Updates in the Treatment of Anal Cancer

Jennifer Leinicke, MD, MPHS, FACS, FASCRS
Associate Professor of Surgery
Division of Colon and Rectal Surgery

University of Nebraska Medical Center

Disclosures

- I have no financial disclosures

Objectives

- Anal cancer prevention
- Treatment
  - Local excision
  - Chemoradiation
  - HIV
- Functional outcomes after chemoradiation
- Salvage surgery for treatment failure/recurrence

Anal cancer prevention

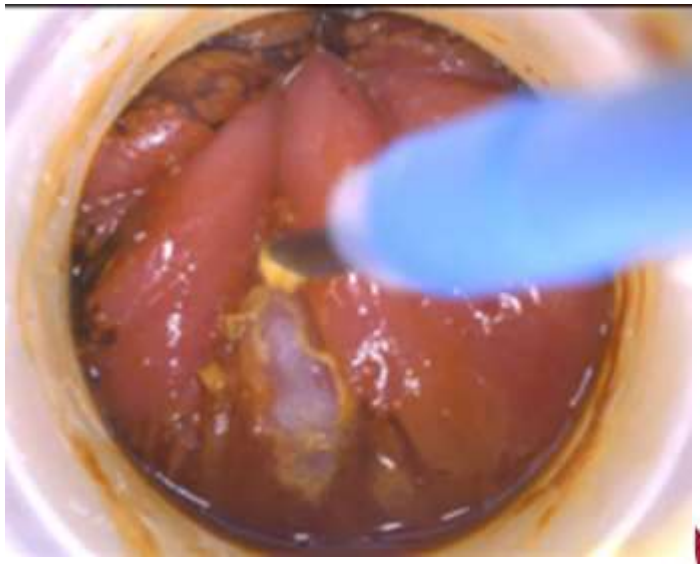
University of Nebraska Medical Center

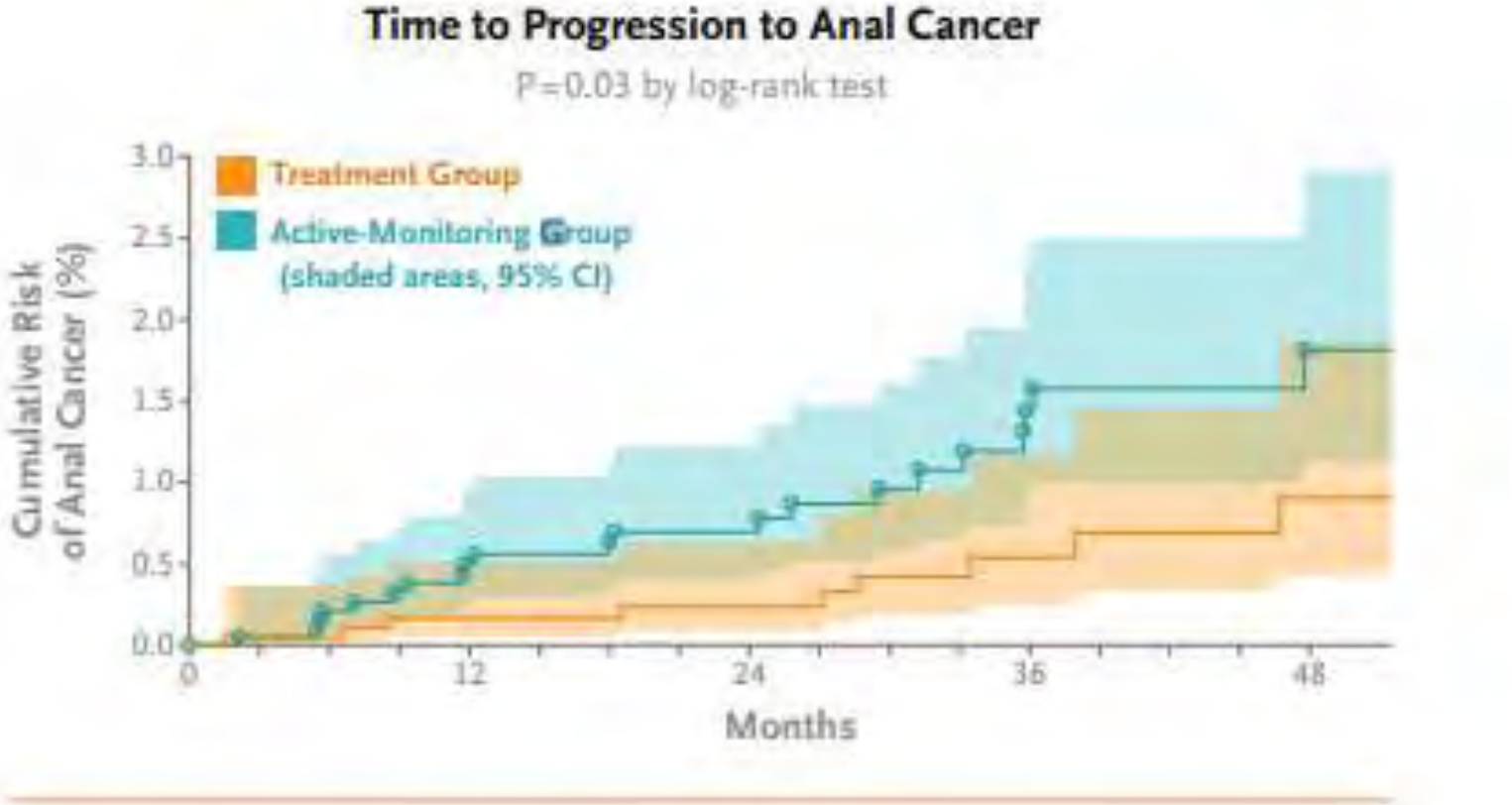
Treatment of Anal High-Grade Squamous Intraepithelial Lesions to Prevent Anal Cancer

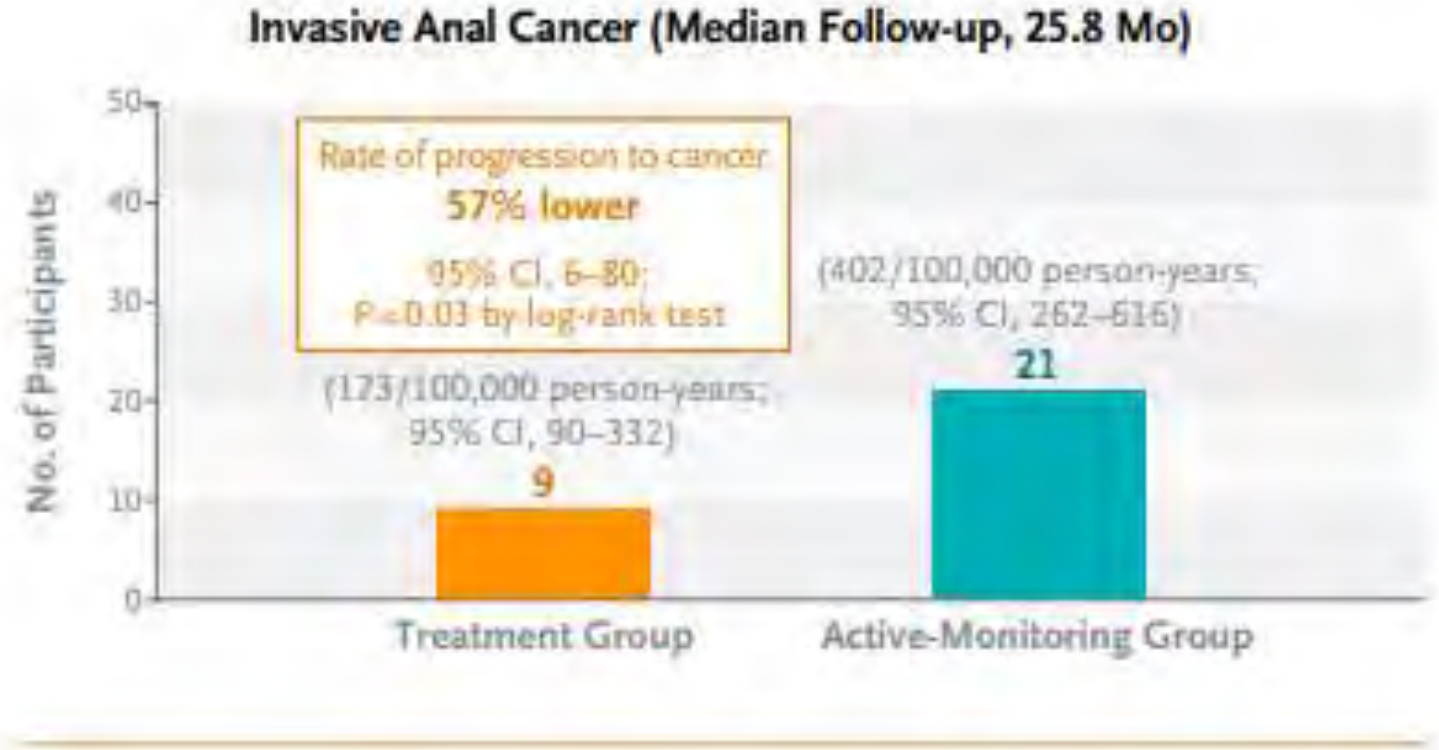
Authors: Joel M. Palefsky, M.D., C.M., Jeannette Y. Lee, Ph.D., Naomi Jay, R.N., Ph.D., Stephen E. Goldstone, M.D., Teresa M. Darragh, M.D., Hillary A. Dunlevy, M.D., Isabella Rosa-Cunha, M.D., +26, for the ANCHOR Investigators Group* Author Info & Affiliations

Published June 15, 2022 | N Engl J Med 2022;386:2273-2282 | DOI: 10.1056/NEJMoa2201048 | VOL. 386 NO. 24

What is high resolution anoscopy?



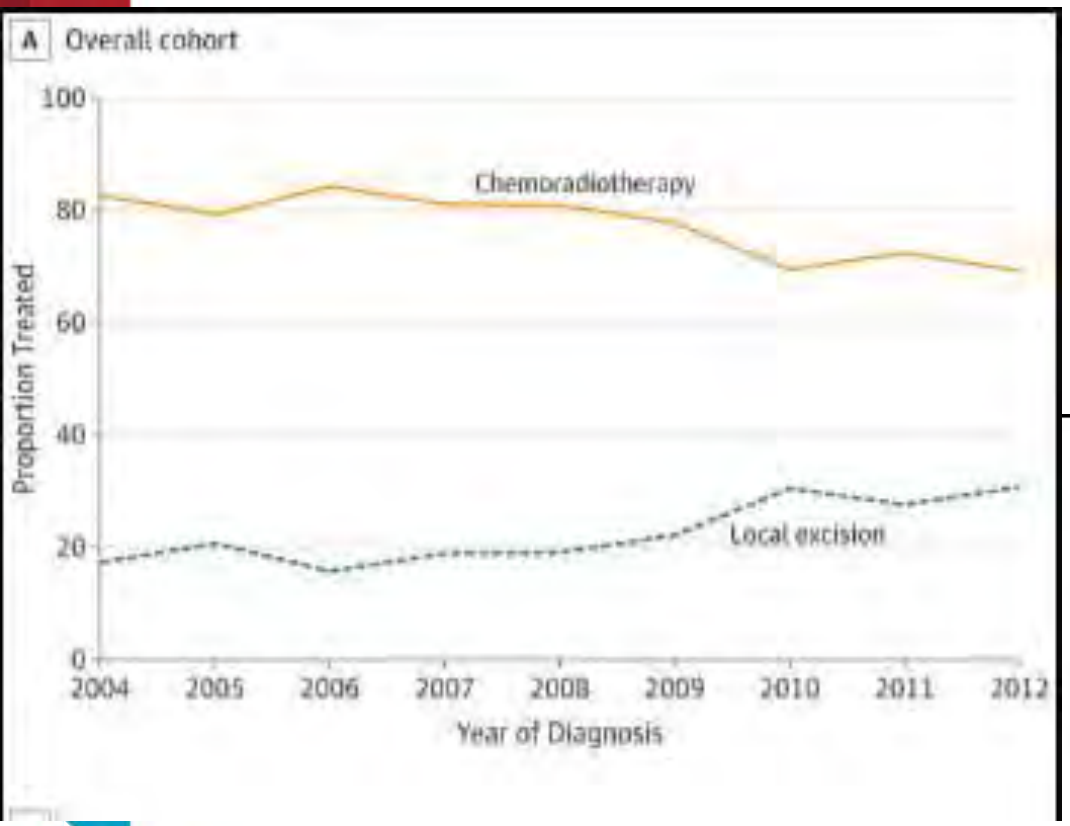

Time to Progression to Anal Cancer
P=0.03 by log-rank test
Treatment Group
Active-Monitoring Group
(shaded areas, 95% CI)
Cumulative Risk of Anal Cancer (%)
3.0
2.5
2.0
1.5
1.0
0.5
0.0
0
12
24
36
48
Months

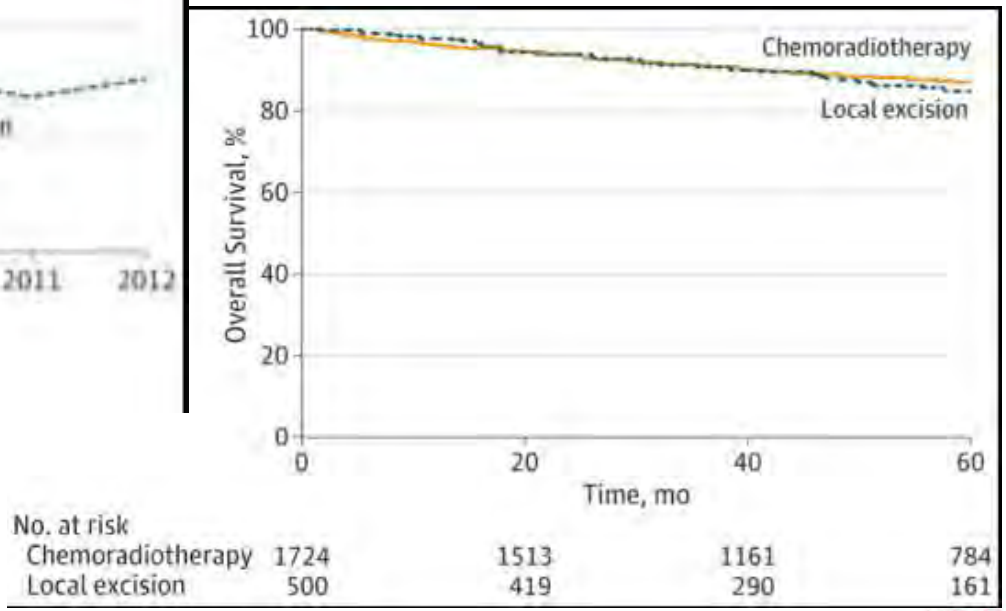

Invasive Anal Cancer (Median Follow-up, 25.8 Mo)
No. of Participants
50
40
30
20
10
0
Rate of progression to cancer
57% lower
95% CI, 6–80;
P=0.03 by log-rank test
(173/100,000 person-years;
95% CI, 90–332)
9
(402/100,000 person-years;
95% CI, 262–616)
21
Treatment Group
Active-Monitoring Group

Local excision

Comparative Study > JAMA Surg. 2018 Mar 1;153(3):209-215. doi: 10.1001/jamasurg.2017.3151.

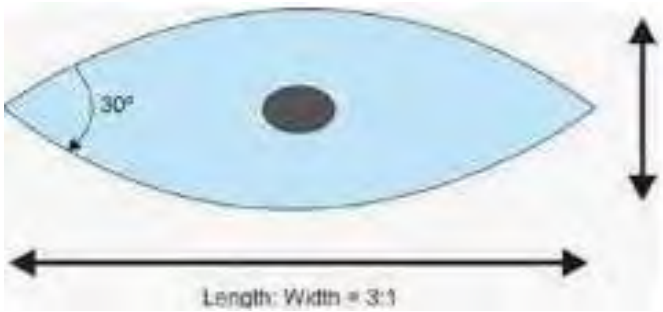
Management of Stage I Squamous Cell Carcinoma of the Anal Canal





NCCN guidelines: local excision for T1 tumors

- Appropriate for superficially invasive SCC
  - Completely excised lesion
  - < 3 mm basement membrane invasion
  - Maximal horizontal spread of 7 mm.



- Post treatment surveillance is important!

- Chemoradiotherapy for recurrence

Chemoradiotherapy

Nigro Protocol

- Originally published 1974
- 5FU+mitomycin+radiation

Norman D. Nigro

Cisplatin vs mitomycin C

- Early uncontrolled studies were promising

April 23 2008

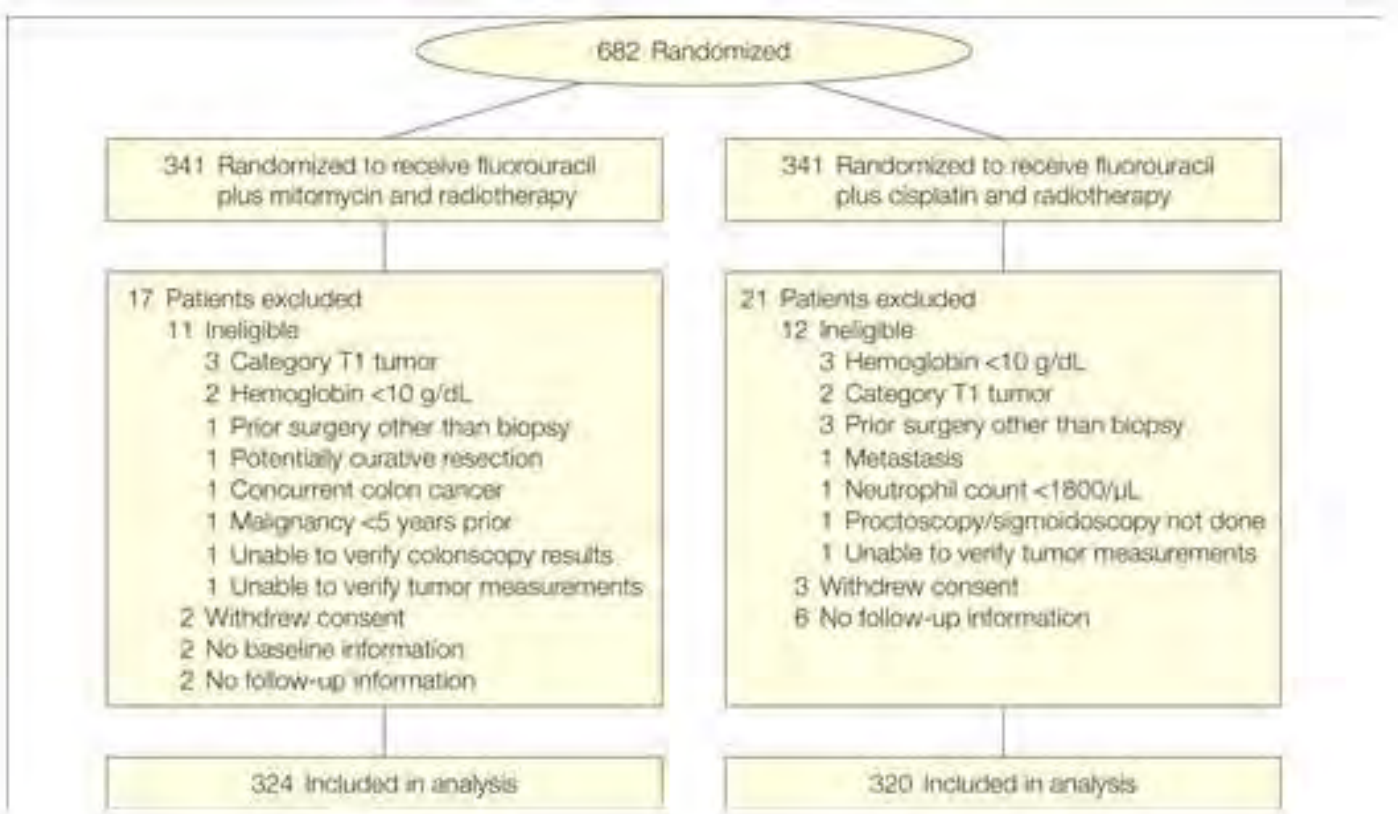
Fluorouracil, Mitomycin, and Radiotherapy vs Fluorouracil, Cisplatin, and Radiotherapy for Carcinoma of the Anal Canal

A Randomized Controlled Trial

Jaffer A. Ajani, MD; Kathryn A. Winter, MS; Leonard L. Gunderson, MD; et al

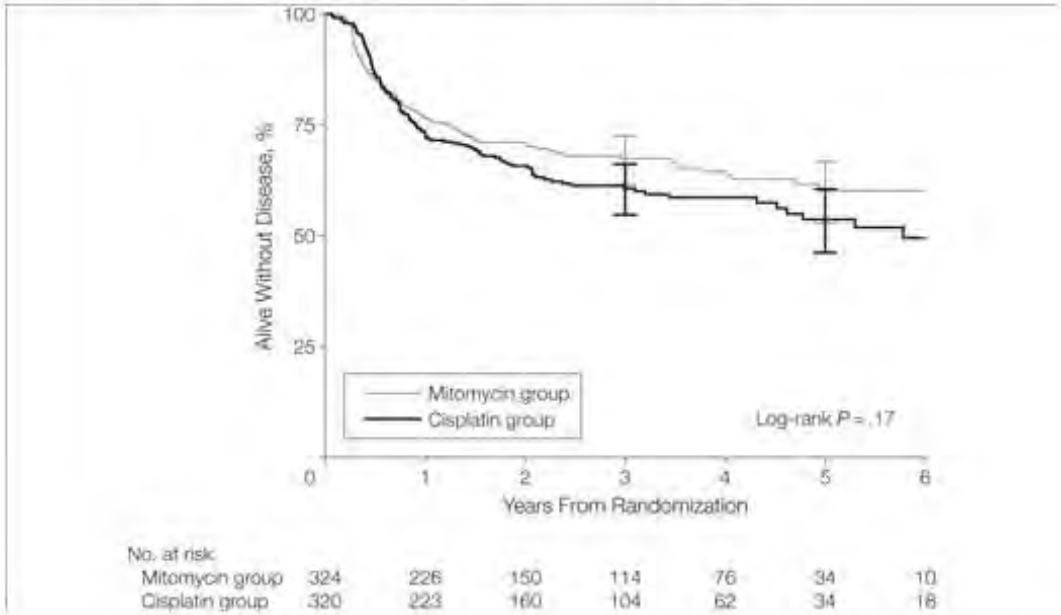
» Author Affiliations | Article Information

JAMA. 2008;299(16):1914-1921. doi:10.1001/jama.299.16.1914



No improvement in DFS with cisplatin

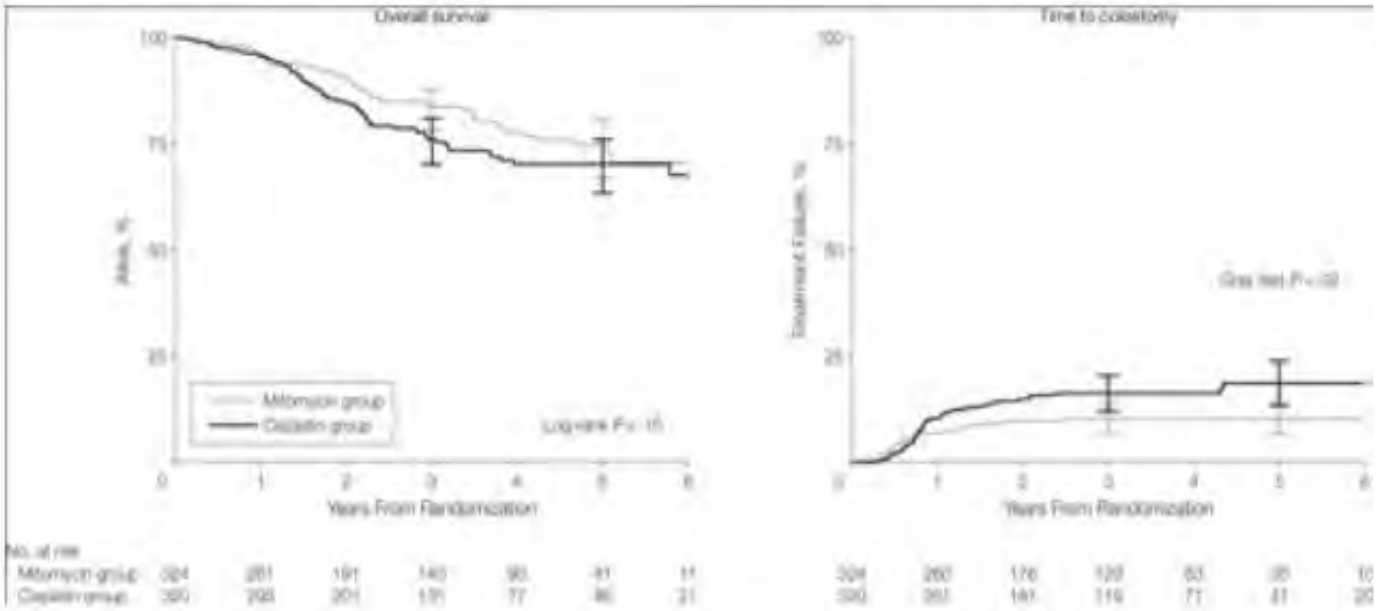
Figure 2. Disease-Free Survival in the Mitomycin- and Cisplatin-Based Groups



Incidence of treatment failure was 105 of 324 with mitomycin-based treatment and 127 of 320 with cisplatin-based treatment. Error bars indicate 95% confidence intervals.

Significantly worse colostomy rate with cisplatin

Figure 3. Overall Survival and Cumulative Incidence of Colostomy in the Mitomycin- and Cisplatin-Based Groups

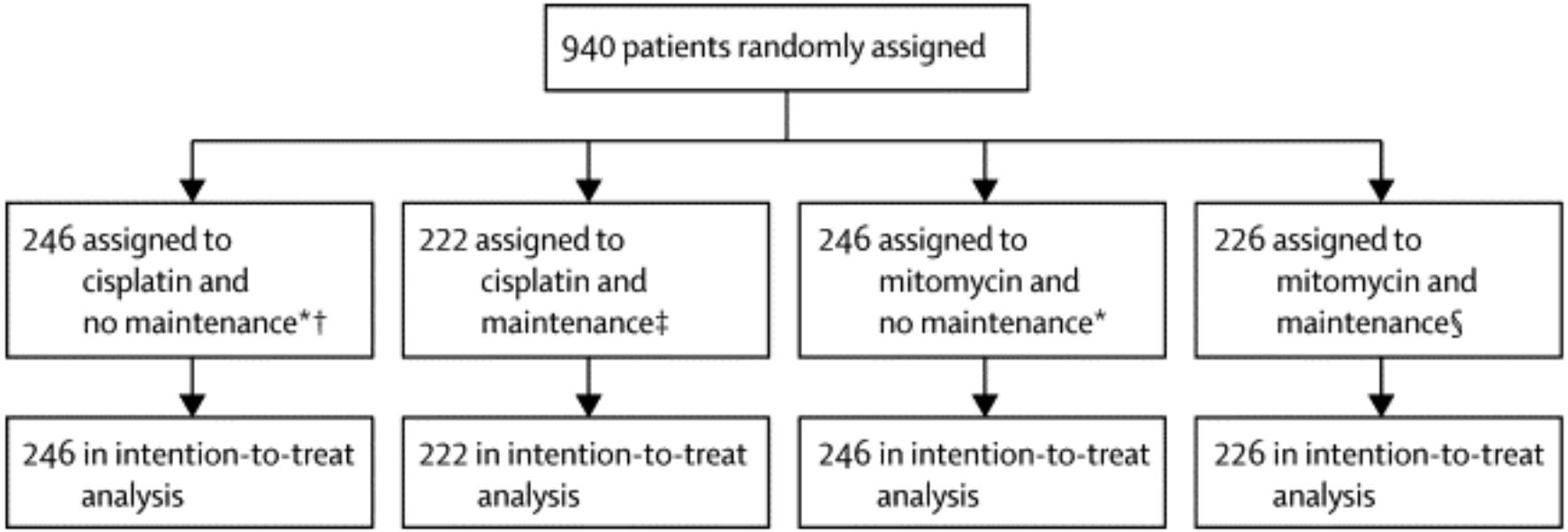


Mortality rates were 53 of 324 with mitomycin-based treatment and 72 of 320 with cisplatin-based treatment. Error bars indicate 95% confidence intervals. Incidence of treatment failure (persistent tumor, relapsed tumor, or colostomy) was 30 of 324 with mitomycin-based treatment and 50 of 320 with cisplatin-based treatment.

ARTICLES · Volume 14, Issue 6, P516-524, May 2013 · *Open Access*

Mitomycin or cisplatin chemoradiation with or without maintenance chemotherapy for treatment of squamous-cell carcinoma of the anus (ACT II): a randomised, phase 3, open-label, 2×2 factorial trial

Prof Roger D James, FRCP [a,†] · Dr Robert Glynne-Jones, FRCR [b,†] · Helen M Meadows, MSc [c] · Prof David Cunningham, MD [d] · Arthur Sun Myint, FRCR [e] · Mark P Saunders, FRCR [f] · et al. Show more



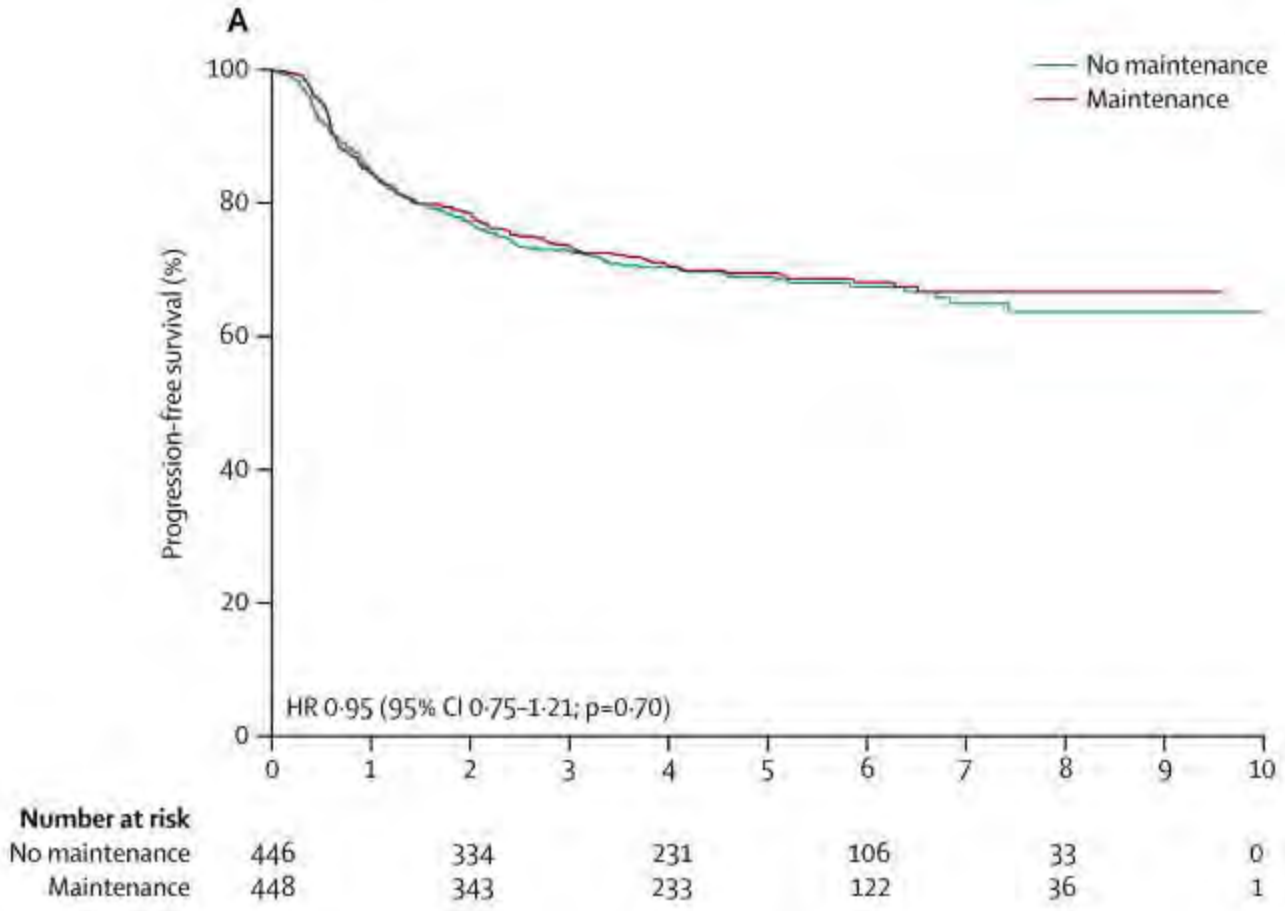
No difference in primary tumor response

	Mitomycin group (n=432)	Cisplatin group (n=431)
Complete response	391 (90·5%)	386 (89·6%)
Partial response	14 (3·2%)	24 (5·6%)
Stable disease	5 (1·2%)	6 (1·4%)
Progressive disease	22 (5·1%)	15 (3·5%)

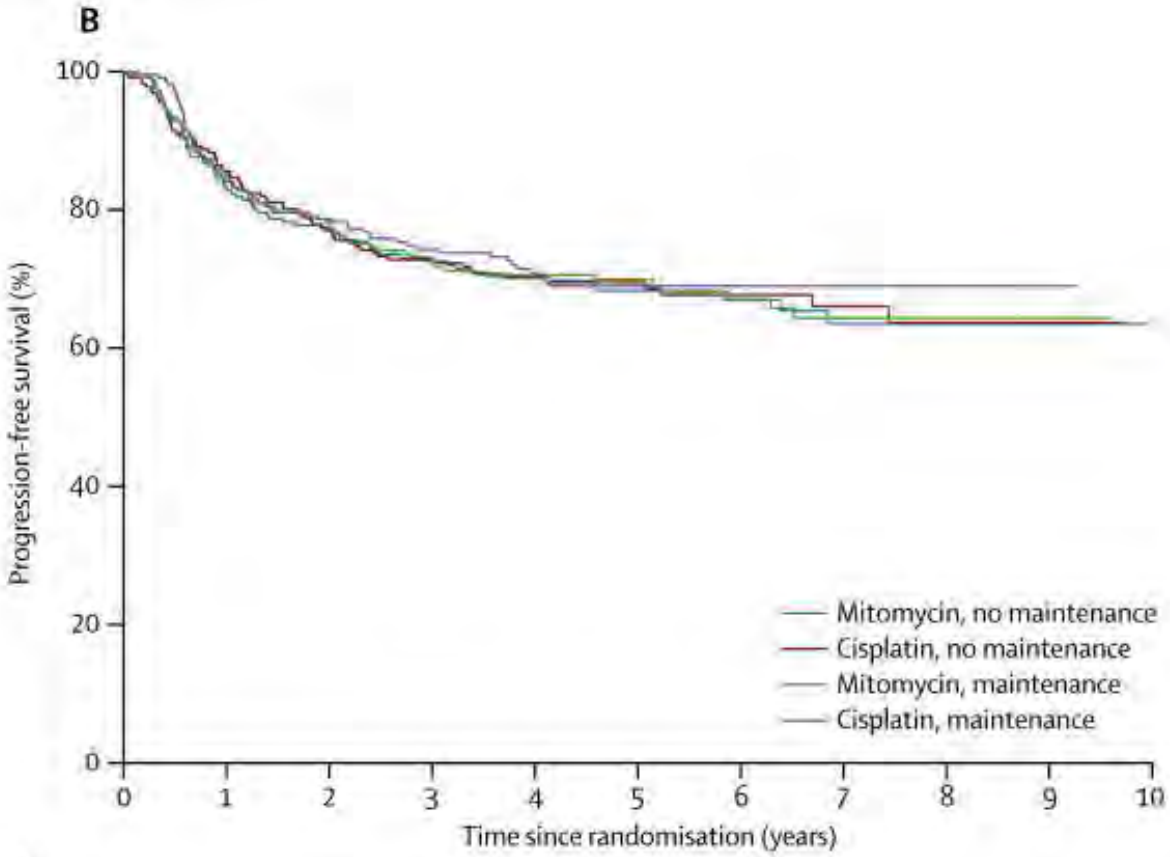
Table 2

Primary tumour response at 26 weeks

Maintenance did not improve PFS



Maintenance did not improve PFS



Number at risk						
Mitomycin, no maintenance	223	266	117	48	15	0
Cisplatin, no maintenance	223	268	114	58	18	0
Mitomycin, maintenance	226	273	119	59	20	0
Cisplatin, maintenance	222	170	114	64	16	1

5FU + Mitomycin remains standard of care for chemotherapy

- NCCN guidelines:

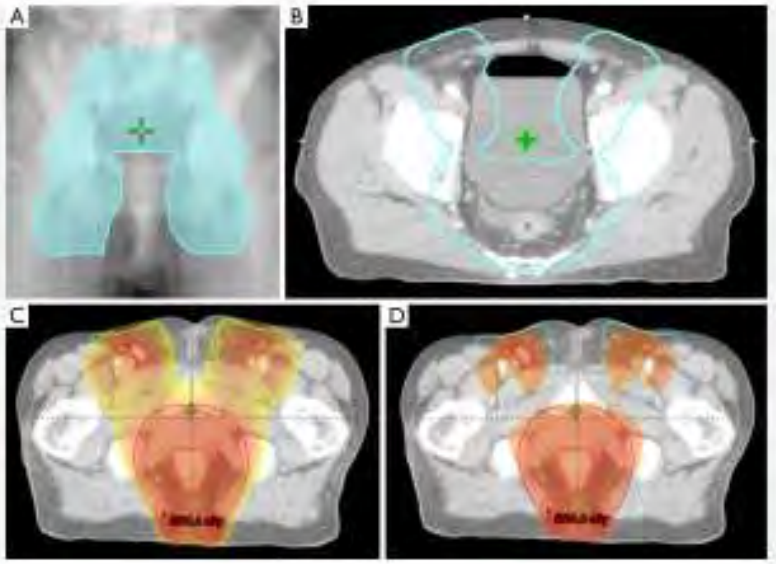
  Infusional 5FU 1000 mg/m^2 on days 1 to 4 and 29 to 32

  PLUS

  Mitomycin 10 mg/m^2 on days 1 and 29, maximum 20 mg per dose

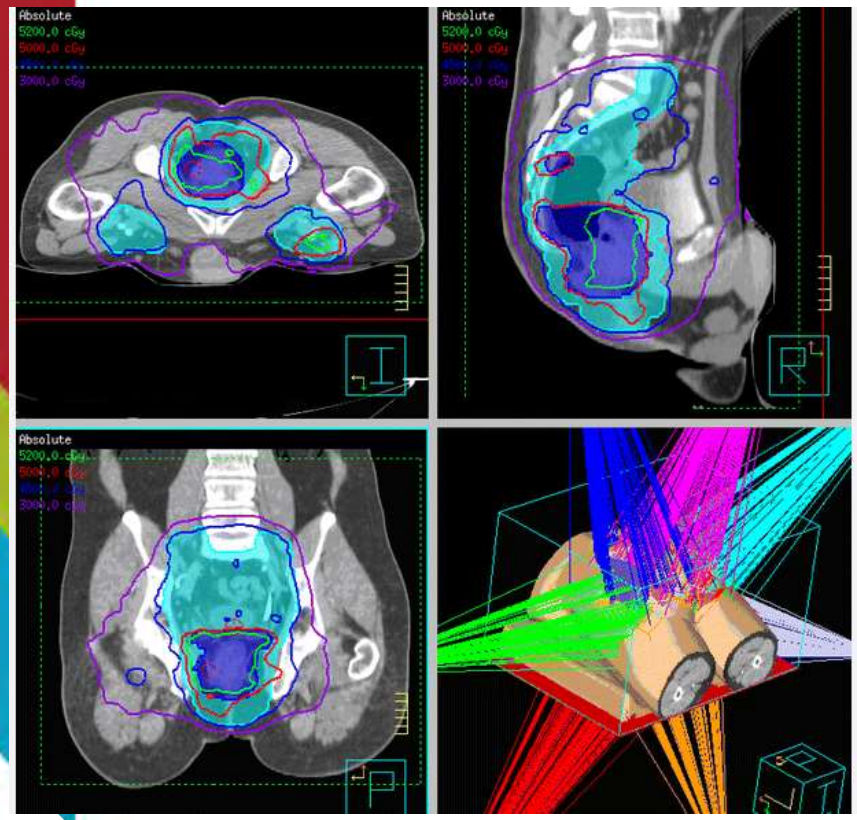
Radiation fields and dosage

- Pelvis from S1-S2
- Inguinal lymph nodes
- Anus



- Minimum dose recommended by NCCN
  - 45 Gy
- Balance long term toxicity vs disease response and survival

IMRT is preferred to 3D-CRT



- 3D RT planning
- Variable, computer-controlled intensities of each beam

People living with HIV (PLWH)

University of Nebraska Medical Center

Anal SCC in PLWH is treated similarly to non-HIV+ individuals

- Screen for HIV on diagnosis of anal SCC

- Response to therapy, local control, and survival are as good in PLWH on ART as non-HIV infected patients

- Patients with active HIV/AIDS may require treatment modification.

Functional outcomes after chemoradiation

AKA

Late Treatment Toxicities of Pelvic Radiation

University of Nebraska Medical Center

Colostomy-free Survival

- 65-86% at 5 years

Pelvic Radiation has long term consequences!

- Bowel, bladder, and sexual dysfunction
- Chronic pain
- Osteoporosis

Fecal incontinence

- 43% have FI
- 64% have fecal urgency

Vaginal stenosis (VS) is a big problem!

- Dysparunia
- Pain with dilator use
- Vaginal dryness
- Difficult pelvic exam

- 79% had VS

- Proactive treatment:
  - Early/ongoing dilator use
  - Moisturizers/lubricants
  - Topical estrogen (unless contraindicated)

Salvage Surgery

University of Nebraska Medical Center

Treatment Failure

- Clinically persistent disease after initial 8-12 week post-treatment evaluation can be watched for up to 6 months

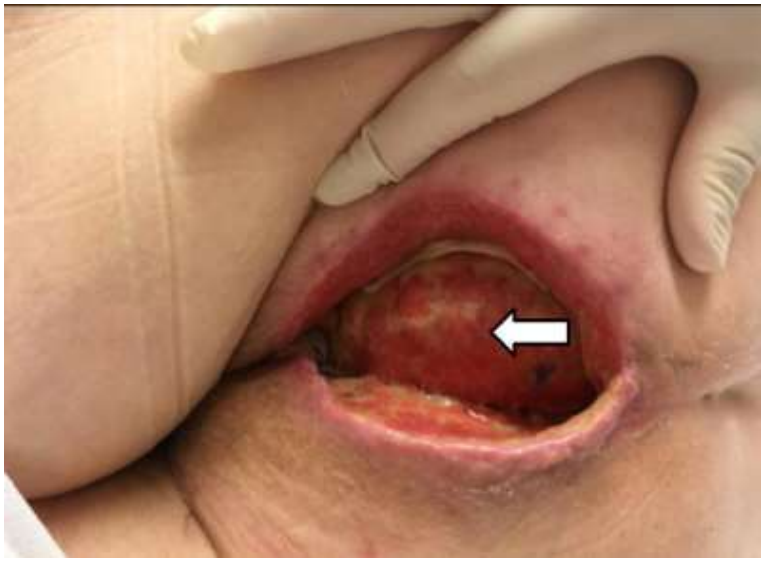
- Treatment Failure:
  - Progression
  - Persistent disease at 6 months

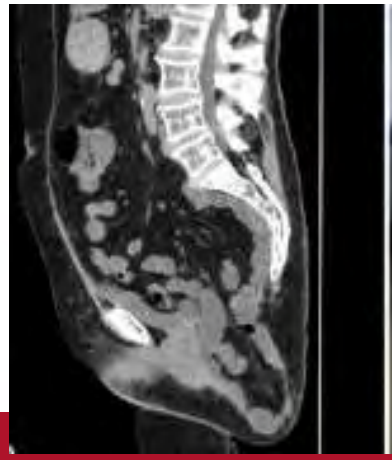
- **Biopsy**

- Surgical salvage: APR with tissue flap reconstruction

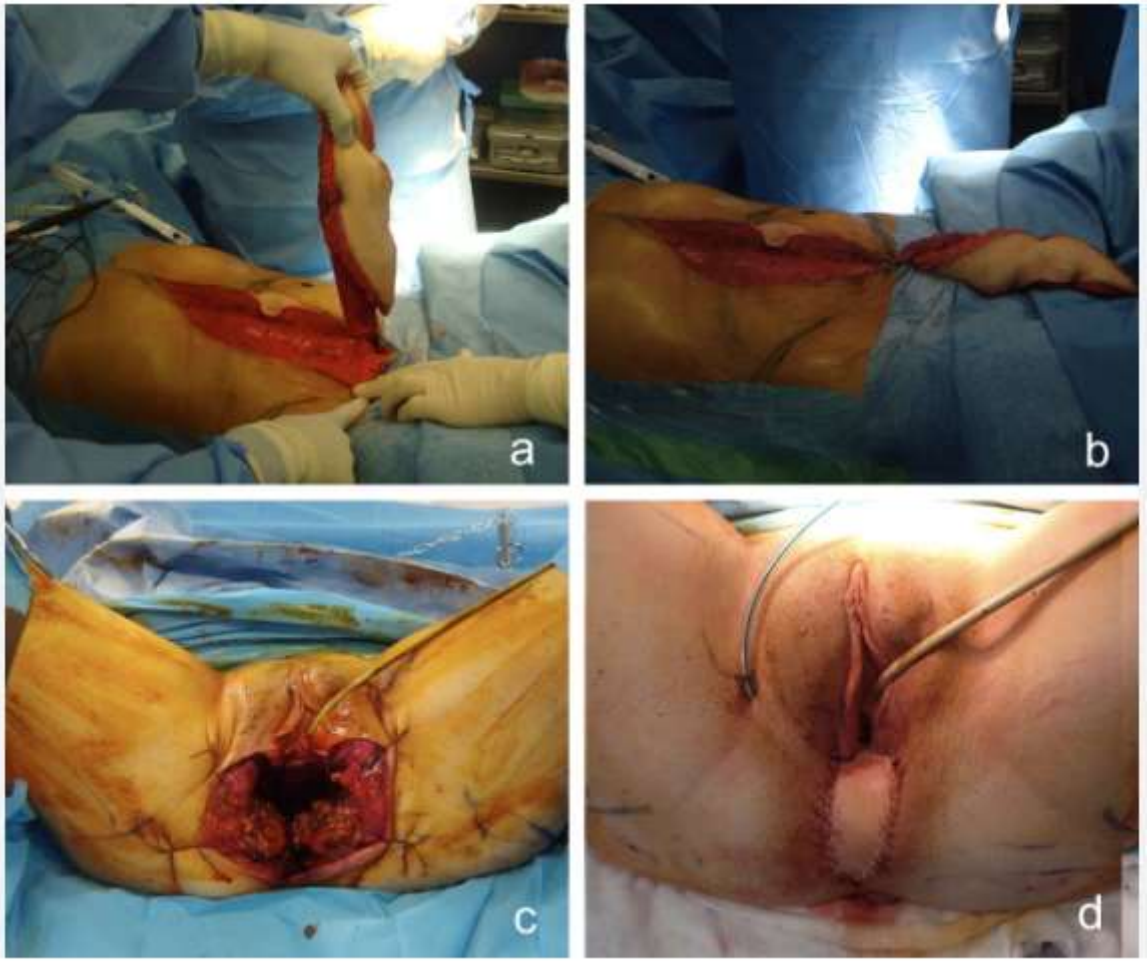
APR has a HIGH risk of perineal wound complications

- 50-80% risk of wound complications





VRAM flap reconstruction



Gracilis flap reconstruction

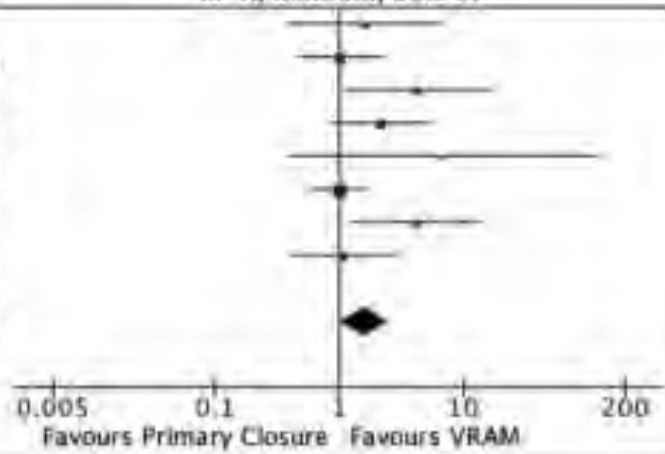
Review > Ir J Med Sci. 2024 Aug;193(4):1721-1728. doi: 10.1007/s11845-024-03651-3. Epub 2024 Mar 27.

Primary closure versus vertical rectus abdominis myocutaneous (VRAM) flap closure of perineal wound following abdominoperineal resection–a systematic review and meta-analysis

Hugo C Temperley [1] [2], Poorya Shokuhi [3], Niall J O'Sullivan [3], Benjamin Mac Curtain [4],

Study or Subgroup	Primary Closure Events	Total	VRAM Events	Total	Weight	Odds Ratio M-H, Random, 95% CI
Althumairi 2016	21	56	3	11	7.7%	1.60 [0.38, 6.71]
Butler 2008	35	76	16	35	17.4%	1.01 [0.45, 2.26]
Chessin 2005	26	59	3	19	8.6%	4.20 [1.10, 15.98]
Lefevre 2009	19	43	11	41	14.8%	2.16 [0.86, 5.40]
Sheckter 2016	33	127	0	9	2.2%	6.74 [0.38, 118.91]
Spasojevic 2018	94	260	25	69	25.2%	1.00 [0.57, 1.73]
Touny 2014	14	30	5	29	10.1%	4.20 [1.26, 13.96]
Woodfield 2017	21	37	17	31	13.9%	1.08 [0.41, 2.83]
Total (95% CI)		**688**		**244**	**100.0%**	**1.61 [1.04, 2.49]**
Total events	263		80			

Heterogeneity: $Tau^2 = 0.12$; $Chi^2 = 10.25$, df = 7 (P = 0.17); $I^2 = 32\%$
Test for overall effect: Z = 2.11 (P = 0.03)



Summary

- Treatment of dysplasia in high-risk patients decreases risk of anal cancer
- 5FU+mitomycin C and concurrent radiation remains standard of care
  - High rates of cure
  - High rates of long-term local toxicity
- Perineal reconstruction with tissue flap should be strongly considered if salvage APR is necessary

University of Nebraska℠ Medical Center

BREAKTHROUGHS FOR LIFE.®