

## Long-Term Update of U.S. GI Intergroup RTOG 98-11 Phase III Trial for Anal Carcinoma: Concurrent Chemoradiation With 5FU-Mitomycin vs 5FU-Cisplatin Improves Disease-Free and Overall Survival

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### Background

- Initial analysis of U.S. GI Intergroup RTOG 98-11 found that concurrent chemoradiation (CCRT) with 5FU + mitomycin (MMC) had a decrease in colostomy failure (10% vs 19%, p=0.02) when compared with induction plus concurrent 5FU+cisplatin (CDDP).
- The intent of the current analysis is to determine the long-term impact of treatment on survival (disease-free [DFS], overall [OS], colostomy-free [CFS]), relapse (local-regional [LRF], distant [DM]), and colostomy failure (CF).

### Methods

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

### Results

- Of 682 patients accrued, 649 were analyzable for outcomes by treatment arm.
- OS, DFS were statistically better for RT+5FU/MMC vs RT+5FU/CDDP as seen in Table 1 and Figure 1 (5-yr DFS, 67.7% vs 57.6%, p=0.0044; 5-yr OS, 78.2% vs 70.5%, p=0.021).
- LRF, CFS, and CF: There was a trend toward a statistically significant improvement with RT+5FU/MMC vs RT+5FU/CDDP as seen in Tables 1-2 and Figures 2A, 3A-B (5-yr LRF, 20% vs 26.5%, p=0.089; 5-yr CFS, 71.8% vs 64.9%, p=0.053; 5-yr CF, 11.9% vs 17.3%, p=0.075).
- Multivariate analyses: Revealed similar results (Tables 3-4).

Table 1: Impact of Treatment Arm on Survival

Treatment Arm	No. Pts	DFS		OS		CFS	
		Total Failures	5yr, % (95% CI)	Total Deaths	5yr, % (95% CI)	Total Failures	5yr, % (95% CI)
RT+5FU/MMC	325	117	67.7 (62.2, 72.6)	80	78.2 (73.1, 82.4)	101	71.8 (66.4, 76.5)
RT+5FU/CDDP	324	156	57.6 (51.8, 62.9)	108	70.5 (65.0, 75.3)	126	64.9 (59.3, 69.9)
Log-rank p-value		0.0044		0.021		0.053	

Table 2: Impact of Treatment Arm on Relapse and Colostomy Failure

Treatment Arm	No. Pts	LRF		DM		CF	
		Total Failures	5 yr, % (95% CI)	Total Failures	5 yr, % (95% CI)	Total Failures	5 yr, % (95% CI)
RT+5FU/MMC	325	67	20.0 (15.6, 24.4)	45	13.1 (9.3, 16.8)	38	11.9 (8.3, 15.4)
RT+5FU/CDDP	324	86	26.5 (21.6, 31.4)	60	17.8 (13.6, 22.1)	55	17.3 (13.1, 21.5)
Gray's test p-value		0.089		0.12		0.075	

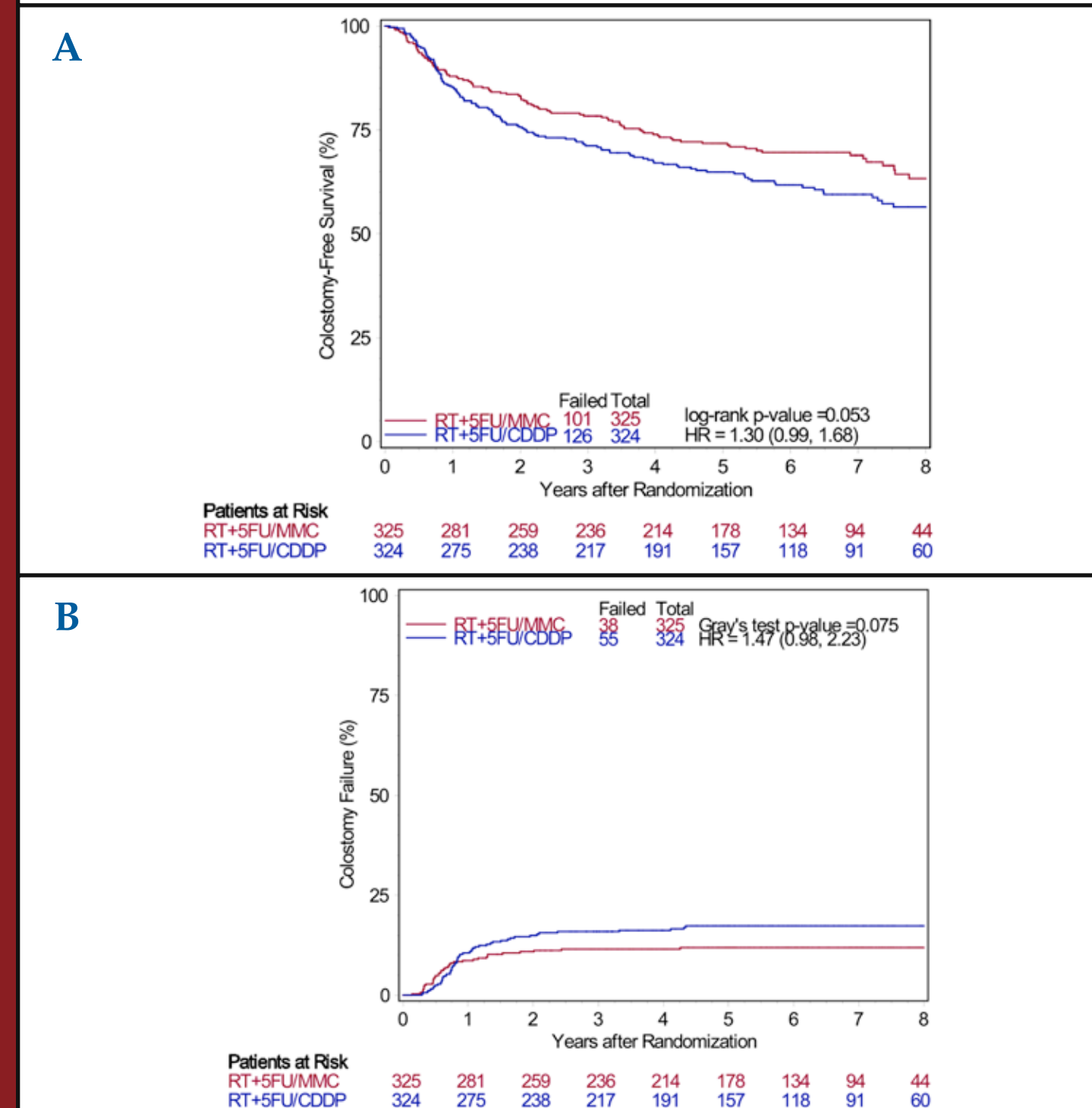
Table 3: Multivariate Analysis for DFS

Variable	Comparison	Adjusted HR (95% CI)	p-value
Treatment	5FU/MMC vs 5FU/CDDP	1.42 (1.11, 1.80)	0.0043
Gender	Female vs Male	1.30 (1.01, 1.67)	0.045
Primary size	>2-5 cm vs >5 cm	1.54 (1.20, 1.98)	0.0008
Clinical node status	Negative vs Positive	1.84 (1.43, 2.37)	<0.0001

Table 4: Multivariate Analysis for OS

Variable	Comparison	Adjusted HR (95% CI)	p-value
Treatment	5FU/MMC vs 5FU/CDDP	1.42 (1.06, 1.89)	0.019
Gender	Female vs Male	1.40 (1.04, 1.89)	0.029
Primary size	>2-5 cm vs >5 cm	1.40 (1.03, 1.91)	0.030
Clinical node status	Negative vs Positive	1.84 (1.37, 2.49)	<0.0001

Figure 3A-B: Impact of RT+5FU/MMC vs RT+5FU/CDDP on (A) CFS (p=0.053) and (B) CF (p=0.075)



### Conclusions

- CCRT with 5FU/MMC has a significant impact on DFS and OS (p=0.0044 and 0.021).
- RT+5FU/MMC has borderline statistical significance for CFS, LRF, and CF (p=0.053, 0.089 and 0.075).
- Male gender, >5 cm tumor diameter and clinical N+ are independent poor prognostic factors for DFS and OS.
- RT+5FU/MMC remains the standard of care for patients with anal canal carcinoma.
- Potential strategies to improve outcomes include: Treatment intensification and individualized, molecular-based treatment approaches.

Figure 1A-B: Impact of RT+5FU/MMC vs RT+5FU/CDDP on (A) DFS (p=0.0044) and (B) OS (p=0.021)

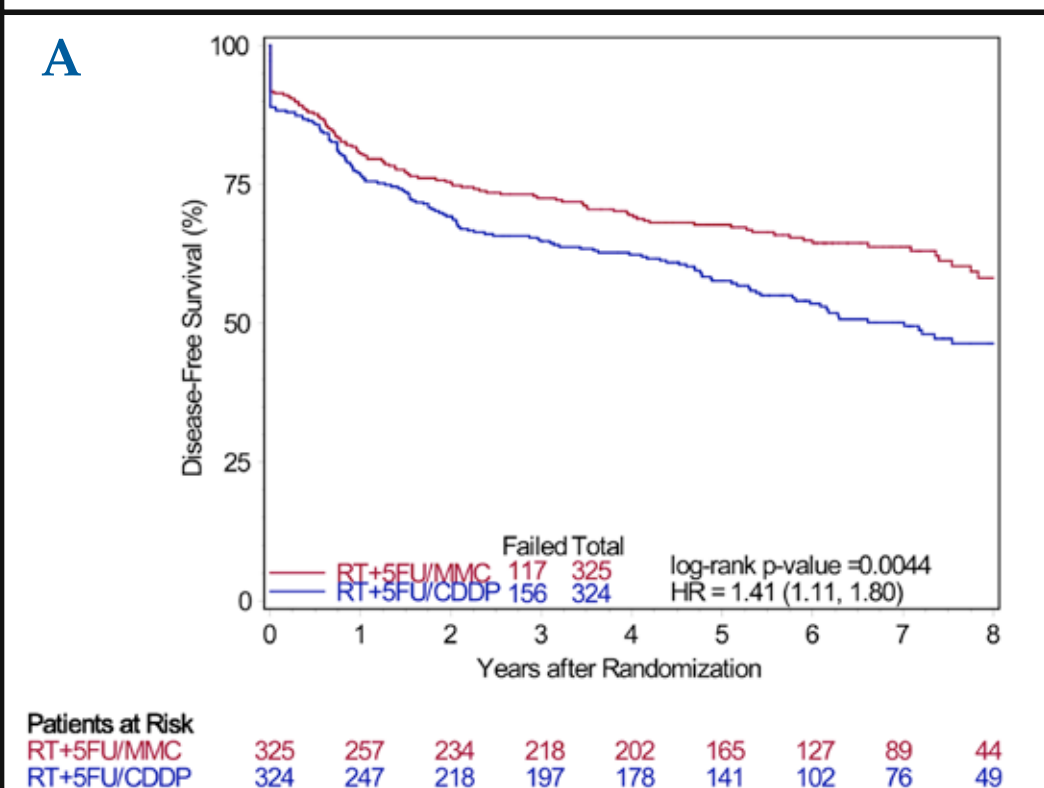


Figure 2A-B: Impact of RT+5FU/MMC vs RT+5FU/CDDP on (A) LRF (p=0.092) and (B) DM (p=0.12)

