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Underwriting Cancer: All You Wanted To Know But Were Too Shy to Ask

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Underwriting cancer takes a deep understanding of staging and grading. A good foundation of these primary elements along with other key prognostics can provide a better determination of mortality risk. This workshop with give foundations of clinical and pathological staging, grading along with the prognostic value of emerging biogenetics in its approach to underwriting most cancer cases with emphasis on breast, prostate and lymphoma. The workshop will conclude with practical case examinations in an interactive setting.

Agenda

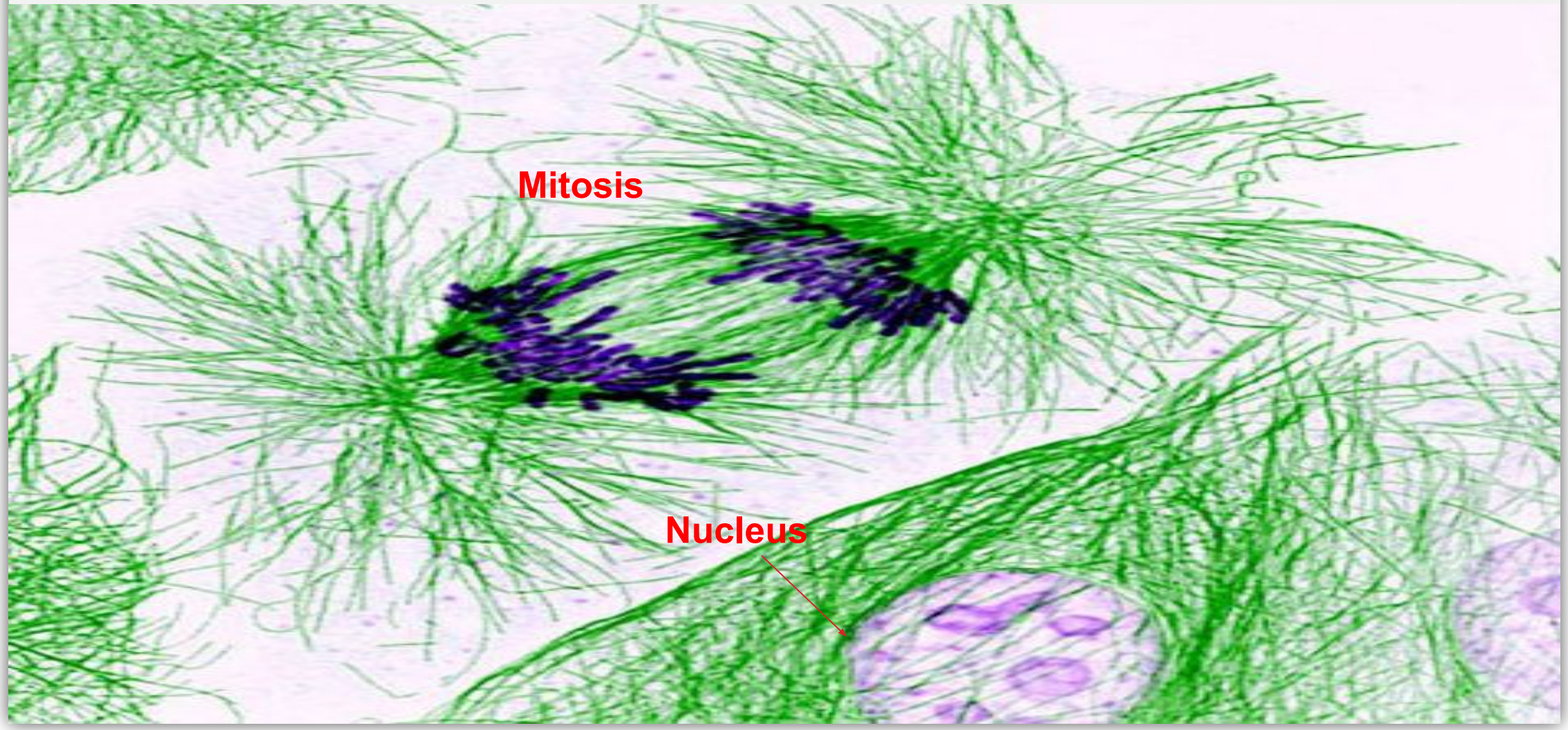
- What is Cancer
- Causes of Cancer
- Epidemiology
- Grading and Staging
- Breast Cancer Pearls
- Prostate Cancer Pearls
- Lymphoma Pearls
- Case Studies

Cancer Introduction: What is Cancer

- Cancer is the second leading cause of death in the U.S. behind cardiovascular disease
- Cancer is ALREADY the number one cause of death in the insured population, due primarily to its unpredictability
- Cancer definition: The loss of normal cellular growth control
  - Just about all cells in the body grow, divide and replace the cells that die with 200 different types of cells
  - Normal cell life cycle is controlled by biochemical proteins that signal when to divide, when to stop dividing, and when to die (apoptosis)
  - If those biochemical protein signals stop working, cancer can develop
  - The development of cancer is often a multi-step process, possibly taking several years
  - With 200 normal cell types, there are 200 different types of cancers

Diagram of Normal Cell Division

The chromosomes (purple) have already replicated, and the duplicates are being pulled apart by fibers of the cell skeleton known as microtubules (green).



Development of Cancer

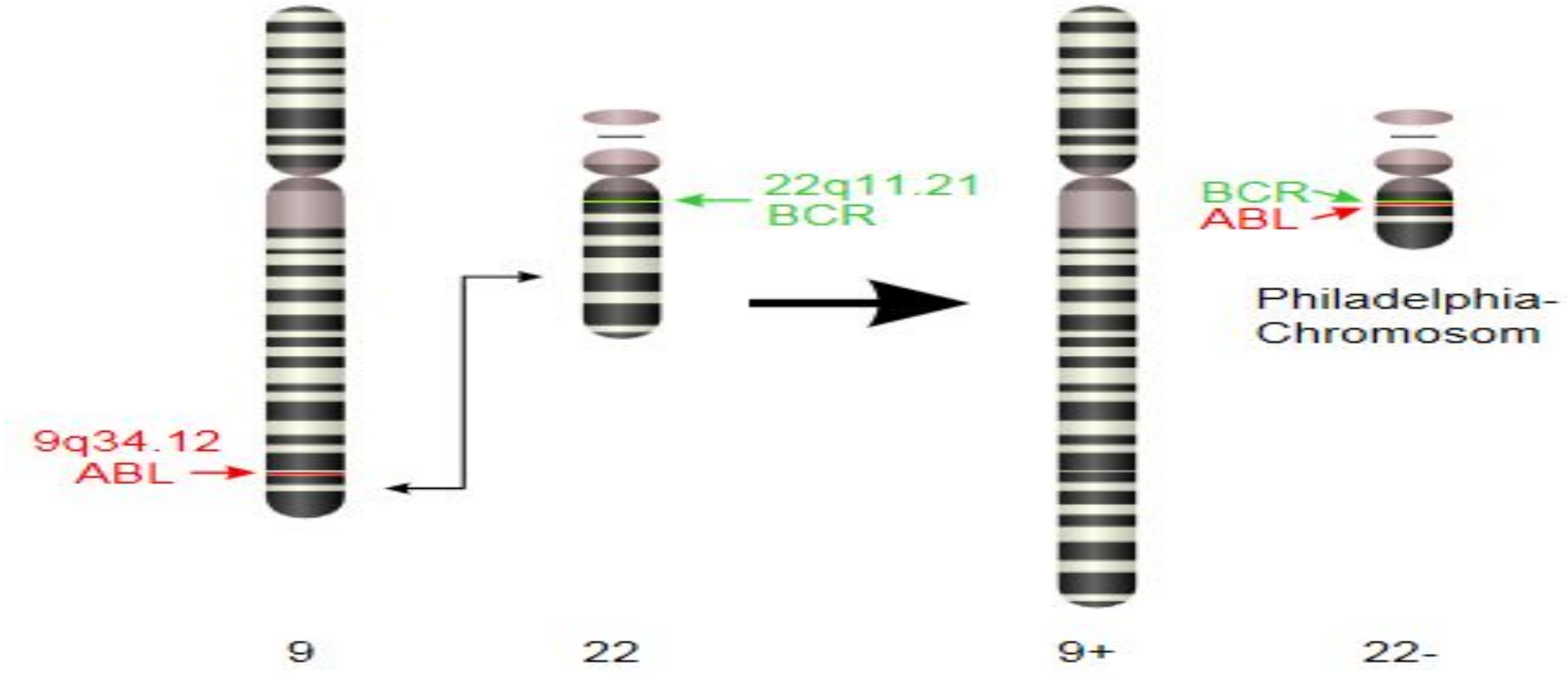
Genetic Causes

GENETIC ALTERATIONS

- **Chromosomal translocations** – rearrangement of portions of non-homogeneous chromosomes – ex.portion of chromosome 4 fusing with chromosome 20
- **Amplifications** – a response to a stress in environment whereby extra copies of a gene are made inside a cell
- **Point mutations** or single base modifications – single nucleotide base substitution, insertion, or deletion of genetic material; usually takes place during DNA replication

Chromosomal Translocation

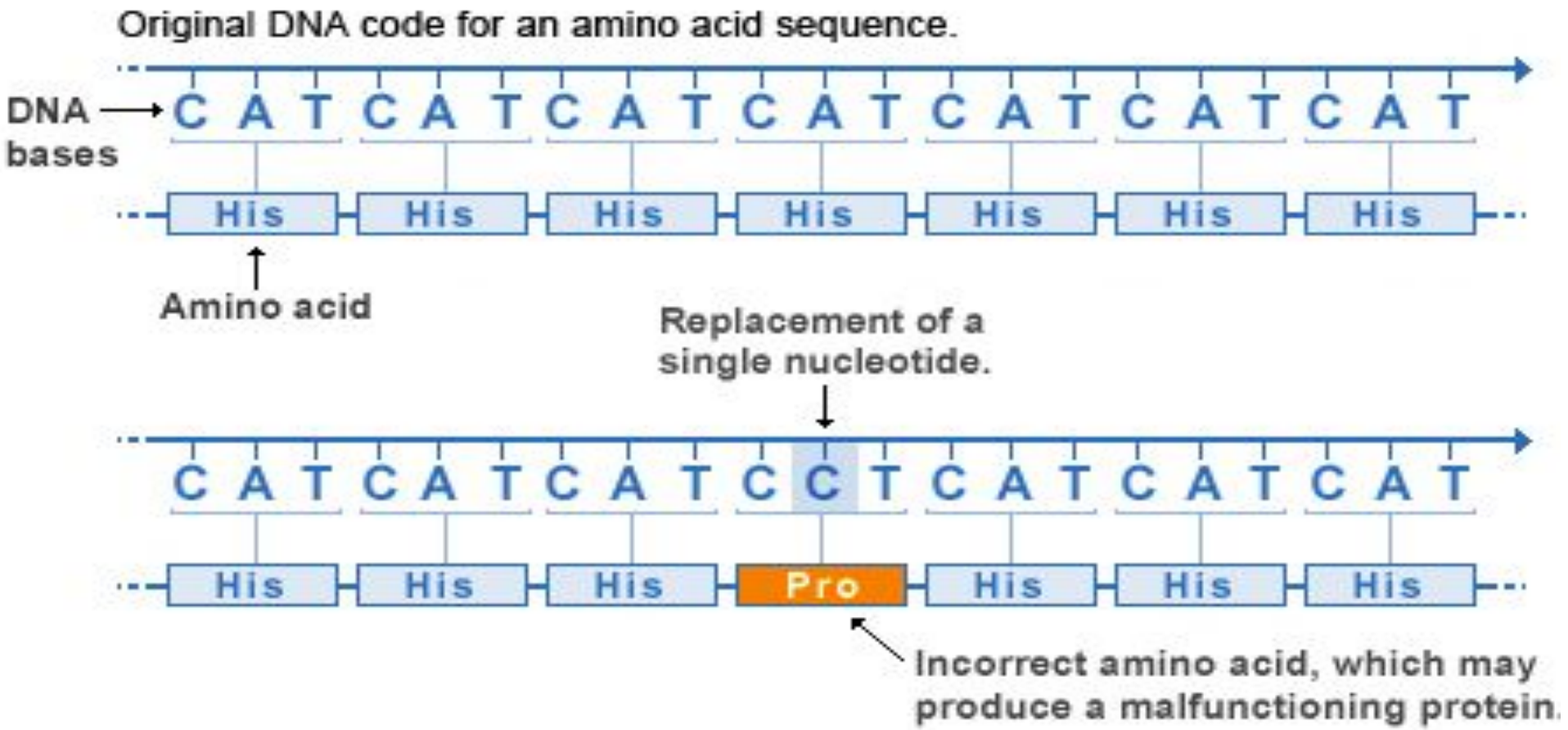
Philadelphia chromosome – genetic abnormality causing Chronic Myelogenous Leukemia (CML)



BCR-ABL codes for a tyrosine kinase signaling protein that is always ON, causing the cell to divide uncontrollably

Point Mutation

Missense Mutation – when nucleotides are replaced by another



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Point Mutation

Examples of a single gene mutation

- Cystic Fibrosis
- Sickle Cell Anemia
- Tay-Sachs disease
- Phenylketonuria
- Color Blindness
- Huntington's Disease
- p53 – Responsible for making protein that stops mutated cells from dividing
- BRCA 1 and BRCA 2 – Tumor-suppressor proteins

Development of Cancer

ENVIRONMENTAL CAUSES

Ionizing radiation (e.g., x-rays, gamma rays, alpha rays and ultraviolet light)

Linked to:

- Skin cancer
- Lung cancer
- Bone cancer
- Liver cancer
- Leukemia
- Thyroid cancer
- Breast cancer

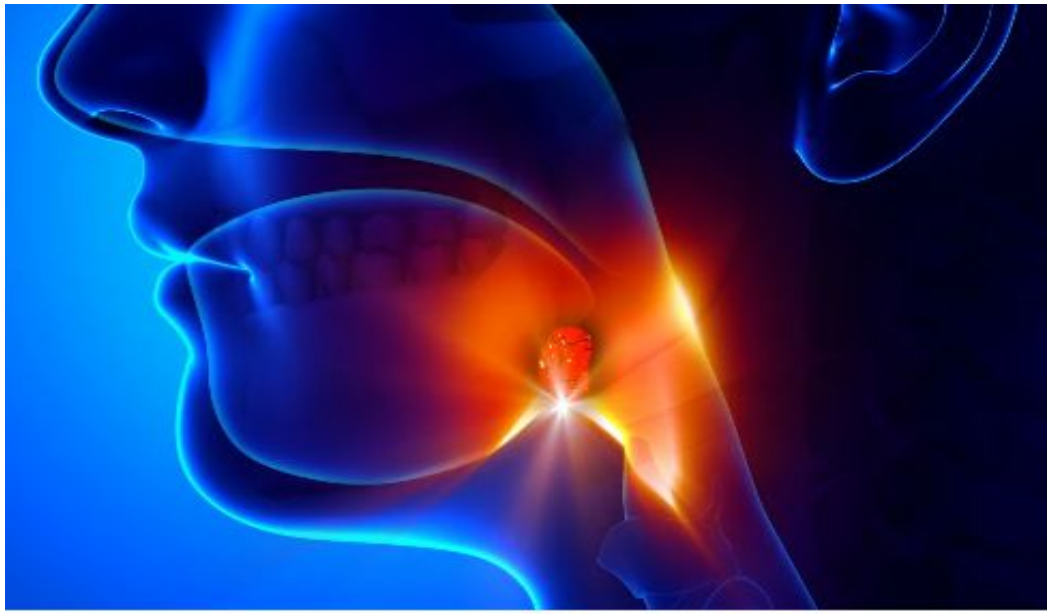
Development of Cancer

Intruders Into Our Normal Cells

VIRUSES

- Account for about 1 in 7 cancers worldwide
- 80% are caused by two DNA viruses
  - **Hepatitis B** causes hepatocellular carcinoma
  - Human papillomavirus **(HPV**) causes cervical cancer
- Another DNA virus, Epstein-Barr virus, has been linked to Burkitt's lymphoma
- RNA viruses linked to cancer are HTLV-1 and HTLV-2, which can cause human T-cell leukemia
- Hepatitis C is also associated with hepatocellular cancer
- HIV is associated with Kaposi's sarcoma

NEWS SHOWS VIDEO CBSN MORE



By RYAN JASLOW / CBS NEWS / *June 3, 2013, 12:42 PM*

Oral sex and throat cancer: Michael Douglas HPV report spotlights "epidemic"

Michael Douglas

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Development of Cancer

TOXIC AGENTS

Chemical causes of cancer may be due to genetic damage as well as non-genotoxic causes. Examples include:

- Nitrosamines
- Polycyclic aromatic hydrocarbons
- Alkylating agents
- Vinyl chloride…. Such as trichloroethylene (TCE)… in that county in Indiana
- Aromatic amines
- Urethane
- Some of the chemicals found in cigarette smoke

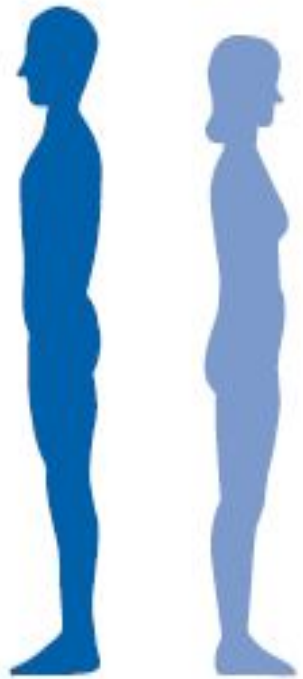
Pop Question #1

Which cancers are associated with a virus?

Options	Answers
a. Kaposi Sarcoma	1. All of the above
b. Burkitt's Lymphoma	2. All except e
c. Chronic Myelogenous Leukemia	3. All except c
d. Cervical Cancer	4. All except b
e. Squamous Cell Ca of oropharynx	
f. Hepatocellular carcinoma	

Leading Sites of New Cancer Cases - 2018 estimates

Male			Female		
Prostate	164,690	19%	Breast	266,120	30%
Lung & bronchus	121,680	14%	Lung & bronchus	112,350	13%
Colon & rectum	75,610	9%	Colon & rectum	64,640	7%
Urinary bladder	62,380	7%	Uterine corpus	63,230	7%
Melanoma of the skin	55,150	6%	Thyroid	40,900	5%
Kidney & renal pelvis	42,680	5%	Melanoma of the skin	36,120	4%
Non-Hodgkin lymphoma	41,730	5%	Non-Hodgkin lymphoma	32,950	4%
Oral cavity & pharynx	37,160	4%	Pancreas	26,240	3%
Leukemia	35,030	4%	Leukemia	25,270	3%
Liver & intrahepatic bile duct	30,610	4%	Kidney & renal pelvis	22,660	3%
All sites	856,370	100%	All sites	878,980	100%



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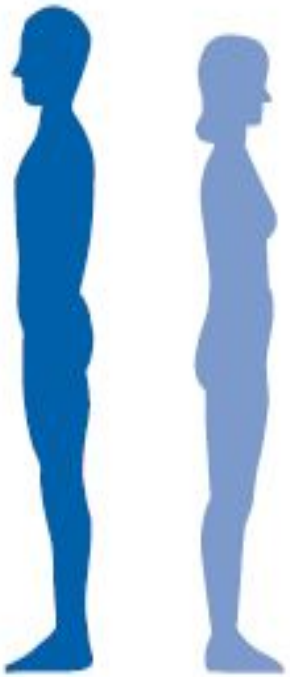
Leading Sites of Cancer Deaths – 2018 Estimates

Male			Female		
Lung & bronchus	83,550	26%	Lung & bronchus	70,500	25%
Prostate	29,430	9%	Breast	40,920	14%
Colon & rectum	27,390	8%	Colon & rectum	23,240	8%
Pancreas	23,020	7%	Pancreas	21,310	7%
Liver & intrahepatic bile duct	20,540	6%	Ovary	14,070	5%
Leukemia	14,270	4%	Uterine corpus	11,350	4%
Esophagus	12,850	4%	Leukemia	10,100	4%
Urinary bladder	12,520	4%	Liver & intrahepatic bile duct	9,660	3%
Non-Hodgkin lymphoma	11,510	4%	Non-Hodgkin lymphoma	8,400	3%
Kidney & renal pelvis	10,010	3%	Brain & other nervous system	7,340	3%
All sites	323,630	100%	All sites	286,010	100%



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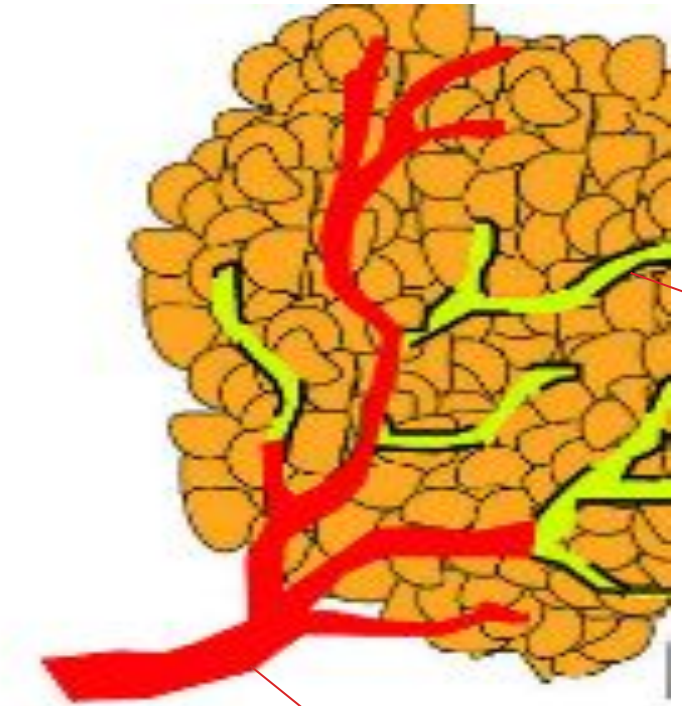
What Do Cancers Cells Actually Do?

- Primary function of cancer cells is to metastasize – take over the universe!
  - The mechanism of metastasis is:
    - Progressive proliferation of neoplastic cells is initially supported with nutrients supplied from the primary organ microenvironment
    - Neovascularization must take place for the tumor to grow, which is promoted by the secretion of angiogenic molecules such as endothelial growth factors (like an irrigation system)
    - Tumor cells deregulate cohesive molecules, which normally cause cells to adhere to one another; so deregulating this, allows cancerous cells to cross over into thin-walled capillaries and lymphatic channels
    - Single tumor cells embolize through the blood or lymphatic channels and then arrest in capillary beds of these distant organs they embolize to
    - Metastatic cells must find ways to evade destruction by the immune system
    - Metastases must develop their own vascular network to exceed a mass of greater than 1 - 2 mm

Neovascularization

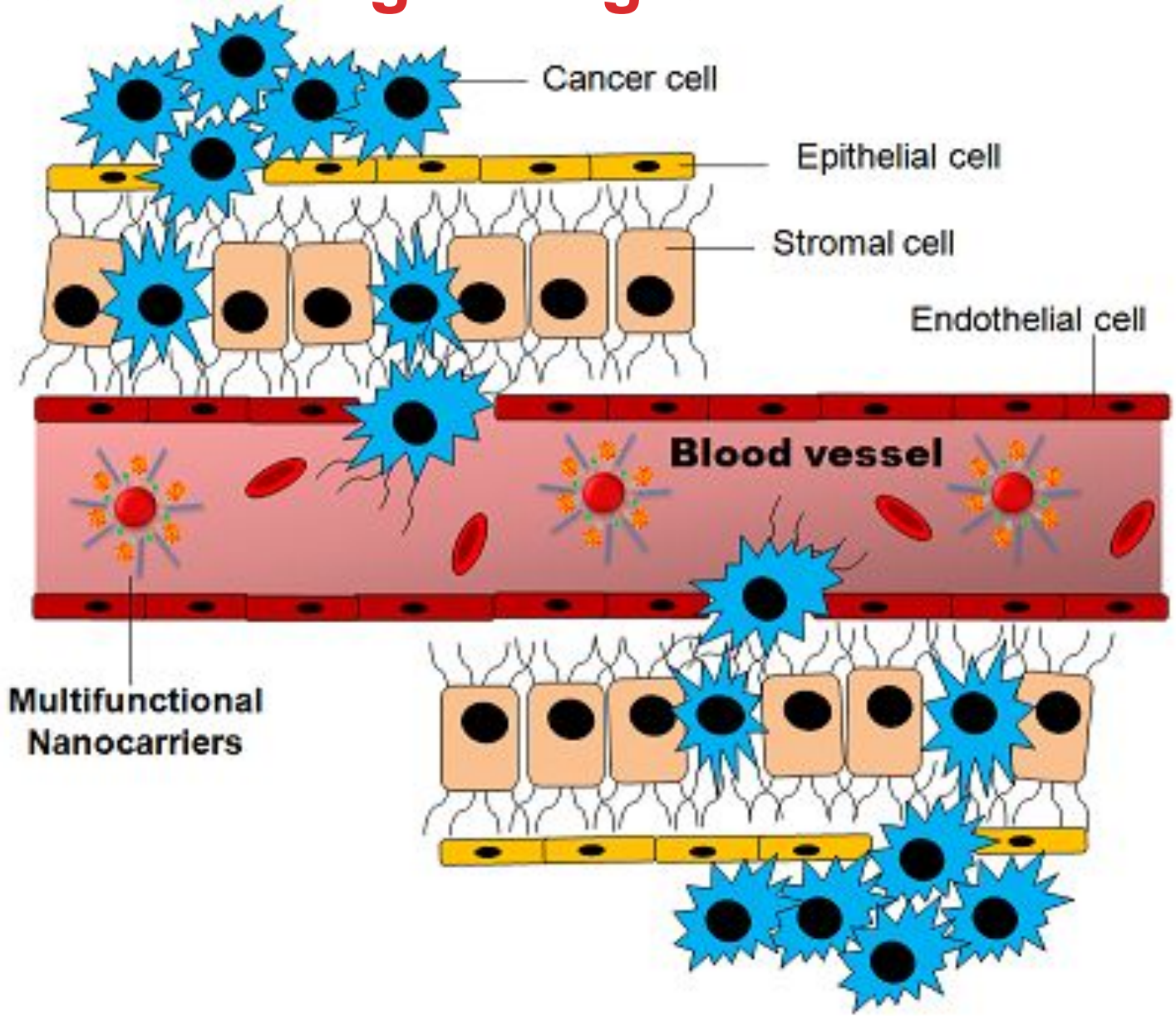


Cancer cell

Angiogenesis

Regular Blood Vessels

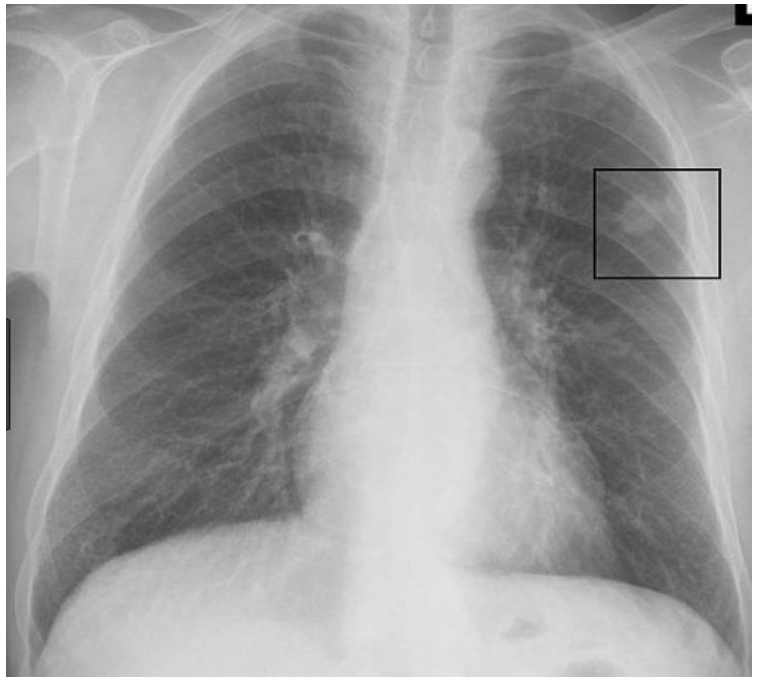
Tumor Cells Deregulating Cohesive Molecules

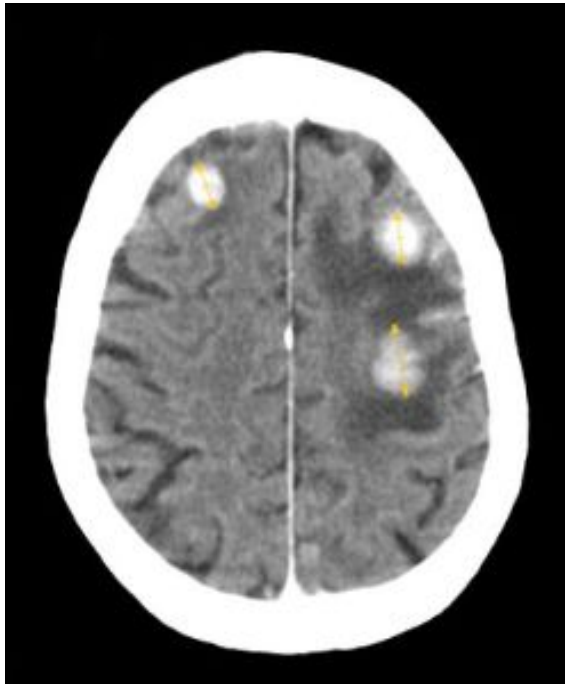


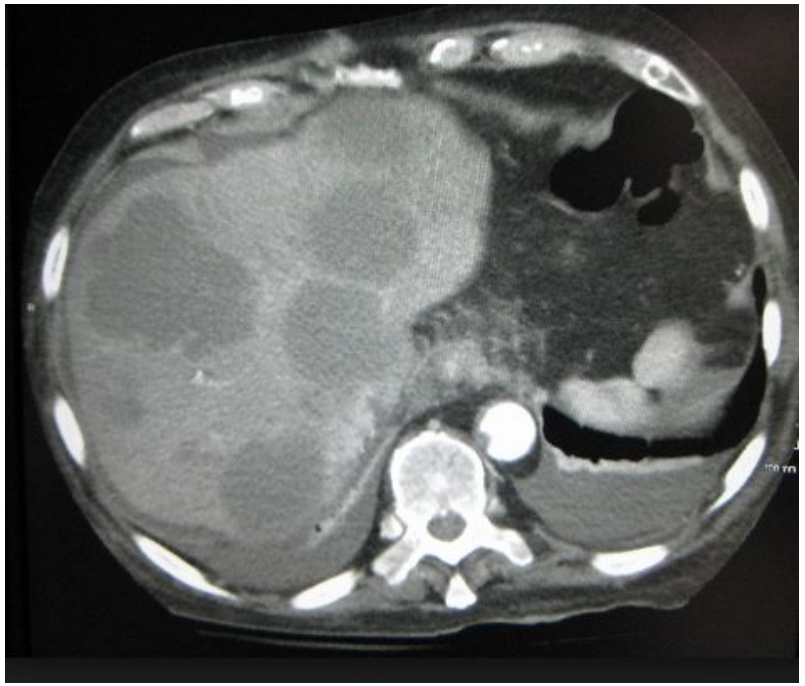
Cancer- How Does It Kill

When growth control is lost

- Tumor enlarges invading local structures
- May move (metastasize) via blood or lymph to distant organs







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How Does It Kill

- Death from cancer may be due to several different events, for example:
  - Invasion or destruction of a vital organ, for example:
    - Brain
    - Lungs
    - Other vital organs or structures
  - Consumes the body's nutrients and blood supply
    - Causes "wasting" – severe weight loss and malnutrition, often complicated by infection due to immunocompromised state
  - Blood clots
    - Associated with hypercoagulable state - blood clots especially in those with solid tumors of the abdomen
    - Result in pulmonary embolism or stroke
  - Effects of treatment
    - Severe immune system suppression with opportunistic infections
    - Damage to vital organs (heart, lungs)
    - Complications of surgery

Like the old saying:" The treatment was a success but the patient died"

Cancer – How it is Detected

Screening vs. Diagnostic testing

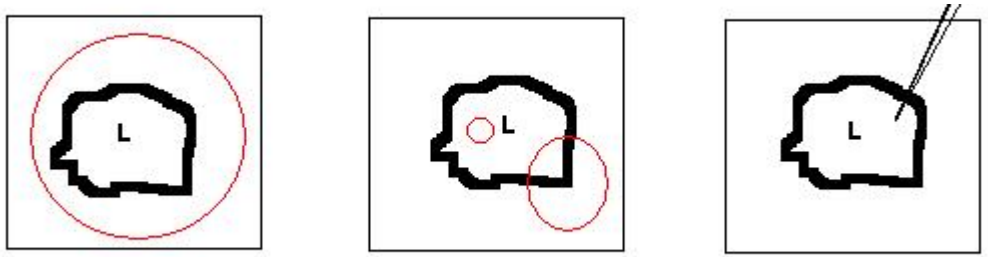
- Screening (may or may not want to postpone an offer)
  - Testing done routinely, without regard to symptoms or signs of disease
    - Mammogram for breast cancer
    - PSA tests for prostate cancer
    - Colonoscopy for colorectal cancer
- Diagnostic testing (would want to postpone any offer)
  - Testing done to evaluate a particular complaint or problem
    - A chest X-ray done on a smoker complaining of weight loss
    - A blood count done on a patient complaining of easy bruising/bleeding
    - A biopsy done to evaluate a worrisome skin lesion

Specific Radiological Tests

- Almost any type of radiology test can detect a tumor
  - Ultrasound
  - MRI
  - PET scans
  - X-rays
- Cancerous lesions typically
  - Grow more rapidly than benign lesions
  - Invade nearby structures
  - Spread to distant sites
  - Are more “metabolically active” than benign lesions
    - “Light up” on PET scan

Cancer – How is it Detected

- Radiological test can only *suggest* the diagnosis of cancer
- A firm diagnosis of cancer generally requires that tissue be obtained and examined by a pathologist
  - The oncologist's motto: "No meat, no treat"
  - Usually this tissue is obtained surgically, via a biopsy
- Biopsies can be excisional, incisional, or needle
  - Excisional – the entire lesion is removed, may be intended to treat as well as diagnose
  - Incisional – only a piece of the lesion is removed, for diagnosis only
  - Needle – only a core of tissue, which can be obtained by a cutting needle, is removed



Cancer - Diagnosis

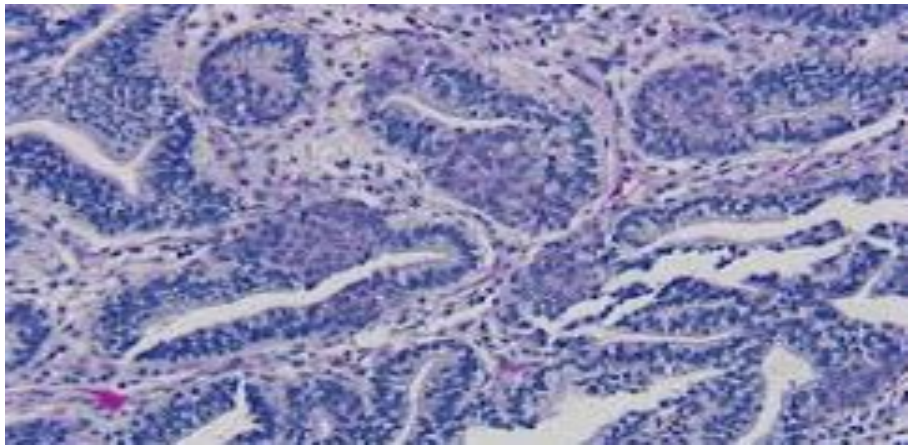
- The next step is to determine how far the cancer has spread (stage), and how fast it appears to be growing (grade)
  - In most cancers, the prognosis depends greatly on stage and grade
  - Stage cannot be determined by pathology alone, usually requires other studies (CT scans, bone scans, etc)
  - Grade is determined by pathology alone

Cancer Grade

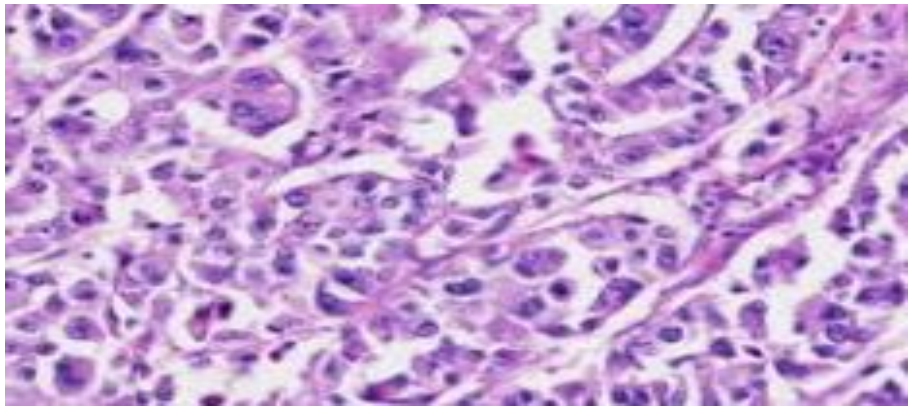
- Grade: degree of differentiation of the tumor tissue
  - How abnormal the tumor cells look under a microscope
  - Indicator of how quickly a tumor will grow and likelihood that it will spread
  - As cells lose control over their growth, their phenotype or appearance changes from normal (similar to cell of origin) to more generic type of cell, called undifferentiated
  - Think of Mendelian genetics and how kids look like their parents… if change their DNA, they would lose any resemblance. Same goes for a cell
  - The degree of changes in appearance of cancer cells is the tumor grade
    - **Low grade or Grade 1= well differentiated** = looks much like the parent cell
    - **High grade or Grade 3 = poorly or undifferentiated** = looks nothing like the parents
    - **Grade 2 is moderately differentiated**, somewhere in between low and high

Cancer Grade – an example

Well-differentiated lung cancer



Poorly differentiated lung cancer



Cancer - Grade

Chinese shar-pei

Cancer Stage

- Stage
  - How much cancer is in the body
  - Location of cancer
  - Extent of spread

TNM is just one very common staging used

Cancer Stage: TNM grouping

- T: size and extent of primary tumor
  - Tx: primary tumor cannot be excluded
  - T0: no evidence of primary tumor
  - Tis: carcinoma in situ (early cancer that has not spread to neighboring tissue)
  - T1-4: size and/or extent of the primary tumor
- N: involvement of lymph nodes
  - Nx: regional lymph nodes cannot be evaluated
  - N0: no regional lymph node involvement
  - N1-3: involvement of regional lymph nodes (number and/or extent of spread)
- M: presence or absence of distant metastasis
  - M0: no distant metastasis
  - M1: distant metastasis

TNM Groupings

- Patients with similar prognosis expectations are assigned specific stage groups
  - **Stage 0**
    - Carcinoma in situ with no metastatic potential, as determined by pathologic examination
  - **Stage I**
    - Cancers that are small or less deeply invasive, with **negative nodes**
  - **Stage II and III**
    - Cancers with increasing tumor spread or nodal extent
  - **Stage IV**
    - Cancers with distant metastasis at diagnosis
- Each type of cancer has its own particular definitions for the various stages
- The American Joint Committee on Cancer or AJCC is responsible for developing these staging systems (cancerstaging.org)

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Staging and Grading

Conceptual Example

Grade 1

Grade 2

Grade 3

Grade 4

Stage

Stage and Grade Determine Prognosis

Prognosis

- Higher stage cancers usually have a worse prognosis
- Grade varies: In most cancers, high grade carries a worse prognosis; however in others, higher grade tumors are more susceptible to chemotherapy and radiotherapy
- Prognosis also dependent on
  - Age at diagnosis
  - Overall health status- whether any comorbidities
  - Type of treatment received
  - Molecular markers

Pop Question #2

- Which grade cancer is associated with a well differentiated cell type?

A. Grade 1

B. Grade 3

C. Grade 2

Pop Question #3

- Which of these TNM grouping is associated closest with stage III cancer

A. T1N0M0

B. T2 N0M0

C. T2N2M0

Trick questions

- Which of the above has a tumor size of 2 cm??
- Which equates with Stage IV? T1, T2 or T4 or neither

Changes in Staging Criteria

The 8th Edition AJCC came out January 2018 American Joint Committee on Cancer

- Historically, staging was based solely on anatomic parameters such as the physical dimensions of the tumor or the local spread of the tumor
- Currently, there is an increasing reliance on non-anatomic factors such as:
  - Duration of symptoms
  - Gender
  - Age
  - Health status
  - Type and grade of cancer
  - Specific biological properties of the cancer

Difference Between Clinical and Pathological Staging

- **Clinical Staging**
  - Any information obtained about the extent of the cancer before initiation of definitive treatment such as surgery, radiation, surveillance or palliative care, which may be noted as cT, cN, cM
- **Pathological Staging**
  - Any information obtained about the spread of the cancer through completion of definitive surgery or identified within 4 months after the date of diagnosis (and prior to systemic or radiation therapy), which may be noted as pT, pN, pM

Additional Value of Pathological Staging

- Not all tumors are pathologically staged, for a variety of reasons (e.g., prostate cancer)
- Pathological staging is defined by all of the same diagnostic studies as clinical staging, but includes the following information from the noted sources:
  - Full surgical resection
  - Histologic examination of the surgically removed tissues
- Often need pathology reports on both initial biopsy and full surgical excision

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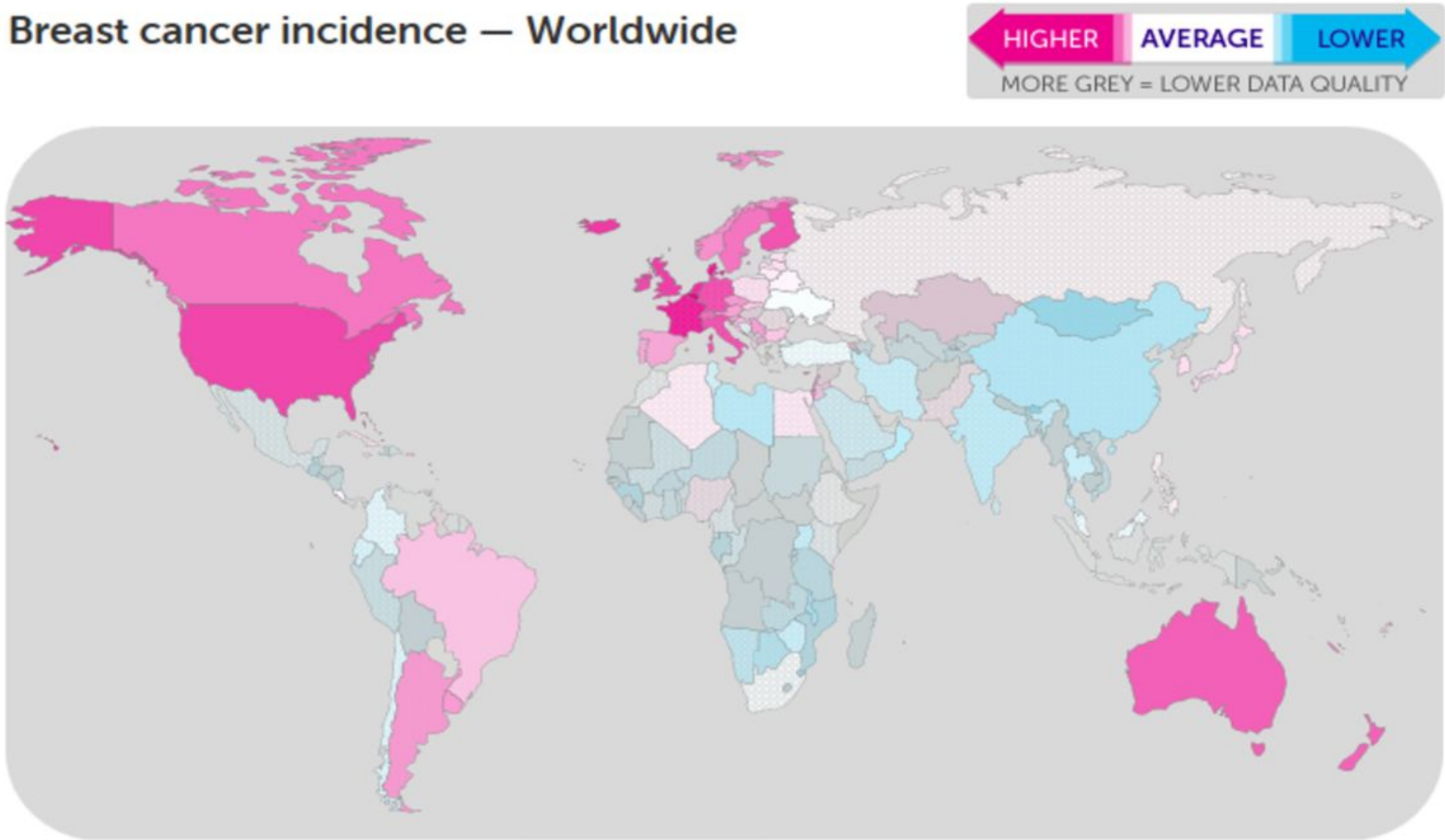
BREAST CANCER

Breast Cancer



Risk Factors

- **BRCA-1 or BRCA-2 mutations**
  (2.9% Caucasians, 10% of Ashkenazi, 3.5% Hispanic, 0.5% Asian Americans for BRCA1)
- Family history of breast or ovarian cancer
- Personal history of prior breast, endometrial or ovarian cancer
- **Increasing age**
- Nulliparity or late age at first pregnancy (age over 30)
- Absence of breast feeding
- Early menarche
- Late menopause
- Hormone replacement therapy
- **Hyperplasia, multiple papillomatosis, sclerosing adenosis, fibroadenomas with proliferative change and atypical hyperplasia**
- Radiation to breast area
- **No added risk for fibrocystic breast disease, simple fibroadenomas without proliferative change, duct ectasia and solitary papillomas**

BI-RADS

- Breast Imaging-Reporting and Data System
  - BI-RADS 0: incomplete; further imaging or information is required, such as compression or magnification views or ultrasound
  - BI-RADS I: negative; no suspicious findings
  - BI-RADS II: benign findings, such as fibroadenomas, lipomas or simple cysts
  - BI-RADS III: probably benign, short interval (6 month) follow up suggested
  - BI-RADS IV: abnormality suspicious for malignancy
    - BI-RADS IVa – low level of suspicion for malignancy
    - BI-RADS IVb – intermediate suspicion for malignancy
    - BI-RADS IVc – moderate level of suspicion for malignancy
  - BI-RADS V: highly suggestive of malignancy; action should be taken
  - BI-RADS VI: known biopsy-proven malignancy

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Newer Staging Strategy

TNM Staging System – what has been added?

- Tumor – size
- Regional lymph nodes
- Metastasis

Micrometastasis and Isolated Tumor Cells

pN0(i+) means isolated tumor cells no greater than 0.2 mm and are prognostically similar to node negative

pN1mi refers to micrometastasis and would think worse prognosis, however this class has only slight increase in recurrence rate

Data on SLN indicates that there was 0% additional positive nodes with ITC; 27% had additional positive node for mi

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Well-Known Prognosticators

- Age
- Size
- Nodal Status
- Localized or Metastasized
- Histological grade
- Estrogen and progesterone receptor status
- HER 2 status
- Mitotic Index

Newest Prognosticators - Genomics

Require Tissue Evaluation

- **Oncotype DX**

  Looks at 21 genes; provides ***recurrence score or RS***

- **Genome sequencing**
  - Introduced in 2009
  - Compares DNA from breast cancer tissue to the woman's own normal breast tissue; reveals areas of chromosomal rearrangement and mutations/deletions of individual genes

Morbidity

- Chemotherapy effects:
  - Neurotoxicity- peripheral neuropathy from certain chemo agents such as Cisplatinum
  - Cardiomyopathy from Trastuzimab
  - Cardiomyopathy from Adriamycin
- Surgical complications:
  - Chest wall and breast complications-seromas, fat necrosis, recurrent skin infection
  - Lymphedema 2% in SLN and 13% in axillary lymph node

Morbidity (Continued)

- Radiation therapy effects:
  - Premature CAD, especially left-sided breast radiation
  - Secondary malignancies: increase risk for esophageal and lung cancer as well as sarcomas, leukemias, myelodysplastic syndrome
    - Occurs within 5-7 years post treatment in 1.5% of patients
- General or other related adverse effects:
  - Long-term effects for primary therapy include cognitive dysfunction, fatigue, insomnia, pain and debilitating menopausal symptoms
  - Pulmonary – cough, dyspnea
  - Fatigue
  - Chemo brain-real or Memorex

Recap

- Characterize these Prognostics

1. ER positive
2. HER 2 positive
3. Low Oncotype DX score of 10
4. Grade 3
5. Triple negative (ER, PR and HER 2 negative)
6. Sentinel node with micrometastasis
7. Sentinel node with isolated tumor cells
8. Diagnosis of cancer after age 50

Breast Cancer Case #1

55 year old female dentist applying for $500,000 of term life insurance

- Mother with breast cancer at 50, she is still alive.
- BRCA testing (-).
- Because of this family history, she started screening mammography at age 40 and in August, 2006 suspicious calcifications were noted prompting a biopsy that showed infiltrating ductal breast cancer.
- She had a lumpectomy & sentinel node bx:
  - Final path: 1.6 cm high grade infiltrating ductal breast cancer, clear margins, ER (-), PR (-), Her 2/neu ab (+); nodes (-). Dx: T1c,N0, M0.
- She was treated at Johns Hopkins receiving 6 months of chemotherapy completing treatment in April, 2007.
- She is followed yearly with mammograms which have been normal.

How would you assess the risk?

Case 1 (Continued)

Risk Issue: Early stage breast cancer in young female >10 yrs ago s/p optimal treatment and without recurrence.

- Favorable Factors:
  - Young age
  - BRCA (-)
  - Early stage breast cancer
  - Her 2/neu ab +
  - Appropriate treatment & follow-up
- Unfavorable Factors:
  - Young age
  - High grade histology
  - Hormone receptors (-)
- Risk Assessment: **Life – Low Substandard**

Same Case 1 except with complication from chemo

55 year old female dentist applying for $500,000 of term life insurance

- Mother with breast cancer at 50, she is still alive. BRCA testing (-).
- Because of this family history, she started screening mammography at age 40 and in August, 2006 suspicious calcifications were noted prompting a biopsy that showed infiltrating ductal breast cancer.
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- She was treated at Johns Hopkins receiving 6 months of chemotherapy completing treatment in April, 2007.
- **Her treatment was complicated by CHF d/t a drug-induced cardiomyopathy that has resolved. Most recent echo WNL. (Or maybe not an echo, but probnp is 30)**
- She is followed yearly with mammograms which have been normal.

Would this scenario alter the rating?

Breast Cancer Case #2

67 year old female radiologist applying for $5,000,000 WL

- In 2008, she had an abnormal mammogram with suspicious calcifications noted in the left upper quadrant of her right breast; biopsy showed DCIS.
- She underwent a lumpectomy which confirmed a single, grade 2, 12 mm DCIS with clear wide margins, ER (+), PR (+), HER2 (-). No comedonecrosis.
- She just completed 10 years of tamoxifen.
- She is followed closely with yearly mammograms; her most recent this year was BIRADS 2.

How would you assess the risk?

Case 2 (Continued)

Risk Issue: DCIS in older woman

- Favorable Factors:
  - Older age applicant
  - DCIS – small, single lesion & without comedonecrosis
  - Optimal treatment with surgery with wide clear margins
  - Good follow-up without recurrence
- +/- Prognostic Factor:
  - Hormone receptors (+)
- Unfavorable Factors:
  - Grade 2
- Risk Assessment: **Life – Standard**

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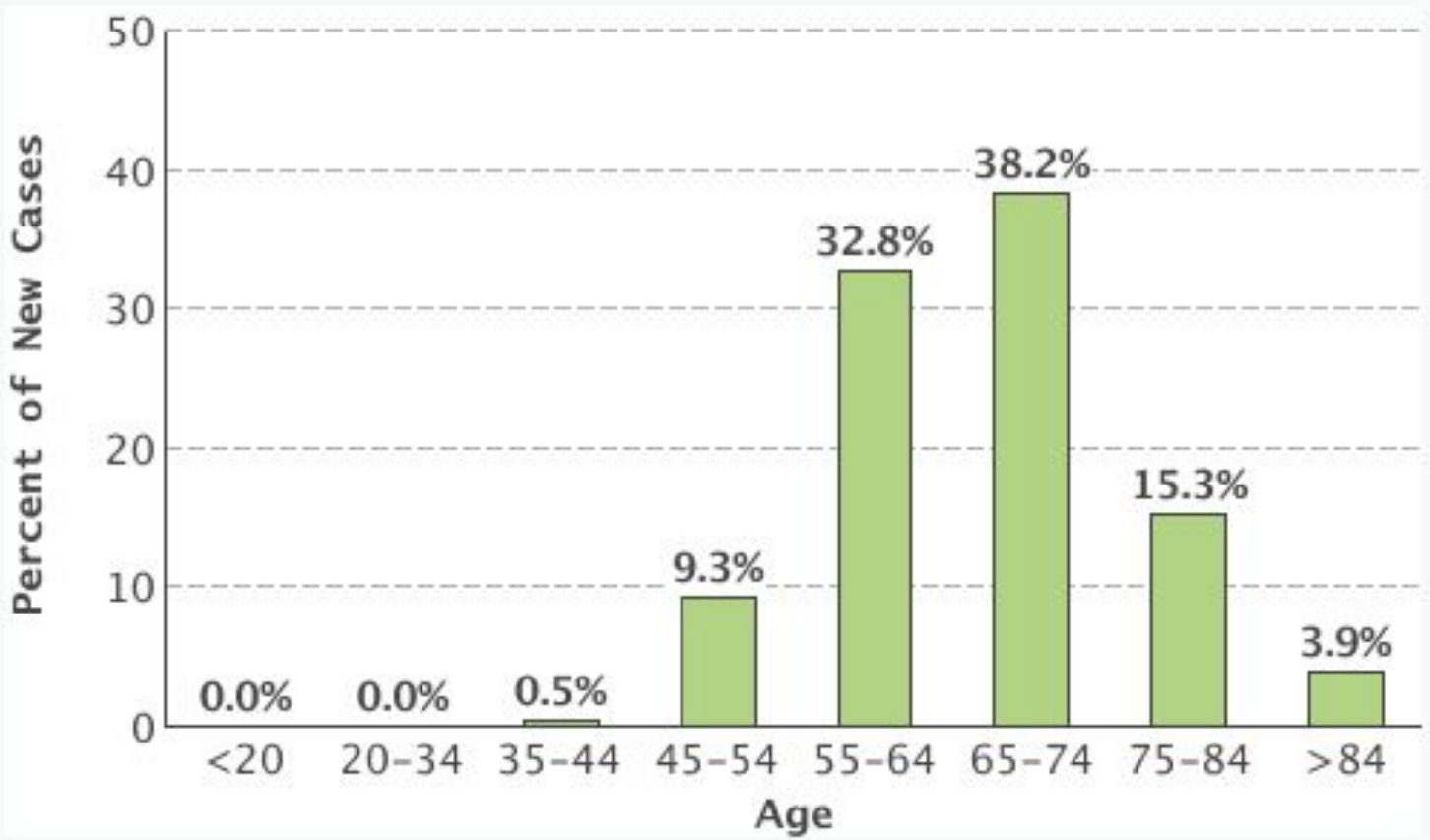
Prostate Caner

Epidemiology

Percent of New Cases by Age Group: Prostate Cancer



Prostate cancer is most frequently diagnosed among men aged 65–74.

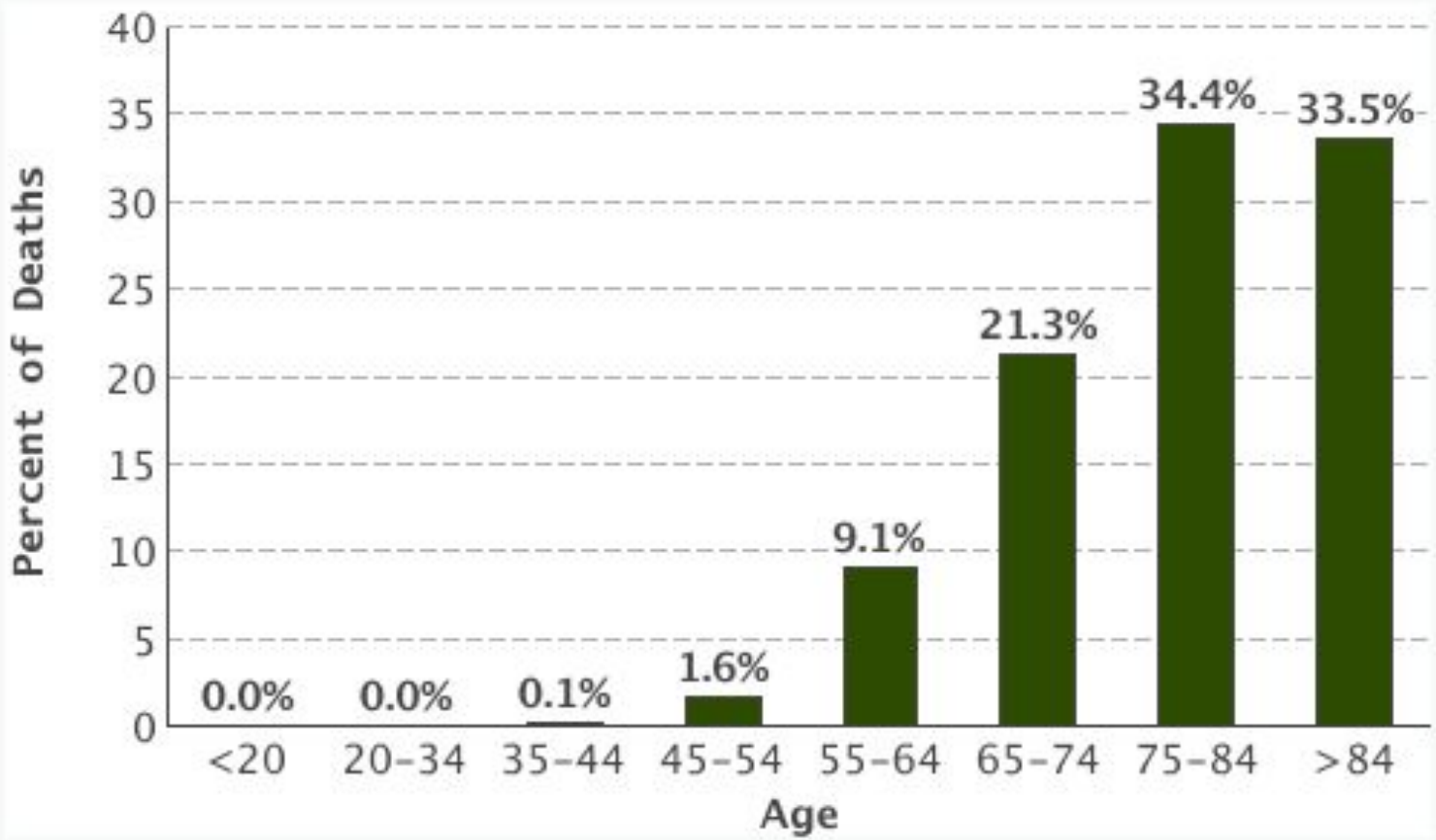
Median Age At Diagnosis

66

SEER 18 2010–2014, All Races, Males

Epidemiology

Percent of Deaths by Age Group: Prostate Cancer



The percent of prostate cancer deaths is highest among men aged 75–84.

Median Age At Death

80

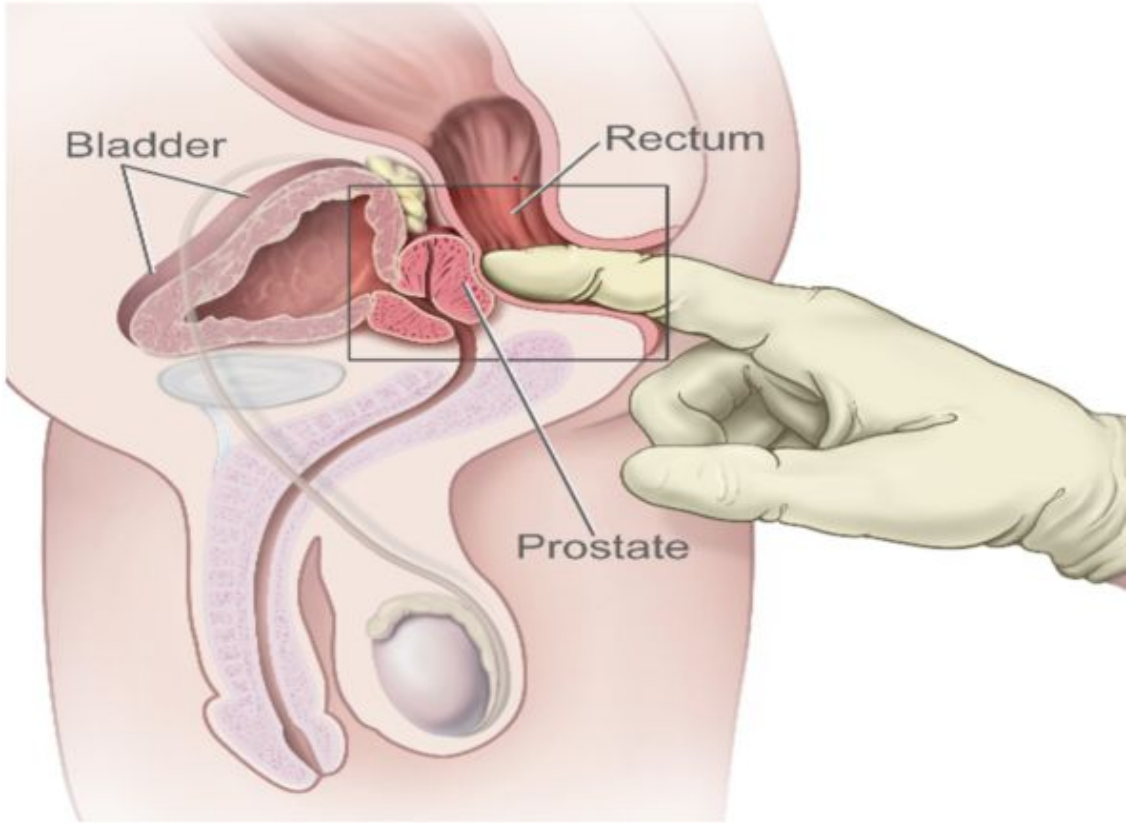
U.S. 2010–2014, All Races, Males

RGA

Historical Review
Digital Rectal Exam: 1904

Hugh Hampton Young, M.D.

Promoted the use of digital rectal exam for prostate cancer screening **NOTE 60% Stage T4!!! An UW PEARL**



- 60% Stage T4
- 20% Stage T3
- 20% Stage T2

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Prostate Specific Antigen PSA and PSA Density

- Normal range 0.0 – 4.0 ng/ml
- Lowered normal range to < 2.5 ng/ml for men with + FHX Prostate Cancer family, men < 60 years of age, and African-American men
- PSA rises < 0.5 ng/ml/yr (normal PSA velocity) **Most company manuals don't like to see velocity > 0.75 ng/ml/yr**

Underwriting Pearl:

Question: 5 Alpha reductase inhibitors such as finasteride (Proscar) can decrease the PSA by 50%. So How Valid is Free PSA ratio?

Answer: **%free PSA remains valid!!**

RGA

PSA Density

- Normal PSA density (PSA/Prostate Volume) is < 0.15 ng/ml/ml. **Most with bx proven prostate cancer had PSA density averaging 0.3 ng/ml/ml**

70 yr old male with 2+ prostate on APS per DRE.

Volume estimated to be 60 ml.

Question: Would you worry about a PSA of 6?

How about a PSA of 12?

Prostate Specific Antigen PSA And Its Pitfalls

Underwriting Pearl

- Elevated levels seen with:
- Benign Prostatic Hyperplasia *(usually < 10, so suspect malignancy if > 10)*
- Advanced Age
- DRE
- Urinary Tract infection
- Prostatitis
- GU instrumentation
- Recent Sexual Activity

PSA Screening Dilemma In Underwriting Risk

6% of men 50 - 70 years of age have a PSA level >4 or an abnormal DRE

LET'S DO THE MATH!!!!

- Would need to screen 250 men to find 15 men with an abnormal PSA or DRE for TRUS/NBP
- Would find 5 cases of prostate cancer in the 15 men undergoing a TRUS/NBP
- Would need to treat all 5 men to prevent one prostate cancer related death
- 3 men would survive regardless of treatment, 1 man would be saved and 1 would develop metastatic disease

SO WHY NOT JUST TREAT THEM ALL? Heard of Over Treatment?!

- Operation was a success but the patient died!
- Similar to the over diagnosis and over treatment of breast cancer.

RGA

Adverse Effects of Prostate Cancer Treatment

- Urinary Dysfunction
- Bowel Dysfunction
- Erectile Dysfunction
- Loss of Fertility
- Side Effects of Hormone Therapy
- Side Effects of Chemotherapy

Prostate Cancer Clinical Staging

- T1a: Found incidentally on TURP, <5%, Normal DRE
- T1b: Found incidentally on TURP, >5%, Normal DRE
- T1c: Found on TRUS – NBP for an elevated PSA, Normal DRE
- T2a: Palpable nodule on DRE, < ½ of one lobe
- T2b: Palpable nodule on DRE, > ½ of one lobe
- T2c: Palpable nodule bilaterally on DRE, both lobes
- T3a: Palpable outside the prostate but not seminal vesicles
- T3b: Palpable outside the prostate invading seminal vesicles
- T4: Locally invading the sphincter, rectum, bladder or pelvic wall

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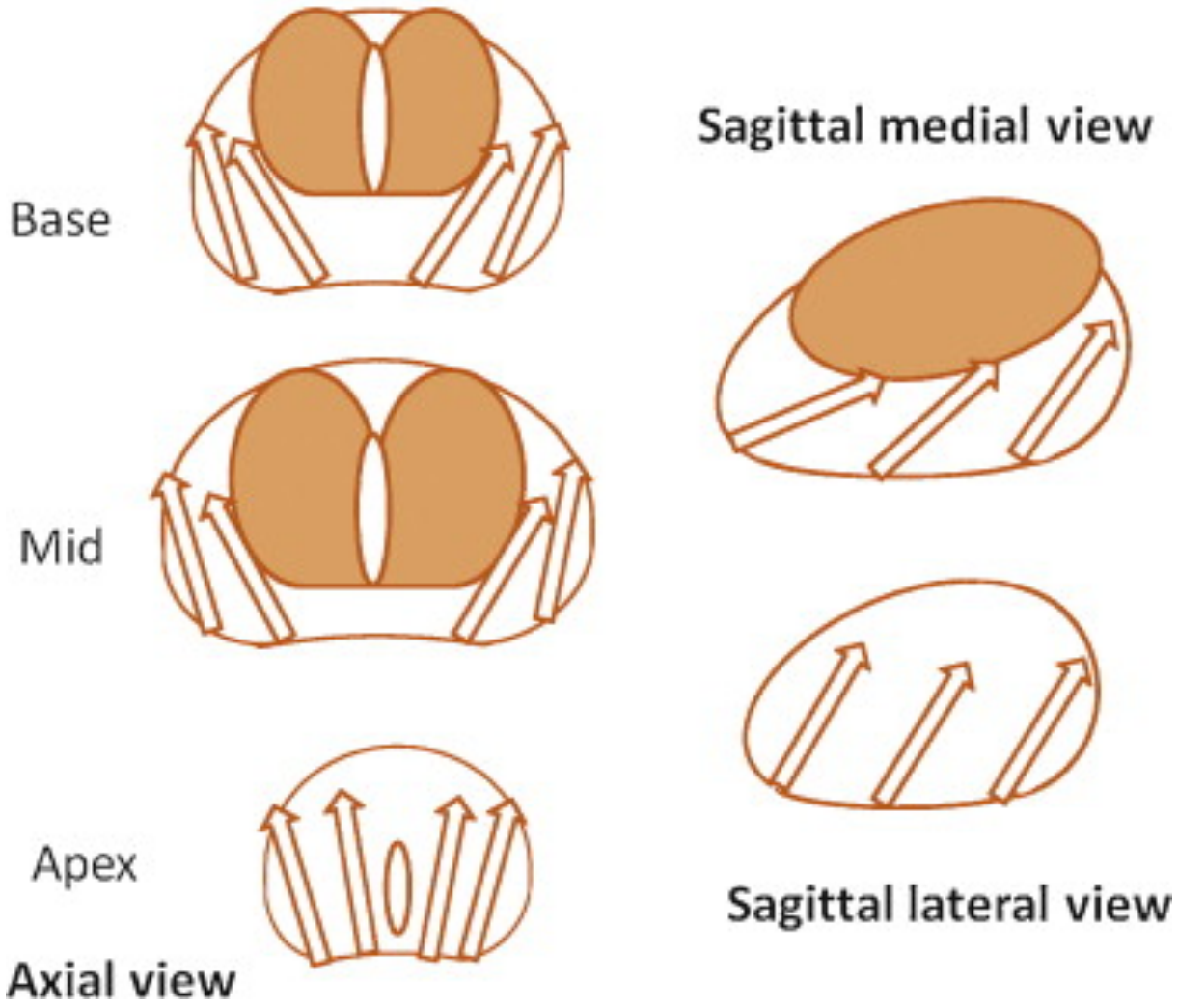
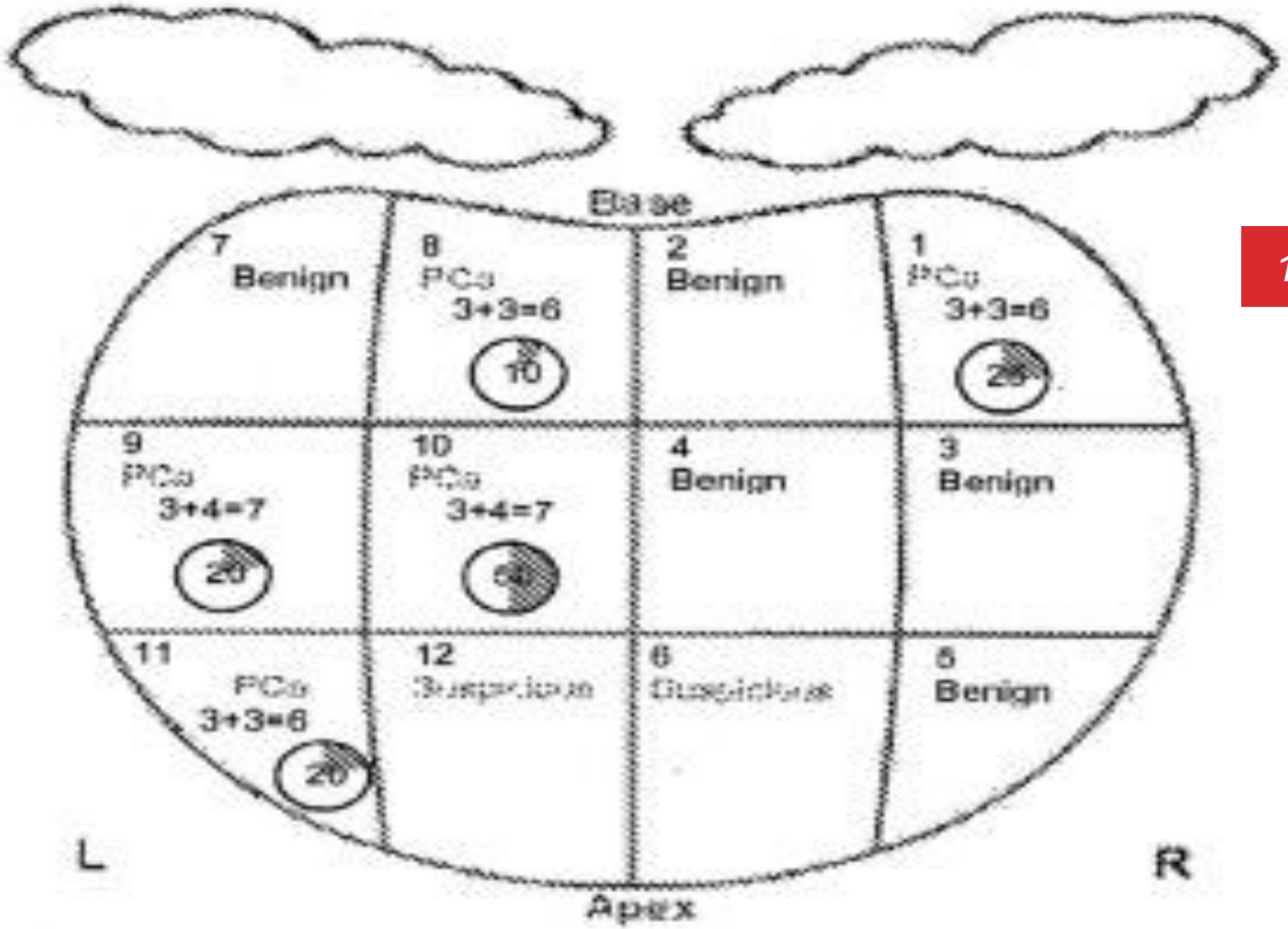
TRUS – NBP

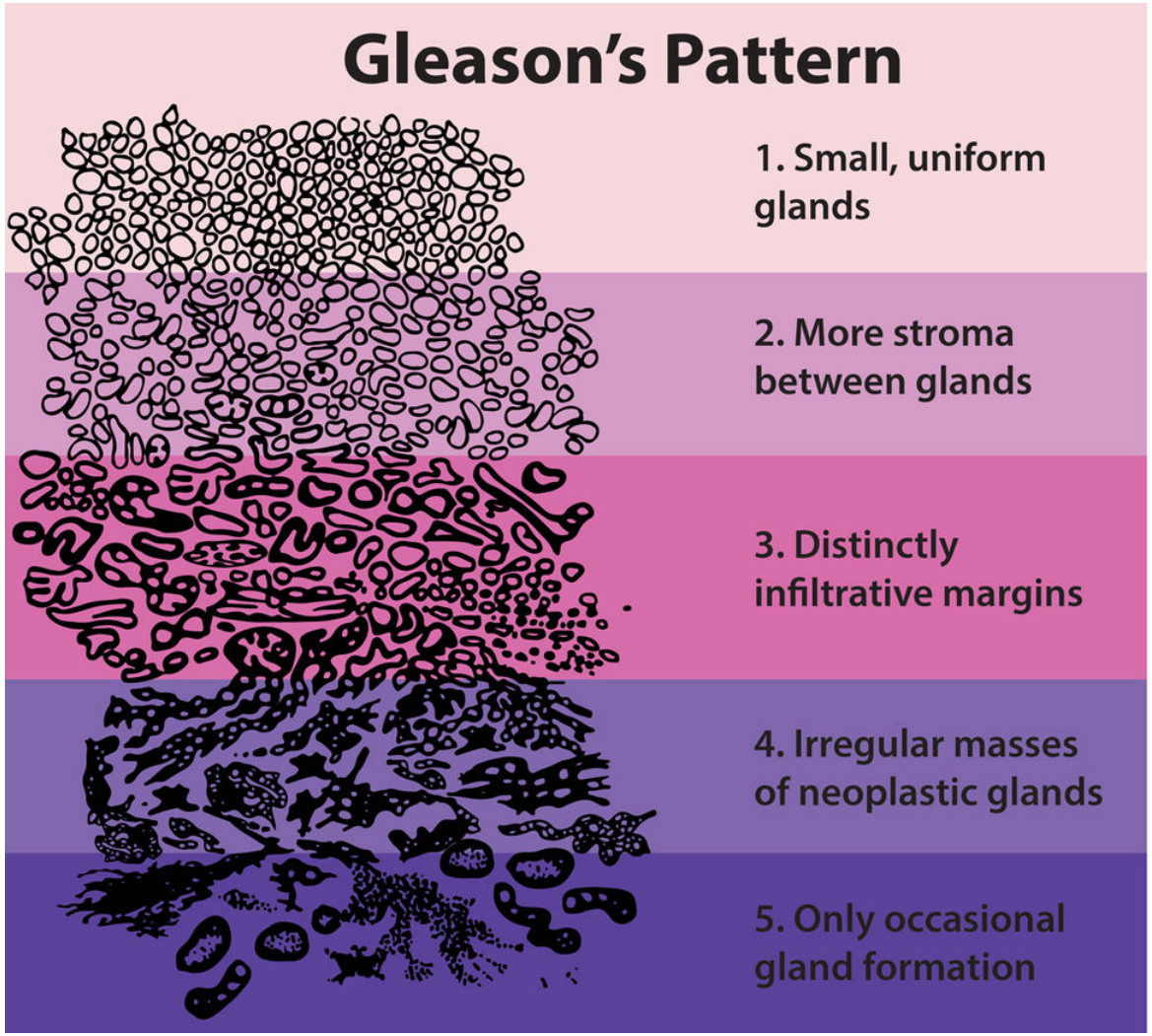

Base
Mid
Apex
Axial view
Sagittal medial view
Sagittal lateral view

TRUS - NBP



12 Core biopsy sites

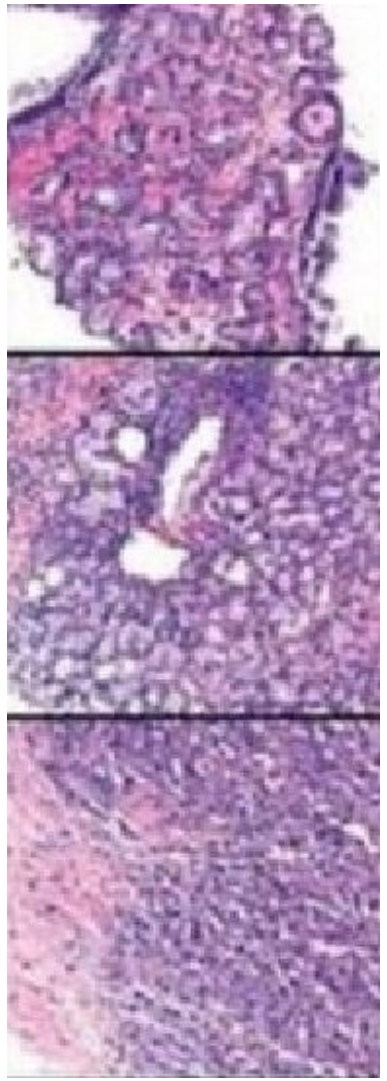
Prostate Cancer Grading



Well differentiated

Moderately differentiated

Poorly differentiated/ Anaplastic



Newer Grading for Prostate Cancer Emerging

Gleason 7 made up of 3+4 or 4+3 with prognostic differences. Likewise there is prognostic difference between Gleason 8 and Gleason 9 and 10

New Grading in use currently along side Gleason Scoring

- Grade Group 1 = Gleason 6 (or less)
- Grade Group 2 = Gleason 3+4=7
- Grade Group 3 = Gleason 4+3=7
- Grade Group 4 = Gleason 8 (4+4, 3+5, 5+3)
- Grade Group 5 = Gleason 9-10 (4+5, 5+4, 5+5)

And remember… Grade reflects behavior… Think of spring break. The worse the behavior, the worse the consequences!!

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Prostate Cancer Risk Groups: Stage, Grade and PSA

Risk Profile	Criteria†	Approximate Proportion of Newly Diagnosed Cases‡
Favorable		
Very Low Risk	• T1c • Gleason score 6 • PSA < 10 ng/ml • Fewer than 3 biopsy cores positive, ≤50% cancer in any core • PSA Density < 0.15 ng/ml/cc	35%
Low Risk	• T1 or T2a • Gleason score 6 • PSA < 10 ng/ml	
Intermediate	• T2b-T2c or • Gleason score 7 or • PSA 10-20 ng/ml	33%
High	• T3a or • Gleason score 8-10 or • PSA > 20 ng/ml	32%

1/3

1/3

1/3

†Adapted from Mohler, J., et al., *Prostate cancer, Version 3.2012: featured updates to the NCCN guidelines.* J Natl Compr Canc Netw, 2012. **10**(9): p. 1081-7. and based on T stage, Gleason score, PSA, PSA density, number and percentage of biopsy cores with cancer; T1c (non palpable cancer), T2a (minimally palpable cancer in one lobe), T2b-T2c (substantial palpable cancer felt to be localized to prostate gland), T3a (palpable cancer thought to have extended beyond the prostate gland).

‡Proportions from Surveillance, Epidemiology, and End Results Program of NCI as reported by Shao, Y-H, et al., *Risk profiles and treatment patterns among men diagnosed as having prostate cancer and a prostate-specific antigen level below 4.0 ng/ml.* Arch Intern Med, 2010. **170**(14): p. 1256-61.

RGA

Anatomic Stage/Prognostic Groups per ACS 7th edition

ANATOMIC STAGE/PROGNOSTIC GROUPS[6]					
Group	T	N	M	PSA	Gleason
I	T1a–c	N0	M0	PSA <10	Gleason ≤6
	T2a	N0	M0	PSA <10	Gleason ≤6
	T1–2a	N0	M0	PSA X	Gleason X
IIA	T1a–c	N0	M0	PSA <20	Gleason 7
	T1a–c	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA ≥10<20	Gleason ≤6
	T2a	N0	M0	PSA <20	Gleason 7
	T2b	N0	M0	PSA <20	Gleason ≤7
	T2b	N0	M0	PSA X	Gleason X
IIB	T2c	N0	M0	Any PSA	Any Gleason
	T1–2	N0	M0	PSA ≥20	Any Gleason
	T1–2	N0	M0	Any PSA	Gleason ≥8
III	T3a–b	N0	M0	Any PSA	Any Gleason
IV	T4	N0	M0	Any PSA	Any Gleason
	Any T	N1	M0	Any PSA	Any Gleason
	Any T	Any N	M1	Any PSA	Any Gleason

RGA

AJCC 8th Edition Prostate Cancer Prognostic Groups

AJCC	T	N	M	Gleason Score	PSA	Grade Group
I	cT1a-c, cT2a	N0	M0	≤6	<10	1
	pT2	N0	M0	≤6	<10	1
IIA	cT1a-c, cT2a	N0	M0	≤6	≥10 <20	1
	cT2b-c	N0	M0	≤6	<20	1
IIB	T1-2	N0	M0	7 (3+4)	<20	2
IIC	T1-2	N0	M0	7 (4+3)	<20	3
	T1-2	N0	M0	8	<20	4
IIIA	T1-2	N0	M0	≤8	≥20	1-4
IIIB	T3-4	N0	M0	≤8	Any	1-4
IIIC	Any T	N0	M0	9 or 10	Any	5
IVA	Any T	N1	M0	Any	Any	Any
IVB	Any T	N0	M1	Any	Any	Any

Approaches to Prostate Cancer Treatment

From Indolent Prostate Cancer to Lethal Prostate Cancer

- Watchful Waiting
- Active Surveillance
- Immediate Treatment

Definition of Active Surveillance and Watchful Waiting

- Active Surveillance is also called "Active monitoring". The aim is to properly time curative treatment or the active decision not to treat the patient immediately. Treatment is held up until a predefined threshold is reached that prompts treatment. This takes into account the patient's life expectancy into consideration. Treatment options are intended to be curative.

- Watchful Waiting is also known as "symptom guided treatment". This was the pre-PSA screening era's form of conservative management of prostate cancer until the development of local or systemic progression. At this point the patient would be treated palliatively with TURP or hormonal therapy or radiotherapy for palliation of metastatic lesions.

Now we use the terms pretty much interchangeably

RGA

Prostate Cancer - Treatment

Radiation

- Radiation will kill the tumor cells and shrink the prostate, but since the gland is still present, the PSA will fall but perhaps not to zero
- The PSA often falls initially, then “bounces” (cause unknown) then continues to decline and reaches a steady state
- PSA bounce can be for up to 1-2 years
- Failure to decline below 1.0 may indicate treatment failure, whereas a sudden rise during follow up (except for the “bounce”) may indicate recurrence

Prostate Case #1

- 63 yr old with no family hx of Pro CA. Had LUTS due to BPH on Flomax. Luts symptoms controlled. Had the biopsy in 2014 when diagnosed with BPH. PSA at time of 10/2014 bx was 7.6 ng/ml. As of 6/17 PSA rose to 10.2 ng/ml. DRE no nodules. Slightly enlarged.
- 4K score on 7/17 was 23% which was in the higher risk category and PSA on that date was 12.9 ng/ml (possibly jumped due to the DRE)
- Subsequently had MRI Prostate 7/17 that reportedly noted suspicious area at right posterolateral transition zone at base/mid junction.

Would you make an offer NOW???

Case 1: continued

- Underwent prostate biopsy on 9/17- taking 10 cores from right and 6 from left, urologist stating he cognitively chose sites corresponding to the MRI report. Prostate Volume was calculated to be 45 mls

- Pearl: Nml prostate volumes are in range of 20-30 mls
- Question: Can someone calculate the PSA density for me??

Pathology

DIAGNOSIS:
09/05/17 JAF:ra

PROSTATE, NEEDLE BIOPSIES:

1. RIGHT BASE:	BENIGN PROSTATE TISSUE.
2. RIGHT MID:	BENIGN PROSTATE TISSUE.
3. RIGHT APEX:	BENIGN PROSTATE TISSUE.
4. RIGHT LATERAL BASE:	BENIGN PROSTATE TISSUE.
5. RIGHT LATERAL MID:	BENIGN PROSTATE TISSUE.
6. RIGHT LATERAL APEX:	BENIGN PROSTATE TISSUE.
7. LEFT BASE:	BENIGN PROSTATE TISSUE.
8. LEFT MID:	BENIGN PROSTATE TISSUE.
9. LEFT APEX:	BENIGN PROSTATE TISSUE.
10. LEFT LATERAL BASE:	BENIGN PROSTATE TISSUE.
11. LEFT LATERAL MID:	BENIGN PROSTATE TISSUE.
12. LEFT LATERAL APEX:	BENIGN PROSTATE TISSUE.

Comment: All tissue has been examined in multiple levels. Patchy atrophy and acute and chronic inflammation are noted throughout the biopsies. Features diagnostic of adenocarcinoma are not identified in any of the biopsy specimens.

Case 1: Underwriting Assessment: Insurance 2/18 PSA is 10.8 (Recall 6/17 was 10.2)

- What is the PSA velocity?

Case 1: Continue

- PSA Velocity
- Simple algebra I

8 months/0.6ng/ml = 12 months/x ng/ml

8x = 7.2

x= 0.9 ng/ml/yr

Case 1: Underwriting Assessment: Insurance 2/18 PSA is 10.8 (Recall 6/17 was 10.2)

- Who would take case now?
- And if not, what would you require?

Subsequent Plan on Case 1 per Urologist

Assessment	Elevated PSA (R97.20).
Patient Plan	He and his wife and I had a complete discussion about his results, and the fact that his PSA still concerns me and I want to keep close watch on him. I suggested a trial of Finasteride to help downregulate and maybe drop PSA below normal after adjustment, and he has agreed. I talked about side effects and he will call if any occur. I will see him in 6mo for repeat PSA. If still high or higher after adjustment, I will try to find a MR fusion biopsy location for him.

Prostate Case #2:

- 72 year old male with insurance PSA of 7.0 ng/ml on 4/18. % free PSA is 22%
- On Proscar (Finasteride) 5 mg/day since 4/16 for urinary retention due to BPH. His PSA at that time just prior to Proscar initiation was 13 ng/ml when he was noted to have a post void residual of 100 cc and prostate volume/size was calculated to be 80 ml. DRE noted markedly enlarged prostate 3+ size without nodules.
- What is your underwriting decision as is?

Prostate Case #3

- 58 yr old male with strong family hx of prostate cancer in a brother and paternal uncle. Both relatives are alive.
- Has had screening PSA and DRE since age 50.

Annual PSA values since age 50 are as follows:

- Age 50: PSA 1.5 ng/ml
- Age 52: PSA 2.0
- Age 54 PSA 3.5
- Age 56 PSA 3.8
- Age 57 PSA 4.5

Current insurance PSA 6.2

Who would make an offer?

Case 3: Continued

- He called urology and placed on 10 days of Cipro and instructed to come into office for repeat PSA. PSA drawn and then had DRE which was normal.
- Repeat PSA was 5.9

Why did urologist place him on antibiotics and then have office draw PSA prior to performing DRE?

Who would take the case now?

Case 3: continued

- Urologist recommended TRUS bx.

- BX results: 1 core at right apex Gleason 4+3

  1 core at left apex Gleason 3+3

  All other cores were negative.

Pelvic imaging negative.

Bone scan negative

So what is the stage here? What is the Grade Group? What is the prognostic risk group?

AJCC 8th Edition Prostate Cancer Prognostic Groups

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I	cT1a-c, cT2a	N0	M0	≤6	<10	1
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IIA	cT1a-c, cT2a	N0	M0	≤6	≥10 <20	1
	cT2b-c	N0	M0	≤6	<20	1
IIB	T1-2	N0	M0	7 (3+4)	<20	2
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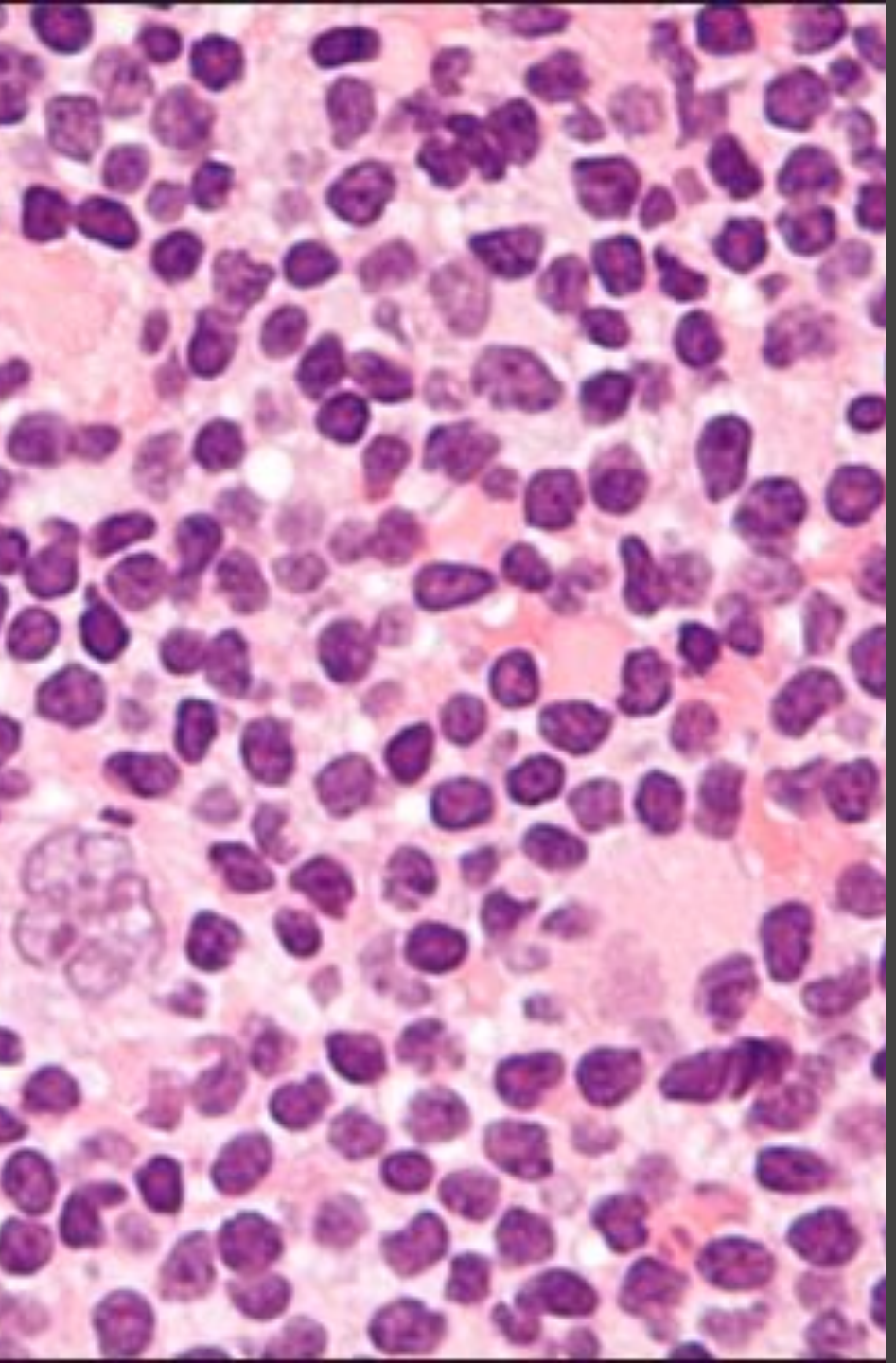
	T1-2	N0	M0	8	<20	4
IIIA	T1-2	N0	M0	≤8	≥20	1-4
IIIB	T3-4	N0	M0	≤8	Any	1-4
IIIC	Any T	N0	M0	9 or 10	Any	5
IVA	Any T	N1	M0	Any	Any	Any
IVB	Any T	N0	M1	Any	Any	Any



RGA

LYMPHOMA

Lymphoma Staging

Staging

Ann Arbor Staging System	
Stage 1	Involvement of single lymph node of a single extralymphatic organ or site
Stage 2	Involvement of 2 or more lymph nodes on the same side of diaphragm or localized involvement of an extralymphatic organ or site
Stage 3	Involvement of lymph node regions on both sides of diaphragm or localized involvement of an extralymphatic organ or site or spleen or both
Stage 4	Diffuse or disseminated involvement of one or more extralymphatic organs with or without associated lymph node involvement

Identification of the presence or absence of symptoms should be noted with each stage designation. A = asymptomatic, B= fever, sweats or weight loss > 10% body weight

Hematologic Cancers

Hodgkin's Lymphoma

Key Points

- B cell lymphocyte tumor characterized by the Reed-Sternberg cell
- Bimodal peak incidence: age 15-35 and less frequent increase >45
- Strong evidence that infectious agent is contributing cause (EBV)
- Genetic component also (identical twin of affected has 99-fold increase risk)
- Most relapses will occur within 2 years after completion of therapy but can be up to 13 yrs post RX
- Long term complications dictated by type of treatment
  - Chemo associated with 1-3% risk of acute leukemia w/in 5-10 years
  - Radiation associated with solid tumors depending on radiation field
  - Thyroid, lung, breast, colon, bone
  - Mantle radiation (radiation above the diaphragm) associated with CAD

Hodgkin's Staging and Survival

- Staging based on:
  - History
  - Physical exam
  - CXR, CT scans of chest, abdomen and pelvis
  - Bone marrow biopsy
  - Other staging from staging laparotomy (splenectomy, liver and all major lymph nodes)
  - “B” symptoms associated with advanced disease-60% have stage III or IV
- 10-year survival according to stage

Stage	Percentage
I	80-92%
II	75%
III	60% (approximately)
IV	40% (approximately)

Hematologic Cancers

Non Hodgkin's Lymphoma

Key Points
▪ 6th most common cause of cancer related deaths in U.S. with average age at DX 42
▪ 5 times more common than Hodgkin's
▪ Etiology: congenital and acquired immunodeficiency states – including those on immunosuppressive; infective agents such as HIV, EBV, Herpes, H.Pylori; autoimmune disorders such as RA, SLE, Sjogrens; chemicals such as herbicides, radiation and prior chemo
▪ Indolent types such as B cell lymphoma can be controlled but not often cured – act like chronic lymphocytic leukemia
▪ Some are extremely indolent AND resistant to therapy
▪ Some aggressive if caught at stage I or II and treated can be curable (they just soak up the chemo and DIE)
▪ Aggressive can be cured but succumb to the risk of secondary cancers later in life, which explains higher rating

Non Hodgkin's Lymphoma

Survival

Prognostic Factors	
Better Prognosis	**Worse Prognosis**
Age <60	Age >60
LDH normal	LDH abnormal
Ann Arbor State I or II	Ann Arbor Stage III or IV
Asymptomatic	Symptomatic
Small size of tumor	Bulky tumor (as defined by pathologist)
Small number of nodes	Large number of nodes
No extranodal involvement	Extranodal involvement

Lymphoma Case

- Case:
  - 45-year-old male with prior history of Hodgkin's treated a decade ago with chemo and radiation to subclavicular nodes
  - Presents with incidental findings of hypoechoic, irregular left thyroid nodule measuring 1.5 cm. FNA performed showing nondiagnostic findings.

- How would you rate case: standard, substandard or decline?