Anal Neoplasia: Screening and Prevention

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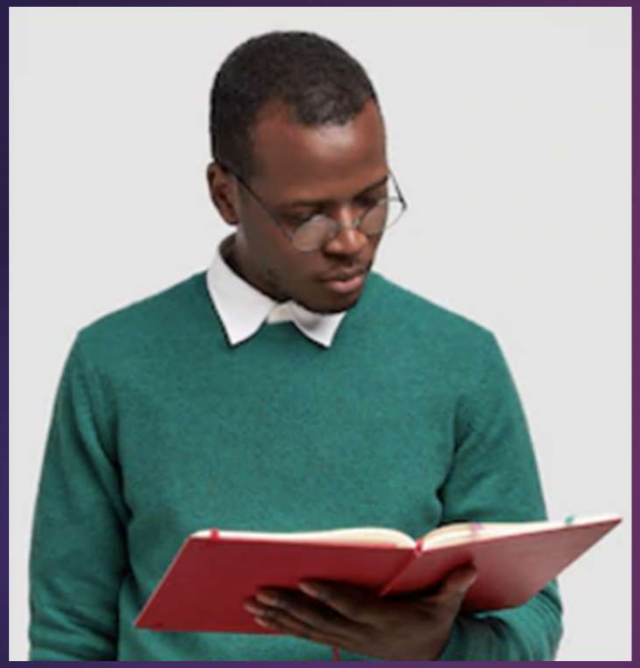
INFECTIOUS DISEASES

This is Tom, he is a 36 years old MSM (men-sleep-men) who is HIV positive, CD4 around 500 and viral load not detectable. He is excited and getting ready for his quarterly appointment with his HIV physician.



Yesterday, Tom was reading about a new study called ANCHOR, which screens patients, especially MSM, for pre-malignant anal lesions that could result in anal cancer. As part of the study, he has to do an anal pap.He knows his sister undergoes her cervical paps, but an anal pap? He has no idea what that meant, and he was not that excited to know either.

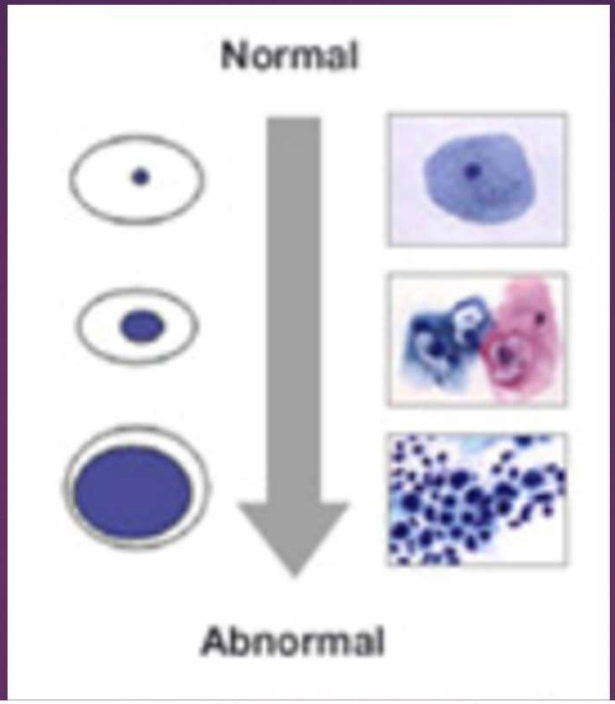
Screening- the Cervical Pap Smear

- Identify precancerous lesions
  - Early treatment of these lesions has been shown to prevent the development of cervical cancer.
- The routine use of cytology screening with the Papanicolau (Pap) smear test has lead to a significant decrease of mortality from cervical cancer in the U.S. In countries where screening for cervical cancer is not routinely done the incidence and mortality of cervical cancer is much greater.

What is a Pap Smear?

- The name "Pap smear" comes from Dr. Georgios Papanikolaou, who invented the test.
- A Pap smear removes a microscopic sample of cells from the cervix to test for cancer and precancer.
- ThinPrep Pap test: A modified Pap test technique that removes contaminants such as blood and mucus which frequently obscure cells in the traditional Pap smear.

Thin prep



Normal cells have small nuclei (centre of the cell), while abnormal cells have larger and darker nuclei (left). The ThinPrep Imager 'directs' the laboratory professional towards larger and darker cells, which are more likely to be abnormal (right).[2]

http://www.paptest.com.au/info/thinprep-pap-test/thinprep-imaging-system.cfm

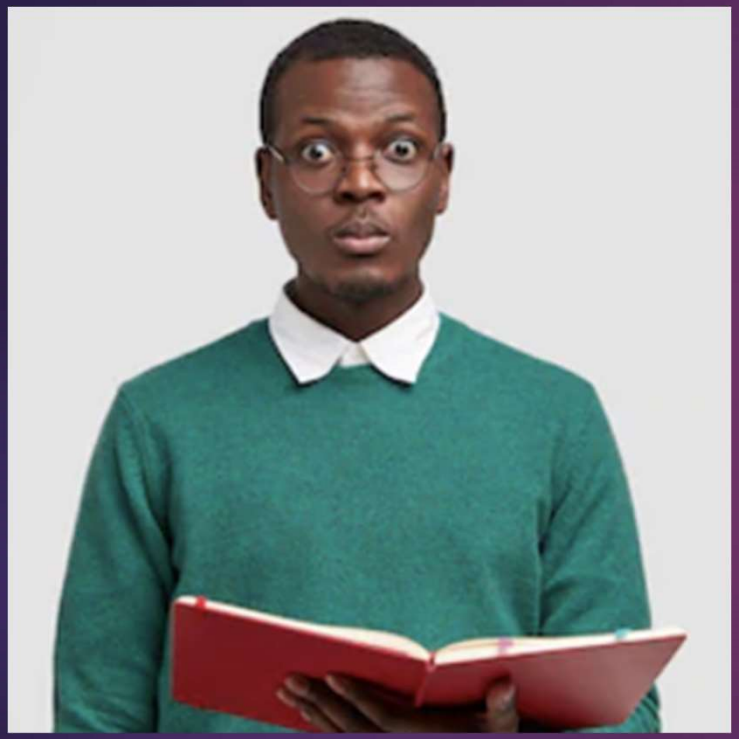
Screening

- Anal cancer and cervical cancer share many similar characteristics. Both anal cancer and cervical cancer develop from precursor lesions:
  - anal intraepithelial neoplasia (AIN)
  - and cervical intraepithelial neoplasia (CIN) respectively.

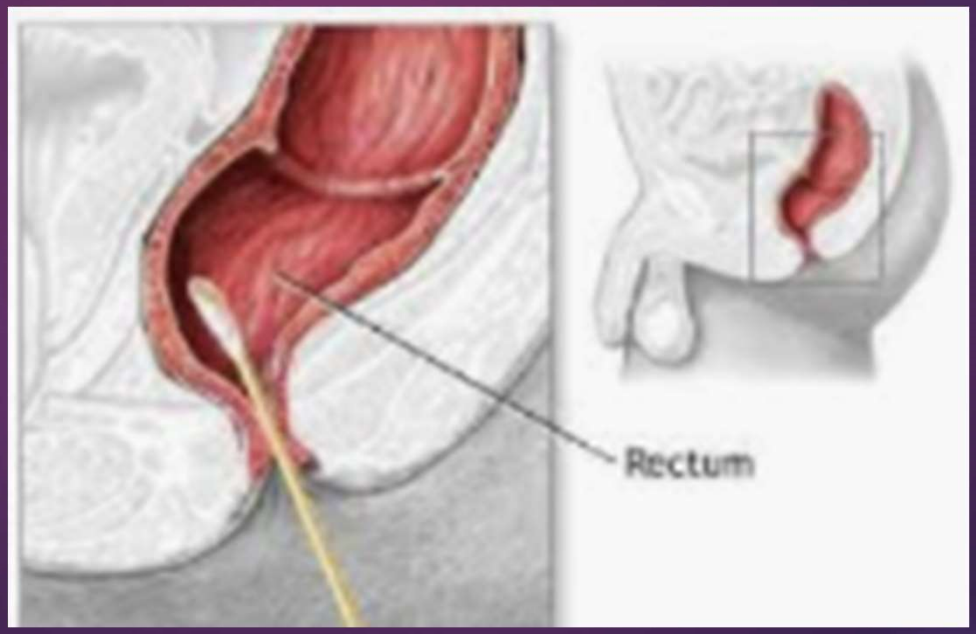
Screening- Anal Cancer

- Screening is performed using anal cytological exams, similar to those performed in cervical cancer screening programs, along with direct tissue evaluation and biopsy via high resolution anoscopy (HRA).
- Both Palefsky et al (1997) and Goldstone et al (2001) showed that over 70%-90% of HIV+ MSM had some abnormal cytology on anal pap.
- Because there is poor correlation between anal pap and HSIL biopsy, all lesions noted on HRA should be biopsied.

Both Palefsky et al (1997) and Goldstone et al (2001) showed that over 70%-90% of HIV+ MSM had some abnormal cytology on anal pap [17], [18].

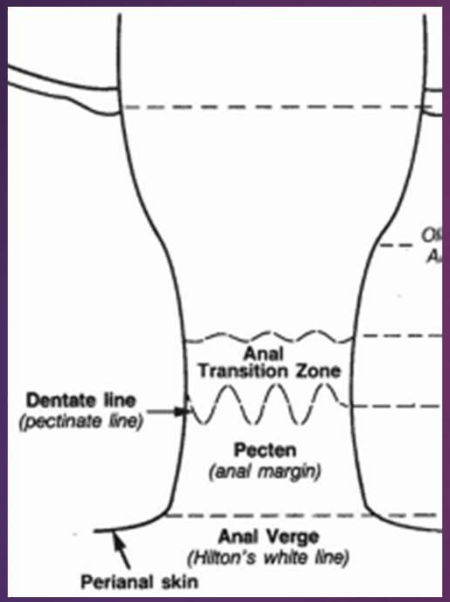


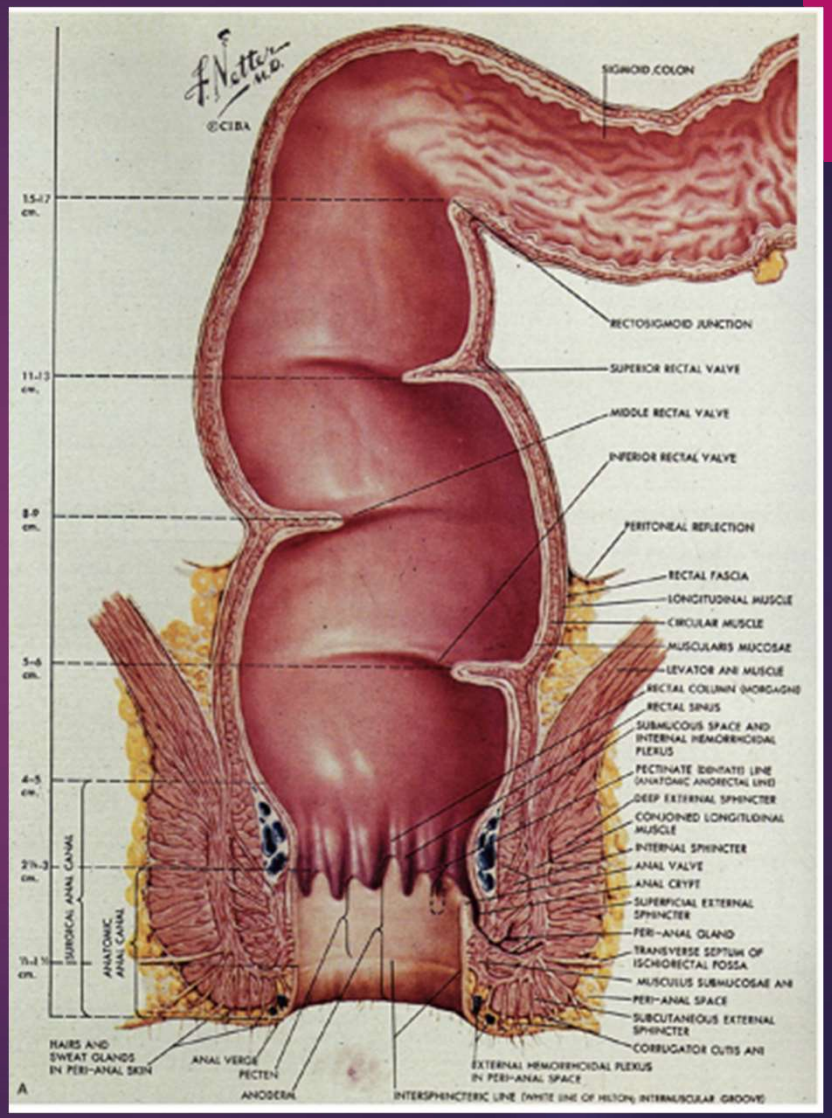
Tom kept reading and found out that he needs a stick up his bottom so the doctor can get samples of cells from his anal canal for microscopic evaluation.


Rectum

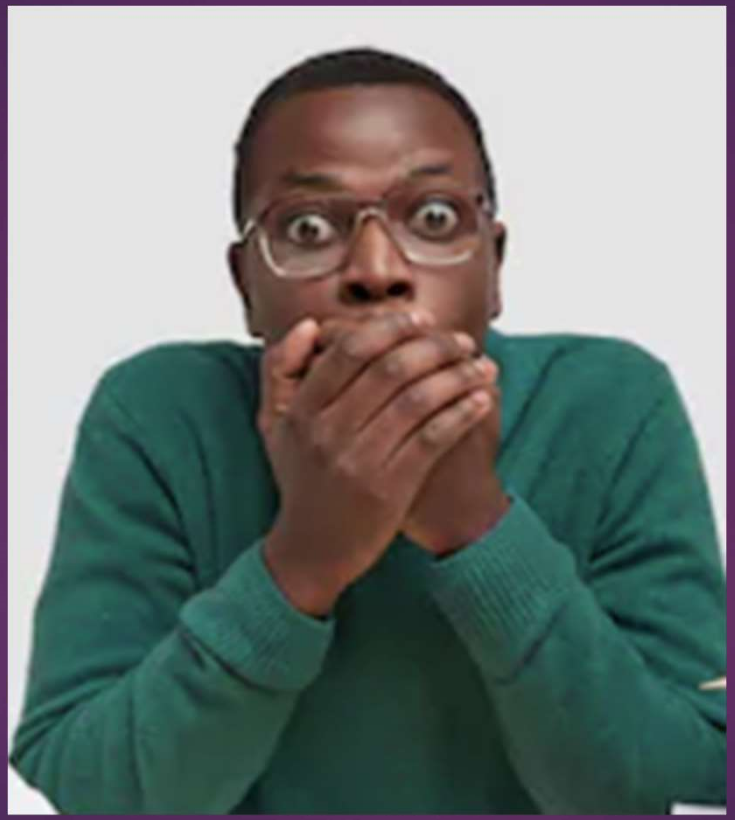
Anal Pap Sample

Anal Anatomy





https://basicmedicalkey.com/the-anal-canal/



Presenting symptoms
Itching – especially at night
Bleeding
Pain/soreness (e.g. on defecation, constant/intermittent, generalized/localized sharp/dull)
Lumps (e.g. warts)
Concerns of patients re symptoms (especially anxiety and embarrassment)
Past medical history, for example, Crohn's disease, atopy and HIV
Family history of skin disease, for example, psoriasis and atopic dermatitis
Drug history including topical medication
General habits including use of soaps, shower gel, baby wipes and deodorants

Perianal Complaints

White patches
Vitiligo
Lichen sclerosus
AIN (see premalignant conditions)
Lichen simplex

Red lesions
Dermatitis/eczema
Atopic
Contact
Irritant/chemical
Allergic
Seborrhoeic
Psoriasis
Infection – bacterial or fungal
Vascular tumours, e.g. hemangioma

Fissures of the skin
Crohn's (multiple, ± anal canal fissure)
Psoriasis
Dermatitis
Herpes simplex virus (HSV)
Itching – see Pruritus Ani Chap. 21

Anal Fissure

https://basicmedicalkey.com/the-anal-canal/

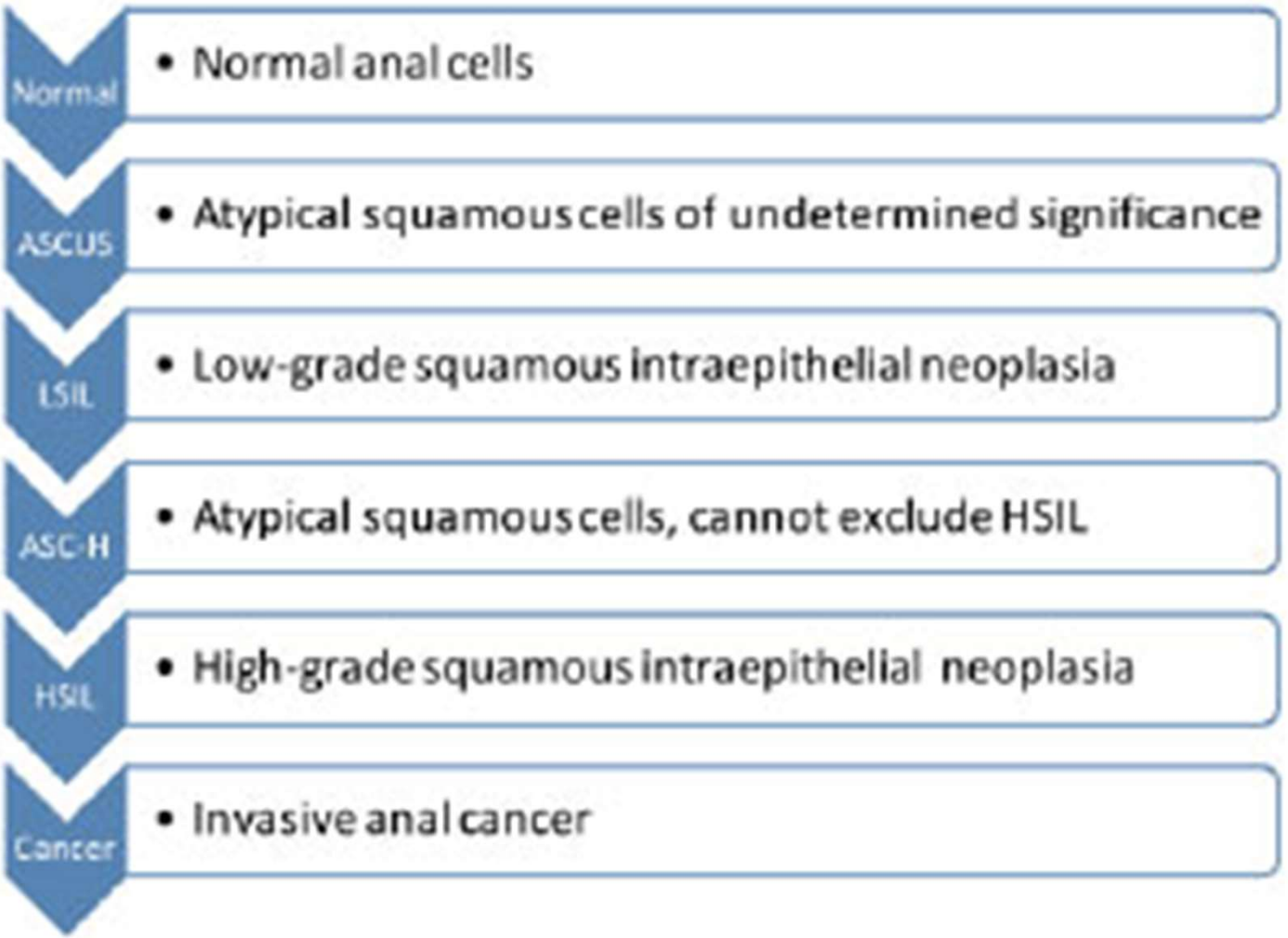
Ulcer
Herpes (HSV)
Syphilis
Lymphogranuloma venereum (LGV)
Human immunodeficiency virus (HIV)
Malignancy (see Malignant Disease)
Crohn's disease
Varicella zoster
Cytomegalovirus (CMV)
Nicorandil
Behçet's disease
Trauma/factitious
Deep mycoses
Chancroid
Donovanosis (granuloma inguinale)

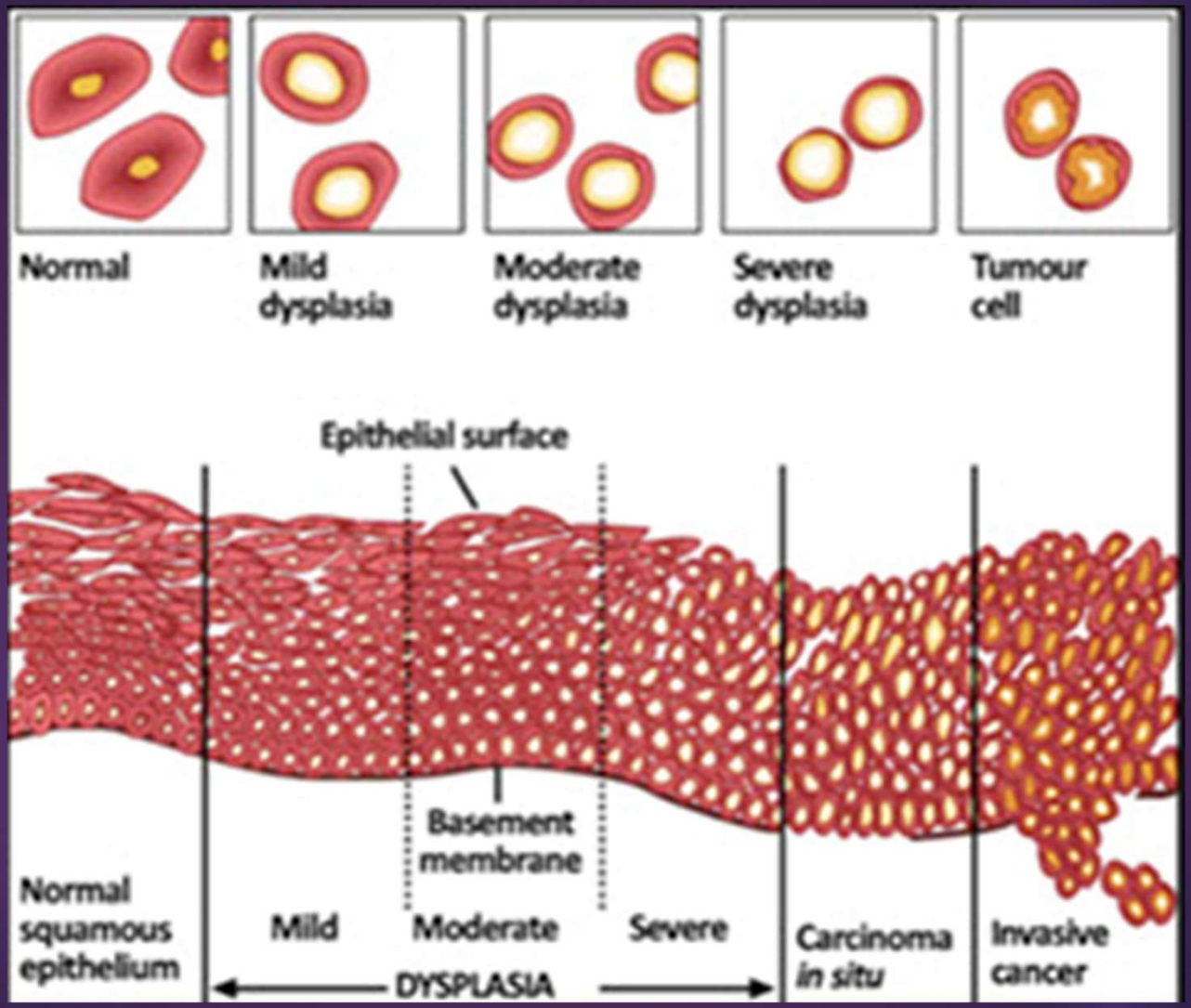
Perianal Complaints

https://basicmedicalkey.com/the-anal

Blistering disorders
Vesicles
Varicella including varicella-zoster virus
Herpes simplex
Stevens-Johnson syndrome
Bullae
Pemphigus vulgaris
Bullous drug eruption, e.g. fixed drug eruption
Lumps
Lipoma
Epidermoid cyst
Dermoid cyst/teratoma
Warts (condylomata acuminata)
Molluscum contagiosum
Condylomata lata
Seborrhoeic keratoses
AIN/bowenoid papulosis
Pseudofolliculitis (ingrowing hairs)
Prominent skin folds

Tom decides he wants an anal pap screening test for anal cancer. He gets his results back and hope his doctor won't order a High Resolution Anoscopy (HRA) for him.


Normal
• Normal anal cells
ASCUS
• Atypical squamous cells of undetermined significance
LSIL
• Low-grade squamous intraepithelial neoplasia
ASC-H
• Atypical squamous cells, cannot exclude HSIL
HSIL
• High-grade squamous intraepithelial neoplasia
Cancer
• Invasive anal cancer

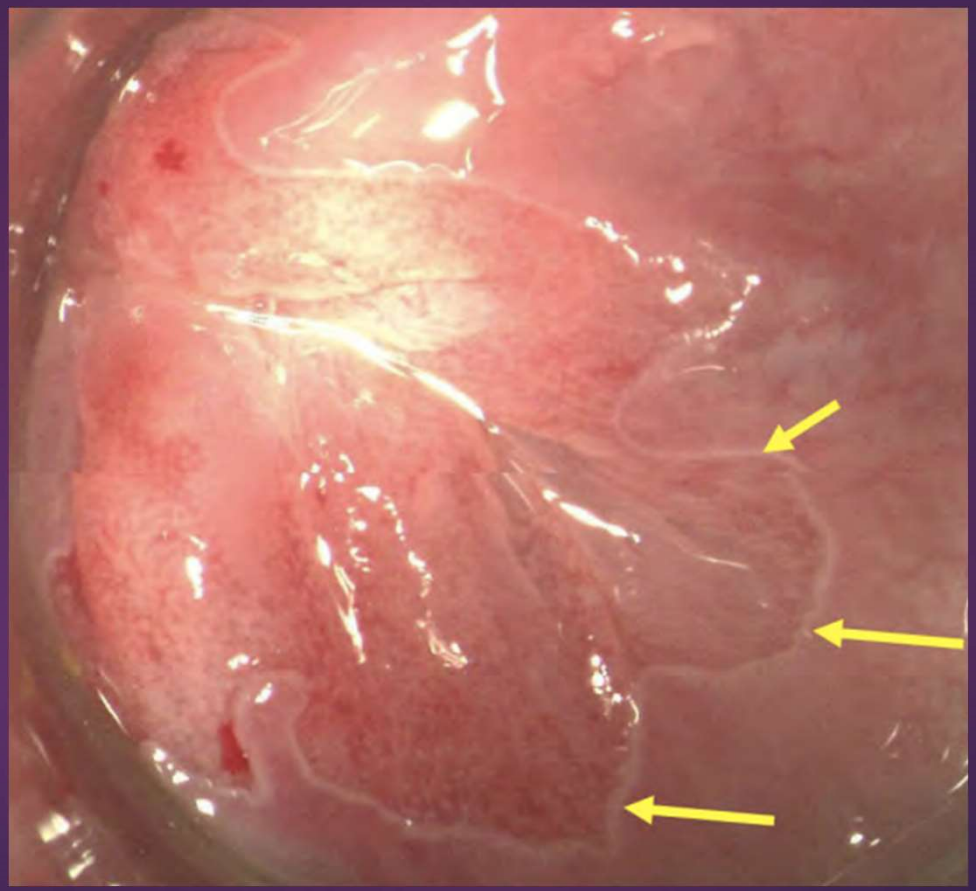

Normal
Mild dysplasia
Moderate dysplasia
Severe dysplasia
Tumour cell
Epithelial surface
Basement membrane
Normal squamous epithelium
Mild
Moderate
Severe
DYSPLASIA
Carcinoma in situ
Invasive cancer

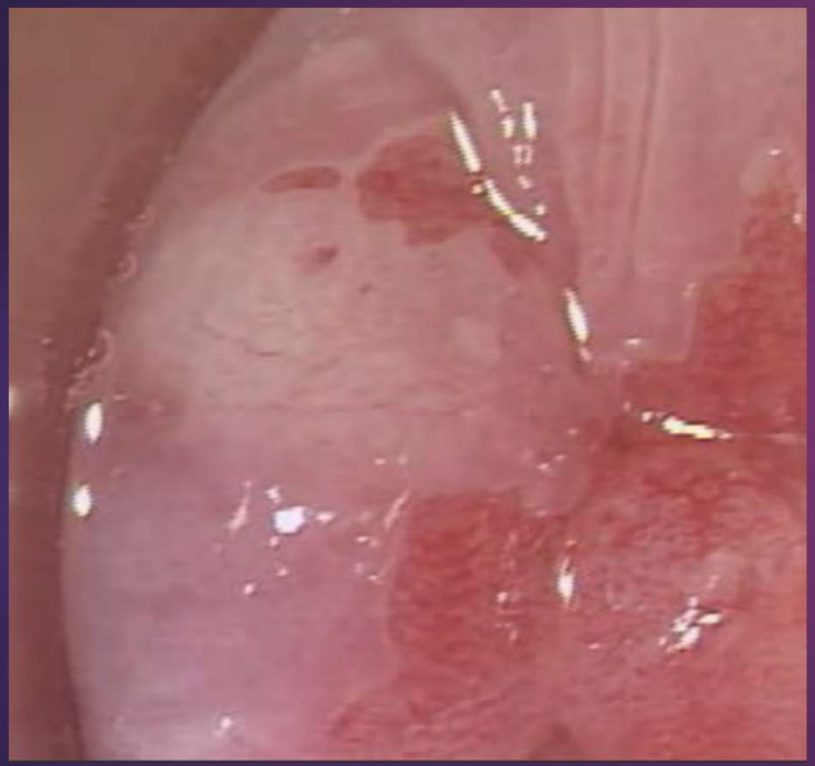
Tom’s results came back as ASCUS

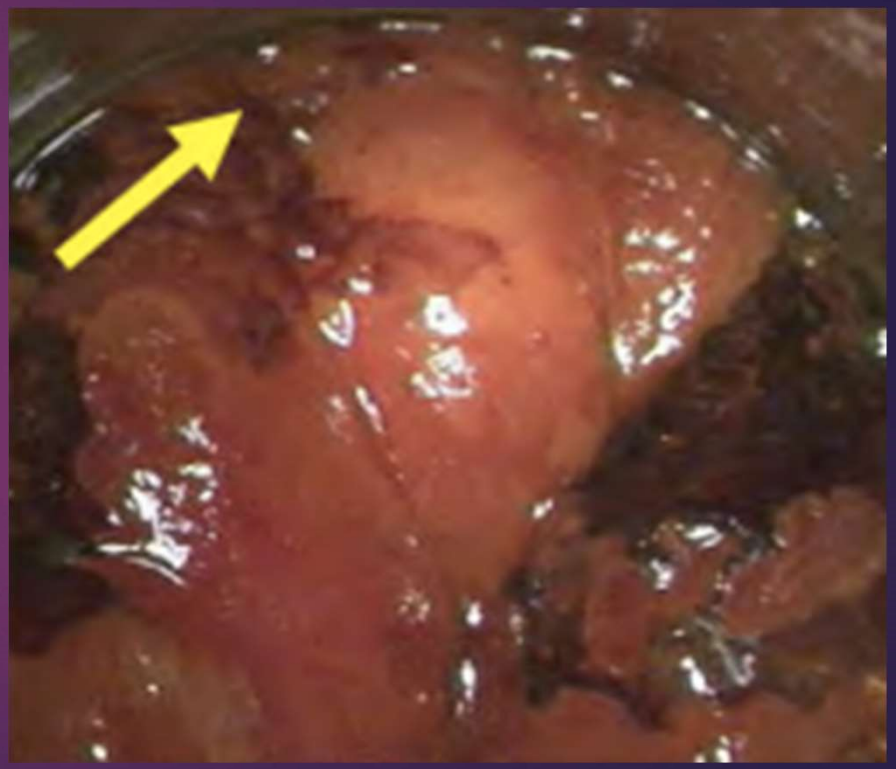
High-resolution anoscopy

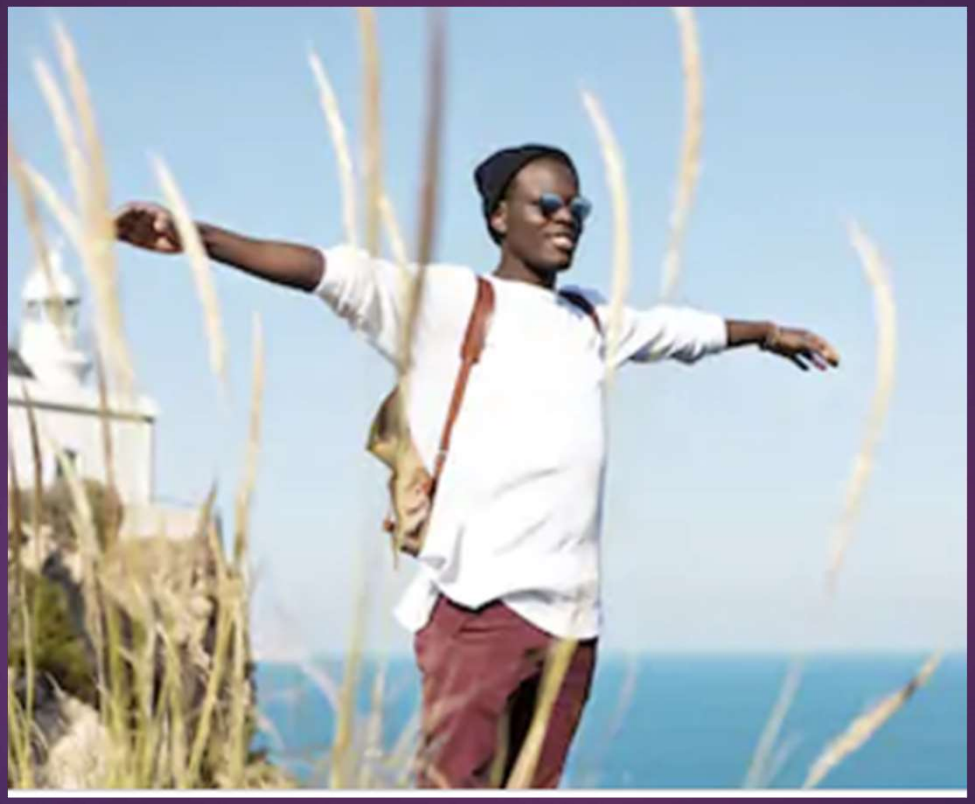
- High-resolution anoscopy, similar to colposcopy, uses acetic acid to identify dysplasia in the perianal area and anal canal. Anoscopy with targeted destruction uses electrocauterization and excisional biopsy both to remove lesions and to provide tissue for biopsy. The two methods are equally effective in diagnosing anal cancer or dysplasia, and the choice between them is based on the individual surgeon's preference.[3]


Fixative
Monsel's
3% Vinegar
Iodine
Lignocaine
gel (4%)
Mops









Anal Cancer

- Anal cancer used to be a rare cancer traditionally associated with elderly women. Now, with the rise of the HIV epidemic anal cancer is on the rise in the U.S and the number of anal cases documented has quadrupled in the past 20 yrs.
- Incidence of anal cancer: 40 to 80 times higher in the HIV+ population.
  - With the advent of HAART pts are living longer and less are progressing to AIDS. As a consequence non AIDS defining cancers such as anal cancer are on the rise.
- HIV+ patients tend to get anal cancer at a younger age, are more frequently men, and more frequently homosexual men who practice RAI.

Incidence- Anal Cancer

- Each year: +/- 6000 new cases of anal cancer
  - 2/3 occur in women.
  - 800 deaths per year.
- The most common cancer of the anus (80-90% of all anal cancers) is squamous cell carcinoma (SCC).

Risk Factors

Which of the following is the greatest risk factor for the development of SCC of the anus?

A. Smoking
B. Age >55 years
C. Human papillomavirus (HPV) infection
D. History of colon cancer

Human Papilloma Virus

- Infection with this virus and its integration into the patient's genome is the single greatest risk factor for the development of anal cancer.
- Anal intraepithelial neoplasia (AIN) is a premalignant lesion (dysplasia) of the anal mucosa that is a precursor to anal cancer.
- This dysplasia is divided into two categories:
  - Low-grade anal intraepithelial neoplasia (LGAIN)
  - High-grade anal intraepithelial neoplasia (HGAIN)- direct precursor lesion to anal squamous cell carcinoma (SCC).

Human Papilloma Virus

- **HPV is most commonly acquired and transmitted through sexual intercourse**. However, it can be spread through many types of genital contact—intercourse is not necessary.
- In addition, it may take only 1 encounter to be infected with the virus. Individuals can acquire HPV from others who are infected but who don't have visible disease or lesions.

HPV-related cancer and disease cases	Total percent contribution of HPV[b]
Cervical cancer[4]	100%[4]
Vulvar cancer[5]	30%[5]
Vaginal cancer[6]	70%—75%[6]
Anal cancer[7]	85%—90%[7]
High-grade cervical precancers[8,c]	90%[8]
Low-grade cervical lesions[8]	75%[8]
Genital warts[9]	90%[9]

[b]Percentages include all HPV types, not just Types 6, 11, 16, 18, 31, 33, 45, 52, and 58.

[c]High-grade cervical precancers defined as CIN 2/3.

CIN=cervical intraepithelial neoplasia.

CIN 3

Anal cancer

Vulvar cancer[d]

Vaginal cancer[d]

Female genital warts

Male genital warts[e]

[d]Reproduced with permission from Professor RW Jones.

[e]Reproduced with permission from DermNetNZ.org.

Risk Factors- HPV

- The strongest HPV-associated risk factors are
  - HIV infection
  - Receptive anal intercourse
  - High risk sexual behavior.
  - History of HPV-mediated genital cancer (infection with an oncogenic HPV strain)

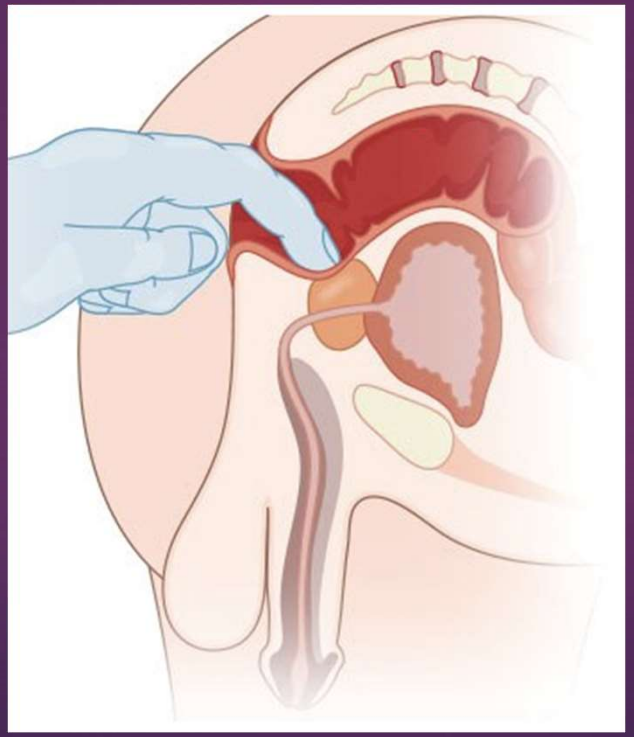
Other risk factors

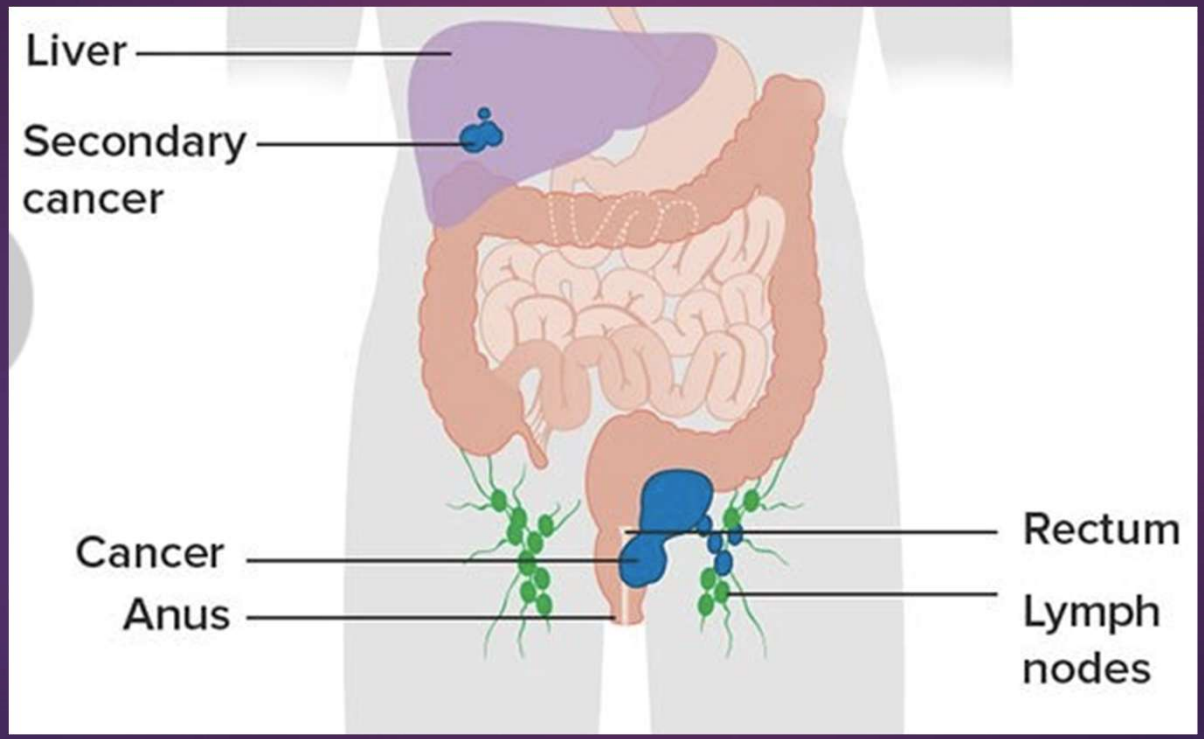
- Age greater than 55 years
- Receptive anal intercourse
- Concomitant sexually transmitted disease (STD)
- Immunosuppression (as in transplant recipients or individuals with HIV infection)
- Pelvic irradiation
- Smoking

Squamous Cell Carcinoma

- Anal intraepithelial neoplasia (AIN) is a premalignant lesion of the anal mucosa and is a precursor to anal cancer.
- Besides palpable lesions, patients may also present with bleeding, itching, discharge, or altered bowel habits
- Squamous cell carcinoma of the anus is thought to arise from a precancerous lesion. Similar to cervical cancer, a Bethesda staging criteria has been devised for precursor anal lesions. AIN1 represents a low grade squamous intraepithelial lesion (LSIL) whereas AIN 2, 3 are high grade squamous intraepithelial lesion (HSIL).

Digital Rectal Exam




Liver
Secondary cancer
Cancer
Anus
Rectum
Lymph nodes

Treatment

- In the past, if HSIL was detected treatment was offered
  - either medical ablation or surgical excision.
- However, we still don't know if we are preventing the development of anal cancer by treating early lesions. Actually, the Anchor study is about this. There is no current recommendation on whether a patient with a pre-cancerous lesion (which is not cancer) should be treated.
- If AIN is to be treated the following tx modalities can be used: topical therapies such as imiquimod, 5-flurouracil, and trichloroacetic acid; ablative therapies such as electrocautery and laser therapy.

Treatment- Squamous Cell Carcinoma of the Anus

- In the past: the standard of care was surgery
  - Colostomy (sphincter loss)
- Now: There have been multiple prospective randomized trials that have shown improvement in local control, disease free survival, and sphincter preservation with the addition of chemotherapy to RT, (with surgery only as salvage)
  - Mitomycin C (MMC), 5-fluorouracil (5-FU), RT

Modified Nigro Protocol

Treatment	Dose	Schedule
5-Fluorouracil (5-FU)	1 g/m^2/day	Start day 1, and continue for 4 days; repeat 4-day infusion starting day 28
Mitomycin C	10-15 mg/m^2 IV bolus	Day 1 only
External radiation therapy	50 Gy to primary tumor, 35-45 Gy to inguinal nodes	Start day 1, and deliver 2 Gy/day, 5 days/wk for 5 wk

Treatment

- The approximate duration of therapy is 4 weeks. The anal canal should be reexamined 4-6 weeks after the completion of therapy. If anal cancer persists or recurs after treatment according to the Nigro protocol, it can be treated by means of radical surgical resection
- The Nigro protocol yields 5-year cancer-free rates in the range of 70-90%. Even if anal cancer does recur after treatment with this protocol, APR is potentially curative. This procedure involves removal of the anus, the rectum, and a portion of the perineum, as well as creation of a permanent colostomy.

Potential Complications of Treatment

- Radiation-related - Ulceration, skin damage, anal stenosis
- Chemotherapy-related - Nausea, hair loss, lung inflammation
- Surgical - Bleeding, infection, damage to normal healthy tissue
- There is also a risk of death associated with chemotherapy and surgery.

Follow Up

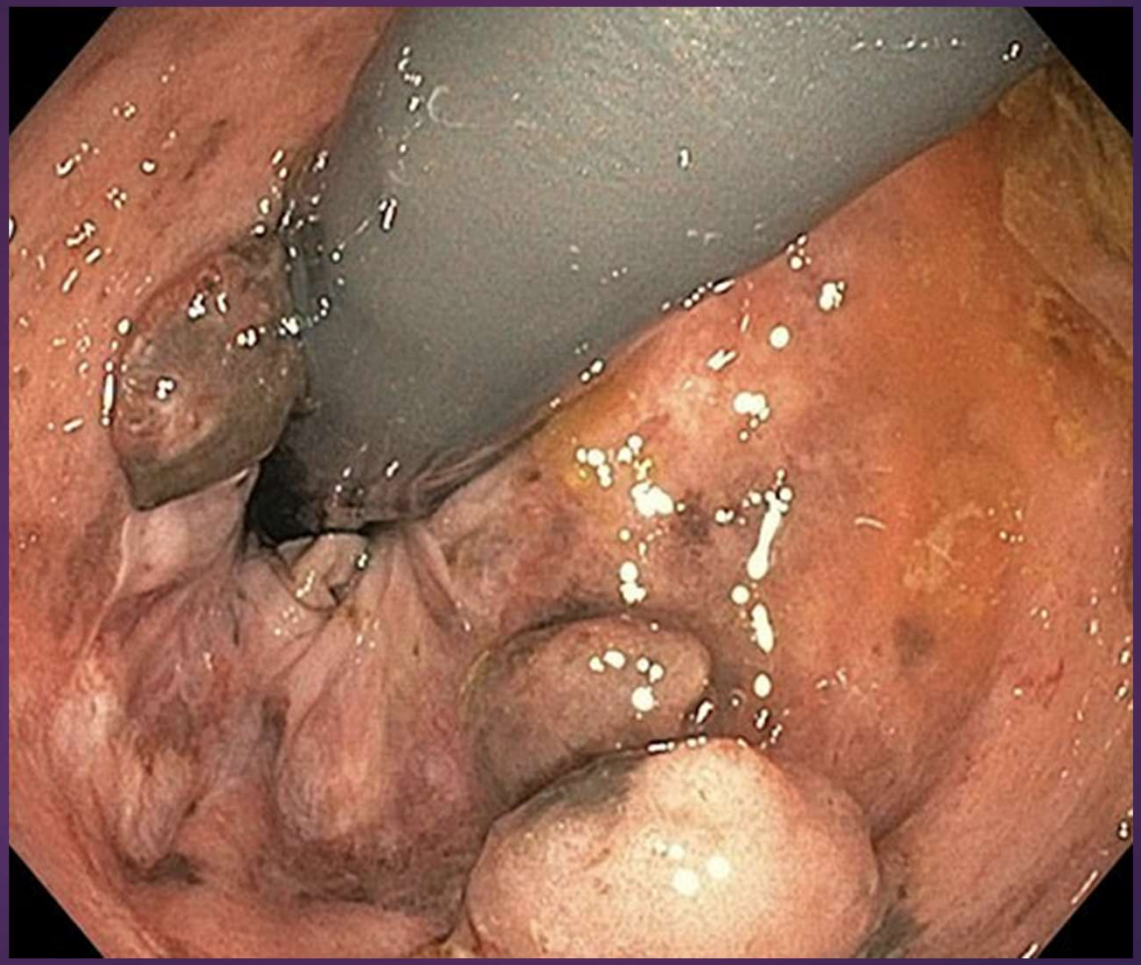
- After successful treatment with chemotherapy and radiation therapy, patients should be examined by means of DRE (shown) or anoscopy at regular intervals. It is recommended that these patients be seen and examined every 3-6 months for the first 2 years, then every 6-12 months for up to 5 years. After this time, patients should be seen on a yearly basis.

Other types of anal cancer- Adenocarcinoma

- Adenocarcinoma accounts for approximately 3-9% of all anal cancers. There are three subtypes of anal adenocarcinoma, as follows:
- Rectal type
- Anal gland type
- Anorectal fistula type

Melanoma of anus

- Melanoma is a very rare type of anal cancer, accounting for fewer than 1% of anal malignancies. Despite the exceeding rarity of melanoma in the anus, the anal canal is the third most common location for this cancer, after the skin and eyes.
- Is difficult to treat and does not respond to the chemotherapy, radiation therapy, or immunotherapy typically used for other melanomas. The prognosis is poor, and surgical excision is the only treatment, though it does not offer any survival benefit.



Summary

- Although anal cancer is a rare malignancy, it is fairly prevalent in certain at-risk populations. These populations should be screened carefully, with early referrals to colorectal surgeons as indicated. Anal cancer is treatable, and it is curable if diagnosed early. The gold standard of treatment is the Nigro protocol, which combines radiation therapy with chemotherapy. Excision is indicated for perianal and recurrent disease. Close surveillance is required after therapy to monitor for recurrence. There are several other subtypes of anal cancer that are exceedingly rare but warrant referral to a colorectal surgeon if suspected.

Prevention

- Reductions in AIN and anal cancer rates have been shown in studies where high-risk populations were vaccinated against the oncogenic strains of HPV.
- Currently, the CDC recommends both high-risk and average-risk populations be vaccinated against HPV infection using the quadrivalent or nonavalent vaccines. It is important for clinicians to be familiar with AIN and the role of HPV vaccination, particularly in high risk populations.

Why 9 HPV Types?

Broader disease coverage due to more HPV types

Worldwide estimated type contribution for certain HPV-related cancer and disease cases	4 HPV types cause: (6, 11, 16, and 18)	5 HPV types cause an additional: (31, 33, 45, 52, and 58)	9 HPV types cause a total of: (6, 11, 16, 18, 31, 33, 45, 52, and 58)
Cervical cancer[2]	70%[2]	20%[2]	90%[2]
Vulvar cancer[3,a]	75%[3]	15%[3]	90%[3]
Vaginal cancer[4,a]	65%[4]	20%[4]	85%[4]
Anal cancer[5,a]	85%[5]	5%–10%[5]	90%–95%[5]
High-grade cervical precancers[6,a,b]	50%[6]	30%[6]	80%[6]
Low-grade cervical lesions[6,a]	25%[6]	25%[6]	50%[6]
Genital warts[7]	90%[7]	No contribution[7]	90%[7]

[a]Not all cervical precancers and lesions, and vulvar, vaginal, and anal cancer cases are caused by HPV. Approximately 90% of high-grade cervical precancers,[8] 75% of low-grade cervical lesions,[8] 30% of vulvar cancer cases,[3] 70% to 75% of vaginal cancer cases,[4] and 85% to 90% of anal cancer cases[5] are HPV related.

[b]High-grade cervical precancers defined as CIN 2/3.

Original 4 HPV types

Established efficacy for HPV Types 6, 11, 16, and 18

Efficacy against diseases caused by HPV Types 6, 11, 16, and 18 for GARDASIL 9 was inferred from a non-inferiority comparison of geometric mean titers (GMTs) versus GARDASIL® [Human Papillomavirus Quadrivalent (Types 6, 11, 16, and 18) Vaccine, Recombinant].

In clinical studies of young men and women 16 to 26 years of age naïve to HPV Type 6, 11, 16, or 18, efficacy of GARDASIL was[a]:

98% efficacy	**CERVICAL CANCER** HPV 16- and 18-related CIN 2/3 or AIS
100% efficacy	**VULVAR/VAGINAL CANCER** HPV 16- and 18-related VIN 2/3 and VaIN 2/3
75% efficacy	**ANAL CANCER** HPV 6-, 11-, 16-, and 18-related AIN 2/3
89% efficacy in males **99%** efficacy in females	**GENITAL WARTS** HPV 6- and 11-related

Dosage and Administration for GARDASIL 9

Recommended Dosing

Age	Regimen	Schedule
9 through 14 years	2-dose	0, 6 to 12 months[a]
	3-dose	0, 2, 6 months
15 through 45 years	3-dose	0, 2, 6 months

[a]If the second dose is administered earlier than 5 months after the first dose, administer a third dose at least 4 months after the second dose.

As in the clinical trial

If using the 2-dose schedule, the **first dose must be administered before the child's 15th birthday.**[9]

https://www.merckvaccines.com/Products/Gardasil9/hpv-types


GARDASIL 9
Suspension for injection
MERCK

Bibliography

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