

***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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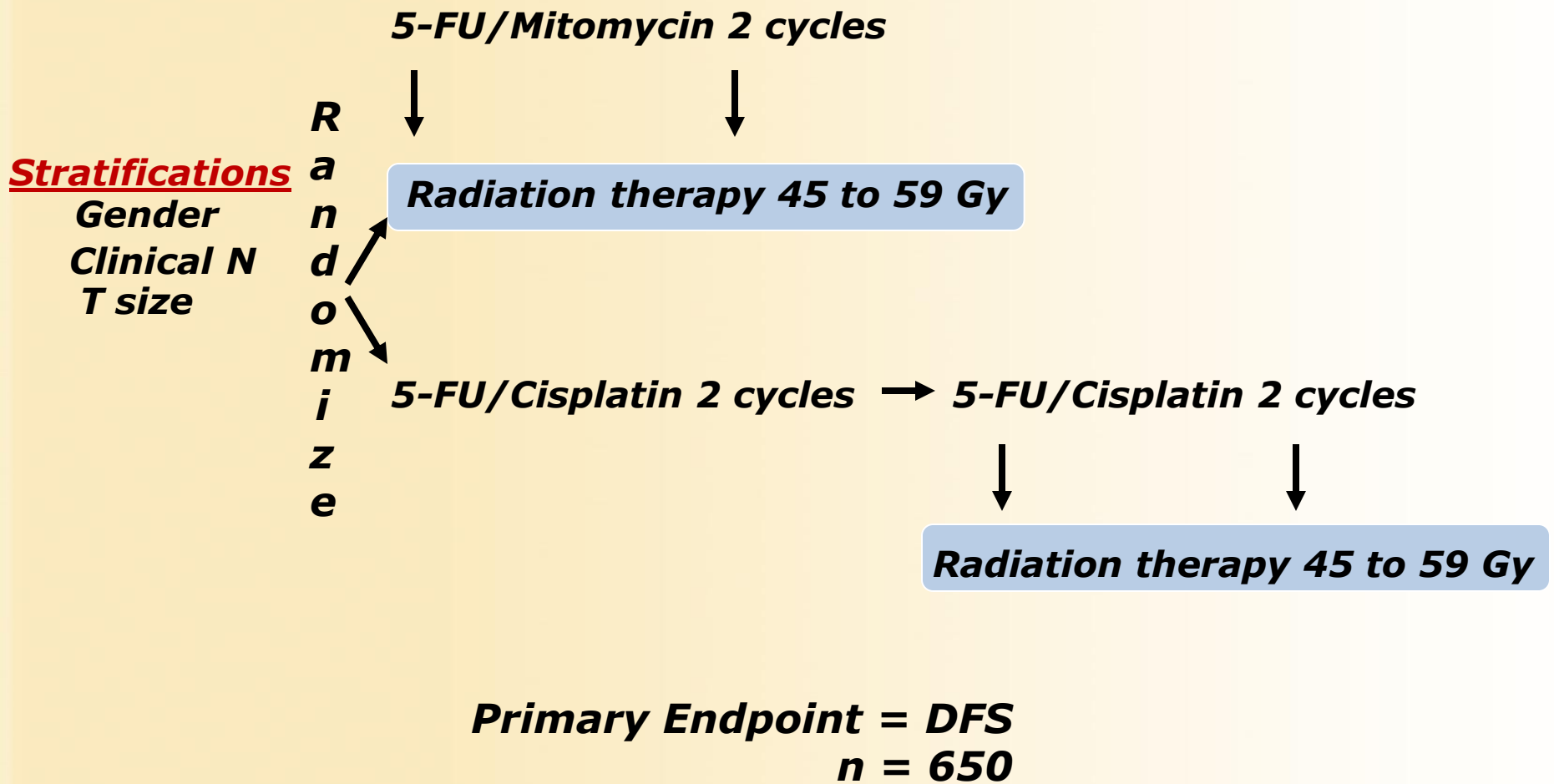
***Supported by RTOG grant U10 CA21661 and CCOP grant U10 CA37422 from the National Cancer Institute (NCI).***

# U.S. GI Intergroup RTOG 98-11

## Participating Cooperative Groups

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

# U.S. GI Intergroup RTOG 98-11 Schema



# U.S. GI Intergroup RTOG 98-11

## 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
  - $\geq 18$  years of age
  - KPS  $\geq 60$
  - 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      |
|-----------------------------------|------------|-------------|------------|
| <b>Total patients entered</b>     | <b>341</b> | <b>341</b>  | <b>682</b> |
| <b>Ineligible</b>                 | <b>12</b>  | <b>13</b>   | <b>25</b>  |
| <b>Withdrew consent</b>           | <b>2</b>   | <b>4</b>    | <b>6</b>   |
| <b>No follow-up info</b>          | <b>2</b>   | <b>0</b>    | <b>2</b>   |
| <b>Eligible, Current Analysis</b> | <b>325</b> | <b>324</b>  | <b>649</b> |
| <b>On-study information</b>       | <b>325</b> | <b>324</b>  | <b>649</b> |
| <b>Early toxicity info</b>        | <b>325</b> | <b>324</b>  | <b>649</b> |
| <b>Late toxicity info</b>         | <b>321</b> | <b>317</b>  | <b>638</b> |
| <b>No protocol treatment</b>      | <b>0</b>   | <b>5</b>    | <b>5</b>   |



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## Selected Pretreatment Characteristics

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

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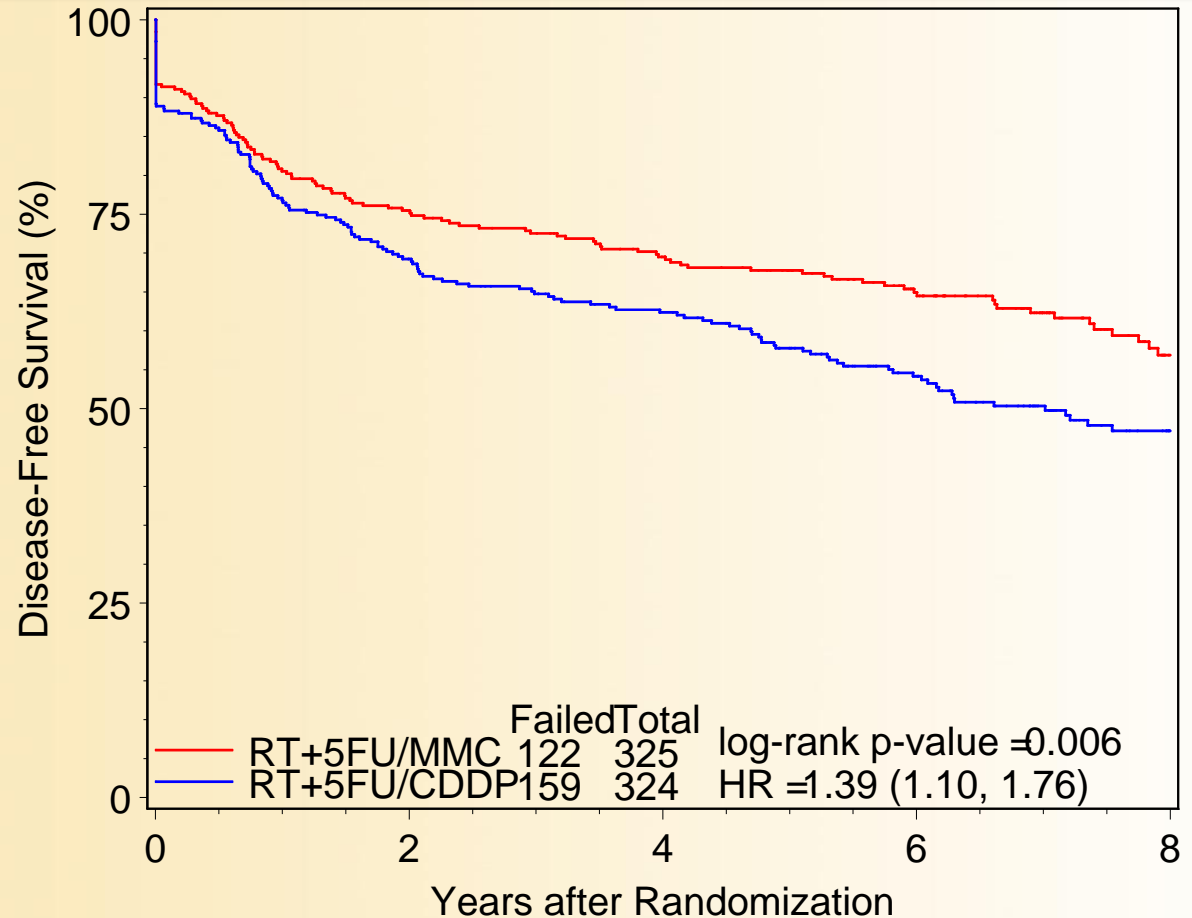
## Disease-Free Survival

| Year         | RT+5FU/MMC<br>(n=325) | RT+5FU/CDDP<br>(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<br>(95% CI) | p-value* |
|----------------------|--------------------------|-------------------------|----------|
| Treatment            | 5FU/MMC vs.<br>5FU/CDDP  | 1.40<br>(1.10-1.77)     | 0.0055   |
| Gender               | Female vs.<br>Male       | 1.29<br>(1.01-1.66)     | 0.044    |
| Primary Size         | >2-5 cm vs.<br>>5 cm     | 1.56<br>(1.21-2.00)     | 0.0005   |
| Clinical Node Status | Negative vs.<br>Positive | 1.80<br>(1.40-2.31)     | <0.0001  |

\*Cox proportional hazards model

# U.S. GI Intergroup RTOG 98-11

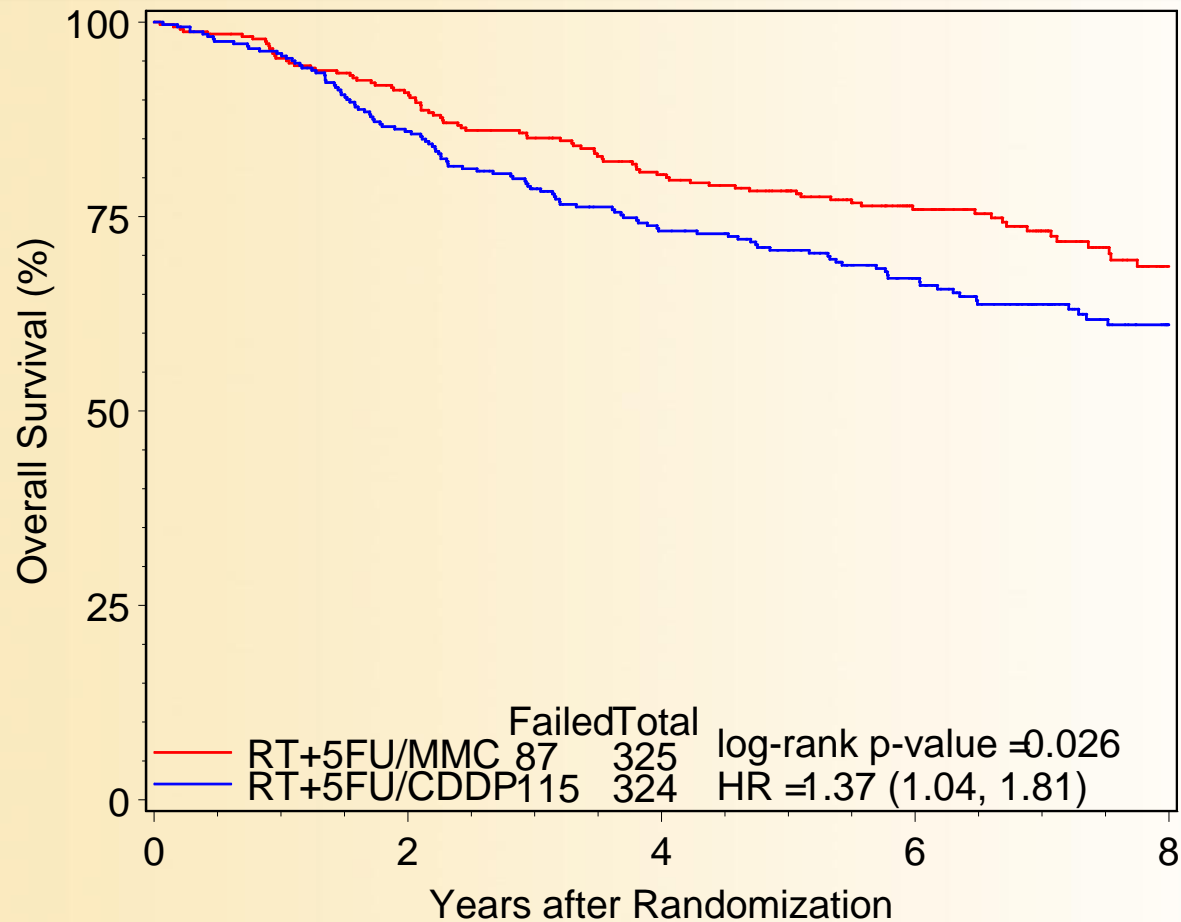
## Overall Survival

| Year         | RT+5FU/MMC<br>(n=325) | RT+5FU/CDDP<br>(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 |     |     |     |     |    |
|------------------|-----|-----|-----|-----|----|
| 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<br>(95% CI) | p-value* |
|----------------------|--------------------------|-------------------------|----------|
| Treatment            | 5FU/MMC vs.<br>5FU/CDDP  | 1.38<br>(1.05-1.83)     | 0.023    |
| Gender               | Female vs.<br>Male       | 1.39<br>(1.04-1.86)     | 0.027    |
| Primary Size         | >2-5 cm vs.<br>>5 cm     | 1.32<br>(0.98-1.78)     | 0.065    |
| Clinical Node Status | Negative vs.<br>Positive | 1.86<br>(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,%<br>(95% CI)    | TF        | 5yr,%<br>(95% CI)    | TF        | 5yr,%<br>(95% CI)    |
| RT + 5FU/MMC        | 325     | 67         | 20.0<br>(15.6, 24.4) | 46        | 13.1<br>(9.3, 16.8)  | 38        | 11.9<br>(8.3, 15.4)  |
| RT + 5FU/CDDP       | 324     | 86         | 26.4<br>(21.5, 31.3) | 61        | 18.1<br>(13.8, 22.4) | 55        | 17.3<br>(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<br>(n=325) | RT+5FU/CDDP<br>(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                   |
| <b>Total Failed</b> | <b>38</b>               | <b>55</b>              |

**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*