

Anal Cancer

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Cancer Care
Alliance**

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UW Medicine

UW SCHOOL
OF MEDICINE

Outline

Background

- Pathogenesis

- Epidemiology

- Anatomy

Staging and Workup

Treatment

- Local Disease

- Recurrent Disease

- Metastatic Disease

Classification

WHO classification of anal cancer

Anal canal
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
Anal margin
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

- 8,590 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

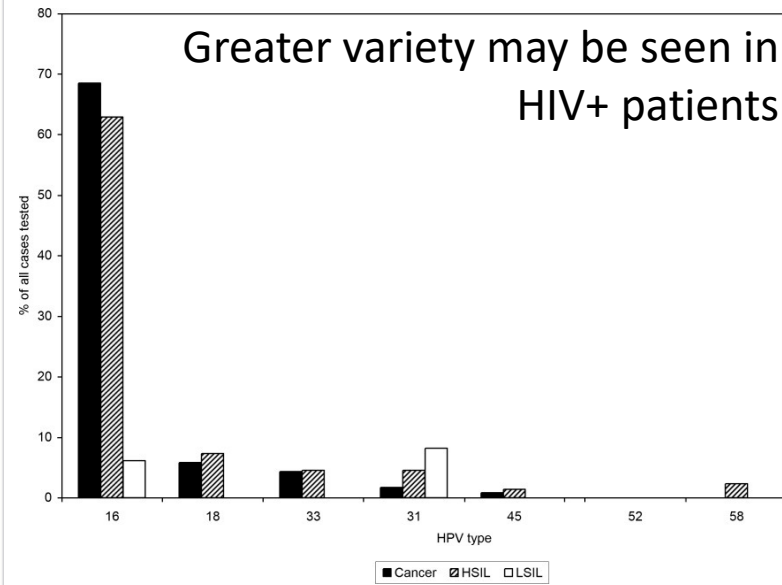
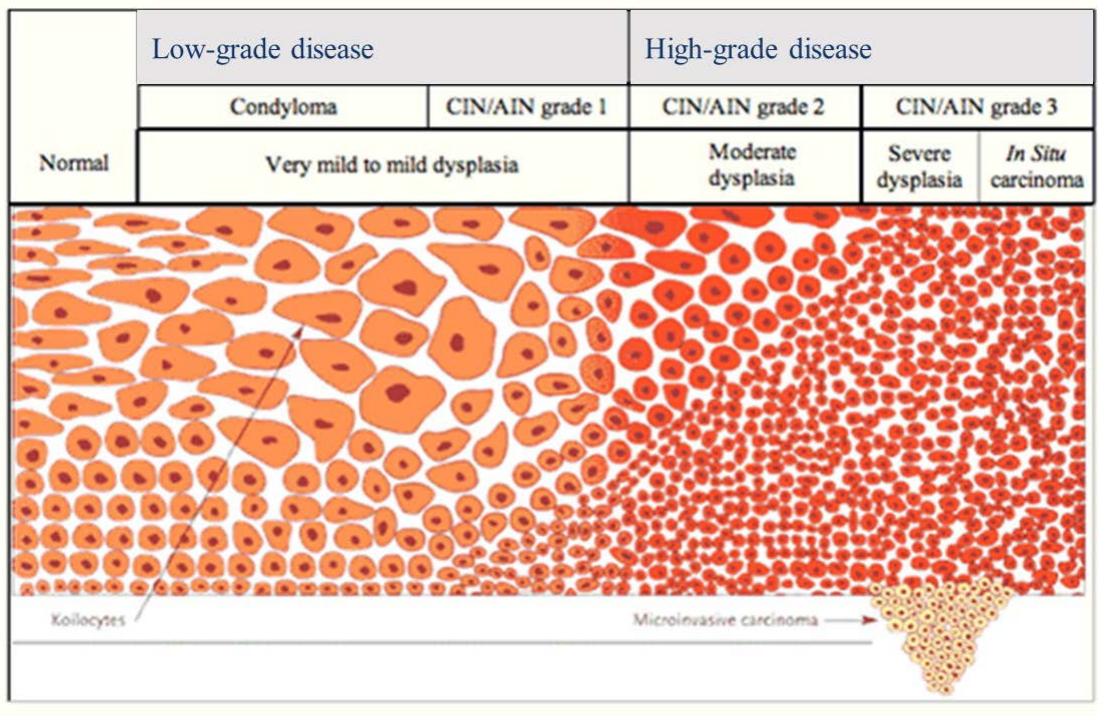
CLINICAL PRESENTATION

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

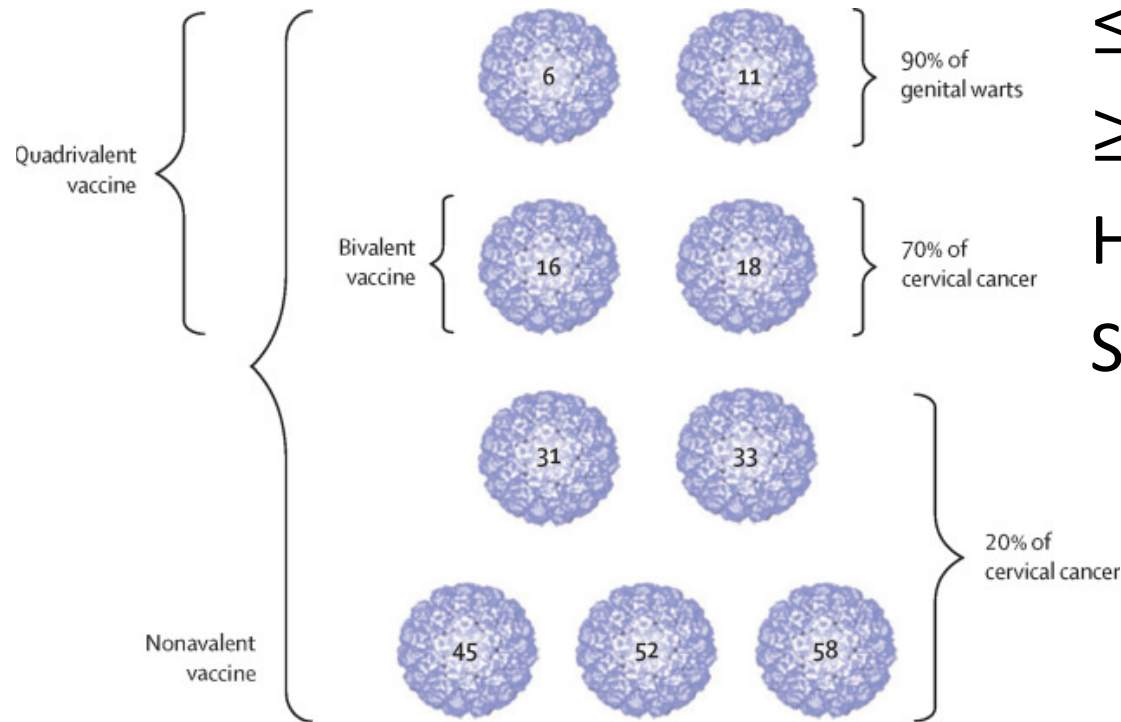
Pathogenesis

- 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



≤ 14 yo: 0 and 6 **or** 12 m

≥ 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 Men and Women

HIV-negative MSM

Woman with High Grade Cervical/Vulvar Lesion/Cancer

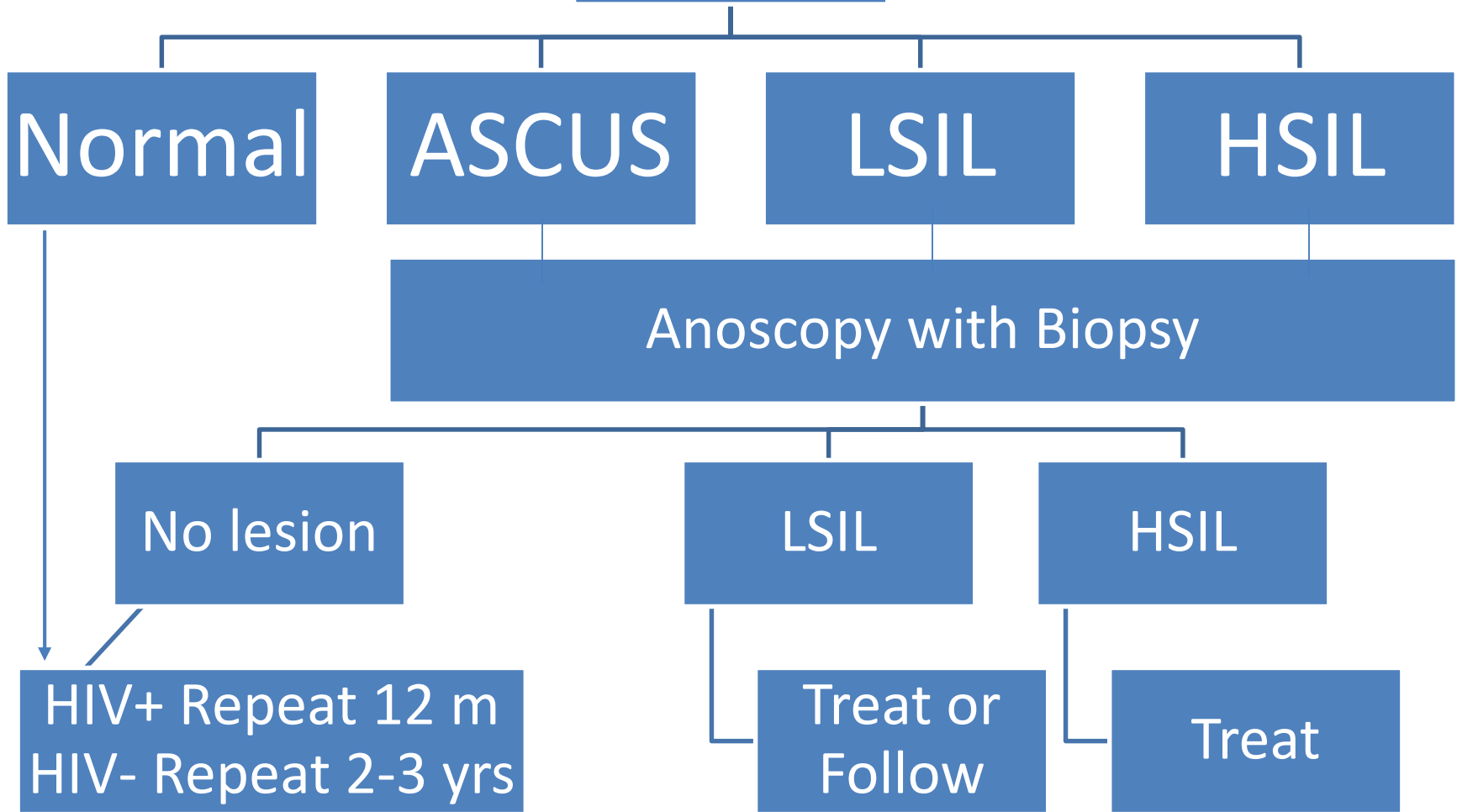
Woman and Men with Perianal Condyloma

Solid Organ Transplant Recipients

Over 25 if immunosuppressed

Over 40 if immunocompetent

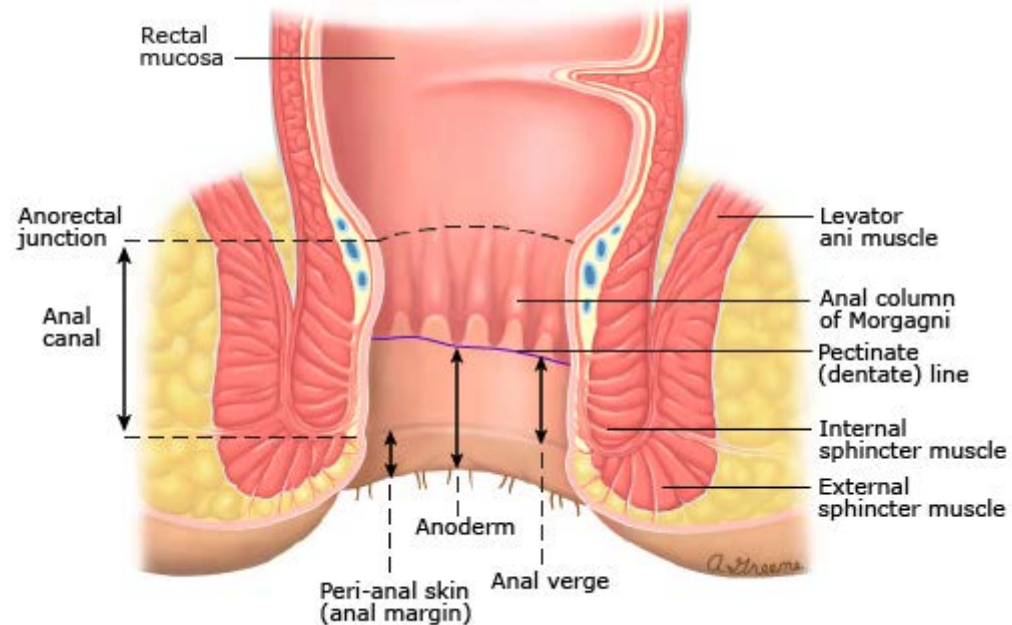
Screen



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.



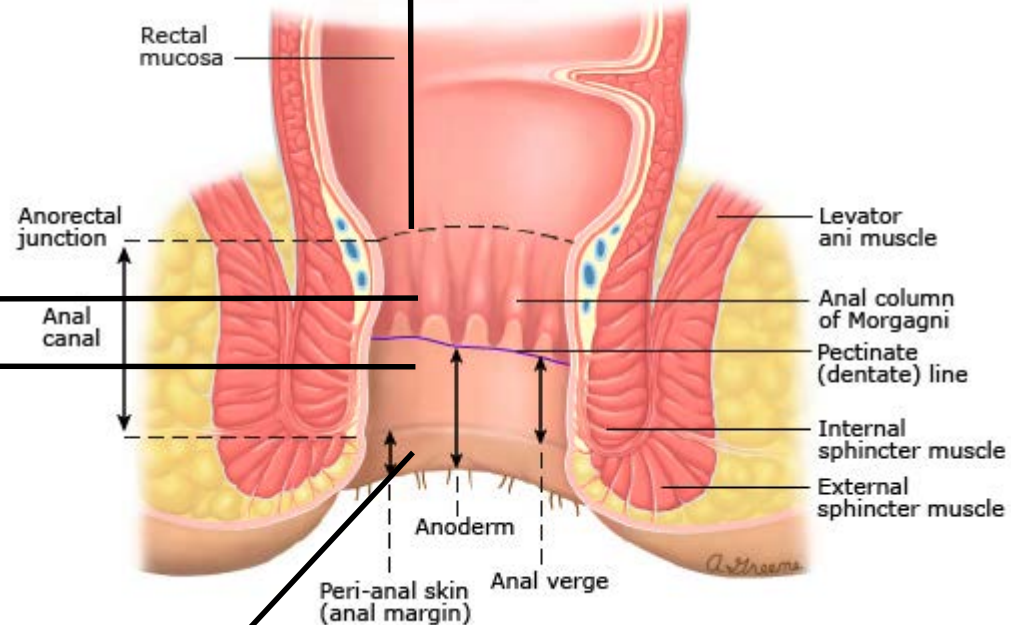
Anatomy: Nodal Drainage

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
M1 (12%)	4	

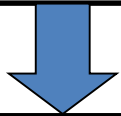
	5 y OS
T1	86%
T2	86%
T3	60%
T4	45%
N0	80%
N1	60%
M1	30%

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

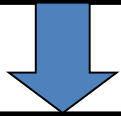
Non-SCC do worse.

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)



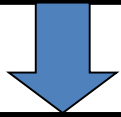
Metastatic
Disease



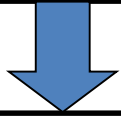
Metastatic
Treatment

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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

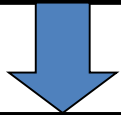
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Metastatic
Disease

Metastatic
Treatment

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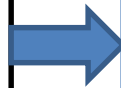


Biopsy Confirms SCC



EVALUATION

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T1-4, N0
Tx, Node +



Definitive

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Metastatic
Disease



Metastatic
Treatment

MMC Improves

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

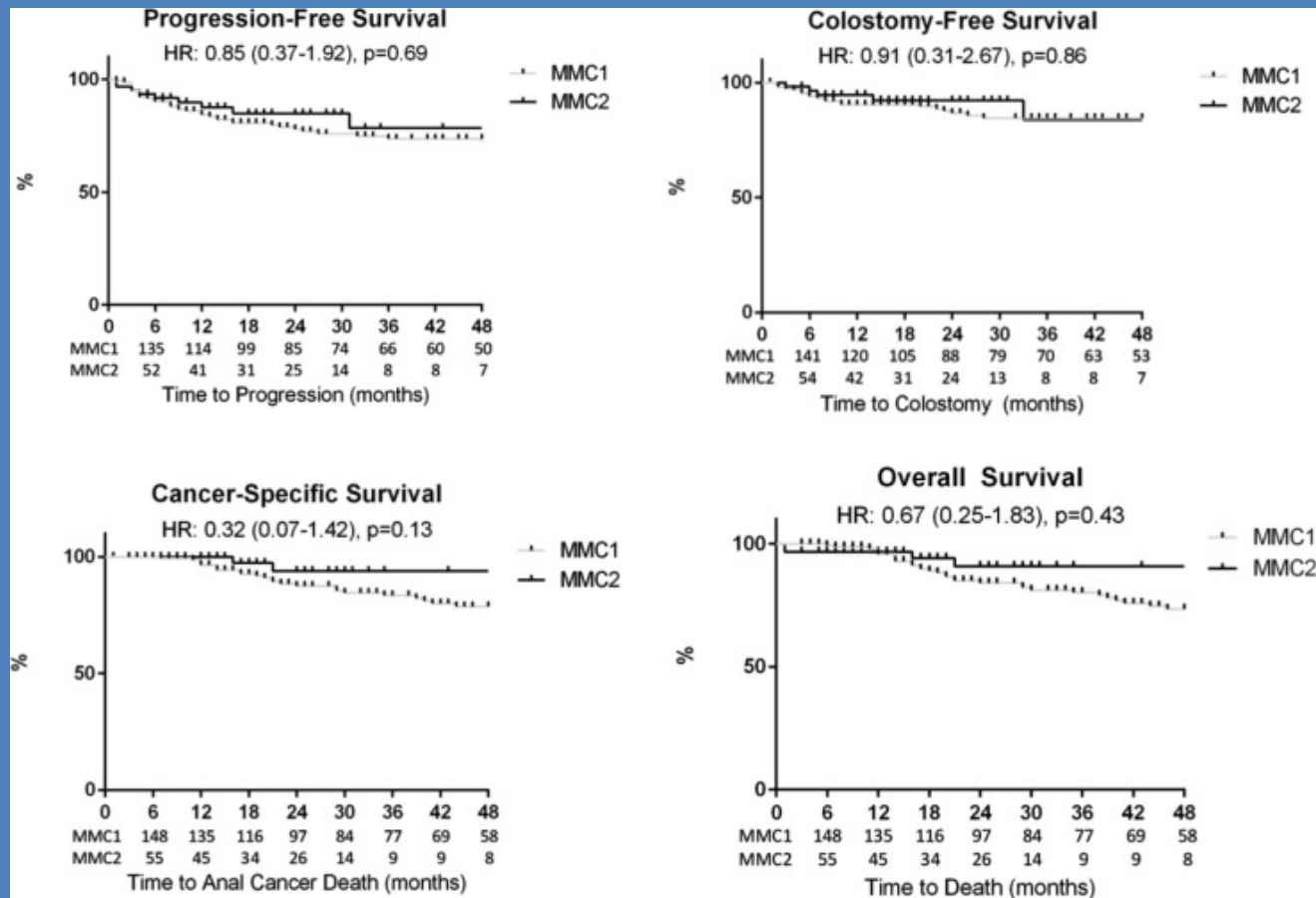
(JCO 1996; 14:2527)

NCCN Guidelines: Anal Carcinoma

Anal Canal Cancer Suspected

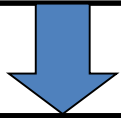
MMC Improves

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

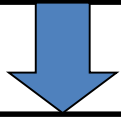


NCCN Guidelines: Anal Carcinoma

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
- CT Chest/Abd + CT or MRI Pelvis Consider PET for **T2-4, N0** or Tx, N+
- Consider HIV testing

Well or Moderately Differentiated

T1 N0
T2 (select) N0



Local Excision

Adequate Margins (1cm)

NO



Re Excision or

Definitive

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



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

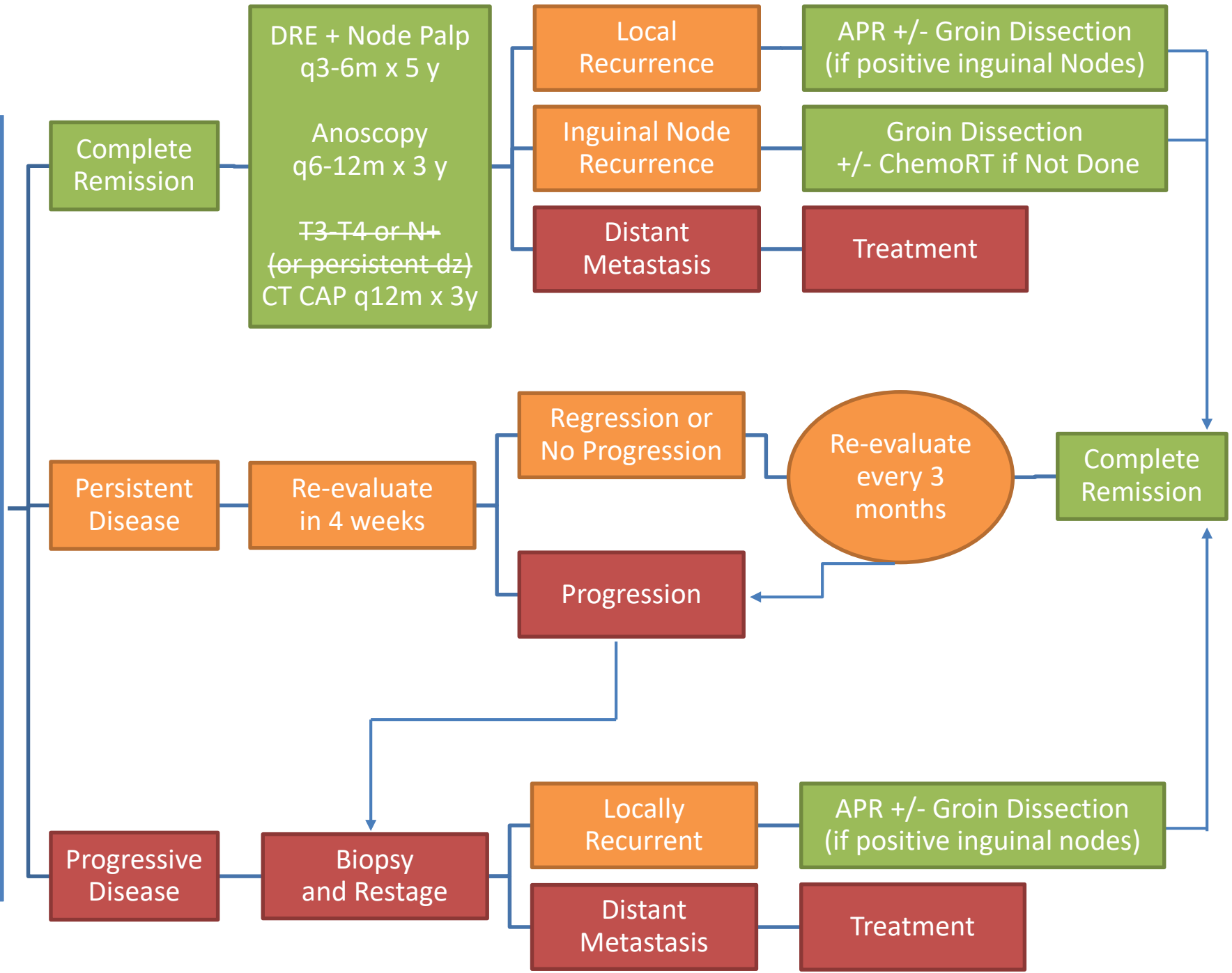


Metastatic Disease

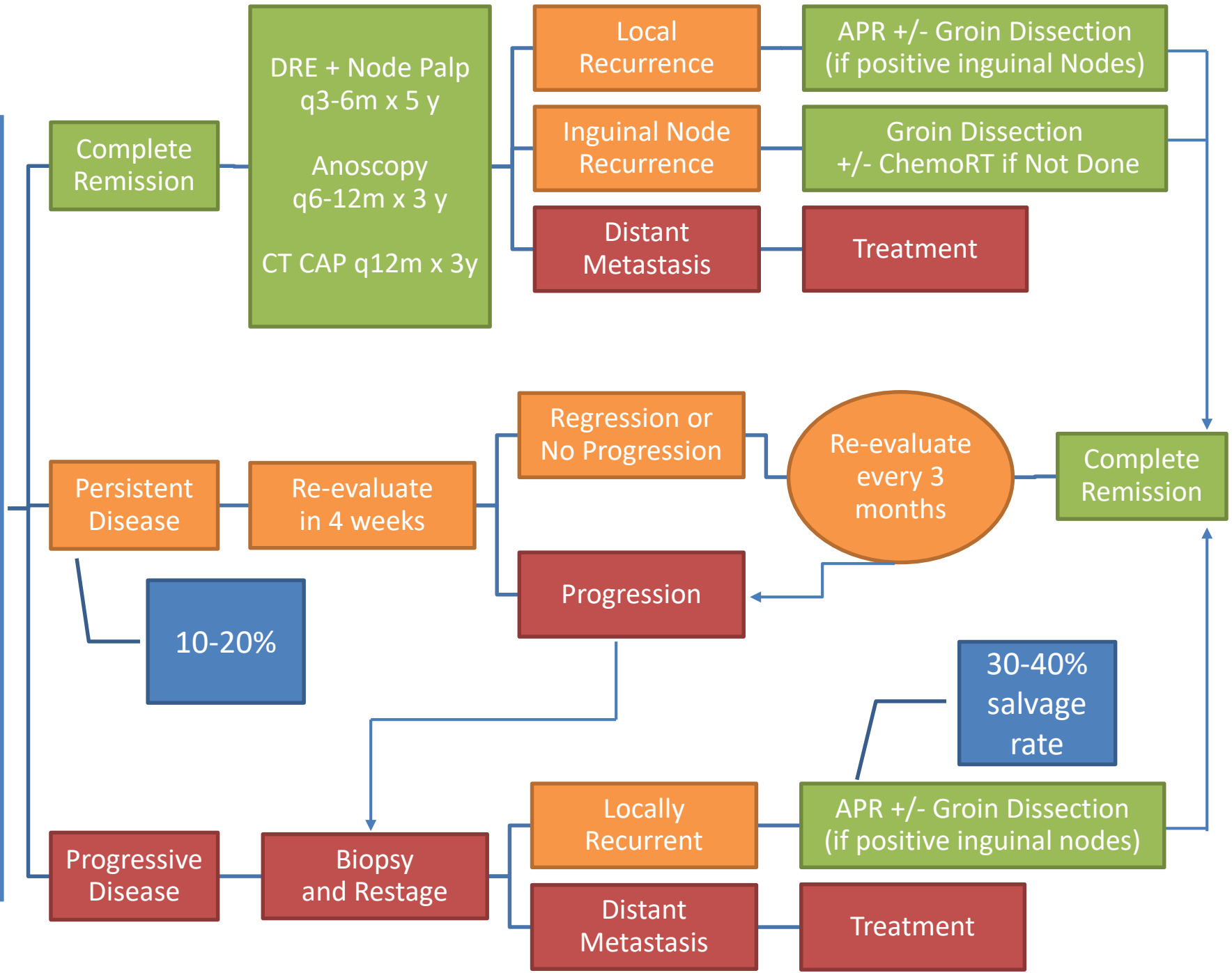


Metastatic Treatment

Evaluate 8-12 weeks with exam and DRE



Evaluate 8-12 weeks with exam and DRE



Treatment

APR was routinely performed

– 5 Year OS was 40-70%

Chemoradiation

– Local Failure: 15-35%

5 Yr OS 72-90%

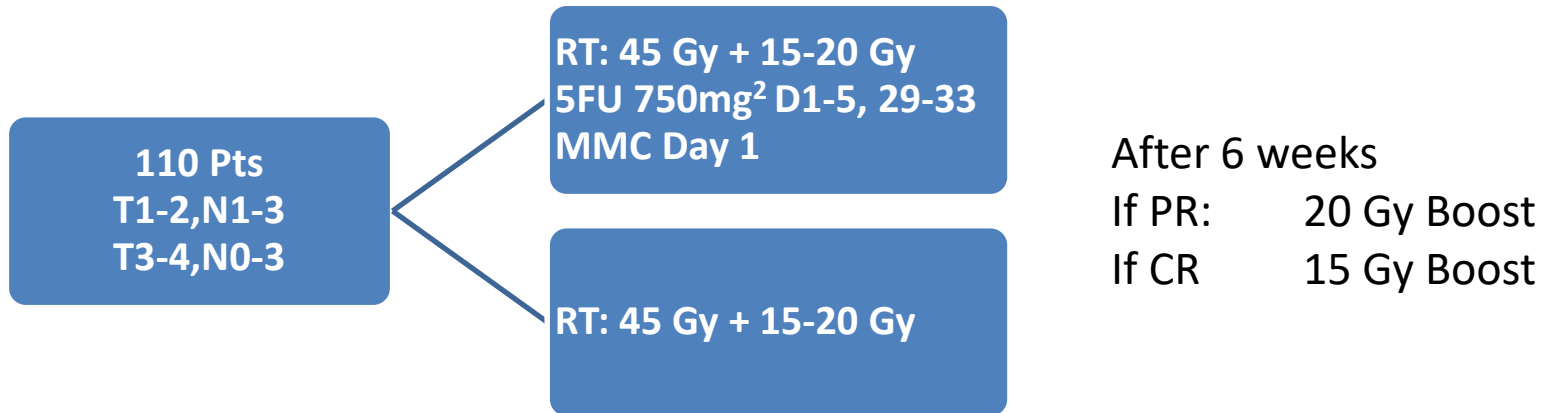
Chemoradiation

5FU/Capecitabine + Mitomycin C

5-FU 1000mg/m ²	Days 1-4, 29-32
or	
Capecitabine 825mg/m ²	M-F on RT Days
+	
Mitomycin C 10mg/m ²	Days 1 and 29
or	
Mitomycin C 12mg/m ²	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

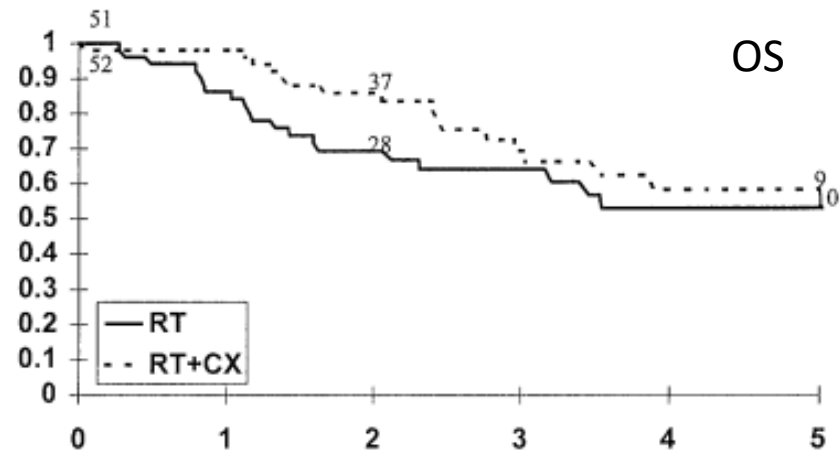
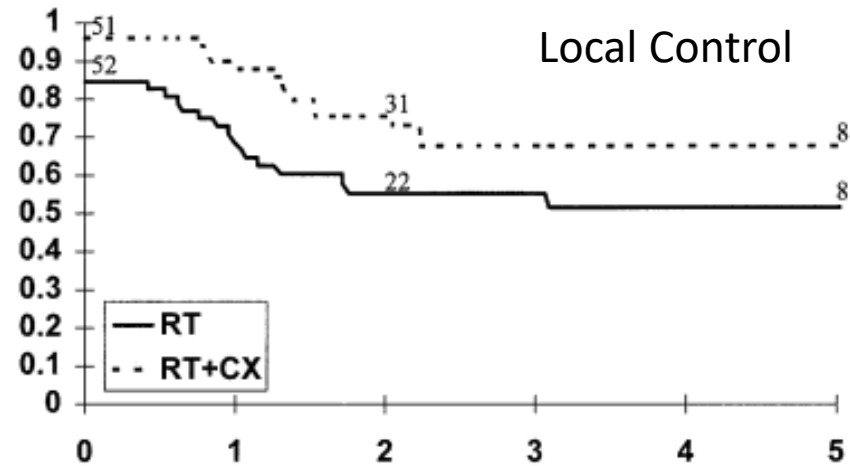
RT vs ChemoRT

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

RT: 45 Gy + 15-20 Gy
5FU 750mg² D1-5, 29-33
MMC Day 1

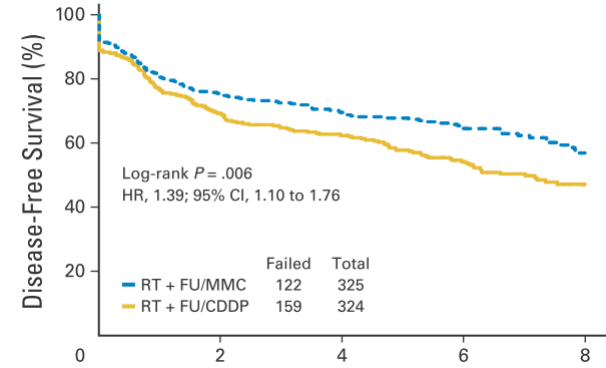
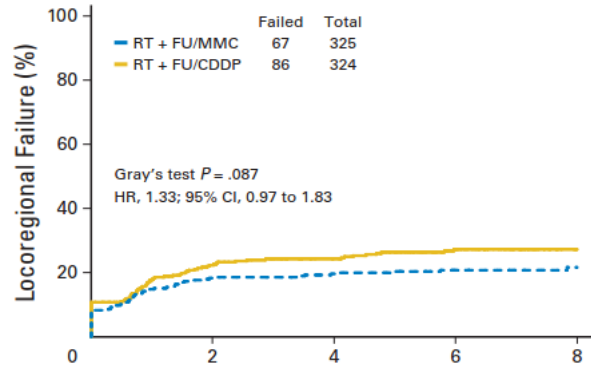
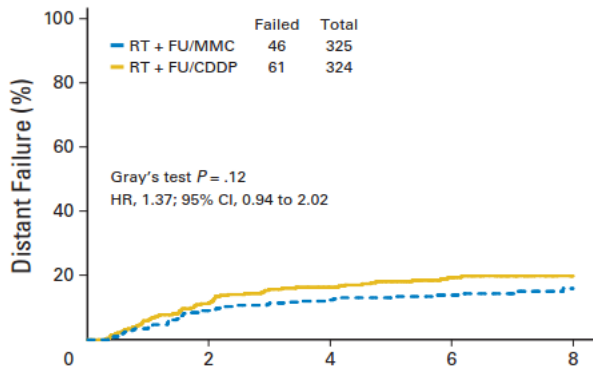
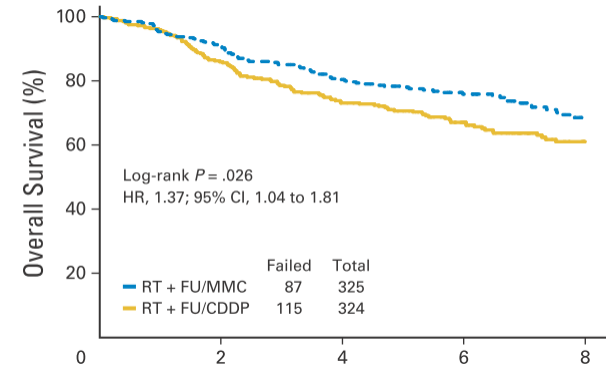
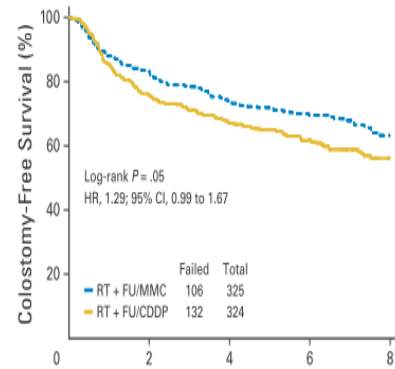
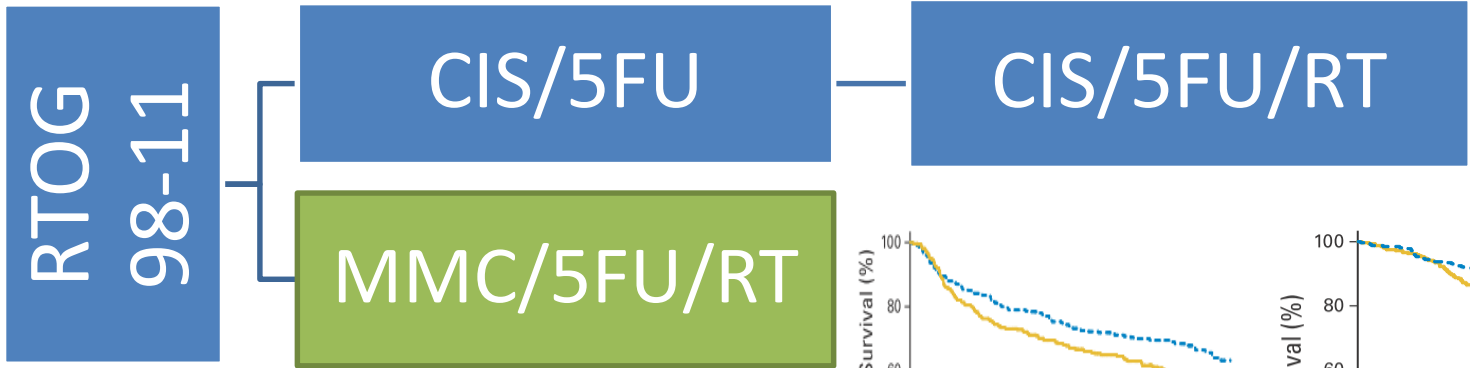
RT: 45 Gy + 15-20 Gy

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



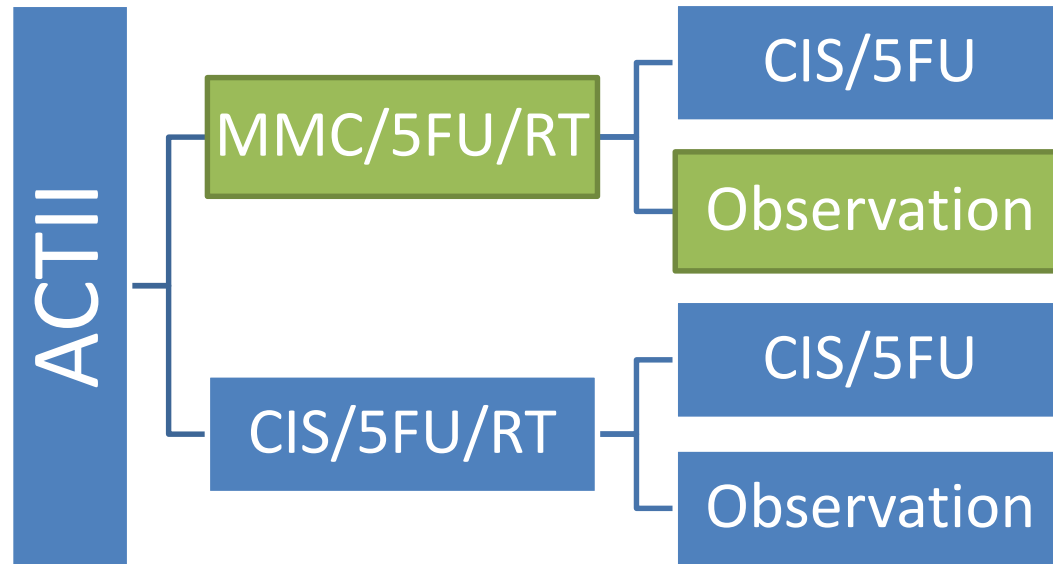
Mitomycin C vs Cisplatin

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

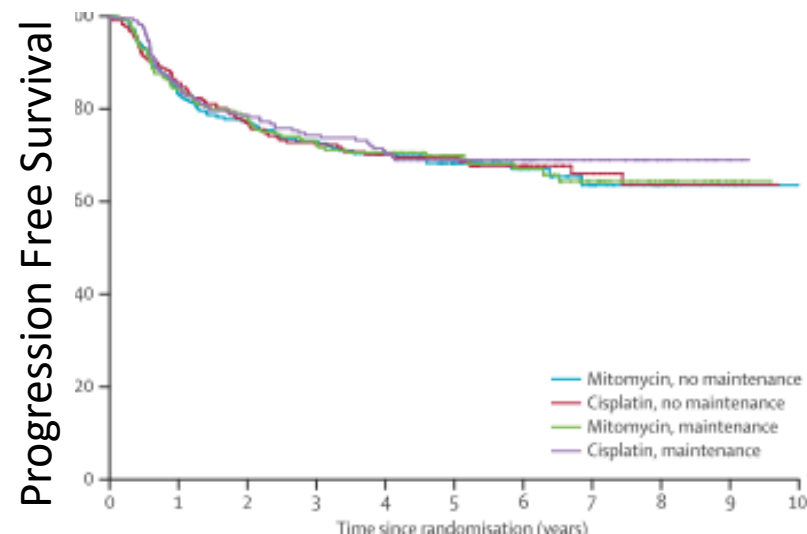


Mitomycin C vs Cisplatin

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



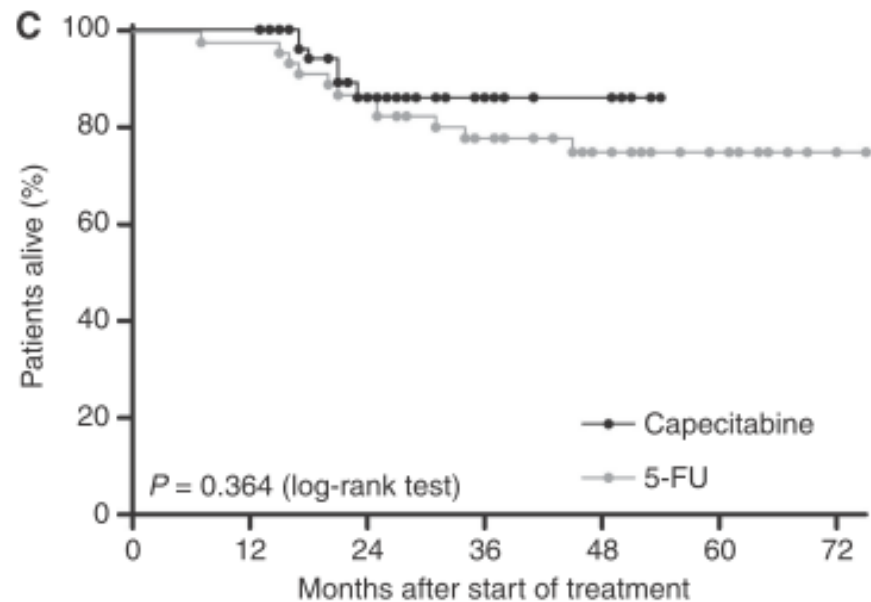
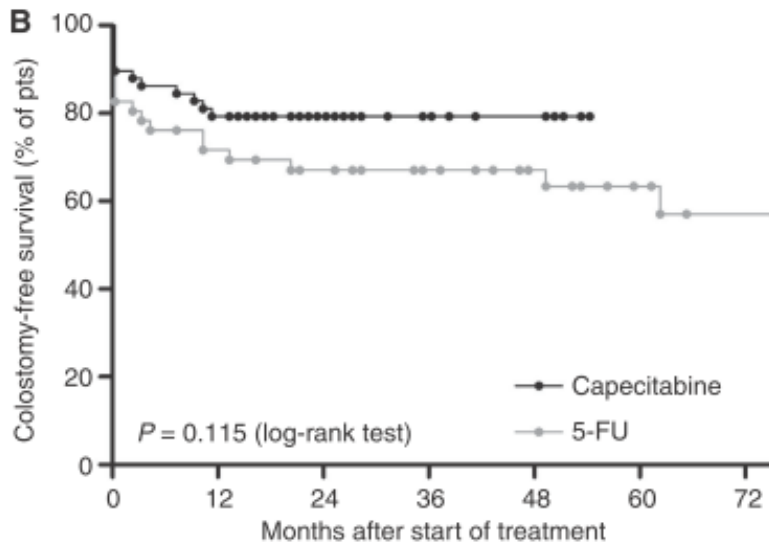
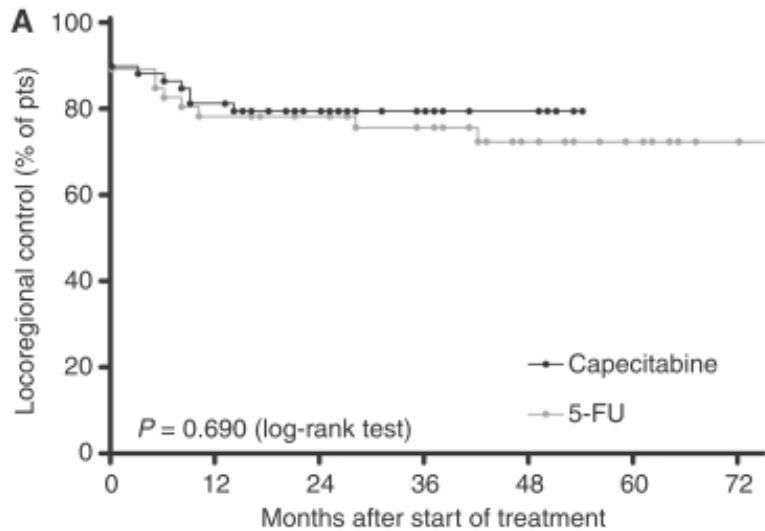
Complete Response	90%
Partial Response	5%
Stable Disease	1%
Progressive Disease	5%



Mitomycin C vs Cisplatin

- 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

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

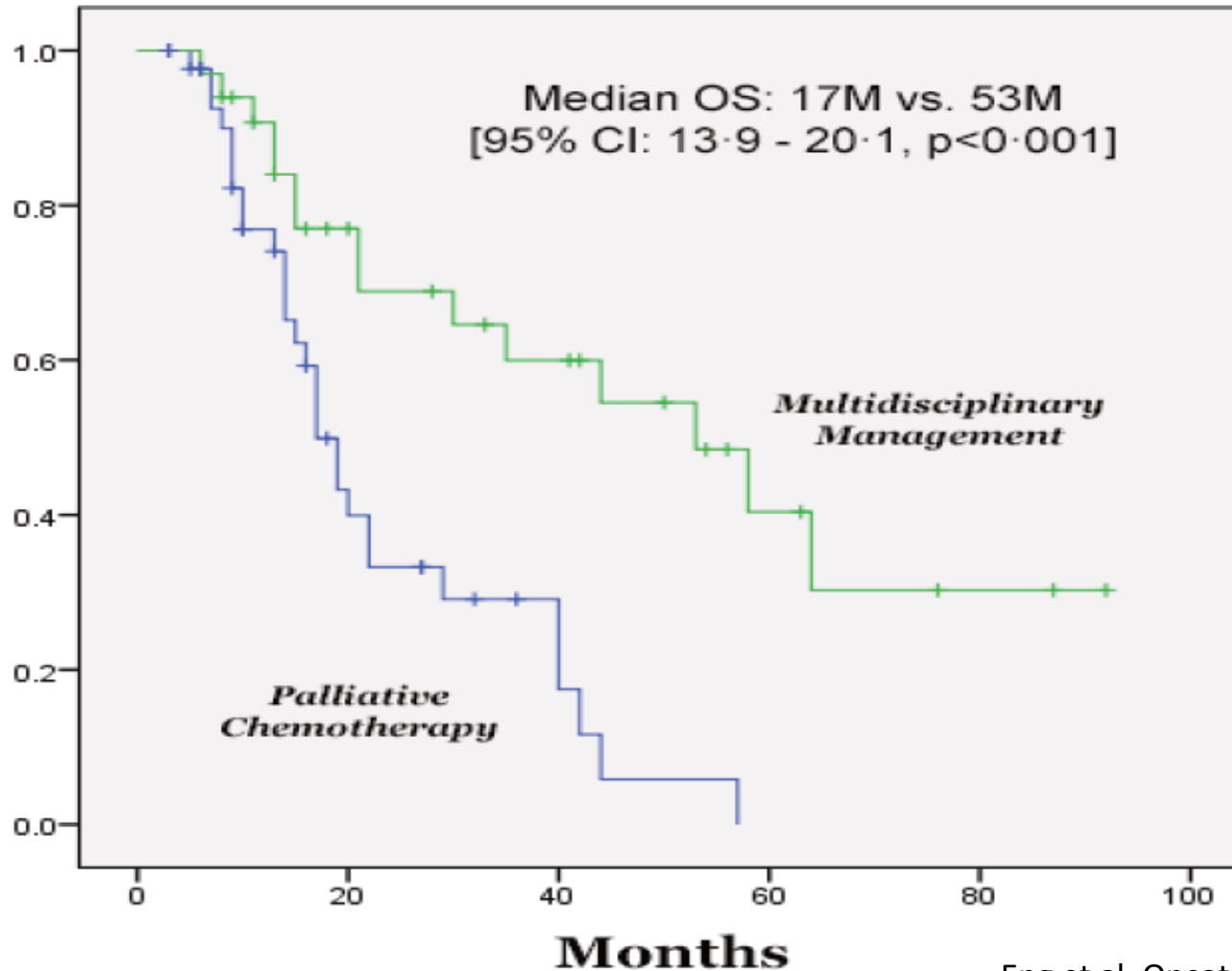
- Reports of long-term outcome with metastasectomy and radiation to oligometastatic disease

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

First Line Therapy +/- RT

Carboplatin + Paclitaxel (NCCN Preferred)

5FU + Cisplatin (more toxic)

FOLFOX6 (NCCN case report, adeno)

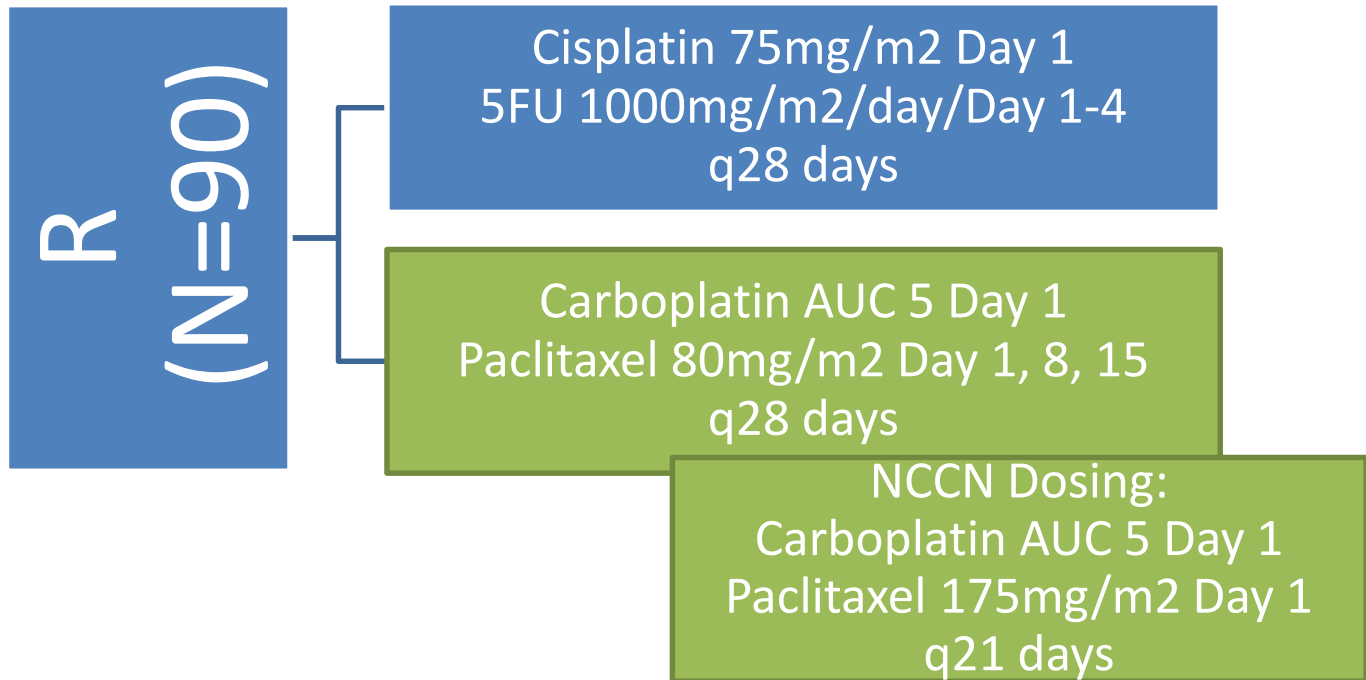
FOLFCIS

mDCF

Second Line Therapy

Nivolumab or Pembrolizumab

InterAACT: 1st Line Trial



Primary:

RR

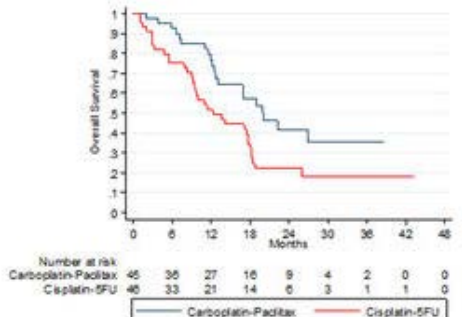
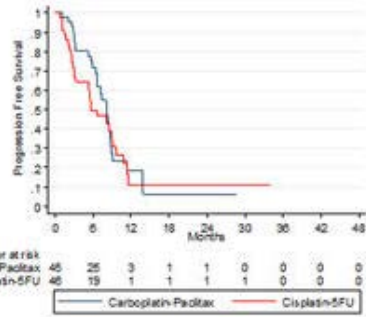
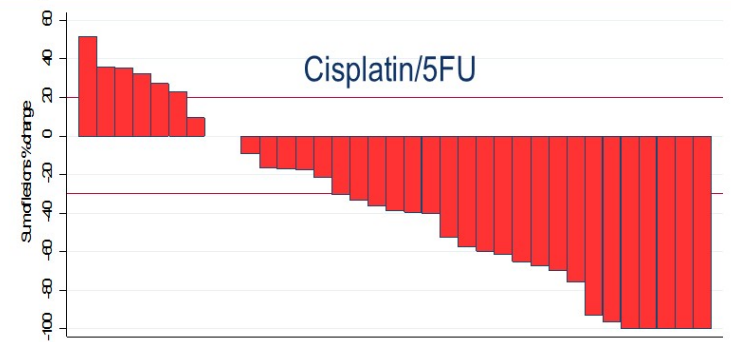
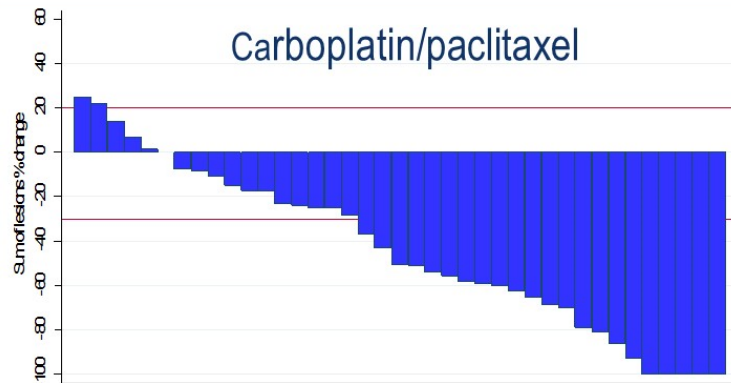
Secondary:

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/m² Day 1

Cisplatin 40mg/m² Day 1

Fluorouracil 2400mg/m² over 48 hours

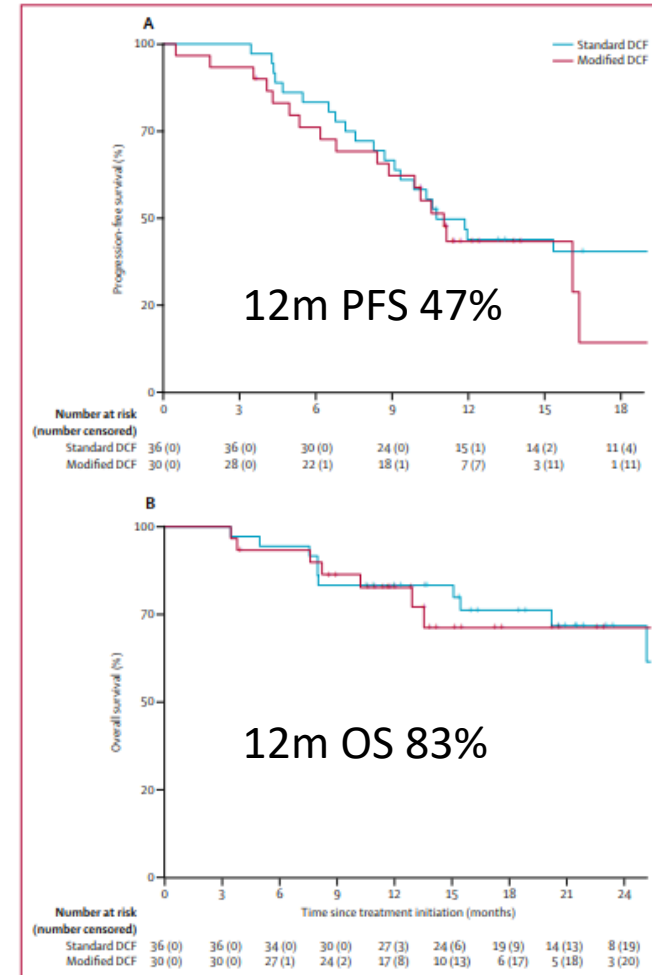
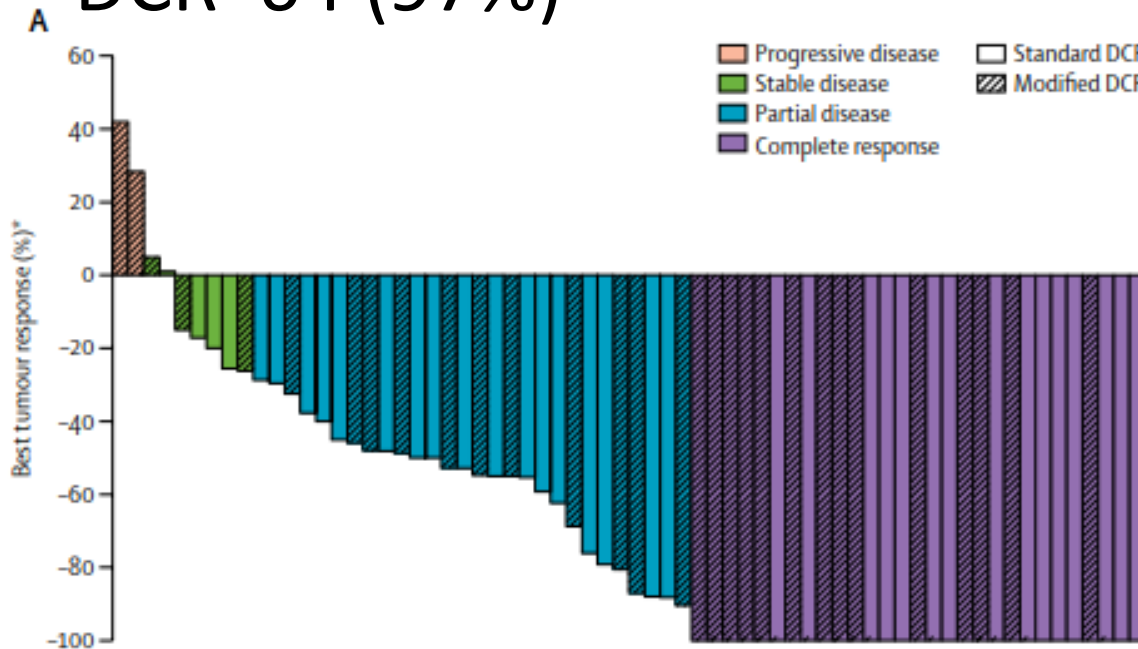
DCF/mDCF (Epitopes HPV02)

Lancet Oncol 2018

CR 30 (45%)

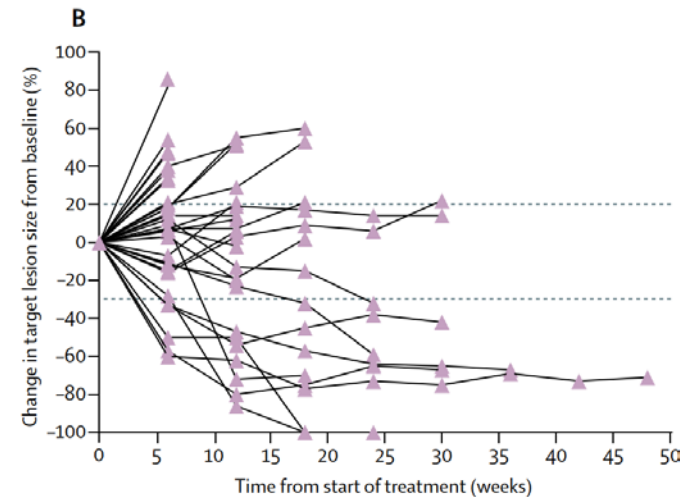
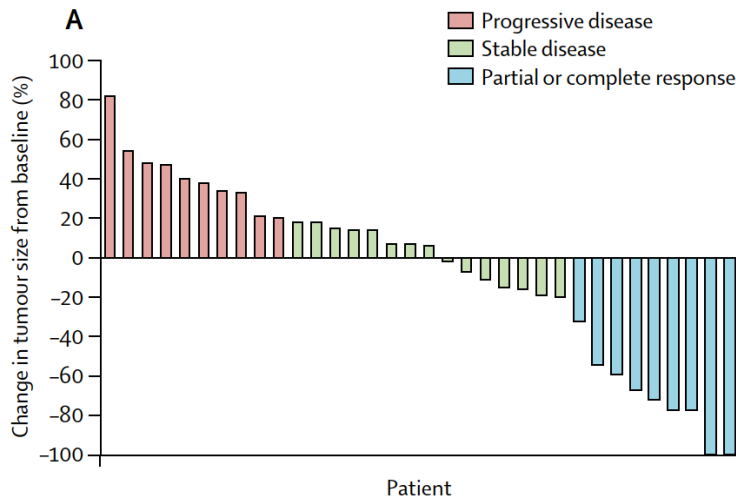
ORR 59 (89%)

DCR 64 (97%)

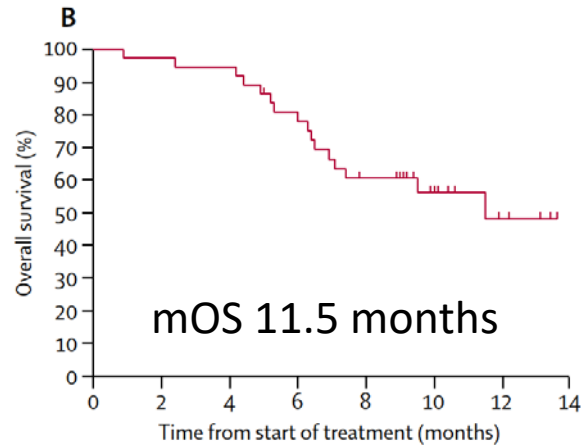
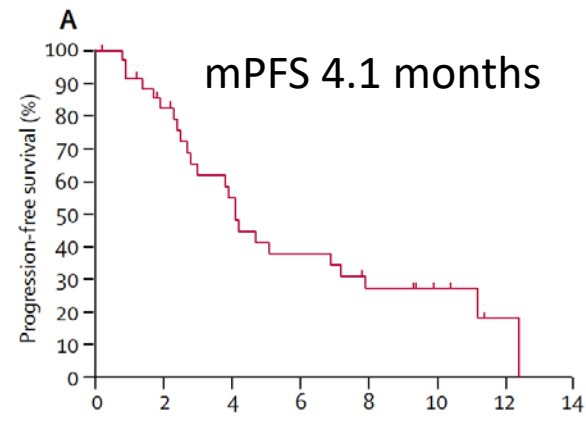


Nivolumab

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



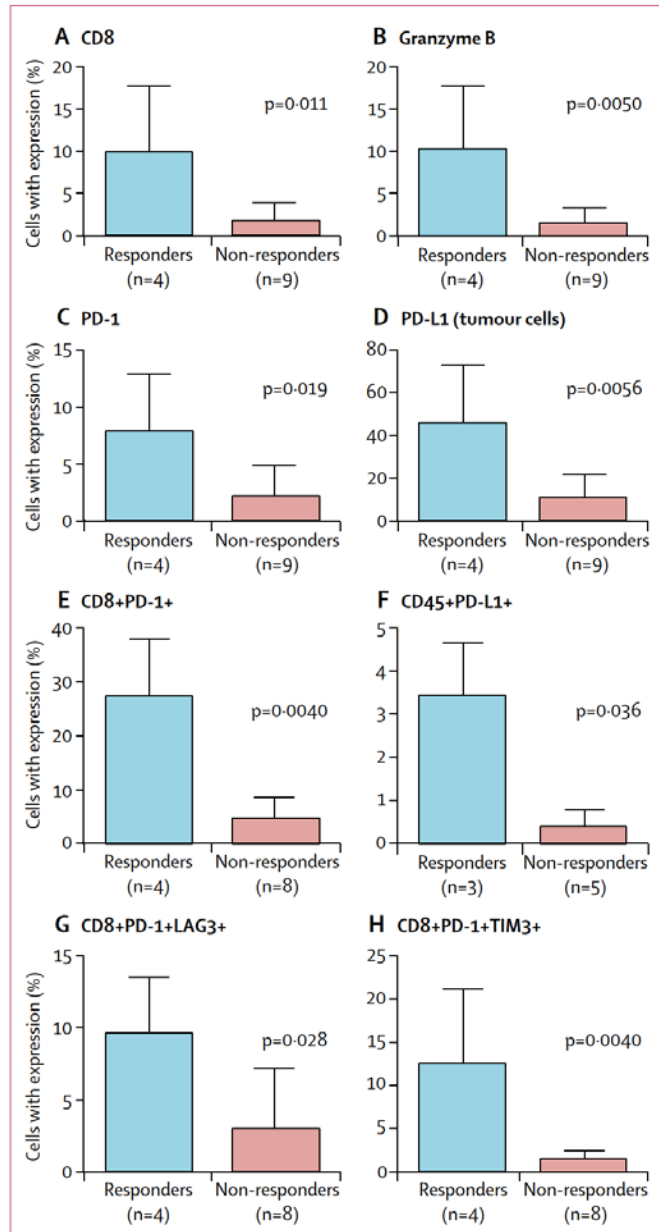
Nivolumab



	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

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