

# Anal Cancer

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**2021**

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# Outline

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## Background

- Pathogenesis

- Epidemiology

- Anatomy

## Staging and Workup

## Treatment

- Local Disease

- Recurrent Disease

- Metastatic Disease

# Classification

## WHO classification of anal cancer

<b>Anal canal</b>
Squamous cell (cloacogenic) carcinoma
Large cell keratinizing
Large cell nonkeratinizing (transitional)
Basaloid
Adenocarcinoma
Rectal type
Of anal glands
Within anorectal fistula
Small cell carcinoma
Undifferentiated
<b>Anal margin</b>
Squamous cell carcinoma
Giant condyloma
Basal cell carcinoma
Others
Bowen's disease
Paget's disease

# Epidemiology and Clinical Features

Updated, SEER, UpToDate  
Glynn-Jones et al. Annals of Oncology. 2010 21(s5)

## EPIDEMIOLOGY

- 9,090 cases US annually
- Increasing incidence 2-3%
- 80-85% SCC

## RISK FACTORS

- Female (2:1 F:M)
- HPV (70%+ HPV related)
- Genital warts
- # sexual partners
- Cigarette use
- HIV?
- Receptive anal intercourse

## CLINICAL PRESENTATION

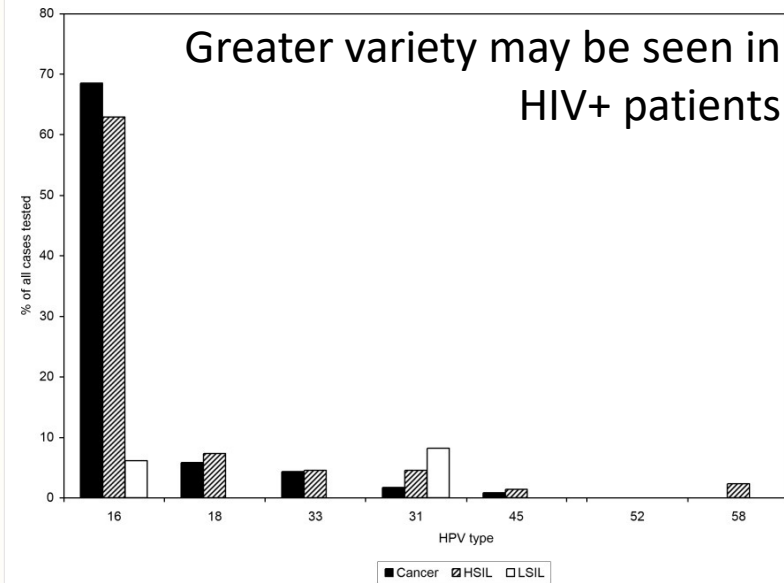
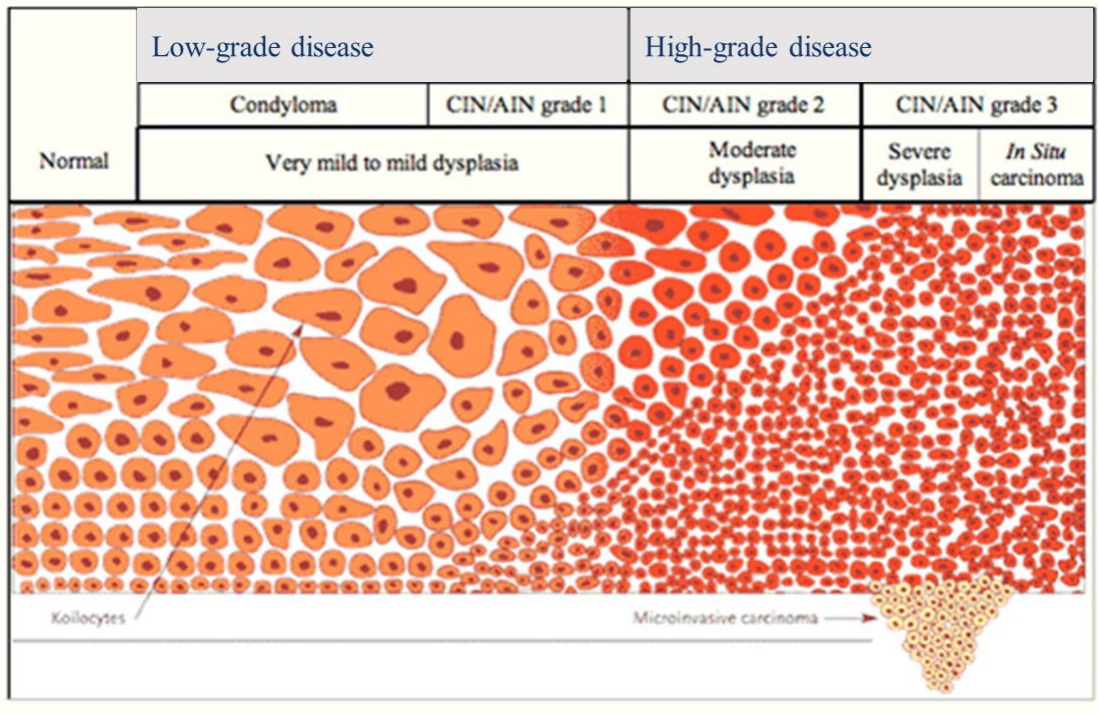
- Rectal bleeding  
(most common)
- Anorectal pain
- Itching
- Sensation of mass
- 20% asymptomatic
- History of anorectal condyloma
- Most patients present with T1-2 N0 disease

# Pathogenesis

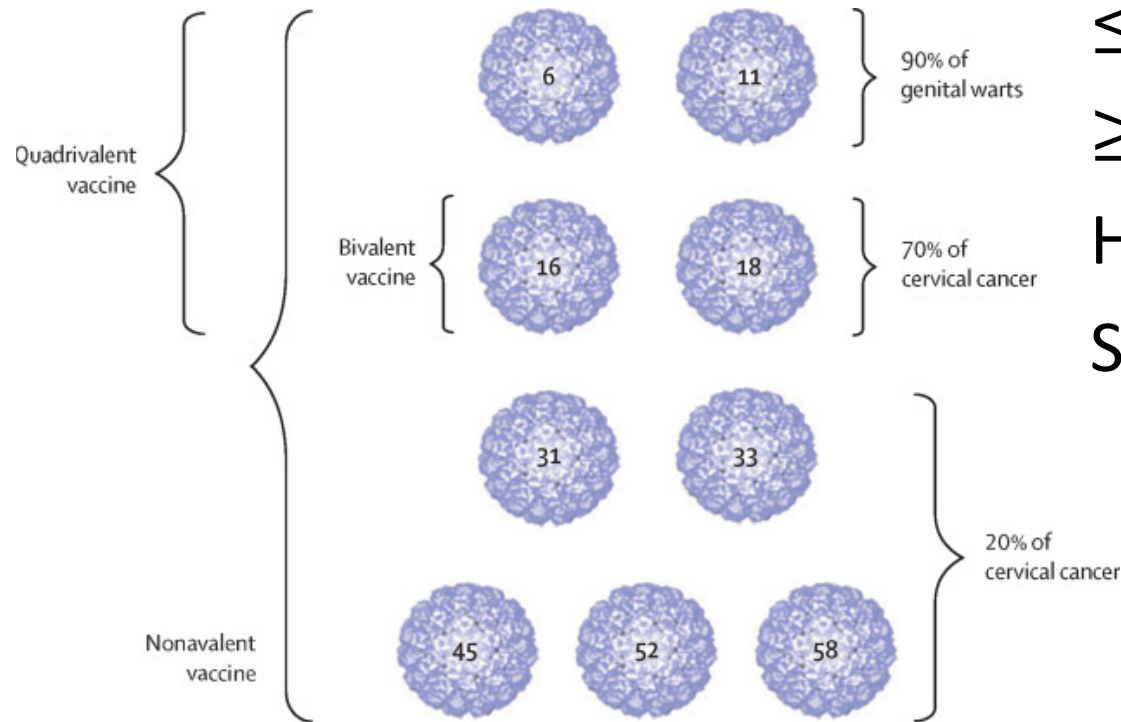
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- Human Papillomavirus
  - HPV DNA has been isolated from 46 to 100 percent of in situ and invasive SCCs of the anus
  - Anal Intraepithelial Neoplasia (AIN) is the precursor lesion
- Cigarettes
  - Cigarettes increase anal cancer (and cervical)

# Pathogenesis



# Prevention: Vaccination



$\leq 14$  yo: 0 and 6 **or** 12 m

$\geq 15$  yo: 0, 2 and 6 m

HIV+: 0, 2 and 6 m

Still efficacious at 15+ yrs

# Screening

Joel Palefsky, ASCO 2019, Educational Session

**There is NOT data to support screening,  
But recommended for high risk groups:**

HIV-positive Patients

HIV-negative MSM

Patients with High Grade Cervical/Vulvar Lesion/Cancer

Patients with Perianal Condyloma

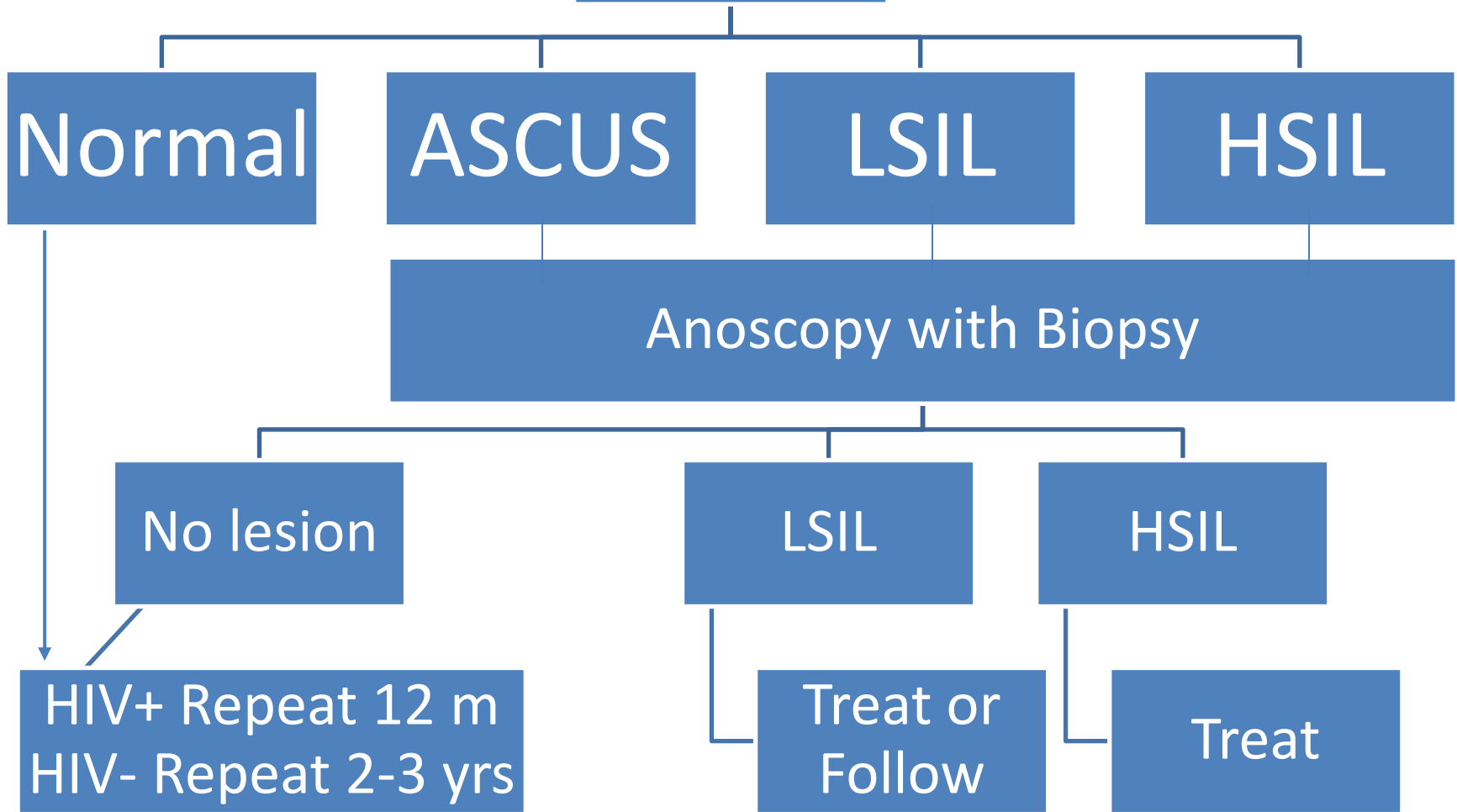
Solid Organ Transplant Recipients

Over 25 if immunosuppressed

Over 40 if immunocompetent



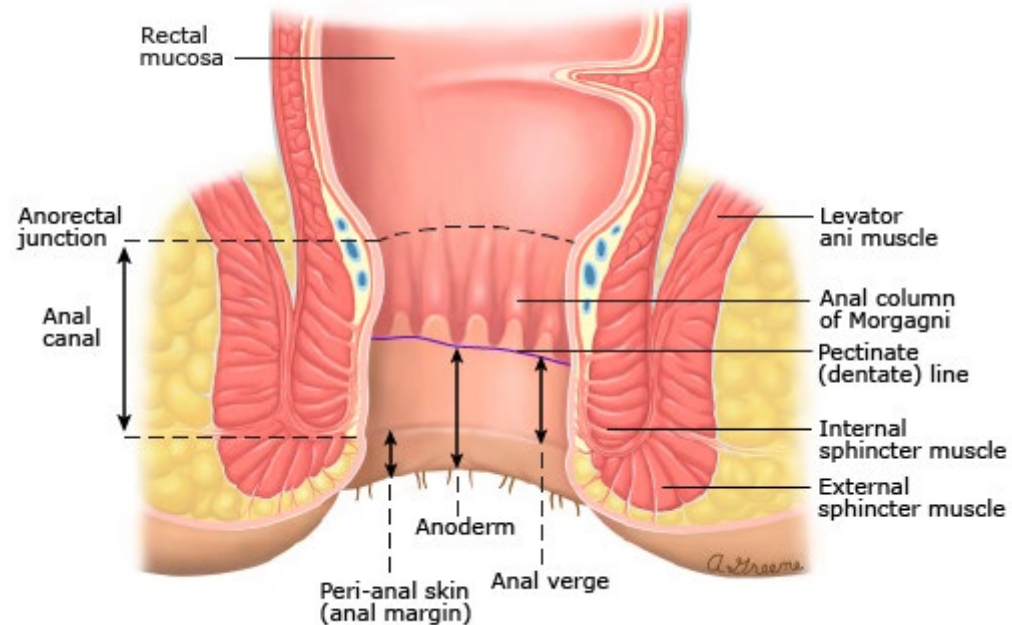
# Screen



ASCUS: Atypical Squamous Cells of Undetermined Significance  
LSIL/HSIL: Low/High grade Squamous Intraepithelial Lesion

# Anatomy

- 3-4 cm anal canal
  - Anorectal ring to anal verge
  - Dentate line located in middle of canal
- Perianal Skin Cancers are now staged and treated like anal canal cancers.



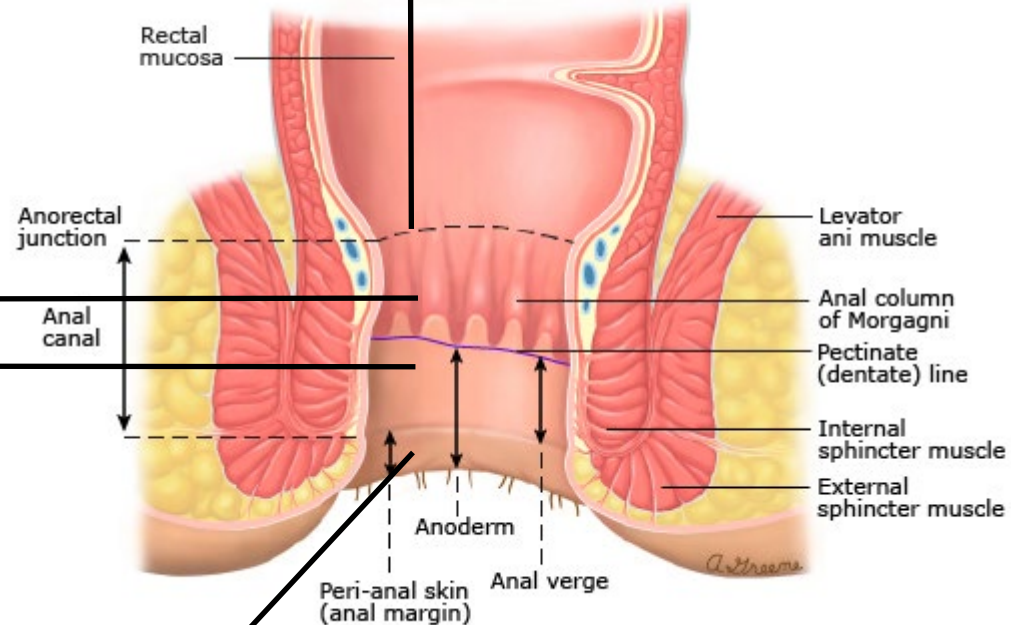
# Anatomy: Nodal Drainage

Non keratinizing SCC  
Perirectal Nodes

Internal Pudendal Nodes  
Internal Iliac Nodes

Keratinizing SCC  
Inguinal Nodes  
Femoral Nodes  
External Iliac Nodes

Anal Margin (Perianal) SCC  
Keratinized squamous cells  
(Treat as Primary Skin SCC)



# Staging

T0	No evidence of primary tumor
Tis	High grade squamous epithelial lesion
T1	≤ 2 cm
T2	> 2 cm ≤ 5 cm
T3	> 5 cm
T4	Invades adjacent organs (e.g. vagina, urethra, bladder)

N0	No regional lymph node metastasis
N1	Metastasis in inguinal, mesorectal, internal iliac, or external iliac nodes
N1a	Metastasis in inguinal, mesorectal, or internal iliac lymph nodes
N1b	Metastasis in external iliac lymph nodes
N1c	Metastasis in external iliac with any N1a nodes

M0	No distant metastasis
M1	Distant metastasis

# Stage Grouping

Stage	N0 (50%)	N1 (30%)
Tis	0	
T1	1	3a
T2	2a	3a
T3	2b	3c
T4	3b	3c
<b>M1</b> (12%)	4	

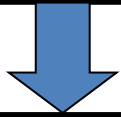
	5 y OS
T1	86%
T2	86%
T3	60%
T4	45%
N0	80%
N1	60%
M1	30%

	ACTII	3 y PFS
T1		85%
T2		80%
T3		65%
T4		63%
N0		76%
N1		60%

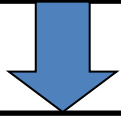
Non-SCC do worse.

# NCCN Guidelines: Anal Carcinoma

Anal **Canal** Cancer Suspected



Biopsy Confirms SCC



## EVALUATION

- Digital Rectal Exam and Inguinal Node Palpation (Biopsy or FNA if Suspicious)
- Gynecologic exam if female with cervical cancer screening
- CT Chest/Abd + CT or MRI Pelvis Consider PET for **T2-4, N0** or Tx, **N+**
- Consider HIV testing



T1-4, N0  
Tx, Node +



## Definitive

Mitomycin C  
5-FU / Cape  
Radiation  
(45-59 Gy)



Metastatic  
Disease



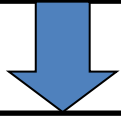
Metastatic  
Treatment

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## PET Scan:

Sensitivity 60% Specificity 90%  
Changed Nodal Status 20%  
Changed TNM Stage 40%

Caldarella, et al. Sci Wrlld Jrnl 2014; 1960-68  
Jones, et al. Ann Surg Oncol 2015;22:3574

T1-4, N0  
Tx, Node +

## Definitive

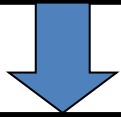
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Metastatic  
Disease

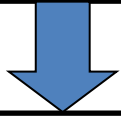
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T1-4, N0  
Tx, Node +



**Definitive**  
Mitomycin C  
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Radiation  
(45-59 Gy)



Metastatic  
Disease



Metastatic  
Treatment

MMC Improves

- DFS at 4 years (73% vs 51%)
- Colostomy rate (9% vs 22%)
- OS at 4 years Not Different

(JCO 1996; 14:2527)

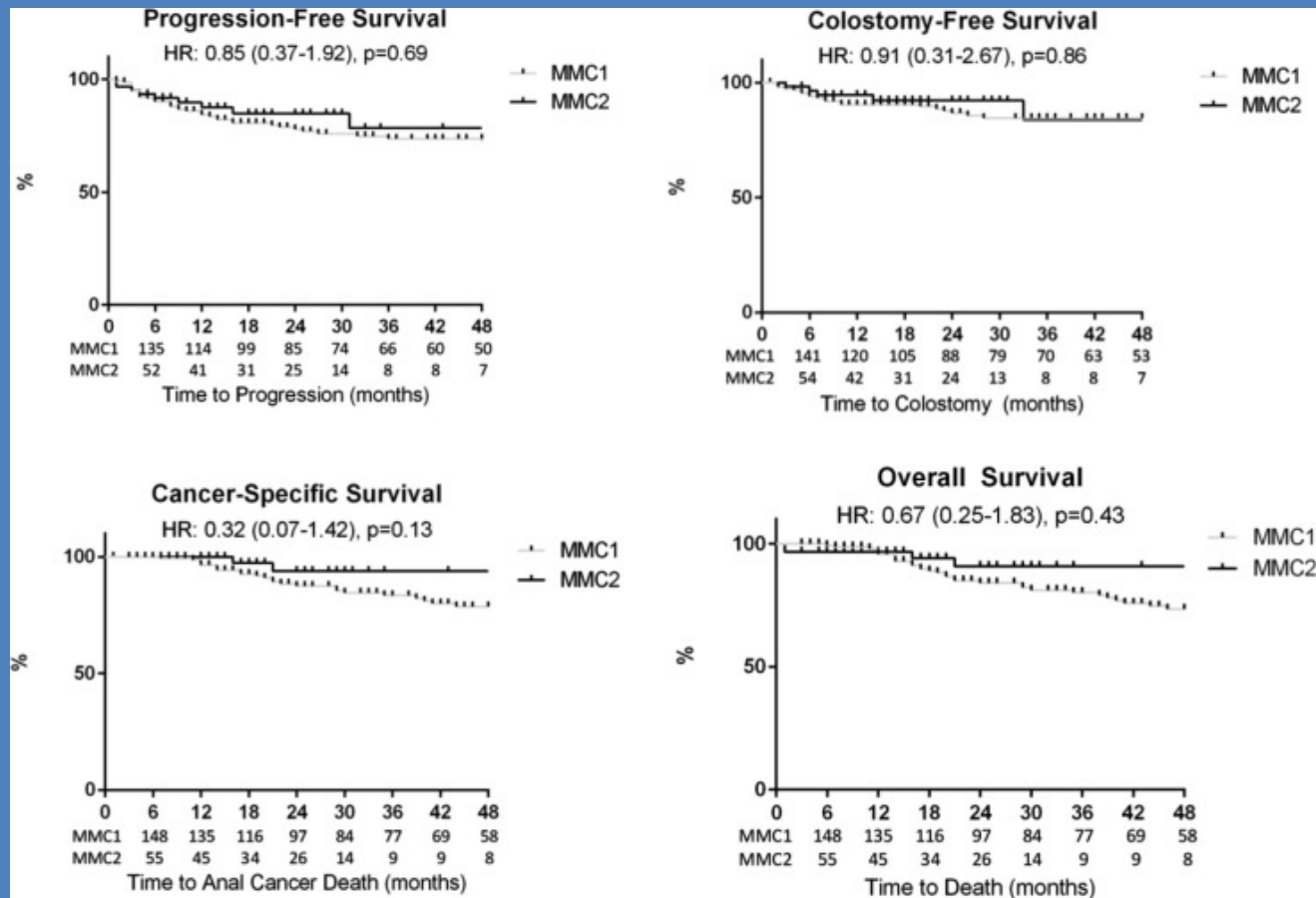


# NCCN Guidelines: Anal Carcinoma

Anal Canal Cancer Suspected

MMC Improves

One vs Two Doses (White et al Radiother Oncol 2015)

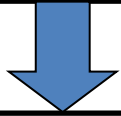


# NCCN Guidelines: Anal Carcinoma

**Perianal Cancer Suspected**



**Biopsy Confirms SCC**



## **EVALUATION**

- Digital Rectal Exam and Inguinal Node Palpation (Biopsy or FNA if Suspicious)
- Gynecologic exam if female with cervical cancer screening
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- Consider HIV testing

**Well or Moderately Differentiated**  
**T1 N0**  
**T2 (select) N0**



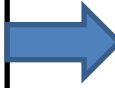
**Local Excision**

**Adequate Margins (1cm)**



**Re Excision or**

**Definitive**  
**Mitomycin C**  
**5-FU / Cape**  
**Radiation**  
**(45-59 Gy)**



**T1, Poorly Diff**  
**T2-4, N0**  
**Tx, N+**

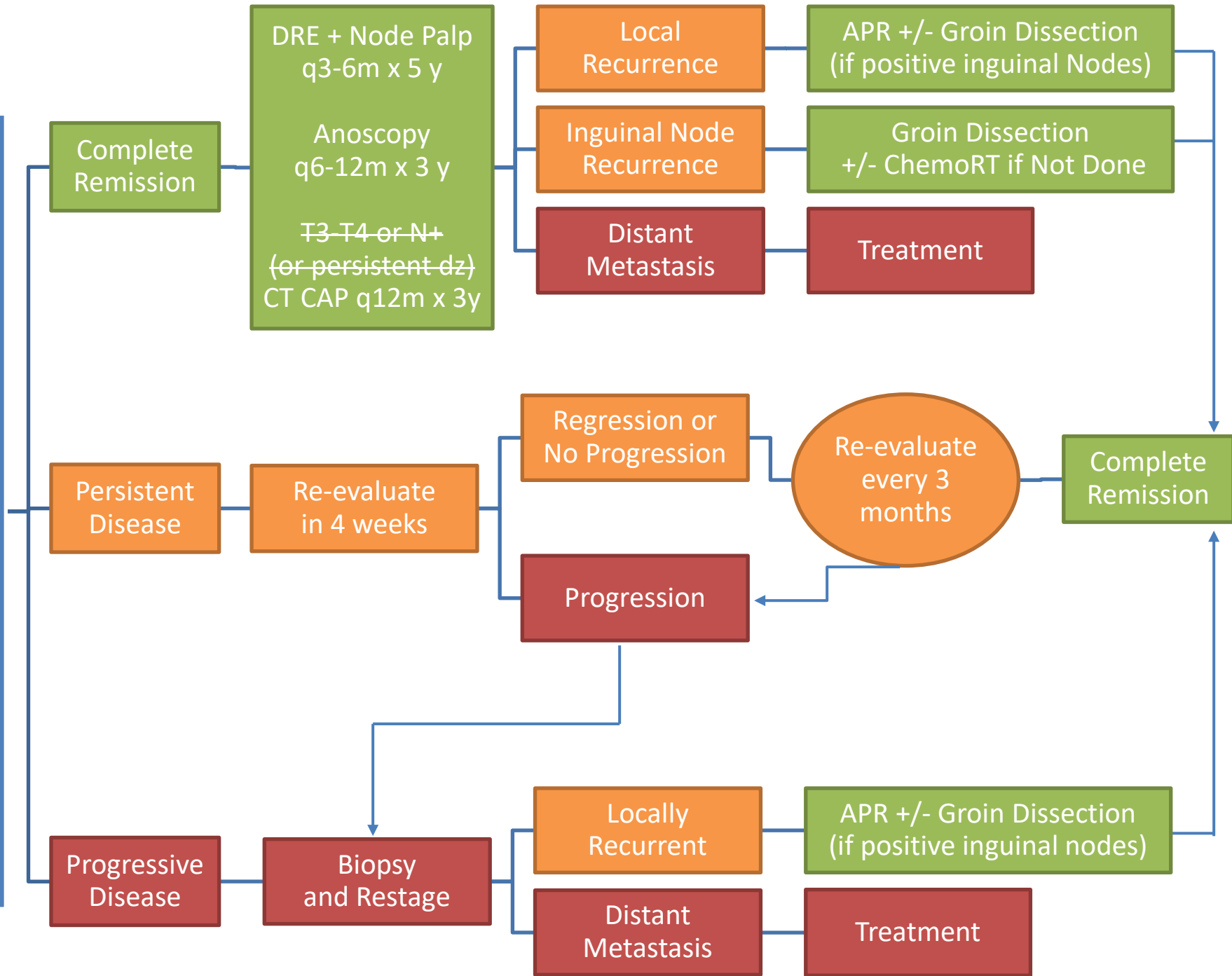


**Metastatic Disease**

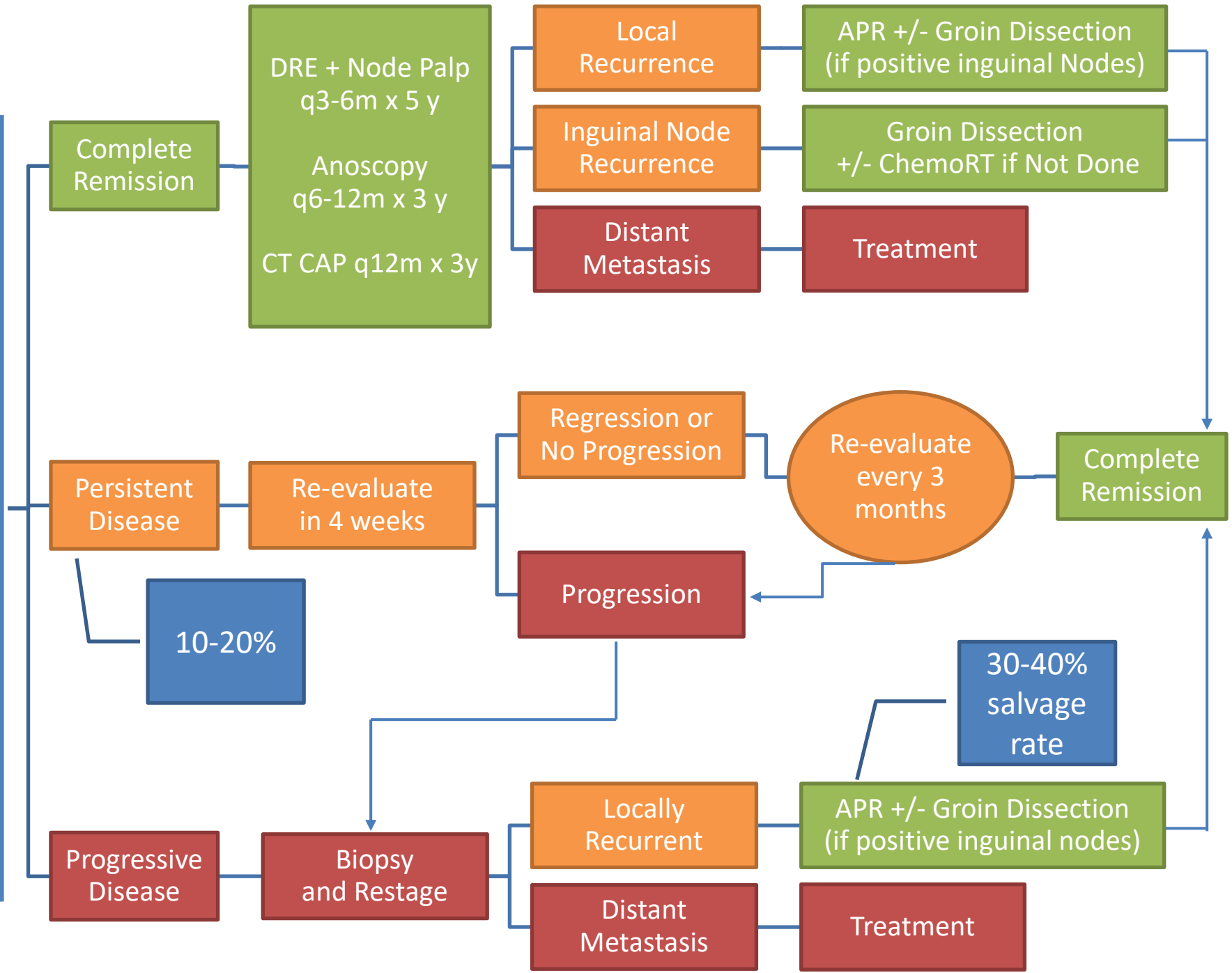


**Metastatic Treatment**

Evaluate 8-12 weeks with exam and DRE



Evaluate 8-12 weeks with exam and DRE



# Treatment

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APR was routinely performed

– 5 Year OS was 40-70%

## **Chemoradiation**

– Local Failure: 15-35%

5 Yr OS            72-90%

# Chemoradiation

## 5FU/Capecitabine + Mitomycin C

5-FU 1000mg/m<sup>2</sup> Days 1-4, 29-32

or

Capecitabine 825mg/m<sup>2</sup> M-F on RT Days

+

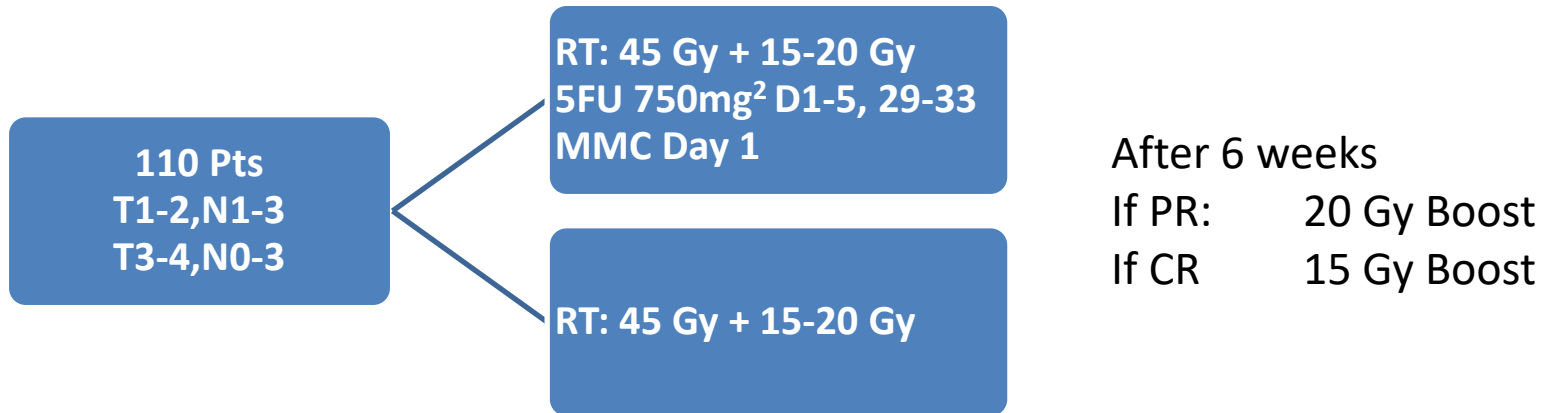
Mitomycin C 10mg/m<sup>2</sup> Days 1 and 29

or

Mitomycin C 12mg/m<sup>2</sup> Days 1

## Radiation to 45-59 Gy

# RT vs ChemoRT



AEs		XRT	XRT + CT
Diarrhea	Gr 2	16	15
	Gr 3	4	10
	Gr 4	0	0
Skin	Gr 2	18	13
	Gr 3	26	28
	Gr 4	0	1

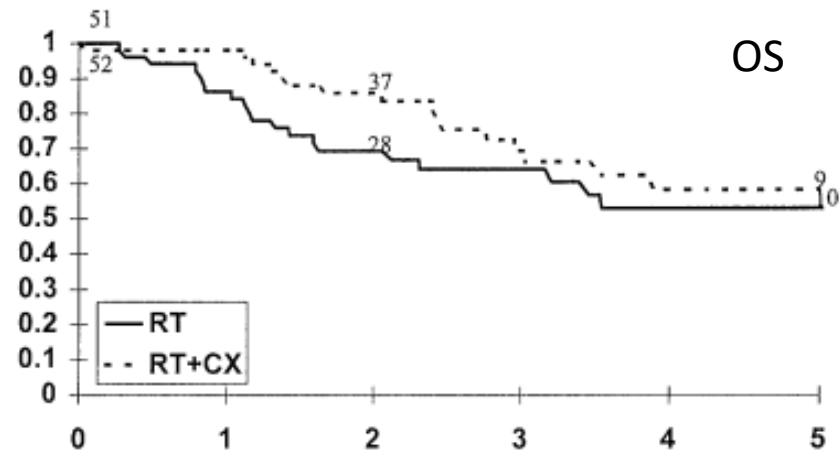
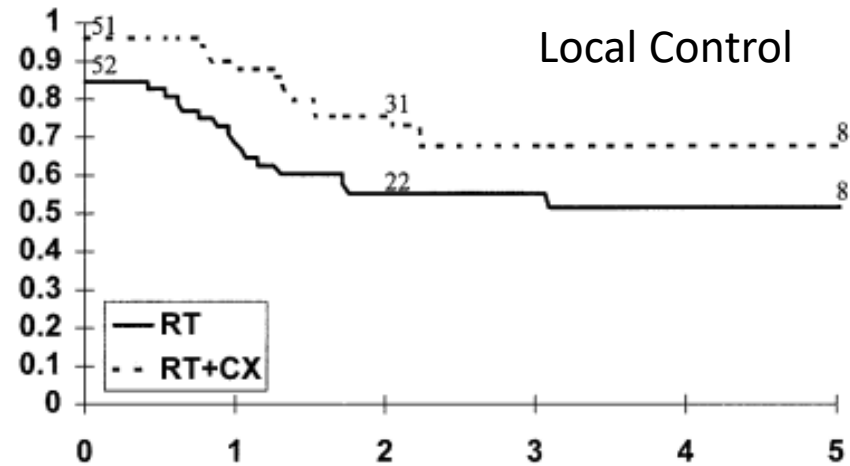
# RT vs ChemoRT

110 Pts  
T1-2,N1-3  
T3-4,N0-3

RT: 45 Gy + 15-20 Gy  
5FU 750mg<sup>2</sup> D1-5, 29-33  
MMC Day 1

RT: 45 Gy + 15-20 Gy

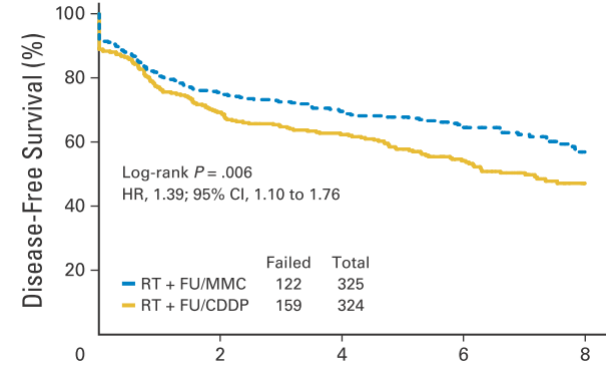
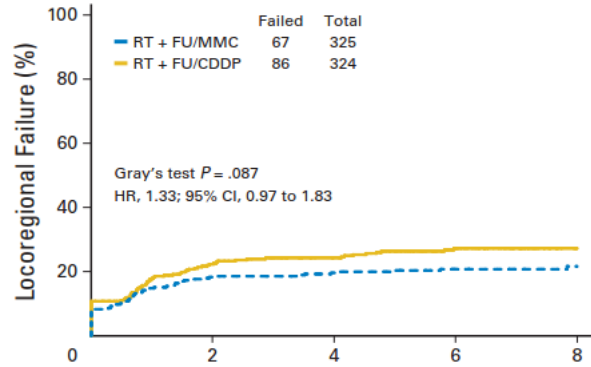
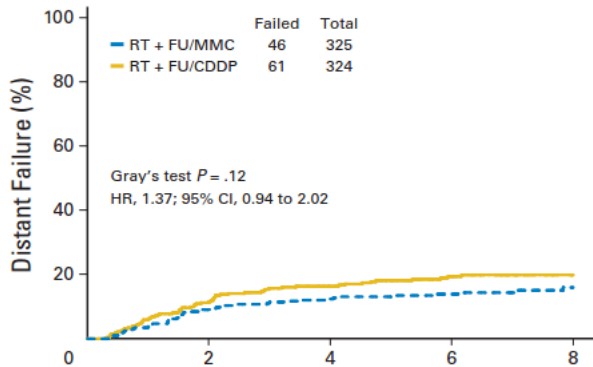
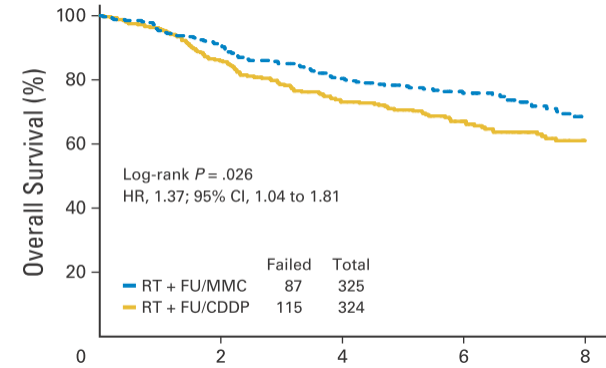
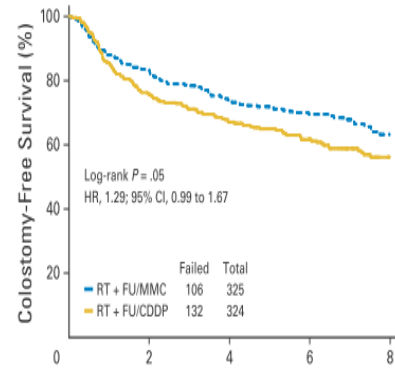
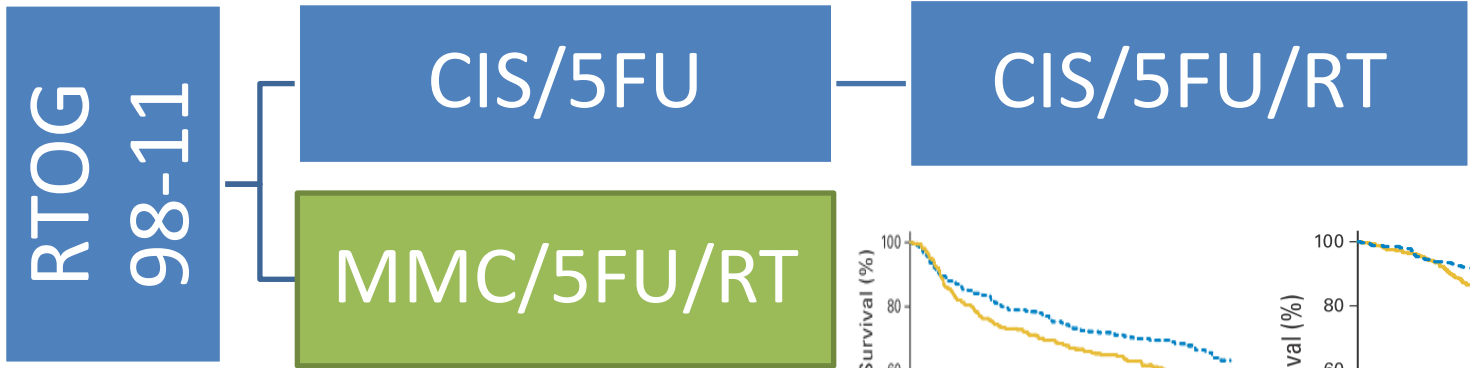
Complete Response:	80% vs 54%
CR after Surgery:	96% vs 85%
Colostomy Free Rate	32% improvement
Locoregional Control	18% improvement





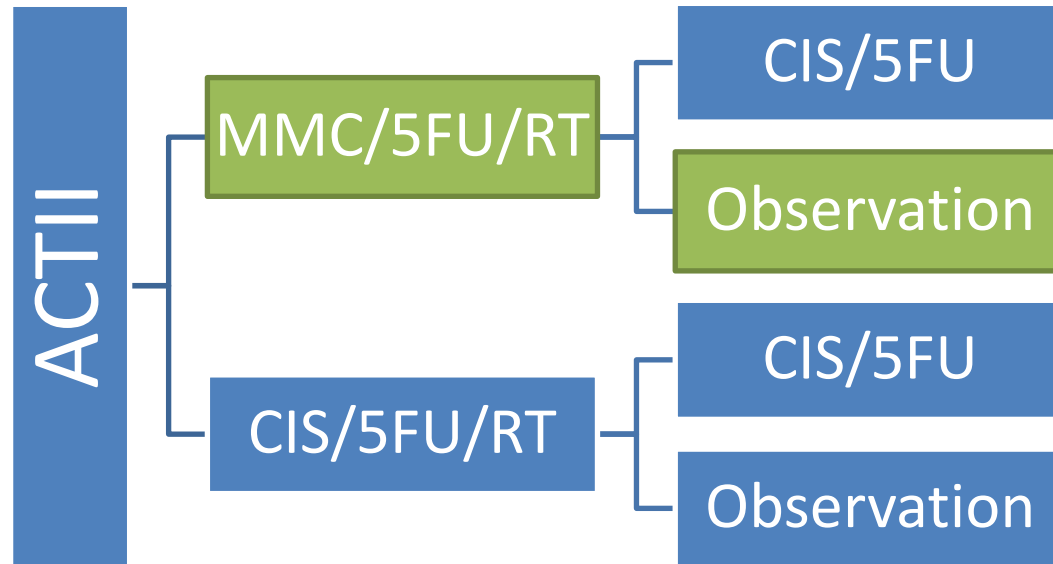
# Mitomycin C vs Cisplatin

Ajani, J. A. et al. JAMA 2008;299:1914-1921  
 Gunderson, L et al. J Clin Oncol. 2012; 30(35)

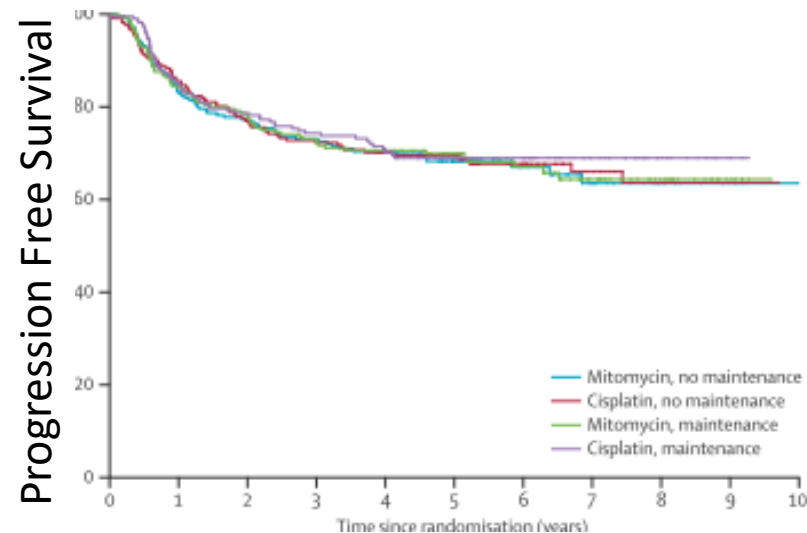


# Mitomycin C vs Cisplatin

Lancet Oncol. 2013 May;14(6):516-24



Complete Response	90%
Partial Response	5%
Stable Disease	1%
Progressive Disease	5%

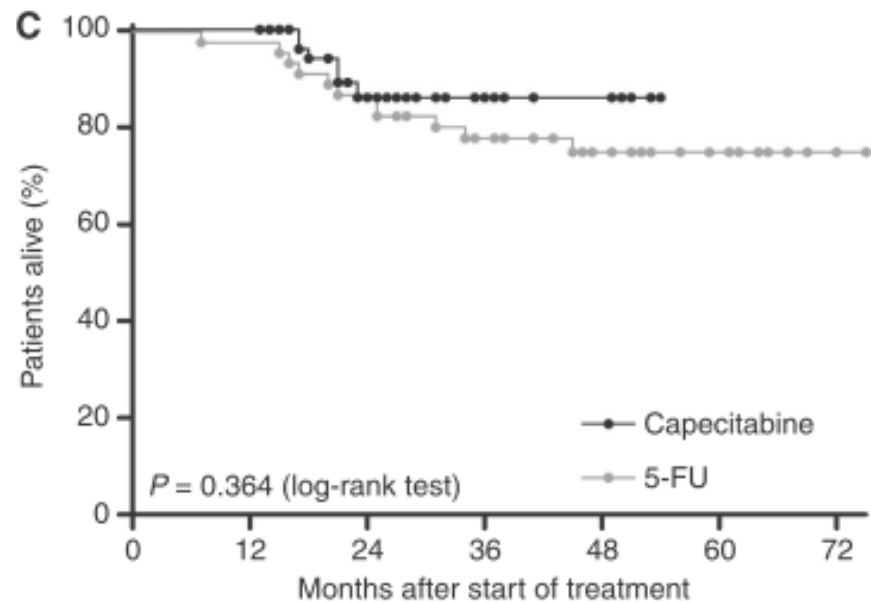
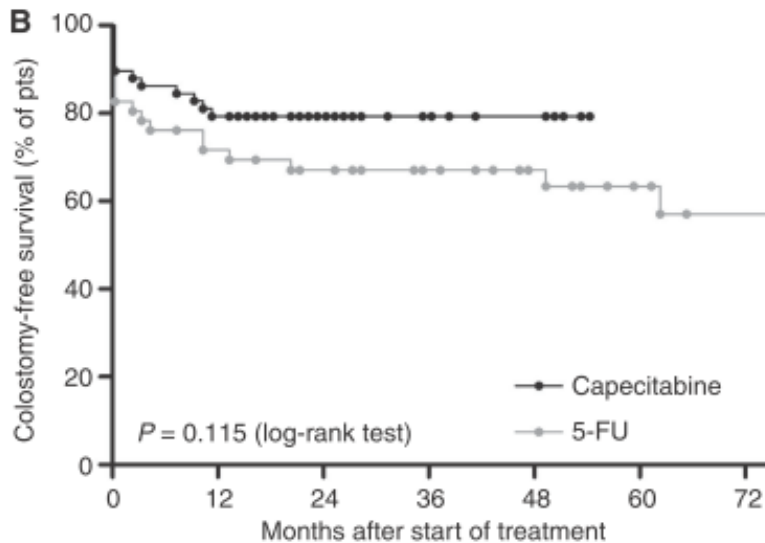
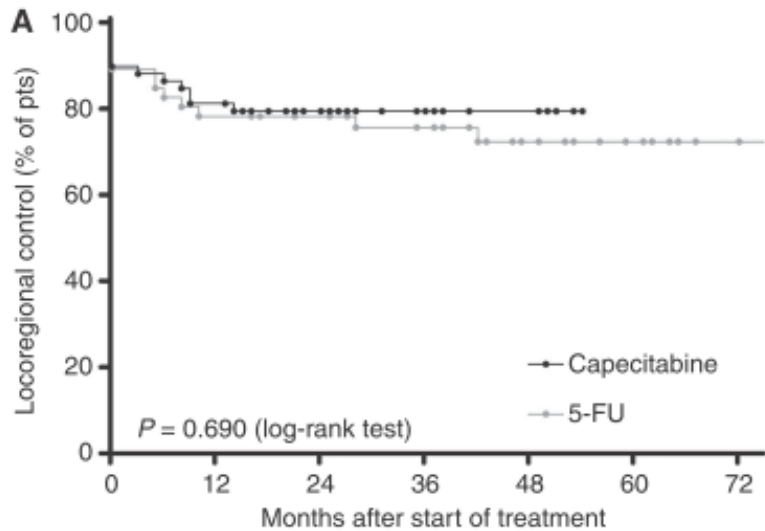


# Mitomycin C vs Cisplatin

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- Any Grade 3-4 Toxicity 71% vs 72%
- Hematological Grade 3-4 26% vs 16%

# Capecitabine vs 5-FU



# Capecitabine

Table 2. Acute toxicity according to treatment group

Type of toxicity	5-FU + MMC (n = 47)		Capecitabine + MMC (n = 58)		P-value <sup>a</sup>
	No.	%	No.	%	
<b>Dermatological toxicity</b>					
No toxicity	0	0	0	0	0.035
Grade 1–2	41	87	40	69	
Grade 3–4	6	13 <sup>b</sup>	18	31	
<b>Gastrointestinal toxicity</b>					
No toxicity	17	36	4	7	1.000
Grade 1–2	29	62	52	90	
Grade 3–4	1	2	2	3	
<b>Haematological toxicity</b>					
No toxicity	7	15	7	12	1.000
Grade 1–2	37	79	47	83	
Grade 3–4	3	6	3	6	
<b>Genitourinary toxicity</b>					
No toxicity	34	72	28	48	0.586
Grade 1–2	11	24	29	50	
Grade 3–4	2	4	1	2	

# Metastatic Disease

Bull Cancer. 1999;86(10):861.

Risk Factors for Residual/Recurrent Disease:

T > 4cm, N+

Approximately 5-20% of cases

Liver > Lung > Extra Pelvic Nodes

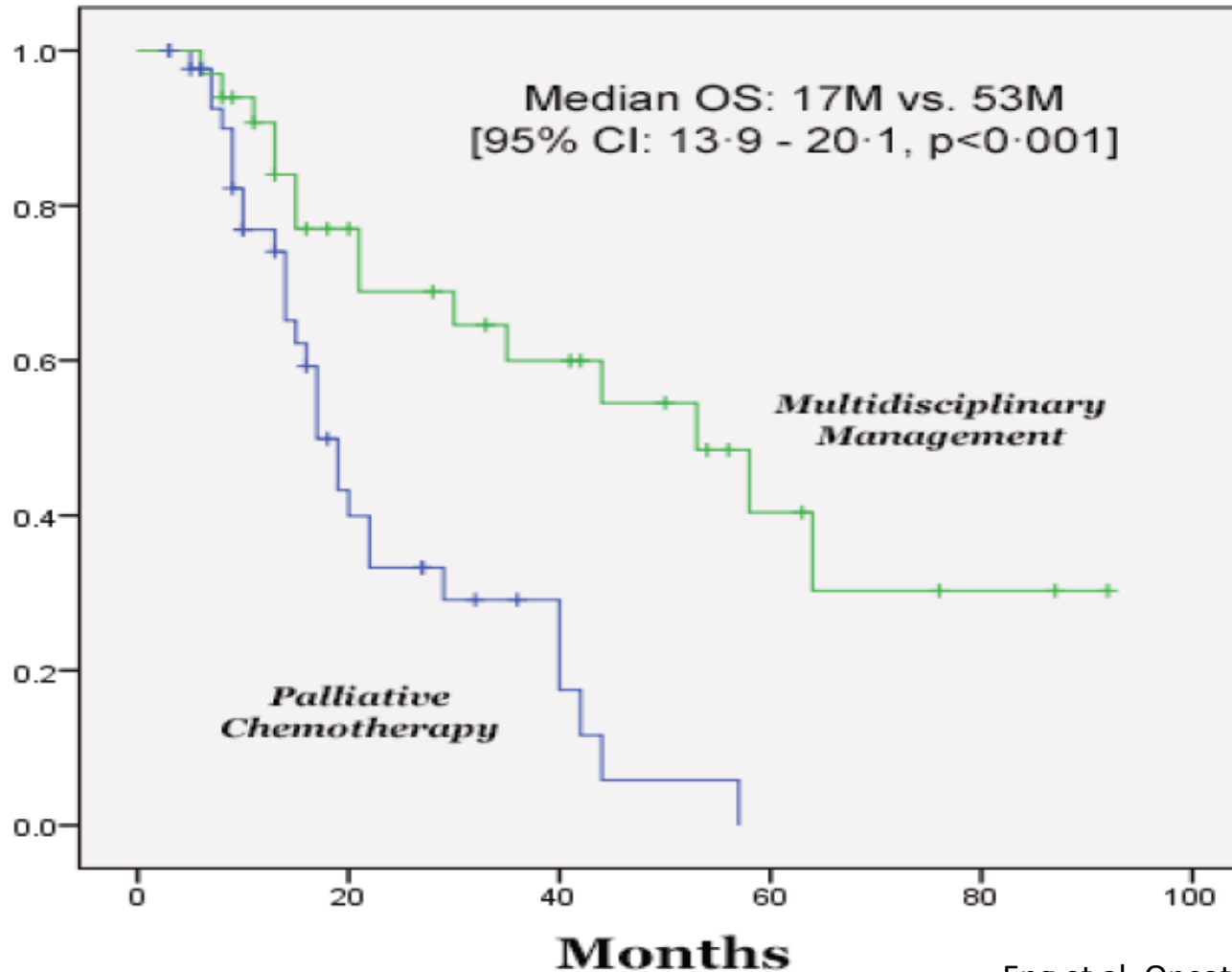
- Reports of long-term outcome with metastasectomy and radiation to oligometastatic disease

Limited data on chemotherapy

Cisplatin / fluoropyrimidine combinations most studied

- Up to 50% response rates, Median OS 15-33 months
- OS is 62% at 1 year and 32% at 5 years
- 3 patients alive at 4, 5 and 7 years benefited from local treatment

# Multidisciplinary Treatment



**2000 - 2012**  
77 patients total

## **5FU Cis (42)**

SD 29%  
PR 57%  
PD 14%

## **Carbo Paclitaxel (24)**

SD 21%  
PR 33%  
PD 46%

# NCCN: Metastatic Disease

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## First Line Therapy +/- RT

Carboplatin + Paclitaxel (NCCN Preferred)

5FU + Cisplatin (more toxic)

FOLFOX6 (NCCN case report, adeno)

FOLFCIS

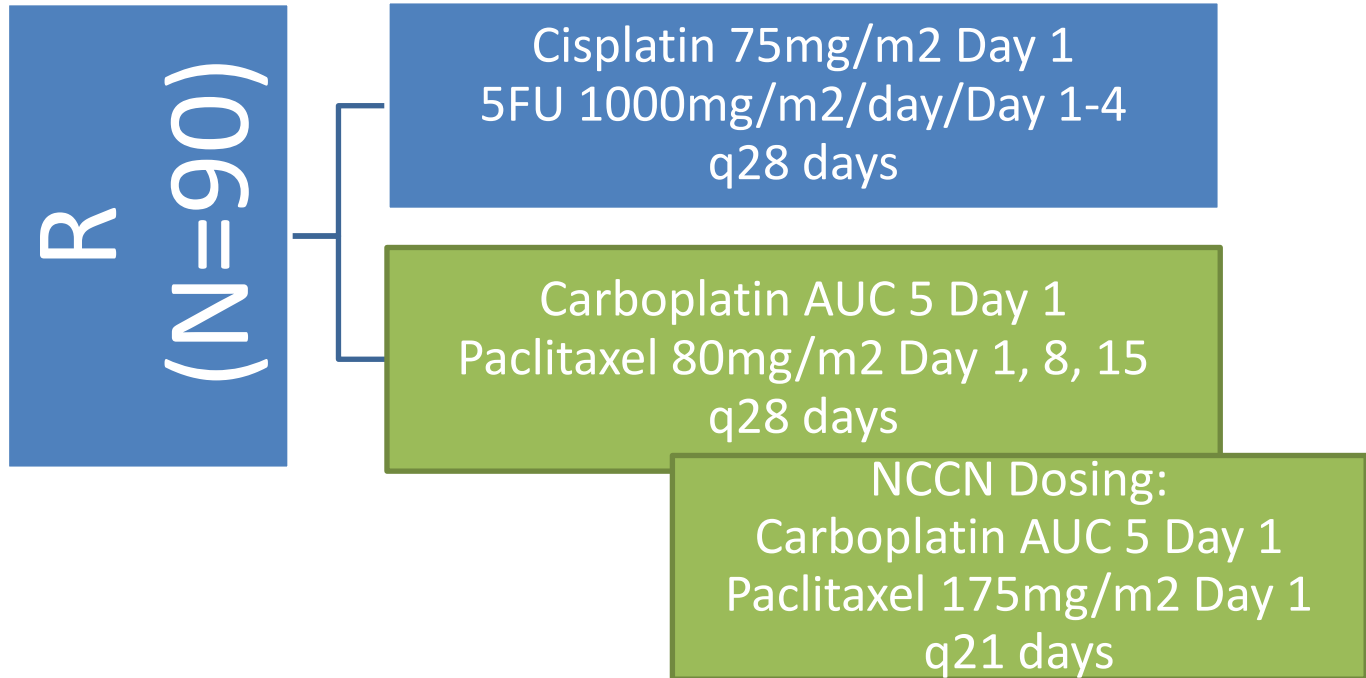
mDCF

## Second Line Therapy

Nivolumab or Pembrolizumab



# InterAACT: 1<sup>st</sup> Line Trial



Primary:

RR

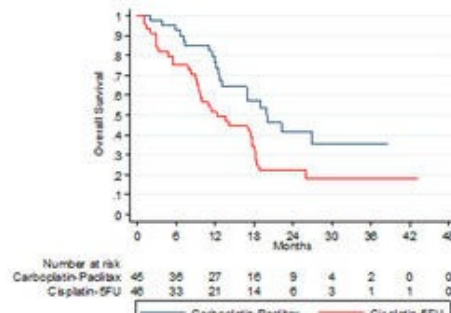
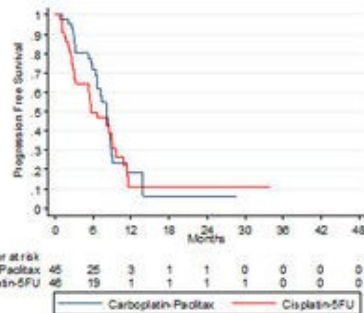
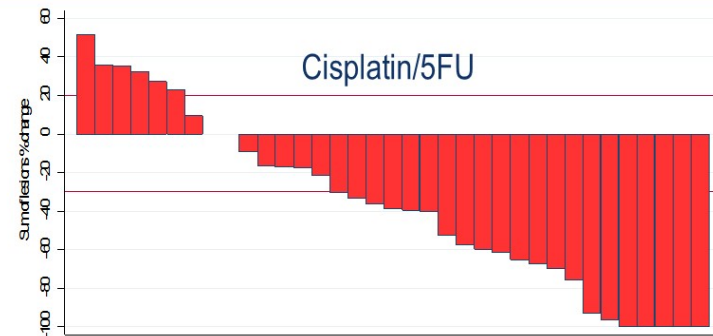
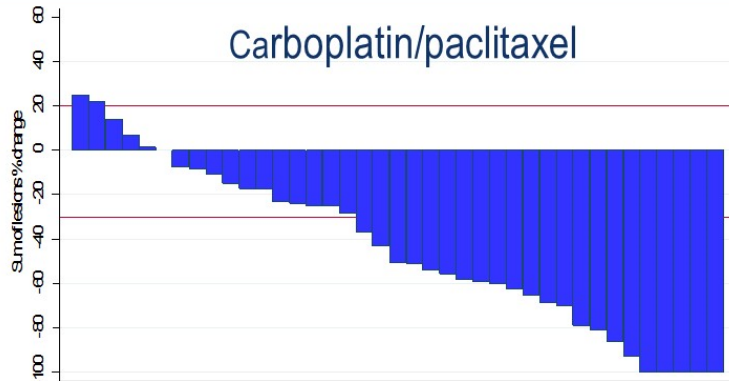
Secondary:

PFS, OS, Correlatives, QOL

# InterAACT: AEs

Toxicity $\geq$ Grade 3	Carboplatin + Paclitaxel (N=42) %	Cisplatin-5FU (N=42) %
Anemia	10	5
Diarrhea	2	5
Fatigue	10	19
Febrile Neutropenia	5	10
Mucositis	0	26
Nausea	2	17
Neuropathy	2	0
Thromboembolism	2	12
Overall	71	76
SAEs	36	62

# InterAACT: Results



	Carboplatin Paclitaxel (N=39)	Cisplatin 5FU (N=35)
CR	13 %	14 %
PR	46 %	43 %
SD	25 %	20 %
PD	15 %	23 %
RR	59 %	57 %
DCR	84 %	77 %
PFS	8.1 months	5.7 months
OS	20 months	12.3 months

# DCF/mDCF (Epitopes HPV02)

Kim, et al. Lancet Oncol 2018

Single Arm, Multicenter, Phase 2

- 66 pts (36 DCF, 30 mDCF)
- 97 SAE (69 DCF, 28 mDCF)



mDCF every 14 days

Docetaxel 40mg/m<sup>2</sup> Day 1

Cisplatin 40mg/m<sup>2</sup> Day 1

Fluorouracil 2400mg/m<sup>2</sup> over 48 hours

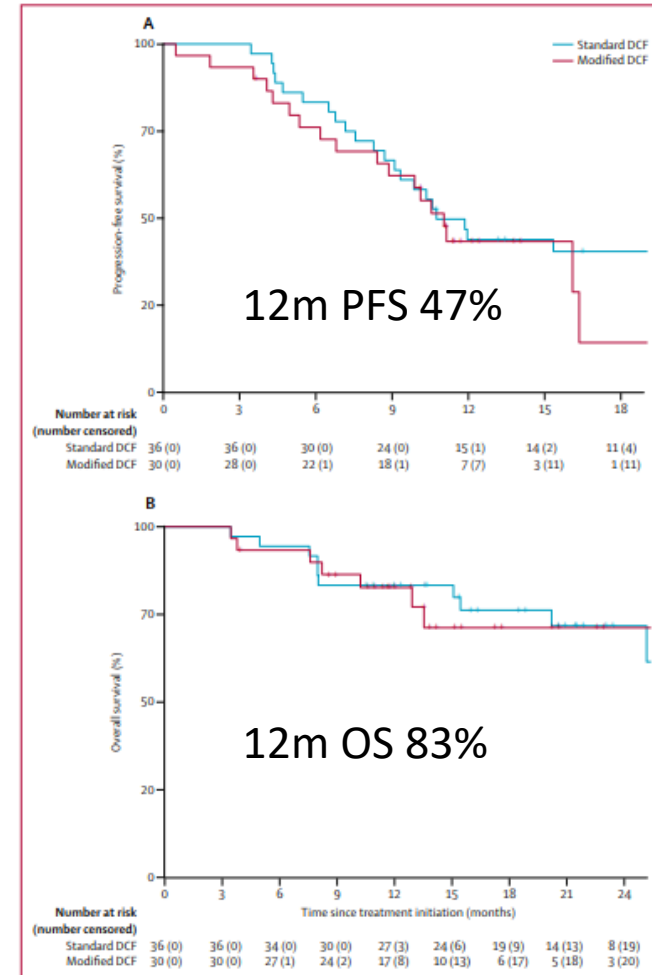
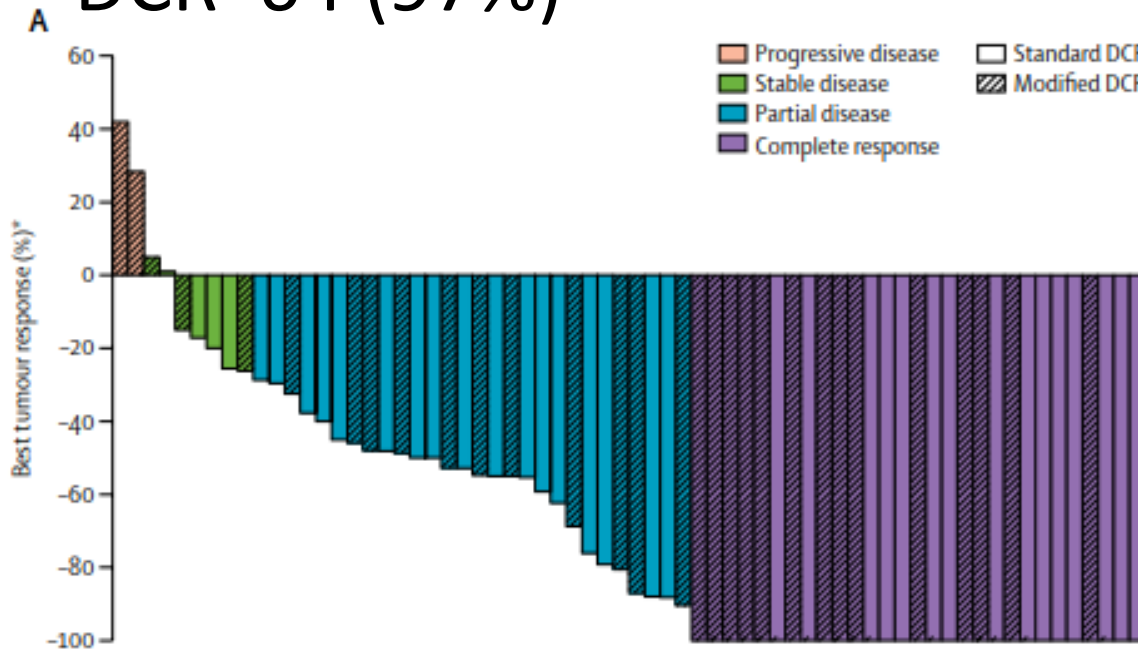
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Lancet Oncol 2018

CR 30 (45%)

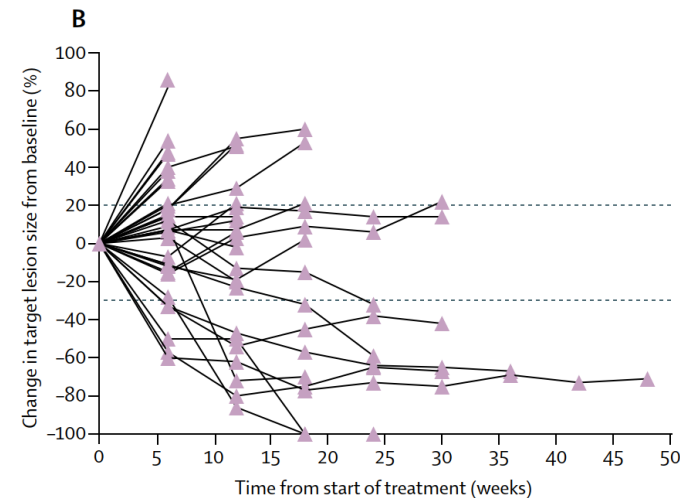
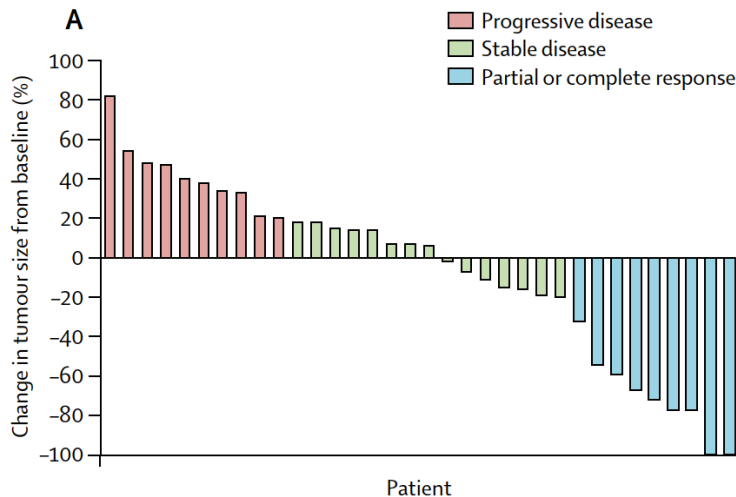
ORR 59 (89%)

DCR 64 (97%)

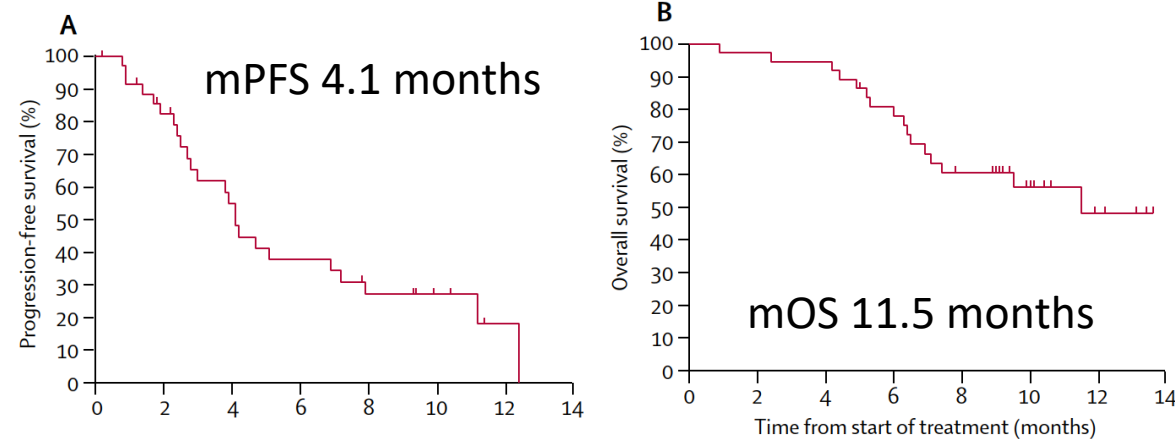


# Nivolumab

- Phase II of 37 patients.
- Primary endpoint was RECIST Response
- 9 patients (24%) responded (2 CR, 7 PR)



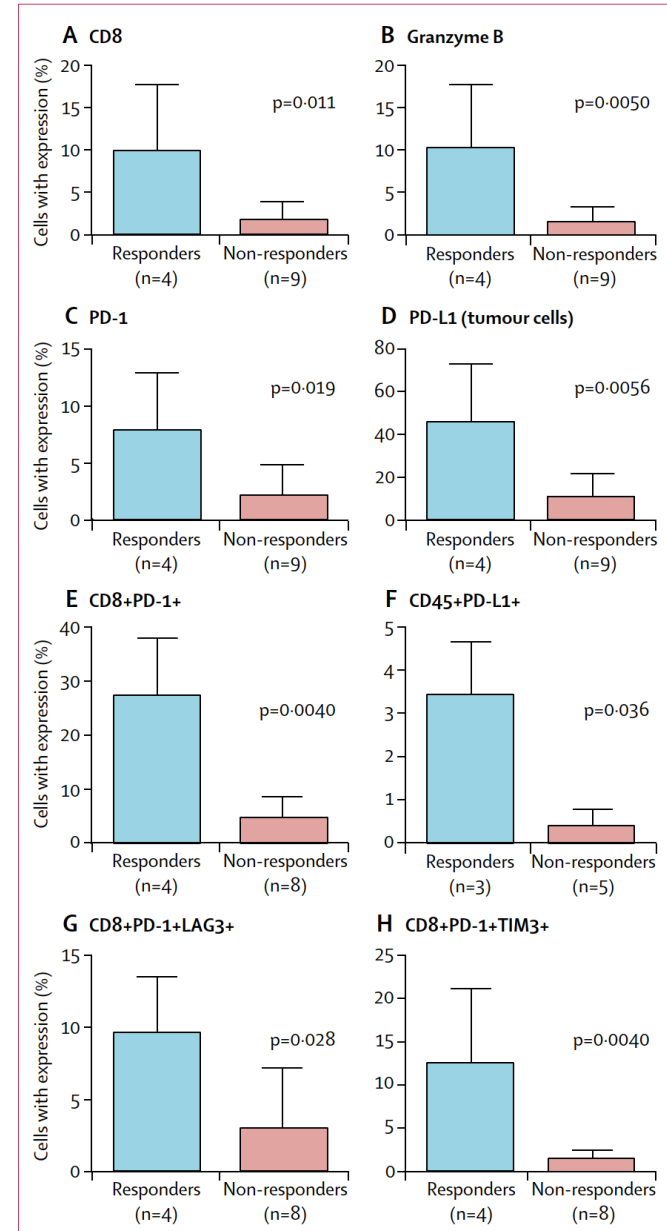
# Nivolumab



	Grade 1	Grade 2	Grade 3
Anaemia	13 (35%)	11 (30%)	2 (5%)
Fatigue	17 (46%)	7 (19%)	1 (3%)
Rash	8 (22%)	2 (5%)	1 (3%)
Constipation	8 (22%)	2 (5%)	0
Anorexia	5 (14%)	4 (11%)	0
Diarrhoea	8 (22%)	0	0
Weight loss	5 (14%)	1 (3%)	0
Arthralgia	3 (8%)	3 (8%)	0
Hyperglycaemia	3 (8%)	1 (3%)	0
Hypothyroidism	1 (3%)	1 (3%)	1 (3%)
Lymphoedema	1 (3%)	1 (3%)	0
Nausea	2 (5%)	0	0
Pneumonitis	0	1 (3%)	0

Data are n (%). n=37.

**Table 2: All adverse events**



# Summary

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## Local Disease

- **Definitive chemoradiation** is standard.  
**5-FU or Capecitabine / Mitomycin / Radiation**
- Adjuvant Nivolumab trial via ECOG (at SCCA)
- Surgery is for salvage

## Metastatic Disease

- **First Line:** ~~5-FU/Cis~~ Carboplatin + Paclitaxel
- **Second Line** Immunotherapy (Phase II data)  
SCCA / DFCI have Phase II Pembrolizumab Trial