

*APPROVED*

# Male Genital Pathology

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Spring 2010

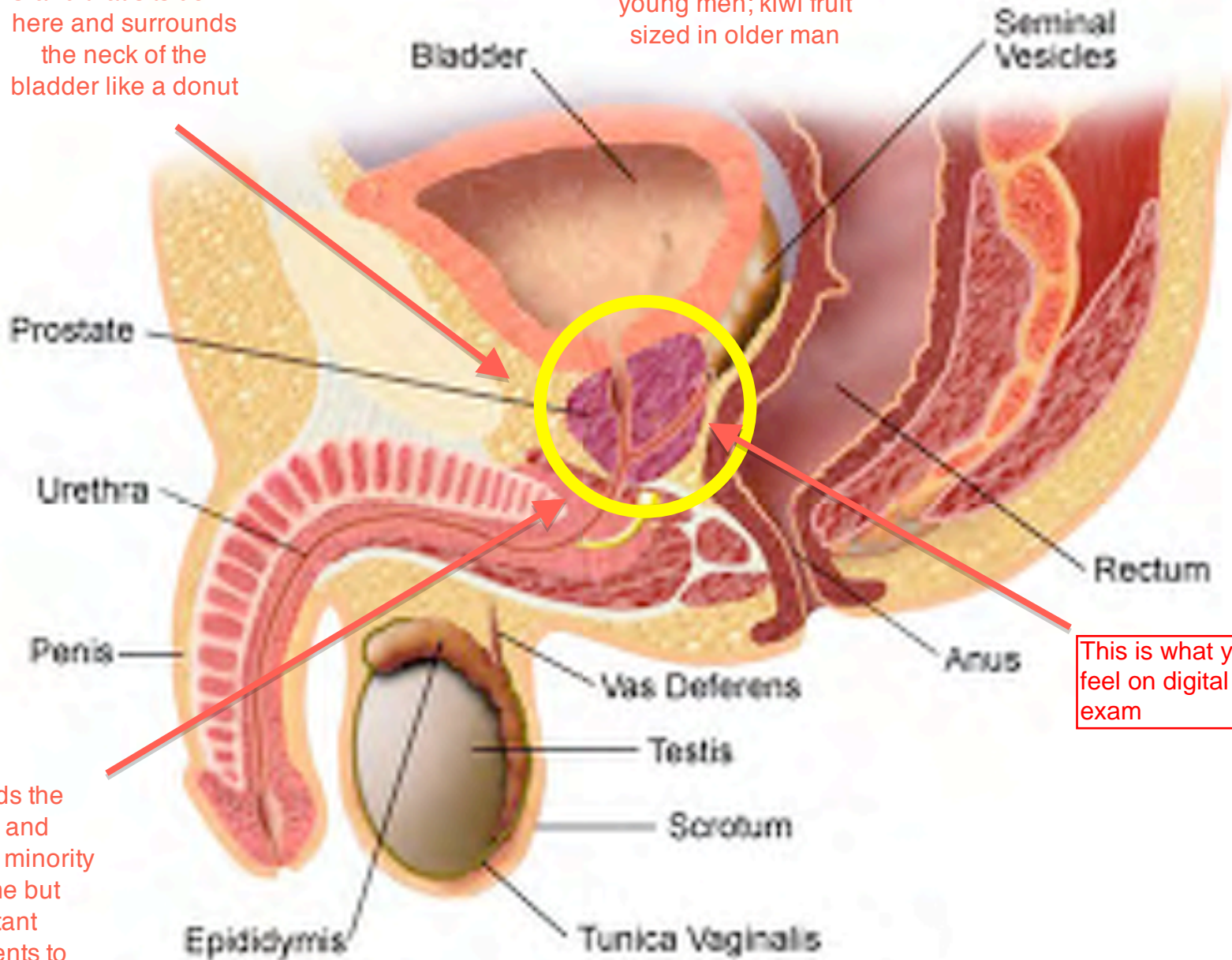
# Prostate

# Male Reproductive Tract

Summary: The prostate sits at the neck of the bladder. You palpate the posterior edge in a rectal exam

Gland that sits down here and surrounds the neck of the bladder like a donut

Walnut sized in young men; kiwi fruit sized in older man

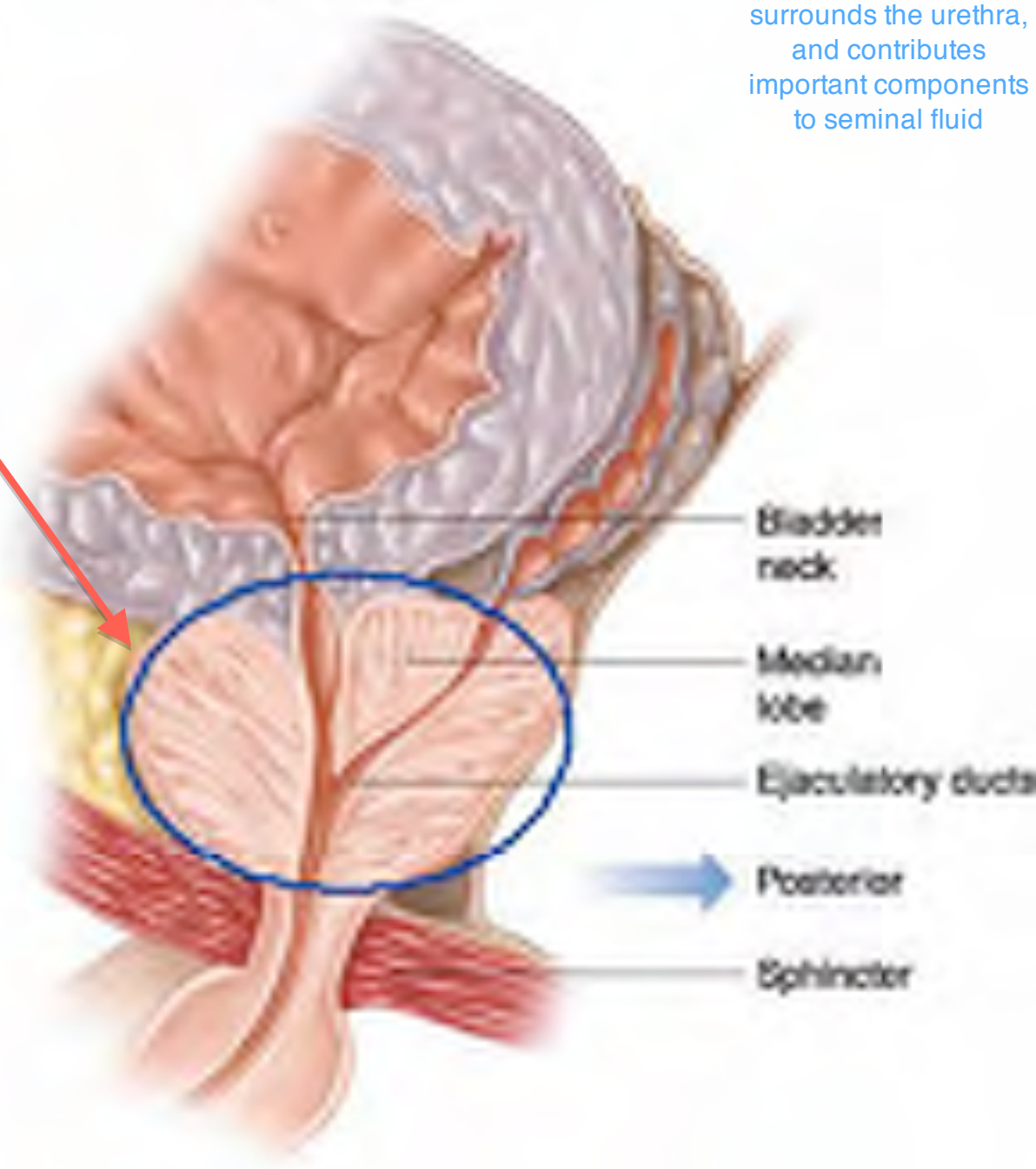


This is what you feel on digital rectal exam

Surrounds the urethra and contributes minority of volume but important components to seminal fluid

# Side View

Summary: the prostate surrounds the urethra, and contributes important components to seminal fluid



Bladder neck

Median lobe

Ejaculatory ducts

Posterior

Sphincter



Summary- prostatitis is a common, benign condition that can be bacterial (same bugs as UTIs), abacterial (most common), or granulomatous

Benign condition that affects the prostate. Its a fairly common complaint

# Prostatitis

- Bacterial prostatitis
  - Same pathogens as UTI

i.e. enteric pathogens (GNR like Proteus, E. Coli etc)

- Chronic abacterial prostatitis
  - Most common type
  - Etiology elusive

Often bacteria is not culturable and the etiology is debated

- Granulomatous prostatitis
  - Most “nonspecific”
  - Tuberculosis, blastomycosis

Most common cause of granulomatous prostatitis at Duke is people who are getting BCG for bladder cancer

Not serious but often seen on biopsy

Also can result from instrumentation of biopsy

Summary: BPH presents with urinary obstruction, is common, and is due to decades of androgen stimulation

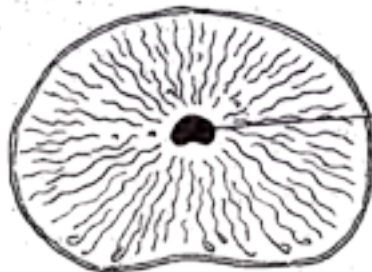
# Benign prostatic hypertrophy

Main symptom

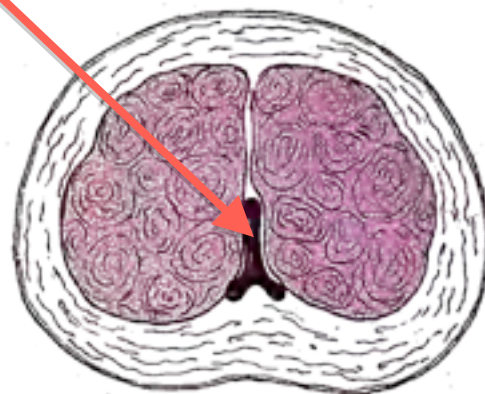
- **Urinary obstruction**
  - Involves periurethral zone
- High prevalence
  - ↑ rapidly after **age 40**
  - **>90% by age 80**
- Androgen dependence

Decades of androgen stimulation causes hypertrophy

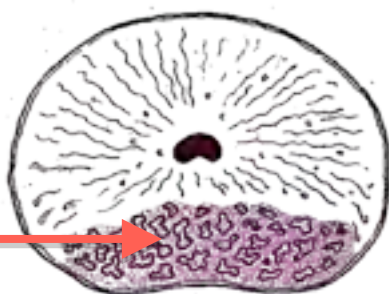
The compression of the urethra is the problem



NORMAL PROSTATE



BENIGN PROSTATIC HYPERPLASIA



CARCINOMA OF PROSTATE

Most carcinomas are accessible to digital exams

Prostate is a compound gland embryologically. There are 3-4 glands that fuse together.

In mice and rodents the lobes are actually independent glands (quasi-important because much prostate research is done on small rodents)

Decades of androgen stimulation causes hypertrophy of the anterior side of the prostate (the opposite side of where you feel during a rectal exam)

Summary- BPH squishes the urethra, causing the symptoms. BPH is anterior, while carcinoma is posterior

Older mans prostate

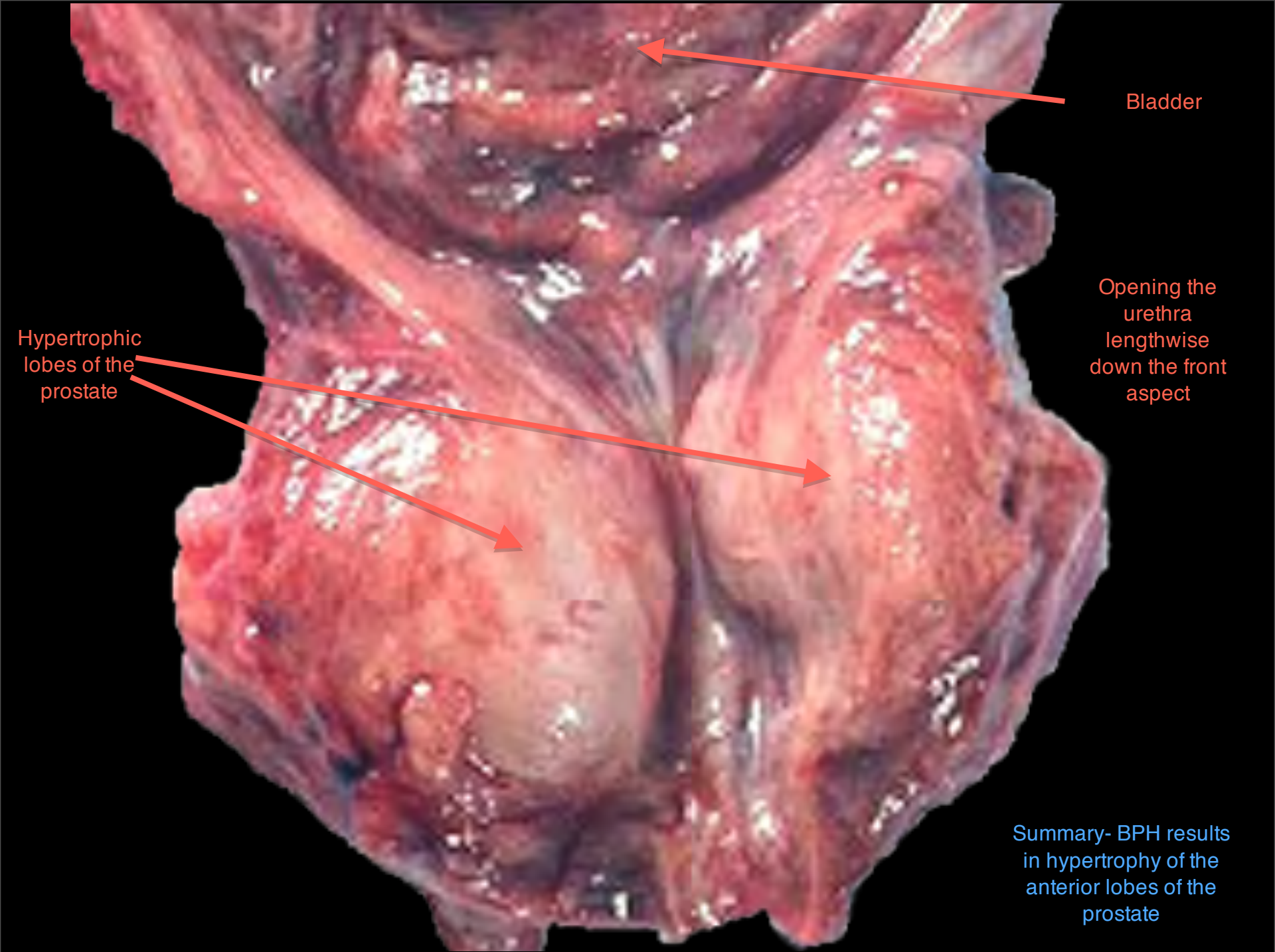
The geometry is a bit bizarre; just note all the enlargments caused by hypertrophy of the prostate. The next slide has a better section



Summary- on gross exam a BPH prostate looks nodular







Bladder

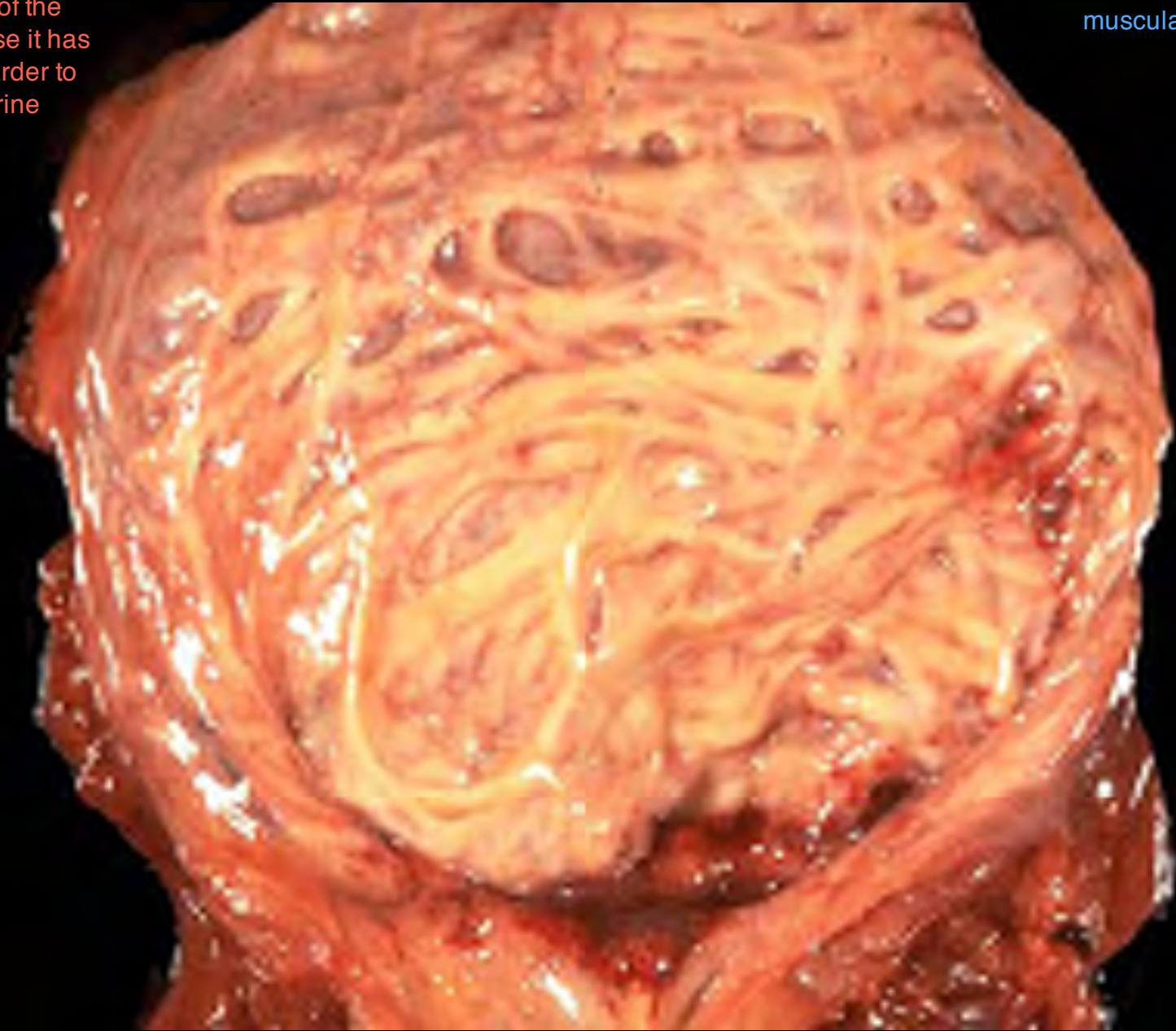
Opening the urethra lengthwise down the front aspect

Hypertrophic lobes of the prostate

Summary- BPH results in hypertrophy of the anterior lobes of the prostate

End result is muscular hypertrophy of the bladder because it has to squeeze harder to push out urine

Summary- BPH can cause bladder muscular hypertrophy



Summary- there are lot of  
BPH therapies  
(nonmedical,  
pharmacological, surgical)

# BPH therapies

- Herbs, diet, clean living, earnest prayer, etc.
- Alpha blocker i.e. silodosin,  
tamsulosin
- 5-alpha reductase inhibitor
- Transurethral resection of prostate (TURP)
- Heat ablation (microwave, hot water, etc.)
- Photoselective vaporization (PVP)
- Simple prostatectomy

Other  
surgical  
procedures



Summary: prostatic adenocarcinoma is common, especially in older African Americans with a family history who eat a high fat diet

# Prostatic adenocarcinoma

- Most common male cancer

- Lifetime risk

- For diagnosis: 1 in 6

- For death: 1 in 34

This is a critical point to note. Many men have prostate cancer, but don't die from it

- Risk factors

- Age (rare before 50)

If you get it before 50 its more aggressive

- Race (black > white)

- Family history

- High fat diet



# Estimated new cases and deaths from prostate cancer in the United States in 2009

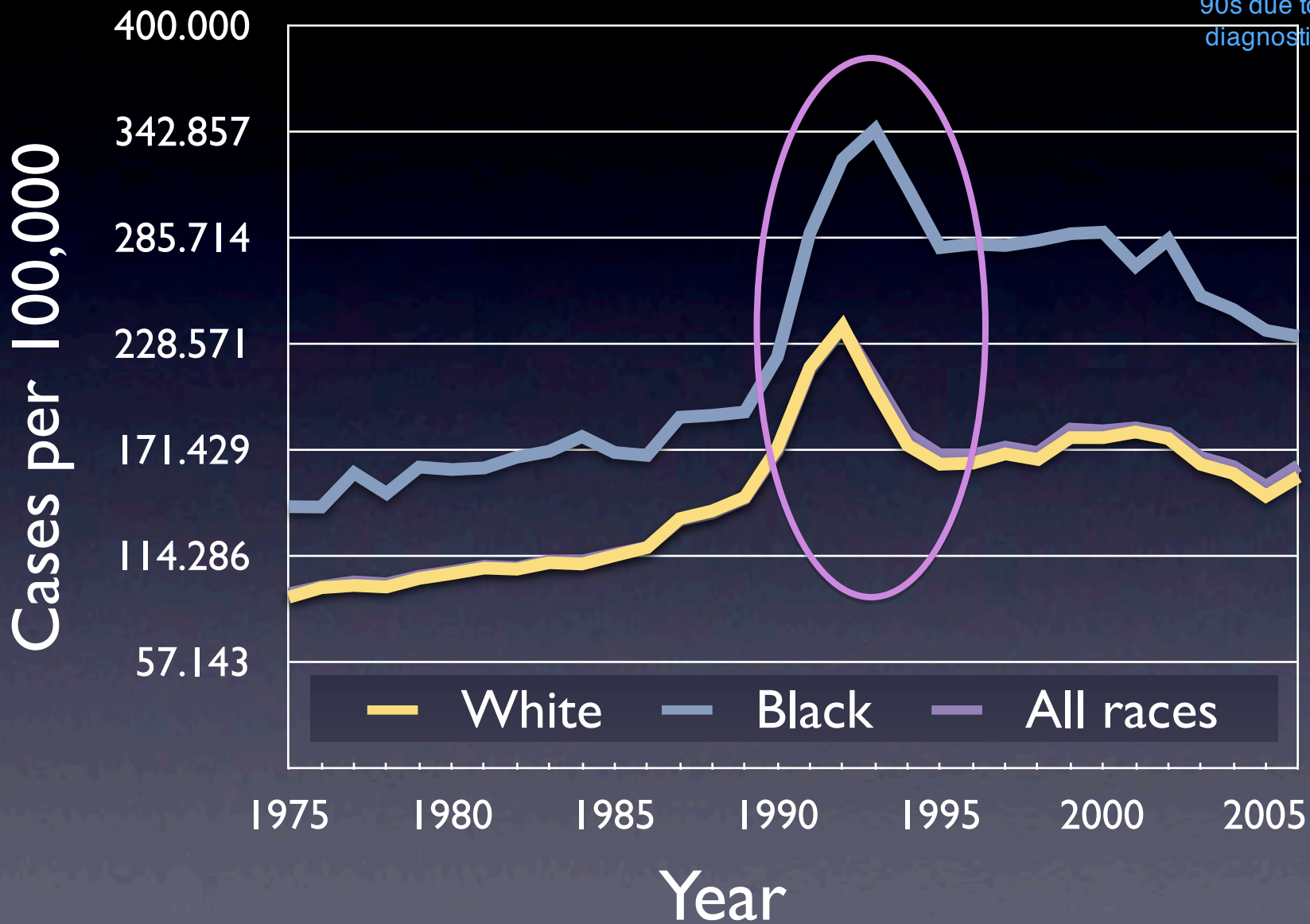
- New cases: 192,280
- Deaths: 27,360

- New cases: Deaths :: 7:1

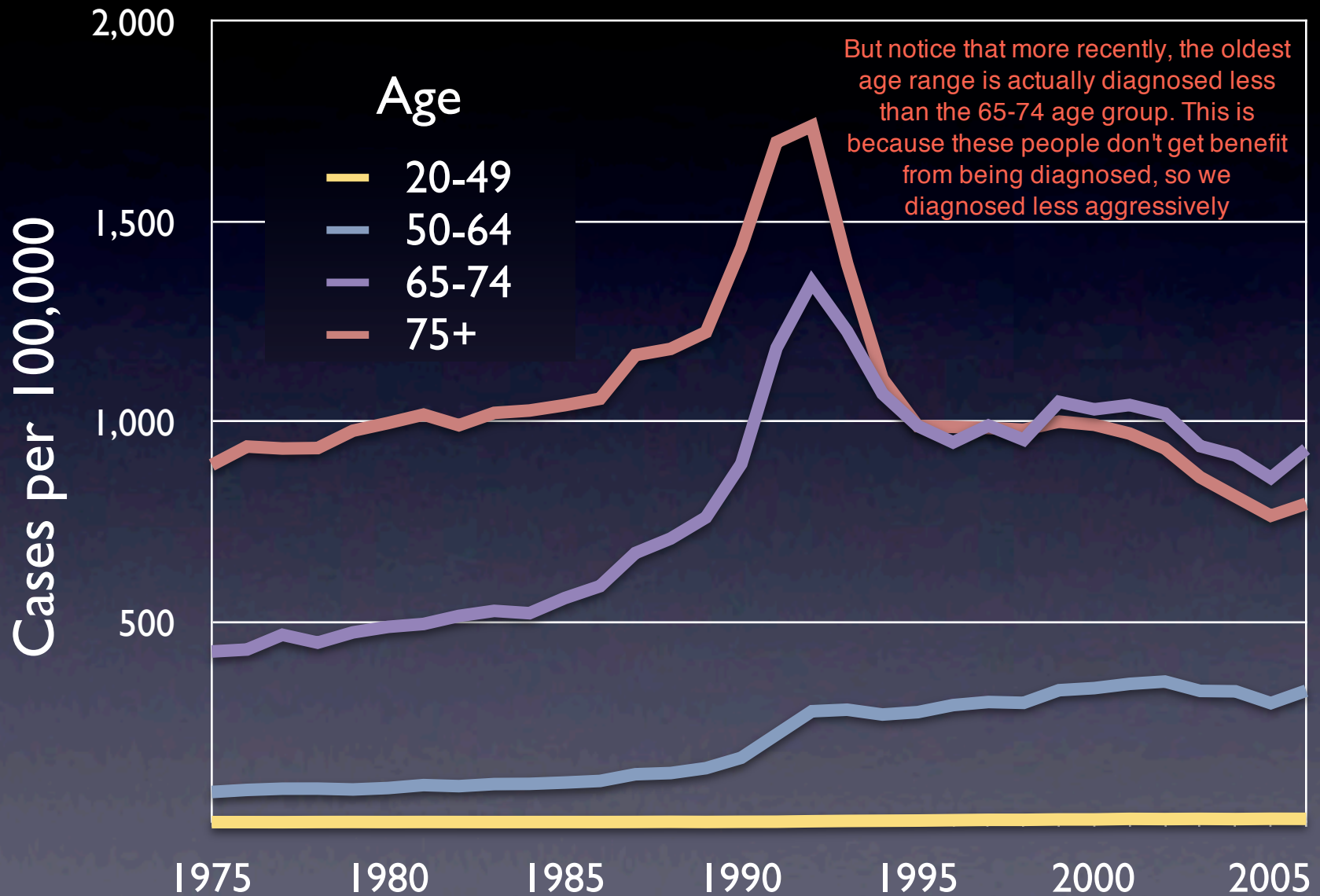
Again, many more people are  
diagnosed than actually die  
from it

# Prostate cancer incidence

Summary-incidence is increasing, and there was a sharp spike in the early 90s due to improved diagnostic methods



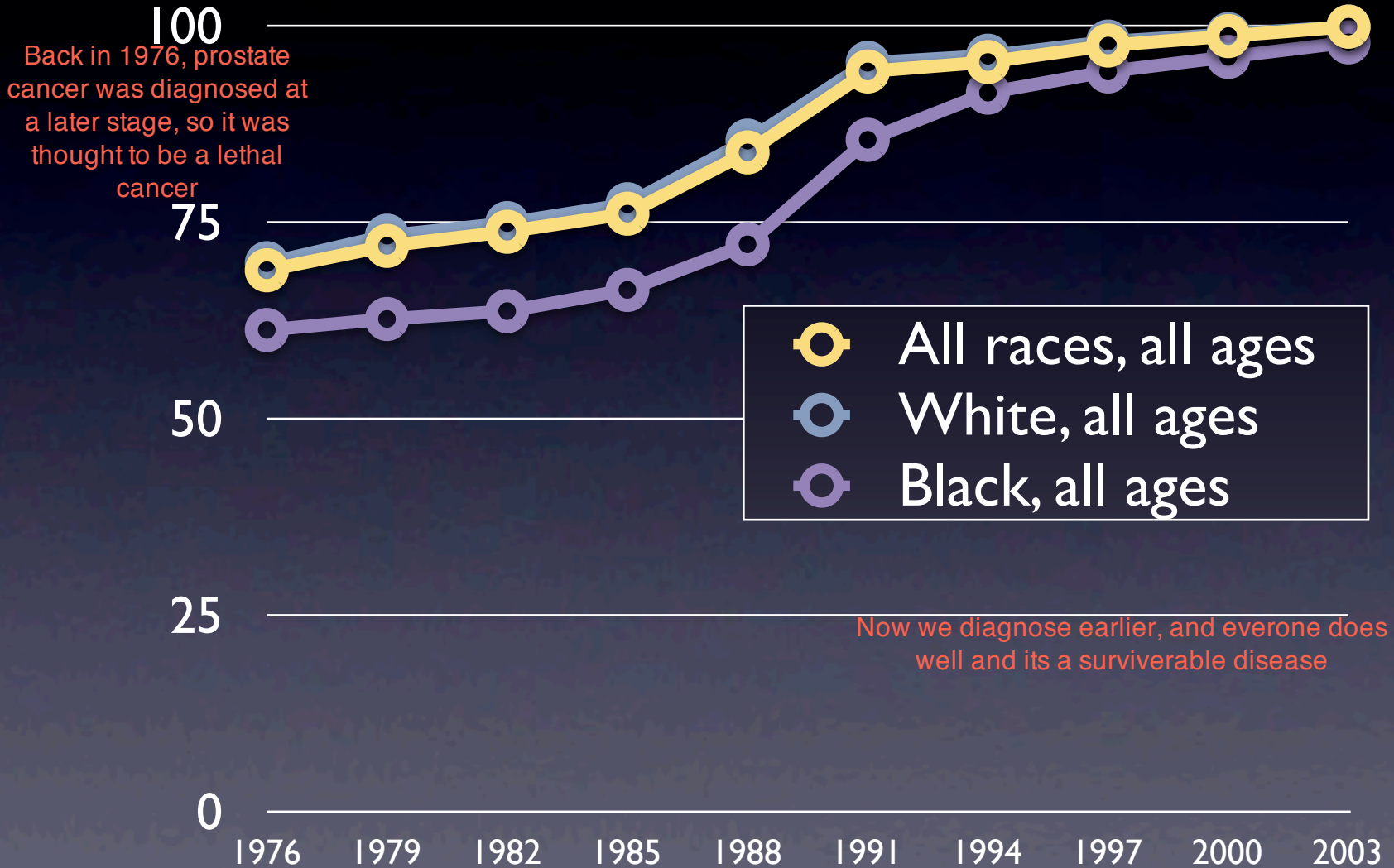
# Prostate cancer incidence by age group



Summary- survival from prostate cancer is good. Across age and race

# 5-year survival

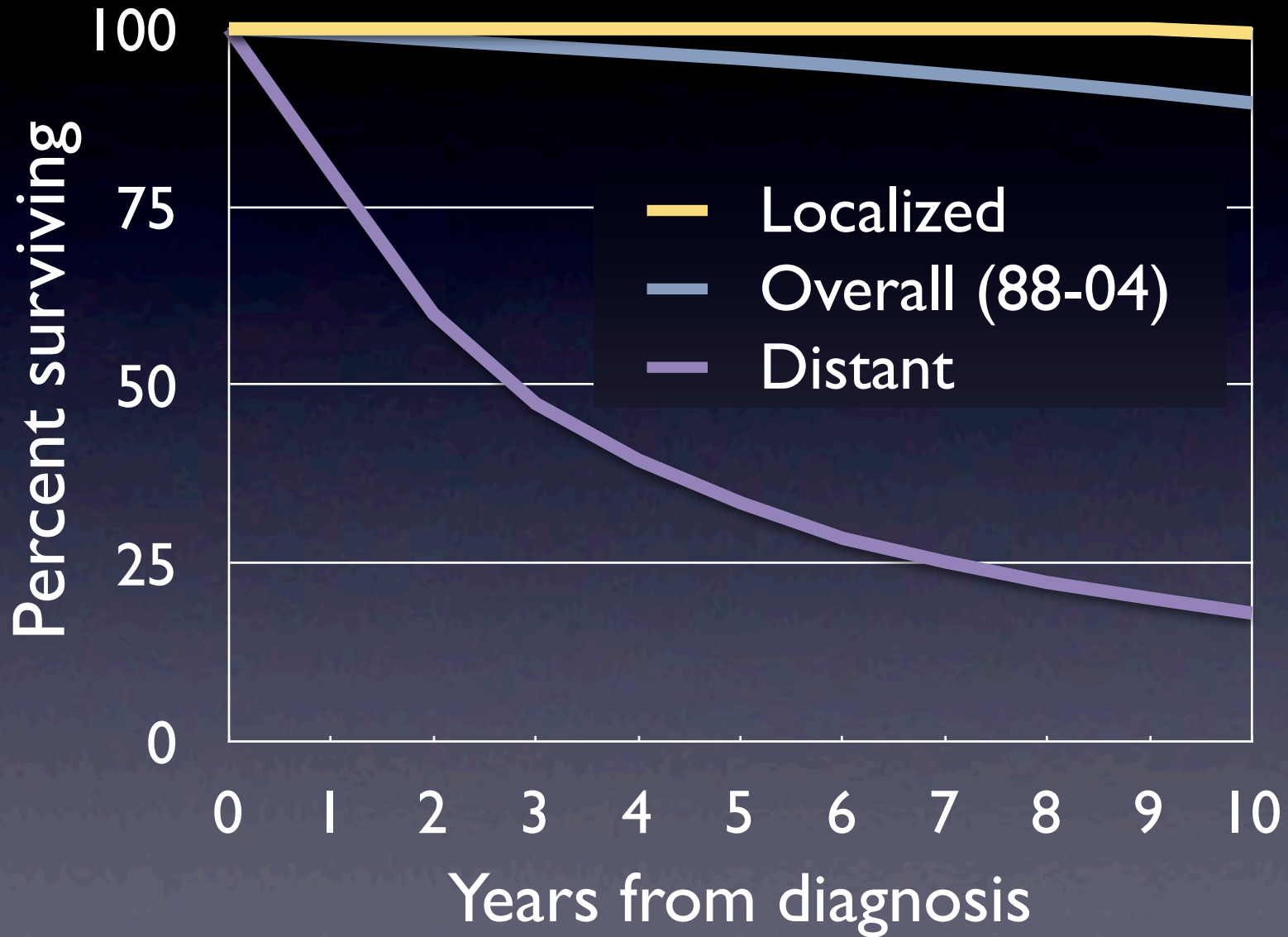
Important



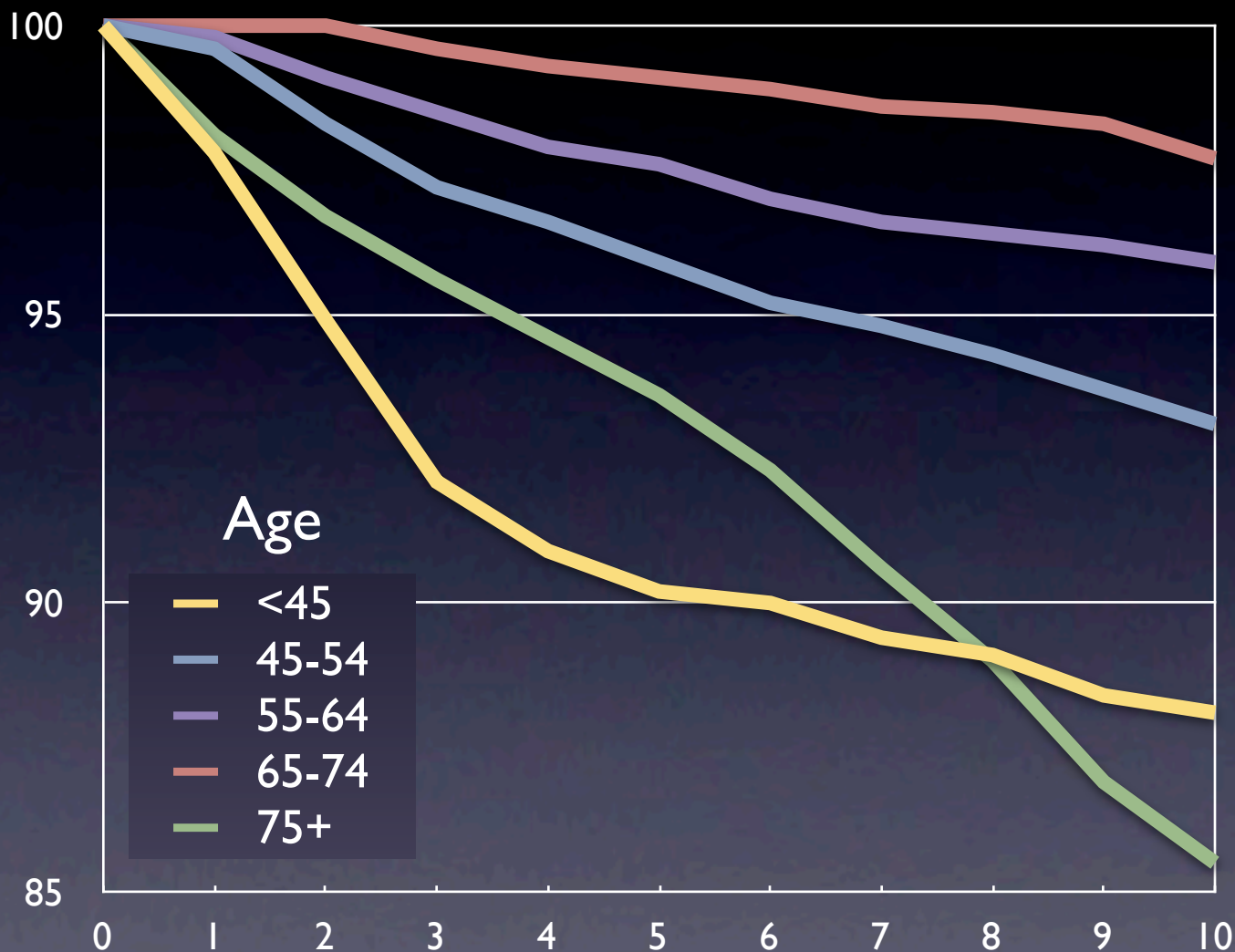


Summary- As expected, metastatic cancer is bad compared to localized cancer

# Prostate cancer survival by stage (1988-2002)

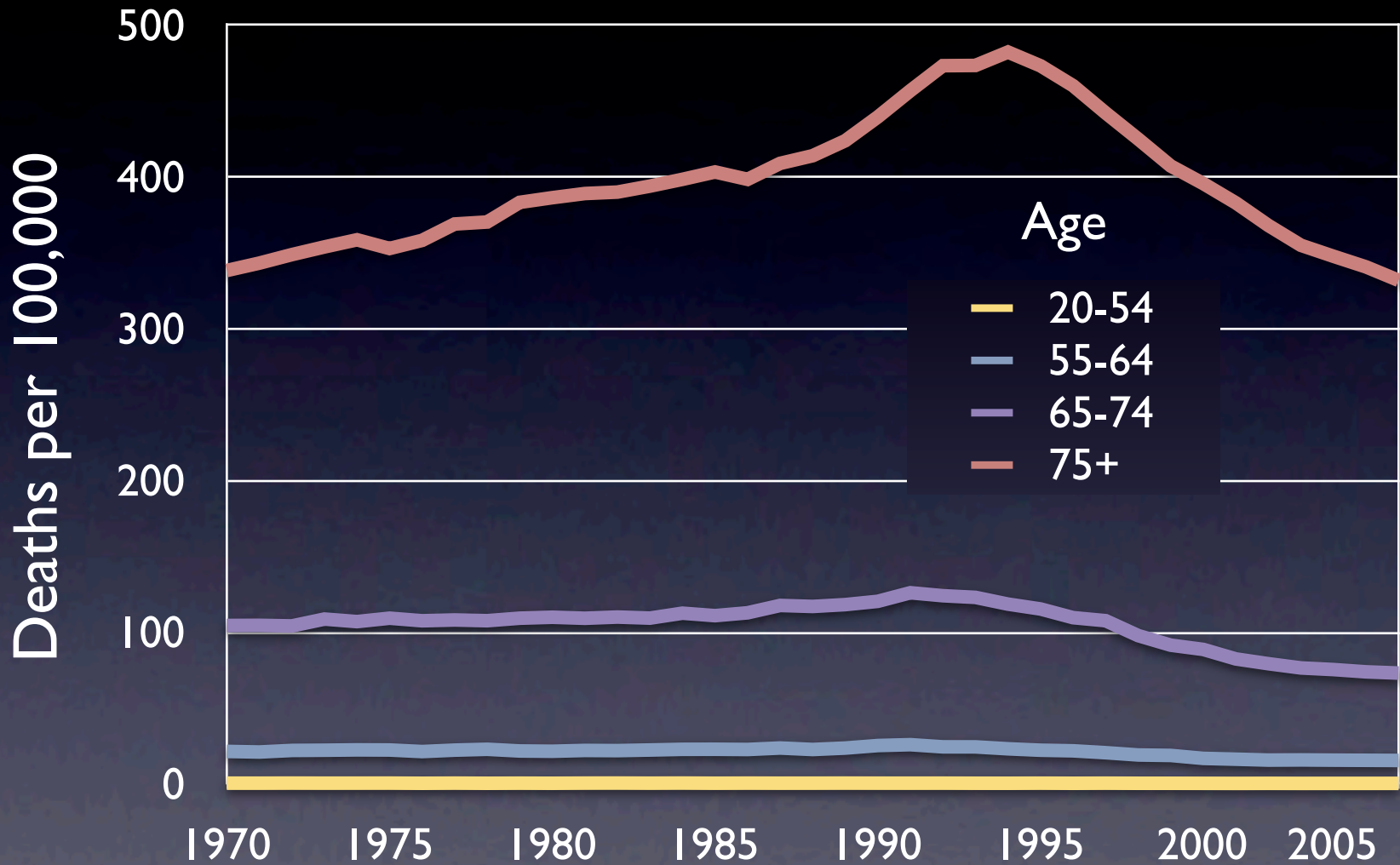


# Prostate cancer survival by age (1988-2002)



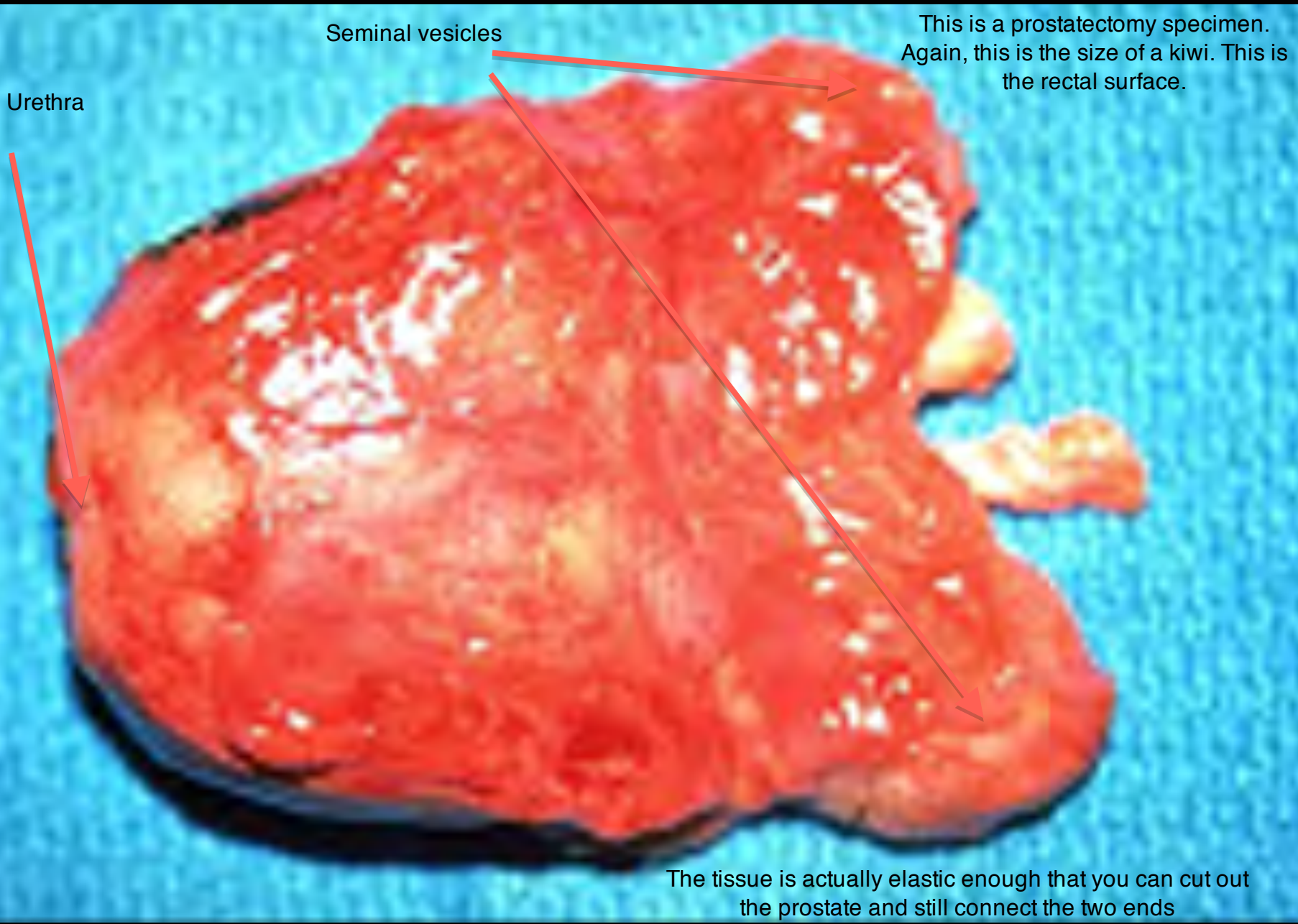
I actually think this is kind of important, because it goes back to his point he made earlier that prostate cancer in younger men is more aggressive- notice how their survival curve is lower than the older age groups

# Prostate cancer mortality by age group



This is showing that in absolute numbers, older people die more frequently of prostate cancer than younger people

Summary- you can remove the prostate and reconnect the two ends of the lower urinary tract because of the tissue elasticity



This is a prostatectomy specimen. Again, this is the size of a kiwi. This is the rectal surface.

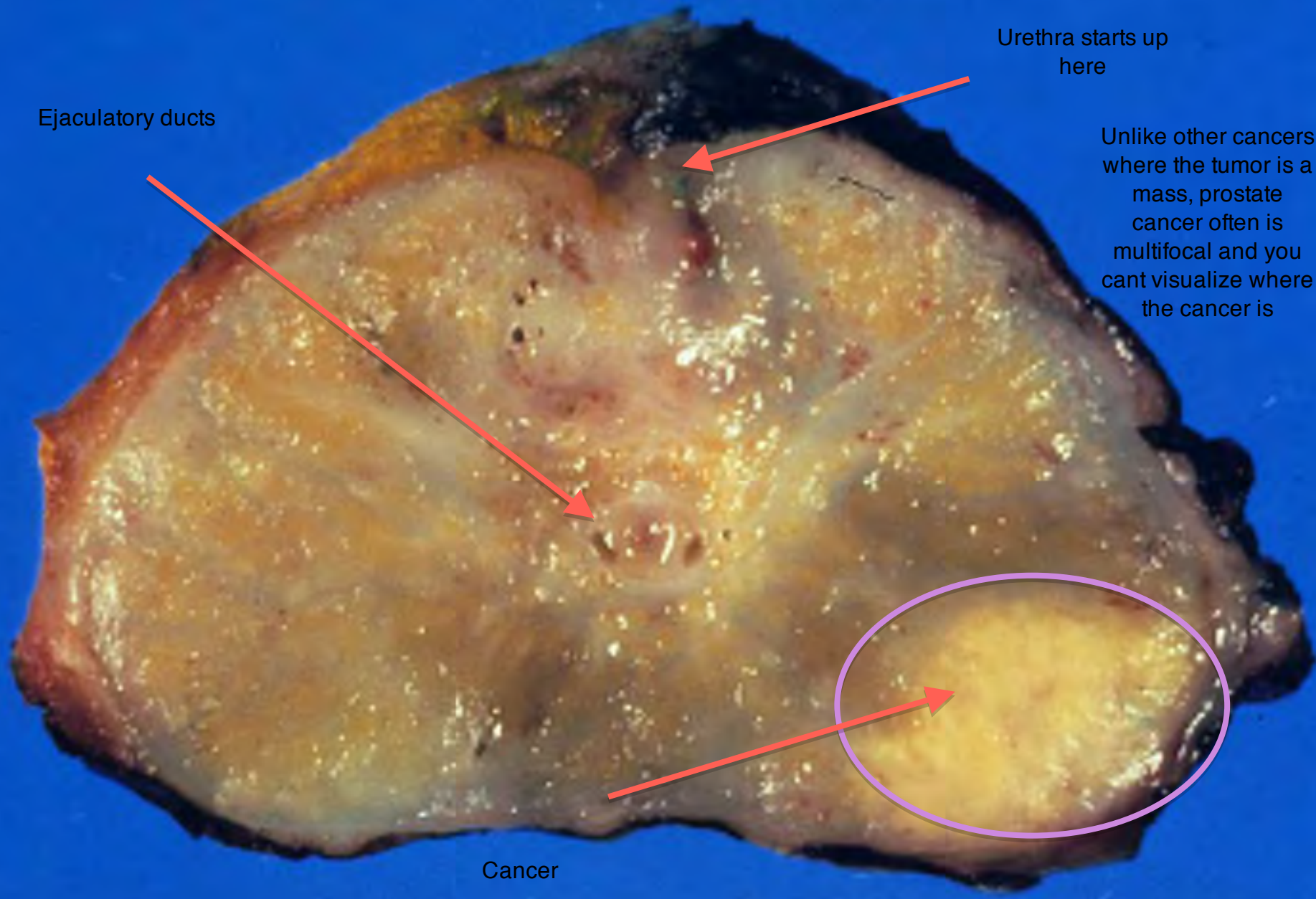
Urethra

Seminal vesicles

The tissue is actually elastic enough that you can cut out the prostate and still connect the two ends



Summary- prostate cancer is a different type of cancer because it is often multifocal and hard to visualize



Ejaculatory ducts

Urethra starts up here

Unlike other cancers where the tumor is a mass, prostate cancer often is multifocal and you cant visualize where the cancer is

Cancer

Jump to Slide 34 to understand the importance of gleason grading

Summary- Gleason grading is important for prognosis, is based on the top two common patterns in a biopsy, and is scored based on differentiation

# Gleason grading

- Most important single prognostic parameter
- Histologic pattern
  - 1 = most differentiated
  - 5 = least differentiated
- “Combined Gleason grade” = sum of two most common patterns in biopsy

You see two numbers between 1 and 5. These come from the two most common biopsy pattern

Gleason's original diagram.

Nice glandular architecture

Summary- Gleason grading is based on how closely the cancer resembles native prostate

# PROSTATIC ADENOCARCINOMA (Histologic Grades)



Just an architectural mess



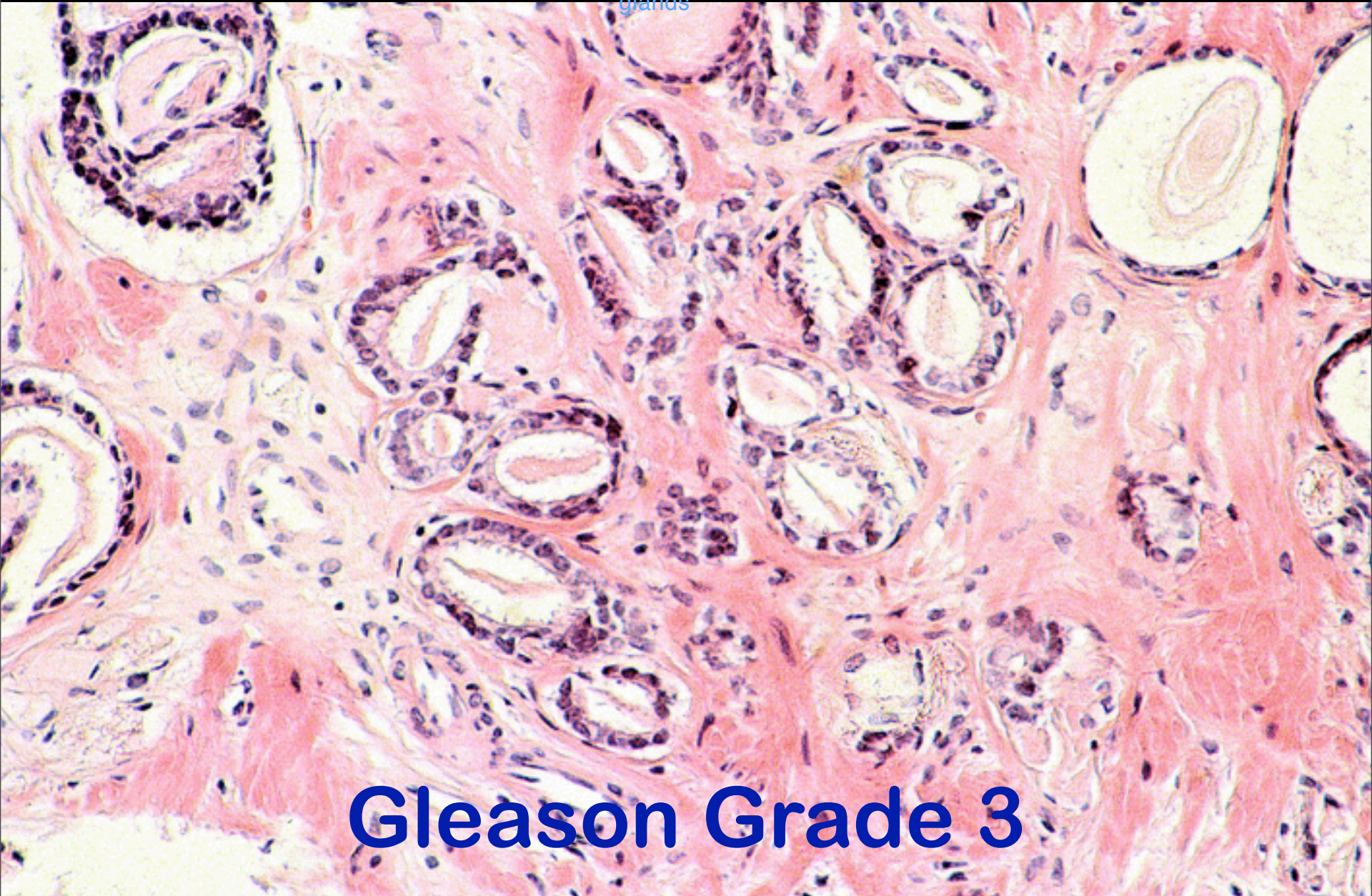
Summary: This is a low grade- resembles normal prostate glands



**Gleason Grade 2**



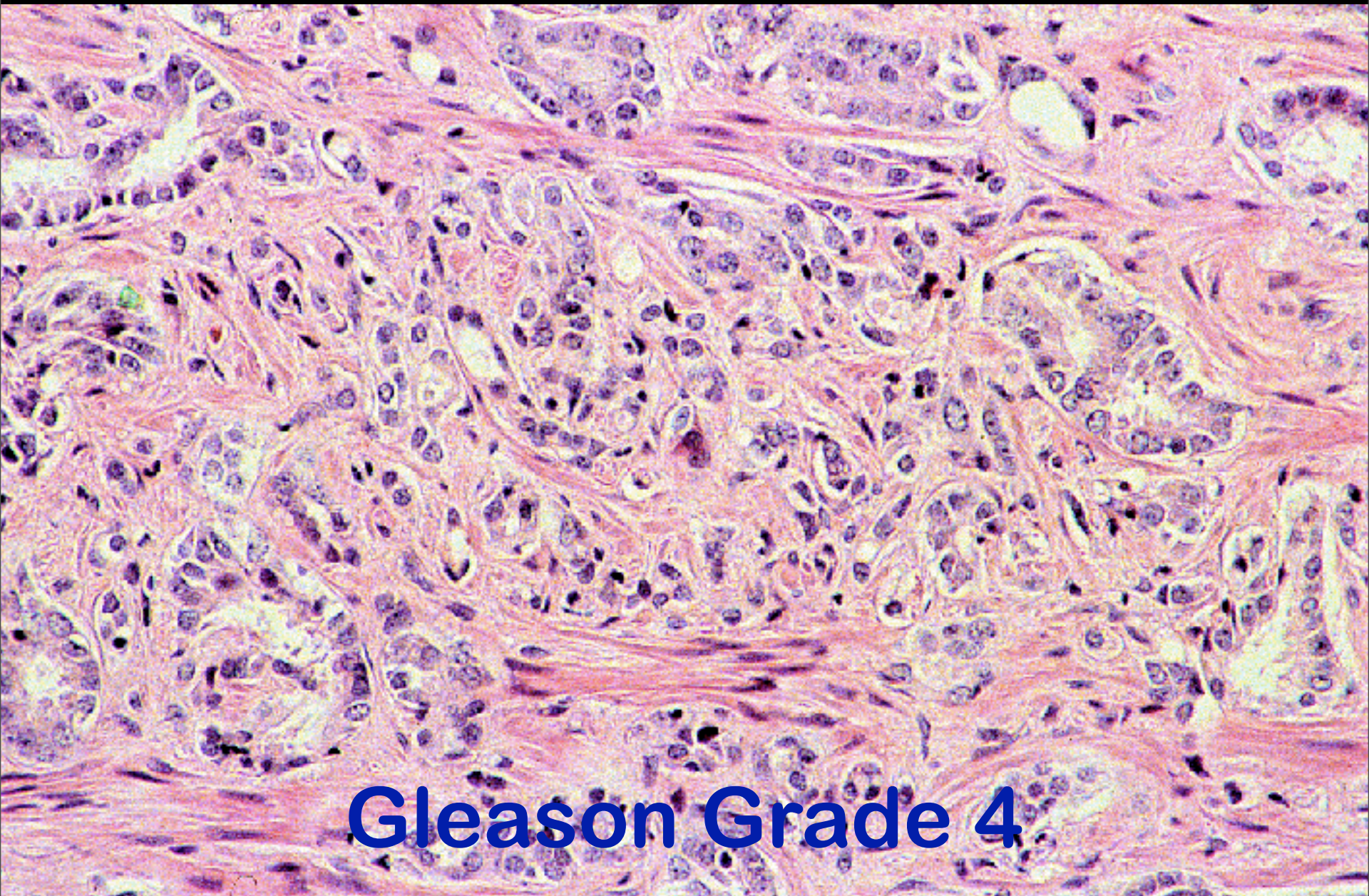
Summary: These are more infiltrative and smaller glands



**Gleason Grade 3**



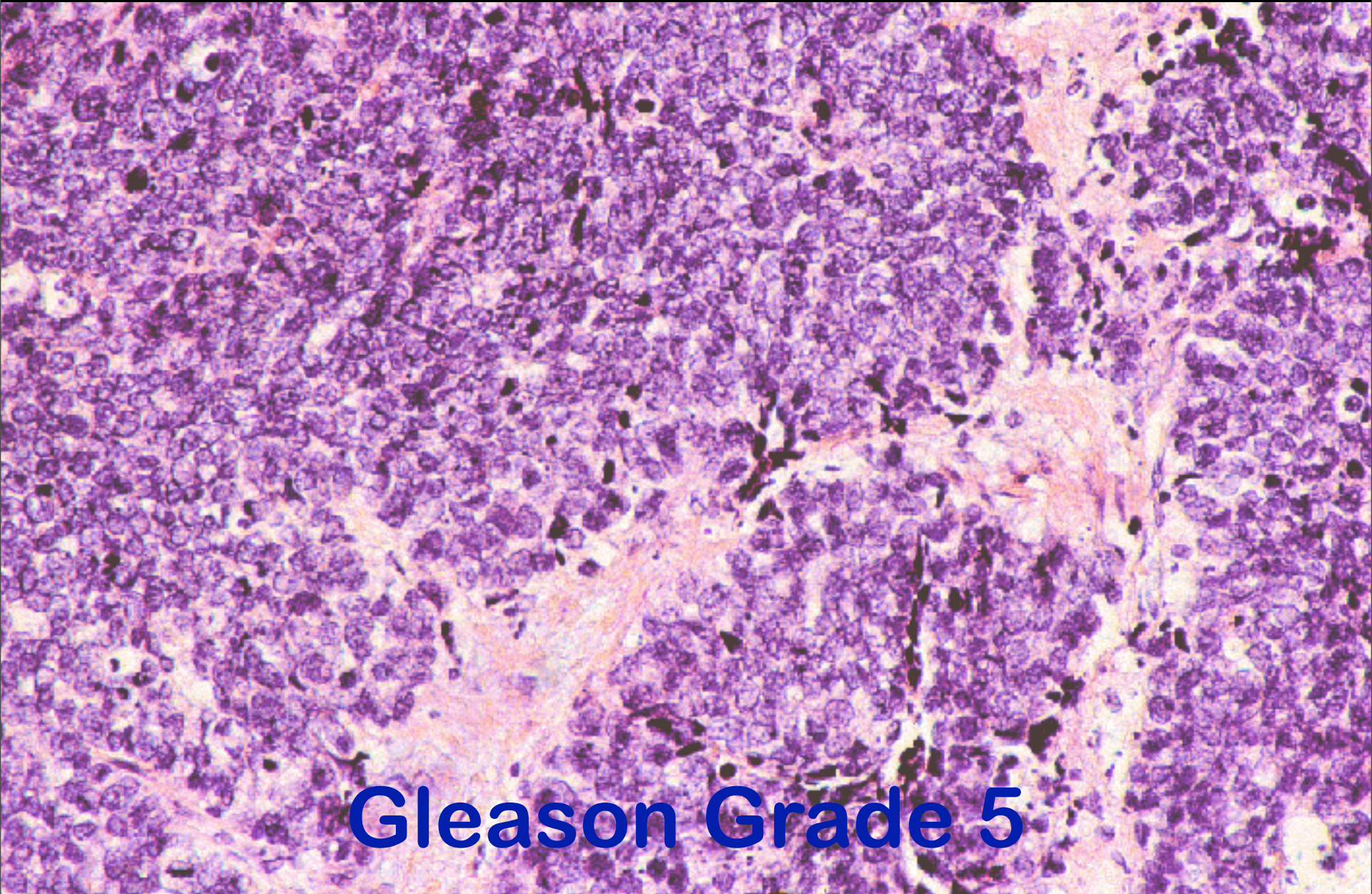
Summary- Little glandular architecture, but some slight resemblance



**Gleason Grade 4**



Summary- Grade 5 is histologically least differentiated and biologically most aggressive

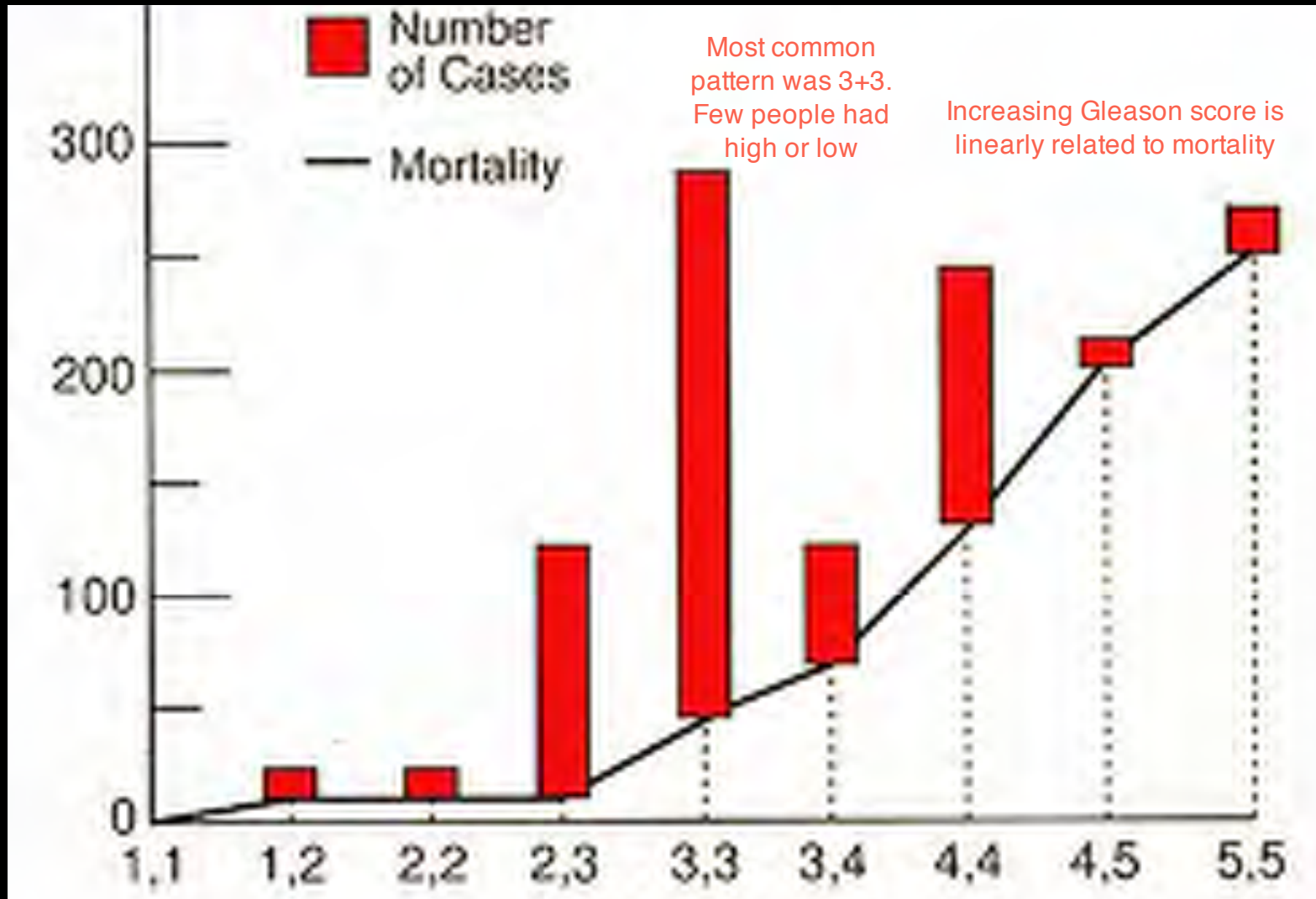


**Gleason Grade 5**



All of this is summarized on the next slide

Some measure of mortality



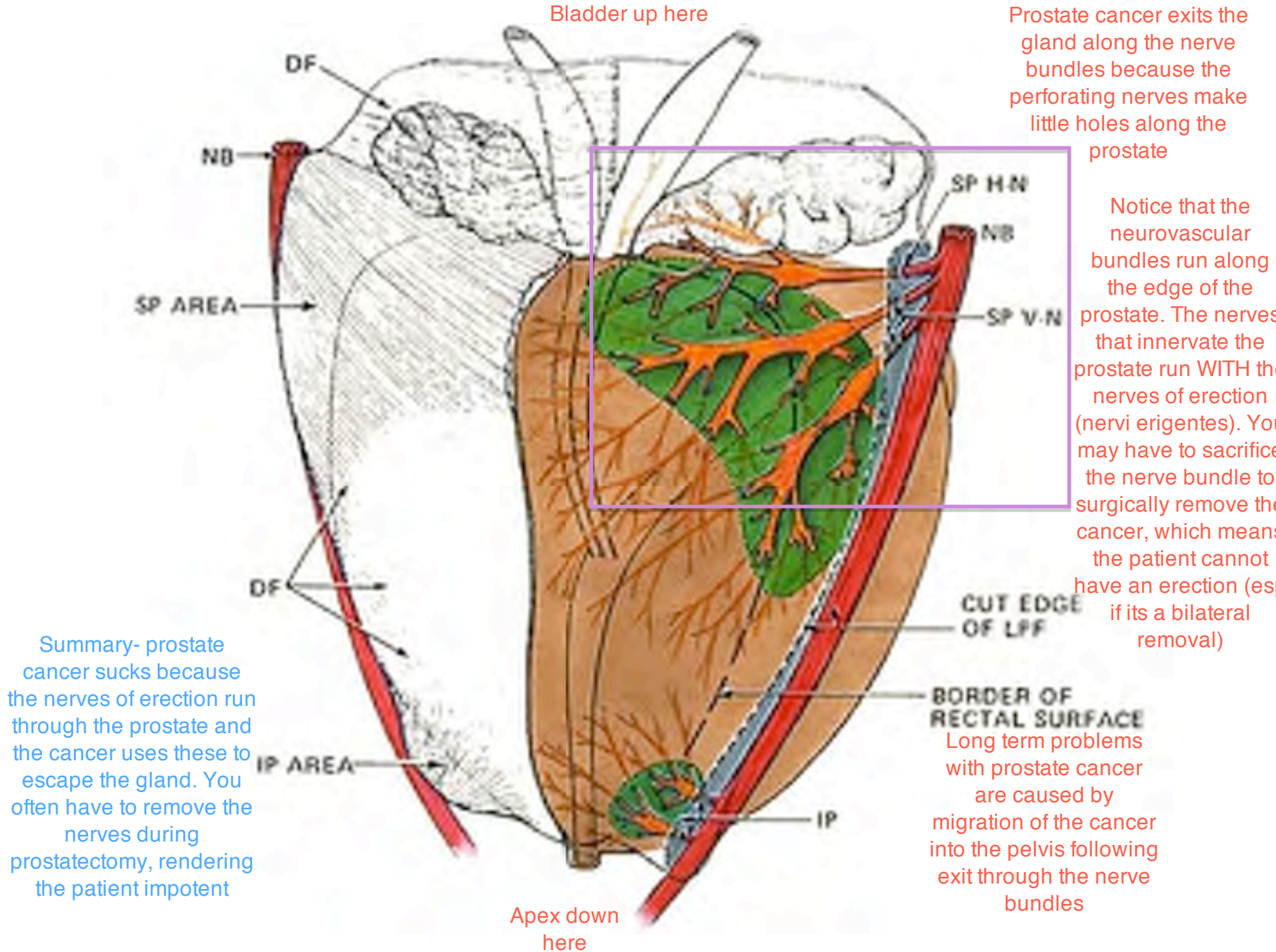
Gleason Scores; more differentiated on the left, less differentiated on the right



Summary- low Gleason scores  
are good prognosis, high is  
bad; but 3 (intermediate) is  
most common

# Implications of Gleason grade

- Gleason grade 1 and 2 tumors are indolent
- Gleason grade 3 = most common pattern, intermediate prognosis
- Any component of Gleason grade 4 or 5 confers markedly worse prognosis



Bladder up here

Prostate cancer exits the gland along the nerve bundles because the perforating nerves make little holes along the prostate

Notice that the neurovascular bundles run along the edge of the prostate. The nerves that innervate the prostate run WITH the nerves of erection (nervi erigentes). You may have to sacrifice the nerve bundle to surgically remove the cancer, which means the patient cannot have an erection (esp if its a bilateral removal)

Summary- prostate cancer sucks because the nerves of erection run through the prostate and the cancer uses these to escape the gland. You often have to remove the nerves during prostatectomy, rendering the patient impotent

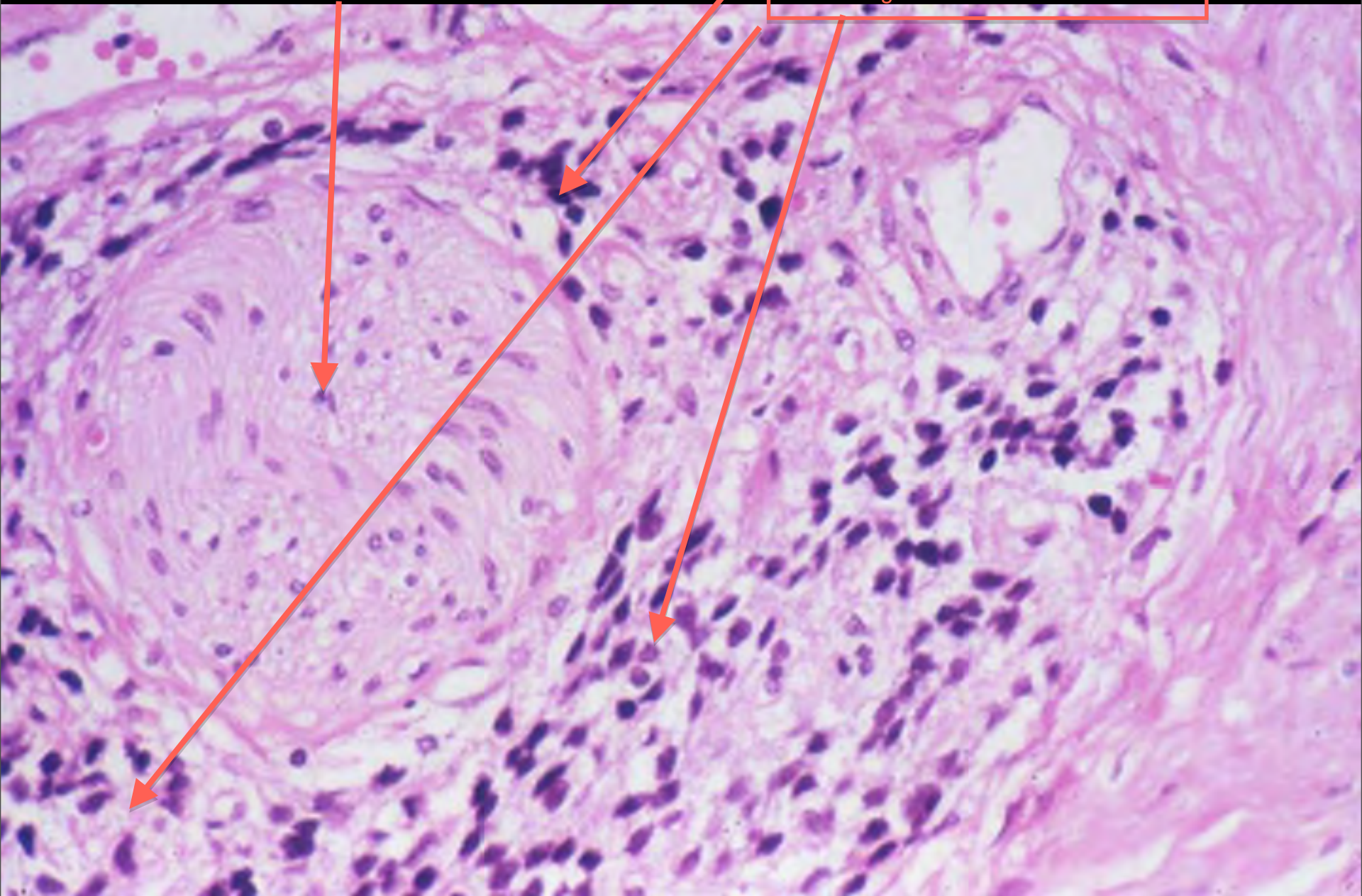
Long term problems with prostate cancer are caused by migration of the cancer into the pelvis following exit through the nerve bundles

Apex down here



Nerve Bundle

Cancer cells are crawling along the edge of the nerve bundle

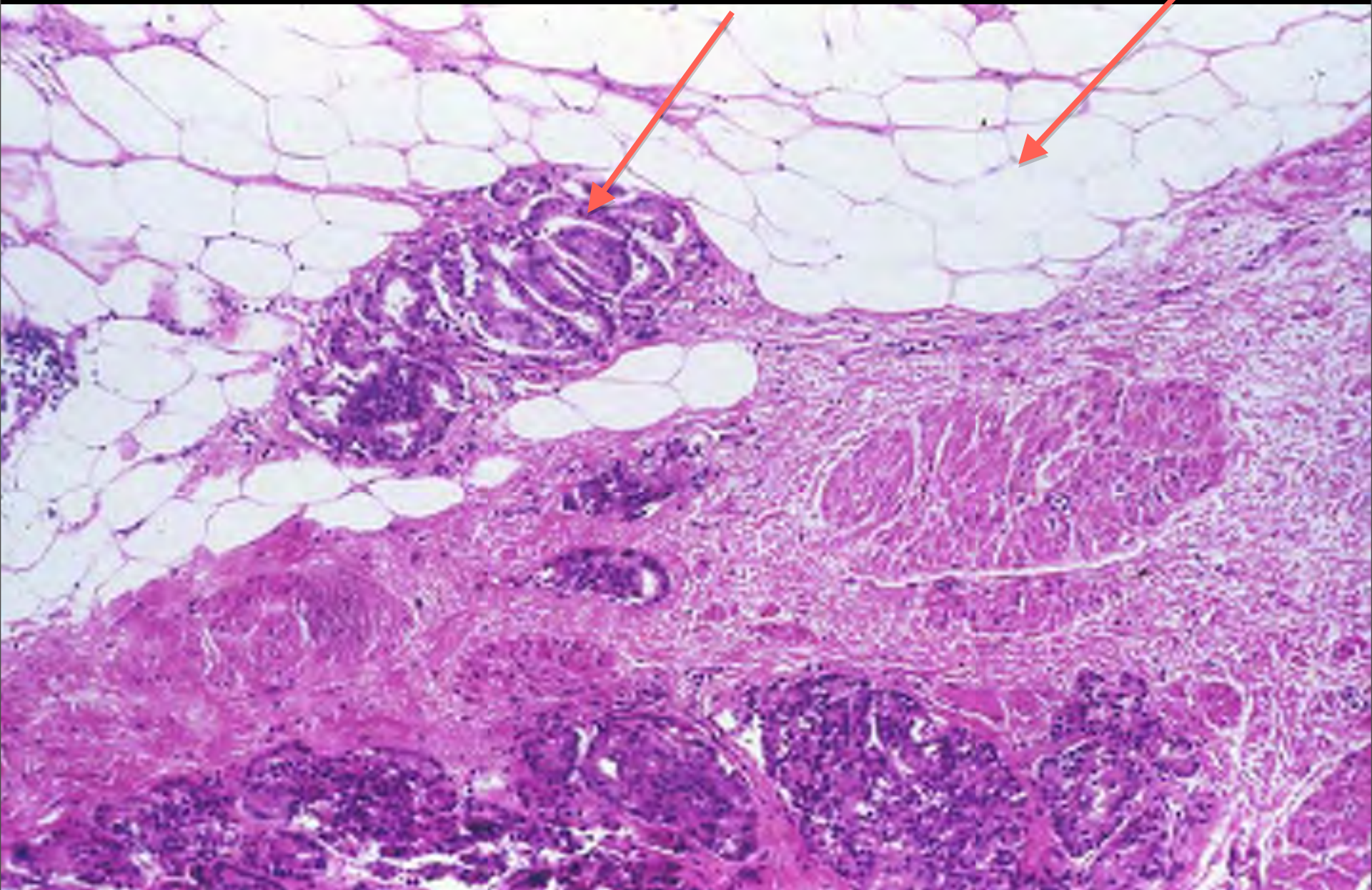


Summary- The point being shown here is that the prostate cancer cells use the nerve bundles as exit sites to migrate away from the glands



Cancer has left the prostate and migrated into the pelvis via a nerve

Pelvic Fat



Summary- again, prostate cancer uses the nerve bundles to escape





Summary- Prostate cancer likes to metastasize into bone, causing osteoblastic bone lesions that are painful. These are managed by hormone therapy

# Therapeutic dilemma of prostate cancer

He just read this slide

- Prostate cancer is very common, prevalence increasing with age
- Most cancers behave indolently, but a minority behave aggressively
- Our ability to predict behavior in a particular case is limited
- Definitive therapy (radical prostatectomy) can have significant negative impact on quality of life

Summary- prostate cancer is common, and usually indolent; however, it is hard to predict behavior and radical prostatectomy is not cool

# Treatment of prostate cancer

- Radical prostatectomy Definitive therapy

- Radiation therapy

- External beam
- Brachytherapy

There are different ways to deliver the radiation, but he didn't discuss the details

- Androgen deprivation

- Anti-androgen drugs But eventually the cancer evolves to grow despite this therapy
- Orchiectomy

- Watchful waiting

aka Active Surveillance. Just don't do anything. Often used for low grade

- Focal therapy Future goal- we are years away

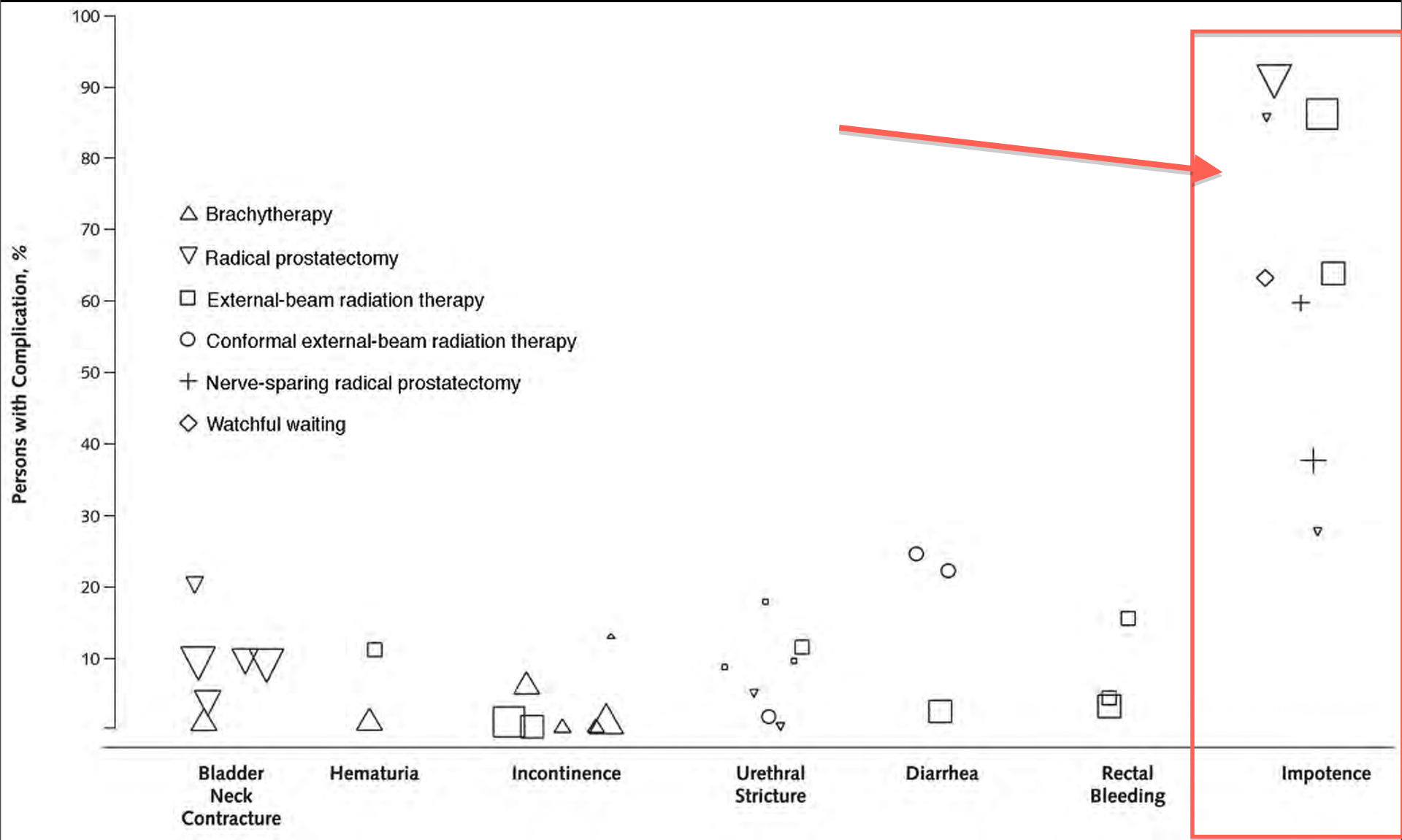
Summary- currently 4 major treatment options for prostate cancer. Radical prostatectomy is the best, radiation therapy is an option, androgen deprivation works until the cancer evolves, and watchful waiting is often used

Summary- there are a lot of complications to prostate cancer therapy, and impotence is the most common

# Complication rate

for a variety of prostate treatment methods (see key)

(Wilt TJ et al. Ann Intern Med 2008; 148:435-445)





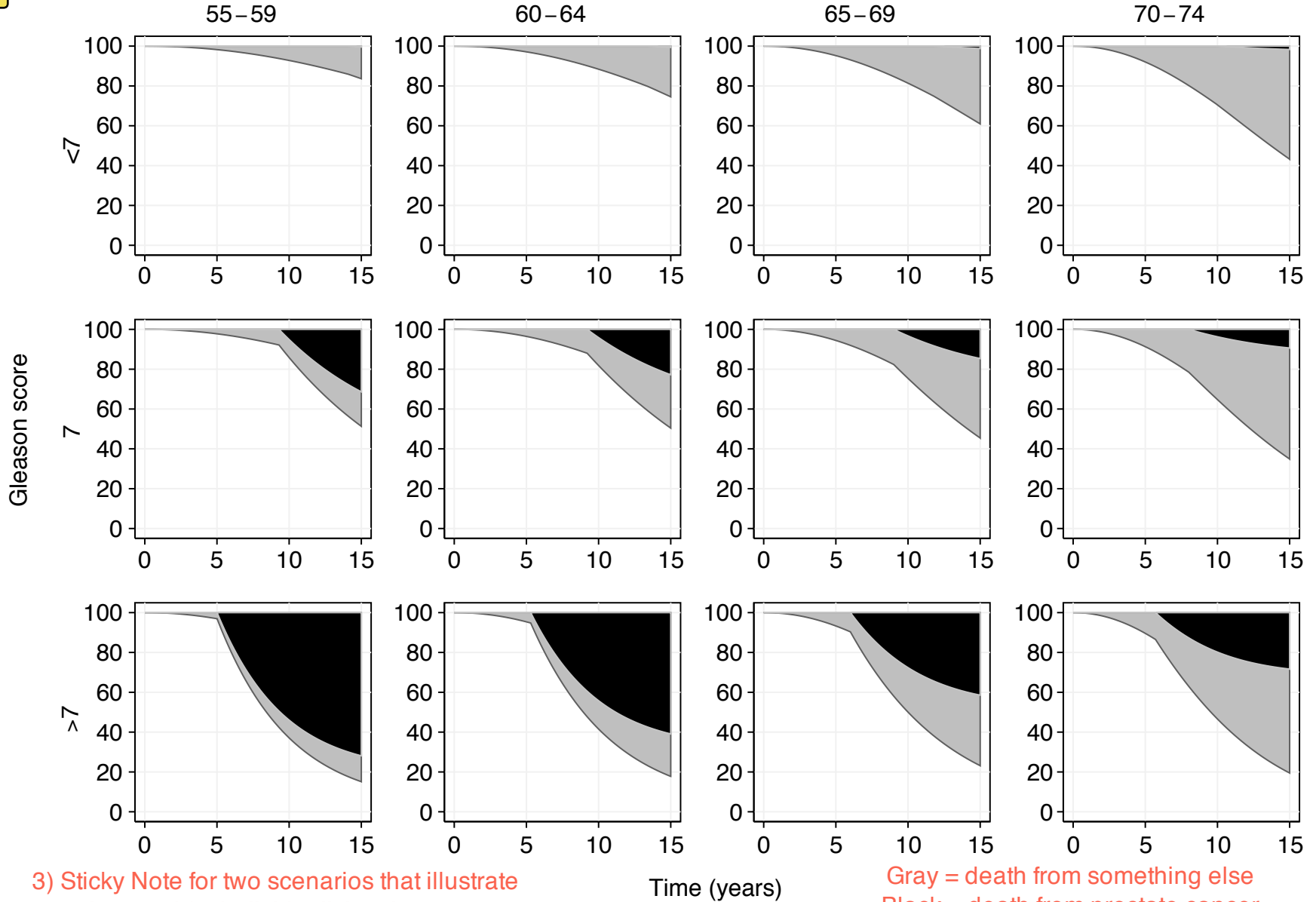
Parker et al. A model of the natural history of screen-detected prostate cancer, and the effect of radical treatment on overall survival. Br J Cancer (2006) vol. 94 (10) pp. 1361-8

1) These graphs are generated by an algorithm based on data

2) The goal was to see what effect watchful waiting has, controlling for Gleason Score and Age



Age at diagnosis (years)



3) Sticky Note for two scenarios that illustrate the need for individualizing therapy

Gray = death from something else  
Black = death from prostate cancer

Watchful Waiting is used a lot in Sweden, Finland, Norway, Denmark etc. A group from there periodically publishes patients from these countries that are out 15 years.

# Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

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Mirja Ruutu, M.D., Ph.D., Hans Garmo, Ph.D., Jennifer R. Stark, Sc.D.,  
Christer Busch, M.D., Ph.D., Stig Nordling, M.D., Ph.D.,  
Michael Häggman, M.D., Ph.D., Swen-Olof Andersson, M.D., Ph.D.,  
Stefan Bratell, M.D., Ph.D., Anders Spångberg, M.D., Ph.D.,  
Juni Palmgren, Ph.D., Gunnar Steineck, M.D., Ph.D.,  
Hans-Olov Adami, M.D., Ph.D., and Jan-Erik Johansson, M.D., Ph.D.,  
for the SPCG-4 Investigators\*

N ENGL J MED 364:18 NEJM.ORG MAY 5, 2011

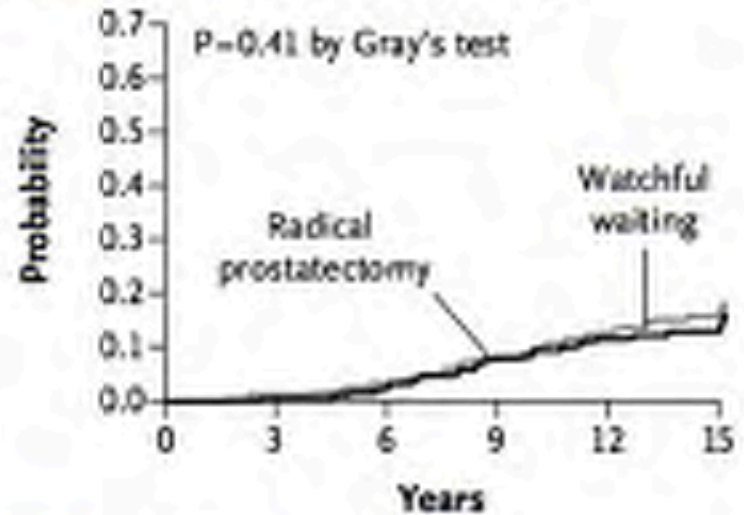
Summary of slides 38-40: watchful waiting may be as good as prostatectomy in older men and men with low grade tumors. In younger men, prostatectomy is better statistically

Notice that there is NO statistical significance between prostatectomy and waiting in men over 65

# All patients mortality

In men UNDER 65, radical prostatectomy had better results. But notice that its a decreased risk of 20% to 10%

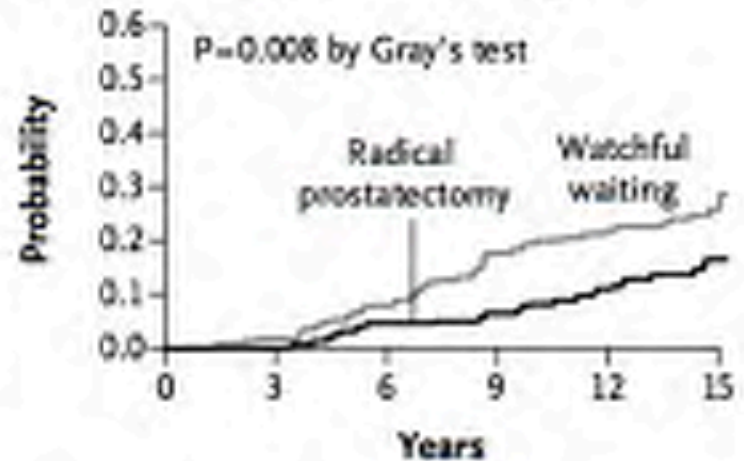
**E** Death from Prostate Cancer, Men  $\geq 65$  Yr of Age



**No. at Risk**

Radical prostatectomy	190	185	166	135	99	42
Watchful waiting	182	177	162	133	101	42

**H** Death from Prostate Cancer, Men <65 Yr of Age

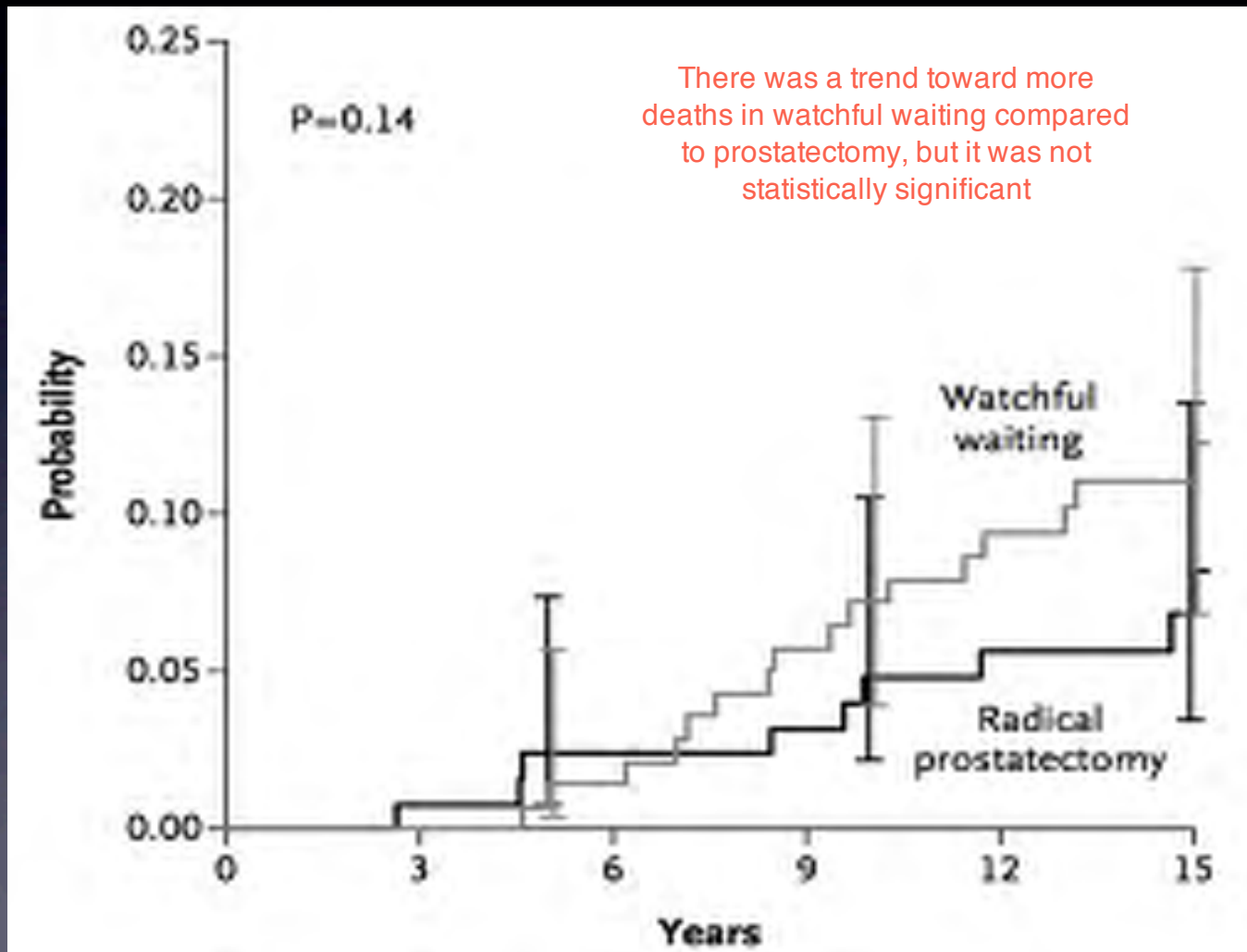


**No. at Risk**

Radical prostatectomy	157	154	145	136	115	67
Watchful waiting	166	157	144	118	91	54



# Low-risk prostate cancer mortality (PSA <10 ng/ml, Gleason <7)



Summary- PSA test is for prostate specific antigen, an enzyme that escapes into the circulation especially during metastasis

# PSA Testing

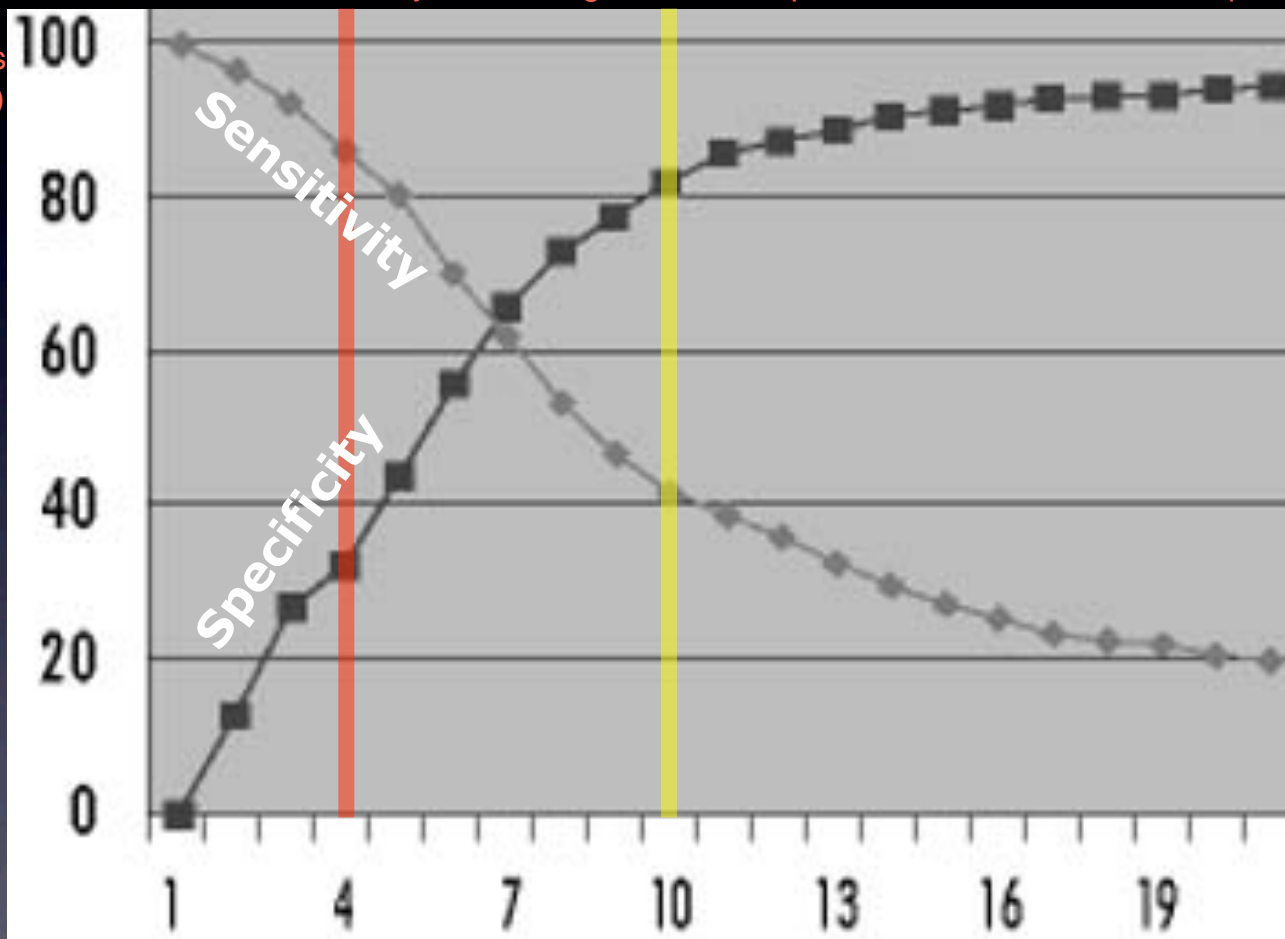
- PSA = “Prostate specific antigen”, normal component of prostate secretions
- Escapes into general circulation in prostate cancer
  - Cancer limited to gland → low serum levels
  - Metastatic cancer → high levels

# PSA sensitivity/specificity

If you were whipping up a test, would you want a sensitive or specific screening test? Generally you want the sensitive one because you want to pick up all the cases of the disease that you can, and you're willing to take false positives too. You can follow up with a specific test

Threshold setting involves a trade-off between sensitivity and specificity. Conventional cutoff is the red line (4 ng/mL)

%



Recall  
- Sensitivity = PID (positive in disease)  
- Specificity = NIH (negative in health)

PSA is widely used as a test, but is NEITHER sensitive NOR specific. It just happens to be the only test we have

Serum PSA (ng/ml)

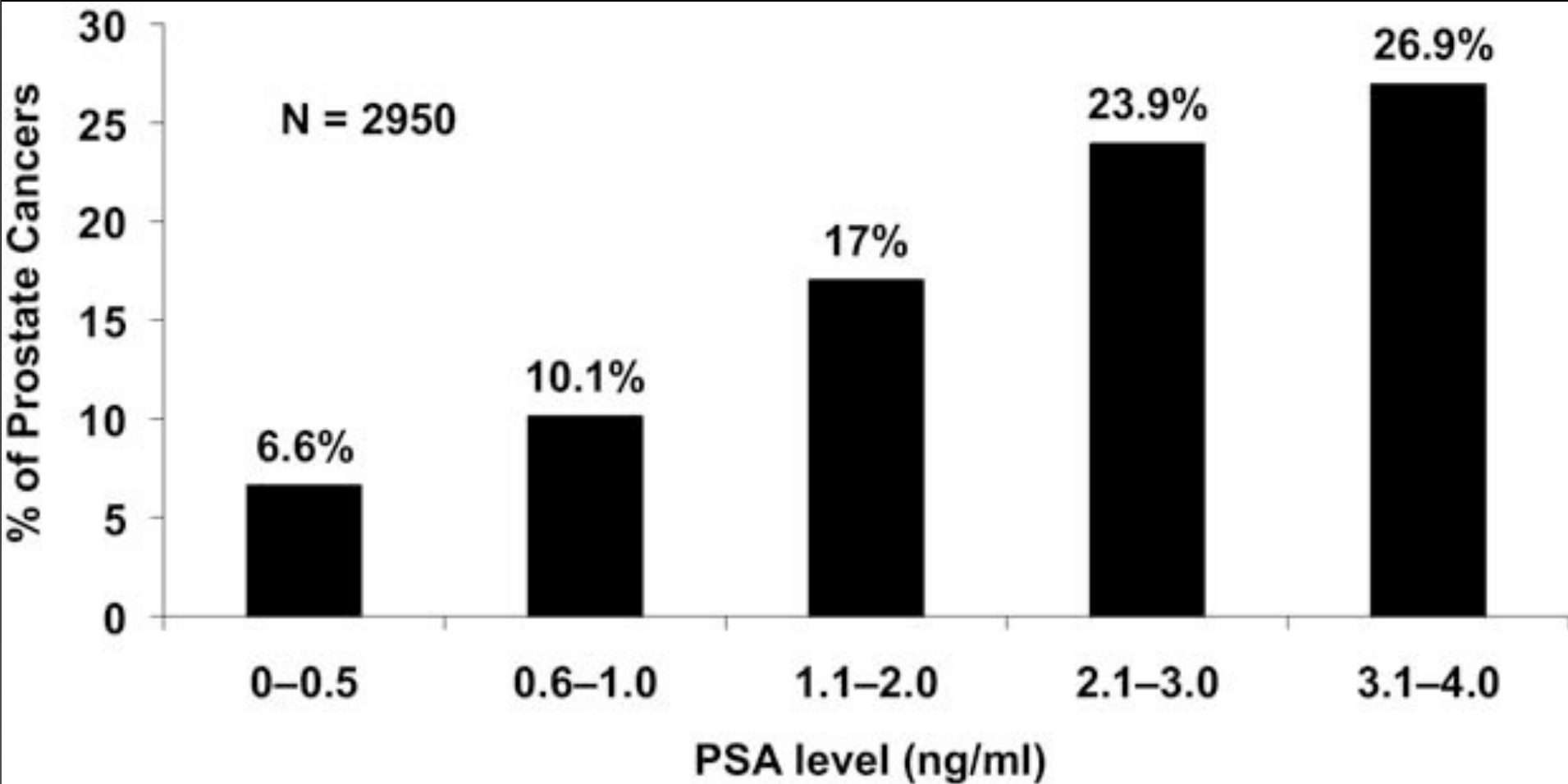
Summary- the PSA test is neither sensitive nor specific



# Over half of prostate cancers are in men with PSA $\leq 4$

Many people with low PSA still have cancer. Therefore, interpreting the result of the test therefore involves some judgement (age, family history, risk factors etc)

Summary- the PSA test is not sensitive



Summary- there is controversy over whether to universally screen for prostate cancer

# Universal prostate cancer screening

## FOR

- American Cancer Society
- American Urological Association
- National Comprehensive Cancer Network

## AGAINST

- American College of Physicians
- US Preventive Services Task Force
- American Society of Internal Medicine
- National Cancer Institute
- CDC
- American Association of Family Practicioners
- American College of Preventive Medicine

# American Cancer Society Recommendations (2005)

- PSA & DRE to be offered annually to men 50 or over with life expectancy  $\geq$  10 years
- Men at high risk should begin testing at age 45, at “very high risk” at age 40

- Men who ask clinician to make the testing decision on their behalf should be tested





Keep your eye  
***on the ball!***

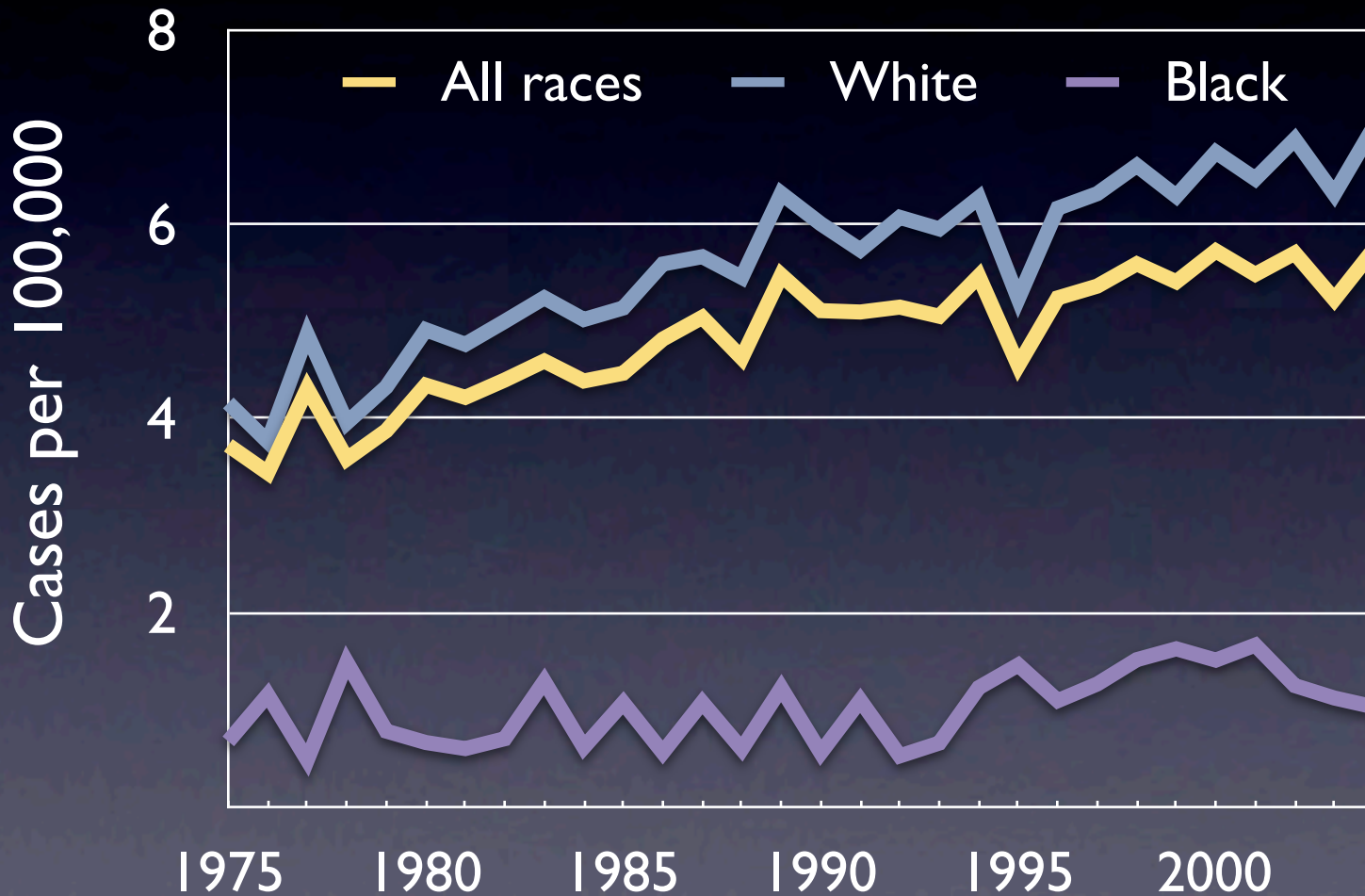
Information on Testicular Awareness - [Click here...](#)

**Check Your  
Johnnies.com**

This material was not covered in the Streaming video available on BlueDocs for ms2016. Nevertheless, you need to know about Testicular cancer and not just because Lance Armstrong had it. There are quiz questions but no biweekly exam questions on this topic. This deficiency will be corrected soon. Dr. H

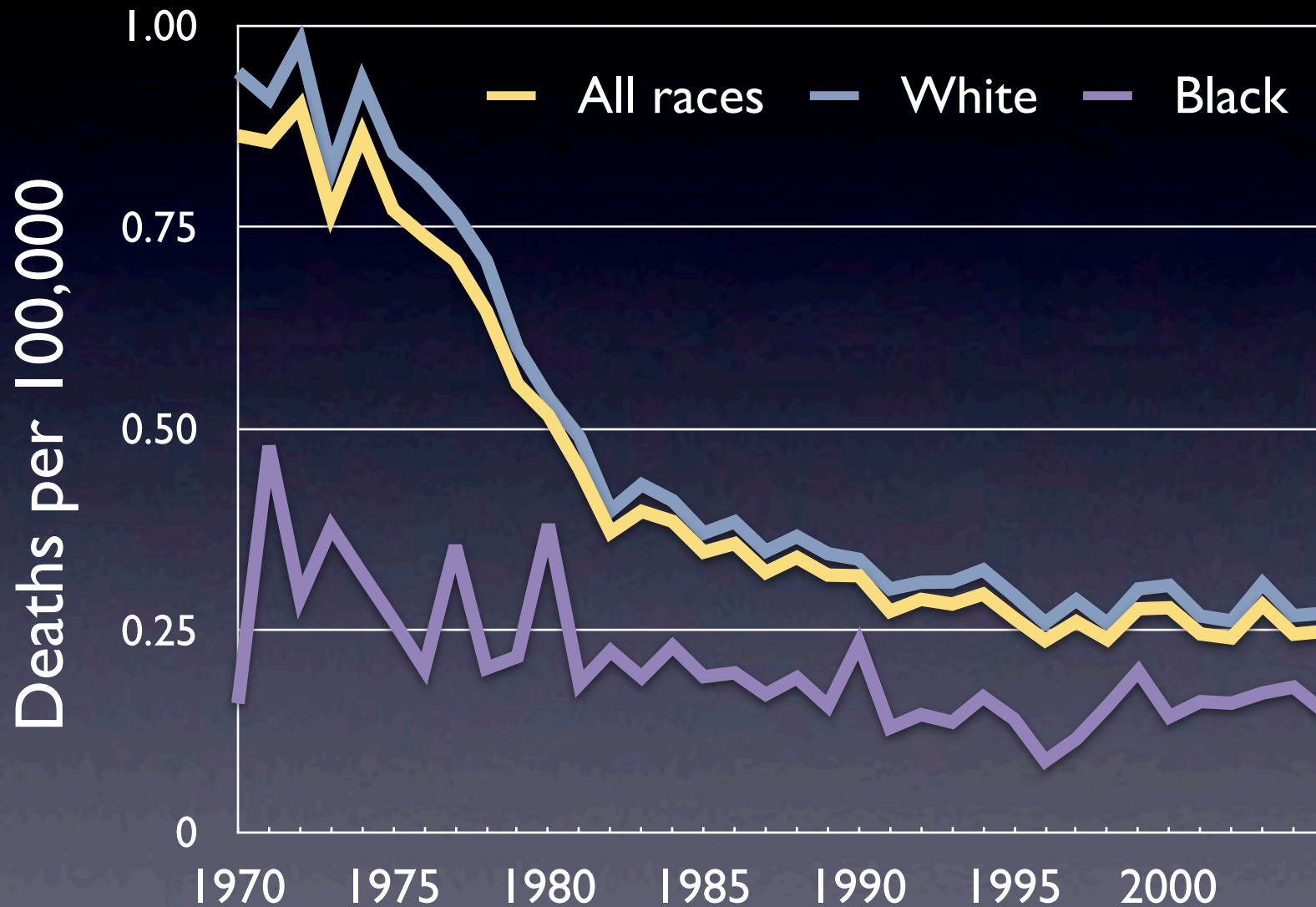
# Testis cancer

# Testis cancer incidence

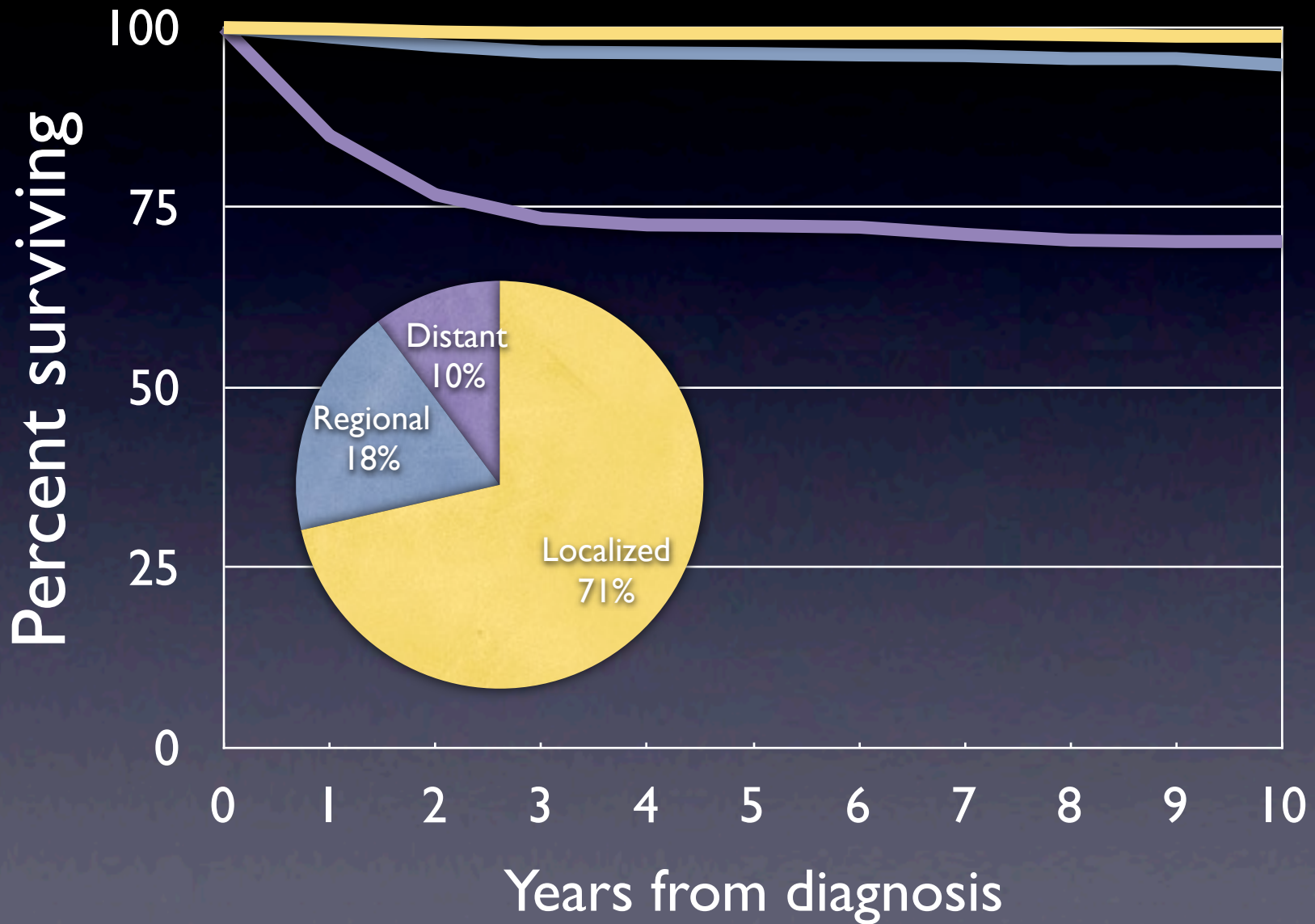




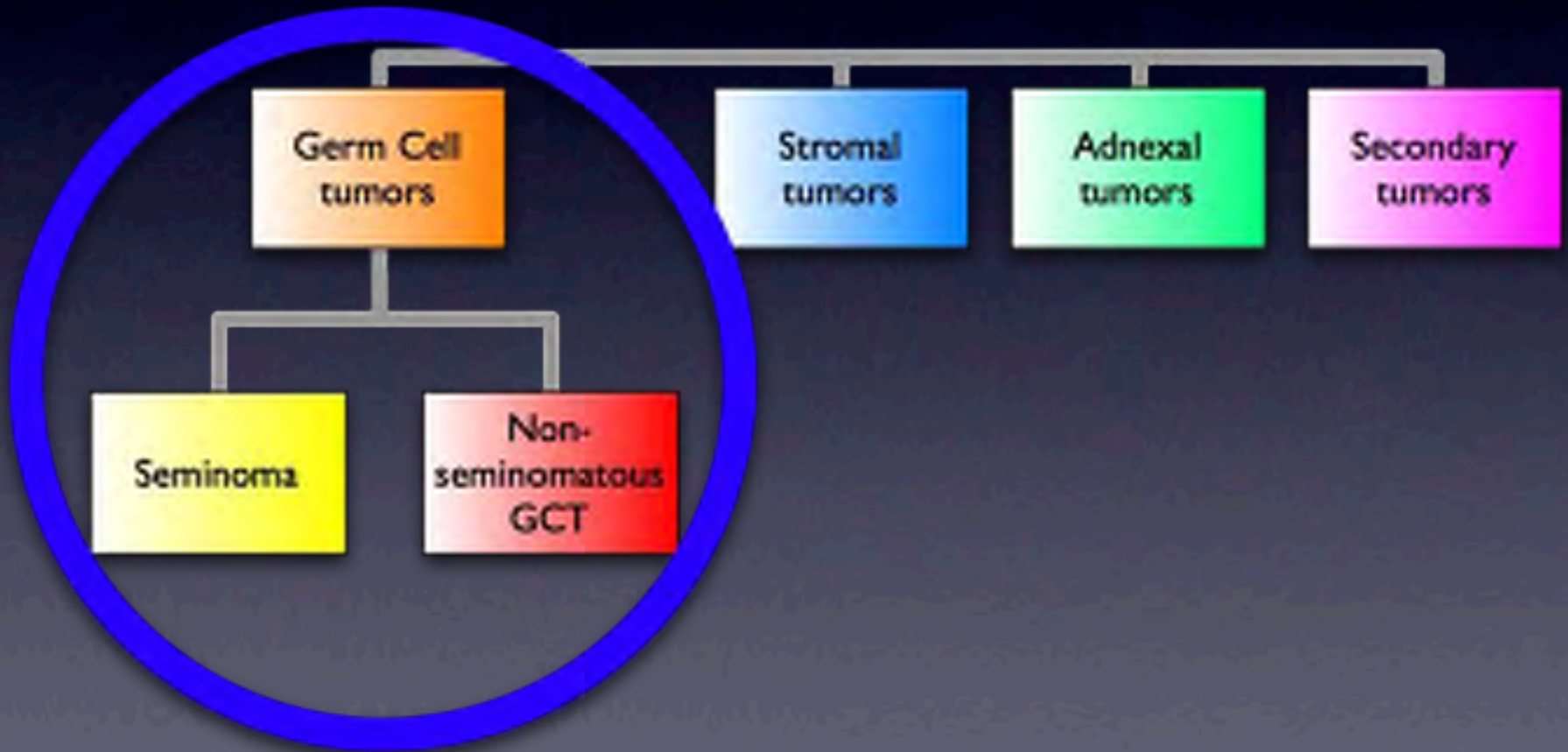
# Testis cancer mortality



# Testis cancer survival



# Testicular Tumors





# Why is testicular cancer increasing?

- Increased incidence worldwide, up to 3-fold in past 30 years
- During same period, average testicular weight and sperm counts declined, and male genital abnormalities increased
- Changes in diagnosis do not explain trend
- What is going on?
  - Sedentary lifestyle → ↑ testicular temperatures?
  - Intrauterine exposure to environmental agents with estrogenic or anti-androgenic activity?
    - “...small genitalia and decreased semen quality have been reported in Florida alligators and American panthers.”

# Germ Cell Tumors

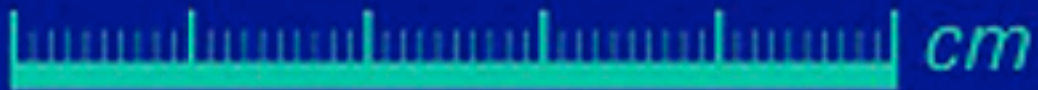
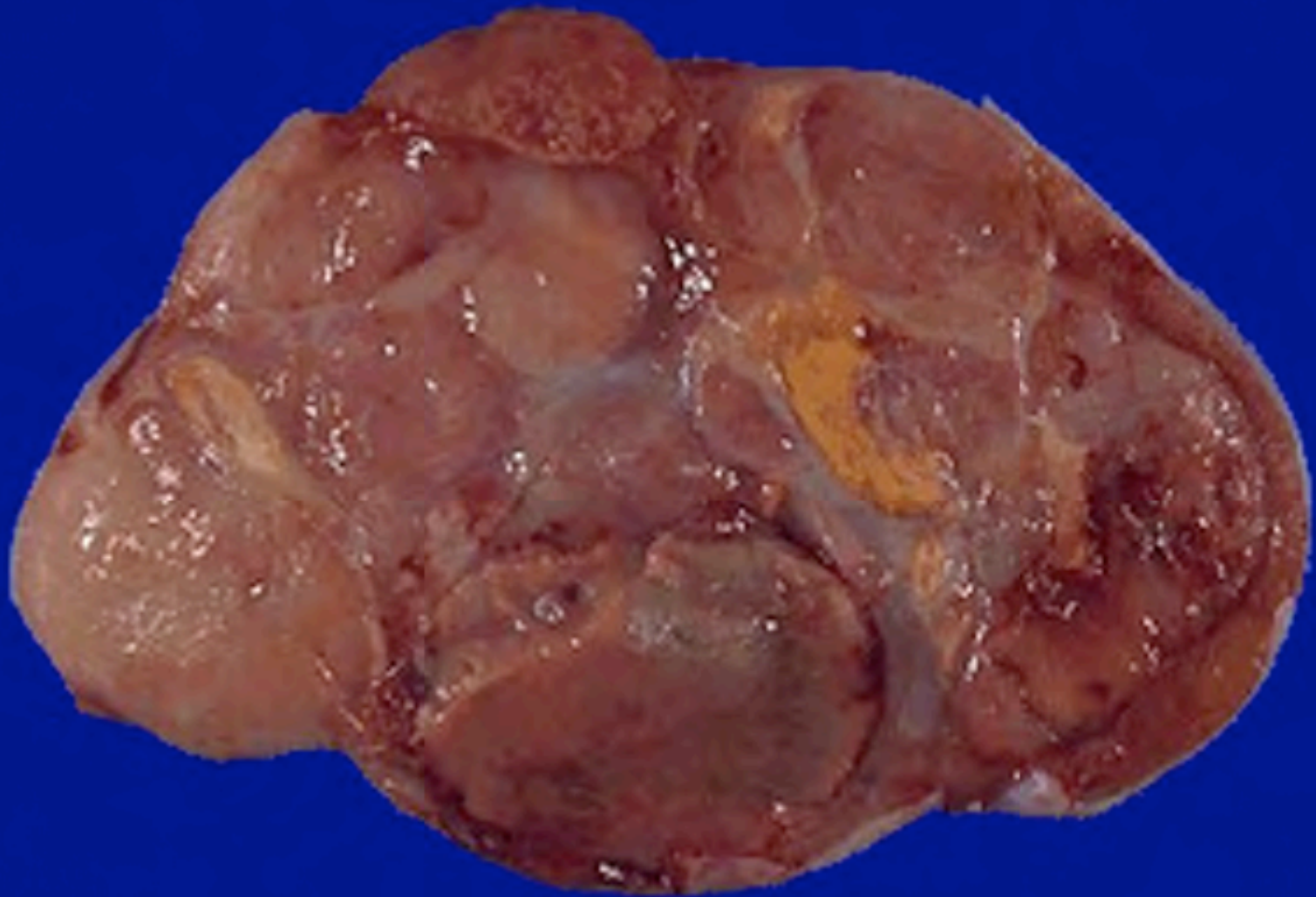
Nonseminomatous (2/3)

Seminoma (1/3)

# Seminoma

- 40% of all germ cell tumors
- Average age 40 years
- Most (75%) stage I at presentation
- About 20% history of cryptorchidism

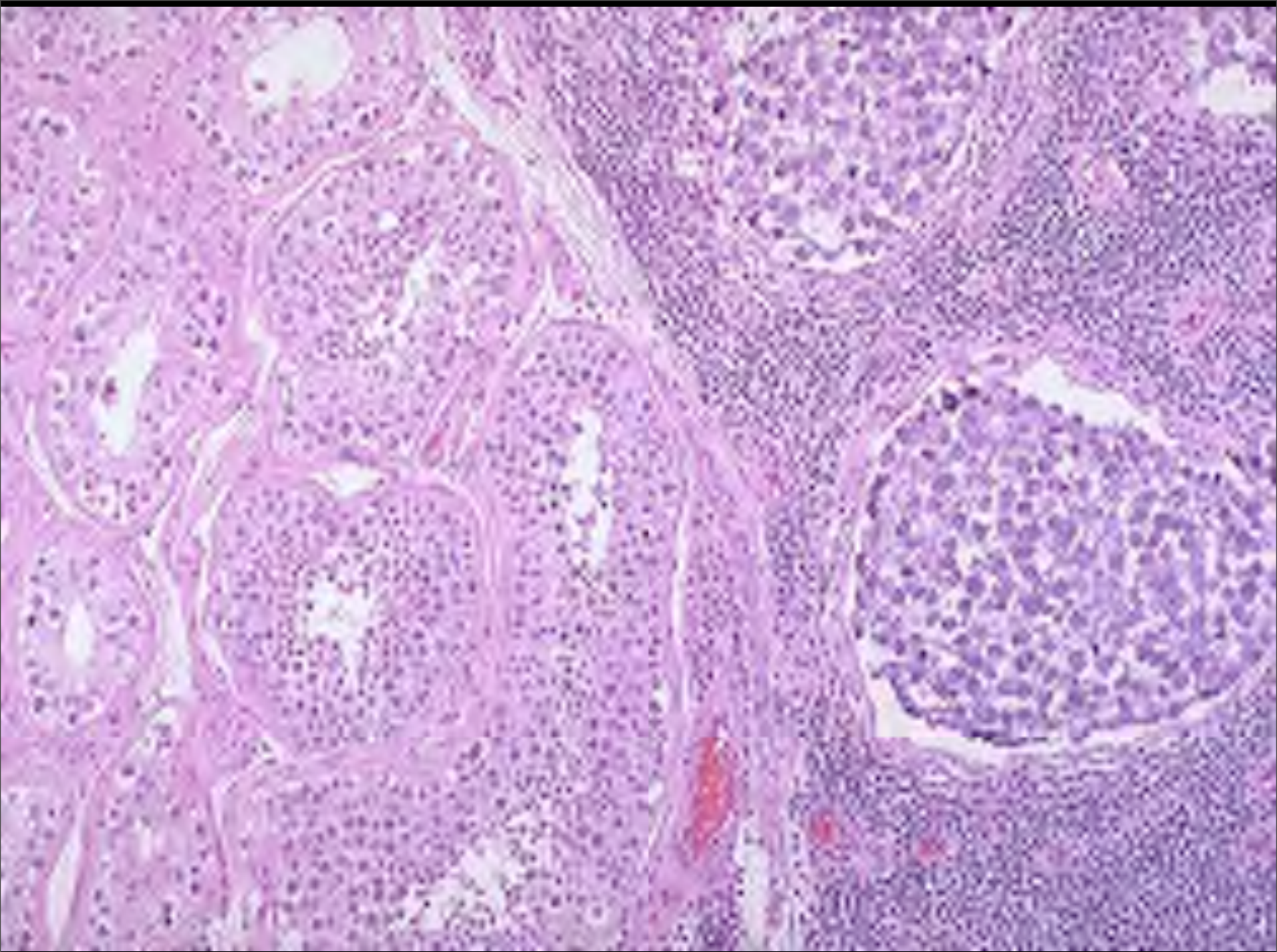




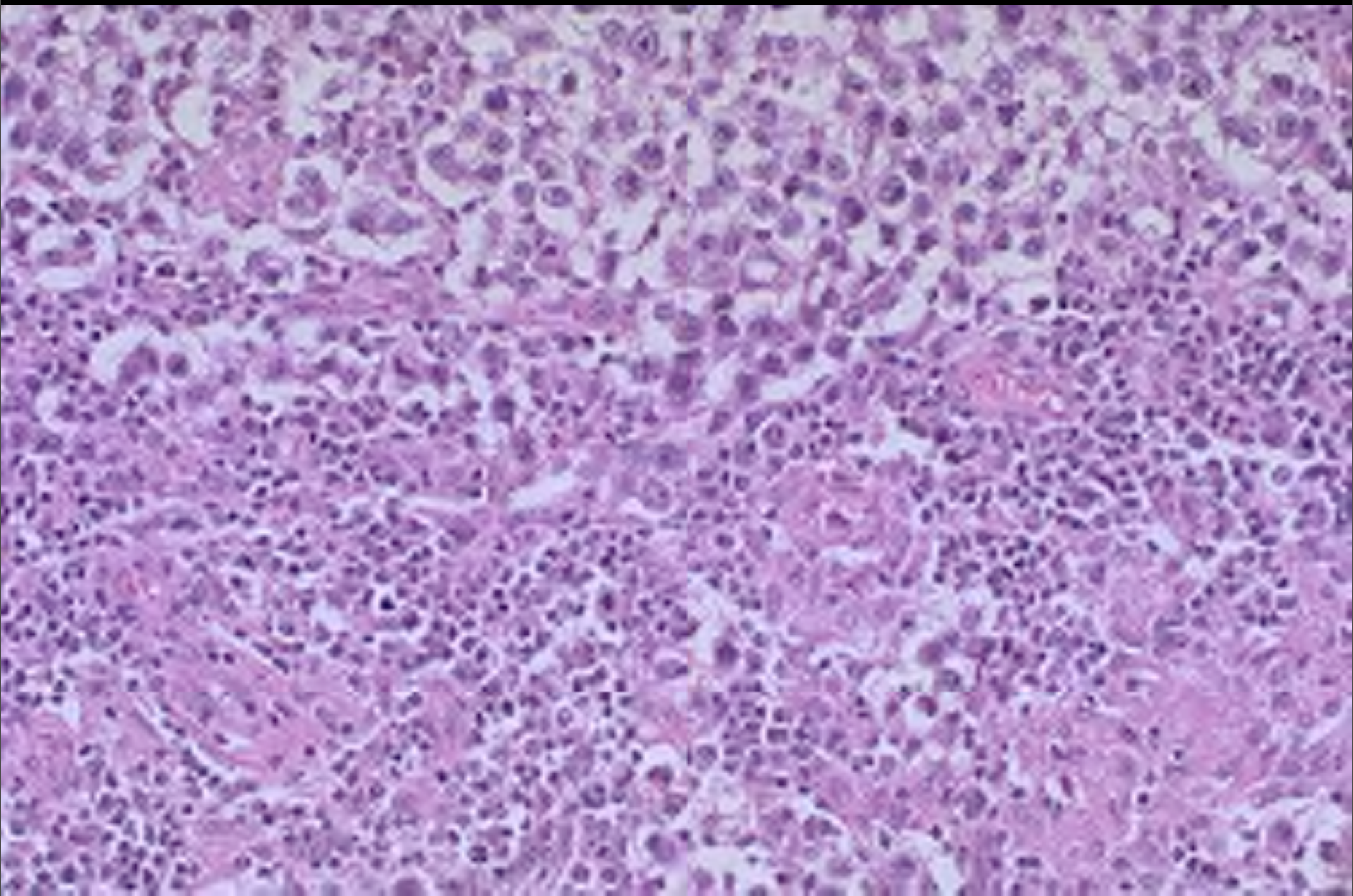
# Seminoma

- Spermatogonium-like nucleus
- Varying degrees of discohesion
- Thin fibrous septa
- Lymphocytes and granulomas
- Coagulative necrosis may occur





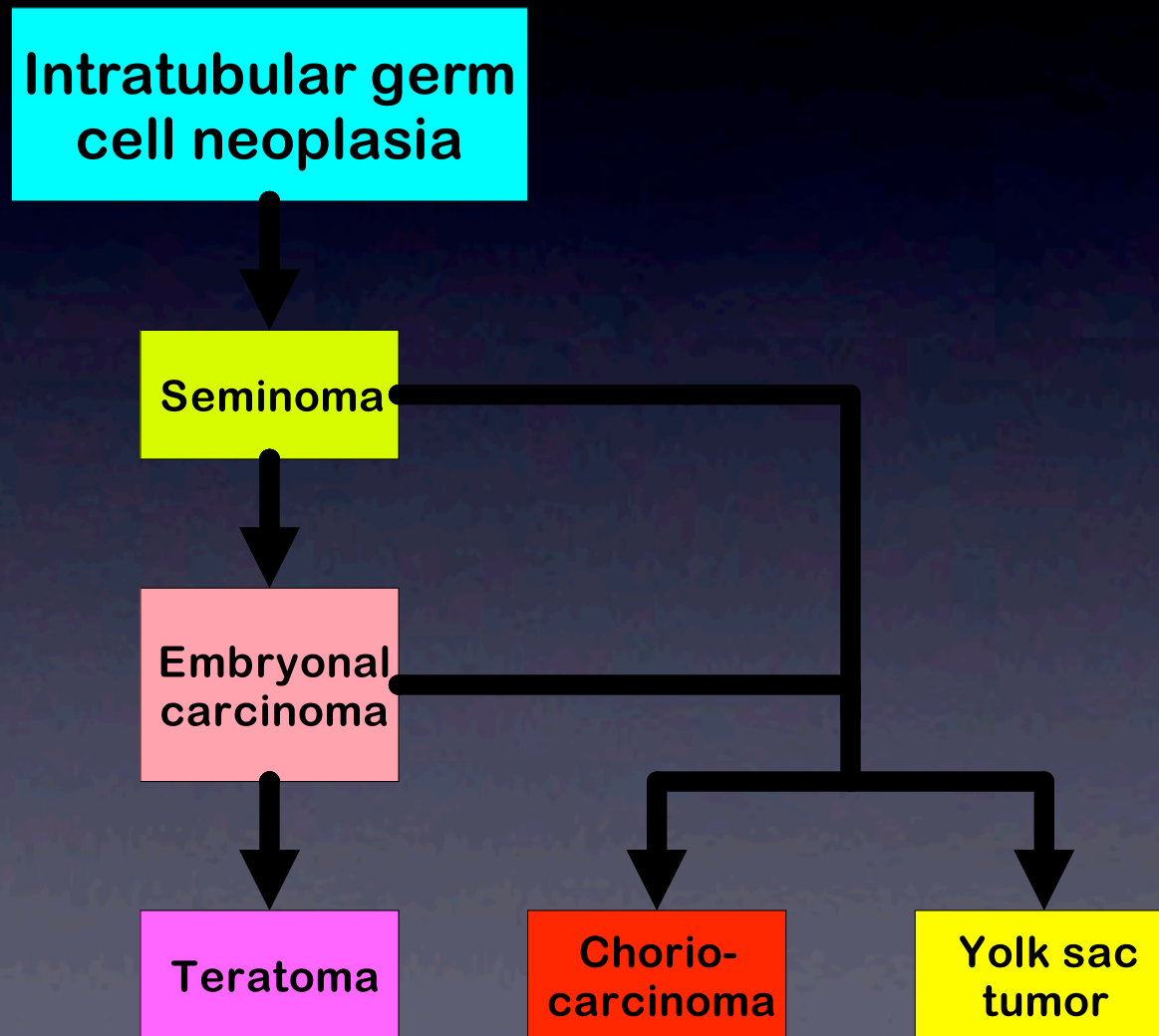




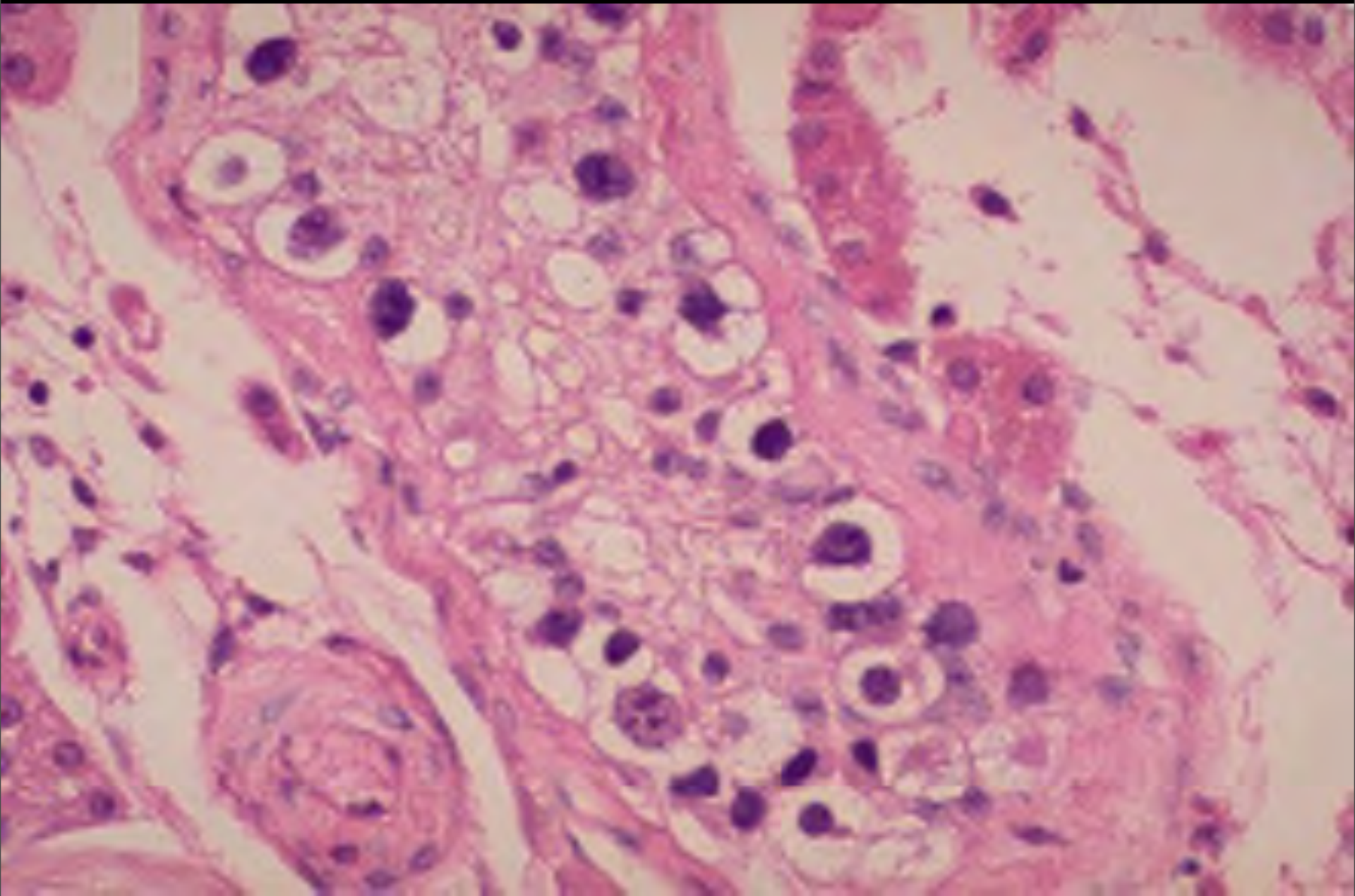
# Treatment of seminoma

- Highly sensitive to radiation and chemotherapy
- Orchiectomy + systemic therapy
  - Retroperitoneal lymph node dissection usually not required
- Survival excellent, even for regional disease

# Histiogenesis







# Nonseminomatous germ cell tumors

Embryonal

Yolk sac

Choriocarcinoma

Teratoma

Other

# Mixed Germ Cell Tumor

- Majority of NSGCT “mixed”, i.e. composites of multiple NSGCT subtype
- Presence of any NSGCT component makes entire tumor NSGCT



# Embryonal Carcinoma

- Average age 32 years
- Some patients have pain
- Stage at presentation
  - 40% limited to testis
  - 40% retroperitoneal nodes
  - 20% remote metastasis
- Some have  $\beta$ -hcG elevation

# Embryonal carcinoma: Gross

- Smaller than seminoma (average ~2.5 cm)
- Hemorrhage, necrosis
- Poorly-circumscribed
- Frequent local extension

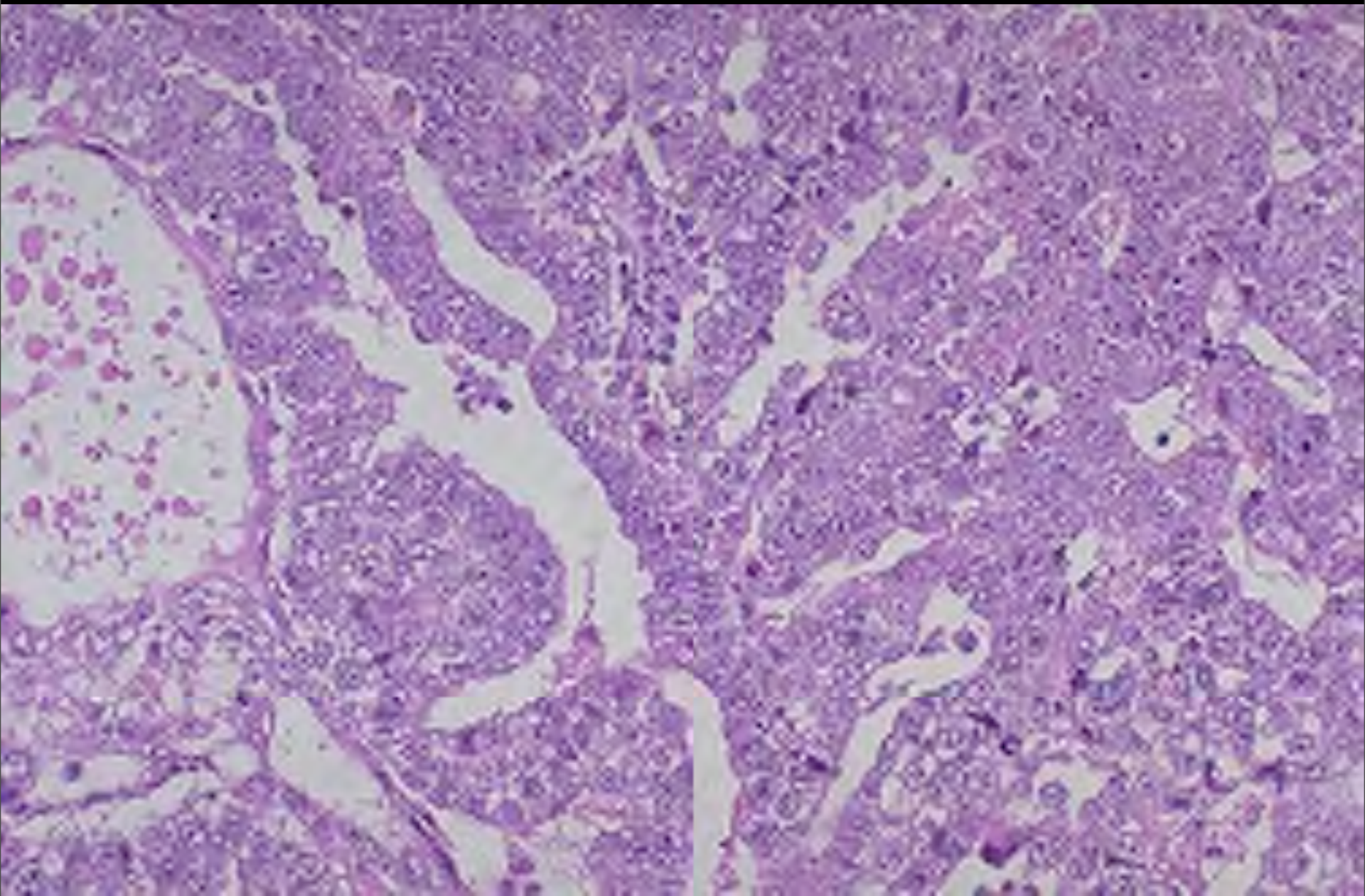


Scale bar: 1 cm

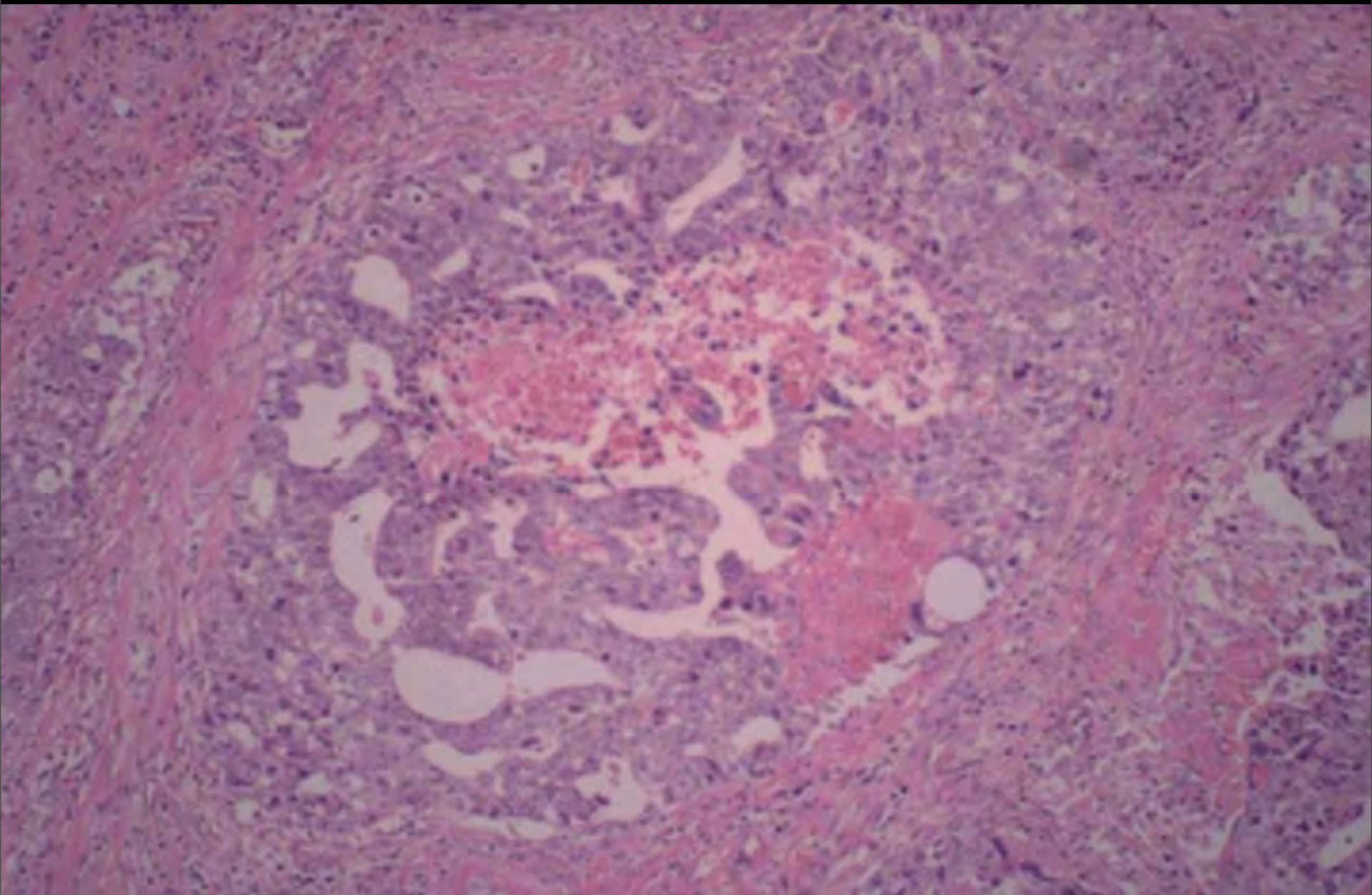


# Embryonal Carcinoma: Microscopic

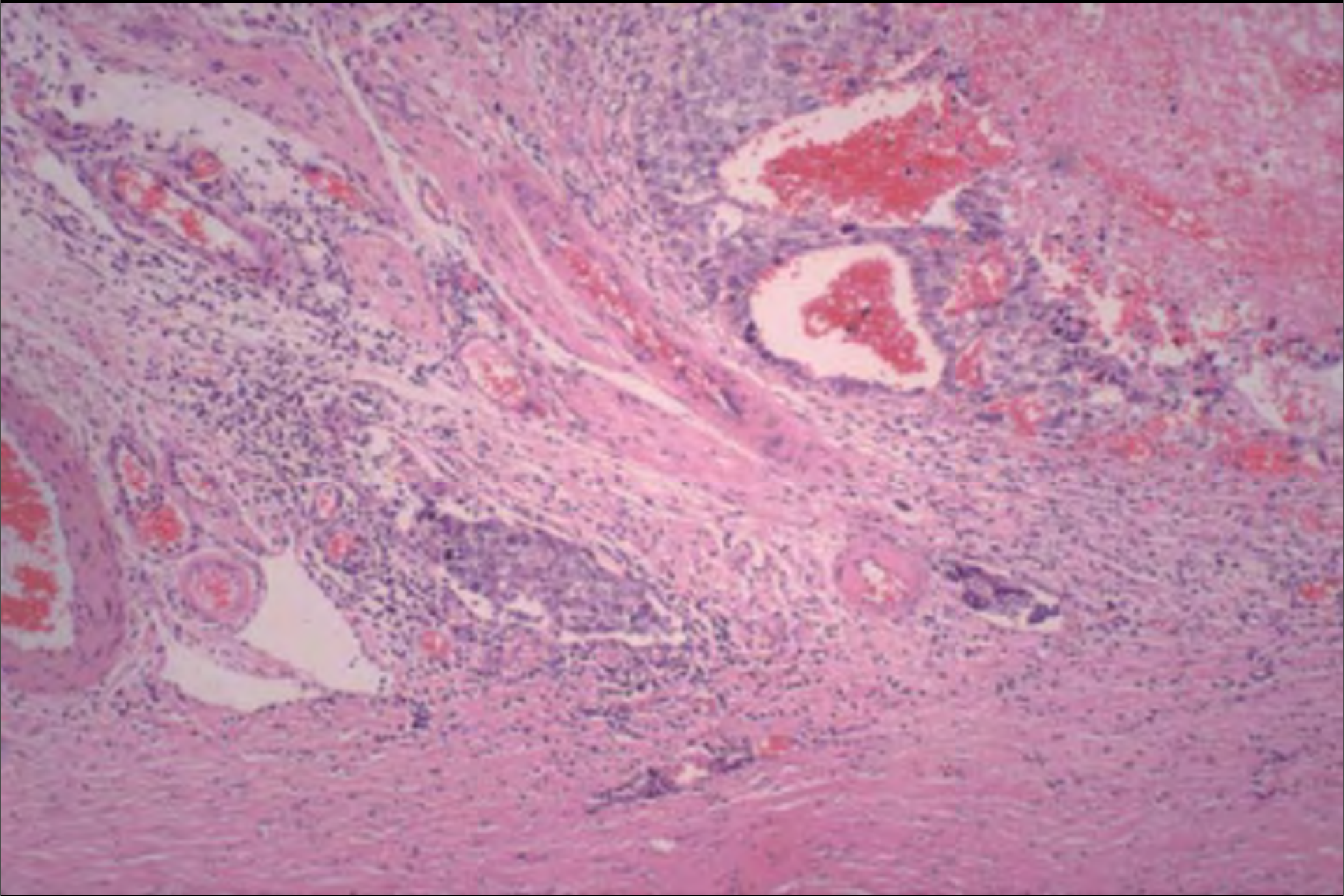
- Variety of patterns
  - Solid (100%)
  - Glandular
  - Papillary
  - “Pseudo-endodermal sinus”
- Absence of fibrous stroma
- Intravascular invasion







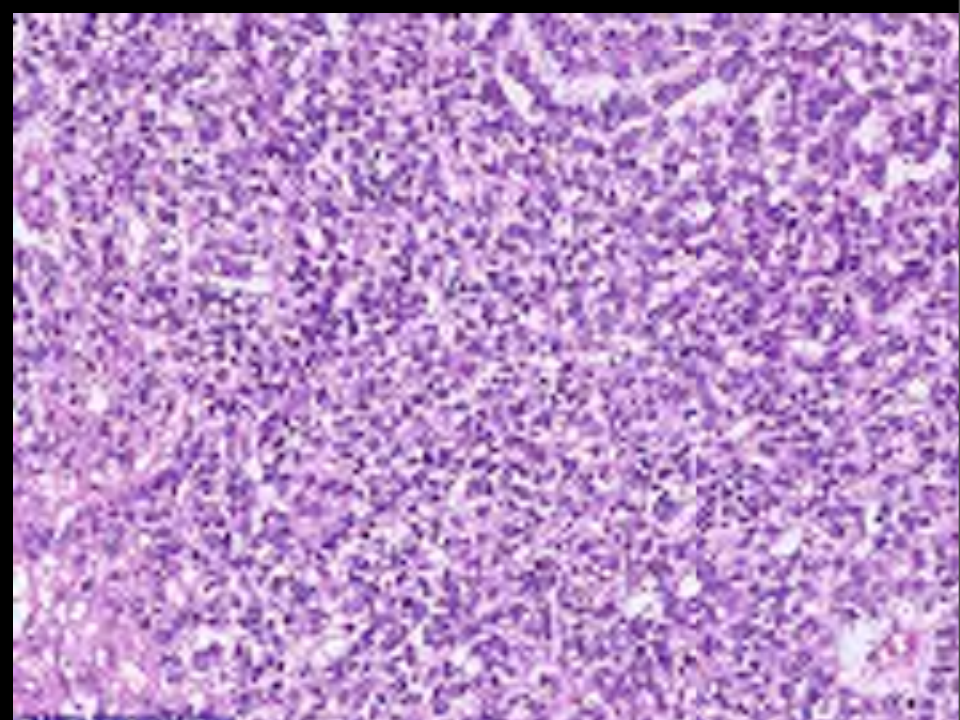
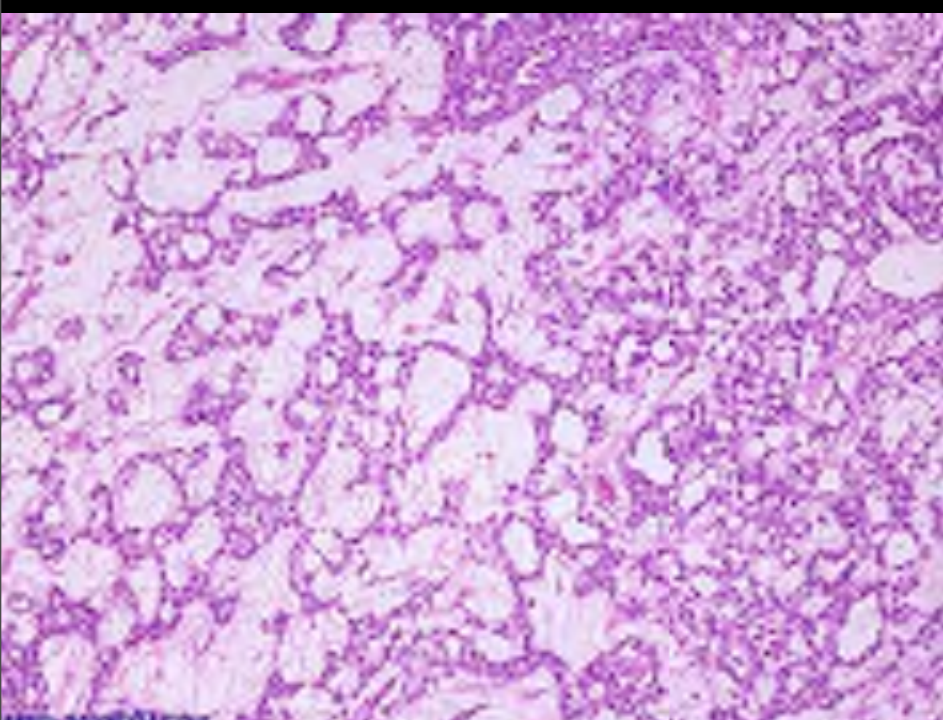
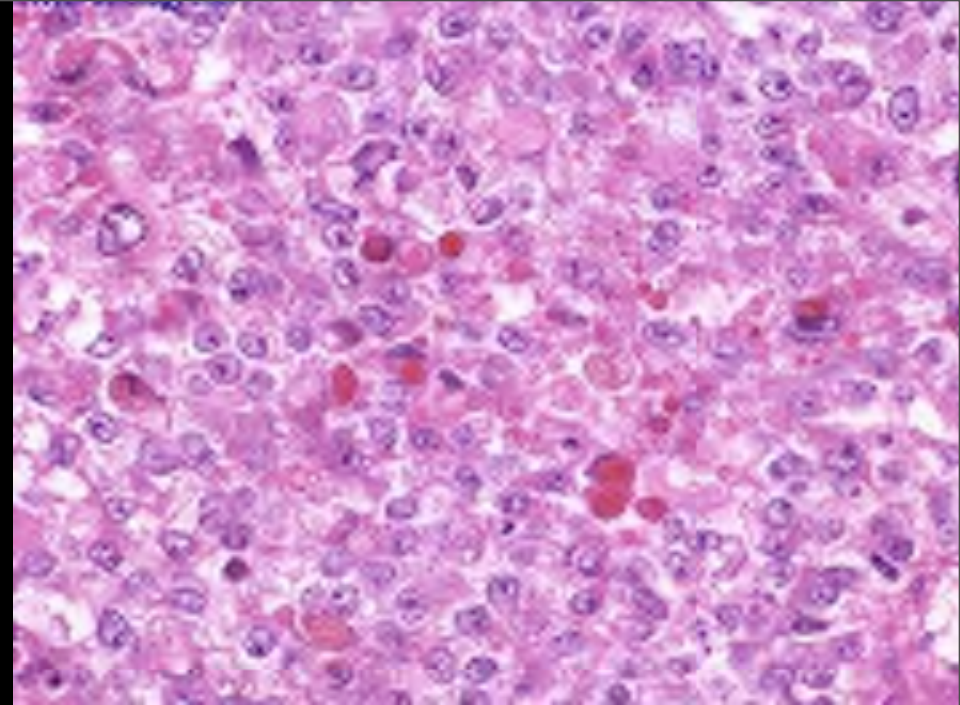
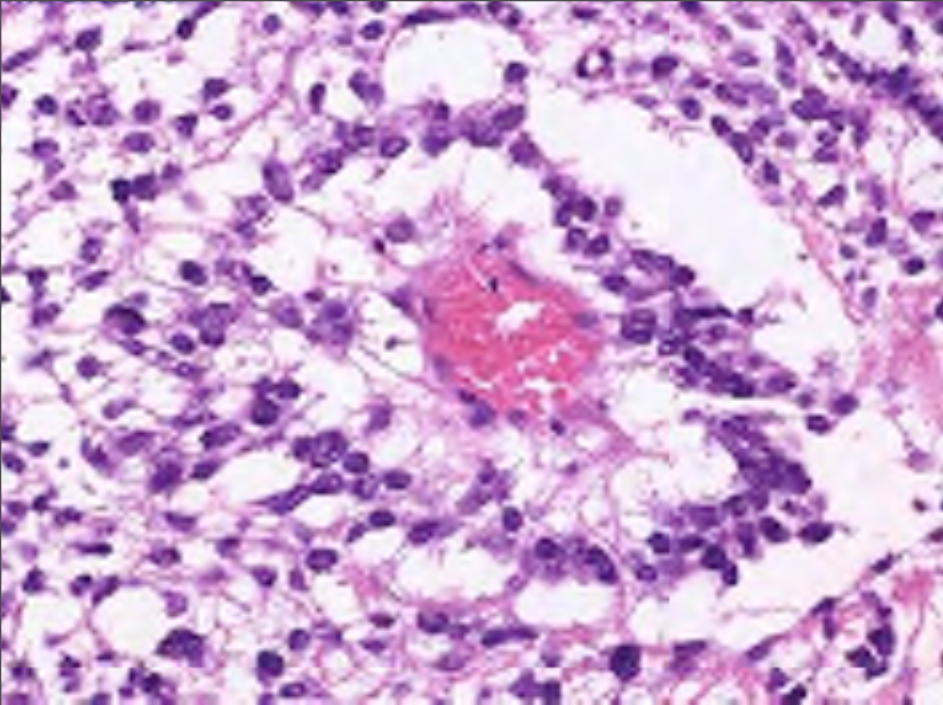




# Yolk sac tumor

- Adult YST
  - Component of mixed NSGCT
  - Prognosis like that of other NSGCT
- Childhood YST
  - Histologically pure YST
  - Low stage
  - Excellent prognosis







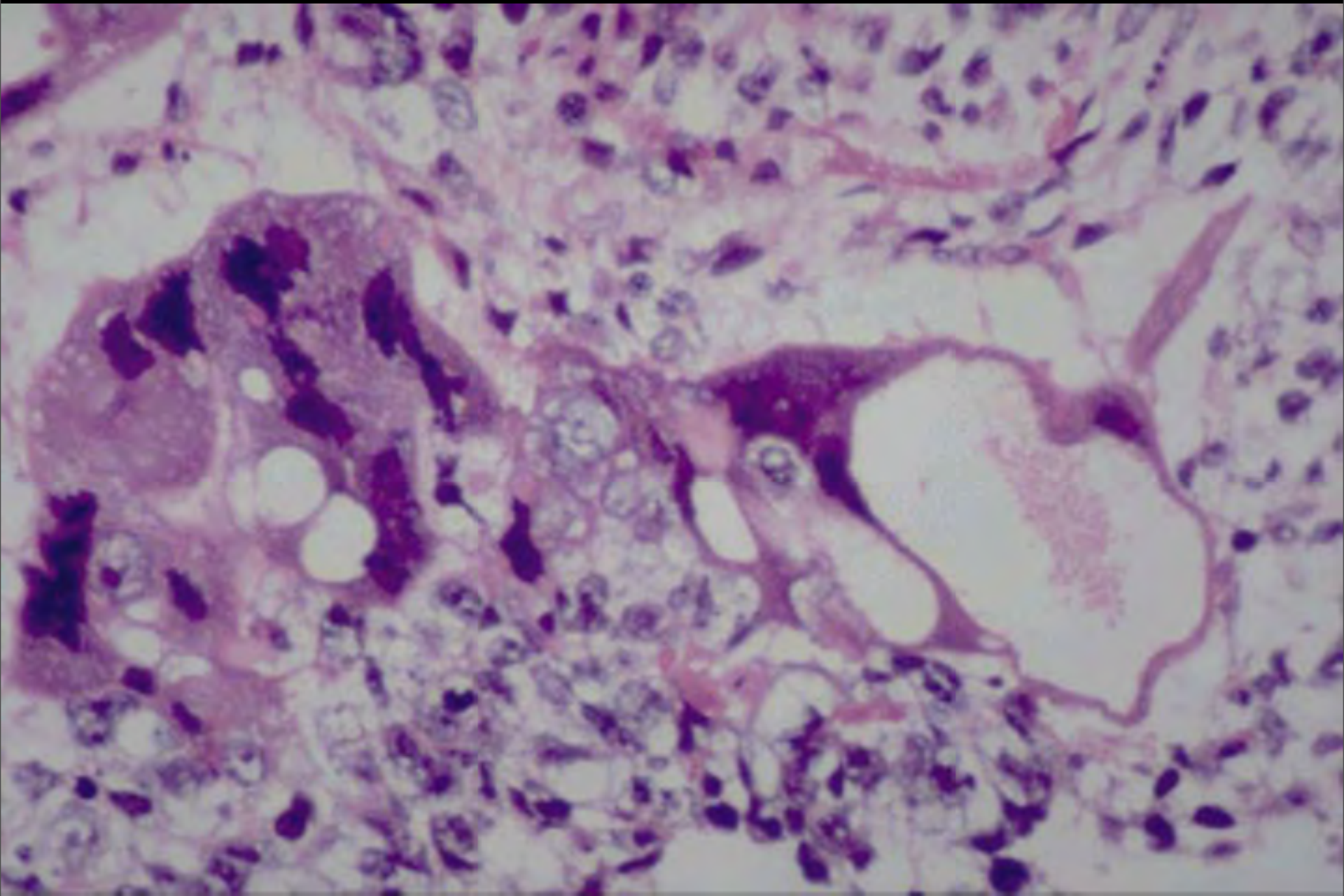
# Choriocarcinoma

- Most common as component of mixed NSGCT
- Rarely, as pure tumor
  - High stage at presentation
  - Usually symptoms of distant metastasis
  - Often, no palpable testicular mass



cm

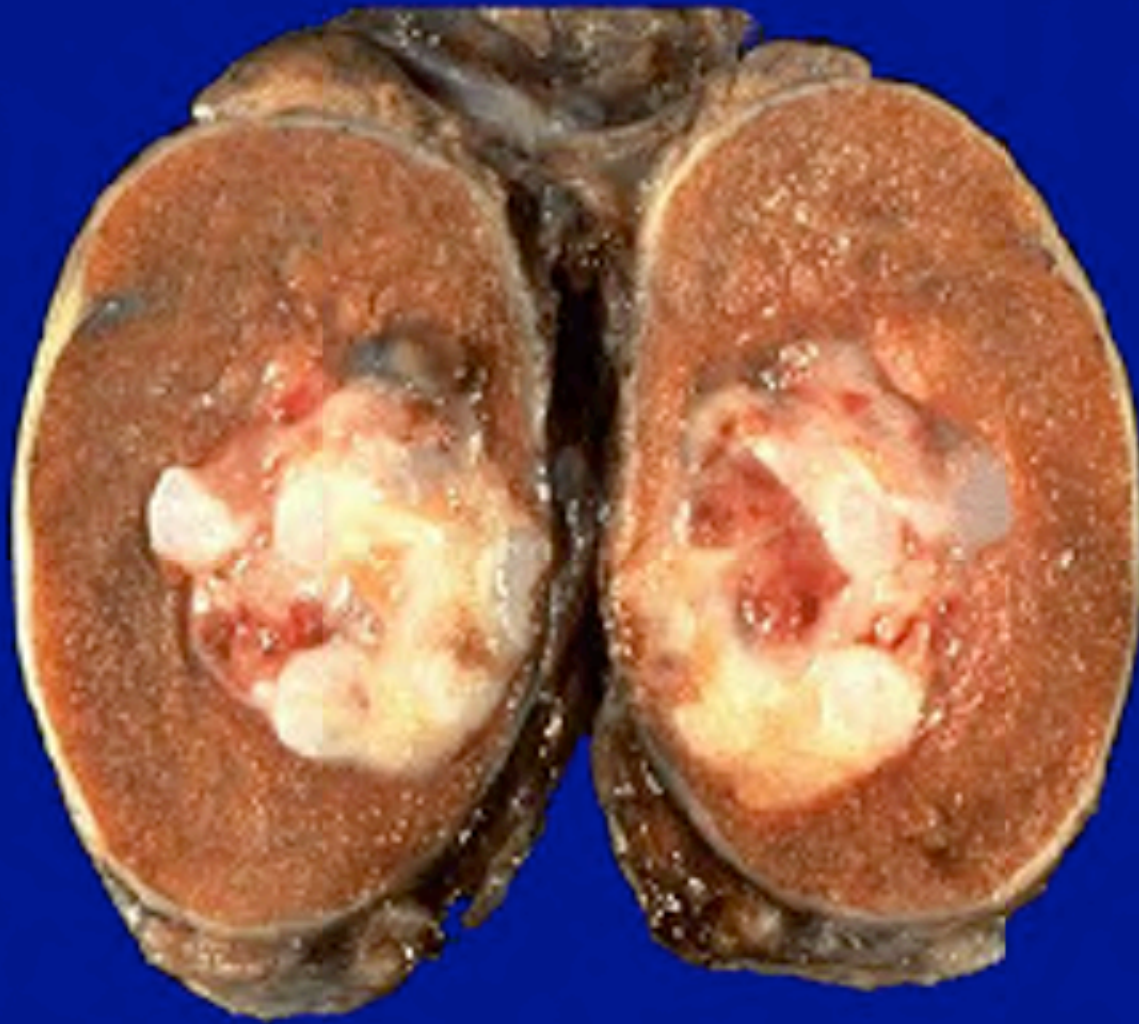
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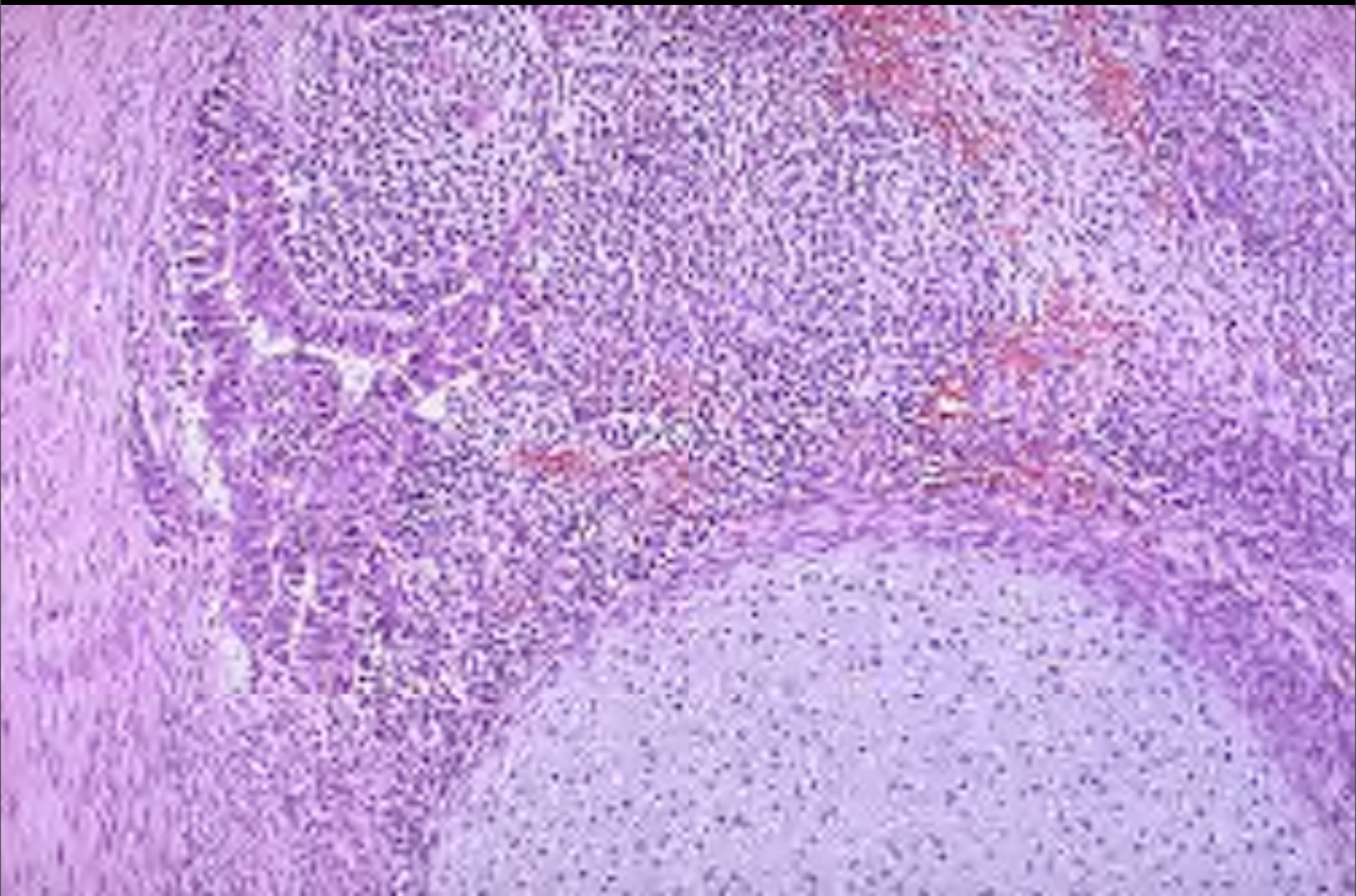


# Teratoma

- Childhood teratoma
  - Benign
- Adult teratoma
  - Usually component of mixed NSGCT
  - Both “mature” and “immature” testicular teratoma has metastatic potential
- Dermoid cyst
  - Rare, purely cystic benign tumor







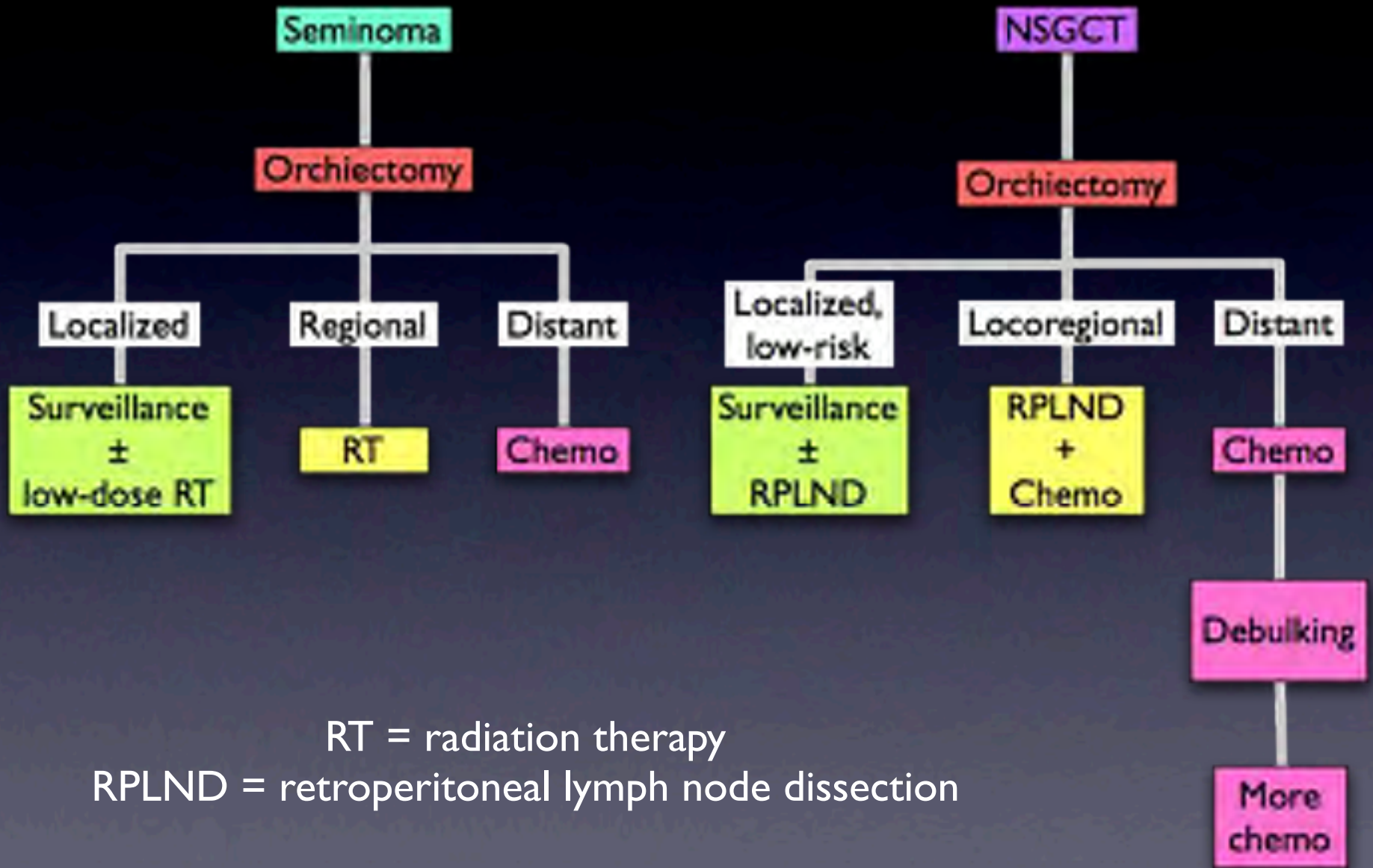


# Testicular Cancer Staging

## Important parameters

- Vascular invasion
- Local invasion (tunica albuginea, spermatic cord, scrotum)
- Number & size of involved nodes
- Distant metastasis
- Serum markers

# Therapeutic approach to testicular germ cell cancer



# Testis cancer survival

