. The cumulative rate of colostomy was significantly better for mitomycin-based than cisplatin-based treatment (10% vs 19%; P=.02). Severe hematologic toxicity was worse with mitomycin-based treatment (P<.001).

Conclusions In this population of patients with anal canal carcinoma, cisplatin-based therapy failed to improve disease-free-survival compared with mitomycin-based therapy, but cisplatin-based therapy resulted in a significantly worse colostomy rate. These findings do not support the use of cisplatin in place of mitomycin in combination with fluorouracil and radiotherapy in the treatment of anal canal carcinoma.

Trial Registration clinicaltrials.gov Identifier: NCT00003596

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ANAL CANAL CARCINOMA IS AN uncommon malignancy in the United States. Among 1 437 180 new cancer diagnoses projected for the year 2008, approximately 5070 will be new cases of anal canal carcinoma.[1] Anal canal carcinoma has a unique clinical biology that can be distinguished from all other gastrointestinal cancers. It is mostly a local-regional cancer, with a metastatic potential in only 15% of patients,[2] and it is highly sensitive to concurrent chemoradiation,[3] resulting in a cure in 60% of cases. The size of the primary tumor has a direct bearing on the cure rates,[4-6] and the 5-year survival rates decrease precipitously for tumors larger than 5 cm in diameter.[7] Similarly, the presence of nodal metastases results in a reduction in the cure rate.[4,8-10] In addition, with larger primary cancers, the likelihood of lymph node metastases increases.[11-14] Approximately 25% of newly diagnosed anal canal carcinomas are larger than 5 cm in diameter and clinically node-positive.

See also Patient Page.

It has been established that chemoradiation is more effective therapy for smaller anal canal carcinomas than for larger ones. This suggests that a strategy that could reduce the burden of cancer in the primary

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tumor and in the lymph node(s) prior to administration of chemoradiation could potentially be quite effective. For the current study, it was hypothesized that disease-free survival might be improved by administering active induction chemotherapy (that would down-stage or downsize cancer) prior to concurrent chemoradiation.

Previous randomized phase 3 trials have established that concurrent chemoradiation with fluorouracil and mitomycin is superior to radiotherapy alone.[15,16] A prior US phase 3 randomized trial (Radiation Therapy Oncology Group [RTOG]/Eastern Cooperative Oncology Group [ECOG]) had demonstrated significant improvement in local control and colostomy-free survival with the addition of mitomycin to concurrent fluorouracil plus radiotherapy[16] and established the use of concurrent fluorouracil-mitomycin plus radiation as the standard primary therapy of local or local-regional anal canal carcinoma. An updated analysis of this trial showed that the 5-year disease-free survival rate after treatment with concurrent fluorouracil-mitomycin plus radiation was approximately 63%.[17] This 63% disease-free survival rate served as the benchmark for the US Gastrointestinal Intergroup RTOG 98-11 trial.

At conception of the Intergroup RTOG 98-11 trial, there was considerable interest in cisplatin as a radiation sensitizer for anal canal carcinoma.[18-21] In addition, 2 studies had piloted the use of induction fluorouracil and cisplatin in patients with anal canal carcinoma with encouraging results.[22,23]

The Intergroup RTOG 98-11 trial was a comparison between (1) fluorouracil plus cisplatin induction chemotherapy followed by the same chemotherapy and concurrent radiation (experimental group) and (2) fluorouracil plus mitomycin and concurrent radiation (control group). Disease-free survival was the primary end point.

METHODS

Organization

The US Gastrointestinal Intergroup RTOG 98-11 trial was coordinated by the RTOG, with participation by the ECOG, Cancer and Leukemia Group B, North Central Cancer Treatment Group, and Southwest Oncology Group.

Hypothesis and Objectives

We hypothesized that induction chemotherapy with fluorouracil and cisplatin would reduce the volume of the primary tumor and that the ensuing concurrent chemoradiation (experimental group) would be more effective for local control and colostomy-free survival compared with traditional up-front concurrent chemoradiation with fluorouracil-mitomycin (control group). The primary objective of this study was to observe an increase in the 5-year disease-free survival rate from 63% to 73%. The major secondary objectives were to detect a 5% or greater difference in the 2-year colostomy rate and to detect a 12% or greater difference in nonhematologic grade 3 or 4 toxic effects.

Patient Eligibility

The protocol was approved by the institutional review board of each participating institution, and all participants provided written informed consent. All patients with histologically documented squamous, basaloid, or cloacogenic carcinoma of the anal canal were eligible if they were at least 18 years of age, had a Karnofsky performance score of at least 60%, had category T2 to T4 tumors (T2=diameter of the primary cancer >2 cm but <5 cm; T3=>5 cm; and T4=invading adjacent organs) with any N category (pelvic or inguinal defined by clinical examination, biopsy, or imaging studies), had adequate organ function, and were willing to provide written consent.

Patients were excluded if they had a T1 or M1 tumor, severe comorbid conditions (including AIDS), or major malignancy (unless successfully treated and disease-free for at least 5 years).

Evaluation

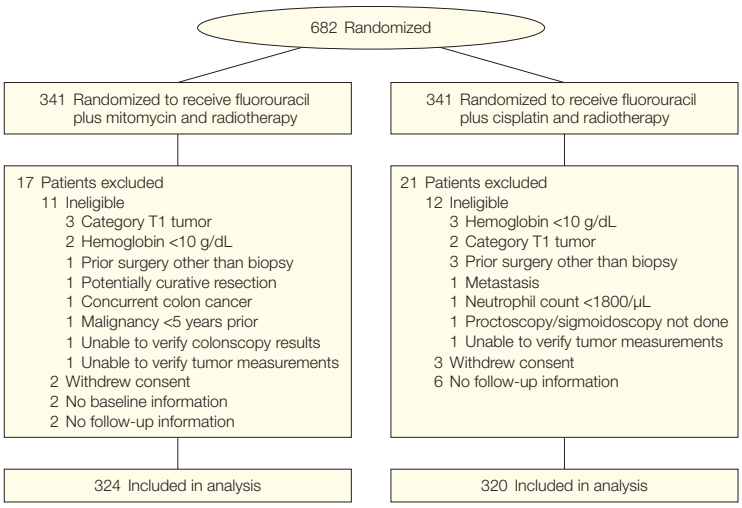
Prior to any therapy, patients had proctoscopy or sigmoidoscopy, chest radiography, and computed tomography or magnetic resonance imaging of the abdomen/pelvis to establish the stage of disease. In addition, blood and serum chemistry evaluations were performed to determine the adequacy of hepatic, renal, and bone marrow functions. Eight weeks after therapy, patients underwent reevaluation similar to baseline except that a full-thickness biopsy was optional. Local-regional treatment failure was defined as histologically documented persistent or recurring cancer in the treated radiation field. Patients were followed up every 3 months for 1 year, every 6 months for the second year, then yearly.

Randomization, Stratification, and Therapy

This study was not blinded. Patients were stratified according to sex, clinical nodal status (positive or negative), and size of the primary tumor (>2-5 cm or >5 cm). Patients were randomly assigned to receive fluorouracil plus mitomycin and concurrent radiation (the control [mitomycin-based] group) or induction fluorouracil plus cisplatin followed by concurrent fluorouracil-cisplatin and radiation (the experimental [cisplatin-based] group) according to the Zelen[24] permuted block randomization method, which ensures that the institutions have the opportunity to treat patients with different protocol groups.

Chemotherapy in the mitomycin-based group included mitomycin, a 10-mg/m^2 intravenous bolus on days 1 and 29 (not to exceed 20 mg per course), and fluorouracil, 1000 mg/m^2/d by continuous infusion on days 1 to 4 and 29 to 32. Chemotherapy in the cisplatin-based group included cisplatin, 75 mg/m^2 intravenously over 60 minutes on days 1 and 29 and repeated on days 57 and 85, and fluorouracil, 1000 mg/m^2/d by continuous infusion on days 1 to 4, 29 to 32, 57 to 60, and 85 to 88 (days 57 and 85 corresponding to days 1 and 29 of radiotherapy). Patients received appropriate premedications and hydration. The doses were modified according to prespecified criteria. In case of grade 4 neutropenia or febrile neutropenia, the doses of cisplatin and fluorouracil were reduced by 50%.

Figure 1. Flow of Trial Participants



All patients received a minimum dose of 45 Gy in 25 fractions of 1.8 Gy over 5 weeks to the primary cancer with supervoltage radiation (photon energy of >6 mV) using anteroposterior-posteroanterior (AP-PA) or multifield techniques. Initial radiation fields were to include the pelvis, anus, perineum, and inguinal nodes, with the superior field border at L5-S1 and the inferior border to include the anus with a minimum margin of 2.5 cm around the anus and tumor. The lateral border of AP fields was to include the lateral inguinal nodes as determined from bony landmarks or imaging (lymphangiogram, computed tomography), but lateral inguinal nodes were not routinely included in the PA fields to allow adequate sparing of the femoral heads. After a dose of 30.6 Gy in 17 fractions, the superior field extent was reduced to the bottom of the sacroiliac joints and an additional 14.4 Gy was given in 8 fractions (total dose of 45 Gy in 25 fractions/5 weeks), with additional field reduction off node-negative inguinal nodes after 36 Gy. For patients treated with an AP-PA rather than 4-field technique, an anterior electron boost (matched to the PA exit field) was used to bring the lateral inguinal region to the minimum dose of 30.6 Gy.

For patients with T3, T4, node-positive disease or patients with T2 residual disease after 45 Gy, the intent was to deliver an additional boost of 10 to 14 Gy in 2-Gy fractions (total dose of 55-59 Gy in 30-32 fractions over 5.5-6.5 weeks). The target volume for boost field 2 was the original primary tumor volume/node plus a 2- to 2.5-cm margin. Treatment field options included a multifield photon approach (AP-PA plus paired laterals, PA + laterals, or other) or a direct perineal boost with electrons or photons with the patient in lithotomy position. Acute toxic effects were recorded according to the National Cancer Institute's Common Toxicity Criteria version 2.0[25] and long-term toxic effects according to the RTOG/European Organization for Research and Treatment of Cancer morbidity scoring system.[26] Temporary suspension of chemoradiation was allowed for grade 3 or 4 neutropenia until recovery to grade 2 or lower.

Statistical Analyses

It was assumed that the mitomycin-based group had a disease-free survival hazard rate of 0.0917 (meaning 5-year disease-free survival of 63%). The study was designed to detect a 33% reduction in hazard for the cisplatin-based group, corresponding to a 5-year disease-free survival of 73% and a hazard ratio (HR) of 1.49, with 80% power, a 2-sided α level of .05, and exponential distribution for survival rates. Adapting the group sequential design[27] with 2 planned interim analyses and a final analysis, 215 events (persistent tumor, local or regional relapse, or colostomy) were required. The O'Brien-Fleming boundary shape, determined using EaST software,[28] was used for the early stopping rules. We further assumed a constant accrual rate for 5 years and a 3-year follow-up period. The total sample size needed was 650.

Patients were analyzed based on the treatment group to which they were randomized, and patients who were determined to be ineligible, withdrew consent, or had inadequate data were excluded. Pretreatment characteristics between the treatment groups were compared using Kruskal-Wallis and χ^2 tests. z Tests were used to test for differences in binomial proportions of grade 3 or higher toxic effects (worst overall, worst nonhematologic, and worst hematologic). Treatment failure was defined for the efficacy end points as follows: for overall survival, death due to any cause; for disease-free survival, local, regional, or distant failure, second primary tumor, or death due to any cause; for local-regional treatment failure, local or regional relapse, progression, or persistence; for distant metastases, appearance of distant metastases; and for colostomy, having a colostomy. All efficacy end points were measured from date of randomization to date of first treatment failure for the given end point or date of last follow-up for patients in whom a given end point did not result in treatment failure. Overall survival and disease-free survival were estimated univariately with the Kaplan-Meier method,[29] and treatment groups were compared using the log-rank test.[30] Time to local-regional treatment failure, distant metastases, and colostomy were estimated by the cumulative incidence method,[31] and treatment groups were compared using the Gray test.[32] All reported P values are 2-sided, with a statistical significance level of $P<.05$. Multivariate analyses were performed with Cox proportional hazard models to test

for treatment differences (mitomycin-based group vs cisplatin-based group) while adjusting for sex, clinical nodal status (no vs yes), and tumor diameter (>2-≤5 cm vs >5 cm). All variables were coded such that an HR greater than 1 indicates an increased risk for the second level of the variable. For example, treatment (mitomycin-based group vs cisplatin-based group) was coded such that an HR greater than 1 indicates an increased risk of treatment failure in the cisplatin-based group and sex was coded such that an HR greater than 1 indicates an increased risk of treatment failure among men. The study was monitored by the RTOG data monitoring committee. SAS software, version 9.1 (SAS Institute Inc, Cary, North Carolina) was used for calculating all analyses.

RESULTS

Patient Characteristics

The study accrued 682 patients from October 31, 1998, to June 27, 2005. All analyses are based on data as of October 2006. There were 23 ineligible patients (3%) and 15 patients who withdrew consent or had inadequate data (2%) (FIGURE 1). Pretreatment characteristics of 644 patients are shown in TABLE 1. Sixty-nine percent of patients were women, 27% had tumors larger than 5 cm in diameter, 35% had T3 or T4 lesions, and 26% had clinically positive nodes. The groups were well-balanced with respect to the pretreatment characteristics, with the exception that there were more cases with a cancer located in the perianal skin and anal canal in the cisplatin-based group ($P=.045$).

Disease-Free Survival

Median follow-up time for all patients was 2.51 years (range, 0.05-7.41 years). At the time of the second interim analysis (summer 2005), 162 events had occurred and the results crossed the futility boundary, indicating that even with the additional specified number of events, the data would not show a statistically significant difference in disease-free survival between the 2 groups. The data monitoring committee therefore recommended reporting study results.

The 3- and 5-year estimated disease-free survival rates were 67% (95% confidence interval [CI], 62%-72%) and 60% (95% CI, 53%-67%), respectively, in the mitomycin-based group and 61% (95% CI, 55%-66%) and 54% (95% CI, 46%-60%), respectively, in the cisplatin-based group ($P=.17$; FIGURE 2). In a multivariate analysis, male sex ($P=.02$), clinically positive nodes ($P<.001$), and tumor size greater than 5 cm ($P=.004$) were independent prognosticators for worse disease-free survival. Type of treatment was not a prognosticator for

Table 1. Baseline Patient Characteristics[a]

Characteristics	Mitomycin-Based Treatment (n = 324)	Cisplatin-Based Treatment (n = 320)	*P* Value[b]
Age, median (range), y	55 (25-83)	55 (31-88)	
Male/female	101 (31)/223 (69)	97 (30)/223 (70)	.81
Karnofsky performance score, %			
60	3 (1)	2 (1)	.74[c]
70	11 (3)	10 (3)	
80	41 (13)	40 (13)	
90	133 (41)	146 (46)	
100	136 (42)	122 (38)	
Tumor location			
Above dentate line	34 (10)	42 (13)	.045
Anal canal	228 (70)	194 (61)	
Perianal skin	8 (2)	7 (2)	
Anal canal and perianal	53 (16)	77 (24)	
Unknown	1 (<1)	0	
Primary (largest) tumor size, cm			
2-5	238 (73)	234 (73)	.92
>5	86 (27)	86 (27)	
Histology			
Squamous cell	278 (86)	273 (85)	.65
Basaloid	18 (6)	21 (7)	
Cloacogenic	24 (7)	19 (6)	
Basaloid/squamous	3 (1)	6 (2)	
Basaloid/squamous/cloacogenic	1 (<1)	1 (<1)	
T category			
T2	204 (63)	212 (66)	.39[c]
T3	86 (27)	84 (26)	
T4	34 (10)	24 (7)	
N category			
N0	227 (70)	221 (69)	.16[c]
N1	40 (12)	24 (8)	
N2	34 (10)	45 (14)	
N3	10 (3)	14 (4)	
NX	13 (4)	16 (5)	
Clinical node status			
Positive	84 (26)	83 (26)	.99
Negative	240 (74)	237 (74)	
AJCC stage[33]			
I	150 (47)	152 (48)	.35[c]
II	62 (19)	53 (17)	
III	33 (10)	24 (7)	
IV-A	67 (21)	76 (24)	
Unknown	12 (4)	15 (5)	

Abbreviation: AJCC, American Joint Committee on Cancer.
[a] Data are expressed as No. (%) of participants unless otherwise specified.
[b] Based on χ^2 test unless otherwise indicated.
[c] Based on Kruskal-Wallis test.

disease-free survival (HR, 1.20; 95% CI, 0.93-1.55; *P*=.17). Tumor location was also not a prognosticator for disease-free survival.

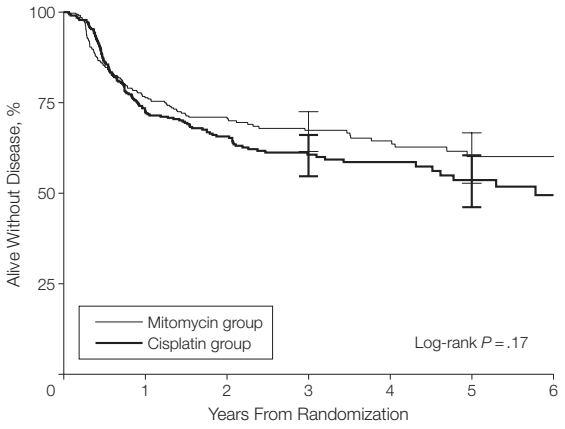
Overall Survival, Local-Regional Failure, Distant Metastases, and Colostomy

Overall survival was not significantly different between the 2 treatment groups (2-sided log-rank *P*=.10; FIGURE 3). The 3- and 5-year overall survival rates were 84% (95% CI, 78%-88%) and 75% (95% CI, 67%-81%), respectively, in the mitomycin-based group and 76% (95% CI, 70%-81%) and 70% (95% CI, 63%-76%), respectively, in the cisplatin-based group. There were more study cancer-related deaths in the cisplatin-based group (54 patients) compared with the mitomycin-based group (28 patients). In a multivariate analysis, male sex (*P*=.02), clinically positive nodes (*P*<.001), and tumor size greater than 5 cm (*P*=.01) independently prognosticated for poor overall survival, but type of treatment did not (HR, 1.28; 95% CI, 0.90-1.84; *P*=.17). There were non–statistically significant results for time to local-regional treatment failure (HR, 1.32; 95% CI, 0.98-1.78; *P*=.07) and distant metastases (HR, 1.38; 95% CI, 0.90-2.10; *P*=.14). There was a statistically significant difference in colostomy rates, with 3- and 5-year cumulative rates of 10% (95% CI, 6%-14%) at both 3 and 5 years in the mitomycin-based group and 16% (95% CI, 12%-20%) and 19% (95% CI, 13%-24%), respectively, in the cisplatin-based group (HR, 1.68; 95% CI, 1.07-2.65; *P*=.02; Figure 3).

Sites of Treatment Failure

The percentages of patients alive without treatment failure at the end of follow-up were 68% and 60% in the mitomycin- and cisplatin-based groups, respectively. Sites of first treatment failure were similar for local (mitomycin-based group, 13% [95%

Figure 2. Disease-Free Survival in the Mitomycin- and Cisplatin-Based Groups

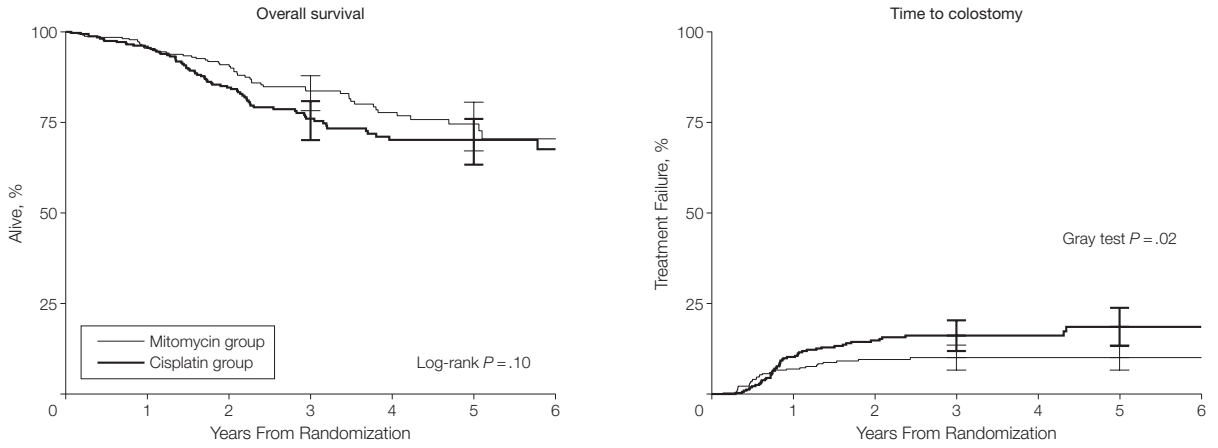


No. at risk

Mitomycin group	324	226	150	114	76	34	10
Cisplatin group	320	223	160	104	62	34	18

Incidence of treatment failure was 105 of 324 with mitomycin-based treatment and 127 of 320 with cisplatin-based treatment. Error bars indicate 95% confidence intervals.

Figure 3. Overall Survival and Cumulative Incidence of Colostomy in the Mitomycin- and Cisplatin-Based Groups



No. at risk

Mitomycin group	324	281	191	140	90	41	11
Cisplatin group	320	293	201	131	77	46	21

324	260	176	129	83	38	10
320	261	181	119	71	41	20

Mortality rates were 53 of 324 with mitomycin-based treatment and 72 of 320 with cisplatin-based treatment. Error bars indicate 95% confidence intervals. Incidence of treatment failure (persistent tumor, relapsed tumor, or colostomy) was 30 of 324 with mitomycin-based treatment and 50 of 320 with cisplatin-based treatment.

CI, 9%-17%] and cisplatin-based group, 19% [95% CI, 15%-23%]), regional (mitomycin-based group, 6% [95% CI, 3%-9%] and cisplatin-based group, 7% [95% CI, 4%-10%]), and distant (mitomycin-based group, 6% [95% CI, 3%-9%] and cisplatin-based group, 8% [95% CI, 5%-11%]), tumors; other types of relapse were rare. The 5-year local-regional recurrence and distant metastasis rates were 25% (95% CI, 20%-30%) and 15% (95% CI, 10%-20%), respectively, for mitomycin-based treatment and 33% (95% CI, 27%-40%) and 19% (95% CI, 14%-24%), respectively, for cisplatin-based treatment.

Adherence

Radiotherapy adherence (per protocol and acceptable variation [only minimum variation in the radiation dose or field]) was 91% in the mitomycin-based group and 88% in the cisplatin-based group. Chemotherapy adherence (per protocol and acceptable variation [only minimum variation in the drug dose, omission of chemotherapy, or nonspecified delay in chemotherapy]) was 95% in the mitomycin-based group and 94% in the cisplatin-based group. The mean and median radiation doses were 55 Gy (range, 9-69 Gy; interquartile range, 45.9-59 Gy) and 55 Gy (range, 14.4-70.2 Gy; interquartile range, 45-59 Gy), respectively, in the mitomycin-based and cisplatin-based groups.

Toxic Effects

The acute and long-term toxic effects are listed in TABLE 2 and TABLE 3. The "worst" toxic effects data represent the sums of patients with highest grades of 1 through 4 in each toxic effects category (hematologic, nonhematologic, and overall). The rate of acute nonhematologic grade 3 or 4 toxicity was 74% in both the mitomycin- and cisplatin-based groups. A post hoc test was statistically significant for differences in severe acute hematologic toxicity (grade

Table 2. Acute Toxic Effects of Chemotherapy and Radiation

	Toxicity Grade, No. (%)							
	Mitomycin-Based Treatment (n = 324)				Cisplatin-Based Treatment (n = 320)			
	1	2	3	4	1	2	3	4
Toxicity category								
Allergy/immunology	6	1	0	0	6	2	1	0
Auditory/hearing	2	1	0	0	10	29	2	0
Blood/bone marrow	33	73	114	85	60	98	86	49
Arrhythmias	5	2	2	0	5	1	1	1
Cardiovascular (general)	22	20	11	1	30	21	23	1
Coagulation	2	0	0	0	1	1	5	0
Constitutional symptoms	94	97	29	2	102	109	38	2
Dermatology/skin	28	113	140	15	30	122	126	6
Endocrine	3	2	0	0	4	5	1	0
Gastrointestinal	56	122	103	12	40	118	138	8
Nausea	106	53	29	0	109	83	56	0
Stomatitis	53	63	18	2	40	90	38	4
Vomiting	29	31	19	1	59	61	48	0
Diarrhea	72	91	73	3	82	76	76	2
Hemorrhage	32	6	1	1	45	7	0	0
Hepatic	41	12	5	0	40	6	6	0
Infection/febrile neutropenia	8	42	51	6	9	50	29	3
Lymphatics	1	0	0	0	2	0	0	0
Metabolic/laboratory	59	18	23	3	62	30	27	5
Musculoskeletal	2	3	2	1	0	4	0	0
Neurology	30	21	13	2	69	44	17	1
Ocular/visual	3	1	1	0	8	2	0	0
Pain	24	71	70	7	33	89	53	2
Pulmonary	18	13	8	2	25	20	3	2
Renal/genitourinary	53	60	10	1	55	63	11	0
Secondary malignancy	0	0	0	0	1	0	0	0
Sexual reproductive function	3	2	4	0	3	6	1	0
Syndromes	0	0	0	0	1	0	0	0
Worst grade								
Hematologic	33 (10)	73 (23)	114 (35)	85 (26)	60 (19)	98 (31)	86 (27)	48 (15)
Nonhematologic	8 (2)	68 (21)	199 (61)	41 (13)	6 (2)	68 (21)	212 (66)	27 (8)
Overall	4 (1)	32 (10)	172 (53)	110 (34)	3 (1)	46 (14)	200 (63)	65 (20)

Table 3. Long-term Toxic Effects of Radiation

	Toxicity Grade, No. (%)							
	Mitomycin-Based Treatment (n = 317)				Cisplatin-Based Treatment (n = 308)			
Toxicity Category	1	2	3	4	1	2	3	4
Small/large intestine	56	28	5	5	41	17	5	1
Skin	52	16	5	5	34	15	3	4
Bladder	17	8	2	0	17	9	1	0
Subcutaneous tissue	18	8	4	1	15	4	2	2
Other	46	42	13	1	39	35	11	5
Worst overall grade	72 (23)	73 (23)	25 (8)	11 (3)	53 (17)	58 (19)	17 (6)	11 (4)

3 or 4, 61% in the mitomycin-based group and 42% in the cisplatin-based group; $P<.001$). The rate of severe long-term toxic effects was similar in both groups (11% vs 10%).

COMMENT

The initial observations that anal canal carcinoma is highly sensitive to concurrent chemoradiation have led the way to drastic alterations in the treatment paradigm for this disease. The current goal is to avoid colostomy, and surgery has become a salvage or secondary therapy.

A series of trials established that concurrent chemoradiation is better than radiation alone[15,16] and that the combination of fluorouracil plus mitomycin given concurrently with radiation is superior to fluorouracil given concurrently with radiation,[17] as noted previously. However, the 5-year disease-free survival rate of approximately 65% has not improved since the early 1990s.

The US Gastrointestinal Intergroup RTOG 98-11 trial was not a pure test of concurrent chemoradiation with fluorouracil-cisplatin vs fluorouracil-mitomycin but, rather, was a test of one strategy vs another. The strategy of induction chemotherapy to reduce the bulk of local-regional anal canal carcinoma had an appeal, and preliminary data suggested considerable sensitivity of anal canal carcinoma to the combination of fluorouracil plus cisplatin. The US Gastrointestinal Intergroup RTOG 98-11 trial was not set up to quantify the actual downsizing of the primary tumor or lymph nodes; instead, it was an assumption that would have translated into improved disease-free survival and decreased colostomy rates, a notion incorporated in the global hypothesis. The data on treatment adherence suggest that the lack of difference in disease-free survival was not related to inadequate therapy in either group. These results also reinforce the importance of randomized controlled trials because the prior assumptions about a treatment strategy based on uncontrolled experiences may turn out to be erroneous.

Clearly, the strategy of induction chemotherapy with fluorouracil-cisplatin followed by concurrent chemoradiation with fluorouracil-cisplatin proved ineffective in improving disease-free survival for patients with anal canal carcinoma compared with the prior standard of concurrent chemoradiation with fluorouracil-mitomycin. Cisplatin-based treatment did not reduce either local-regional or distant relapse compared with mitomycin-based treatment and did not improve disease-free or colostomy-free survival as hypothesized. In fact, trends favoring concurrent chemoradiation with fluorouracil and mitomycin over induction and concurrent fluorouracil and cisplatin existed in a number of outcomes analyses (local-regional relapse: 3-year rate, 23% vs 31%, and 5-year rate, 25% vs 33%; $P=.07$; disease-free survival: 3-year rate, 67% vs 61%, and 5-year rate, 60% vs 54%; $P=.17$; overall survival: 3-year rate, 84% vs 76%, and 5-year rate, 75% vs 70%; $P=.10$). The better cumulative colostomy rate in the mitomycin-based group was statistically significant (3-year rate, 10% vs 16%, and 5-year rate, 10% vs 19%; $P=.02$).

There are no clear explanations for the failure of fluorouracil-cisplatin to improve disease-free survival compared with fluorouracil-mitomycin as a component of treatment for patients with anal canal carcinoma. In theory, induction chemotherapy may have resulted in accelerated repopulation and an increase in the number of clonogens at the onset of radiation despite the decrease in overall tumor volume. Alternatively, mitomycin may be a more effective radiosensitizer than cisplatin, especially in hypoxic areas of the tumor. The increase in the rate of cumulative colostomies may have resulted from a combination of these factors or because of other, unknown reasons. The results of the current trial, however, clearly demonstrate the importance of conducting phase 3 trials to test hypotheses that appear to have merit instead of establishing the alternate treatment as an acceptable standard based on single-institution phase 2 trials.

Cisplatin-based treatment resulted in significantly higher cumulative rates of colostomy and should generally be avoided in this patient population as primary therapy. Exceptions include only a clinical trial setting or patients in whom the combination of fluorouracil and mitomycin would not be tolerable.

The question remains how to further improve disease-free and colostomy-free survival relative to the continued standard of concurrent chemoradiation with fluorouracil and mitomycin. It may be that further manipulations with different classes of cytoxic agents are not likely to produce better results. Options to explore include targeted agents (eg, results with

concurrent cetuximab plus radiation for head/neck cancer[34]), dose escalation with intensity-modulated radiation plus concurrent chemotherapy, and surgical excision of residual cancer after concurrent chemoradiation at an earlier interval, when sphincter preservation may still be feasible in select patients.

In conclusion, the US Gastrointestinal Intergroup RTOG 98-11 trial demonstrates that cisplatin should not replace mitomycin when given with fluorouracil and radiotherapy in the primary treatment of localized anal canal carcinoma.

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