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ORIGINAL REPORT

Long-Term Update of US GI Intergroup RTOG 98-11 Phase III Trial for Anal Carcinoma: Survival, Relapse, and Colostomy Failure With Concurrent Chemoradiation Involving Fluorouracil/Mitomycin Versus Fluorouracil/Cisplatin

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See accompanying article on page 4297

A B S T R A C T

Purpose

On initial publication of GI Intergroup Radiation Therapy Oncology Group (RTOG) 98-11 [A Phase III Randomized Study of 5-Fluorouracil (5-FU), Mitomycin, and Radiotherapy Versus 5-Fluorouracil, Cisplatin and Radiotherapy in Carcinoma of the Anal Canal], concurrent chemoradiation (CCR) with fluorouracil (FU) plus mitomycin (MMC) decreased colostomy failure (CF) when compared with induction plus concurrent FU plus cisplatin (CDDP), but did not significantly impact disease-free survival (DFS) or overall survival (OS) for anal canal carcinoma. The intent of the updated analysis was to determine the long-term impact of treatment on survival (DFS, OS, colostomy-free survival [CFS]), CF, and relapse (locoregional failure [LRF], distant metastasis) in this patient group.

Patients and Methods

Stratification factors included sex, clinical node status, and primary size. DFS and OS were estimated univariately by the Kaplan-Meier method, and treatment arms were compared by log-rank test. Time to relapse and CF were estimated by the cumulative incidence method and treatment arms were compared by using Gray's test. Multivariate analyses used Cox proportional hazard models to test for treatment differences after adjusting for stratification factors.

Results

Of 682 patients accrued, 649 were analyzable for outcomes. DFS and OS were statistically better for RT + FU/MMC versus RT + FU/CDDP (5-year DFS, 67.8% *v* 57.8%; $P = .006$; 5-year OS, 78.3% *v* 70.7%; $P = .026$). There was a trend toward statistical significance for CFS ($P = .05$), LRF ($P = .087$), and CF ($P = .074$). Multivariate analysis was statistically significant for treatment and clinical node status for both DFS and OS, for tumor diameter for DFS, and for sex for OS.

Conclusion

CCR with FU/MMC has a statistically significant, clinically meaningful impact on DFS and OS versus induction plus concurrent FU/CDDP, and it has borderline significance for CFS, CF, and LRF. Therefore, RT + FU/MMC remains the preferred standard of care.

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INTRODUCTION

Phase II[1-3] and subsequent phase III trials[4-9] have established concurrent chemoradiation (CCR) as the preferred initial treatment for most patients with anal carcinoma. CCR achieves sphincter preservation in many patients, with surgical salvage as an option for patients with persistent or recurrent tumors.[10] A phase III trial by the Radiation Therapy Oncology Group (RTOG) and Eastern Cooperative Oncology Group (ECOG) [A Phase III Randomized Study of 5-Fluorouracil (5-FU), Mitomycin, and Radiotherapy Versus 5-Fluorouracil, Cisplatin and Radiotherapy in Carcinoma of the Anal Canal], demonstrated that radiation therapy (RT) with concurrent infusion of fluorouracil (FU) plus mitomycin (MMC) improved local control and had a lower colostomy failure than RT + FU.[4] Phase III trials from the

United Kingdom Coordinating Committee on Cancer Research (UKCCCR) and the European Organisation for Research and Treatment of Cancer (EORTC) found that CCR with FU/MMC was superior to RT alone with regard to local control and colostomy failure (CF), but with no overall survival (OS) advantage.[5,6]

To determine whether concurrent MMC during RT + infusion FU could be replaced with cisplatin (CDDP), a US GI Intergroup phase III trial, coordinated by RTOG (RTOG 98-11), was initiated to test RT + FU/MMC versus RT + FU/CDDP.[7] Disease-free survival (DFS) was the primary end point with secondary end points of OS, CF, and disease relapse. An initial analysis of RTOG 98-11 found a decrease in CF for RT + FU/MMC versus RT + FU/CDDP with 5-year CF rates of 10% versus 19% ($P = .02$) but no impact on either DFS or OS.[7]

Secondary analyses of RTOG 98-11 were performed to evaluate OS, DFS, and time to colostomy (TTC) by various prognostic factors.[8,9] The first analysis found that pretreatment tumor diameter more than 5 cm (independent of nodal status) predicts for TTC ($P = .008$), and the cumulative 5-year colostomy failure was higher for large-diameter tumors than for small-diameter tumors ($P = .0074$).[8] In another secondary analysis, various combinations of tumor size (> 2 to ≤ 5 cm *v* > 5 cm) and clinically involved nodes (N0, N+) were analyzed, which included a four-category blend of tumor size and nodal status. Patients with more than 5-cm tumor and N+ had the worst DFS and OS, and those with ≤ 5 cm N0 tumors had the best DFS and OS.[9] A subsequent secondary analysis was performed to determine the impact of TN category of disease on survival, disease relapse, and CF.[11]

Because the initial analysis of RTOG 98-11 found that RT + FU/MMC (*v* RT + FU/CDDP) decreased CF but had no significant impact on DFS or OS, it was felt that the long-term impact of treatment on survival (DFS, OS, colostomy-free survival [CFS]), CF, and relapse (locoregional failure [LRF], distant metastasis [DM]) should be evaluated.

PATIENTS AND METHODS

Infrastructure, Hypothesis, and Objectives

RTOG 98-11 was a US GI Intergroup trial, coordinated by RTOG, with participation by ECOG, Cancer and Leukemia Group B (CALGB), North Central Cancer Treatment Group (NCCTG), Southwest Oncology Group (SWOG), and RTOG. The primary study objective was to observe an increase in 5-year DFS from 63% with RT + concurrent FU/MMC to 73% with RT + concurrent FU/CDDP. Secondary objectives included OS, LRF, and CF.

The intent of this analysis (February 27, 2011) was to determine the long-term impact of treatment with RT + FU/MMC versus RT + FU/CDDP on survival (DFS, OS, CFS), CF, and relapse (LRF, DM) in this patient group. The protocol was approved by local/institutional human investigations committees, and informed consent was obtained from each participant or their guardian.

Patient Eligibility

Patients with histologically proven squamous, basaloid, or cloacogenic carcinoma of the anal canal were eligible provided they were 18 years of age or older, had Karnofsky performance status ≥ 60, had T2-4 category cancers with any N category (pelvic or inguinal), had adequate organ function, and were willing to provide written consent. Patients were excluded if they had a T1 or M1 cancer, severe comorbid conditions (including AIDS), or major malignancy unless they had been successfully treated and were disease-free for ≥ 5 years.

Evaluations

Before treatment, patients had baseline proctoscopy or sigmoidoscopy, chest film, and computed tomography (CT) or magnetic resonance imaging scans of the abdomen/pelvis to establish stage of disease. Adequacy of hepatic, renal, and bone marrow function were evaluated with blood and serum chemistry studies. HIV testing was not part of standard pretreatment evaluation. After treatment completion, patients underwent re-evaluation similar to baseline evaluation and were then observed every 3 months for four cycles, every 6 months for two cycles, and then yearly.

Random Assignment, Stratification, and Treatment

Patients were randomly assigned to RT + FU/MMC (arm A, the control arm) or induction FU/CDDP followed by RT + FU/CDDP (arm B) by using

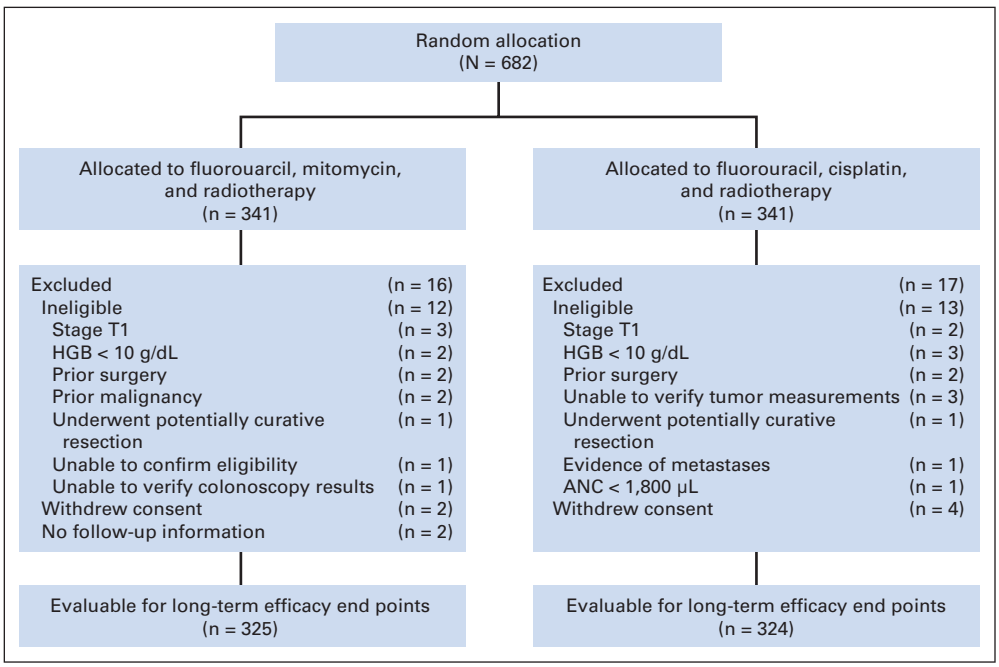

Fig 1. CONSORT diagram. ANC, absolute neutrophil count; HGB, hemoglobin.

Table 1. Impact of Treatment Arm on Survival, Relapse, and Colostomy Failure

		DFS			OS			CFS			LRF			DM			CF		
Treatment	Patient ID	TF	5-Year %	95% CI	TD	5-Year %	95% CI	TF	5-Year %	95% CI	TF	5-Year %	95% CI	TF	5-Year %	95% CI	TF	5-Year %	95% CI
RT + FU/MMC	325	122	67.8	62.3 to 72.6	87	78.3	73.2 to 82.5	106	71.9	66.5 to 76.5	67	20.0	15.6 to 24.4	46	13.1	9.3 to 16.8	38	11.9	8.3 to 15.4
RT + FU/CDDP	324	159	57.8	52.1 to 63.0	115	70.7	65.2 to 75.4	132	65.0	59.4 to 70.0	86	26.4	21.5 to 31.3	61	18.1	13.8 to 22.4	55	17.3	13.1 to 21.5
Log-rank *P*				.006			.026			.05									
Gray's test *P*													.087			.12			.074
HR				1.39			1.37			1.29			1.33			1.37			1.48
95% CI				1.10 to 1.76			1.04 to 1.81			0.99 to 1.67			0.97 to 1.83			0.94 to 2.02			0.98 to 2.23

Abbreviations: CF, colostomy failure; CFS, colostomy-free survival; DFS, disease-free survival; DM, distant metastasis; HR, hazard ratio; ID, [patient] identification; LRF, locoregional failure; OS, overall survival; RT + FU/CDDP, radiation therapy plus fluorouracil/cisplatin; RT + FU/MMC, RT plus fluorouracil/mitomycin; TD, total deaths; TF, total failures.

a permuted randomized block scheme as described by Zelen.[12] Patients were stratified according to sex, clinical node status (N0 *v* N+), and size of primary tumor (> 2 to 5 cm *v* > 5 cm).

The details of both the RT and chemotherapy components of treatment are described in depth in the initial publication and will not be reiterated in detail.[7] All patients were to receive a minimum dose of 45 Gy in 25 fractions of 1.8 Gy (5 days per week) to the primary cancer plus involved nodes with supervoltage irradiation. Noninvolved nodal sites at risk received 30.6 to 36 Gy in 17 to 20 fractions of 1.8 Gy (5 days per week). Patients with T3-4N+ disease or T2 patients with residual disease after 45 Gy in 25 fractions were to receive an additional dose of 10 to 14 Gy in 2 Gy fractions (5 days per week) to the primary tumor/involved nodes (total dose, 55 to 59 Gy in 30 to 32 fractions over 5.5 to 6.5 weeks). Intensity-modulated radiation therapy (IMRT) was not allowed.

Statistical Methods

OS is defined as death resulting from any cause. Events for LRF are defined as any of the following: local disease persistence/recurrence/progression, positive biopsy, surgery for primary, or disease presence/recurrence/progression in lymph nodes. CF events are any of the following: abdominoperineal resection or colostomy for disease, treatment complications, or both. Death, LRF, DM, or second primary are considered failures for DFS. CFS events are either death or CF.

DFS, OS, and CFS were univariately estimated by the Kaplan-Meier method,[13] and treatment arms were compared by the log-rank test.[14] Time to relapse (LRF, DM) and CF were estimated by the cumulative incidence method,[15] and results by treatment arm were compared by using Gray's test.[16]

Multivariate analyses were performed with Cox proportional hazards models[17] to test for treatment differences (RT + FU/MMC *v* RT + FU/CDDP) while adjusting for sex (female *v* male), clinical nodal status (no *v* yes), and maximum tumor diameter (> 2 to 5 cm *v* > 5 cm). All variables were coded such that a hazard ratio [HR] of more than 1 indicates an increased risk for the second level of the variable.

RESULTS

Patient Characteristics

Of the 682 patients who were randomly assigned to the trial, 649 were evaluable for the analysis of long-term outcomes by treatment arm (25 were ineligible, six withdrew consent, and two had no follow-up information; Fig 1).

Duration of treatment from the initiation of CCR was evaluated by treatment arm. For RT + FU/MMC versus RT + FU/CDDP, radiation treatment duration was a median of 49 days (0, minimum; 42, first quartile; 56, third quartile; 100 maximum days) versus 45 days (0, minimum; 37.5, first quartile; 52, third quartile; 107 maximum days). Total treatment duration from beginning of any treatment to the end of treatment: RT + FU/MMC with a median of 49 days (see above data) versus RT + FU/CDDP with a median of 101 days (0, minimum; 93, first quartile; 111, third quartile; 241 maximum days). The patient with 241 days duration delayed the start of CCR to allow treatment of a melanoma on the leg.

Survival and Relapse by Treatment Arm

DFS and OS results are provided in Table 1 and Figures 2A and 2B. Both DFS and OS were statistically better for RT + FU/MMC versus RT + FU/CDDP (5-year DFS, 67.8% *v* 57.8%; HR, 1.39; $P = .006$; 5-year OS, 78.3% *v* 70.7%; HR. 1.39; $P = .026$; two-sided log-rank test). As seen in Figure 2, DFS curves started to separate at approximately 1 year, and OS curves started to separate at approximately 1.5 years. No instance of disease progression during the neoadjuvant cycles of FU/CDDP was reported.

Multivariate analysis for DFS included treatment (RT + FU/MMC *v* RT + FU/CDDP) and the stratification variables of sex (female *v* male), tumor diameter (> 2 to 5 cm *v* > 5 cm) and clinical nodal status (no *v* yes). As detailed in Table 2, treatment with RT + FU/MMC had statistically significantly better DFS after adjusting for the stratification variables (HR, 1.40; $P = .005$). Patients with tumor diameter more than 5 cm had statistically worse DFS (HR, 1.51; $P = .0012$) as did patients with positive clinical nodes (HR, 1.82; $P < .001$; Table 2).

Multivariate analysis for OS used the same variables as for DFS. After adjusting for stratification variables, treatment with RT + FU/MMC had statistically significantly better OS (HR, 1.39; $P = .022$; Table 2). Male patients had statistically worse OS (HR, 1.38; $P = .031$) as did those with positive clinical nodal status (HR, 1.88; $P < .001$).

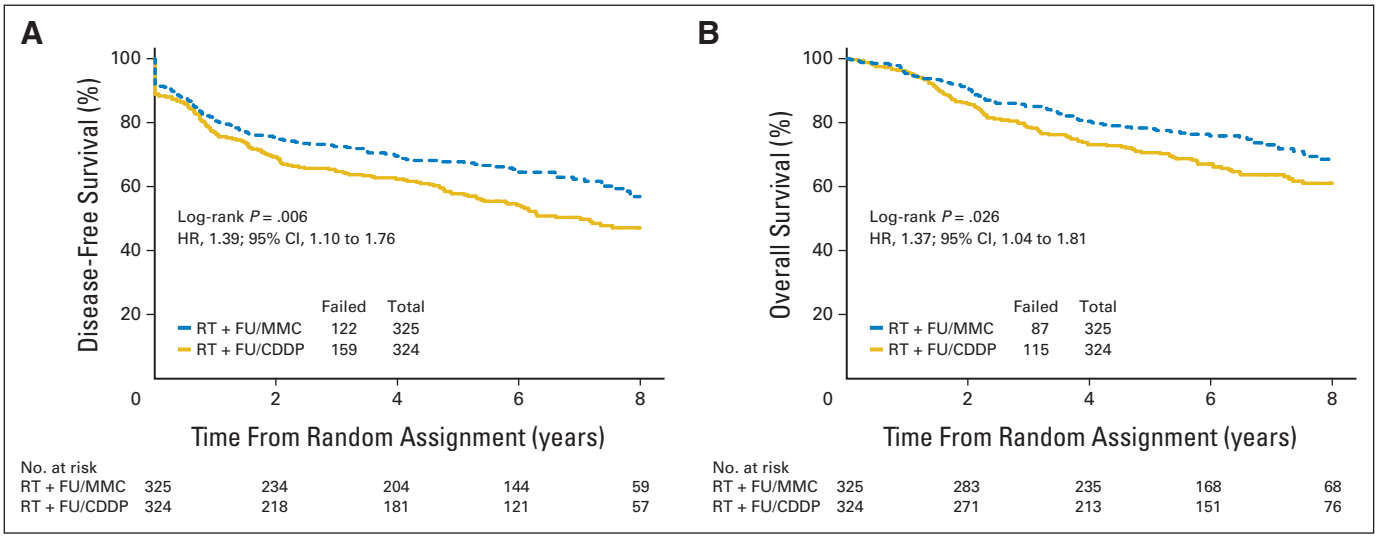

Fig 2. Impact of radiation therapy plus fluorouracil/mitomycin (RT + FU/MMC) *v* radiation therapy plus fluorouracil/cisplatin (RT + FU/CDDP) on (A) disease-free survival ($P = .006$) and (B) overall survival ($P = .026$). HR, hazard ratio.

Table 2. Multivariate Analysis for DFS and OS

Variable	Comparison	DFS			OS		
		Adjusted HR	95% CI	*P*	Adjusted HR	95% CI	*P*
Treatment	RT + FU/MMC *v* RT + FU/CDDP	1.40	1.11 to 1.78	.005	1.39	1.05 to 1.83	.022
Sex	Female *v* male	1.27	0.99 to 1.63	.06	1.38	1.03 to 1.85	.031
Tumor diameter	> 2-5 cm *v* > 5 cm	1.51	1.17 to 1.93	.0012	1.30	0.97 to 1.75	.079
Clinical node status	Negative *v* positive	1.82	1.42 to 2.34	< .001	1.88	1.41 to 2.51	< .001

Abbreviations: DFS, disease-free survival; HR, hazard ratio; OS, overall survival; RT + FU/CDDP, radiation therapy plus fluorouracil/cisplatin; RT + FU/MMC, RT plus fluorouracil/mitomycin.

There was a trend toward statistical significance for LRF, CFS, and CF for patients treated with RT + FU/MMC versus RT + FU/CDDP as detailed in Table 1 and Figures 3A, 4A, and 4B. Five-year CFS was 71.9% versus 65.0% ($P = .05$), 5-year LRF was 20% versus 26.4% ($P = .087$), and 5-year CF was 11.9% versus 17.3% ($P = .074$). Data did not show any statistically significant differences between treatment arms for DM (5-year DM was 13.1% *v* 18.1%; $P = .12$, Fig 3B).

Toxicity by Treatment Arm

The most common types of acute grade 3 or 4 toxicity were hematologic, infection/febrile neutropenia, skin (treatment-related dermatitis), GI, and pain (Appendix Table A1, online only). Hematologic grade 3 or 4 toxicity was higher in the RT + FU/MMC arm (61.8% *v* 42.0%; $P < .001$). Interruption of chemoradiotherapy because of acute toxicity occurred in 200 patients on the RT + FU/MMC arm (median 7 days; 1, minimum; 4, first quartile; 10.5, third quartile; 33 maximum days) and 163 patients on the RT + FU/CDDP arm (median 6 days; 1, minimum; 4, first quartile; 10, third quartile; 34 maximum days). The most common causes of toxicity-related treatment interruption were hematologic/febrile neutropenia, GI, metabolic, or skin reaction.

Grade 3 or 4 late toxicity by type and treatment arm is depicted in Table 3. The data do not show a statistically significant difference in overall late grade 3 or 4 treatment-related toxicities for RT + FU/MMC versus RT + FU/CDDP (13.1% *v* 10.7%; $P = .35$).

DISCUSSION

CCR with FU/based regimens has been the preferred initial treatment in most patients with anal carcinoma for several decades, in view of sphincter preservation probabilities.[1-9] Although differences in local control, CF, and DFS have been noted in prior phase III trials, this has not translated into improvements in OS in view of the ability to accomplish surgical salvage with abdomino-perineal resection.[10]

In the initial analysis of RTOG 98-11, there was a statistically significant decrease in CF for RT + FU/MMC versus RT + FU/CDDP, with 5-year CF rates of 10% versus 19% ($P = .02$) but no impact on either DFS or OS.[7] The intent of this analysis was to evaluate the long-term impact of the two treatment arms on survival, disease relapse, and CF.

On the basis of the long-term updated analysis, RT + FU/MMC has statistically better DFS and OS than RT + FU/CDDP (5-year DFS: 67.8% *v* 57.8%; $P = .008$; 5-year OS: 78.3% *v* 70.7%: $P = .026$). In addition, RT + FU/MMC has trended toward statistical significance for CFS ($P = .05$), LRF ($P = .087$), and CF ($P = .074$). Multivariate analysis was statistically significant for treatment and clinical nodal

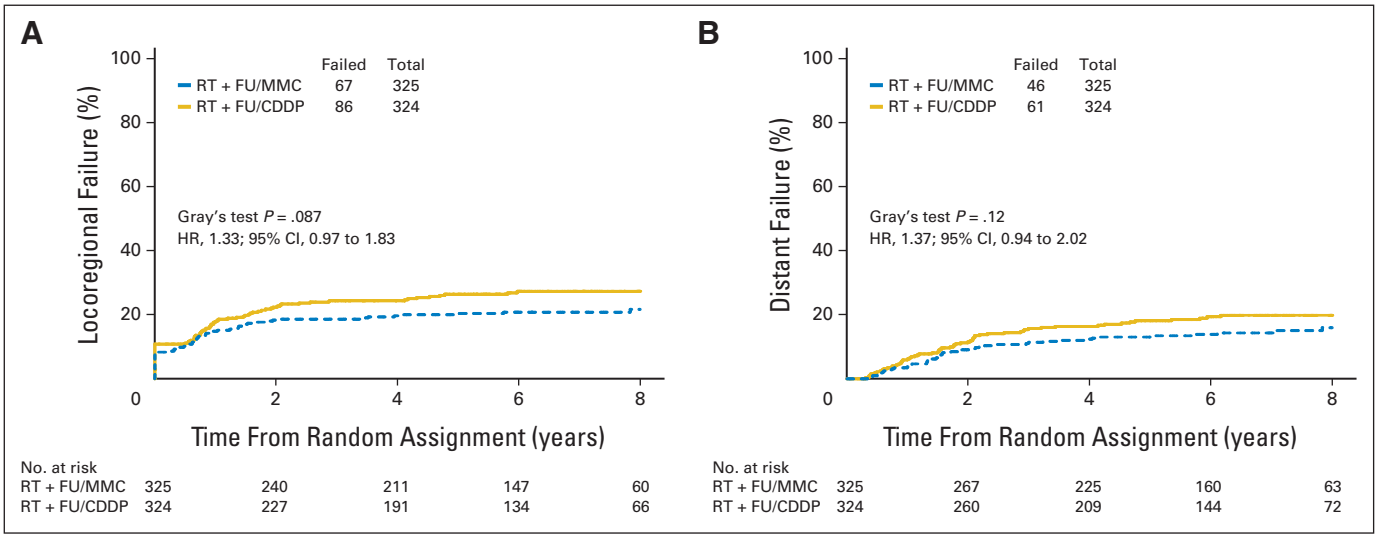

Fig 3. Impact of radiation therapy plus fluorouracil/mitomycin (RT + FU/MMC) *v* radiation therapy plus fluorouracil/cisplatin (RT + FU/CDDP) on (A) locoregional failure ($P = .087$) and (B) distant failure ($P = .12$). HR, hazard ratio.

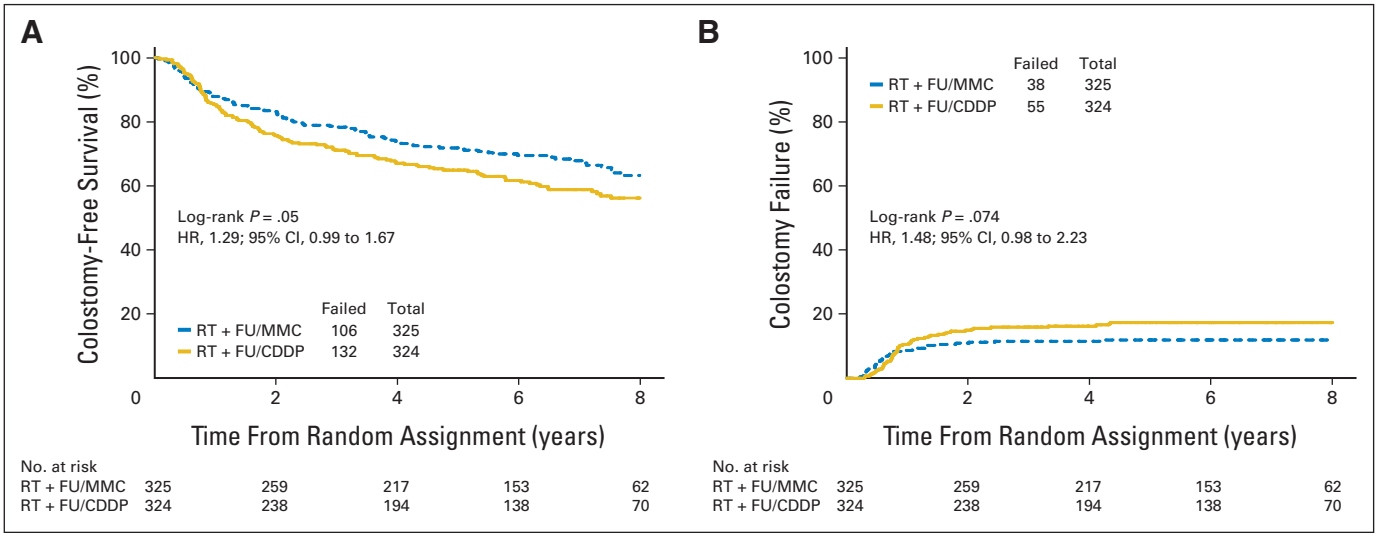

Fig 4. Impact of radiation therapy plus fluorouracil/mitomycin (RT + FU/MMC) *v* radiation therapy plus fluorouracil/cisplatin (RT + FU/CDDP) on (A) colostomy-free survival (P = .05) and (B) colostomy failure (P = .074). HR, hazard ratio.

status for both DFS and OS and was also statistically significant for primary tumor diameter for DFS and for sex for OS.

Possible Reasons for Superiority of RT + FU/MMC

There are several possible reasons for the superiority of RT + FU/MMC over RT + FU/CDDP. The first is that concurrent RT + FU/MMC is simply more effective than concurrent RT + FU/CDDP. This head-to-head comparison was not tested in this trial design; however, patients in the RT + FU/CDDP arm received up to two cycles of neoadjuvant FU/CDDP before receiving CCR. Although the ACT II phase III trial [A Randomized Trial of Chemoradiation Using Mitomycin or Cisplatin, With or Without Maintenance Cisplatin/5FU in Squamous Cell Carcinoma of the Anus] attempted to directly compare CCR with FU/MMC versus FU/CDDP, concurrent MMC was given only on day 1 of RT (12 mg/m^2) whereas concurrent CDDP was given on both day 1 and day 29 of RT (60 mg/m^2 per day). In addition, there was a second random assignment to maintenance FU/CDDP systemic therapy versus no maintenance FU/CDDP. To date, the ACT II trial has shown no difference in 3-year CFS, but the duration of follow-up is more limited than in this study.[18] In this US GI Intergroup trial, MMC was given at 10 mg/m^2 per day on days 1 and 29 of RT, and CDDP was also given at 75 mg/m^2 per day on days 1 and 29 of RT. Infusion FU doses were the same in both trials (1,000 mg/m^2 per day on days 1 through 4 and days 29 through 32 of RT).

Another possible explanation for the superiority of RT + FU/MMC was the use of neoadjuvant FU/CDDP in the experimental arm (up to two cycles). This resulted in delaying definitive CCR and prolongation of overall treatment time, which may have significantly affected outcomes.[19-22] In addition, platin-induced radioresistance may have affected outcomes in this treatment arm.[23-25]

The significant prolongation of the overall treatment time in the experimental treatment arm may have contributed to the observed inferior results, as suggested in a prior pooled analysis of two anal cancer chemoradiation trials.[19] It is a well-established radiobiologic tenet that fractionated RT results in accelerated repopulation. Clinical trials in patients with squamous cell carcinomas of the head and neck treated with definitive RT have conclusively demonstrated that prolongation of the overall treatment time is associated with inferior tumor control.[20] Prolongation of overall treatment time has also been associated with inferior tumor control in patients with cervical cancer[21] and bladder cancer.[22] Preclinical studies have also demonstrated the phenomenon of accelerated population following treatment of rodent tumors with chemotherapy.[26]

Treatment with cisplatin before radiotherapy may have resulted in radioresistance through activation of epidermal growth factor receptor expression or through activation of other signal transduction pathways.[23] Although cisplatin is thought to be a radiosensitizer, there are reports that cisplatin treatment can increase DNA repair and enhance survival of residual tumor clones after radiation exposure resulting in radioresistance.[24,25] Neoadjuvant cisplatin chemotherapy before definitive chemoradiation has failed to improve results despite initial objective tumor response in numerous phase III trials in patients with squamous cell cancers of the head and neck, cervical cancer, esophageal cancer, and non–small-cell lung cancer.[23]

Table 3. Number of Patients With Late Grade 3 or 4 Toxicity by Type and Treatment Arm*

Type	RT + FU/MMC		RT + FU/CDDP	
	Grade 3	Grade 4	Grade 3	Grade 4
Skin	6	6	3	5
Small/large intestine	5	5	7	1
Subcutaneous tissue	4	1	3	2
Other	20	3	14	7

Abbreviations: RT + FU/CDDP, radiation therapy plus fluorouracil/cisplatin; RT + FU/MMC, RT plus fluorouracil/mitomycin.
*Toxicities were graded with Radiation Therapy Oncology Group/European Organisation for Research and Treatment of Cancer late radiation morbidity scoring schema.

Future Possibilities

CCR with FU/MMC has a statistically significant, clinically meaningful impact on DFS and OS versus induction plus concurrent FU/CDDP and borderline significance for CFS, CF, and LRF. Therefore, RT + FU/MMC remains the preferred standard of care for patients with anal canal carcinoma. In addition, the use of induction chemotherapy with FU/CDDP before definitive chemoradiation is not recommended, on the basis of both the earlier analyses and this analysis.

There are several potential strategies for improving outcomes for patients with anal canal carcinoma: treatment intensification, treatment modification based on positron emission tomography (PET)/CT response, and individualized molecular-based treatment. Treatment intensification/modification has implications with regard to each potential component of treatment (RT, chemotherapy, and surgery).

From the perspective of RT, the use of IMRT has been shown to decrease morbidity, including perineal reactions, in both single-institution and multi-institution studies, including the recent phase II RTOG 0529 trial [A Phase II Evaluation of Dose-Painted IMRT in Combination with 5-Fluorouracil and Mitomycin-C for Reduction of Acute Morbidity in Carcinoma of the Anal Canal].[27] Accordingly, RT intensification may be possible as a result of both an increase in RT dose (increase dose within boost field to 65 to 70 Gy) and decrease in treatment duration. As noted previously, RT duration/delays have been shown to have a negative effect on outcomes in a variety of squamous cell cancers including head and neck, cervical, and anal cancer.[19-21]

With regard to systemic components of treatment, further evaluation of the optimal concurrent chemotherapy alone or plus biologics continues to be pertinent. Whether the intense concurrent regimen of FU 1,000 mg/m^2 per day for days 1 through 4 and days 29 through 32 of RT could be replaced by regimens for rectal cancer remains to be determined (ie, protracted venous infusion FU 200 to 250 mg/m^2 per day Monday through Friday each week; capecitabine 825 mg/m^2 twice per day, Monday through Friday each week). Some anal carcinomas express biomarkers of therapy resistance such as sonic hedgehog, nuclear factor kappa B and nuclear Gli1.[28] Thus, these pathways lend themselves to therapeutic exploitation. As local disease control becomes optimized, systemic approaches may have to be re-evaluated for patients with TN category of disease that have higher risks of systemic relapse.[11]

At present, surgery is used mainly as salvage treatment for patients with lack of complete response to CCR. The hope is that salvage surgery is instituted as early as possible so that resection translates to locoregional disease control and cure. However, inferior survival in the RT + FU/CDDP arm in this trial suggests that surgical salvage may not have been used at an optimal interval. For patients at higher risk of local relapse despite CCR, it may be preferable to obtain a baseline PET/CT study and repeat it within 4 weeks of completion of treatment.[11] Patients with less-than-optimal PET/CT response could proceed to early surgical salvage, which may include the possibility of local excision in select patients.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

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