



**Carcinoma of the Anal Canal:
Small Steps in The Paradigm
Shift**

Cathy Eng, M.D., F.A.C.P.
Associate Professor
June 26, 2009

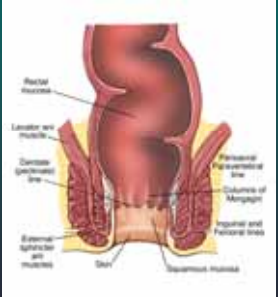
THE UNIVERSITY OF TEXAS
MD ANDERSON
CANCER CENTER
Making Cancer History™

Department of GI Medical Oncology

Discussion Points

- Background
 - Epidemiology, Risk Factors, Histology, Diagnosis, Staging
- Optimizing Chemoradiation Therapy
 - Pivotal Trials
- Incorporation of Novel Agents
- Management of Recurrent/Metastatic Disease

Anatomy of The Anal Cancer




Eng et al; MD Anderson Manual of Clinical Oncology, 2006;

Background of Anal Cancer

- Carcinoma of the anus represents only 4% of all lower GI malignancies
- 2009:
 - Lifetime risk (2003-2005) = 1 in 640 (0.16%)
 - Estimated new cases: 5290
 - Deaths: 720
- 5-Yr OS rate: 67% for all stages
 - Varies by race and geographic region.

Johnson et al; Cancer 101: 281-88, 2004;
Jemal A, et al; CA Cancer J Clin. 2009 Jun 9 [pub].

SEER Anal Cancer Incidence Rates: 1973-2002



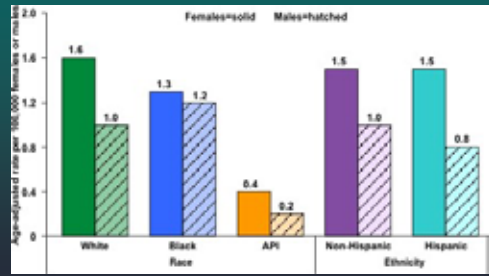
Rate per 100,000 individuals

Year

Legend: Males (blue line), Females (red line)

Source: According to SEER Cancer Incidence Statistics

Age-adjusted incidence rates for anal cancer in the United States during 1998–2003



Race/Ethnicity	Females (solid)	Males (hatched)
White	1.6	1.0
Black	1.3	1.2
API	0.4	0.2
Non-Hispanic	1.5	1.0
Hispanic	1.5	0.8

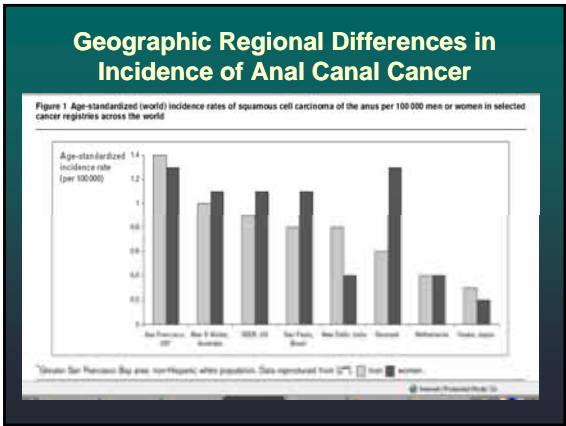
Age-adjusted rate per 100,000 females or males

Race

Ethnicity

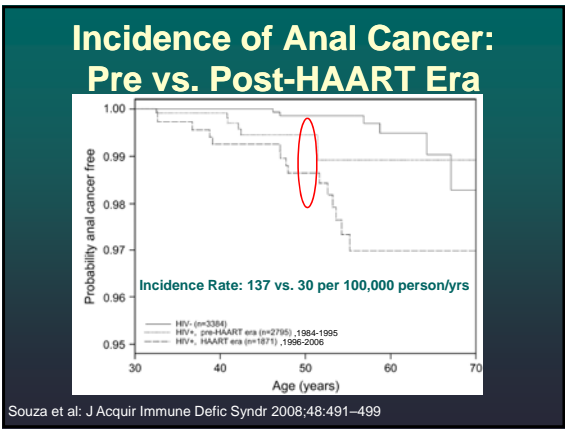
Legend: Females=solid, Males=hatched

<http://www.cdc.gov/cancer/hpv/statistics/anal.htm>; accessed June 20, 2009

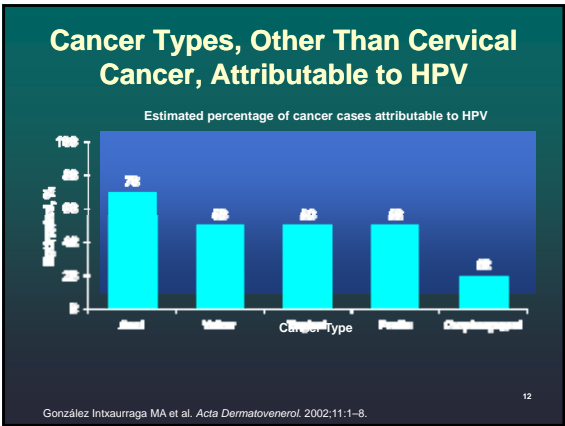


- ### Risk Factors for Anal Canal Cancer
- > 50 years of age
 - > 10 sexual partners
 - Receptive anal intercourse
 - Prior history of gyne malignancy
 - STD's: Chlamydia, gonorrhea, syphilis
 - Human papilloma virus (HPV, subtypes 16, 18, & 31)
 - Chronic immunosuppression:
 - Organ transplant pts
 - 10-fold risk of anal cancer
 - 20-fold for vulva and vaginal cancers.
 - HIV/AIDS
 - **Not** considered an AIDS-defining illness
 - Tobacco use: Linear increase
- C. Eng. MD Anderson Manual of Clinical Oncology, 2006; Frisch et al. J Natl Cancer Inst 92:1500-10, 2000; Frisch M, et al. J Natl Cancer Inst 91:708-15, 1999.

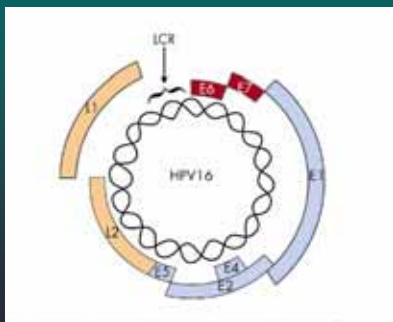
- ### HIV+/AIDS and Anal Cancer
- HIV+ 2-6x's likely to have HPV regardless of sexual practices and have a persistent infection
 - Incidence rate for anal cancer (MSM):
 - HIV+: 70-100 cases/100,000
 - HIV-: 35 cases/100,000
 - MACS: 4.7 fold increase in risk anal cancer in HIV+ pts.
 - Younger age of presentation if HIV+ vs. HIV-
- D'Souza et al. J Acquir Immune Defic Syndr; Aug 2008, 491-499; Chiao et al. JCO, 2008, 26:474-479.



- ### HPV as a Risk Factor for Anal Cancer:
- 20 million are currently infected
 - Estimated that ~75 % of reproductive age women and men have been infected with genital HPV
 - ~ 6.2 million will contract HPV each year.
 - Worldwide prevalence of HPV in anal cancer is 88%
 - HPV latency may be up to 40 yrs
- Bower M, et al. J Acquired Immune Defic Syndr 37(5):1563-5, 2004; HPV Monographs in Medicine, 2008



HPV 16 Genome



Monographs in Medicine: HPV, 2008

Diagnosis

- Complete history
 - Sexual history: STD's including HIV risk factors
- Physical
 - Inguinal lymph node examination and FNA
 - DRE including perianal region, and local extension (prostate/vagina)
- Histologic confirmation
- Proctosigmoidoscopy
- Diagnostic imaging
 - CXR
 - CT scan of the chest, abdomen/pelvis
 - PET?

Schwarz et al. Int J Rad Oncology Biol. Physics. 71: 180-186, 2008
 Nguyen et al. Radio and Onc. Epub, 2008

AJCC 2002 Tumor Staging

T-stage	Tumor Size
T ₁	≤ 2 cm
T ₂	> 2 cm but ≤ 5 cm
T ₃	> 5 cm
T ₄	Invades adjacent organs

N-stage	Nodal Involvement
N ₁	perirectal lymph nodes
N ₂	unilateral internal iliac and/or inguinal lymph nodes
N ₃	perirectal and inguinal lymph nodes and/or bilateral internal iliac and/or inguinal lymph nodes

Treatment for Anal Cancer:

- Anal margin
 - Analogous to skin cancer
 - Surgical excision or radiation alone
- Adenocarcinoma
 - Analogous to treatment for rectal cancer
 - Aggressive
- SCCA of the anal canal
 - Chemoradiation therapy with curative intent
 - Salvage surgery: APR
- Metastatic anal cancer
 - No standard treatment

Pivotal Historical Trials

Wayne State Pilot: Nigro Regimen

- Single-institution study (N=28)
- RT: 30 Gy in 15 fx via AP/PA fields to the pelvis, medial inguinal LN and anal canal
- 5-FU (1000mg/m²/day) x 4 days + MMC (15 mg/m² bolus, Day 1)
- Initially APR planned in all pts
 - 5/6 initial pts had NO residual tumors in APR specimen
 - APR was then reserved as salvage treatment
- Expansion of the study revealed 86% (24/28) pts had a clinical CR to combined chemoradiation therapy alone w/o surgery

Nigro et al. Cancer 51(10):1826-9, 1983

UKCCCR: Radiation Therapy +/- Chemotherapy

Arms	N	Dose	3- yr Local Failure	3- yr Mortality	3-yr OS
RT	200	45 Gy + boost	61%	39%	58%
RT/ 5-FU/MMC	295	1) 5-FU (1000 mg/m ² , D1-4 or 750 mg/m ² , D1-5) during 1 st and last week of RT, 2) MMC 12 mg/m ² day 1 3) 45 Gy + boost	39% <i>(P<.001, HR = 0.54)</i>	28% <i>(P=.02)</i>	65% <i>(P=.25)</i>

UKCCCR: Lancet 348:1049-54, 1996

EORTC: Radiation Therapy +/- Chemotherapy

Arms	N	Dose	CR	3- yr LC	3-yr OS
RT	52	45 Gy + boost	54%	39%	72%
RT/ 5-FU/MMC	51	1) 5-FU (750 mg/m ² , D1-5) during 1 st and last week of RT, 2) MMC 15mg/m ² day 1, 3) 45 Gy + boost	80%	58% <i>(P=.02)</i>	65% <i>(P=.17)</i>

Bartelink et al. J Clin Oncol 15:2040-9, 1997

RTOG/ECOG 87-04: 5-FU + Radiation Therapy +/- MMC

Arms	N	Dose	Neg Bx	4-yr CFS	4-yr DFS
5-FU/RT	145	45 Gy 5-FU (1000 mg/m ² /day, D1-D4)	86%	59%	51%
5-FU/ MMC/RT	146	1) 5-FU (1000 mg/m ² , during 1 st and last week of RT, 2) MMC 10 mg/m ² , Day 1 and 29 3) 45-50.4 Gy	92.2% <i>(P=.135)</i>	71% <i>(P=.014)</i>	73% <i>(P=.01)</i>

Flam et al: JCO 14:1527-39, 1996

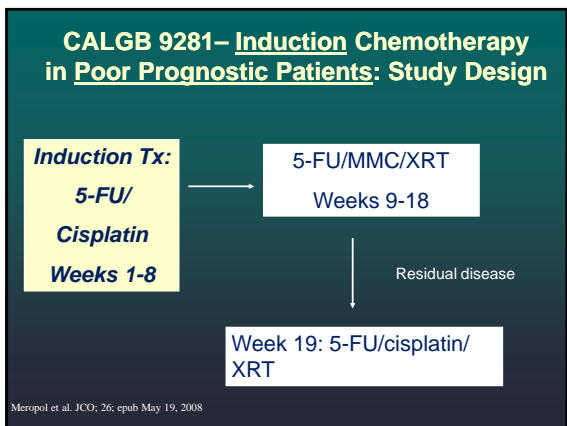
- ### MMC Treatment-Related Morbidity
- Acute:
 - 6 chemotherapy-related deaths were reported in the UKCCCR study.
 - 4 deaths in the RTOG/ECOG MMC arm were attributed to neutropenic sepsis.
 - 23% vs. 7% of pts had grade 4/5 toxicities on MMC arm
 - Chronic:
 - Late morbidity soft tissue necrosis was not uncommon and often resulted in temporary colostomy placement for palliation of pain.
 - Led to search for other radiation sensitizers to MMC
- UKCCCR: Lancet 1996; 348:1049-54; Flam et al: JCO, 1996; 14:1527

- ### Mitomycin C vs. Cisplatin
- | | |
|---|---|
| <ul style="list-style-type: none"> ▪ Myelosuppression ▪ Pulmonary fibrosis ▪ Hemolytic-uremic syndrome ▪ Therapy-related myelodysplastic (MDS) syndrome | <ul style="list-style-type: none"> ▪ Nausea/vomiting ▪ Electrolyte imbalance ▪ Nephrotoxic ▪ Ototoxic ▪ Neuropathy |
|---|---|

MDACC Experience: 5-FU, Cisplatin, XRT (N=92)

Overall survival	85%
DFS	77%
Colostomy-free survival	82%
Locoregional control	83%
Distant mets	9%

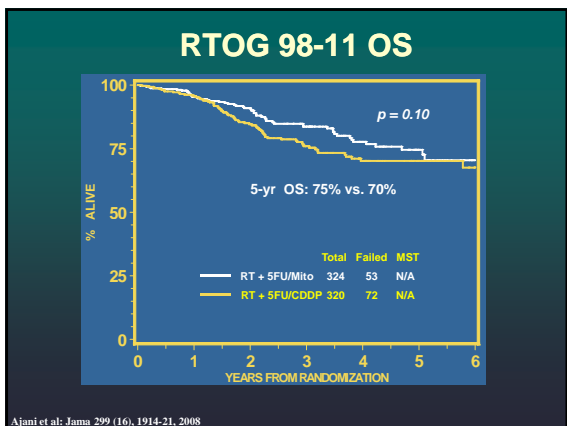
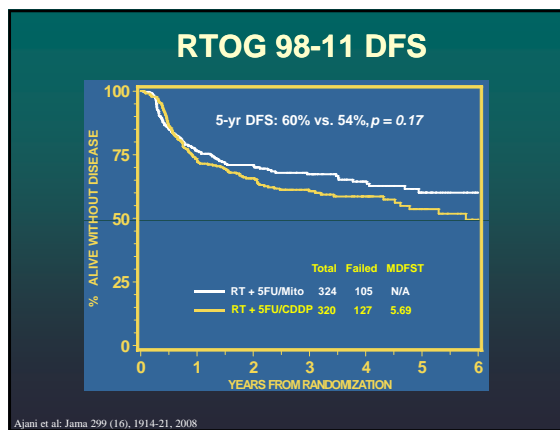
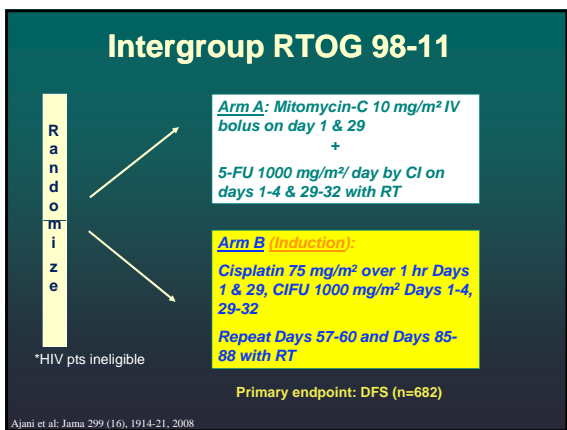
Hung et al: Cancer 2003; 97:1195-202



CALGB 9281 – Induction Chemotherapy in Poor Prognostic Patients: Final Results

N = 45	CR	PR
Phase I: Induction CT	8 (18%)	21 (47%)
Phase II: ChemoXRT (combined)	37 (82%)	4 (9%)
4-yr DFS	61%	

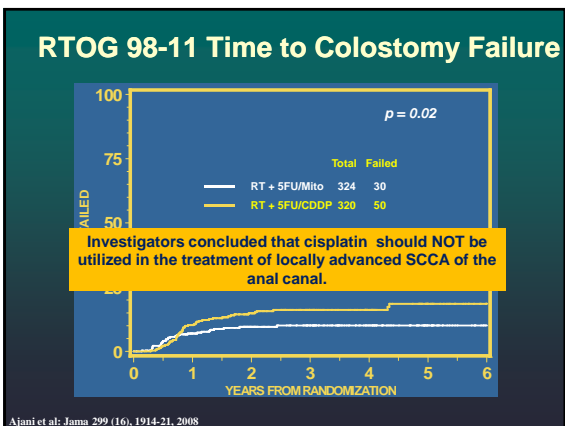
Meropol et al. JCO; 26; epub May 19, 2008



98-11 Acute Toxicity Grade $\geq 3/4$

Toxicity	RT + 5FU Mitomycin (n=324)	RT + 5FU Cisplatin (n=320)	P-Value
Worst hematologic (%)	61	42	0.0005
Worst nonhematologic (%)	74	74	1
Worst Overall (%)	87	83	0.19

Ajani et al. JAMA 299 (16), 1914-21, 2008



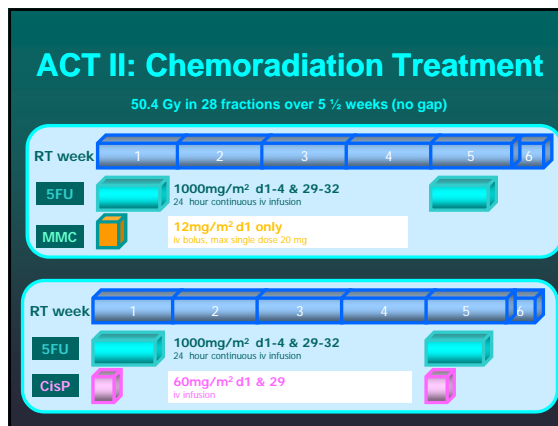
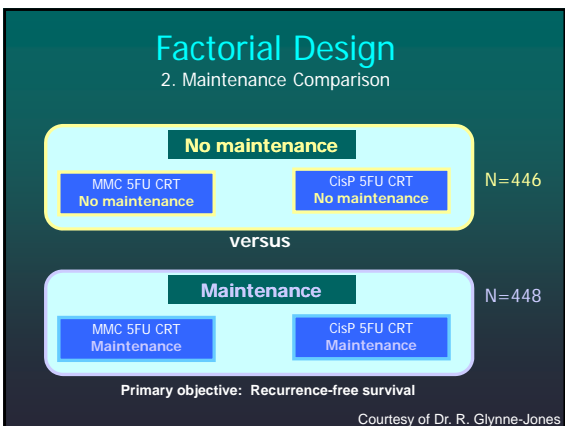
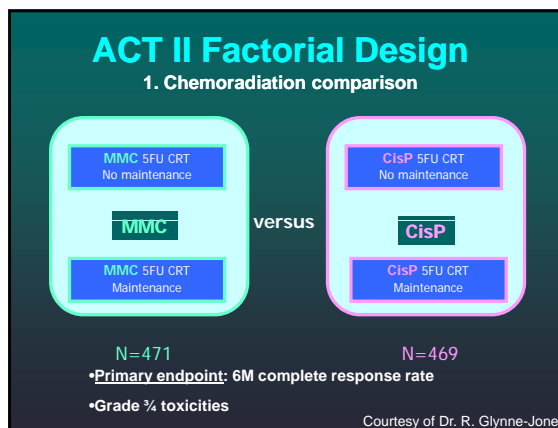
- ### Summary of RTOG 98-11
- NOT a direct comparison between arms
 - Excluded HIV + patients
 - NS difference in DFS, OS, or time to LRF
 - Increased Gr 4 toxicities in the MMC arm
 - Time to colostomy inferior in the cisplatin arm (*p*=0.02)
 - Delay in RT?
 - Difference in radiation sensitization?
 - Induction chemotherapy is not of additional benefit
 - Concluded: 5-FU, MMC with RT remains the standard

ACT II: The Second UK Phase III Anal Cancer Trial

A randomised trial of chemoradiation using mitomycin of cisplatin, with or without maintenance cisplatin/5-FU in squamous cell carcinoma of the anus.

on behalf of the NCRI ACT II Trial Management Group and Investigators
 ASCO, Florida, May 2009. Abstract ID: LBA 4009 (30894)
 Cancer Research UK grant number: C444/A628
 ISRCTN number: 26715889

Courtesy of Dr. R. Glynne-Jones



Maintenance Treatment

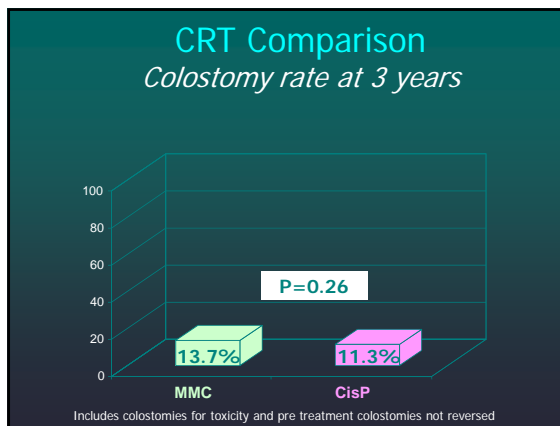
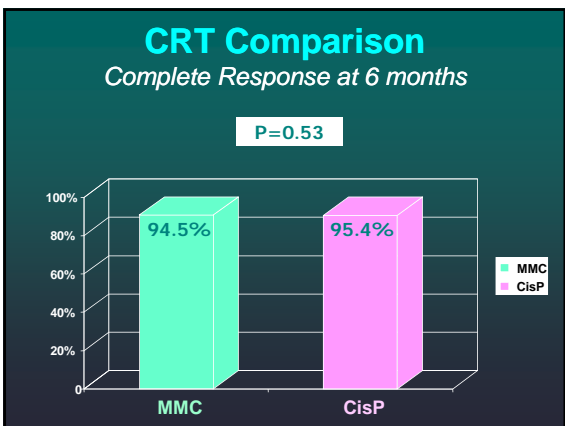
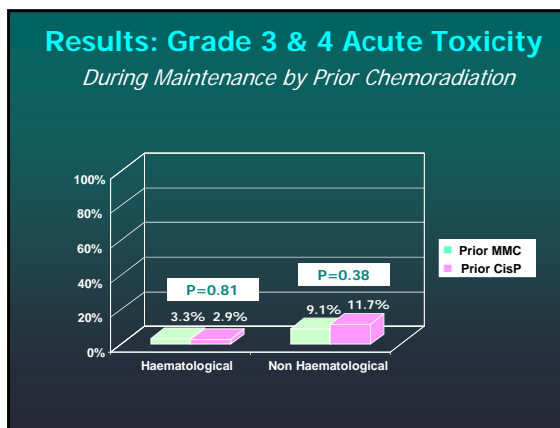
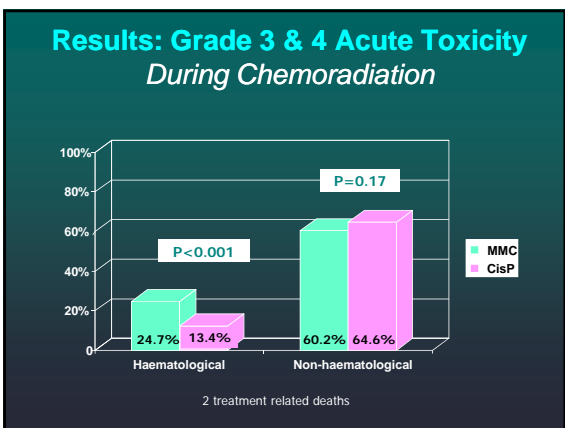
Starts 4 wks after end of primary CRT

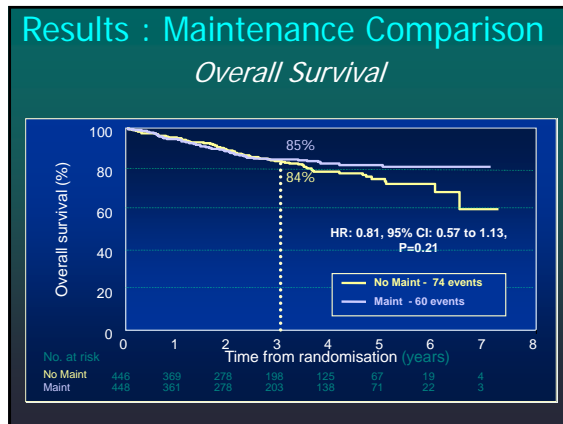
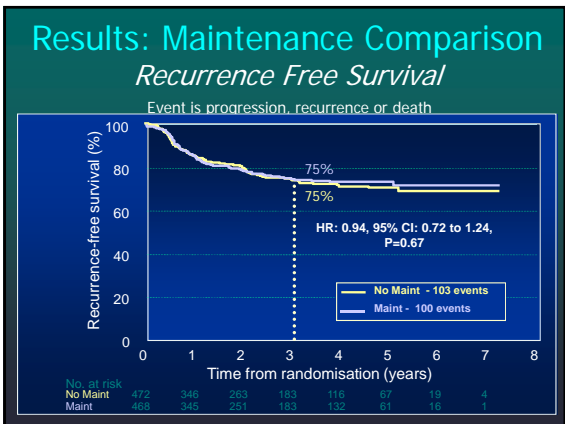
Courtesy of Dr. R. Glynne-Jones

Patient Demographics

* Stratification factor

	MMC No maint n=246	CisP No maint n=246	MMC Maint n=226	CisP Maint n=222
* Site	80%	81%	83%	81%
Canal	16%	15%	14%	14%
Margin	4%	4%	4%	4%
N/K				
* T1	11%	11%	10%	10%
T2	41%	41%	39%	39%
T3	29%	29%	31%	30%
T4	13%	13%	14%	14%
N/K	6%	6%	7%	7%
* Node +ve	29%	29%	31%	30%
Node -ve	63%	63%	61%	61%
N/K	8%	8%	8%	9%





ACT II Trial – Conclusions

Chemoradiation Treatment

- Primary Objective
 - Failed to fulfill primary endpoint of superiority of cisplatin vs. MMC
 - Demonstrated equivalence
- Note no statistically significant difference in colostomy rate vs. RTOG 98-11

Maintenance comparison

- Preliminary data - follow-up ongoing
- No statistically significant difference in RFS, OS or cause specific survival

Comparison of Recent RTOG vs. ACT II Phase III Anal Ca trials

	RTOG 98-11 (N=644)	ACT II (N=940)
Median follow-up	2.51 yrs	3 yrs
Induction	Yes (no benefit)	n/a
Treatment	MMC: 10 mg/m ² , Cisplatin 75 mg/m ² D1 and 29	MMC: 12 mg/m ² , D1 Cisplatin 60 mg/m ² D 1 and 29
Maintenance (adjuvant)	n/a	Yes (early - but unlikely benefit)
Time to Colostomy	10% vs. 19%	13.7% vs. 11.3%

Current Clinical Trials & the Incorporation of Novel Agents

MDACC Phase II: CapeOX/XRT

- Phase II, single institution study
- Goal was 60 patients
- Excluded HIV+ patients
- IMRT was optional
- Interim safety analysis using Bayesian methods: Toxicity and failure-free survival is evaluated after every 10 patients.

Eng et al. ASCO GI Symposium, #216, 2005; Eng et al. ASCO, 2009

Objectives of XELOX-XRT

Primary Objectives:

- Time to treatment failure:
 - Disease persistence or progression, recurrence, or treatment-related mortality
- Determine treatment-related toxicities:
 - ≥ Grade 3 gastrointestinal symptoms
 - Grade 4 XRT dermatitis
 - ≥ Grade 3 hematologic or nonhematologic toxicity
 - Treatment delays > 7 days

Secondary Objectives:

- Rate of complete response (CR), locoregional control (LCR)
- Two-year rates of:
 - Colostomy-free survival
 - OS
 - PFS

XELOX-XRT Eligibility Criteria

- Histologically proven SCCA of the anal canal
- AJCC stage II-IIIB (T₁₋₄N_xM₀ or T_xN₁₋₃M₀)
- ECOG PS 0-1
- Informed consent
- No prior radiation to the pelvis
- No prior surgery for anal carcinoma excluding biopsy
- No peripheral neuropathy ≥ CTC Grade 2 (Ver 3.0)
- Treatment naive to oxaliplatin or 5-FU-based therapy
- No anticoagulation with coumadin
- HIV (+) patients were ineligible

Eng et al. ASCO GI Symposium, #216, 2005; Eng et al. ASCO, 2009

XELOX-XRT: Treatment Regimen(Chemotherapy)

Drug	Route	Dose	Schedule*
Oxaliplatin	Central Line, IV	50 mg/m ² , weekly	Days 1, 8, 22, and 29 during radiation therapy only.
Capecitabine	Oral	825 mg/m ² , twice daily	Given Monday to Fridays only, on days of radiation therapy only. Weeks 1-2 and 4-5 only.
XRT		45 Gy	25 fractions for T ₁ N ₀ lesions
		55 Gy	55 Gy in 30 fractions for T ₂ lesions
		59 Gy	59 Gy in 32 fractions for T ₃₋₄ lesions

* Revised schedule

Eng et al. ASCO GI Symposium, #216, 2005; Eng et al. ASCO, 2009

XELOX-XRT Results

- ❖ 20 patients were enrolled. All patients were evaluable for toxicity; 19 for response.
- ❖ Five of the first 11 patients (Group 1) developed grade 3 treatment-related diarrhea.

	Number of patients	
	Group 1 (N=11)	Group 2 (N=9)
Grade 3/4 Toxicity of interest	7 (78%)	2 (22%)

XELOX-XRT Toxicities of Interest

ADVERSE EVENT	Number of Events			
	Group 1		Group 2	
	N	%	N	%
DEHYDRATION	1	8.3	0	0
DIARRHEA	5	41.7	1	50
FATIGUE	1	8.3	0	0
HEMOGLOBIN	1	8.3	0	0
NAUSEA	0	0	1	50
PAIN (ABDOMEN NOS)	1	8.3	0	0
PAIN (NOS)	2	16.7	0	0
PAIN (PERINEUM)	1	8.3	0	0

XELOX-XRT Response Rates

- ❖ Complete response rates of the primary tumor were 100% in Groups 1 and Group 2.

❖ One patient in Group 1 developed distant disease to the liver 10 months after the completion of chemoradiation therapy.

❖ One patient developed a second microscopic primary SCCA of the anal canal (<1mm focus), 3.5 yrs after completing initial therapy. He was treated with chemoradiation therapy and remains disease-free.

- ❖ Based on the log-rank test (p=0.4), there was no significant difference between the two treatment groups regarding time to treatment failure.

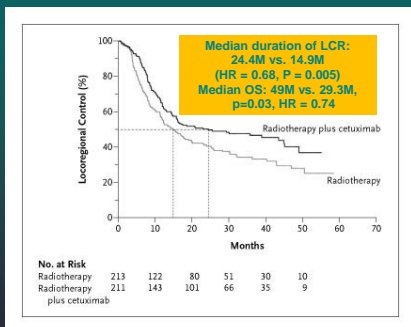
RTOG Phase II : 5-FU, MMC (IMRT)

- Primary objective: Decreased toxicity of 15% in first 90 days of therapy vs. RTOG 98-11
- Second endpoints:
 - Clinical CR at 8 weeks
 - Locoregional failure
 - DFS
 - OS
 - Time to Colostomy

www.rtog.org

The Role of Biologic Agents: Cetuximab

Locoregional Control among Unresectable HNC Patients Randomized to Radiotherapy plus Cetuximab or Radiotherapy Alone



Bonner J et al. N Engl J Med 2006;354:567-578



ECOG 3205 and AMC 045 (HIV+ Consortium) – Study Design

Amendment

~~Induction Tx:
5-FU/
Cisplatin/ Cetuximab~~

Primary Objective:
3-yr Local Failure Rate
Goal: N=47

1. 5FU 1000 mg/m²/day, Days 1-4 and 29-32
2. Cisplatin 75 mg/m² IV on days 1 and 29
3. Cetuximab 400 mg/m² IV day 1, then 250 mg/m² IV days 8, 15, 22, 29, 25 (and days 32 and 39 if RT continues beyond day 25) - a minimum of 6 and a maximum of 8 cycles
4. RT 45 Gy for T1-T2 & 50.4-54 Gy for T3-T4

Options for the Metastatic Anal Carcinoma Patient

Approach to Metastatic Disease

- Develops in < 20% of patients
- Common site of metastases:
 - Bone, liver and lung
- No standard chemotherapy regimen
- Little published data
- Review of existing literature reveals:
 - Small, retrospective studies
 - Case studies

Eng et al, CTOO, 2008 Dec;9(4-6):400-7. Epub 2009 May 29, 2009

Approach to Metastatic Disease

- Identify your objectives of therapy
 - Palliative vs. surgically resectable
- Challenges:
 - Identification of the appropriate chemotherapy regimen
 - Duration of chemotherapy
 - Is there a role for biologic therapy?

Treatment of Metastatic Disease: The MDACC Experience

Type	Patients N=30
Systemic Chemotherapy	
•5-FU/capecitabine + Platinum	70%(21/30)
•Irinotecan (CPT-11) + Platinum	10%(3/30)
•Taxanes + Platinum	20%(6/30)

Eng, et al, ASCO GI, #352, 2008

Treatment of Metastatic Disease: The MDACC Experience

Median PFS: 7.2M

Med OS = 38M

Eng C et al: manuscript in preparation

Is there a role for cetuximab in the metastatic anal carcinoma patient?

5-FU/Platinum +/- Cetuximab in Untreated or Metastatic SCCA HNC

A

Med OS 7.4 vs. 10.1M

Hazard ratio (95% CI): 0.80 (0.64-0.99)
P=0.04

No. at Risk	0	3	6	9	12	15	18	21	24
Chemotherapy (N=220)	220	179	127	83	65	47	19	8	1
Chemotherapy plus cetuximab (N=222)	222	184	153	118	82	57	30	15	3

B

Med PFS 3.3M vs. 5.6M

Hazard ratio (95% CI): 0.54 (0.43-0.67)
P<0.001

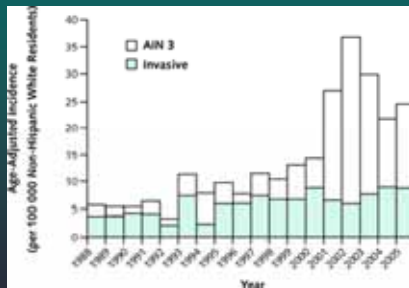
No. at Risk	0	3	6	9	12	15
Chemotherapy (N=220)	220	103	29	8	3	1
Chemotherapy plus cetuximab (N=222)	222	138	72	29	12	7

Vermorken et al. 359 (11): 1116, September 11, 2008

Steps to Prevention?

- Anal pap screening
 - High risk groups
- Role for the HPV vaccine?
 - Bivalent and quadrivalent vaccine available
 - Subtypes of anal cancer appear similar to that of cervical CA
 - No known efficacy in pts infected currently with vaccine type
 - May be best prior to any intercourse.
 - Ideally therapeutic vaccines targeting HPV for prevention
 - Little known re: any efficacy in an HIV+ pt

Age-adjusted incidence of AIN 3 and invasive squamous cell carcinoma of the anus* among non-Hispanic white male residents of San Francisco County, 1988-2005



Katz, K. A. et. al. Ann Intern Med 2009;150:283-284

Annals of Internal Medicine

Conclusions:

- Multidisciplinary management is imperative.
- Acute and chronic toxicities must be monitored closely
- Chemoradiation with curative intent remains gold standard for treatment-naive patients
- Clinical response should be take up to 12 weeks
 - Do not biopsy unless suspicious for residual or PD
- Challenges:
 - Next step for treatment
 - Future role for molecular targeted therapy or just increased toxicities with XRT?
 - Defining appropriate treatment for metastatic patients