XXIII CONGRESSO

AIRO2013

Giardini Naxos - Taormina, 26 - 29 ottobre

# *Carcinoma del Canale Anale*

# Approcci RadioChemioterapici

**Antonino De Paoli**

Oncologia Radioterapica, CRO Aviano

# Anal Cancer
## Epidemiology and Risk Factors

**Uncommon Disease;** 2-4% of all GI Tumors

**Increasing Incidence over last 25 years**

**HPV- Associated in 70-90% of cases**

**Risk Factors:** Immunosuppression
(HIV infection, post-transplantation)

# *Management of Anal Cancer 1st RCTs Generation*

Definitive CT-RT (EBRT+MMC-FU) ND Nigro, *Cancer '83*

Definitive RT+/- CT (EBRT+BRT) J Papillon, DCR '87

- **UKCCR ACT I Trial;** Lancet 1996, *BJC 2010*
  *CT-RT preferred to RT alone*
- **EORTC 22861 Trial;** JCO 1997
  *CT-RT preferred to RT alone*
- **RTOG 87-04 Trial;** JCO 1996
  *(FU+MMC/RT preferred to FU/RT)*

# Management of Anal Cancer
# 1st RCTs Generation - Results

| | UKCCR | | EORTC | | RTOG | |
|---|---|---|---|---|---|---|
| | RT | MMC-FU RT | RT | MMC-FU RT | FU RT | MMC-FU RT |
| Local Failure | 59 % | 36 % | 25 % | 15 % | 34 % | 16 % |
| | P=0.001 | | P=0.02 | | P=0.008 | |
| Colostomy free survival | 61 % | 72 % | 40% | 72% | 59 % | 71 % |
| | P=0.02 | | P=0.02 | | P=0.014 | |
| Overall survival | 58% | 65% | 65% | 72% | 65% | 67% |
| | P=0.25 | | P=0.31 | | P=0.17 | |

# *Management of Anal Cancer 1st RCTs Generation - Results*

**5-FU – MMC + RT 45-59 Gy**

Surgery for salvage

| | | |
|---|---|---|
| 5-years OS | 65%-72% | ( vs 58%-65% p=NS) |
| 5-years CFS | 71%-72% | ( vs 40%-59% p=0.02) |
| Local Failure | 16%-36% | ( vs 25%-59% p=0.02) |

*Acute G3+ Tox: 25%-60% (T. interruption)*

*Late effects: -<10%; 5% colostomy*

# *Management of Anal Cancer*

## 5-FU-DDP + RT _ Phase I-II Studies

| Study | Pts | CT-RT | CR | DFS | OS |
|---|---|---|---|---|---|
| Martenson et al<br>IJROBP '96 (ECOG) | 19 | 36+24Gy<br>FU+DDP 75m/m2 | 79% | - | - |
| Doci et al<br>JCO '96 | 35 | 36+24Gy<br>FU+DDP 100m/m2 | 94% | 94% (3ys) | 97% (3ys) |
| Peiffert et al<br>Ann Oncol '01 | 80 | 45+20Gy<br>*FU+DDP 80m/m2 | 93% | 70% (3ys) | 86% (3ys) |
| Gerard et al<br>Radiother Oncol '01 | 95 | 39+14-28Gy(BRT)<br>FU + DDP 25m/m2/d1- 4 | 90% | - | 84% (5ys) |

* Neoadj FU-DDP x 2 cycles; **5-FU 750-1000 mg/m2, d1-4; DDP 75-100 mg/m2, d1,29**

**CR 79-94%; Colostomy Free 73-86% at 3yrs**

# *Management of Anal Cancer 2nd RCTs Generation*

- **UKCCR ACT2 Trial**
  *DDP vs MMC+FU/RT +/- Maintenance FU-DDP*
- **RTOG 98-11 Trial**
  *FU+MMC/RT vs Neoadj FU-DDP & FU+DDP/RT*
- **ACCORD-03 Trial**
  *Neadj FU-DDP & FU+DDP/RT +HD or LD RT Boost*

# JKCCCR ACT II Trial

CT-RT comparison (CR rate)

CT maint comparison (RFS)

**R**

**Stage**
**T1-T4**
**N0/+**

**Concurrent DDP-5FU/RT**

**50.4Gy/28fr**
**DDP 100mg/m2 d1,28**
**5FU 1000mg/m2 d1-4 (wks 1,5)**

**2xDDP-FU**

**no Chemo**

**Concurrent MMC-5FU/RT**

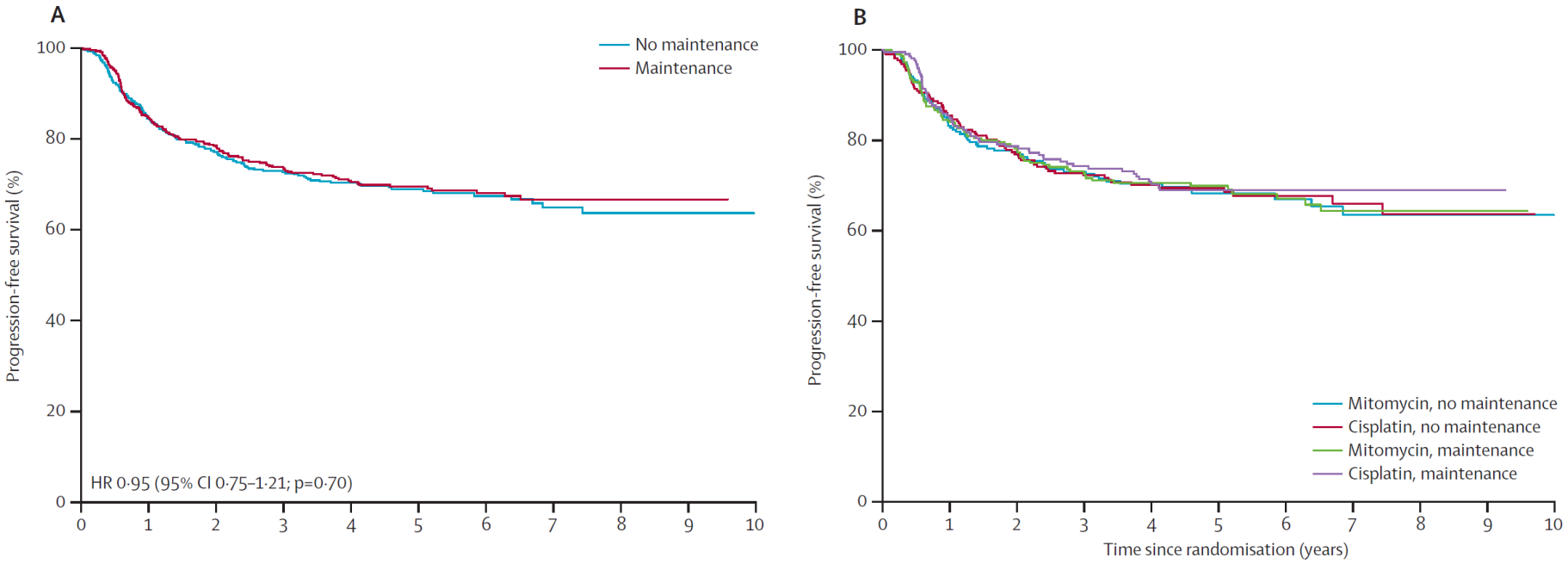
**50.4Gy/28fr**
**MMC 12mg/m2 d1only**
**5FU 1000mg/m2 d1-4 (wks 1,5)**

**2xDDP-FU**

**no Chemo**

# Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial

*Roger D James*, Robert Glynne-Jones*, Helen M Meadows, David Cunningham, Arthur Sun Myint, Mark P Saunders, Timothy Maughan, Alec McDonald, Sharadah Essapen, Martin Leslie, Stephen Falk, Charles Wilson, Simon Gollins, Rubina Begum, Jonathan Ledermann, Latha Kadalayil, David Sebag-Montefiore*



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| | Mitomycin group (n=432) | Cisplatin group (n=431) |
|---|---|---|
| Complete response | 391 (90·5%) | 386 (89·6%) |
| Partial response | 14 (3·2%) | 24 (5·6%) |
| Stable disease | 5 (1·2%) | 6 (1·4%) |
| Progressive disease | 22 (5·1%) | 15 (3·5%) |

***Table 2:*** **Primary tumour response at 26 weeks**

2012

# Optimum time to assess complete clinical response (CR) following chemoradiation (CRT) using mitomycin (MMC) or cisplatin (CisP), with or without maintenance CisP/5FU in squamous cell carcinoma of the anus: Results of ACT II.

Robert Glynne-Jones, Roger James, Helen Meadows, Rubina Begum, David Cunningham, John Northover, Jonathan A. Ledermann, Sandra Beare, Latha Kadalayil, David Sebag-Montefiore and ACT II Study Group

| | Pts with CR | Absolu difference<br>CR rate % |
|---|---|---|
| Week 11 | 429 | 65.6 |
| Week 18 | 527 | 75.4 |
| Week 26 | 582 | 83.5 |

CR 26 w = + 29%

202/695 (29%) pts not in CR at 11 weeks were CR at 26 weeks

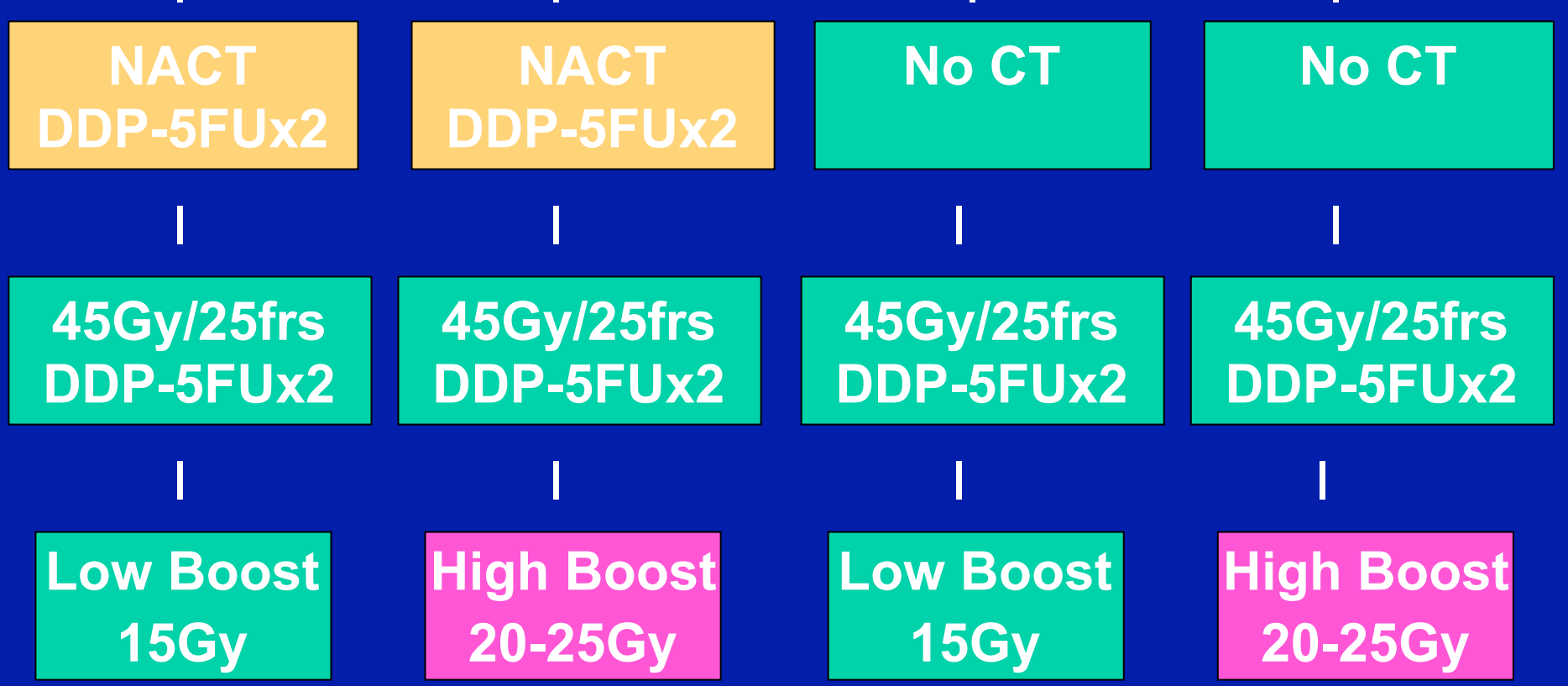
**Optimum time to assess complete clinical response (CR) = 26 weeks**

# ACCORD 03 Trial

Induction CT
High dose RT

R

DDP 100mg/m2 d1,29
5FU 1000mg/m2 d1-4 (wks 1,5)



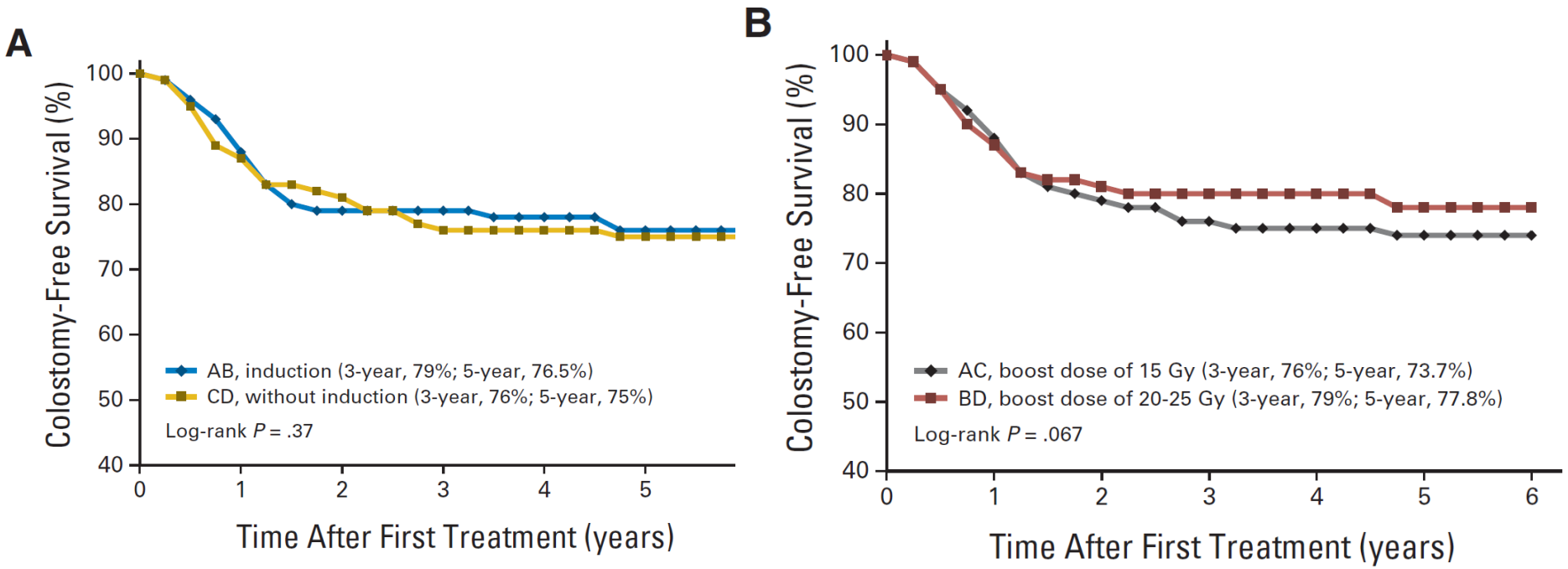
VOLUME 30 · NUMBER 16 · JUNE 1 2012

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Induction Chemotherapy and Dose Intensification of the Radiation Boost in Locally Advanced Anal Canal Carcinoma: Final Analysis of the Randomized UNICANCER ACCORD 03 Trial

*Didier Peiffert, Laetitia Tournier-Rangeard, Jean-Pierre Gérard, Claire Lemanski, Eric François, Marc Giovannini, Frédérique Cvitkovic, Xavier Mirabel, Olivier Bouché, Elisabeth Luporsi, Thierry Conroy, Christine Montoto-Grillot, Françoise Mornex, Antoine Lusinchi, Jean-Michel Hannoun-Lévi, Jean-François Seitz, Antoine Adenis, Christophe Hennequin, Bernard Denis, and Michel Ducreux*



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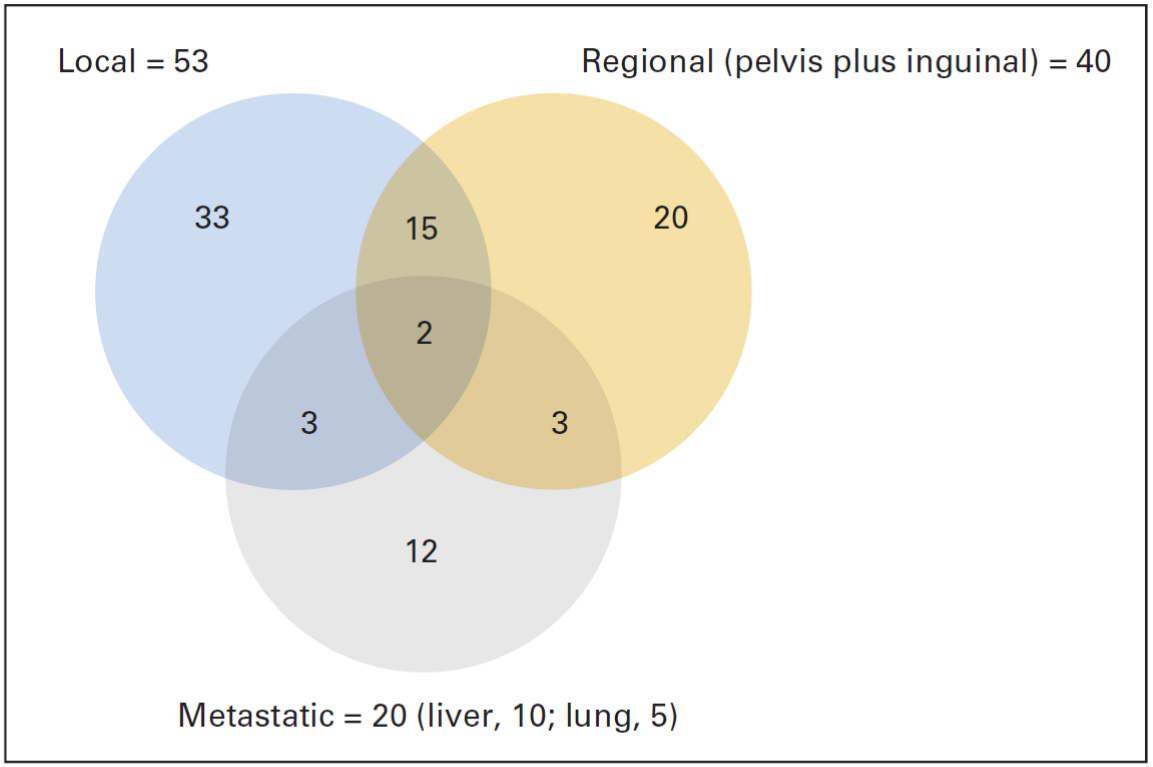


# RTOG 98-11 Trial

Stratification

Gender

Clinical N

T size

R

P. endpoint
DFS

DDP
FU

DDP
FU

Concurrent
DDP-5FU/RT

45 to 59Gy/25-30 frs (break)
DDP 100mg/m2 d1,29
5FU 1000mg/m2 d1-4 (wks 1,5)

Concurrent
MMC-5FU/RT

45 to 59Gy/25-30 frs (break)
MMC 12mg/m2 d1, 29
5FU 1000mg/m2 d1-4 (wks 1,5)

VOLUME 30 · NUMBER 35 · DECEMBER 10 2012

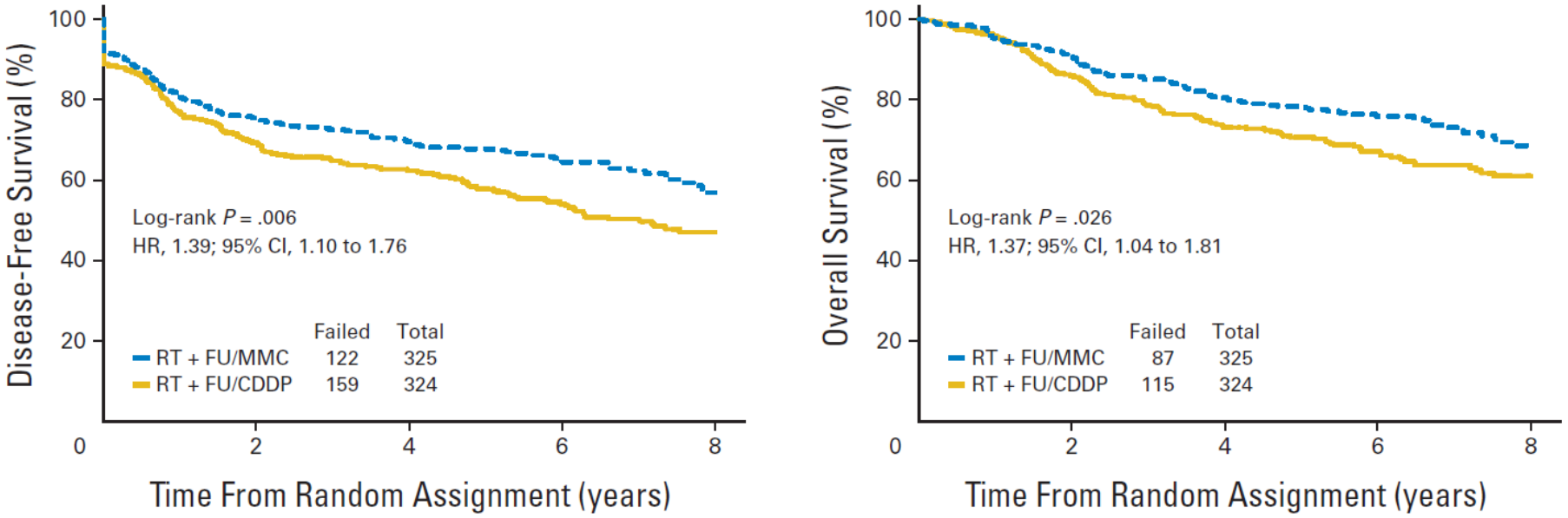
JOURNAL OF CLINICAL ONCOLOGY

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

*Leonard L. Gunderson, Kathryn A. Winter, Jaffer A. Ajani, John E. Pedersen, Jennifer Moughan, Al B. Benson III, Charles R. Thomas Jr, Robert J. Mayer, Michael G. Haddock, Tyvin A. Rich, and Christopher G. Willett*

**A**



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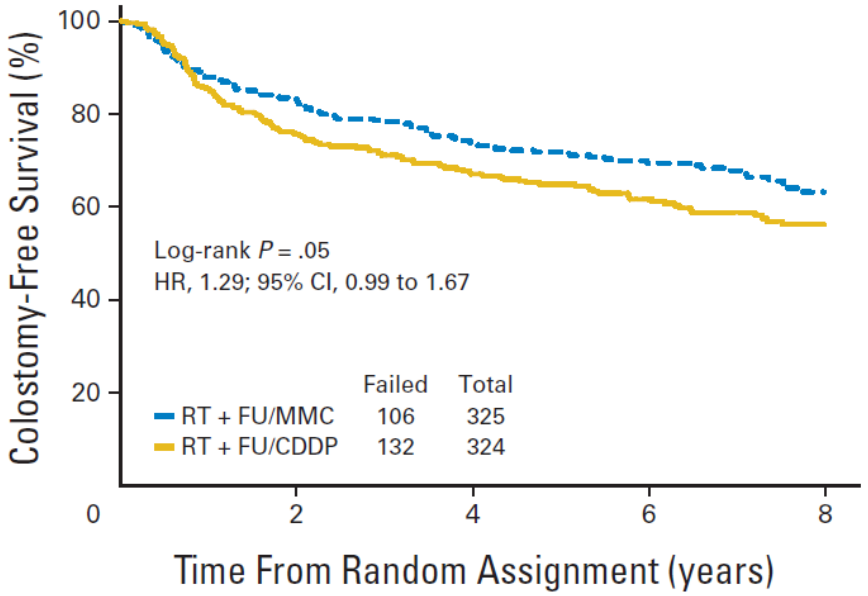


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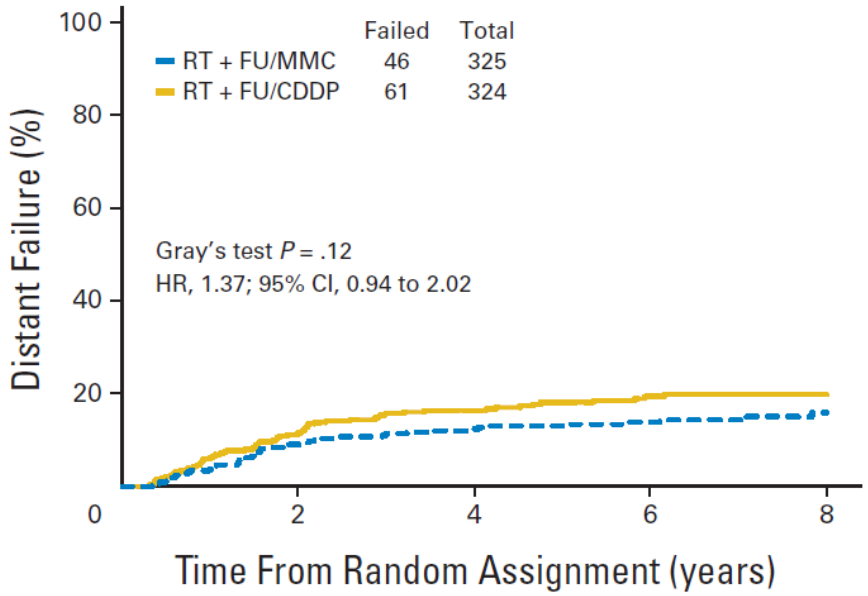


# *Management of Anal Cancer 2nd RCTs Generation*

## Long-Term Results

| | Treatment | CFS (%) | OS (%) | G3-4 hem Tox | G3-4 non-hem Tox | Late Toxic effects |
|---|---|---|---|---|---|---|
| RTOG 98-11 | RT FU-Mito | 72% | 78% | 61% | 74% | Colostomy 1% |
| | RT FU-P | 65% | 71% | 42% | 74% | |
| ACCORD-3 | NACT-RTCT+15Gy | 70% | 75% | 19% | 9% | Colostomy 3% |
| | NACT-RTCT+25Gy | 82% | 71% | | | |
| | RTCT+15Gy | 77% | 71% | 12% | 12% | |
| | RTCT+25Gy | 73% | 74% | | | |
| ACT II | RT FU-P | 72% | 84% | | | Colostomy 2% |
| | RT FU-Mito | 75% | 86% | 26% | 62% | |
| | RT FU-P+ FU-P | 75% | 83% | 16% | 68% | |
| | RT FU-Mito+FU-P | 73% | 82% | | | |

# *Management of Anal Cancer 2nd RCTs Generation-Summary*

*CT-RT comparison*

- **FU-MMC/RT still preferred**

*NACT comparison*

- No superior DFS, OS and CFS
- Impact of OTT, Tumor size / LN involvement

*Maintenance/Intensification comparison*

- No difference in DFS or OS
- No difference in L-R and distant Mets

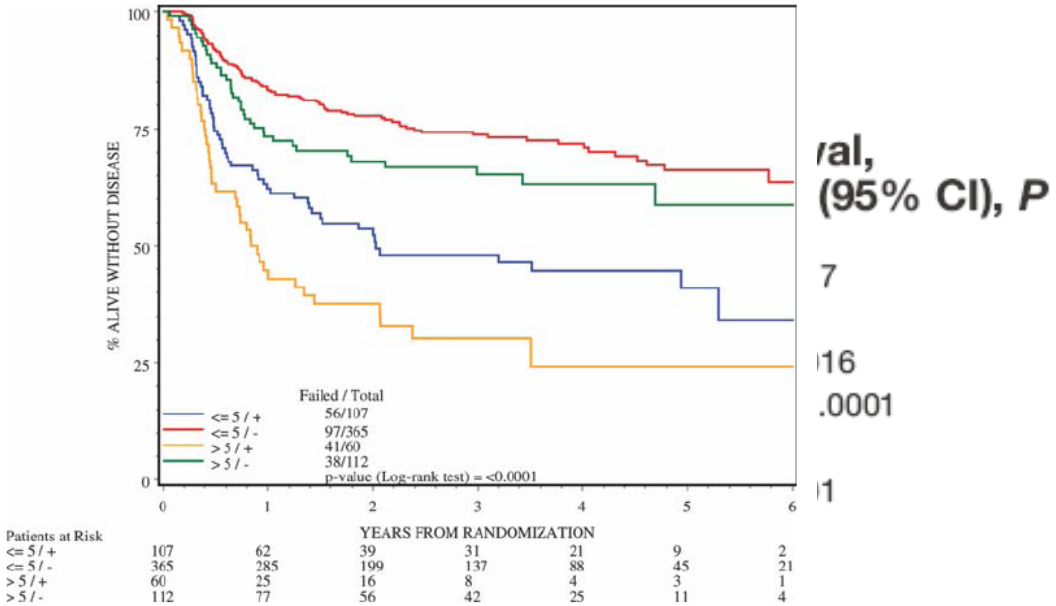
# Prognostic Factors Derived from A Prospective Database Dictate Clinical Biology of Anal Cancer

## The Intergroup Trial (RTOG 98-11)

Jaffer A. Ajani, MD[1]; Kathryn A. Winter, PhD[2]; Leonard L. Gunderson, MD[3]; John Pedersen, MD[4]; Al B. Benson, III, MD[5]; Charles R. Thomas, Jr, MD[6]; Robert J. Mayer, MD[7]; Michael G. Haddock, MD[8]; Tyvin A. Rich, MD[9]; and Christopher G. Willett, MD[10]

**Table 1.** Multivariate Analyses (N=64

| **Adjustment Variables** | **D** / **A** | **ral, (95% CI), *P*** |
|---|---|---|
| Treatment (5-FU/mitomycin-C vs 5-FU/cisplatin) | 1.2 | 7 |
| Sex (female vs male) | 1.3 | 16 |
| Clinical nodal status (negative vs positive) | 2.6 | .0001 |
| Tumor diameter (2-5 cm vs >5 cm) | 1 | 1 |




Cancer September 1, 2010

# PREDICTORS AND PATTERNS OF RECURRENCE AFTER DEFINITIVE CHEMORADIATION FOR ANAL CANCER

PRAJNAN DAS, M.D., M.S., M.P.H.,* SUMITA BHATIA, M.D.,* CATHY ENG, M.D.,†
JAFFER A. AJANI, M.D.,† JOHN M. SKIBBER, M.D.,‡ MIGUEL A. RODRIGUEZ-BIGAS, M.D.,‡
GEORGE J. CHANG, M.D.,‡ PRIYA BHOSALE, M.D.,§ MARC E. DELCLOS, M.D.,*
SUNIL KRISHNAN, M.D.,* NORA A. JANJAN, M.D., M.P.S.A.,* AND CHRISTOPHER H. CRANE, M.D.,*

*Department of Radiation Oncology, †Department of Gastrointestinal Medical Oncology, ‡Department of Surgical Oncology, and §Department of Diagnostic Radiology, The University of Texas M. D. Anderson Cancer Center, Houston, TX

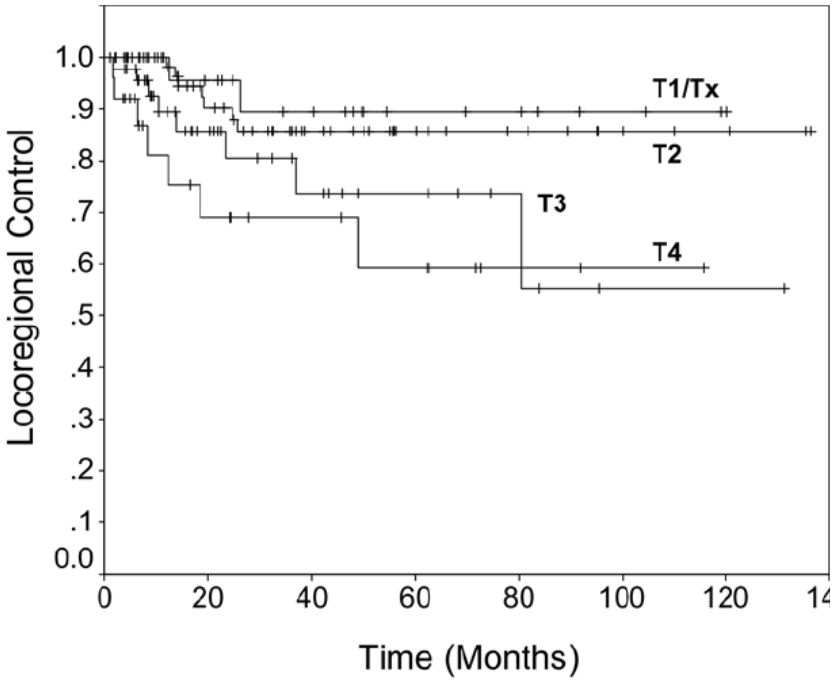



Table 4. Significant predictors on multivariate analysis

| | Hazard ratio (CI) | *p* |
|---|---|---|
| Predictors of locoregional failure | | |
| T stage | 1.71 (1.08–2.71) | 0.023 |
| N stage | 1.47 (1.04–2.08) | 0.030 |
| Predictors of distant metastases | | |
| N stage | 2.03 (1.37–3.01) | <0.001 |
| Basaloid subtype | 4.23 (1.61–11.13) | 0.003 |
| Predictors of overall survival | | |
| N stage | 1.54 (1.18–2.00) | 0.001 |
| HIV positive | 6.45 (1.47–28.36) | 0.014 |

*Abbreviation:* CI = 95% confidence interval.

Time (Months)

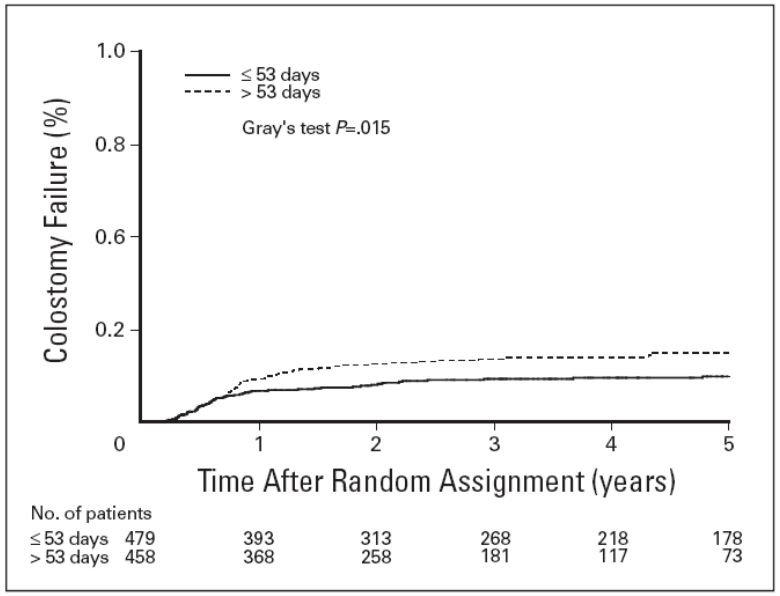
VOLUME 28 · NUMBER 34 · DECEMBER 1 2010

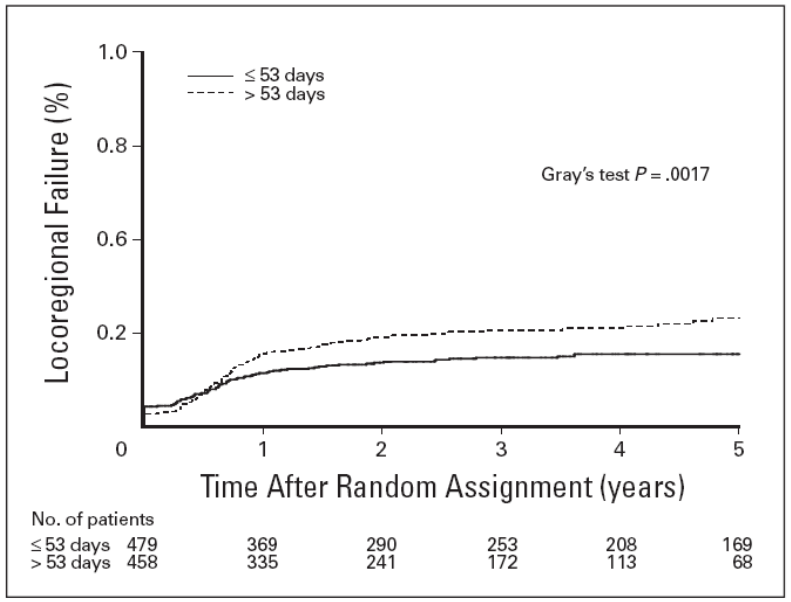
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Impact of Overall Treatment Time on Survival and Local Control in Patients With Anal Cancer: A Pooled Data Analysis of Radiation Therapy Oncology Group Trials 87-04 and 98-11

*Edgar Ben-Josef, Jennifer Moughan, Jaffer A. Ajani, Marshall Flam, Leonard Gunderson, JonDavid Pollock, Robert Myerson, Rani Anne, Seth A. Rosenthal, and Christopher Willett*



# *Management of Anal Cancer Current Issues*

- **Phase I-II CMT programs with new drug/RT modalities: ↑ CR, tolerance, compliance**
  - Tailored RT dose by *Patient Risk Category:*
    Clinical Path predictive factors
  - Influence of OTT of RT course:
    Gap or continuous course
- **Treatment of Vulnerable Pt Population (HIV+)**
- **Salvage strategy for persistent/recur disease**
- **Health-Related Quality of Life**

# Management of Anal Cancer

## New Drug-RT Modalities

## *Phase I-II Studies (selected Series)*

| Study | Pts | CT-RT | CR | DFS | OS |
|---|---|---|---|---|---|
| Glinne-J et al<br>IJROBP ' 08 | 31 | 50.4Gy<br>Cape 825m/m2 bid<br>MMC 12m/m2 d1 | 79% | - | - |
| Eng et al<br>ASCO '09 | 20 | 45-59 Gy<br>Cape 825m/m2bid<br>Oxa 50m/m2 wk | 90% | 100% (3ys) | 100% (3ys) |
| Kachnic et al<br>ASTRO ' 09 | 63 | IMRT 50-54Gy<br>FU+MMC | 93% | - | - |
| Lukan et al<br>Oncology '09 | 77 | 65 Gy<br>FU + DDP<br>Cetuximab | ongoing | | |

# RTOG 0529: A Phase 2 Evaluation of Dose-Painted Intensity Modulated Radiation Therapy in Combination With 5-Fluorouracil and Mitomycin-C for the Reduction of Acute Morbidity in Carcinoma of the Anal Canal

Lisa A. Kachnic, MD,* Kathryn Winter, MS,† Robert J. Myerson, MD,‡ Michael D. Goodyear, MD,§ John Willins, PhD,* Jacqueline Esthappan, PhD,‡ Michael G. Haddock, MD,‖ Marvin Rotman, MD,¶ Parag J. Parikh, MD,‡ Howard Safran, MD,# and Christopher G. Willett, MD**

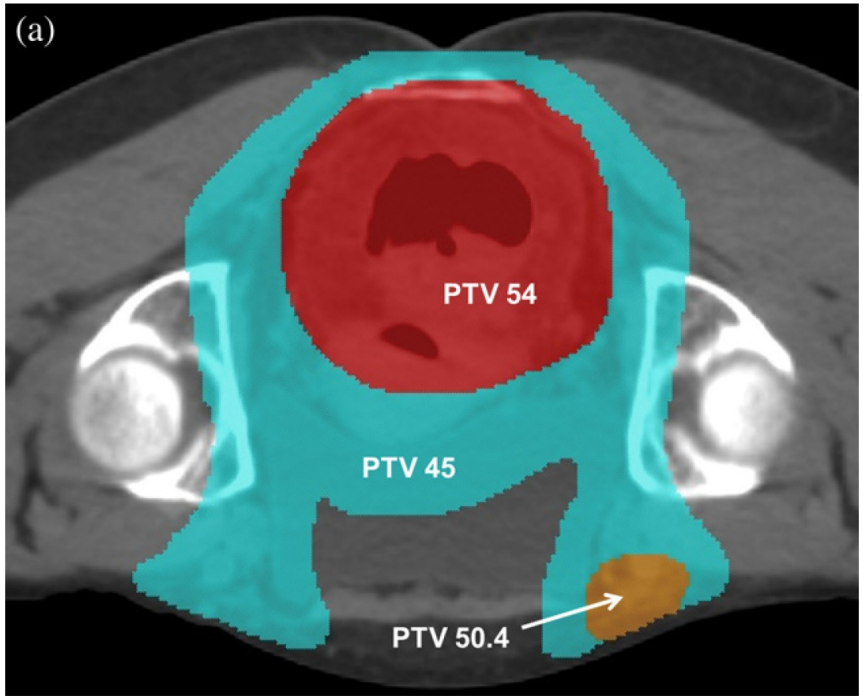



**Table 5** Comparisons of acute treatment-related adverse events*

| Adverse events | 0529 (n=52) | 98-11 (Arm 1†) (n=325) | *P* value (1-sided proportions test§) |
|---|---|---|---|
| Grade 2+ | | | |
| GI/GU‡ | 40 (77%) | 249 (77%) | .50 |
| Derm | 39 (75%) | 271 (83%) | .10 |
| GI | 38 (73%) | 237 (73%) | .50 |
| GU | 8 (15%) | 66 (20%) | .18 |
| Heme | 38 (73%) | 275 (85%) | .032 |
| Overall | 49 (94%) | 318 (98%) | .12 |
| Grade 3+ | | | |
| GI/GU | 11 (21%) | 120 (37%) | .0052 |
| Derm | 12 (23%) | 159 (49%) | <.0001 |
| GI | 11 (21%) | 117 (36%) | .0082 |
| GU | 1 (2%) | 11 (3%) | .32 |
| Heme | 30 (58%) | 201 (62%) | .29 |
| Overall | 43 (83%) | 283 (87%) | .23 |

Int J Radiation Oncol Biol Phys, Vol. 86, No. 1, pp. 27–33, 2013

# STANDARDIZED INCIDENCE RATIO (SIR) of NADCs among 21.951 AIDS* pts,by year of cancer diagnosis. Italy,1986-2004

| Tumor Site | SIR ( 95% CI) 1986-1996 | 1997-2004 |
|---|---|---|
| Hodgkin Disease | 18.0 (13.2-23.9) | 20.7 ( 14.6-28.5) |
| ANUS | 35.5 (12.8-77.7) | 44.0 (21.0-78.9) |
| LUNG | 2.1 (1.2-3.3) | 4.1 (2.9-5.5) |
| LIVER | 2.1 (0.4-6.4) | 6.4 (3.7-10.5) |
| SKIN non-melanoma | 2.1 (1.2-3.3) | 1.8 (1.2-2.6) |

* from 5 yrs before to 10 yrs after AIDS

Dal Maso L. BJC 2009

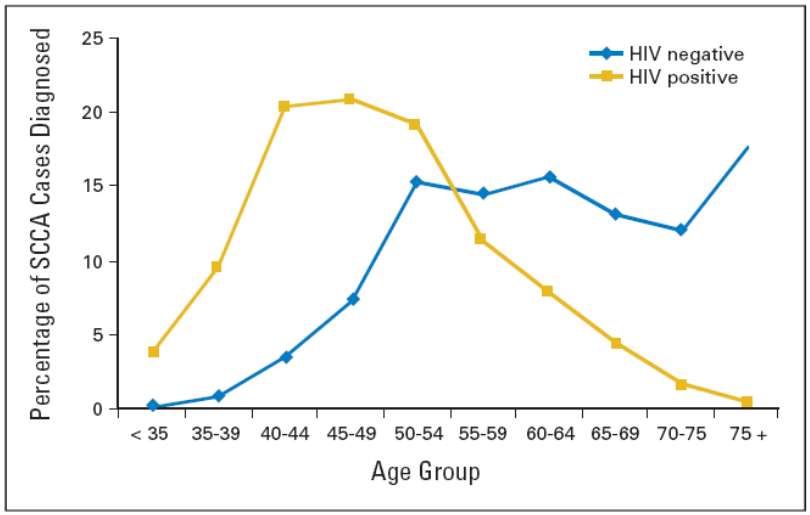
VOLUME 26 · NUMBER 3 · JANUARY 20 2008

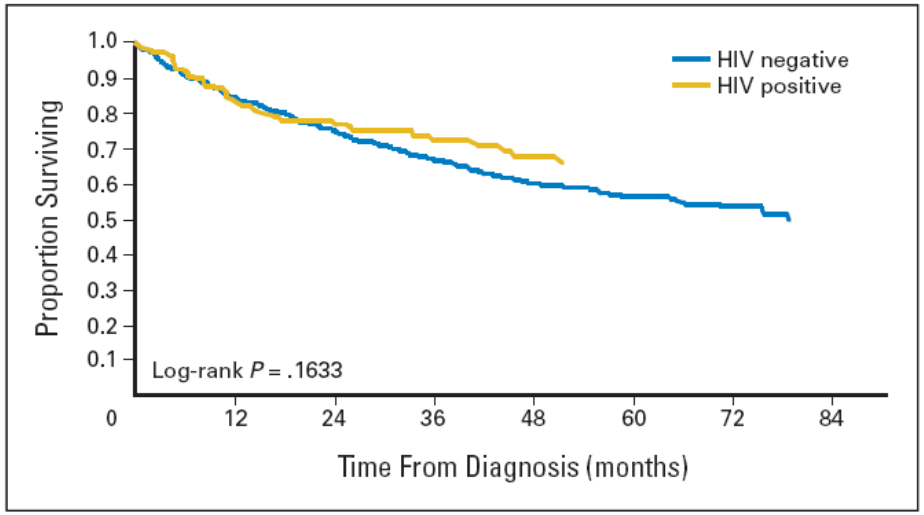
JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

# Human Immunodeficiency Virus–Associated Squamous Cell Cancer of the Anus: Epidemiology and Outcomes in the Highly Active Antiretroviral Therapy Era

*Elizabeth Y. Chiao, Thomas P. Giordano, Peter Richardson, and Hashem B. El-Serag*



# *Management of Anal Cancer*

## New Drug-RT Modalities

## A Pilot Study

### Anal Cancer, EUS-RM Stage I-III (HIV-, HIV+)

Treatment IMRT 45 Gy/25fr PTV1 (elective N)

50-54 Gy/25fr (SIB) PTV2 (Tumor,N+)

Cape 650mg/m2 bid, x 5 wks
MMC 10mg/m2 d1(28)

End-points

Primary Feasibility

Secondary RR, CFS, DFS, OS

CRO 2013

# *Management of Anal Cancer*

## New Drug-RT Modalities

## A Pilot Study (Dec 2011- Jun2013)

***N.Pts 24; 13 Stage T1-2, 11 Stage T3-4; HIV- 19, HIV+ 5***

## Treatment

| | | | |
|---|---|---|---|
| IMRT | Completed planned IMRT | 23/24 | (m52.5Gy, 36-54Gy) |
| Cape | Completed planned dose | 21/23 | (75-100%) |
| MMC | Completed planned cycles | 23/23 | (median 1) |

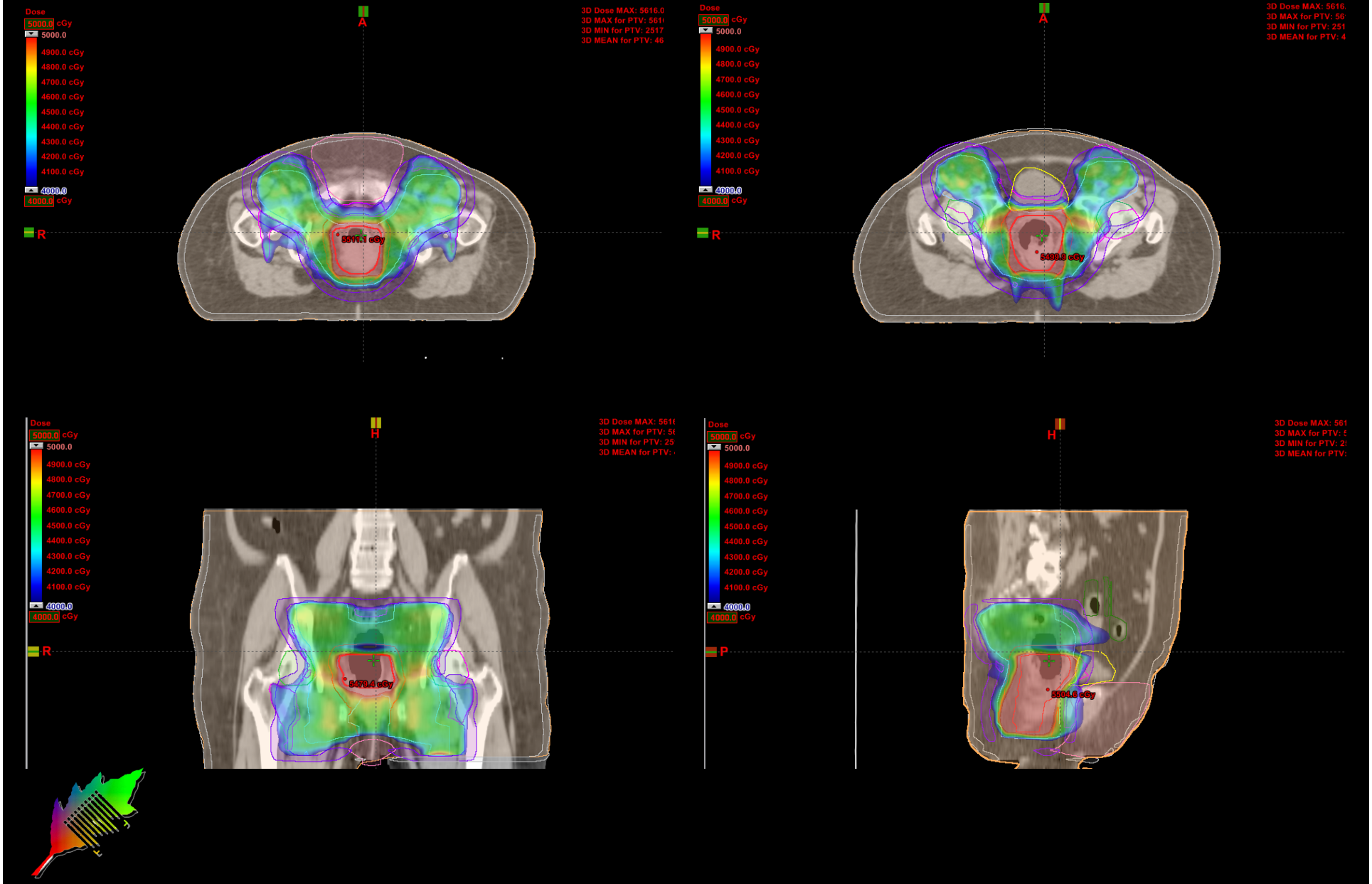
| Toxicity | (HIV-) G1-2 | G3-4 | (HIV+) G1-2 | G3(4) |
|---|---|---|---|---|
| Hemat | 12/19 | 2/19 | - | 1/5 |
| GI | 10/19 | 4/19 | 2/5 | 1/5 |
| GU | 1/19 | - | 1/5 | - |
| Skin | 7/19 | 6/19 | 3/5 | 2/5 |

CRO 2013

# Summary

- Chemoradiotherapy confirms the Gold Standard to cure Anal Cancer Patients
- 5FU-MMC/RT still remains preferred treatment
- New drug-RT modalities (IMRT-IGRT) represent a major area of investigation (Tolerance,Disease control-Organ preservation)
- Vulnerable Pt Population (HIV+) can receive standard treatment
- New modalities of response assessment / prediction are needed (functional imaging, molecular markers) to individualize treatment

# IMRT for Anal Cancer



# UKCCCR TRIAL ACT II

*DDP vs MMC-FU+RT +/- maint. FU-DDP or MMC*

Results

| | MMC | DDP | |
|---|---|---|---|
| CR at 6 mo | 94.5% | 95% | p= ns |
| G3+ Hem Tox | 25% | 13% | p<0.001 |
| no Hem Tox | 60% | 65% | p=ns |
| Colostomy | 14% | 11% | p=ns |

Glynne-Jones, WGIC 2011