Fred Hutch
Cancer Center

Anal Cancer

2024

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UW Medicine

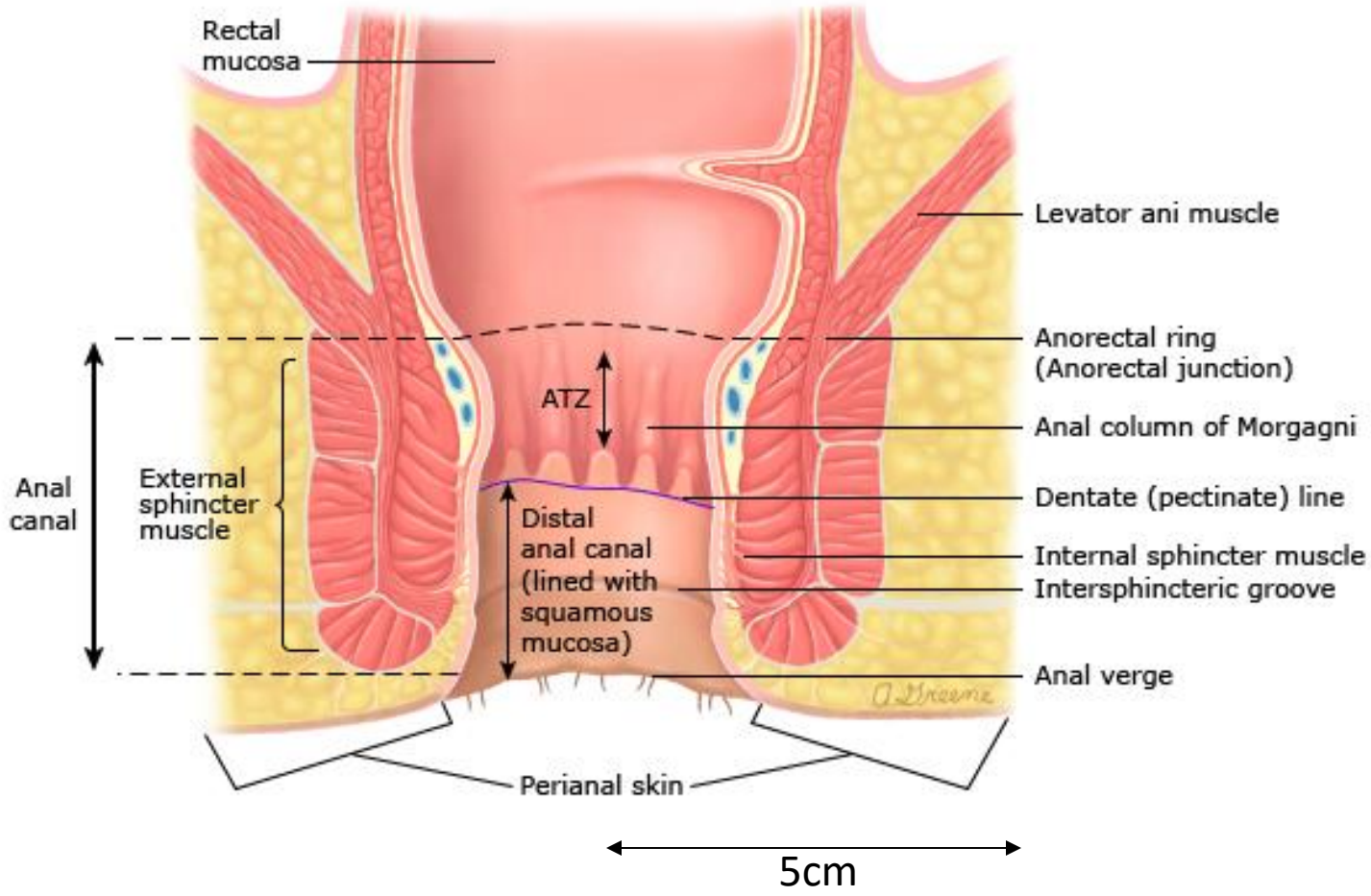
Outline

- Background
  - Pathogenesis
  - Epidemiology
  - Anatomy
- Staging and Workup
- Treatment
  - Local Disease
  - Recurrent Disease
  - Metastatic Disease

World Health Organization (WHO) classification of tumors of the anal canal

Benign epithelial tumors and precursors
Squamous intraepithelial neoplasia, low grade
Squamous intraepithelial neoplasia, high grade
Malignant epithelial tumors
Squamous cell carcinoma NOS
▪ Verrucous squamous cell carcinoma
Adenocarcinoma NOS
Neuroendocrine tumor NOS
▪ Neuroendocrine tumor, grade 1
▪ Neuroendocrine tumor, grade 2
▪ Neuroendocrine tumor, grade 3
Neuroendocrine carcinoma NOS
▪ Large cell neuroendocrine carcinoma
▪ Small cell neuroendocrine carcinoma
Mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN)

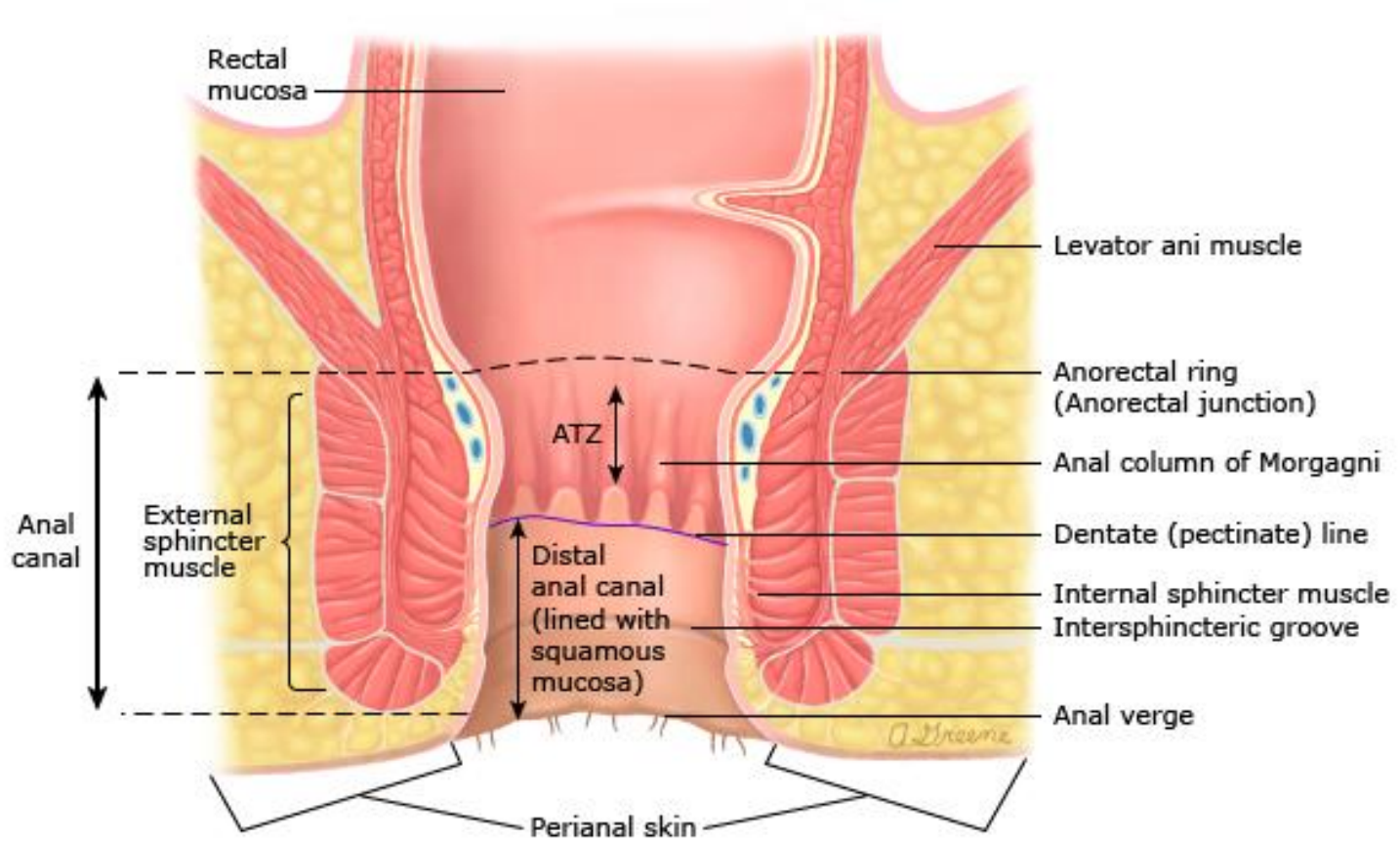
NOS: not otherwise specified.



Anatomy

- 3-4 cm anal canal
- Anorectal ring to anal verge
- Dentate line located in middle of canal

- Perianal Skin Cancers are staged and treated like anal canal cancers.



Picture from UpToDate

Epidemiology and Clinical Features

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

EPIDEMIOLOGY

7,000 in 2014

- 10,000 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
- Smoking/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

Epidemiology and Clinical Features

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

7,000 in 2014

2001-2019 Increasing the most in Females aged > 60

2007-2019 Incidence Decreasing in F 40-44 and males

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Pathogenesis

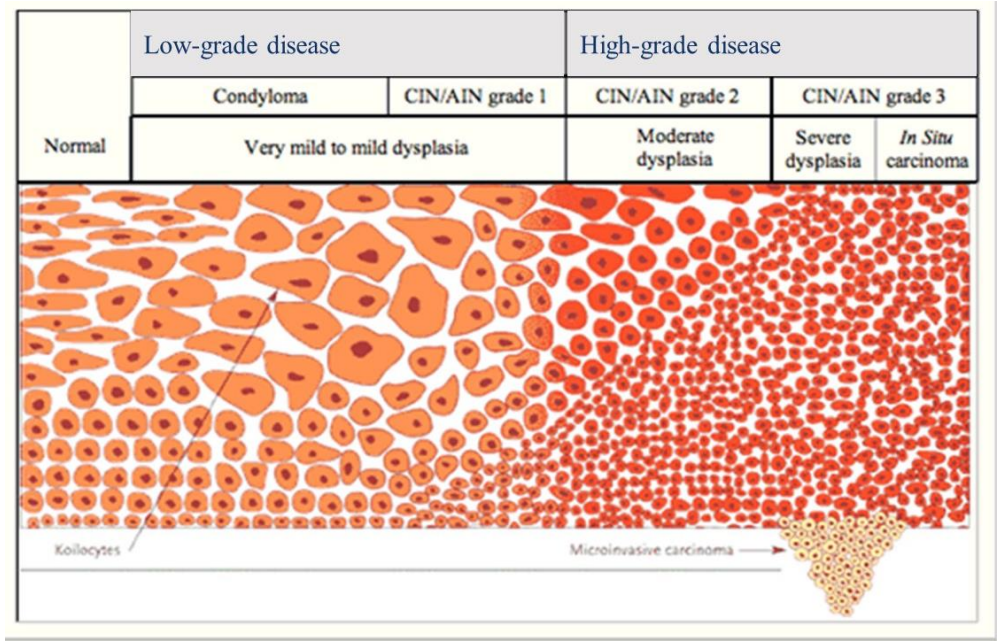
N Engl J Med. 1997;337(19):1350|Hoots etal, Int J Cancer 2009;124:2375

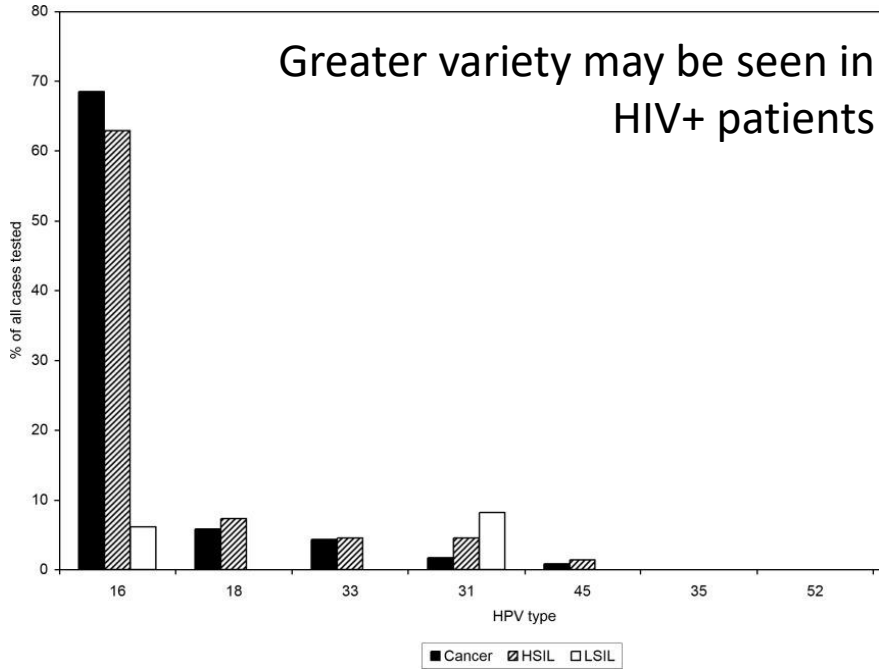
Human Papillomavirus

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

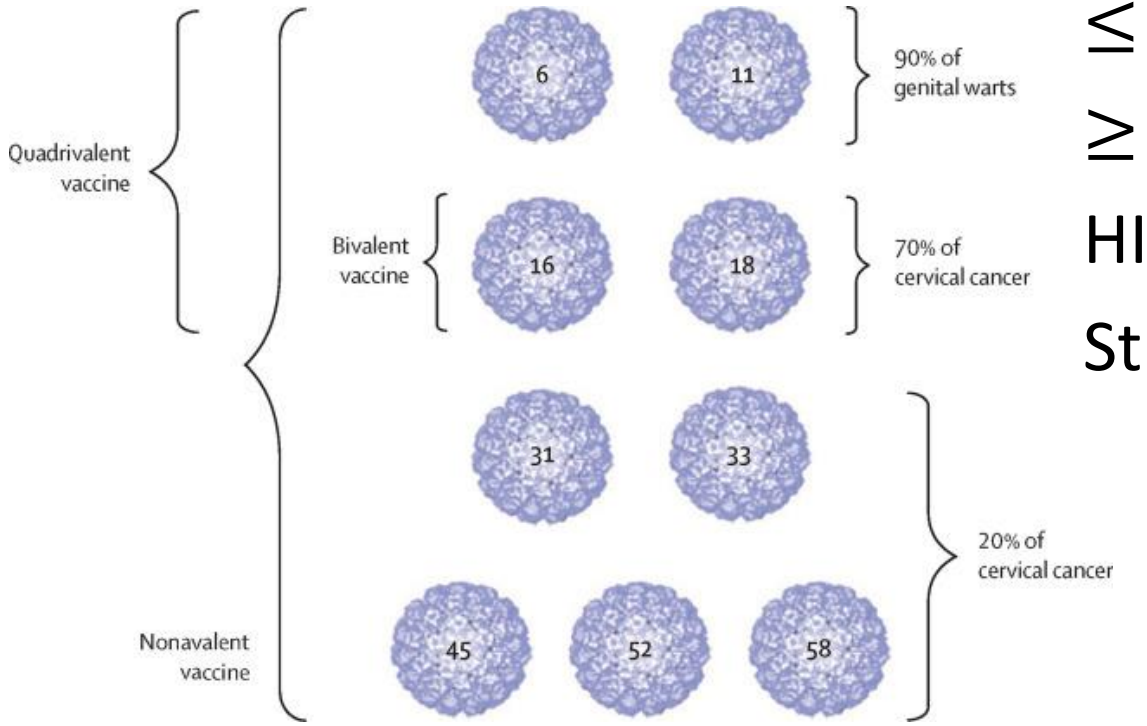
Cigarettes

- Cigarettes increase anal cancer (and cervical)





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

Schiller, Lancet Oncol. 2015 May;16(5):e217-25.

Screening

There are no randomized clinical trials that document the value of screening for anal SIL in at-risk populations.

Instead, the rationale for screening relies on the similarities between the anus and cervix.

HIV-positive Patients

HIV-negative MSM

Patients with High Grade Cervical/Vulvar Lesion/Cancer

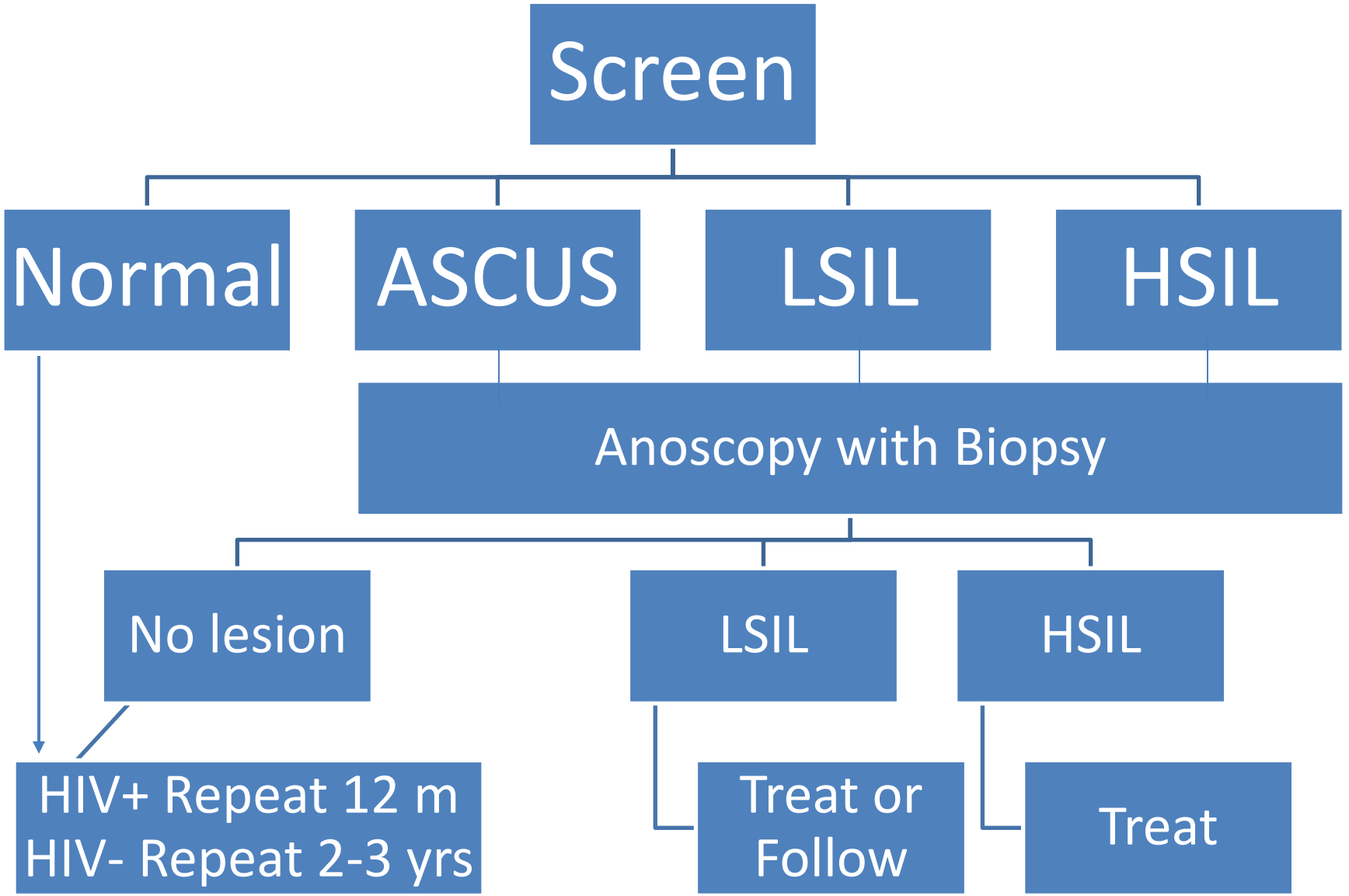
Patients with Perianal Condyloma

Solid Organ Transplant Recipients

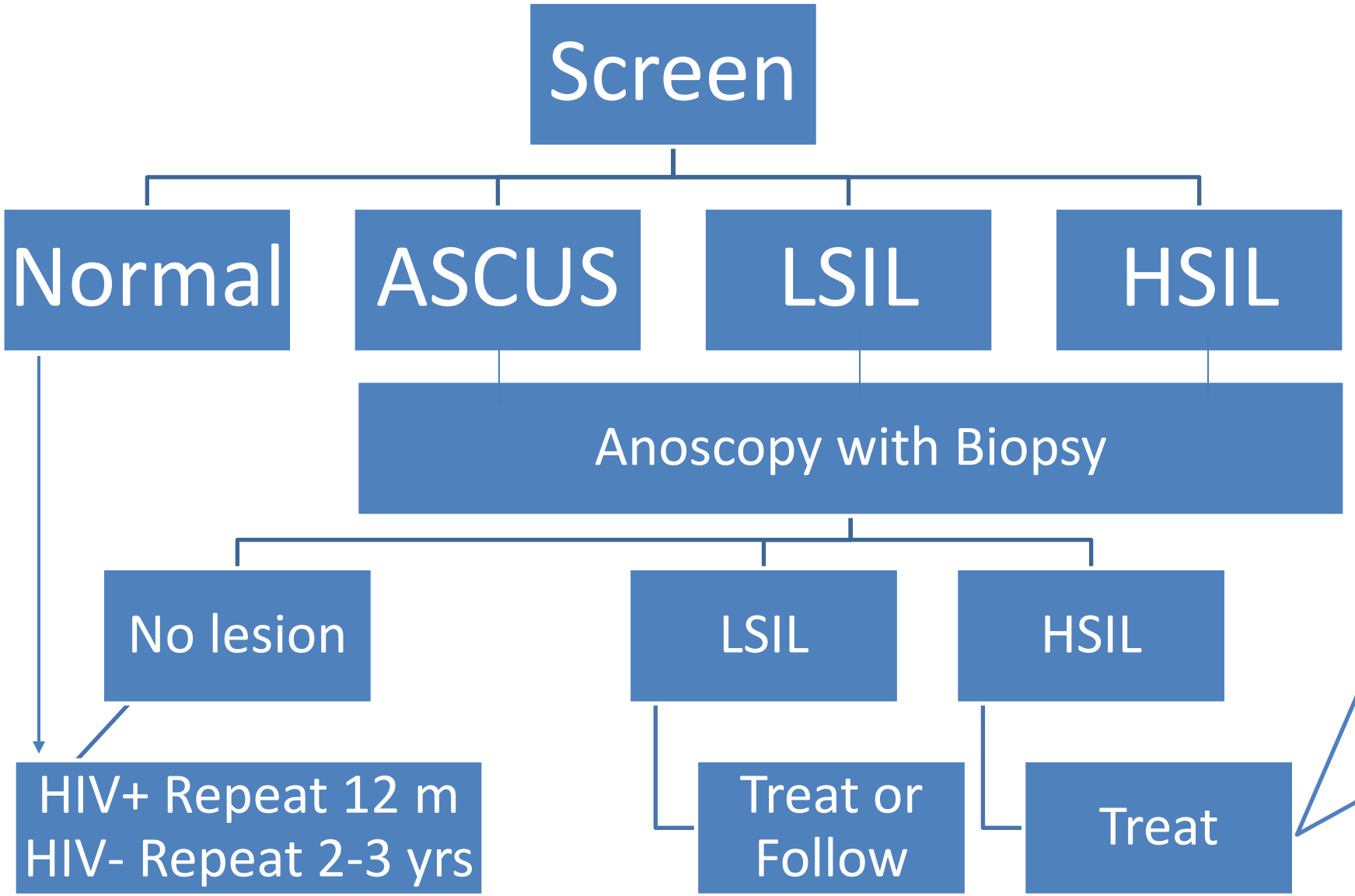
Over 25 if immunosuppressed

? Over 40 if immunocompetent

Joel Palefsky, ASCO 2019, Educational Session



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



Non FDA approved and little to no data:

- 80% trichloroacetic acid
- targeted ablation
  infrared coagulation
  radiofrequency ablation
  electrocautery/hyfrecation
- imiquimod or fluorouracil (FU)

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

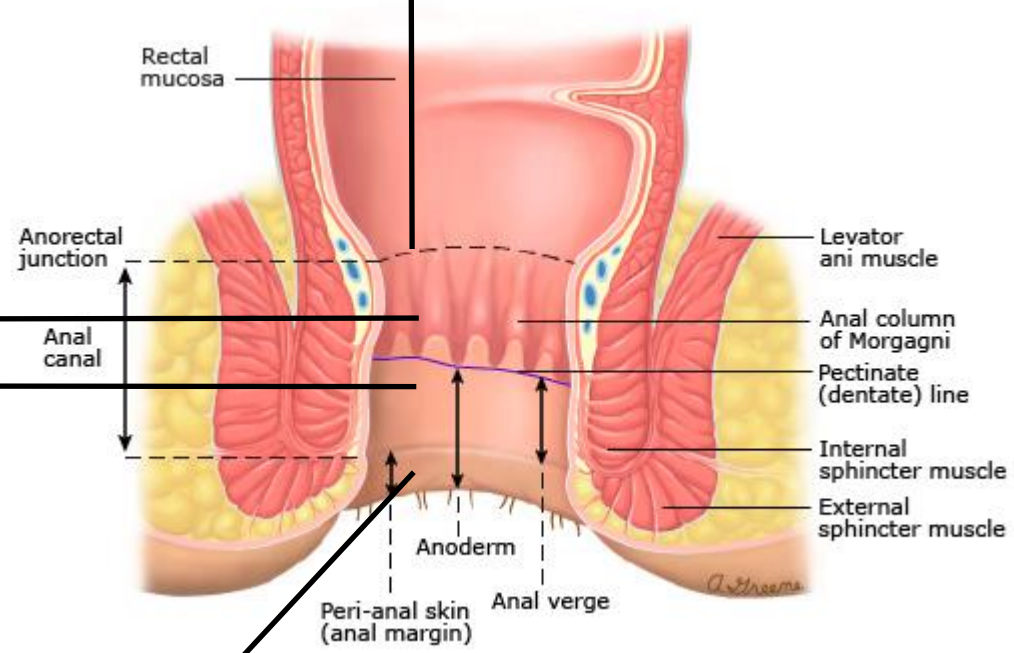
Anatomy: Nodal Drainage

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)~~



Picture from UpToDate
Glynne-Jones et al. Annals of Oncology. 2010 21(s5)

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

	T	N	M
0	Tis		
I	T1		
IIA	T2		
IIB	T3		
IIIA	T1-T2	N1	
IIIB	T4		
IIIC	T3-T4	N1	
IV			M1

AJCC 8th Edition

Stage Grouping

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

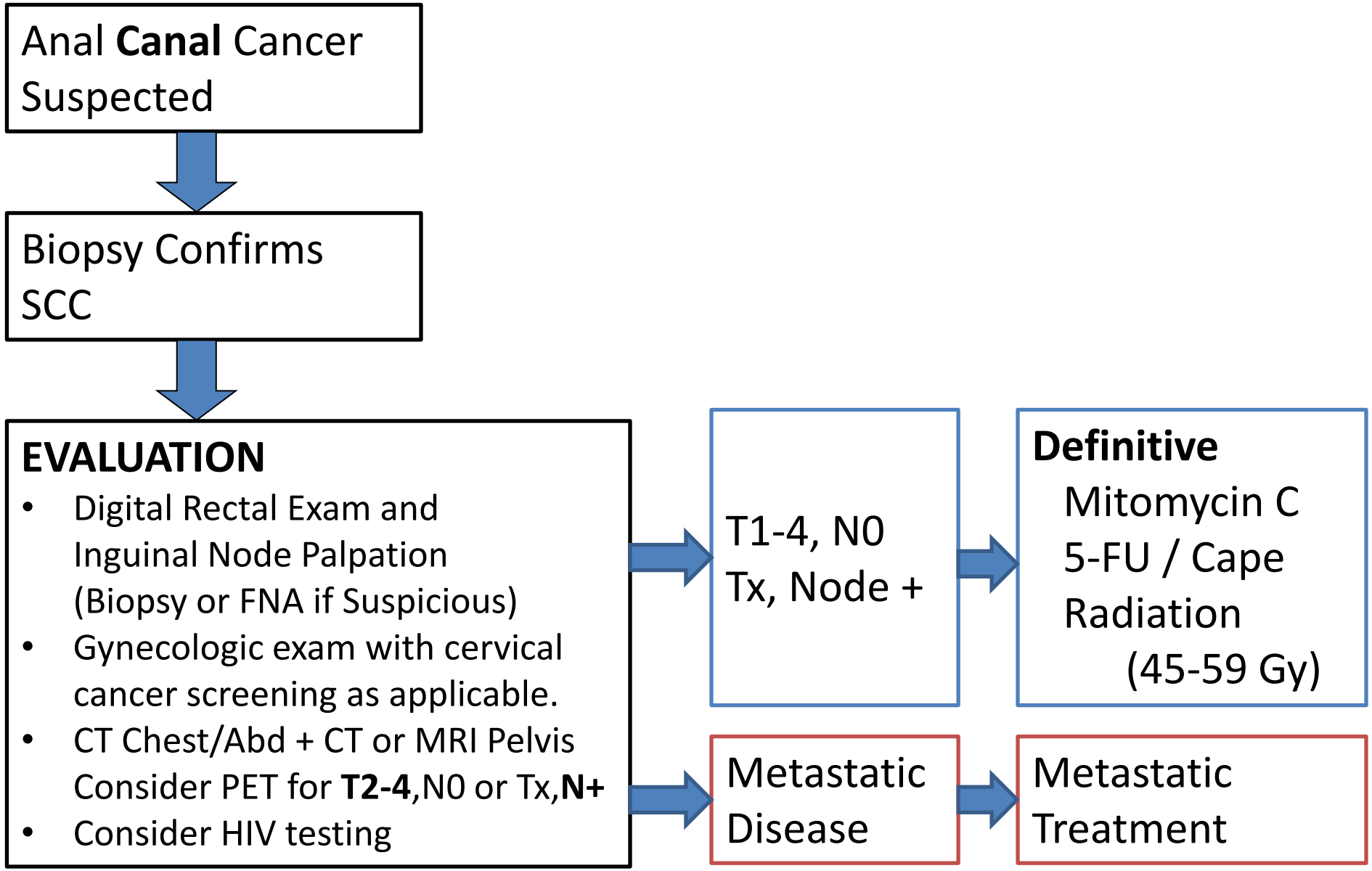
	5 y OS
T1	86%
T2	86%
T3	60%
T4	45%
N0	80%
N1	60%
M1	30%

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

Non-SCC do worse.

NCCN 2018

NCCN Guidelines: Anal Carcinoma



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 with cervical cancer screening as applicable.
- CT Chest/Abd + CT or MRI Pelvis Consider PET for **T2-4**,N0 or Tx,N+
- Consider HIV testing

Superficially Invasive SCC (SISCCA)
Are generally found incidentally in biopsy or excision of what is thought to be a benign lesion (e.g. skin tag, condyloma).

For such lesions, negative margins, selected patients, experienced teams, structured surveillance may be adequate.

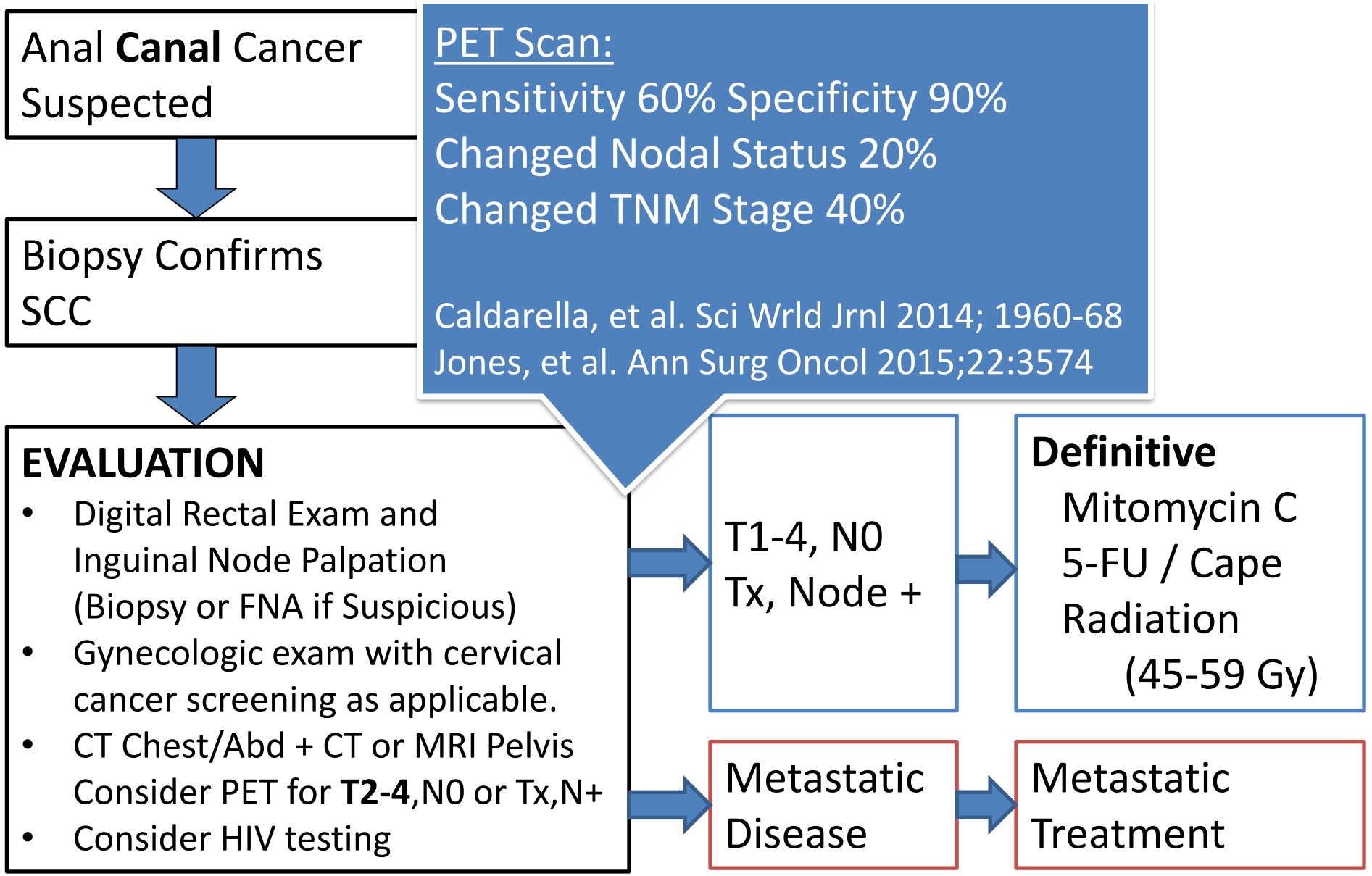
T1-4, N0
Tx, Node +

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

Metastatic Disease

Metastatic Treatment

NCCN Guidelines: Anal Carcinoma



NCCN Guidelines: Anal Carcinoma

Anal **Canal** Cancer Suspected

Biopsy Confirms SCC

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

(JCO 1996; 14:2527)

EVALUATION
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Metastatic Disease

Metastatic Treatment

NCCN Guidelines: Anal Carcinoma

Anal **Canal** Cancer Suspected

Biop
SCC

EVA
- D
  In
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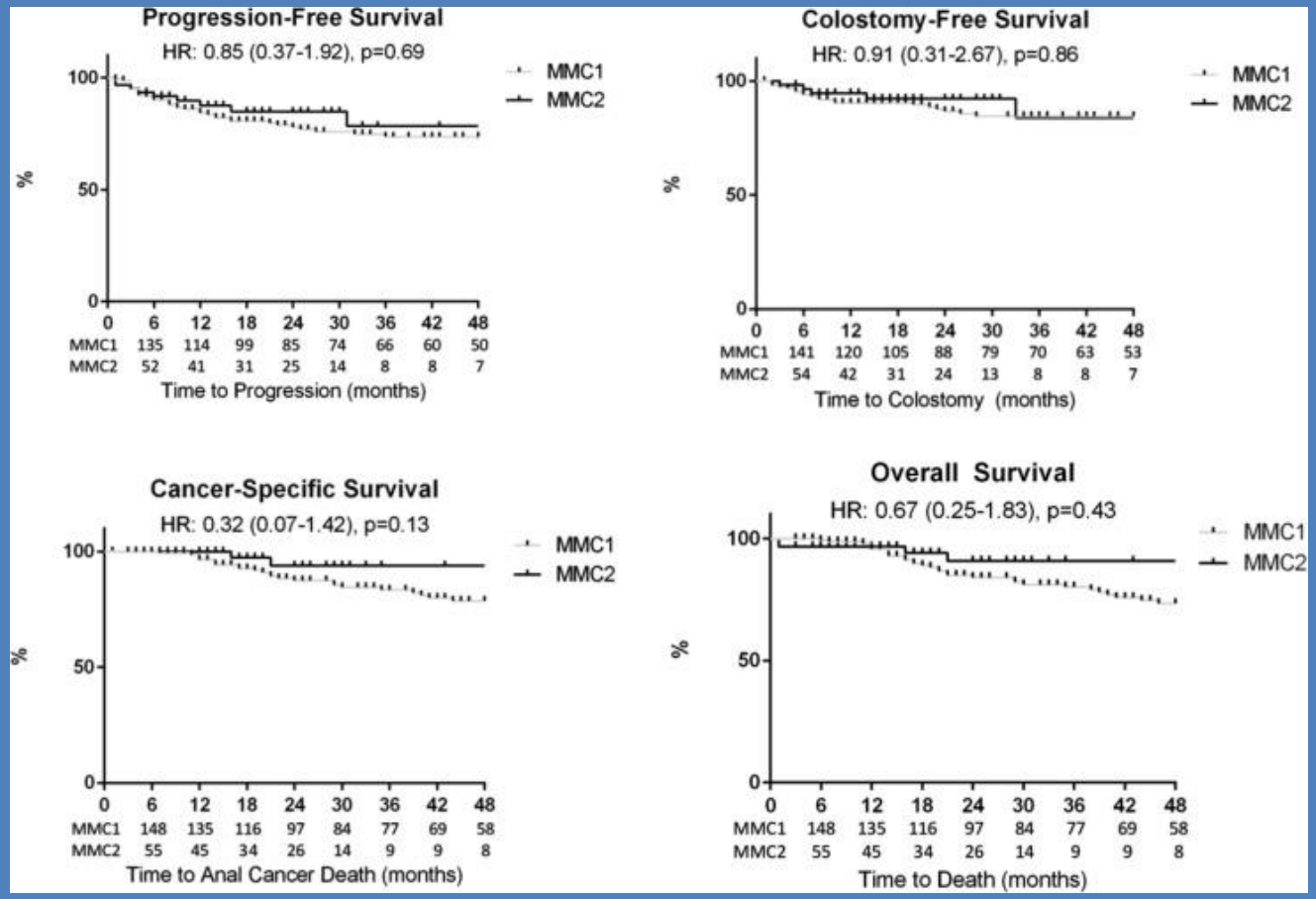
- G
  ca
- C
  C
- C

MMC Improves

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



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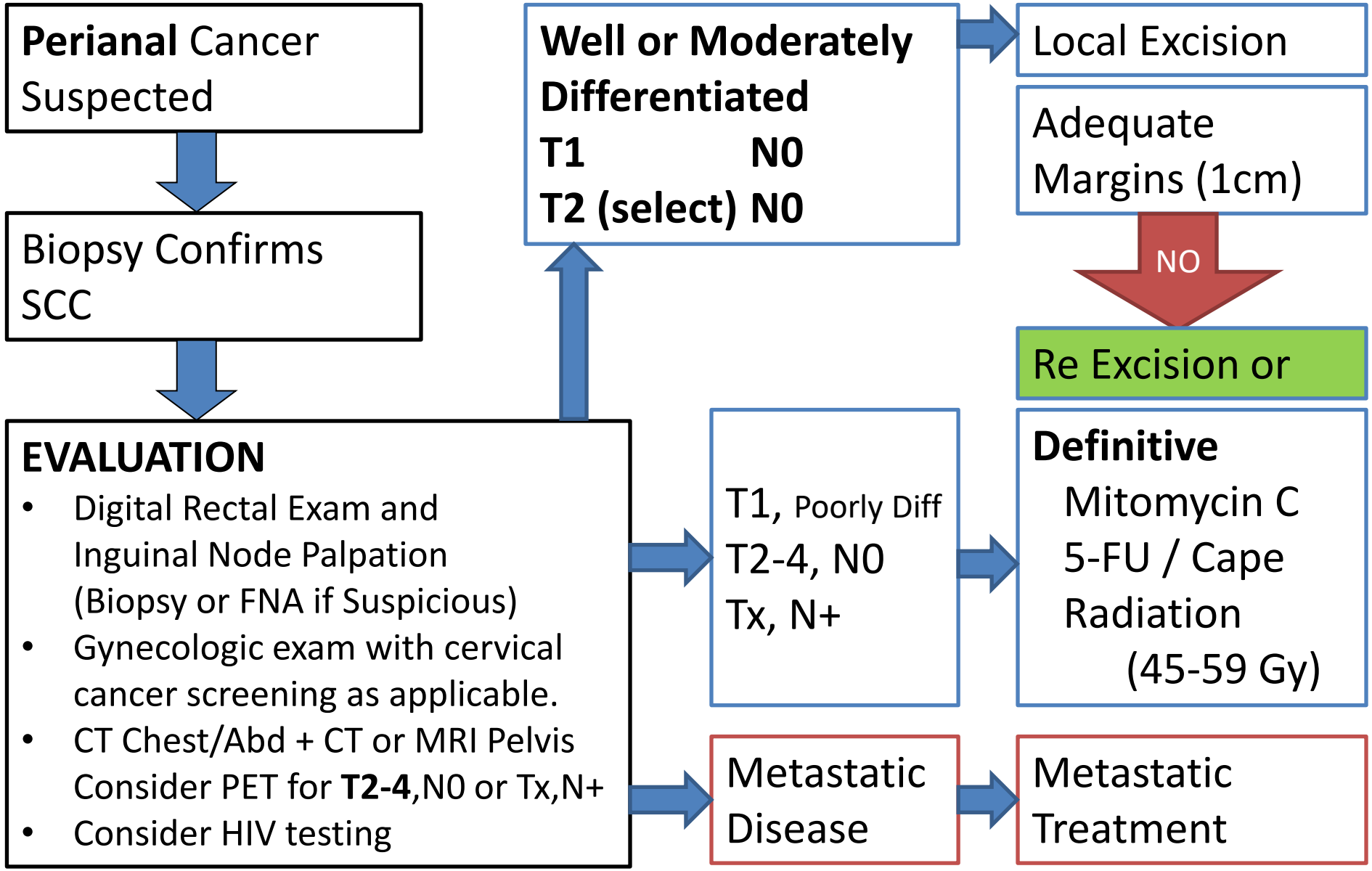
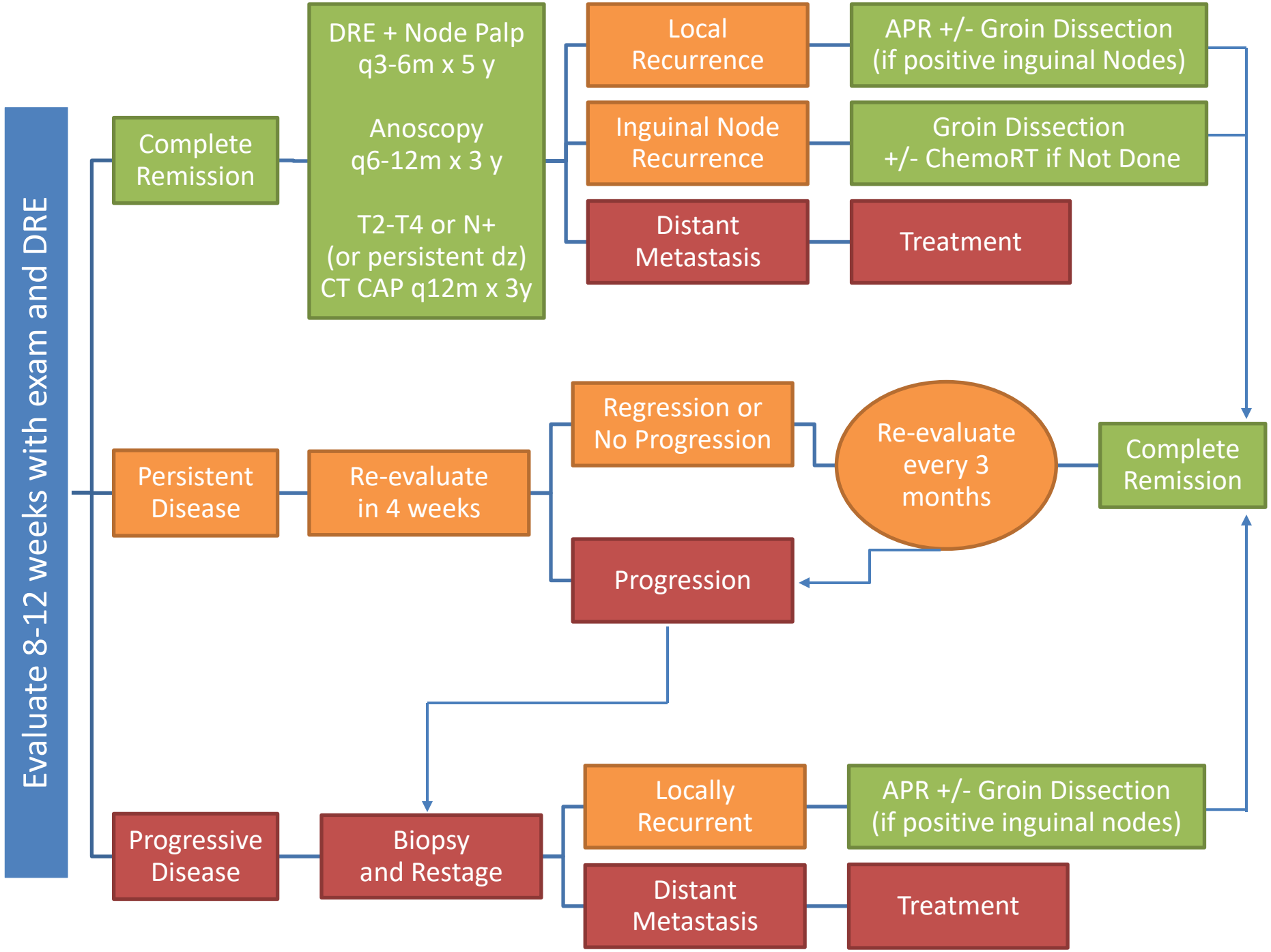
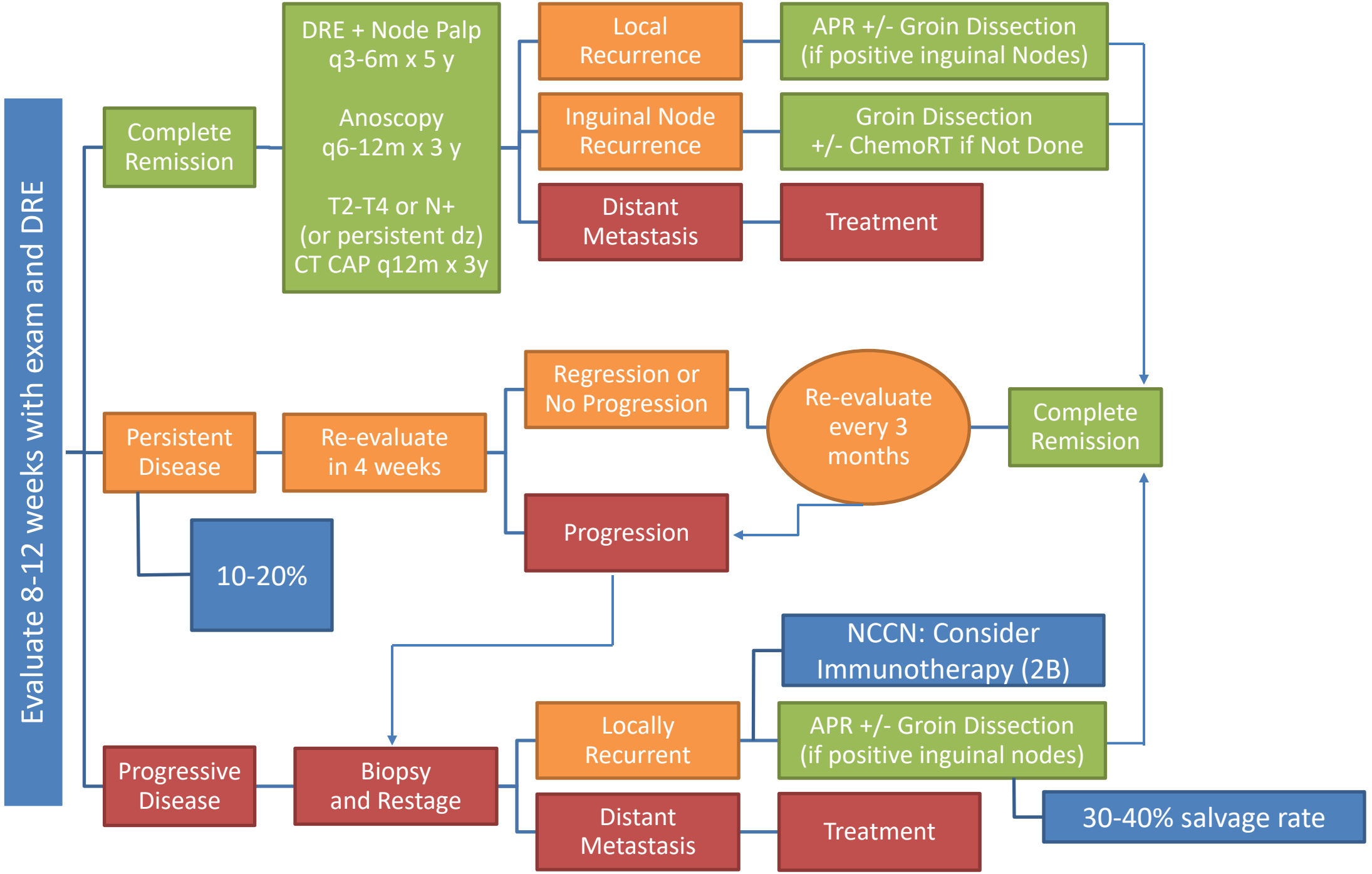



Evaluate 8-12 weeks with exam and DRE
Complete Remission
DRE + Node Palp q3-6m x 5 y
Anoscopy q6-12m x 3 y
T2-T4 or N+ (or persistent dz) CT CAP q12m x 3y
Local Recurrence
APR +/- Groin Dissection (if positive inguinal Nodes)
Inguinal Node Recurrence
Groin Dissection +/- ChemoRT if Not Done
Distant Metastasis
Treatment
Persistent Disease
Re-evaluate in 4 weeks
Regression or No Progression
Re-evaluate every 3 months
Complete Remission
Progression
Progressive Disease
Biopsy and Restage
Locally Recurrent
APR +/- Groin Dissection (if positive inguinal nodes)
Distant Metastasis
Treatment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Treatment
Persistent Disease
Re-evaluate in 4 weeks
Regression or No Progression
Re-evaluate every 3 months
Complete Remission
Progression
10-20%
Progressive Disease
Biopsy and Restage
Locally Recurrent
NCCN: Consider Immunotherapy (2B)
APR +/- Groin Dissection (if positive inguinal nodes)
Distant Metastasis
Treatment
30-40% salvage rate

Treatment

APR was routinely performed

- 5 Year OS was 40-70%

Chemoradiation

- Local Failure: 15-35%
  5 Yr OS 72-90%

NCCN, Nigro et al. Dis Colon Rectum. 1974;17(3):354

Chemoradiation

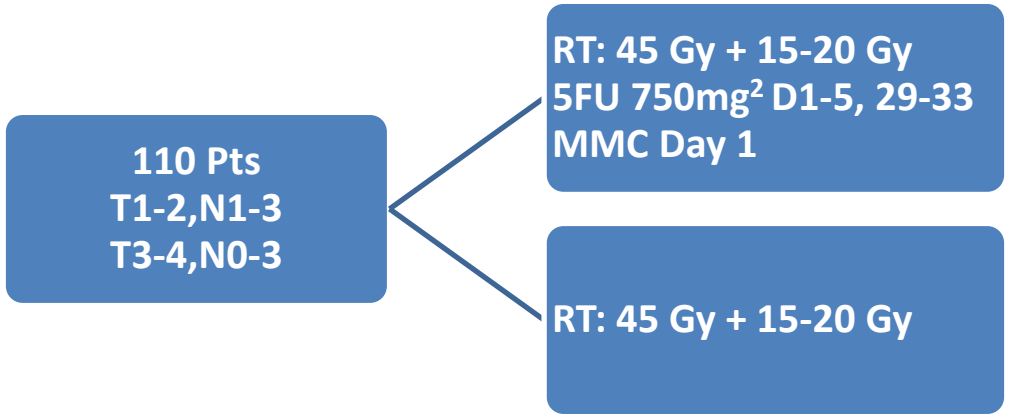
5FU/Capecitabine + Mitomycin C

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 50.4-59.4 Gy

NCCN v1.2024

RT vs ChemoRT



After 6 weeks
If PR: 20 Gy Boost
If CR 15 Gy Boost

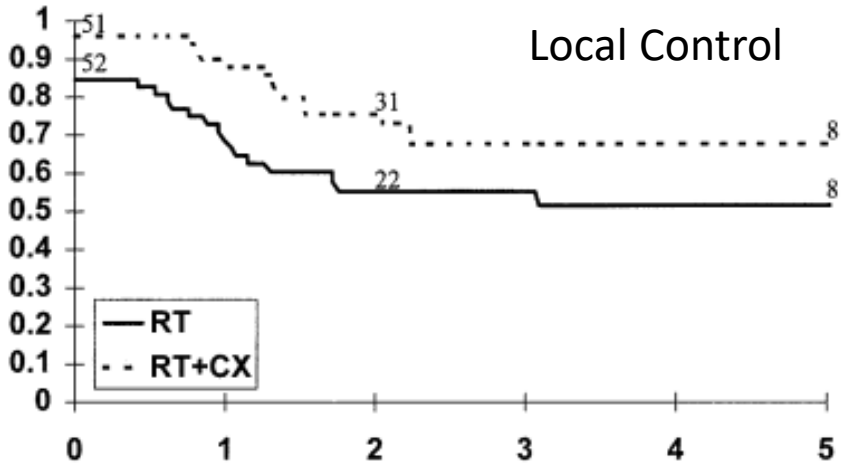
AEs		XRT	XRT + CT
Diarrhea	Gr 2	16	15
	Gr 3	4	10
	Gr 4	0	0
Skin	Gr 2	18	13
	Gr 3	26	28
	Gr 4	0	1

Bartelink et al. JCO 1997 15(5):2040-9

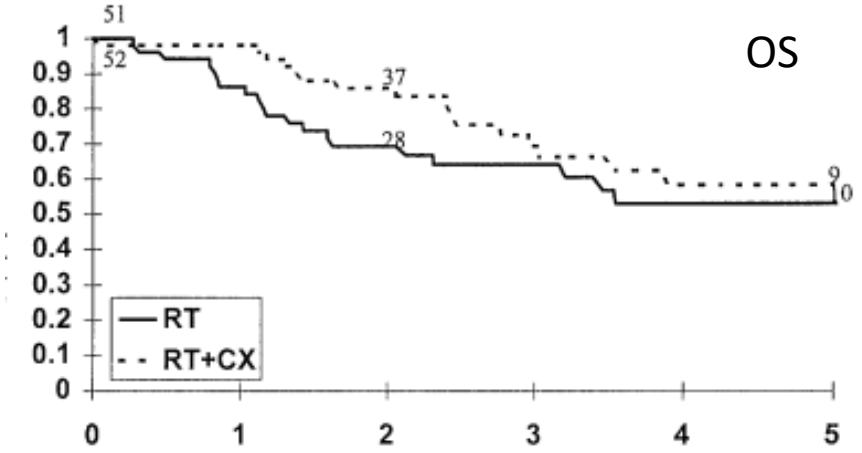
RT vs ChemoRT

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

- **RT: 45 Gy + 15-20 Gy**
  5FU 750mg^2 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



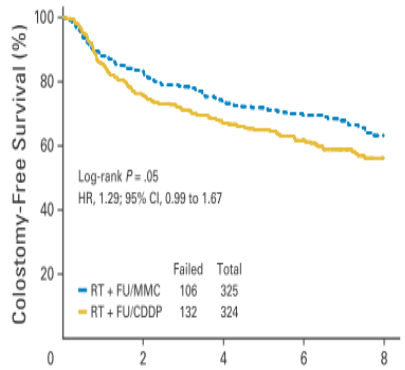
Bartelink et al. JCO 1997 15(5):2040-9

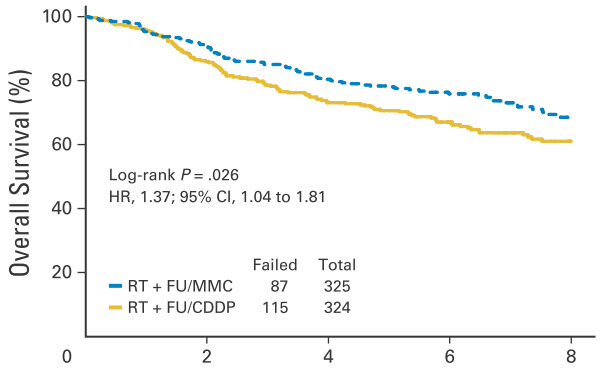
Mitomycin C vs Cisplatin

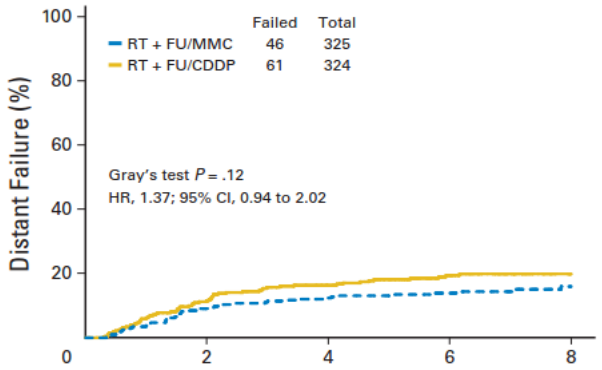
Ajani, J. A. et al. JAMA 2008;299:1914-1921
Gunderson, L et al. J Clin Oncol. 2012; 30(35)

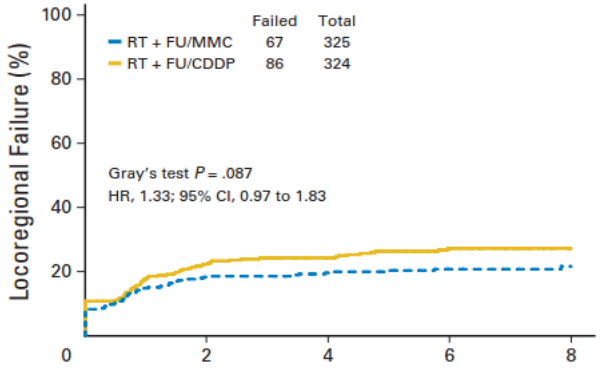
RTOG 98-11

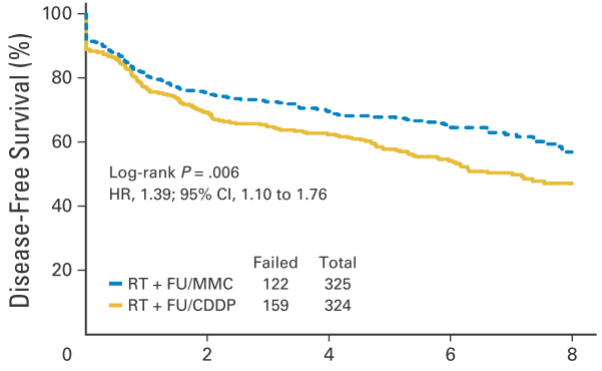
- CIS/5FU → CIS/5FU/RT
- MMC/5FU/RT





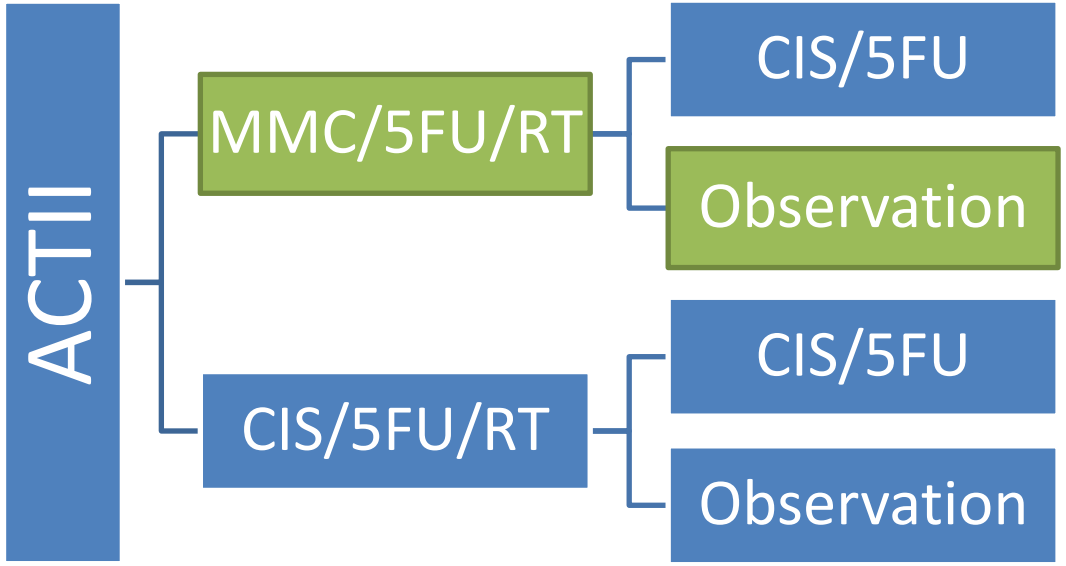




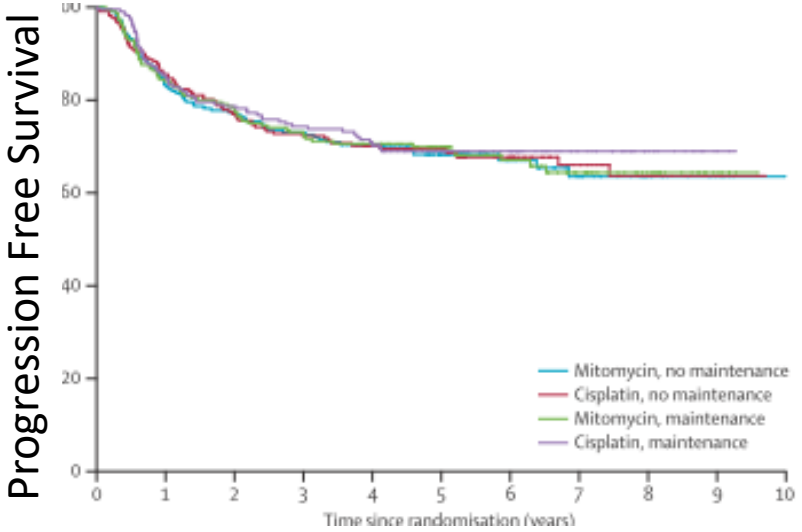


Mitomycin C vs Cisplatin

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



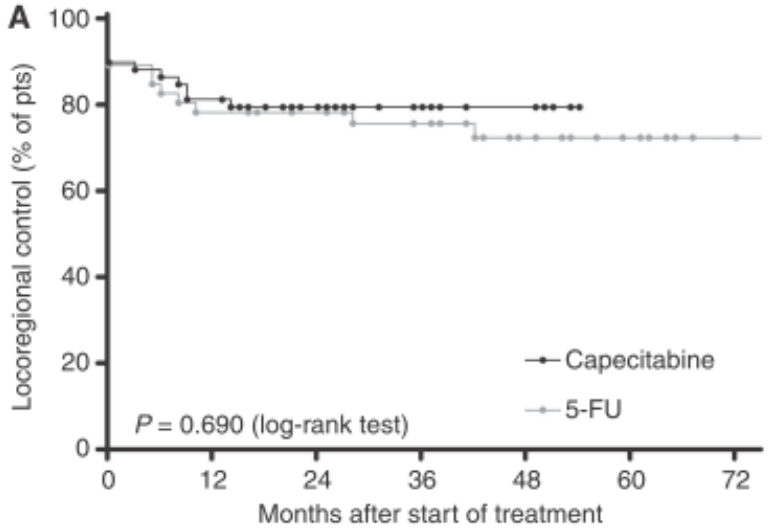
Complete Response	90%
Partial Response	5%
Stable Disease	1%
Progressive Disease	5%

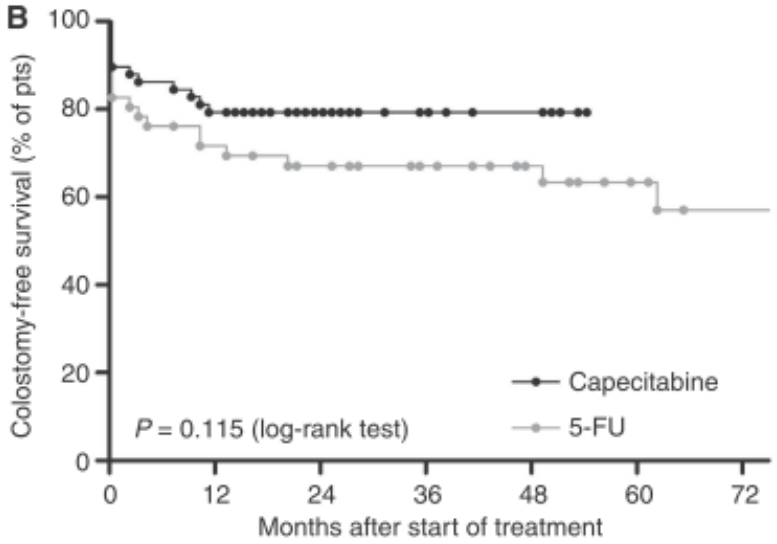


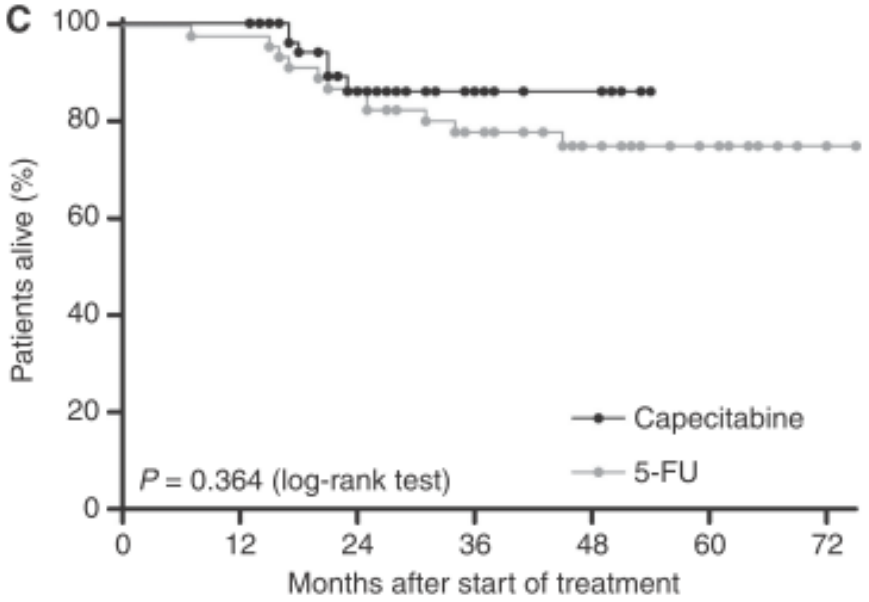
Mitomycin C vs Cisplatin

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

Capecitabine vs 5-FU







Meulendijks, BJC, 2014
Thind, Radiation Oncology, 2014,9:214

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	

Meulendijks, BJC, 2014

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

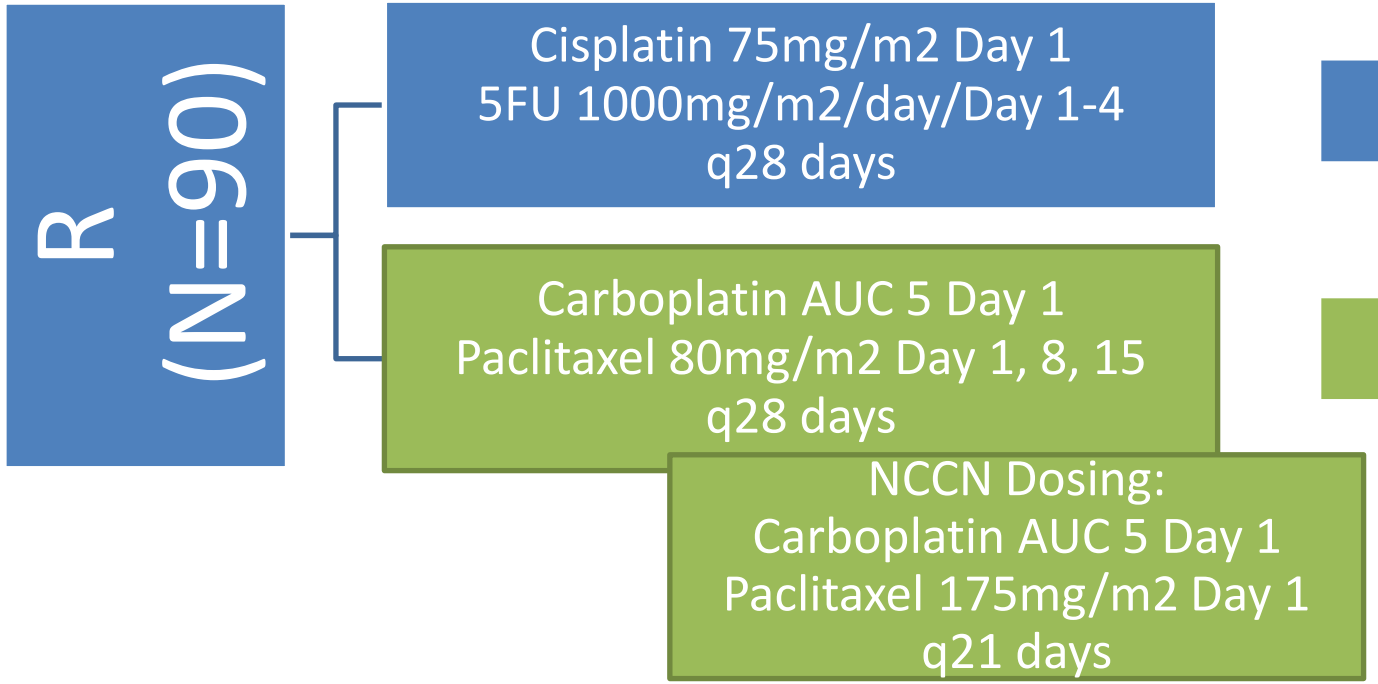
- Reports of long-term outcome with metastasectomy and radiation to oligometastatic disease

Cisplatin / fluoropyrimidine combinations

- 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

InterAACT: 1st Line Trial

Rao et al. JCO 2020



RR (Primary)	PFS	OS
57	5.7	12.3
59	8.1	20

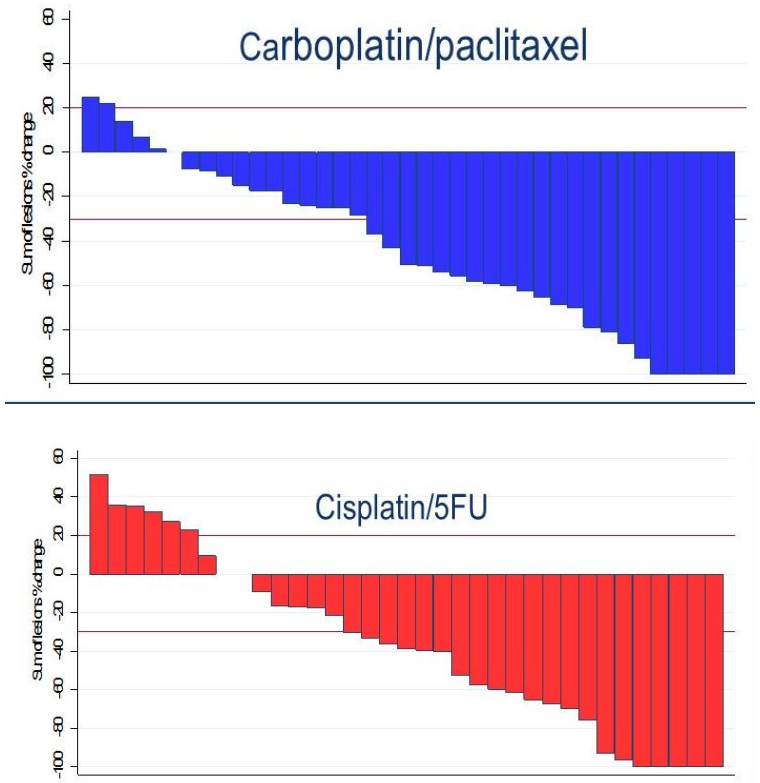
Primary: RR

Secondary: PFS, OS, Correlatives, QOL

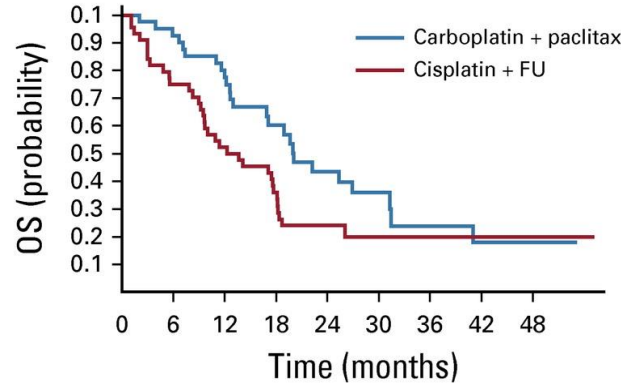
Note NCCN dosing different, ClinicalTrials.gov

InterAACT: Results

Rao et al, JCO 2020

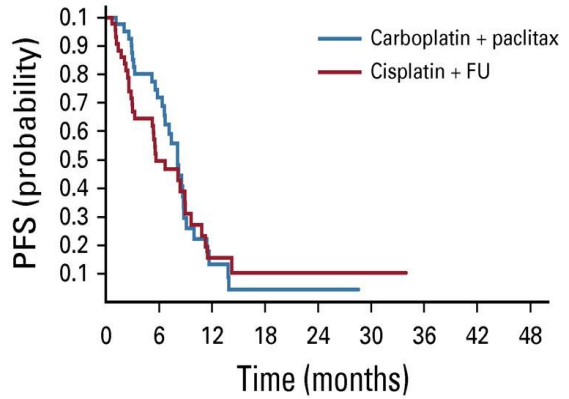


	Carboplatin Paclitaxel (N=39)	Cisplatin 5FU (N=35)
CR	13 %	14 %
PR	46 %	43 %
SD	25 %	20 %
PD	15 %	23 %
RR	59 %	57 %
DCR	84 %	77 %
PFS	8.1 months	5.7 months
OS	20 months	12.3 months



No. at risk:

Carboplatin + paclitax	45	37	31	18	12	7	4	2	1
Cisplatin + FU	46	33	23	15	8	4	3	2	2



No. at risk:

Carboplatin + paclitax	45	26	3	1	1	0	0	0	0
Cisplatin + FU	46	19	3	2	1	1	0	0	0

InterAACT: AEs

Toxicity ≥ 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

Rao et al, ESMO 2018

NCCN: Metastatic Disease

First Line Therapy +/- RT

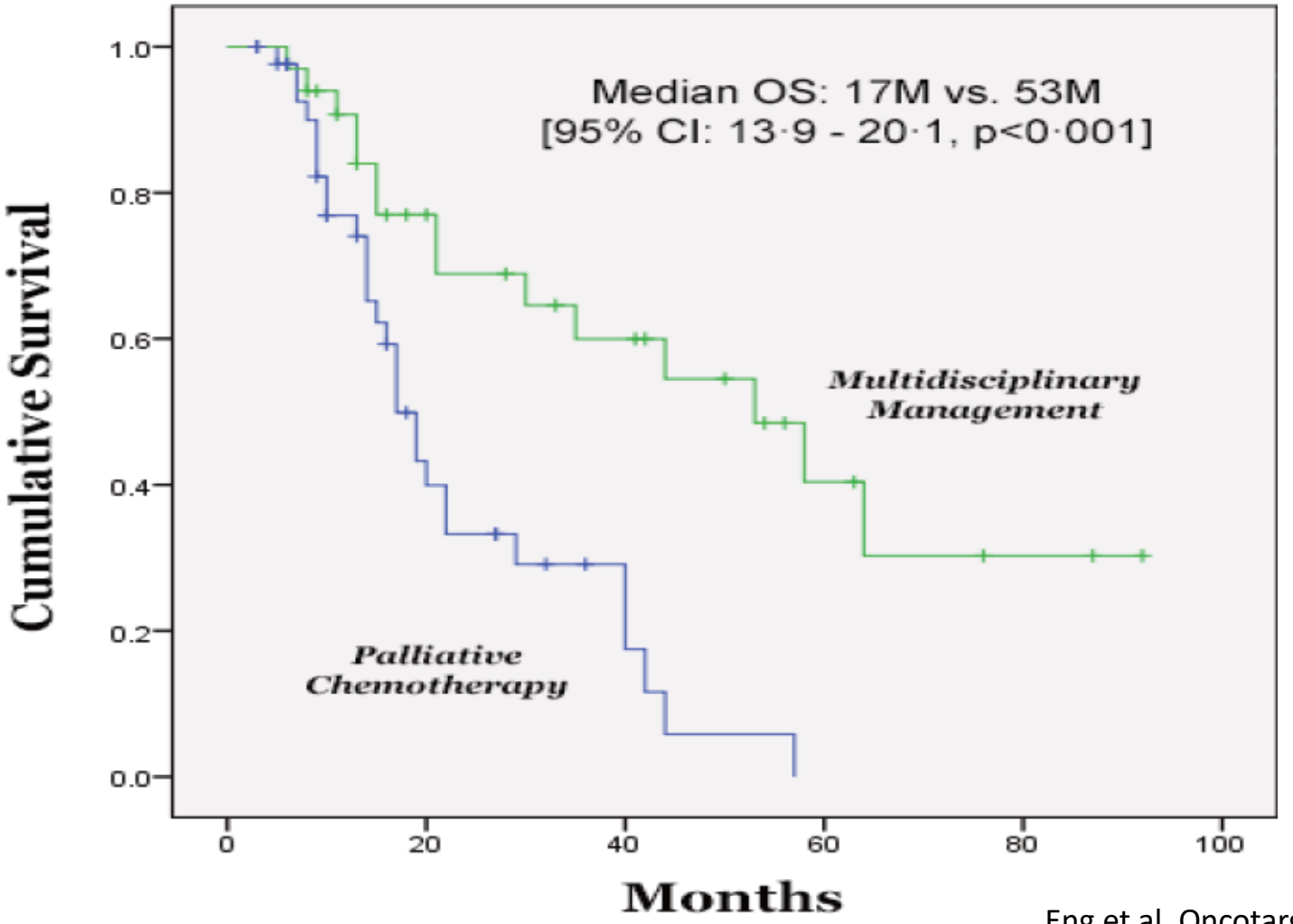
Carboplatin + Paclitaxel	(NCCN Preferred)
5FU + Cisplatin	(more toxic)
FOLFOX6	(NCCN case report, adeno)
FOLFCIS	
mDCF	(NCCN 2b)

Second Line Therapy

Nivolumab or Pembrolizumab

NCCN 2023, Modified

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%

Eng et al, Oncotarget , 2014, Vol.5(22), p.11133

DCF/mDCF (Epitopes HPV02)

Lancet Oncol 2018

Single Arm, Multicenter, Phase 2

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

DCF/mDCF (Epitopes HPV02)

Lancet Oncol 2018

Single Arm, Multicenter, Phase 2

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

DCF/mDCF (Epitopes HPV02)

Lancet Oncol 2018

Single Arm, Multicenter, Phase 2

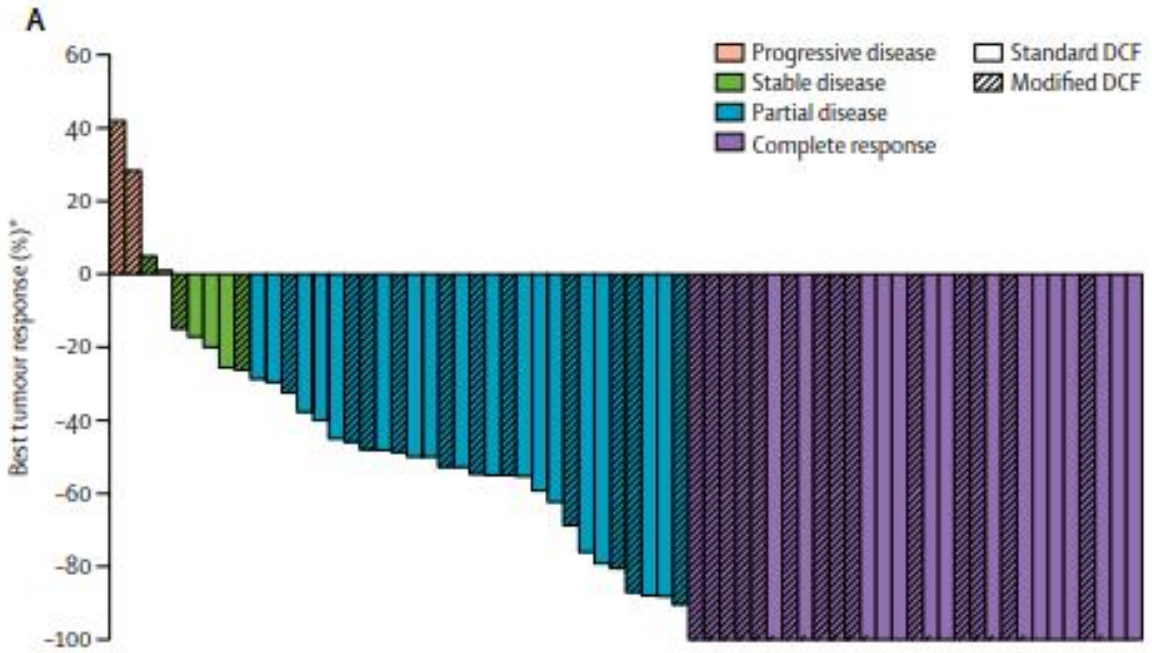
- 66 pts (36 DCF, 30 mDCF)
- 97 SAE (69 DCF, 28 mDCF)

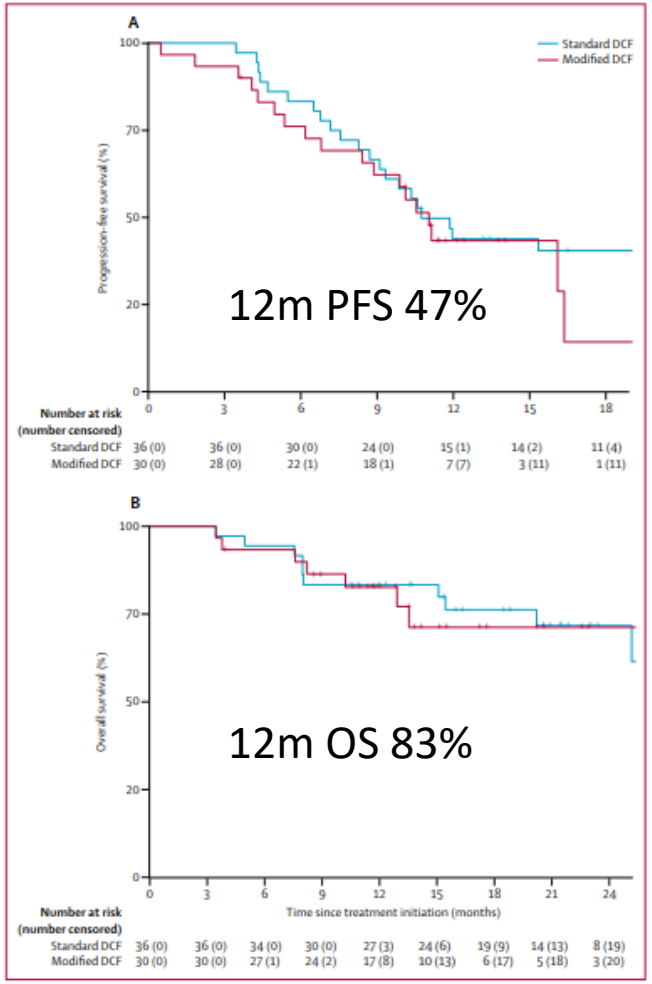
Not Randomized

CR 30 (45%)

ORR 59 (89%)

DCR 64 (97%)





Nivolumab

Phase II (n=37)

RECIST Response

9 patients (24%)

2 CR, 7PR

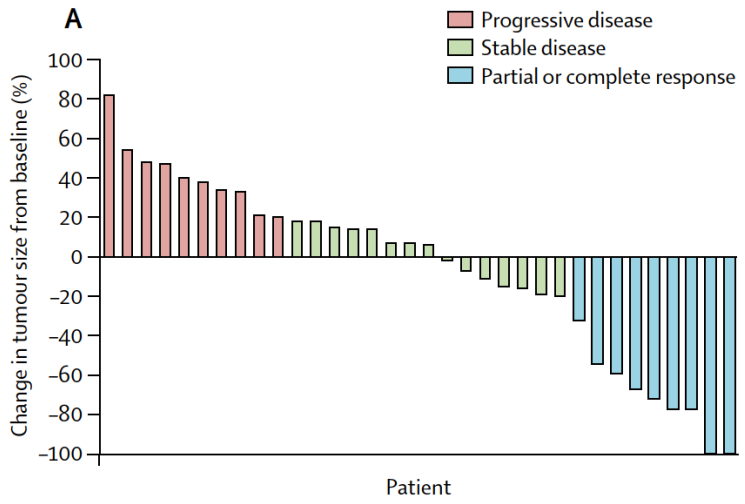
Pembrolizumab

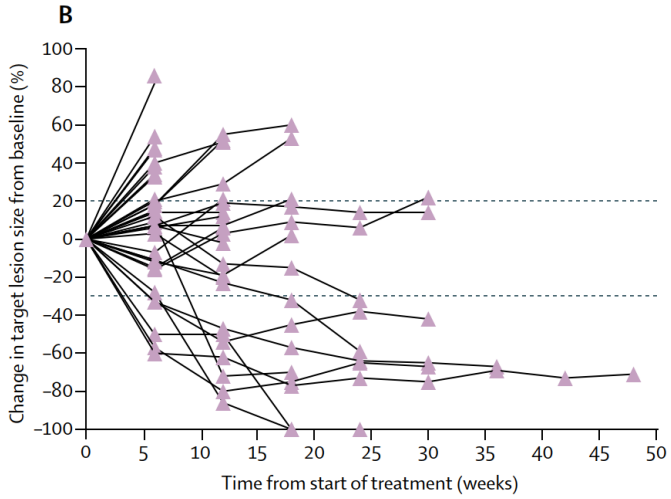
Ib (n=25)

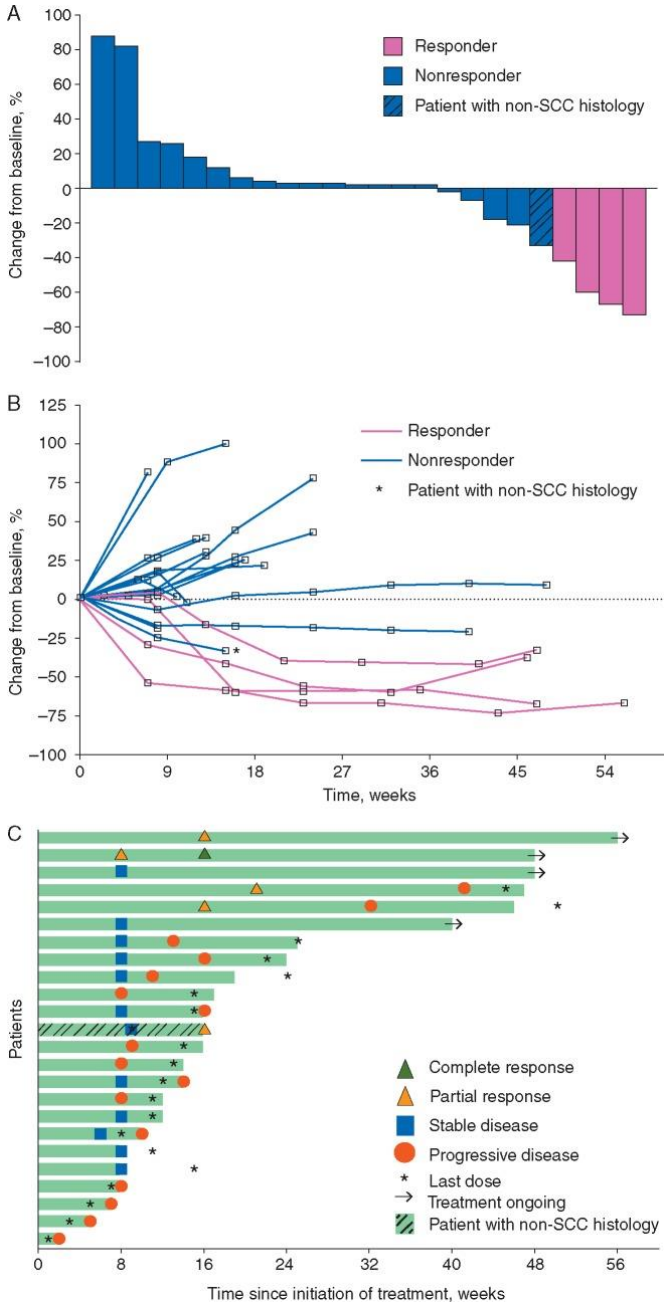
Safety and Response

4 patients (17%)

4 PR

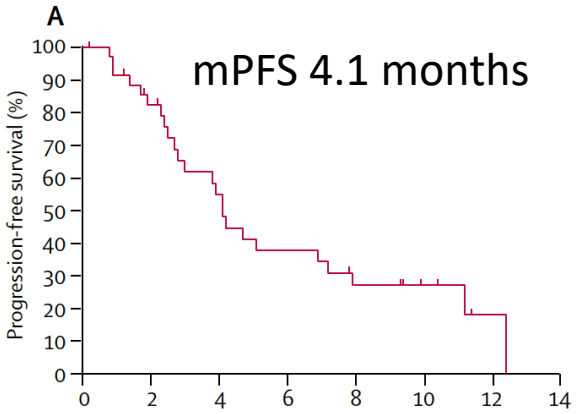


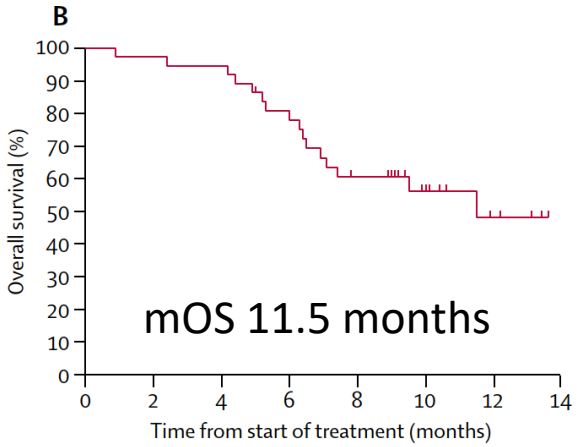




Lancet Oncol 2017; 18: 446–53 | Ann Oncol 2017;28:1036-1041.

Nivolumab

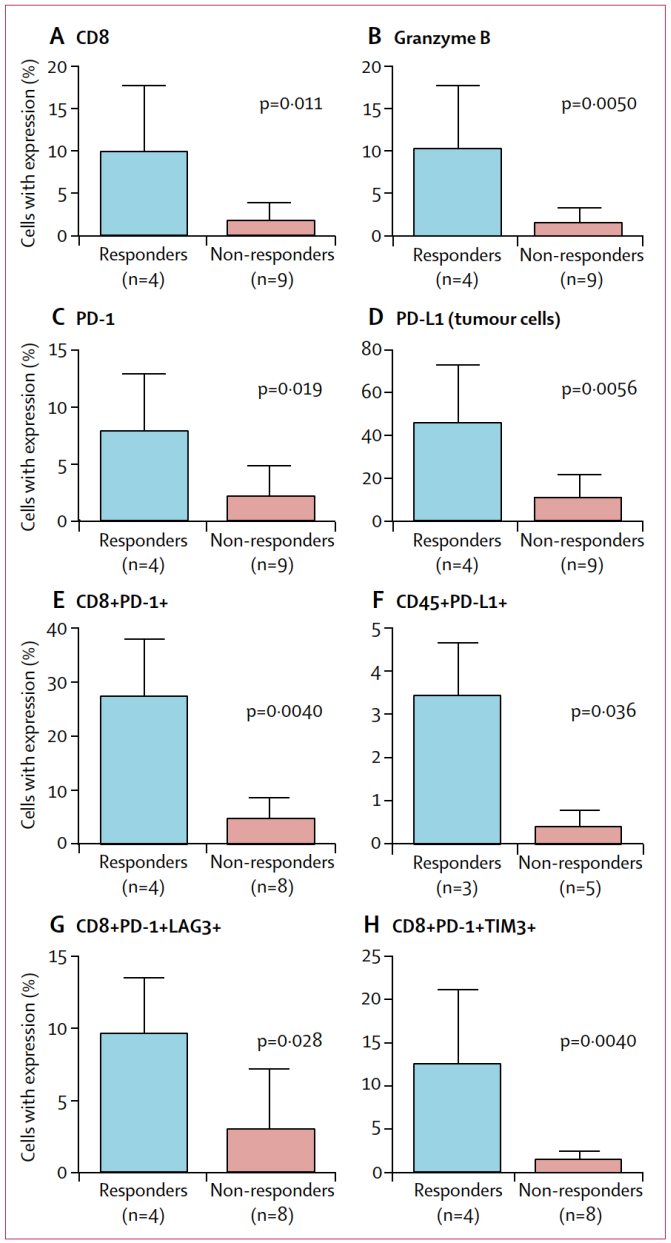




	Grade 1	Grade 2	Grade 3
Anaemia	13 (35%)	11 (30%)	2 (5%)
Fatigue	17 (46%)	7 (19%)	1 (3%)
Rash	8 (22%)	2 (5%)	1 (3%)
Constipation	8 (22%)	2 (5%)	0
Anorexia	5 (14%)	4 (11%)	0
Diarrhoea	8 (22%)	0	0
Weight loss	5 (14%)	1 (3%)	0
Arthralgia	3 (8%)	3 (8%)	0
Hyperglycaemia	3 (8%)	1 (3%)	0
Hypothyroidism	1 (3%)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



Local Disease

- **Definitive chemoradiation** is standard.
  5-FU or Capecitabine / Mitomycin / Radiation
- Adjuvant Nivolumab trial Pending Results
- Surgery is for salvage

Metastatic Disease

- **First Line:** Carboplatin + Paclitaxel
- **Second Line:** Immunotherapy (Phase Ib/II data)