

***Long-term update of US GI Intergroup
RTOG 98-11 Phase III trial for anal
carcinoma: Concurrent chemoradiation
with 5FU-Mitomycin, yields better
disease-free and overall survival than
5FU-Cisplatin***

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U.S. GI Intergroup RTOG 98-11

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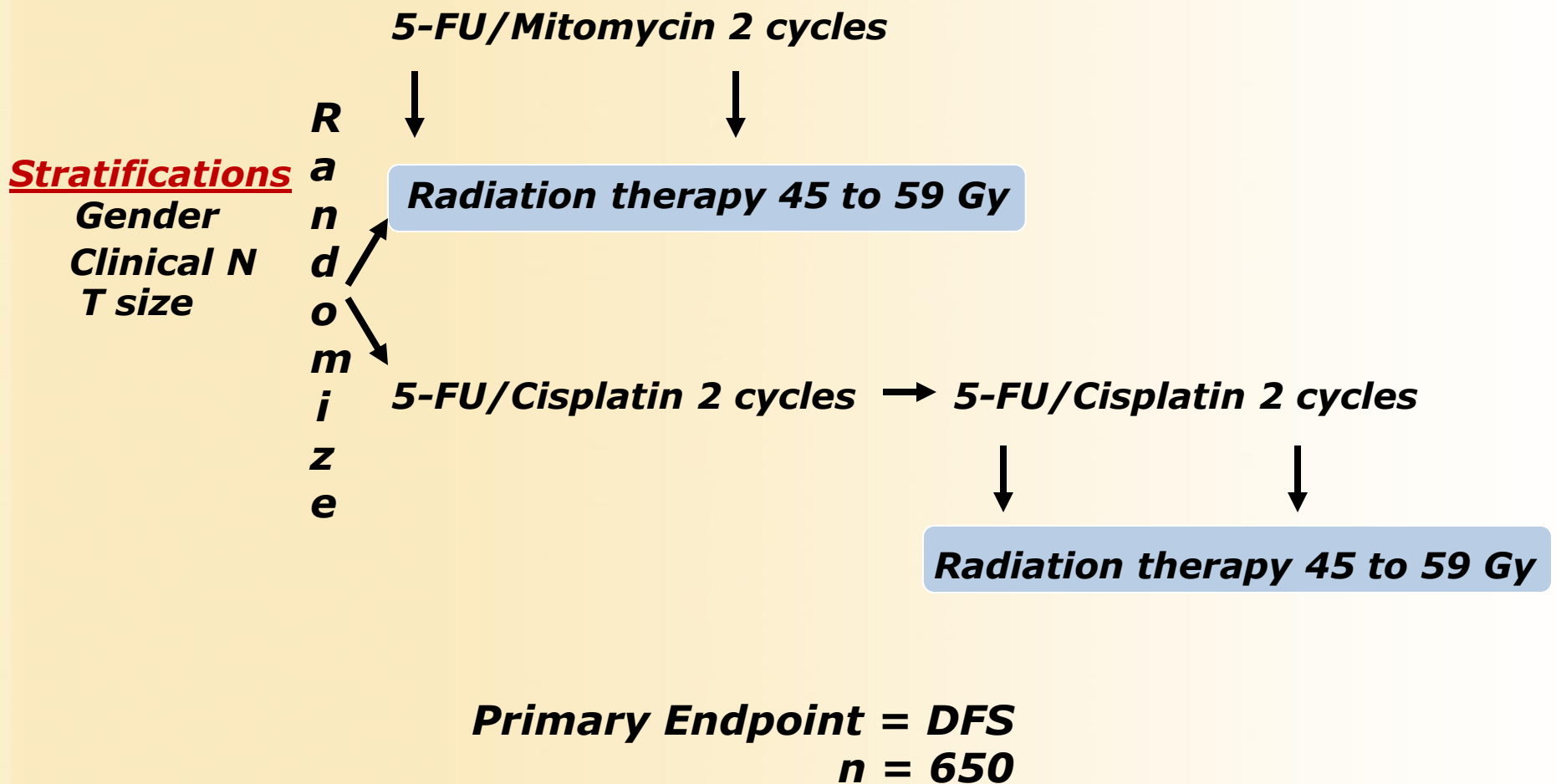
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Participating Cooperative Groups

- CALGB
- ECOG
- NCCTG
- RTOG the Coordinating Group
- SWOG

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Objectives

- **Primary Objective:**
 - **Disease-Free Survival (DFS)**
- **Secondary Objectives:**
 - **Overall Survival (OS)**
 - **Cumulative rate of colostomy**
 - **Rate of local-regional relapse**
 - **Differences in toxicities**

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Eligibility and Stratifications

- **Eligibility**
 - Histologic proof of anal canal carcinoma
 - ≥ 18 years of age
 - KPS ≥ 60
 - T2 to T4 category
 - Any N category (pelvic or inguinal)
 - Adequate organ function
 - Written consent
- **Stratification Factors**
 - Male vs. Female
 - Clinical N+ vs. N0
 - Primary size: >2 to 5 cm vs. > 5 cm

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Background

- **Initial analysis of U.S. GI Intergroup RTOG 98-11 found a decrease in colostomy failure for RT/5FU+mitomycin (MMC) vs. RT/5FU+cisplatin (CDDP), 10 vs. 19%, $p=0.02$, (JAMA 2008; 299:1914-21) but no significant impact on disease-free or overall survival (DFS, OS)**
- **Intent of current analysis - determine long-term impact of treatment on survival (OS, DFS, colostomy-free), disease relapse (local-regional, distant) and colostomy failure**

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Status of Cases, Current Analysis

	RT+5FU/MMC	RT+5FU/CDDP	Total
Total patients entered	341	341	682
Ineligible	12	13	25
Withdrew consent	2	4	6
No follow-up info	2	0	2
Eligible, Current Analysis	325	324	649
On-study information	325	324	649
Early toxicity info	325	324	649
Late toxicity info	321	317	638
No protocol treatment	0	5	5

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Selected Pretreatment Characteristics

Stratification Factor	RT+5FU/MMC (n=325)	RT+5FU/CDDP (n=324)
Gender		
Male	101 (31%)	98 (30%)
Female	224 (69%)	226 (70%)
Primary Size		
>2-5 cm	237 (73%)	236 (73%)
>5 cm	88 (27%)	88 (27%)
Clinical Node Status		
Positive	85 (26%)	85 (26%)
Negative	227 (70%)	223 (69%)
Unknown	13 (4%)	16 (5%)

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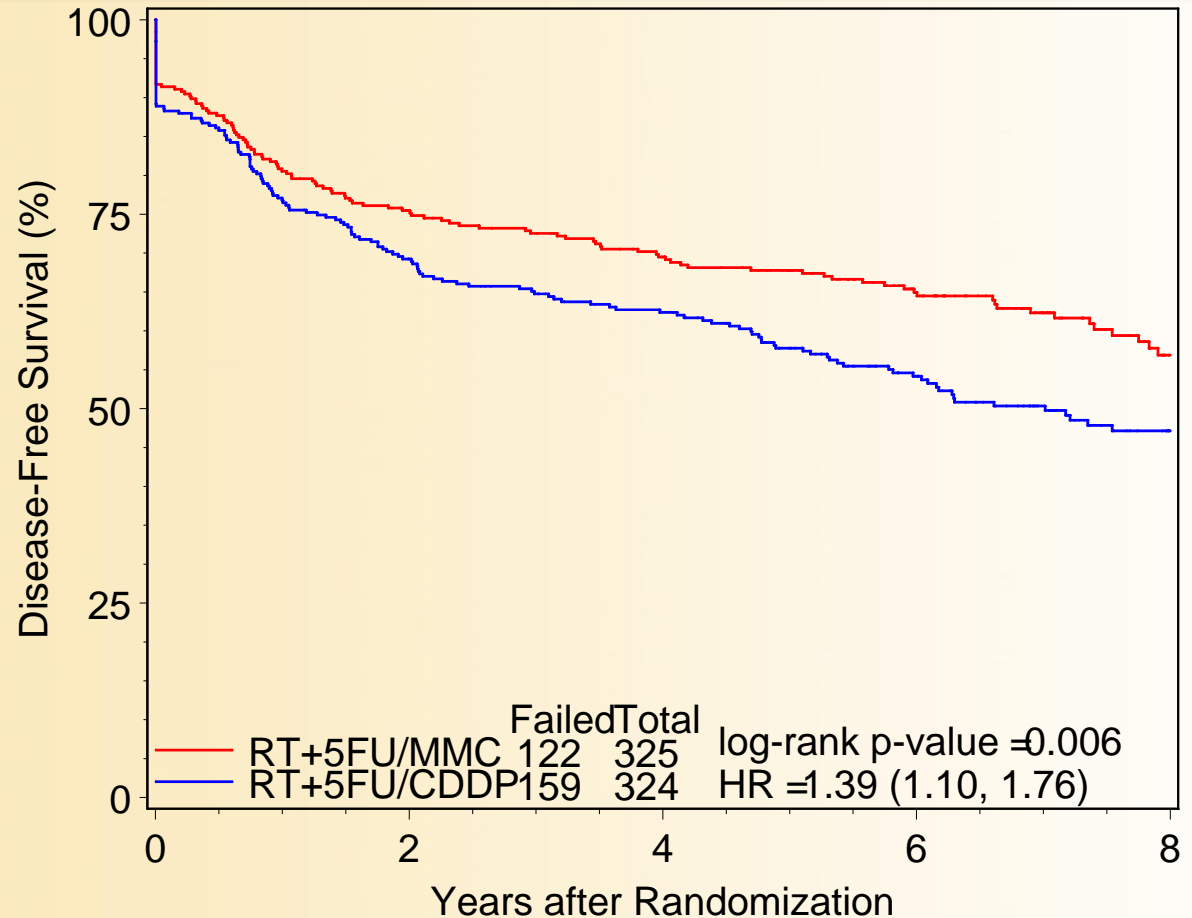
Disease-Free Survival

Year	RT+5FU/MMC (n=325)	RT+5FU/CDDP (n=324)
0	100%	100%
1	80.5	76.8
2	75.5	69.2
3	72.5	64.8
4	69.5	62.4
5	67.8	57.8
	(62.3, 72.6)	(52.1, 63.0)
6	64.9	54.2
7	62.3	50.3
8	56.9	47.1
Total Failed	122	159

p-value = 0.006 (2-sided log-rank)

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Disease-Free Survival



Patients at Risk	0	2	4	6	8
RT+5FU/MMC	325	234	204	144	59
RT+5FU/CDDP	324	218	181	121	57

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Multivariate Analysis for DFS

Adjustment variable	Comparison	Adjusted HR (95% CI)	p-value*
Treatment	5FU/MMC vs. 5FU/CDDP	1.40 (1.10-1.77)	0.0055
Gender	Female vs. Male	1.29 (1.01-1.66)	0.044
Primary Size	>2-5 cm vs. >5 cm	1.56 (1.21-2.00)	0.0005
Clinical Node Status	Negative vs. Positive	1.80 (1.40-2.31)	<0.0001

*Cox proportional hazards model

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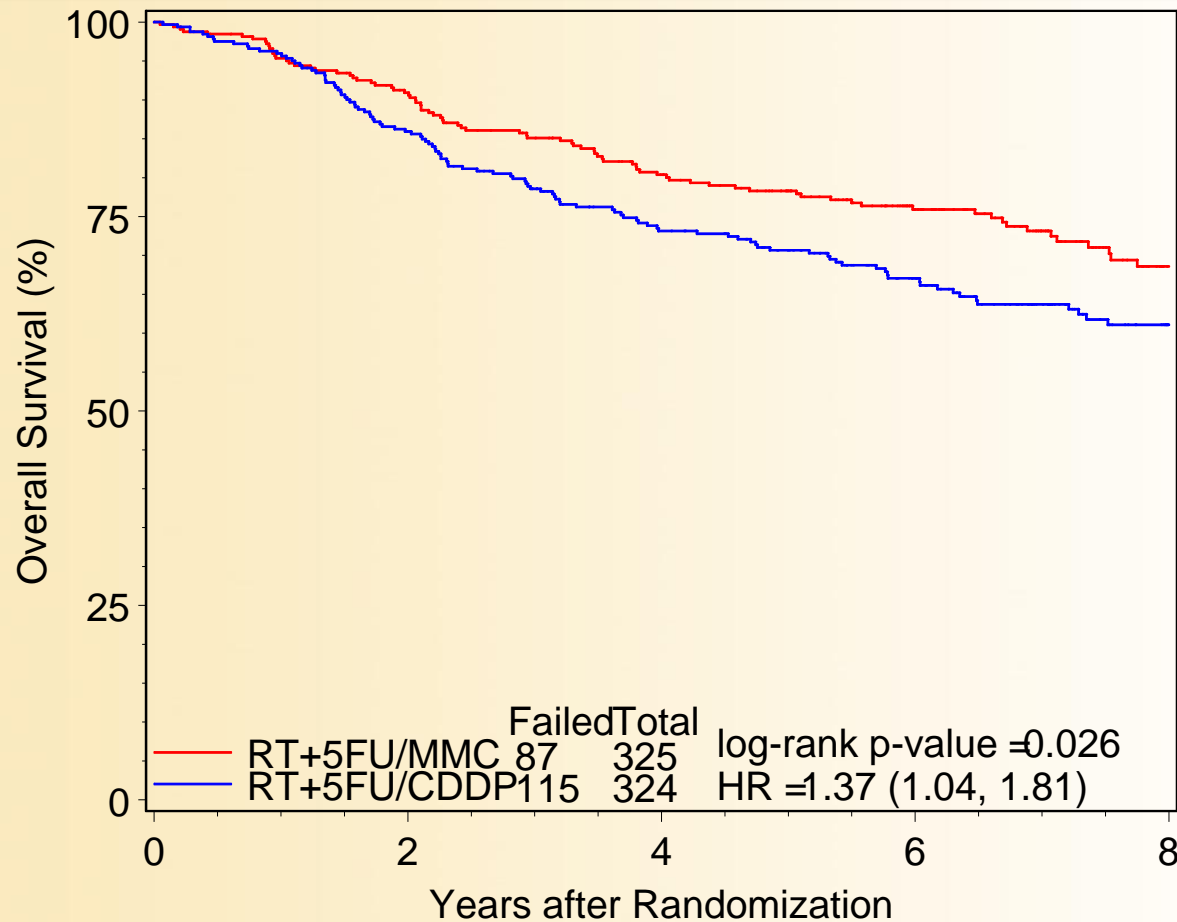
Overall Survival

Year	RT+5FU/MMC (n=325)	RT+5FU/CDDP (n=324)
0	100%	100%
1	95.3	96.0
2	90.9	85.9
3	85.1	78.6
4	80.4	73.2
5	78.3	70.7
	(73.2, 82.5)	(65.2, 75.4)
6	75.9	67.1
7	73.2	63.7
8	68.6	61.1
Total Deaths	87	115

p-value = 0.026 (2-sided log-rank)

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Overall Survival



Patients at Risk	0	2	4	6	8
RT+5FU/MMC	325	283	235	168	68
RT+5FU/CDDP	324	271	213	151	76

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Multivariate Analysis for OS

Adjustment variable	Comparison	Adjusted HR (95% CI)	p-value*
Treatment	5FU/MMC vs. 5FU/CDDP	1.38 (1.05-1.83)	0.023
Gender	Female vs. Male	1.39 (1.04-1.86)	0.027
Primary Size	>2-5 cm vs. >5 cm	1.32 (0.98-1.78)	0.065
Clinical Node Status	Negative vs. Positive	1.86 (1.40-2.49)	<0.0001

*Cox proportional hazards model

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Relapse by Treatment Arm

Treatment Arm	No. Pts	<u>LRF</u>		<u>DF</u>		<u>CF</u>	
		TF	5yr,% (95% CI)	TF	5yr,% (95% CI)	TF	5yr,% (95% CI)
RT + 5FU/MMC	325	67	20.0 (15.6, 24.4)	46	13.1 (9.3, 16.8)	38	11.9 (8.3, 15.4)
RT + 5FU/CDDP	324	86	26.4 (21.5, 31.3)	61	18.1 (13.8, 22.4)	55	17.3 (13.1, 21.5)
Gray's test p-value			0.087		0.12		0.074
HR (95% CI)			1.33 (0.97, 1.83)		1.37 (0.94, 2.02)		1.48 (0.98, 2.23)

Abbreviations: LRF, local-regional failure; DF, distant failure; CF, colostomy failure; TF, total failures; HR, hazard ratio

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Colostomy Failure

Year	RT + 5FU/MMC (n=325)	RT+5FU/CDDP (n=324)
0	0%	0%
1	8.7	10.6
2	10.9	14.9
3	11.5	15.9
4	11.5	16.2
5	11.9	17.3
	(8.3, 15.4)	(13.1, 21.5)
6	11.9	17.3
7	11.9	17.3
8	11.9	17.3
Total Failed	38	55

p-value = 0.074 (Gray's test)

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Conclusions

- RT+5FU/MMC has statistically better DFS & OS than RT+5FU/CDDP**
(5-yr DFS: 67.8 vs. 57.8%, $p=0.006$; 5-yr OS: 78.3 vs. 70.7%, $p=0.026$).
- RT+5FU/MMC has borderline statistical significance for CFS, LRF, and CF ($p=0.05$, 0.087 and 0.074).
- Possible reasons for superiority of RT+5FU/MMC**
 - Concurrent RT + 5FU/MMC more effective than RT+5FU/CDDP**
 - Neoadjuvant 5FU/CDDP**
 - Delay to concurrent chemoradiation
 - Platin-induced radioresistance

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Conclusions; Future Strategies

4. Males, >5 cm tumor diameter, and clinical N+ cancer were independent poor prognosticators for DFS.
5. RT+5FU/MMC remains the standard of care for patients with anal canal carcinoma.
6. Potential strategies to improve outcomes:
 - a) *Treatment intensification*
 - 1) EBRT: IMRT dose escalation, decrease treatment duration
 - 2) Chemo/targeted agents
 - 3) Earlier surgical salvage – PET based
 - b) *Individualized molecular-based treatment*