Fred Hutch
Cancer Center

Anal Cancer

2025

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University of Washington
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UW Medicine

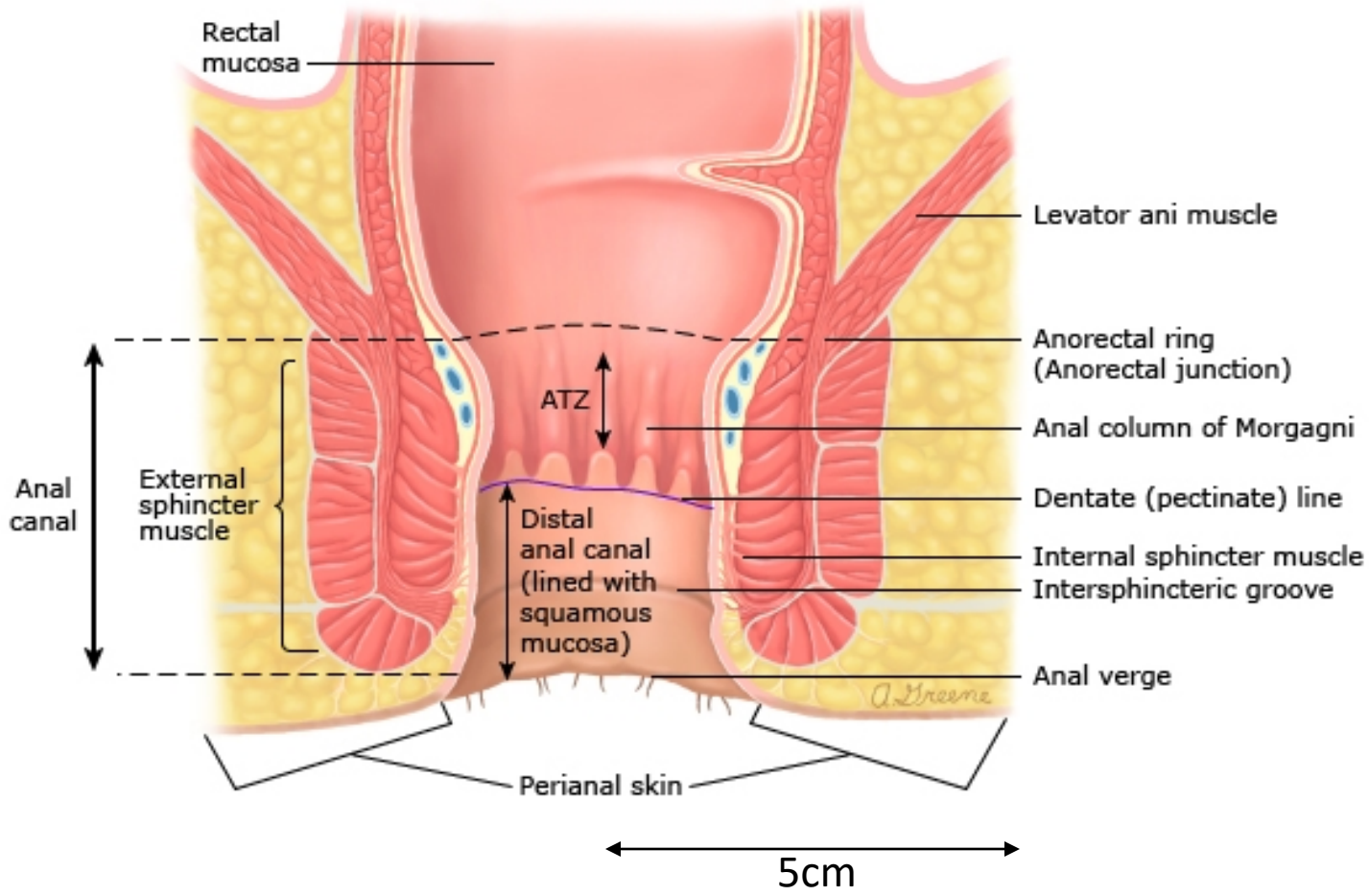
Outline

- 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)

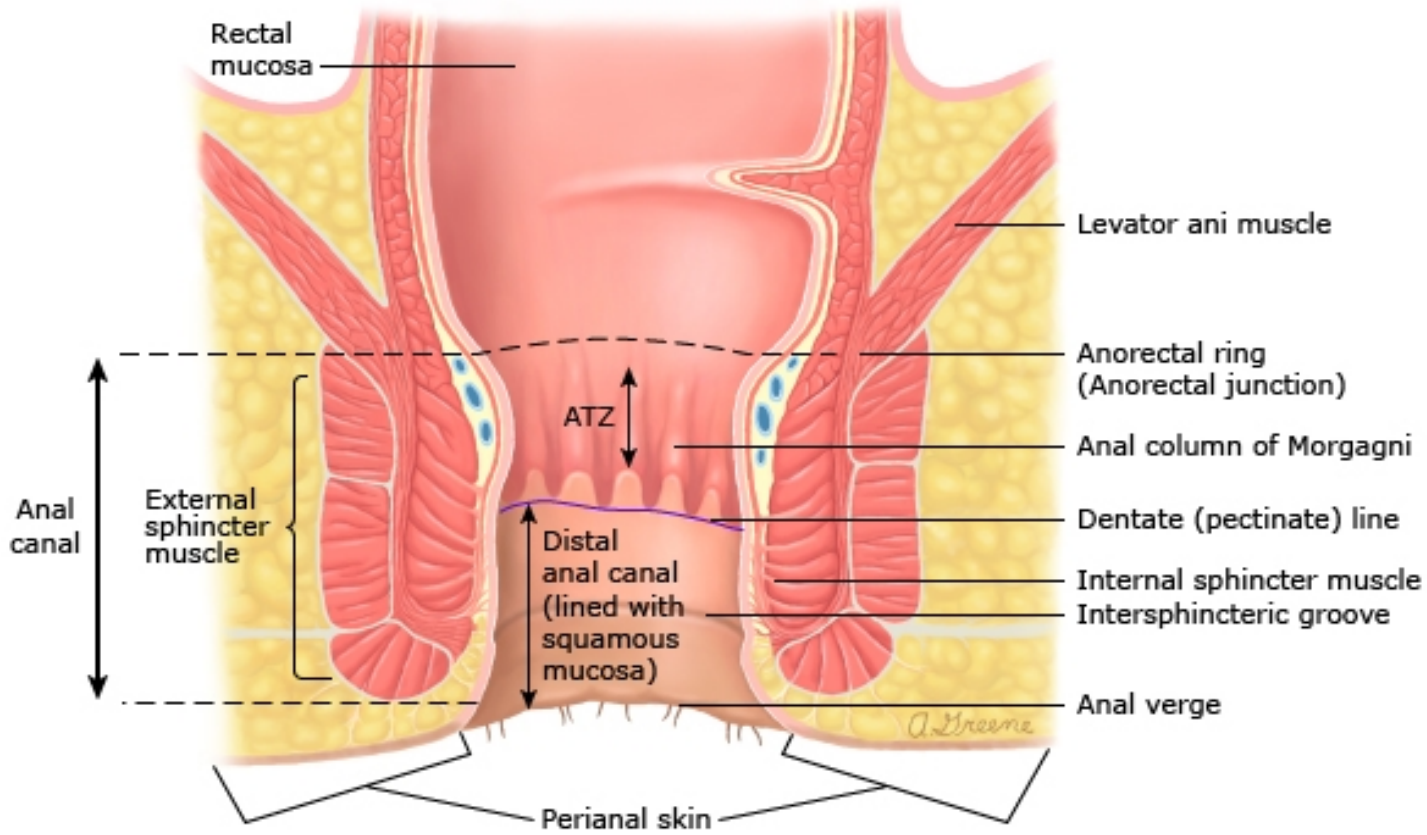
NOS: not otherwise specified.



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

7,000 in 2014

2001-2019 Increasing the most in Females aged > 60

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

EPIDEMIOLOGY

- 10,930 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

Updated, SEER, UpToDate
Glynne-Jones et al. Annals of Oncology. 2010 21(s5)
American Cancer Society. Cancer Facts and Figures 2025.

Pathogenesis

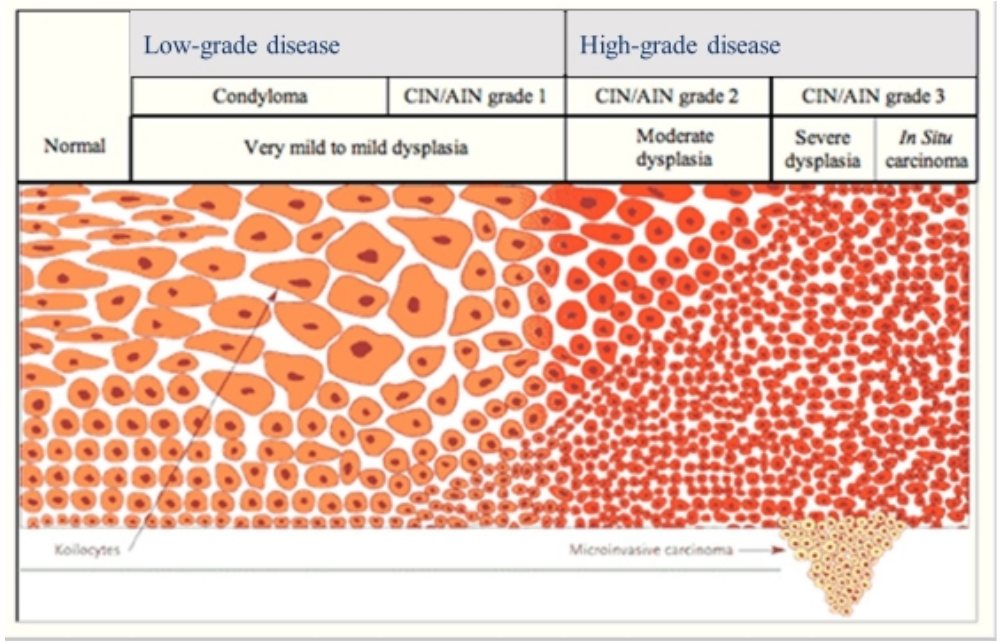
N Engl J Med. 1997;337(19):1350|Hoots etal, Int J Cancer 2009;124:2375

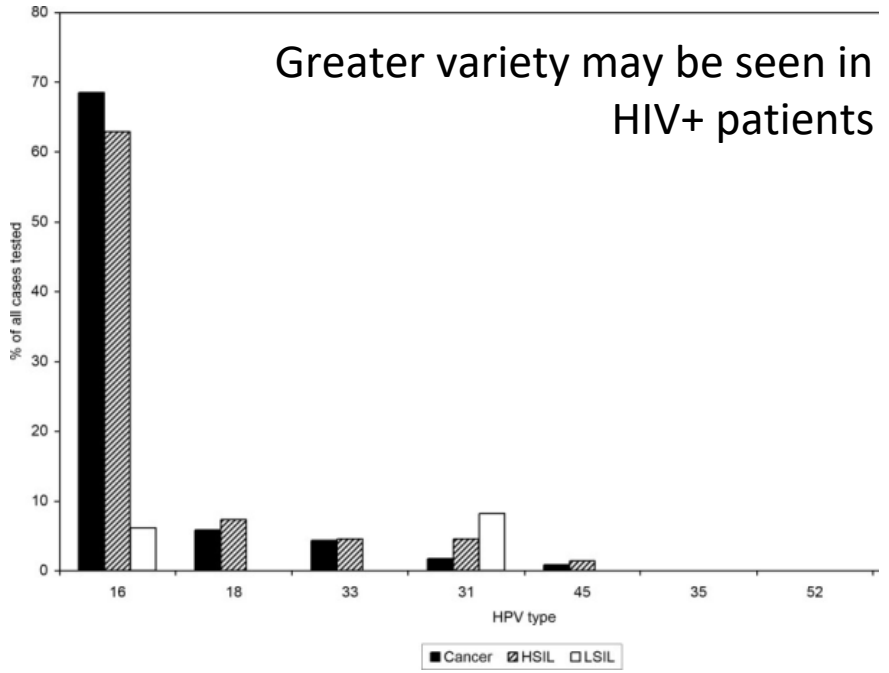
Human Papillomavirus

- 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

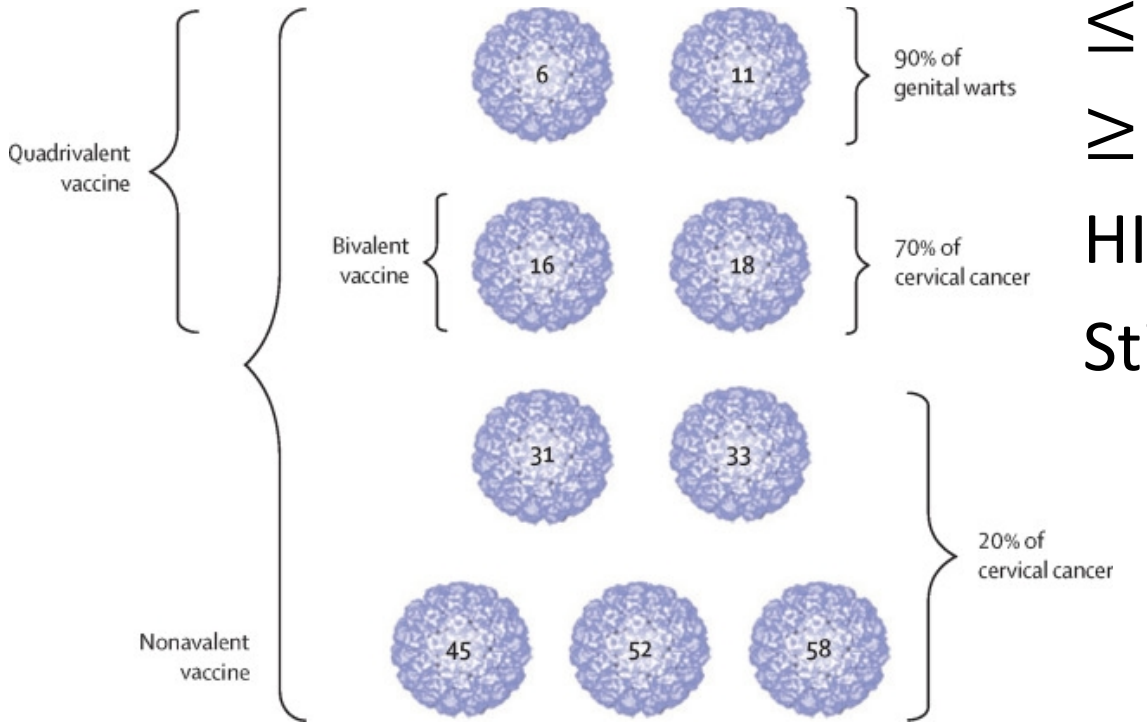
Cigarettes

- 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

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

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

Palefsky JM et al. DOI: 10.1056/NEJMoa2201048

CLINICAL PROBLEM

Anal cancer is caused by human papillomavirus infection and is preceded by high-grade squamous intraepithelial lesions (HSIL). Whether treatment of anal HSIL reduces progression to anal cancer is unknown.

CLINICAL TRIAL

Design: A multisite, randomized, U.S. trial examined the efficacy and safety of HSIL treatment for the prevention of anal cancer in adults living with HIV, a group disproportionately affected by anal cancer.

Intervention: 4446 participants 35 years of age or older with HSIL and without a history of anal cancer received either HSIL treatment until complete resolution (e.g., office-based ablation, ablation or excision under anesthesia, or topical therapies) or active monitoring without treatment. Participants in the treatment group returned for high-resolution anoscopy at least every 6 months, suspicious lesions were biopsied, and recurrences were treated. Participants in the active-monitoring group underwent anoscopy every 6 months, and visible lesions were biopsied annually. The primary outcome was progression to anal cancer in a time-to-event analysis.

RESULTS

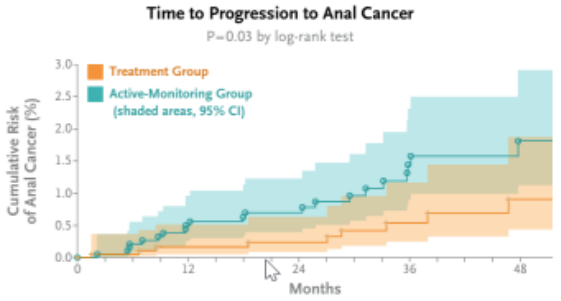
Efficacy: During a median follow-up of roughly 26 months, the rate of progression to anal cancer was significantly lower in the treatment group than in the active-monitoring group.

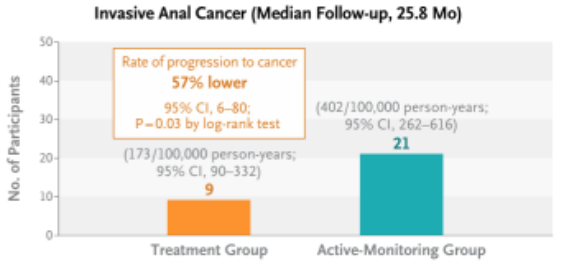
Safety: Trial-related serious adverse events were uncommon.

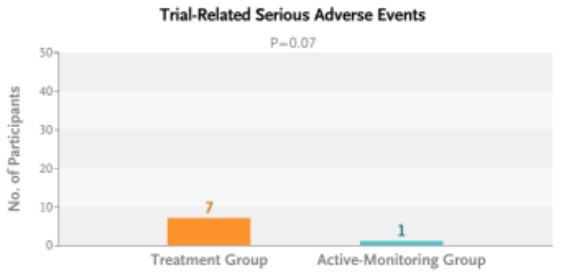
LIMITATIONS AND REMAINING QUESTIONS

- HSIL treatment did not prevent all cancers, which underscores the need for close follow-up and for more effective treatments.
- The results may not be generalizable to settings in which high-resolution anoscopy and treatment are performed by clinicians with less training and support.
- Additional research is warranted to improve screening algorithms for identifying anal HSIL.

Links: Full Article | NEJM Quick Take







CONCLUSIONS

Among adults living with HIV who had anal HSIL, treatment of HSIL reduced the risk of progression to anal cancer, with a low incidence of serious adverse events.

Screening

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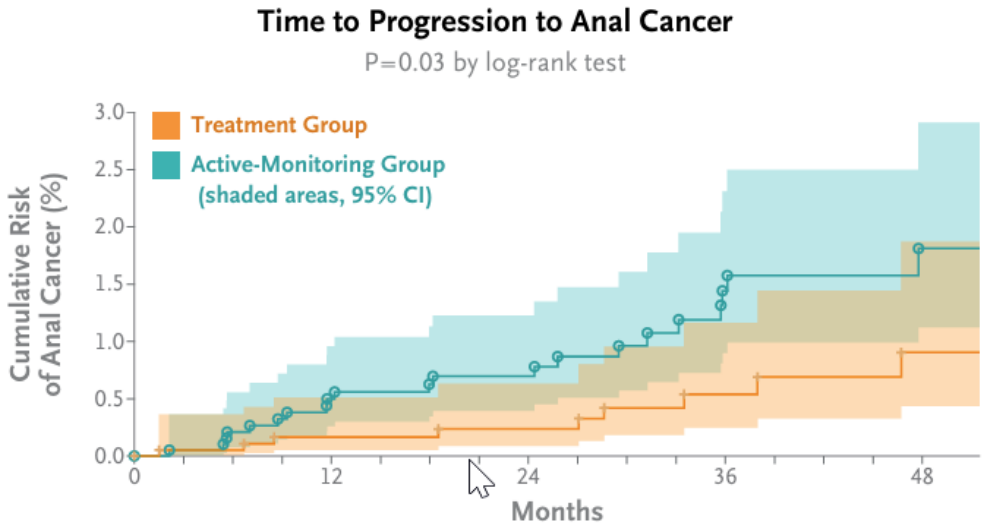

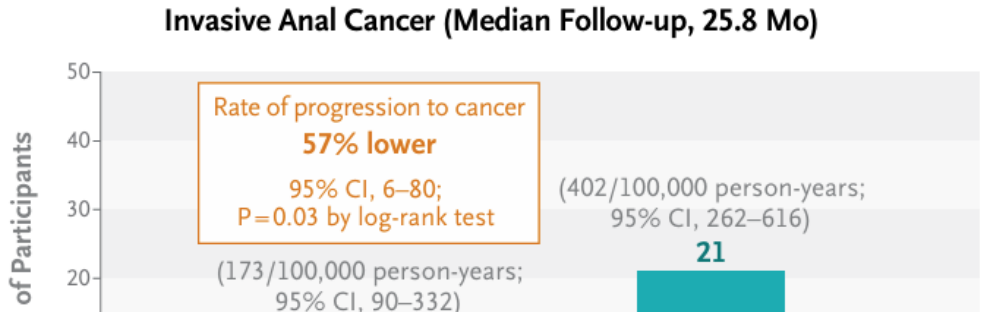

Screening

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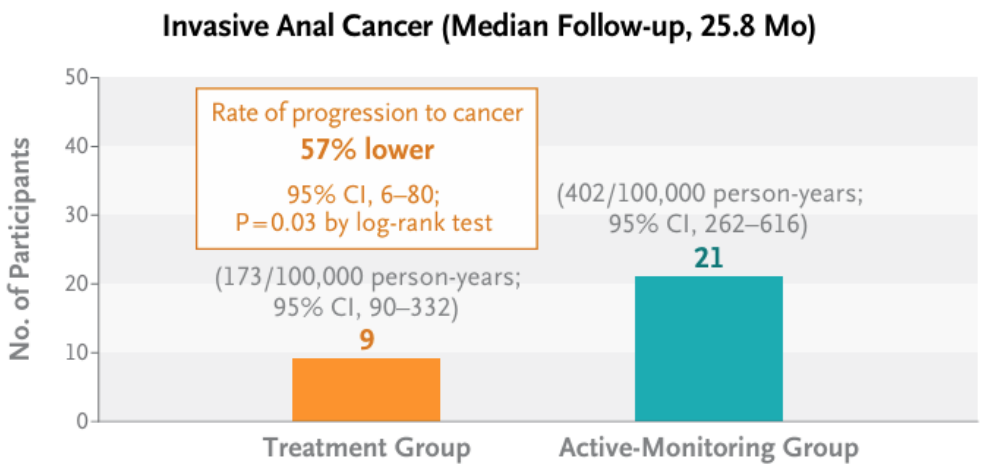

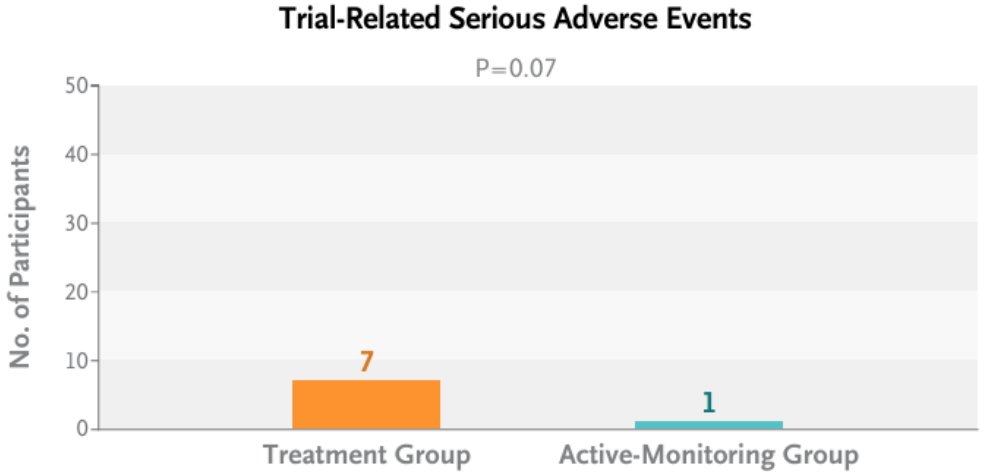

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Screening

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Invasive Anal Cancer (Median Follow-up, 25.8 Mo)

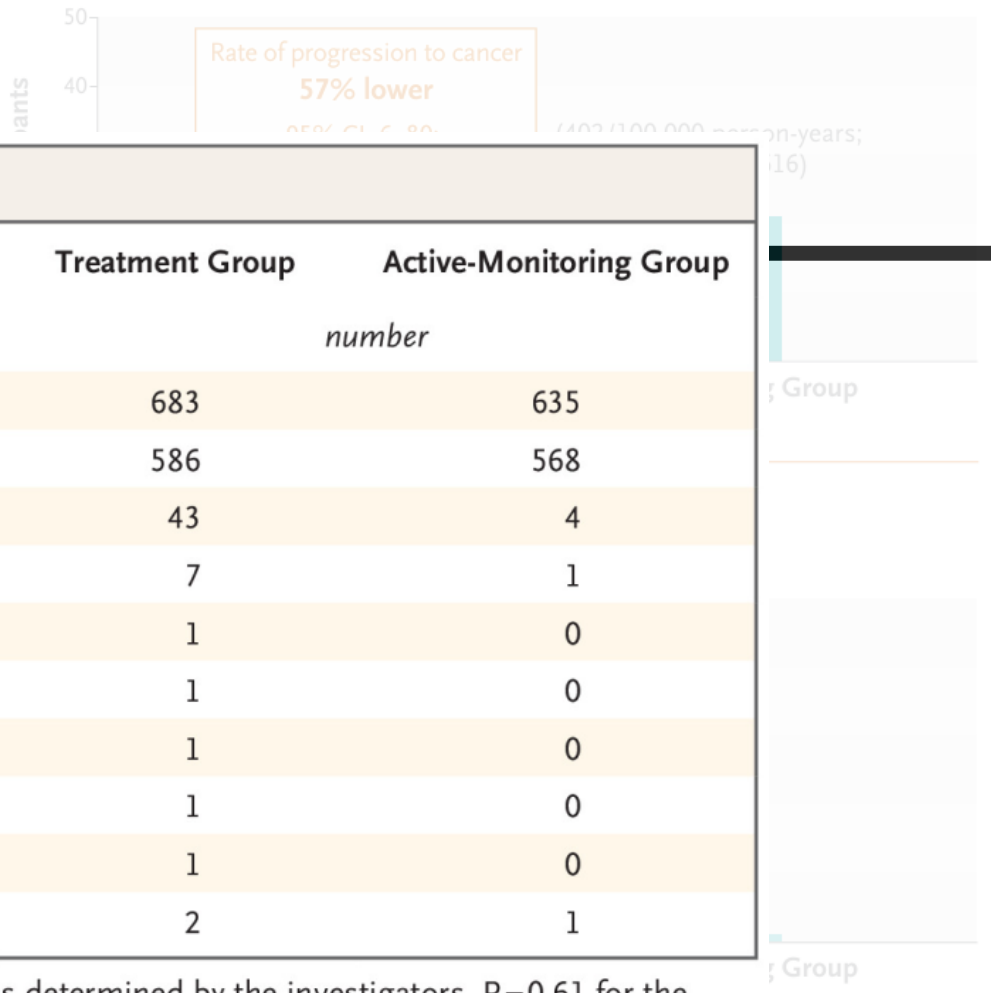


Table 2. Adverse Events.

Events	Treatment Group	Active-Monitoring Group
	number	
Adverse events	683	635
Serious adverse events*	586	568
Trial-related adverse events†	43	4
Trial-related serious adverse events‡	7	1
Skin ulceration due to fluorouracil	1	0
Anal abscess due to electrocautery	1	0
Pain due to electrocautery	1	0
Pain due to treatment under anesthesia	1	0
Pain due to infrared coagulation	1	0
Infection or abscess due to anal biopsy	2	1

* Shown are all serious adverse events regardless of intervention, as determined by the investigators. P=0.61 for the between-group difference.
† Shown are adverse events with a possible, probable, or definite relationship to trial interventions, as determined by the investigators.
‡ Shown are serious adverse events with a possible, probable, or definite relationship to trial interventions, as determined by the investigators. P=0.07 for the between-group difference.

IL, treat-
anal cancer,
with a low incidence of serious adverse events.

Links: Full Article | NEJM Quick Take

Screening

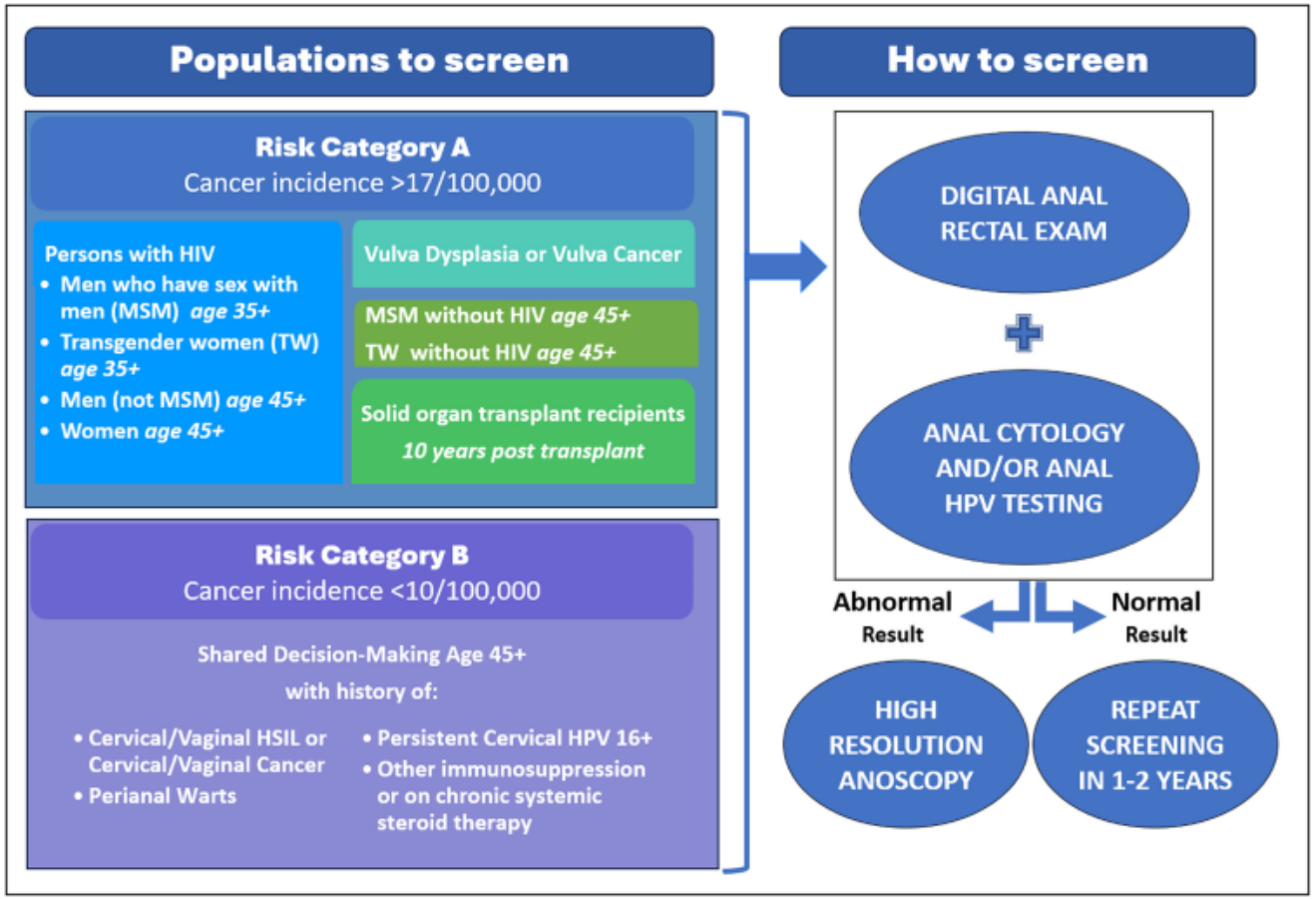
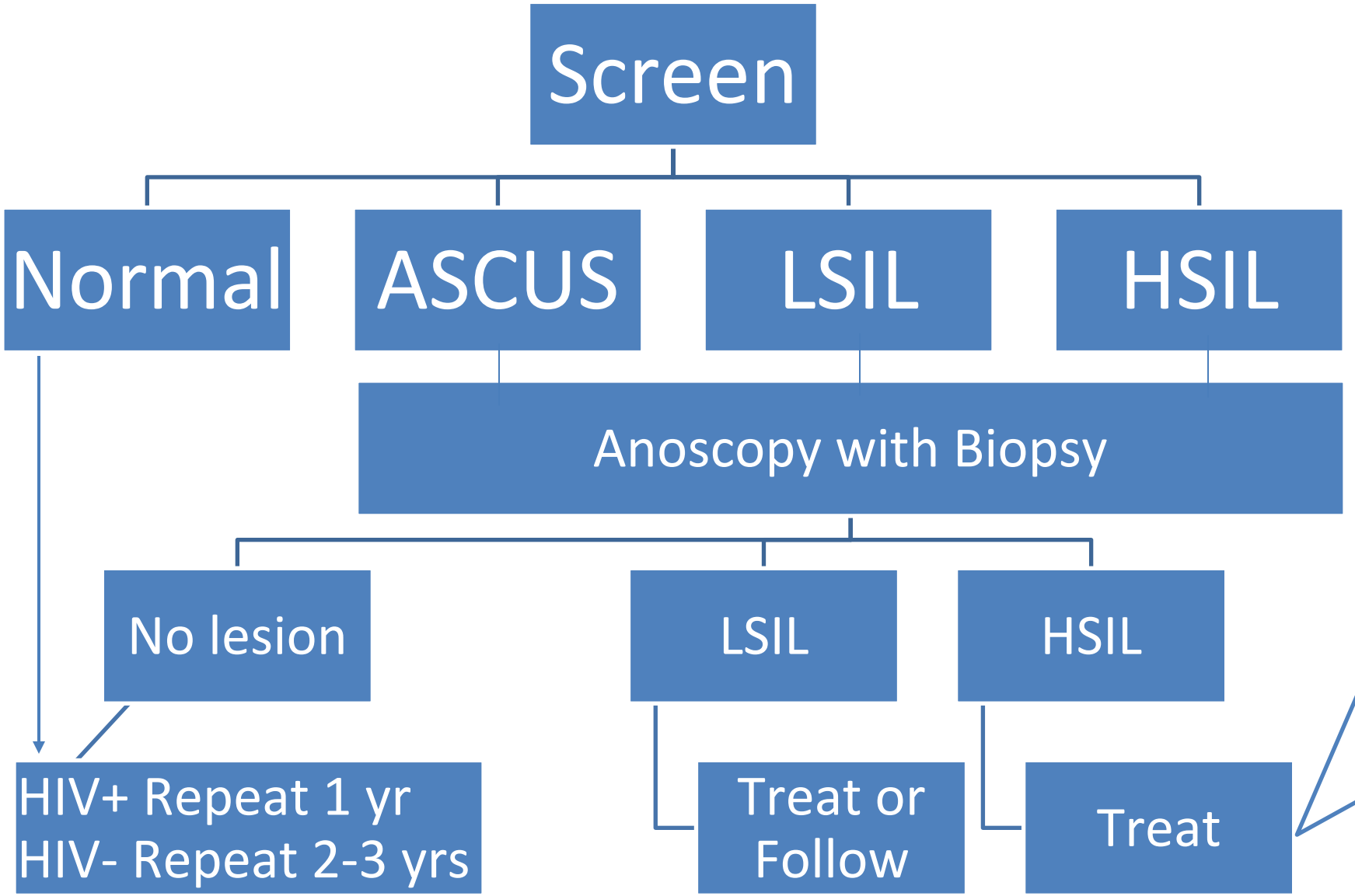


Table 1. Incidence rates of anal cancer by risk group. Based on Clifford et al. *Int J Cancer* 2021.[7]

Risk Group	Incidence rate (per 100,000 persons)
Risk Category A	
MSM and TGF living with HIV age 35+	>70
Vulvar cancer, VIN3	>40
MSW LWH age 45+	40
Women LWH age 45+	25
Solid organ transplant recipients, 10 yrs post-transplant	>25
MSM and TF without HIV age 45+	>18
Risk Category B	
H/o cervical or vaginal precancer or cancer, perianal warts, persistent cervical HPV16+, other immunosuppression	<10

Stier EA, Clarke MA, Deshmukh AA, et al. International Anal Neoplasia Society's consensus guidelines for anal cancer screening. *Int J Cancer*. 2024; 154(10): 1694-1702. doi:10.1002/ijc.34850

MSM Men who have sex with men | TW transgender woman | TGF transgender female
MSW Men who have sex with women | LWH living with HIV



Non FDA approved:

- 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

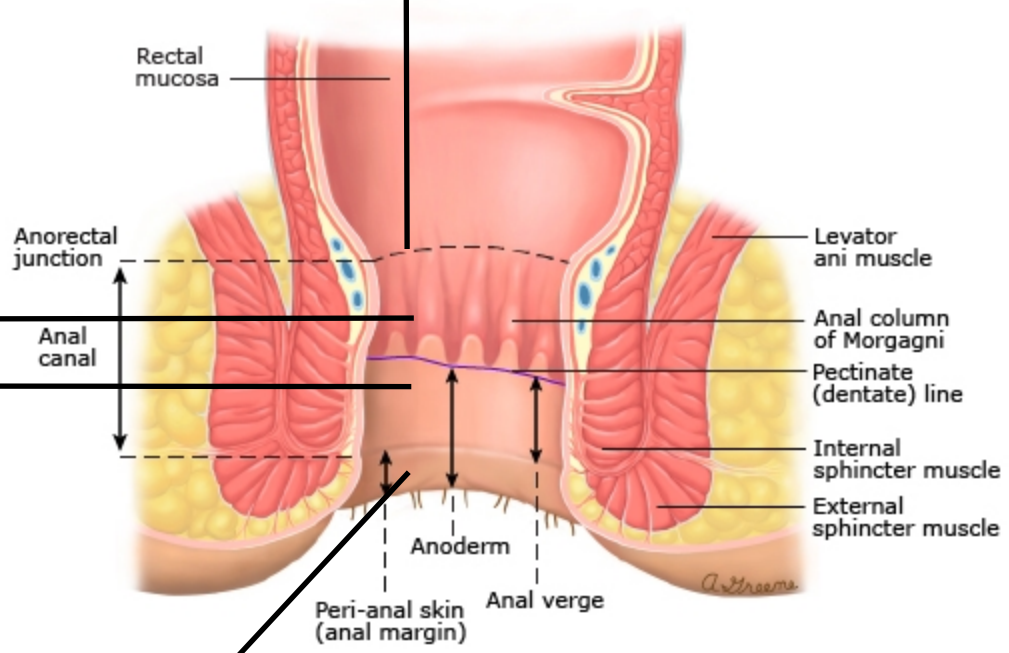
Anatomy: Nodal Drainage

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	

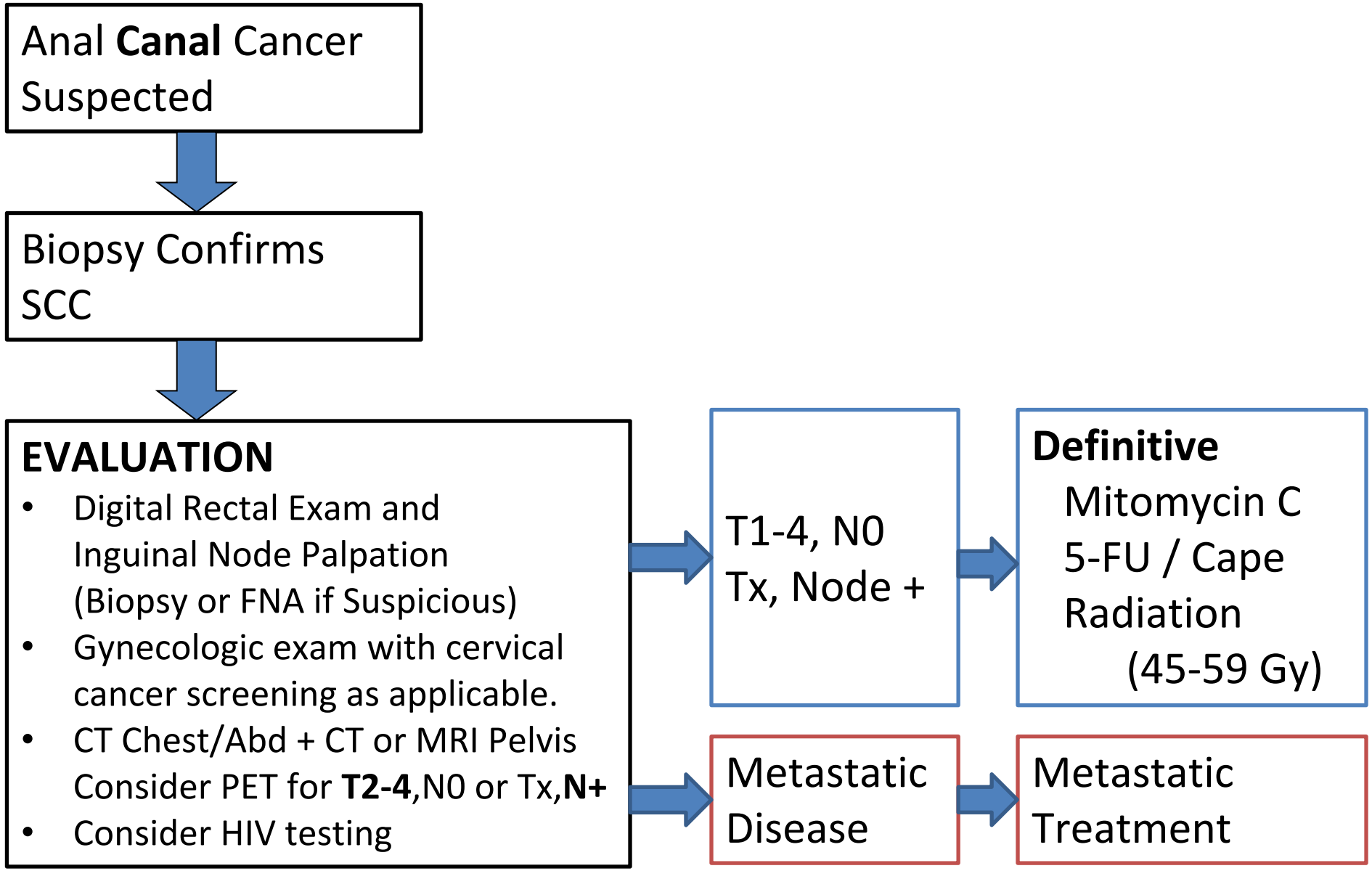
	5 y OS
T1	86%
T2	86%
T3	60%
T4	45%
N0	80%
N1	60%
M1	30%

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.

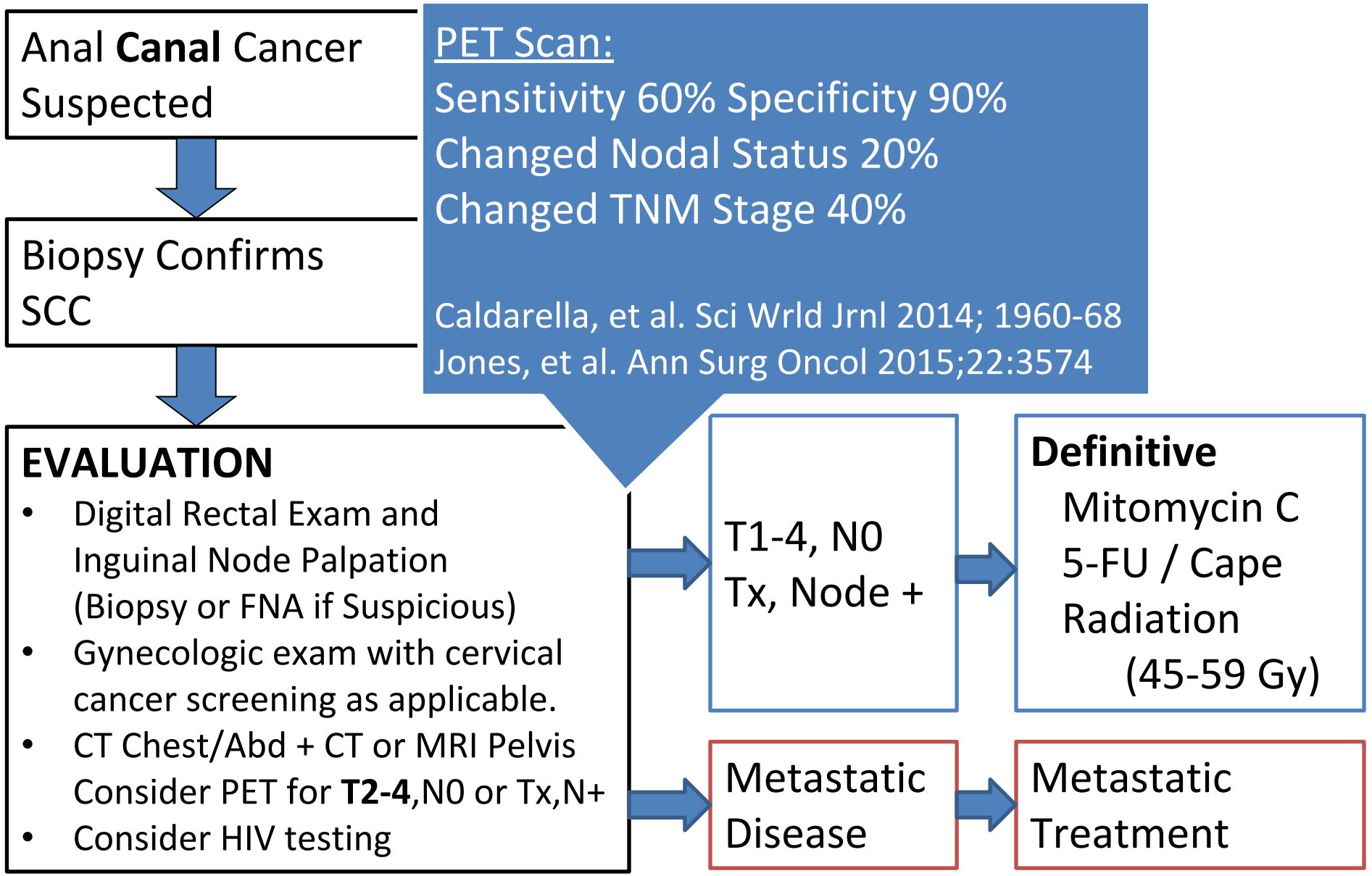
T1-4, N0
Tx, Node +

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

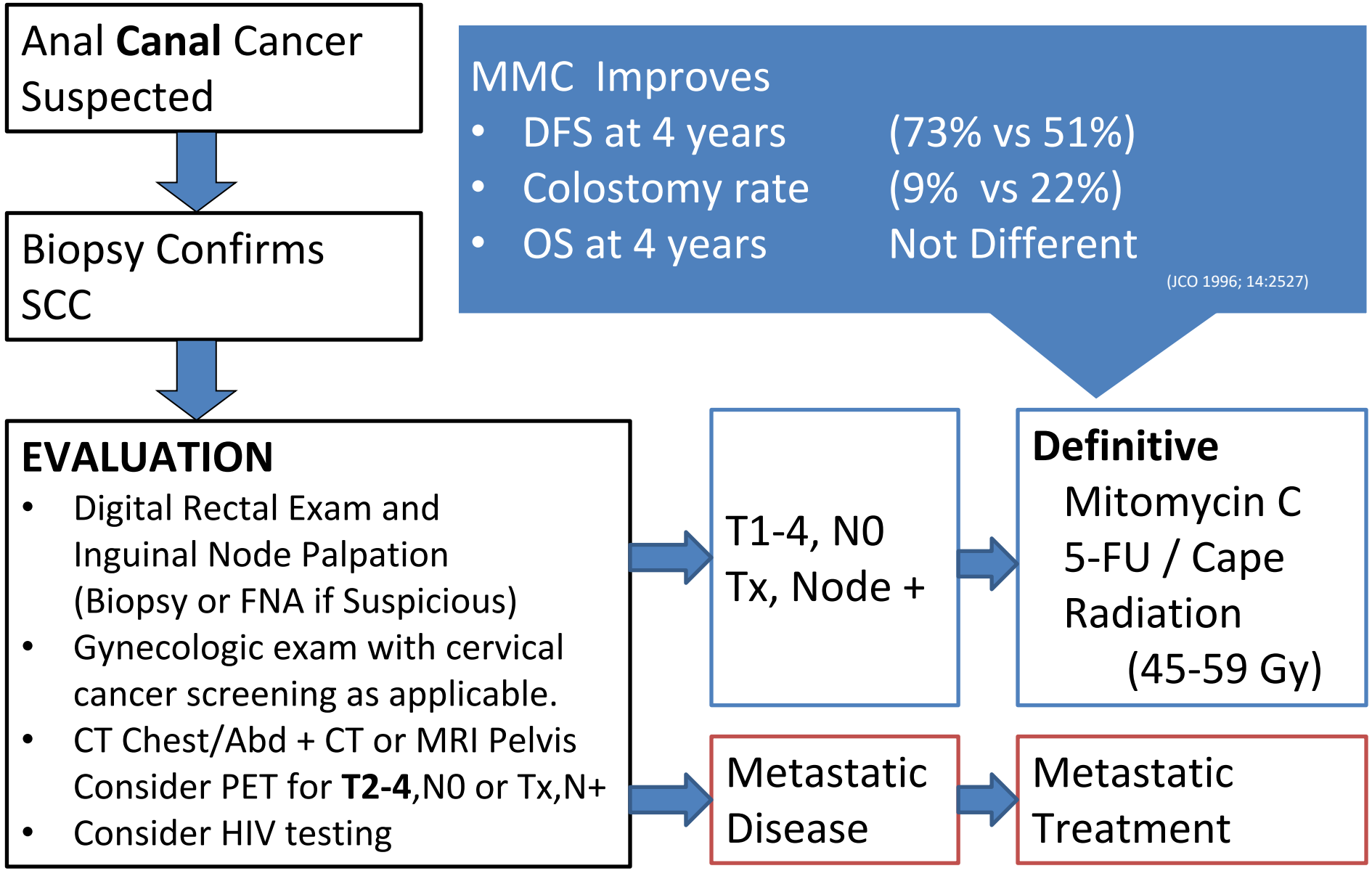
Metastatic Disease

Metastatic Treatment

NCCN Guidelines: Anal Carcinoma



NCCN Guidelines: Anal Carcinoma



NCCN Guidelines: Anal Carcinoma

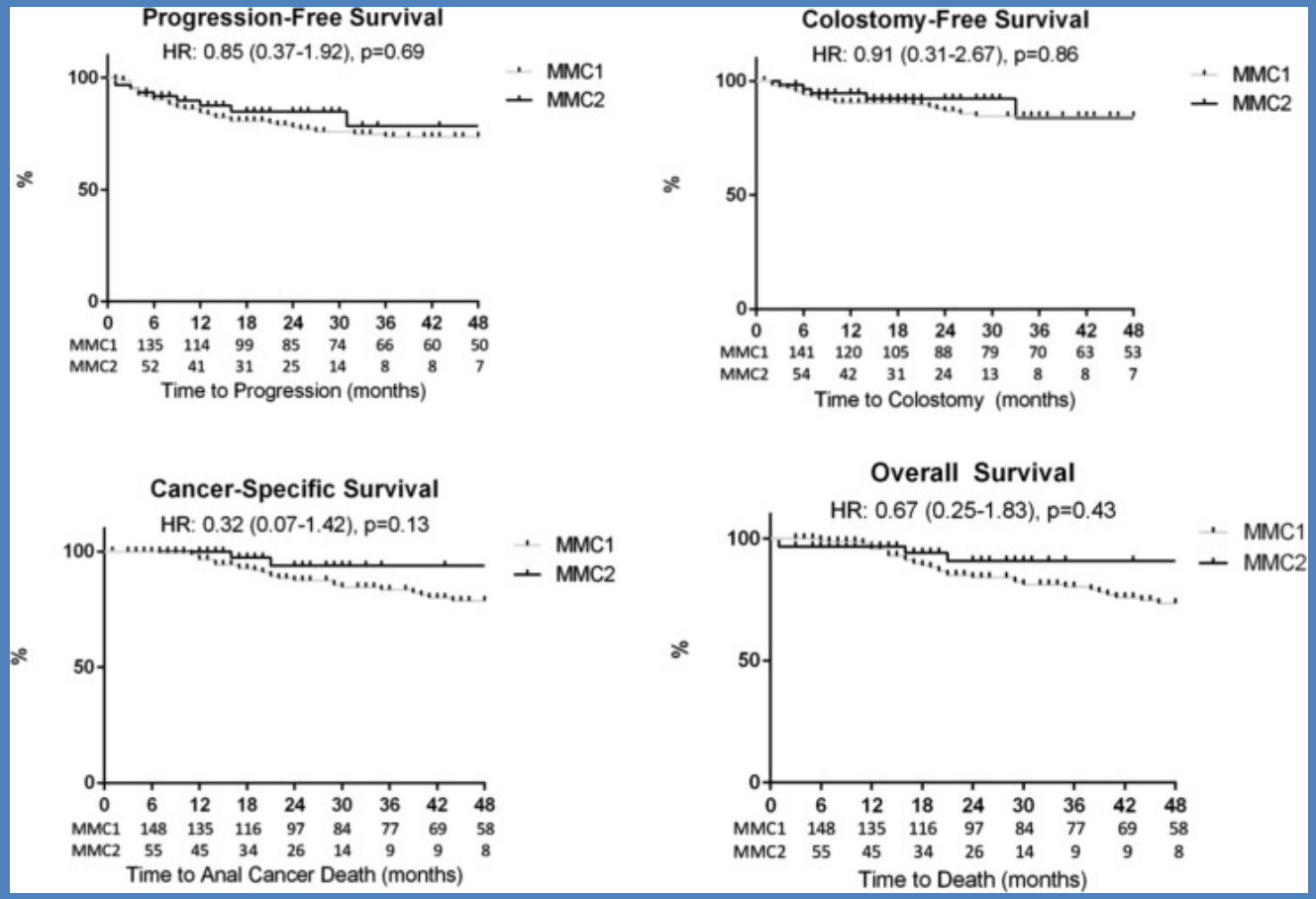
Anal **Canal** Cancer Suspected

Biop
SCC

EVA
- D
  In
  (E
- G
  ca
- C
  C
- C

MMC Improves

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



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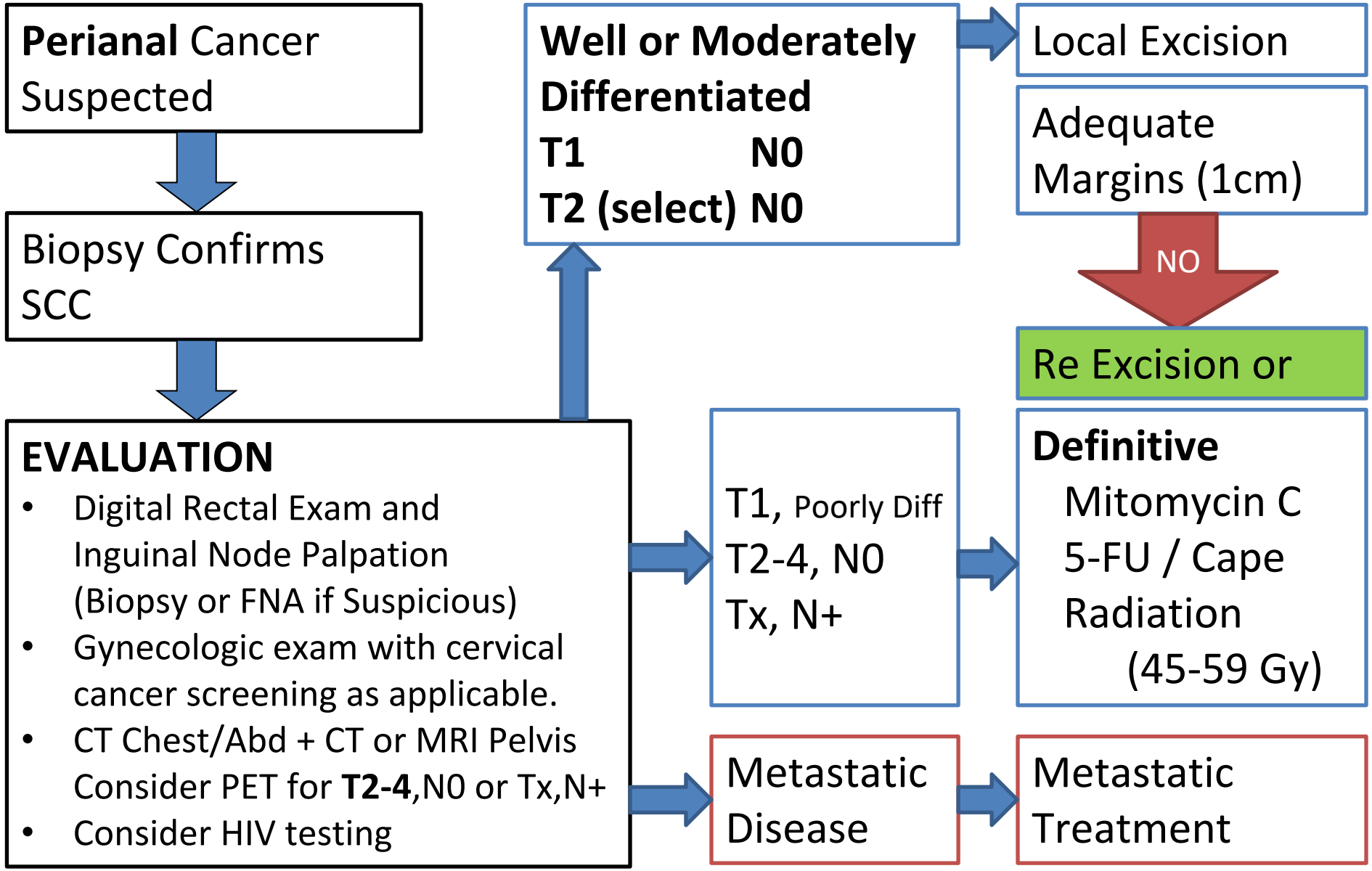
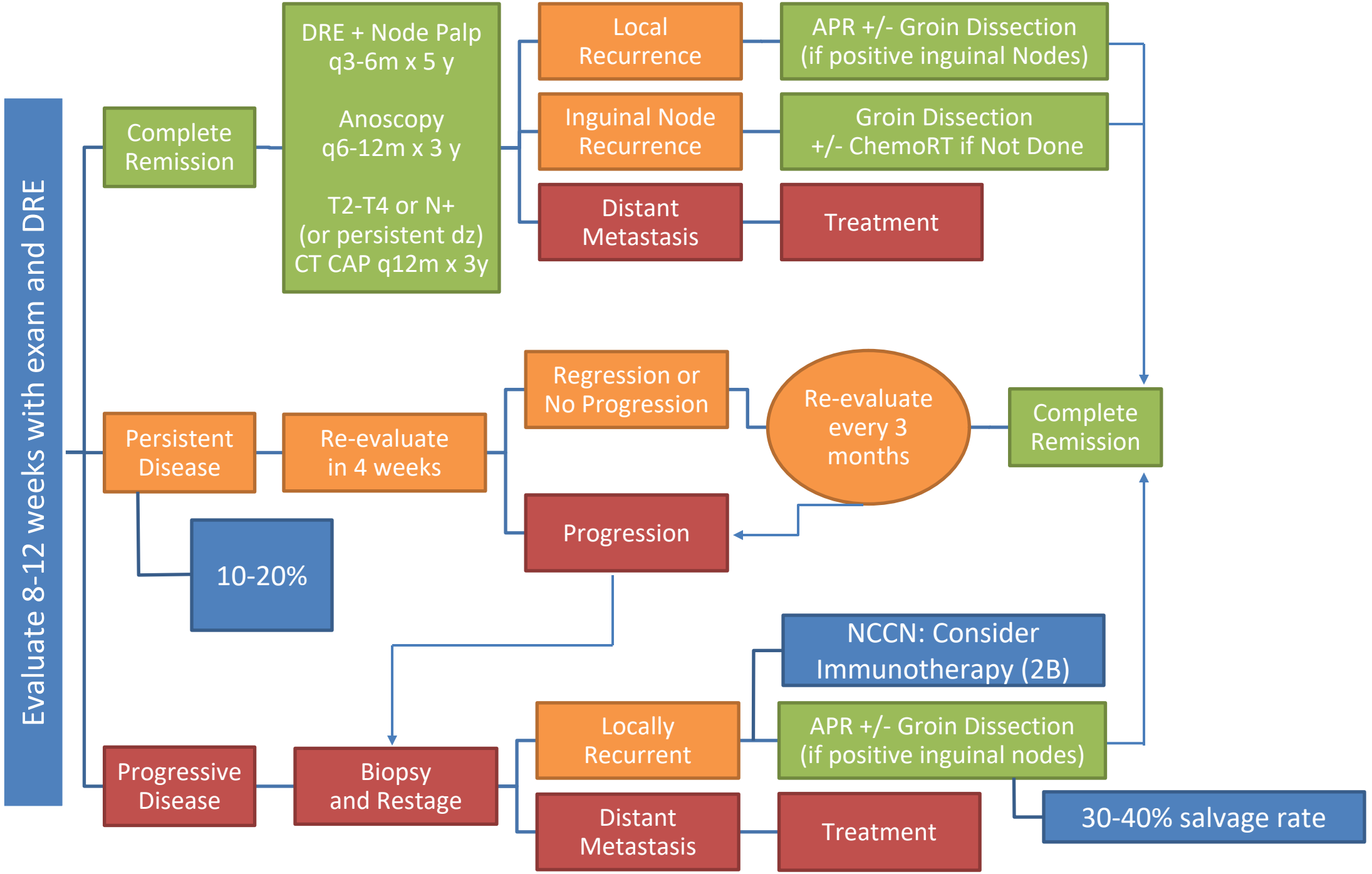



Evaluate 8-12 weeks with exam and DRE
Complete Remission
DRE + Node Palp q3-6m x 5 y
Anoscopy q6-12m x 3 y
T2-T4 or N+ (or persistent dz) CT CAP q12m x 3y
Local Recurrence
APR +/- Groin Dissection (if positive inguinal Nodes)
Inguinal Node Recurrence
Groin Dissection +/- ChemoRT if Not Done
Distant Metastasis
Treatment
Persistent Disease
Re-evaluate in 4 weeks
Regression or No Progression
Re-evaluate every 3 months
Complete Remission
Progression
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: Local Disease

APR was routinely performed

5 Year OS was 40-70%

Chemoradiation

Local Failure: 15-35%

5 Yr OS: 72-90%

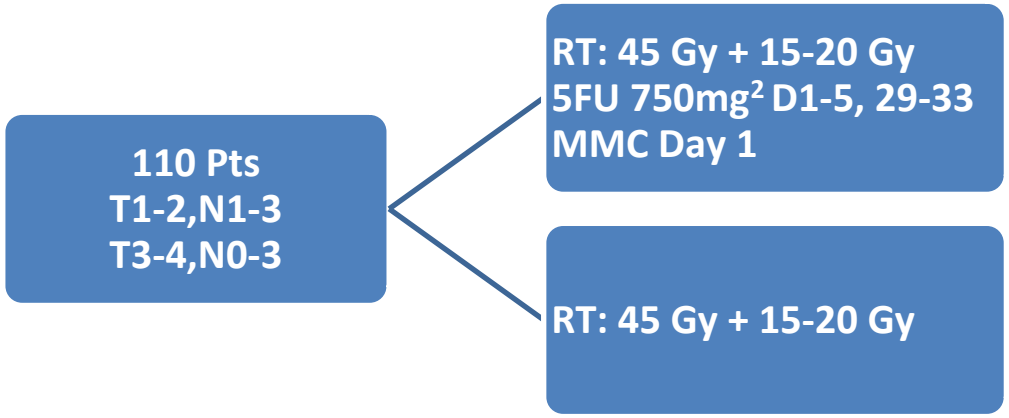
5FU/Capecitabine + Mitomycin C

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

RT vs ChemoRT



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

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

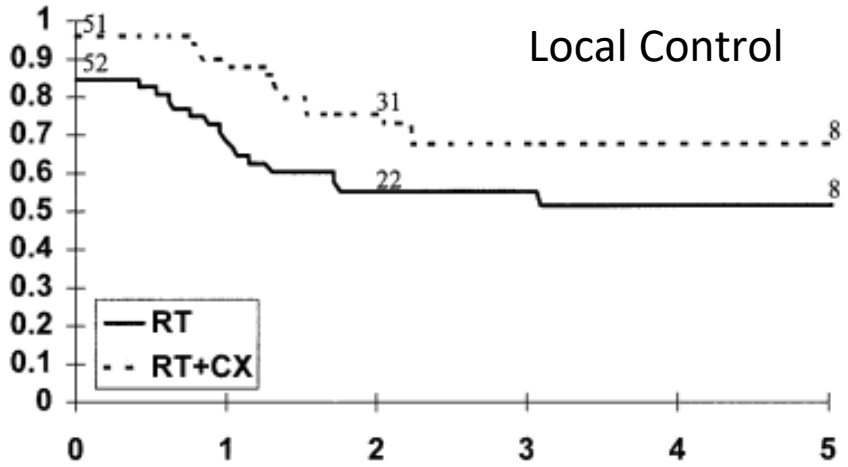
AEs		XRT	XRT + CT
Diarrhea	Gr 2	16	15
	Gr 3	4	10
	Gr 4	0	0
Skin	Gr 2	18	13
	Gr 3	26	28
	Gr 4	0	1

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**



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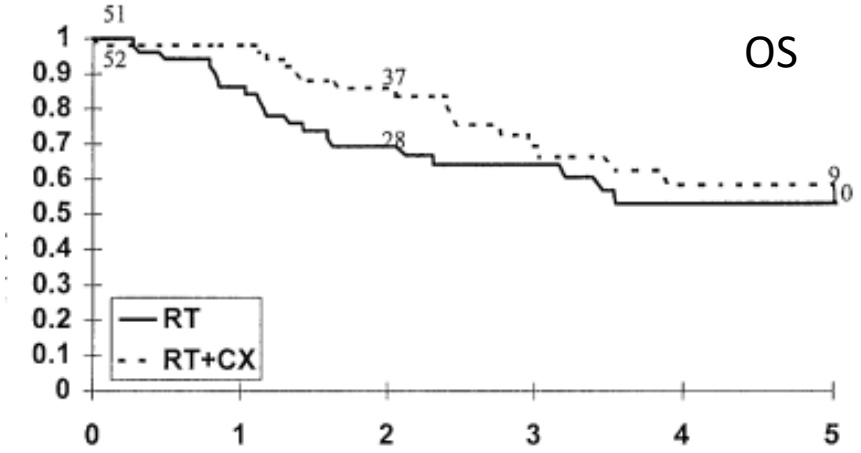


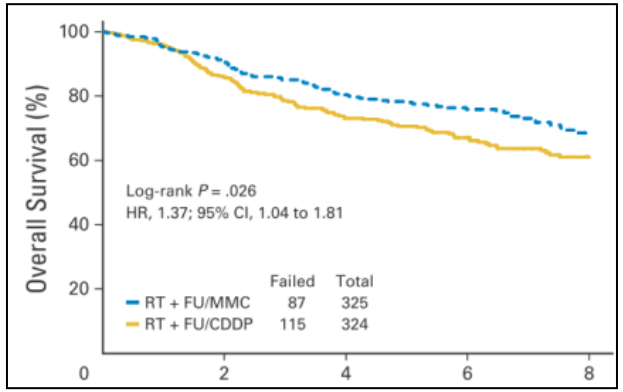
Bartelink et al. JCO 1997 15(5):2040-9

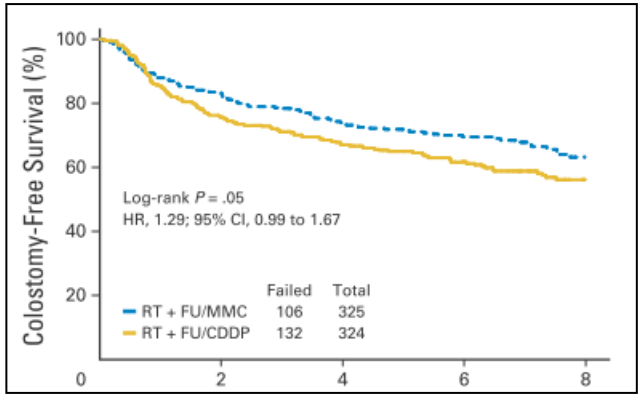
Mitomycin C vs Cisplatin

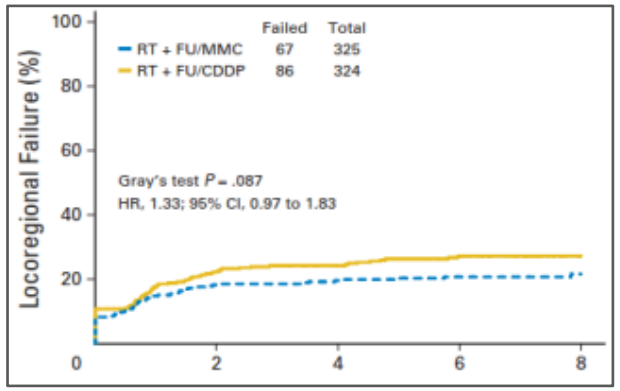
Ajani, J. A. et al. JAMA 2008;299:1914-1921
Gunderson, L et al. J Clin Oncol. 2012; 30(35)

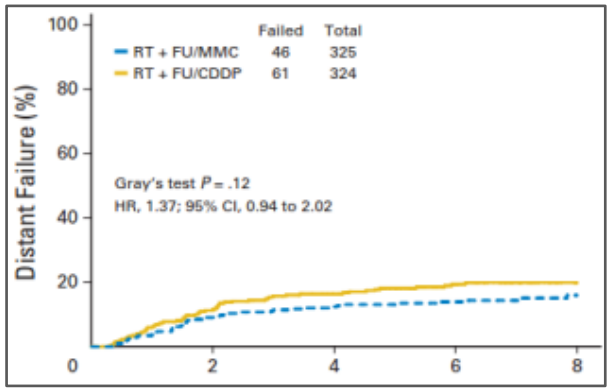
RTOG 98-11

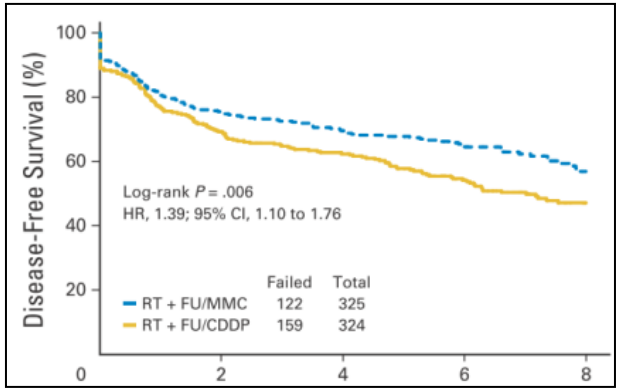
- CIS/5FU → CIS/5FU/RT
- MMC/5FU/RT





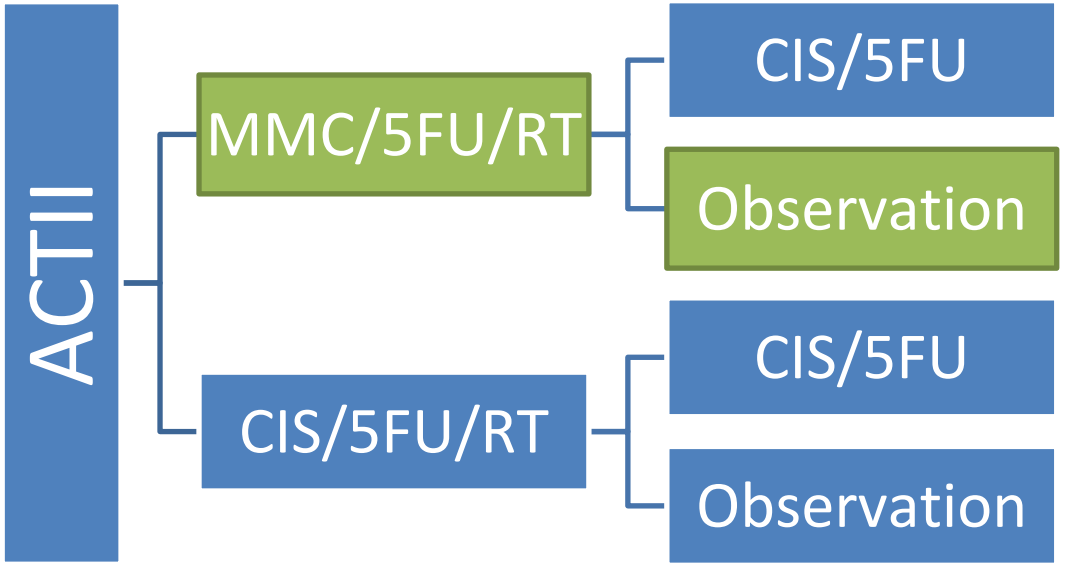






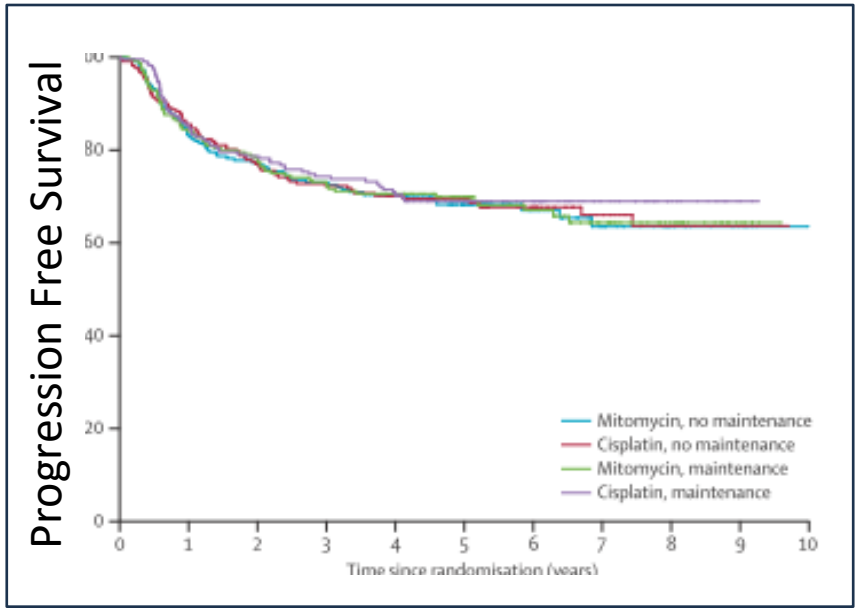
Mitomycin C vs Cisplatin

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



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

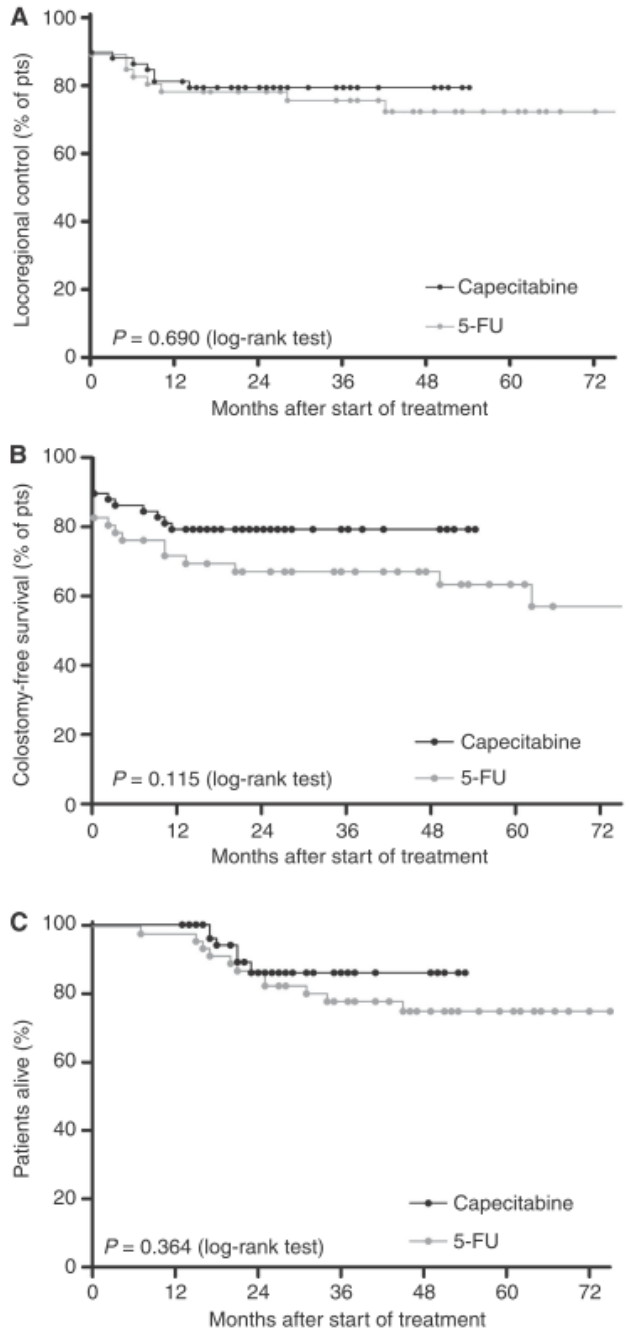
Any Grade 3-4 Toxicity	71%	vs 72%
Hematological Grade 3-4	26%	vs 16%



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
Thind, Radiation Oncology, 2014,9:214

Metastatic Disease

Risk Factors for Residual/Recurrent Disease:

T > 4cm, N+

Stats

Approximately 5-20% of cases

Metastatic Disease

Liver > Lung > Extra Pelvic Nodes

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

Metastatic Disease

Bull Cancer. 1999;86(10):861.
Rao et al. JCO 2020.
Rao et al. Lancet 2025.

Historic: 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

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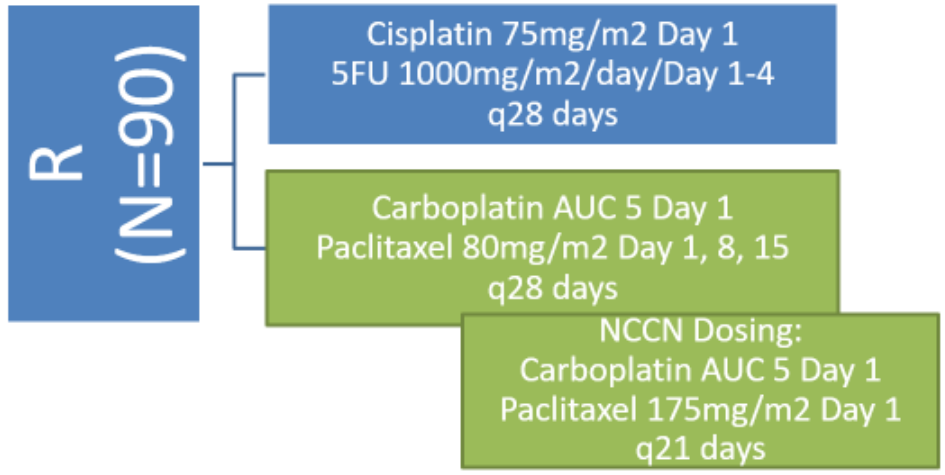
5FU/Cis vs Carboplatin/Paclitaxel

Primary: RR, Secondary: PFS, OS, Correlatives, QOL

	RR	PFS	OS
5FU Cisplatin	57%	5.7	12.3
Carboplatin Paclitaxel	59%	8.1	20



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

Metastatic Disease

Bull Cancer. 1999;86(10):861.
Rao et al. JCO 2020.
Rao et al. Lancet 2025.

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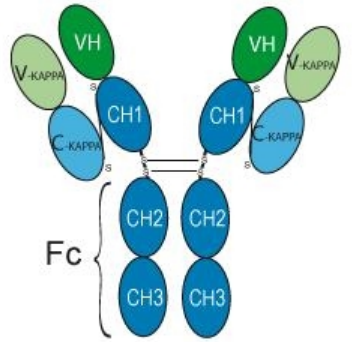
Anti-PD1



Carboplatin/Paclitaxel ± Retifanlimab

Primary: PFS, Secondary: ORR, OS, DCR, Safety

	RR	PFS	OS	HR
Carboplatin Paclitaxel	44%	7.4	23.0	0.63
Carbo/Taxol + Retifanlimab	56%	9.3	29.2	0.70

Retifanlimab 500mg Day 1
Carboplatin AUC 5 Day 1
Paclitaxel 80mg/m^2 Day 1, 8, 15

CP x 24 weeks, R x 52 weeks

Metastatic Disease

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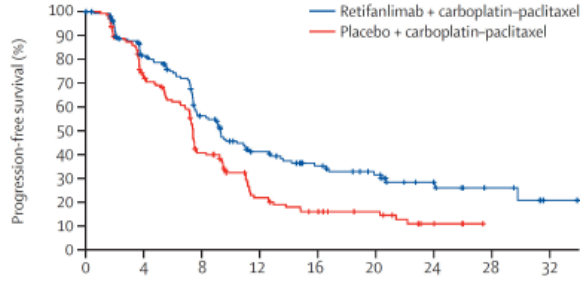
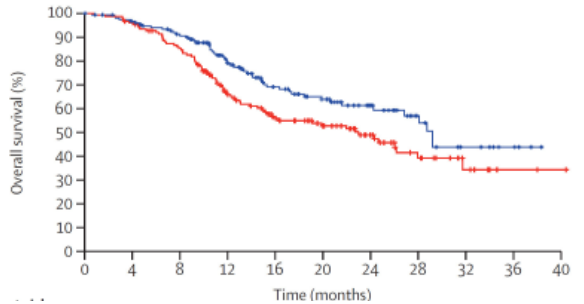
A

	Retifanlimab + carboplatin–paclitaxel	Placebo + carboplatin–paclitaxel
Number of events	92 (60%)	110 (71%)
Number of censored events	62 (40%)	44 (29%)
Median PFS	9·3 months (95% CI 7·5–11·3)	7·4 months (95% CI 7·1–7·7)
Hazard ratio (95% CI)	0·63 (0·47–0·84)	
Median follow-up	7·6 months (range 0·0–33·9)	7·1 months (range 0·0–27·4)

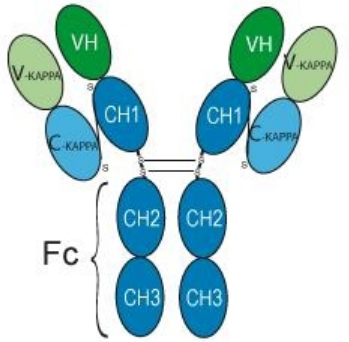


B

	Retifanlimab + carboplatin–paclitaxel	Placebo + carboplatin–paclitaxel
Number of events	53 (34%)	73 (47%)
Number of censored events	101 (66%)	81 (53%)
Median overall survival	29·2 months (95% CI 24·2–NE)	23·0 months (95% CI 15·1–27·9)
Hazard ratio (95% CI)	0·70 (0·49–1·01)	
Median follow-up	14·8 months (range 0·6–38·3)	12·9 months (range 0·0–40·4)



Anti-PD1



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Anal Cancer: Metastatic Disease

First Line Therapy +/- RT

Carboplatin + Paclitaxel + Retifanlimab

Carboplatin + Paclitaxel

5FU + Cisplatin (more toxic)

FOLFOX6 (NCCN case report, adeno)

FOLFCIS

mDCF (NCCN 2b)

Second Line Therapy

Nivolumab or Pembrolizumab (likely not if retifanlimab in first line)

NCCN 2023, Modified

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Second Line Therapy

Nivolumab or Pembrolizumab (likely not if retifanlimab in first line)

NCCN 2023, Modified

Nivolumab

Phase II (n=37)

RECIST Response

9 patients (24%)

2 CR, 7PR

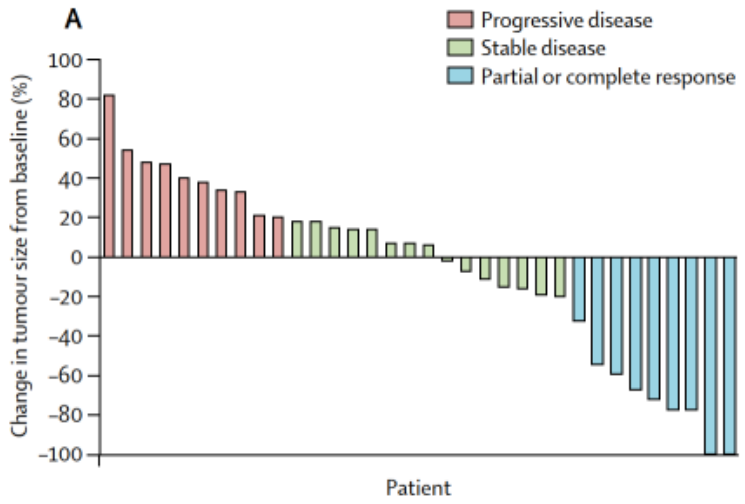
Pembrolizumab

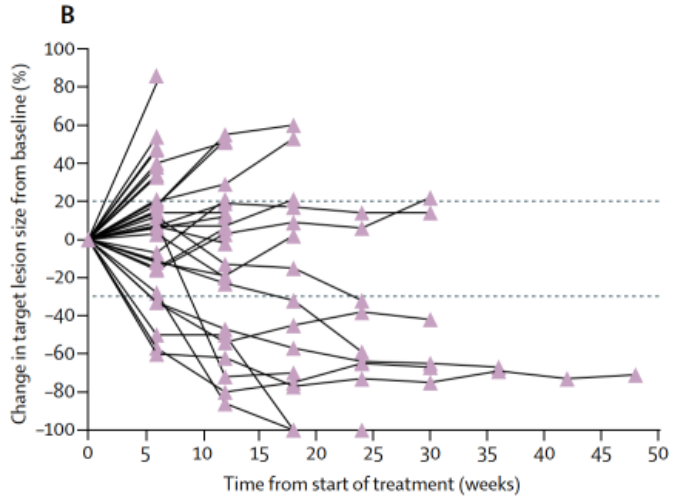
Ib (n=25)

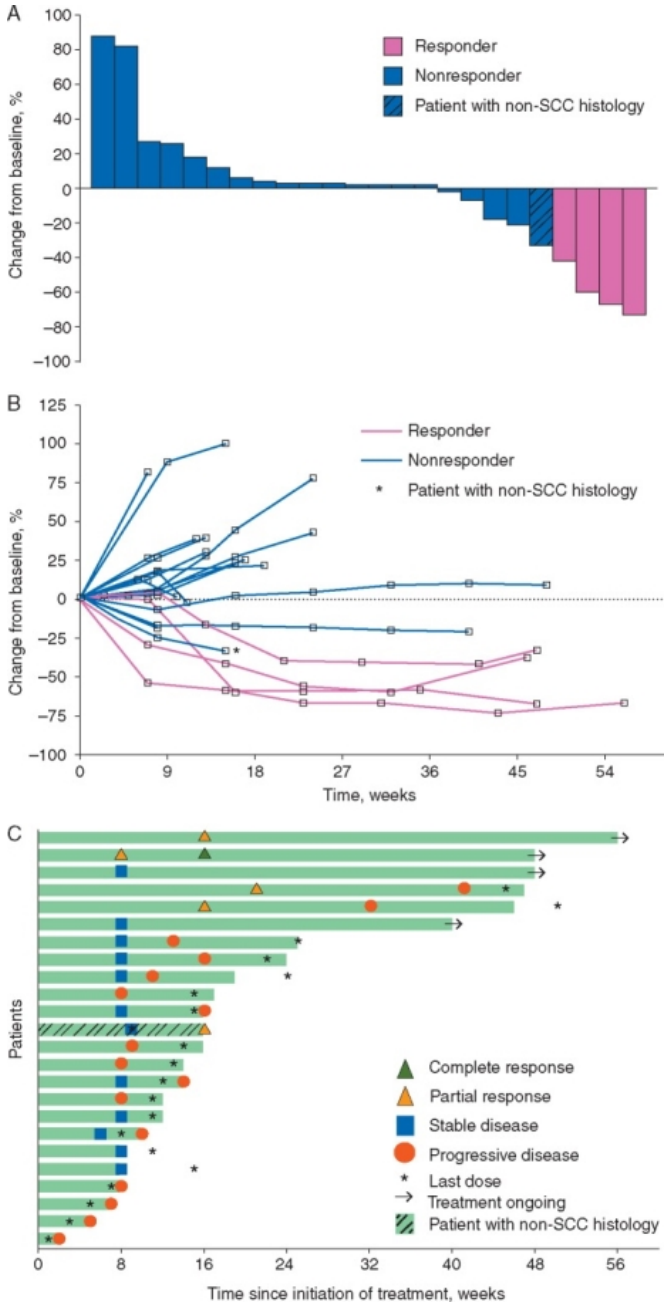
Safety and Response

4 patients (17%)

4 PR

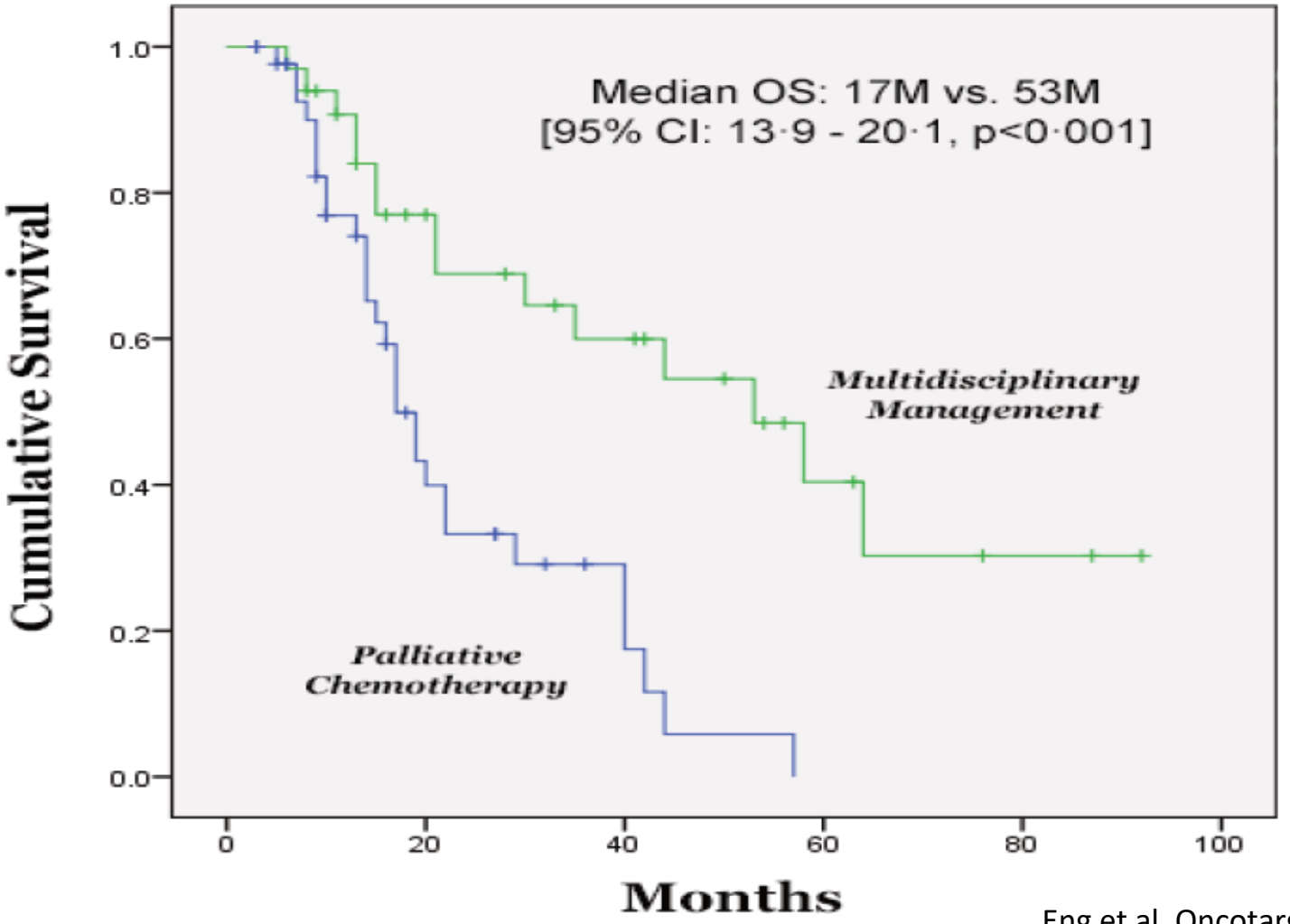






Lancet Oncol 2017; 18: 446–53 | Ann Oncol 2017;28:1036-1041.

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

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 + Retifanlimab