SOLID TUMORS WORKSHOP

An overview of cancers commonly encountered in underwriting

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U.S. Cause of Death

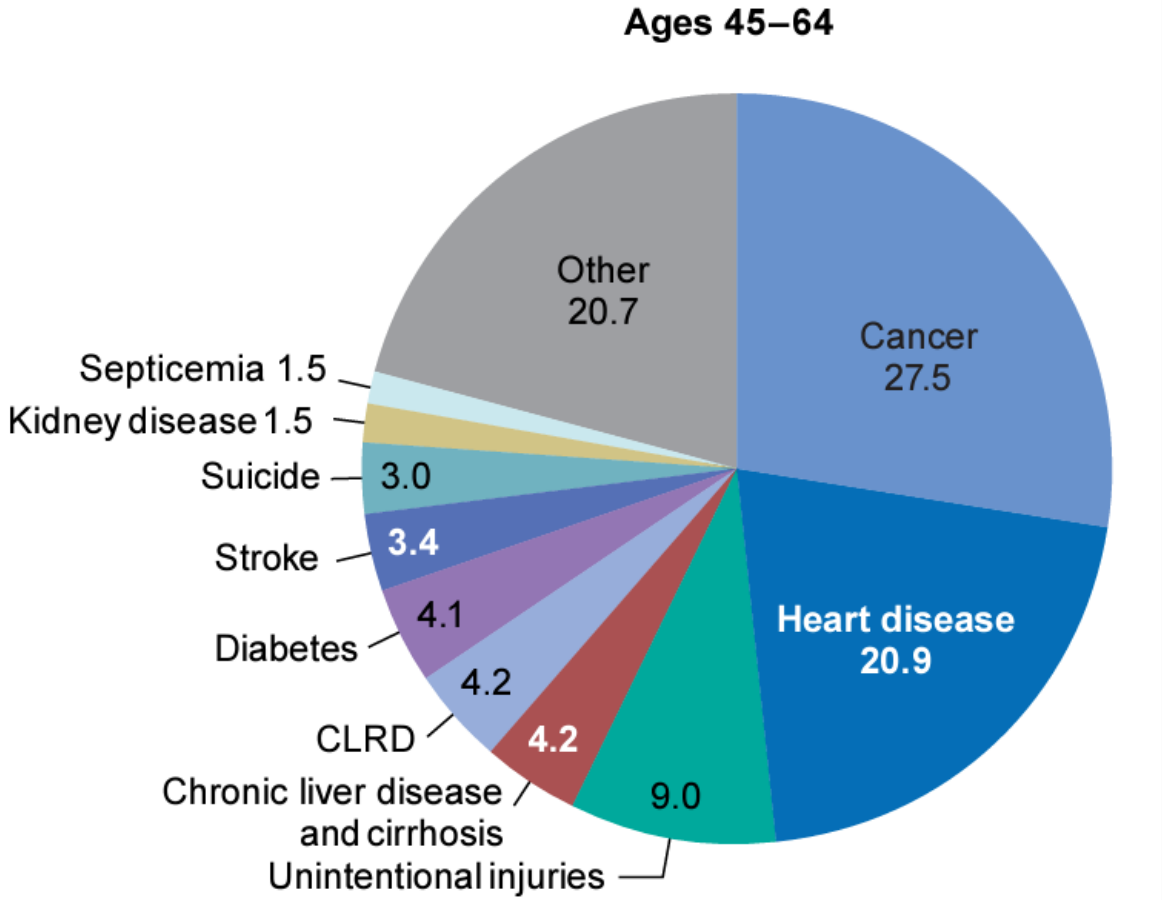
Overall, per CDC:

- Diseases of the heart 23.1%
- Malignant neoplasms 21.1%

However, cancer is the leading cause of death among those age <85

Munich Re 2019 claims review:

- 45% of deaths due to cancer



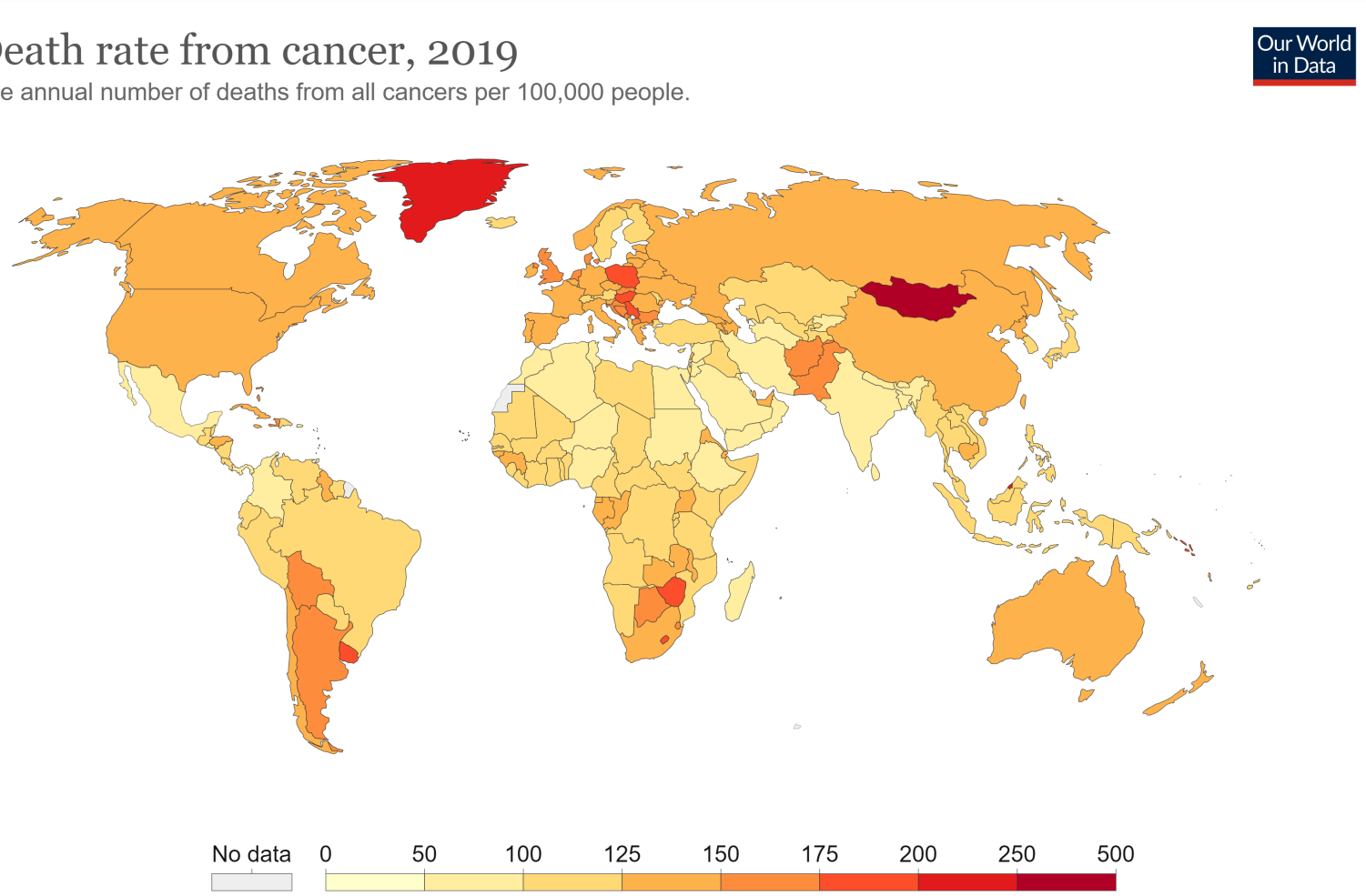
Estimated 18 million people in the U.S. with a history of cancer

Estimated New Cases in 2022	1,918,030
% of All New Cancer Cases	100.0%

Estimated Deaths in 2022	609,360
% of All Cancer Deaths	100.0%

5-Year Relative Survival
68.1%
2012–2018

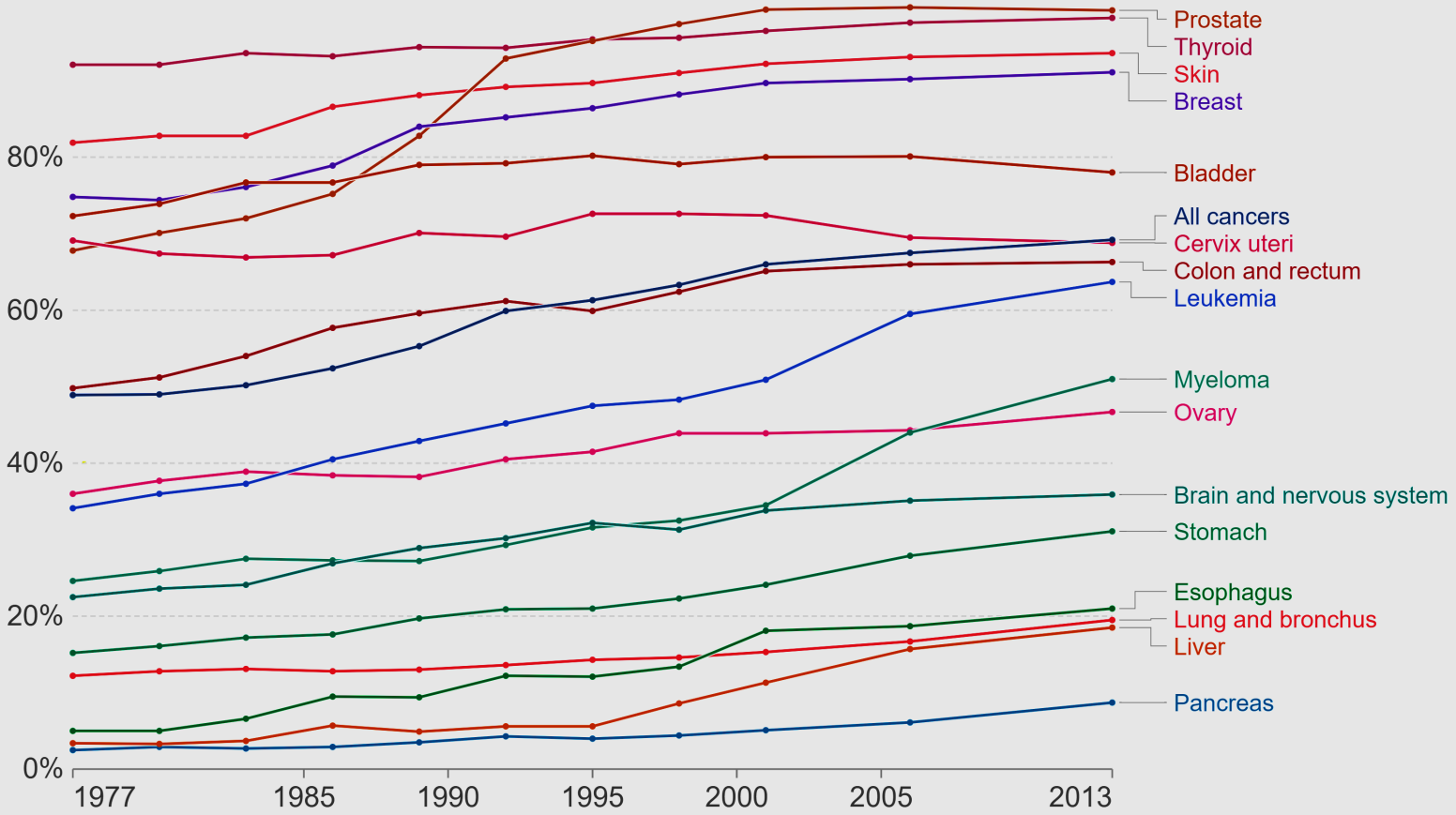
Cancer is a burden worldwide



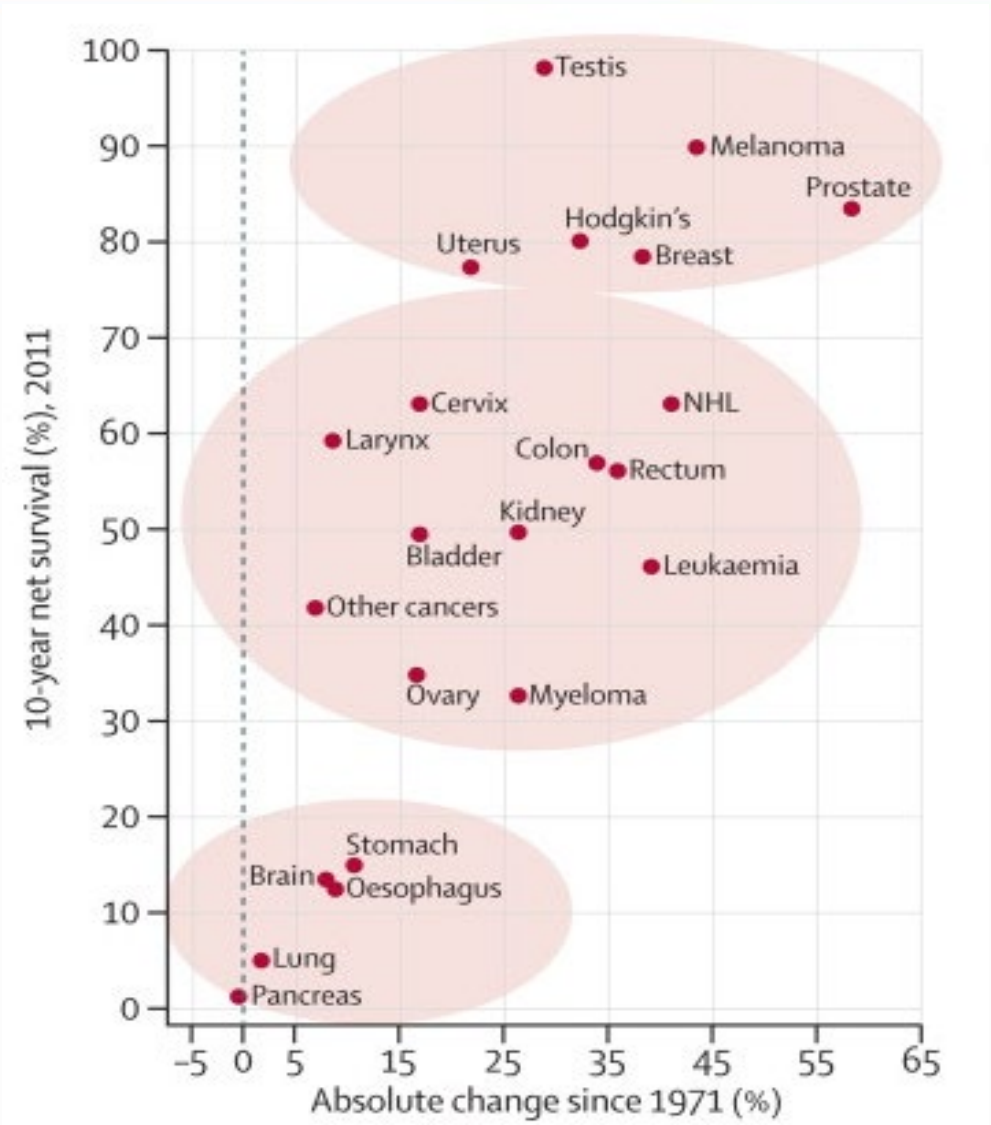
Five-year cancer survival rates in the USA, All races, total, 1977 to 2013

Percentage of cancer patients surviving at least five years since diagnosis, by cancer type. This data is available to view by sex and race.

Our World in Data



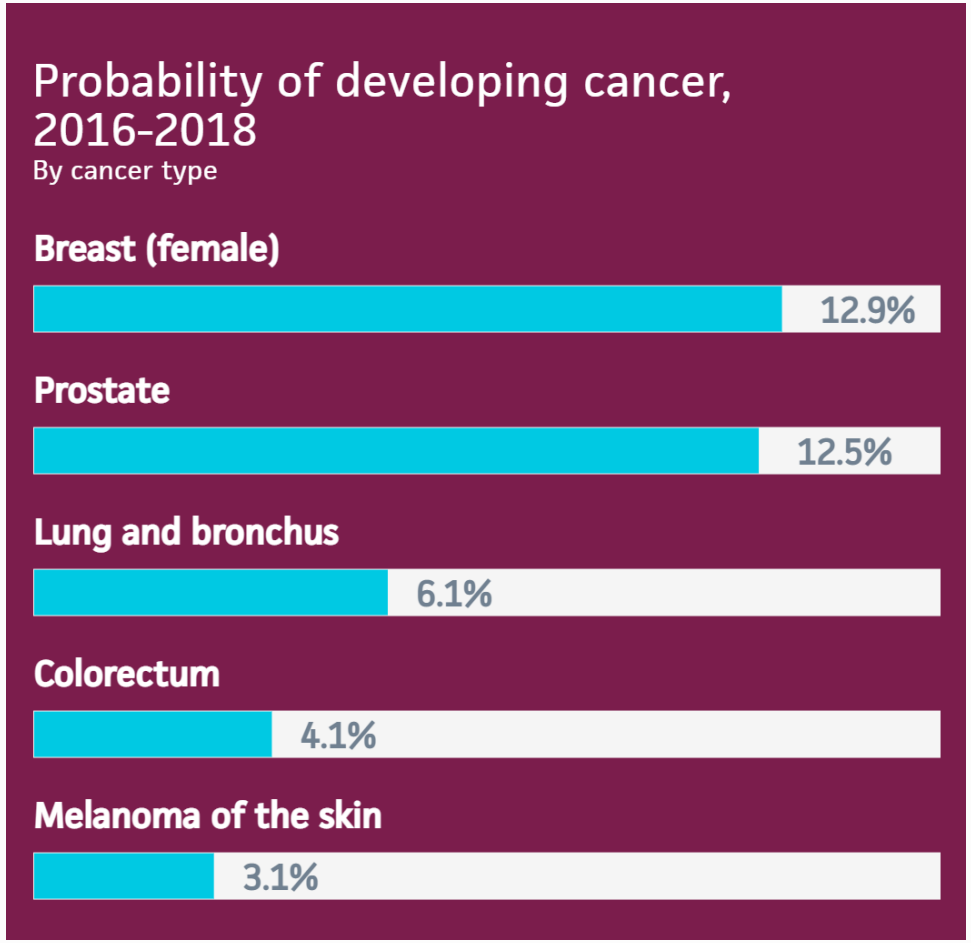
Source: National Cancer Institute



Net survival adjusted for age and sex for each cancer in 2010–11, and absolute change since 1971

All adults (15–99 years), England 10 years after diagnosis

Lifetime risk of top 5 occurring cancers

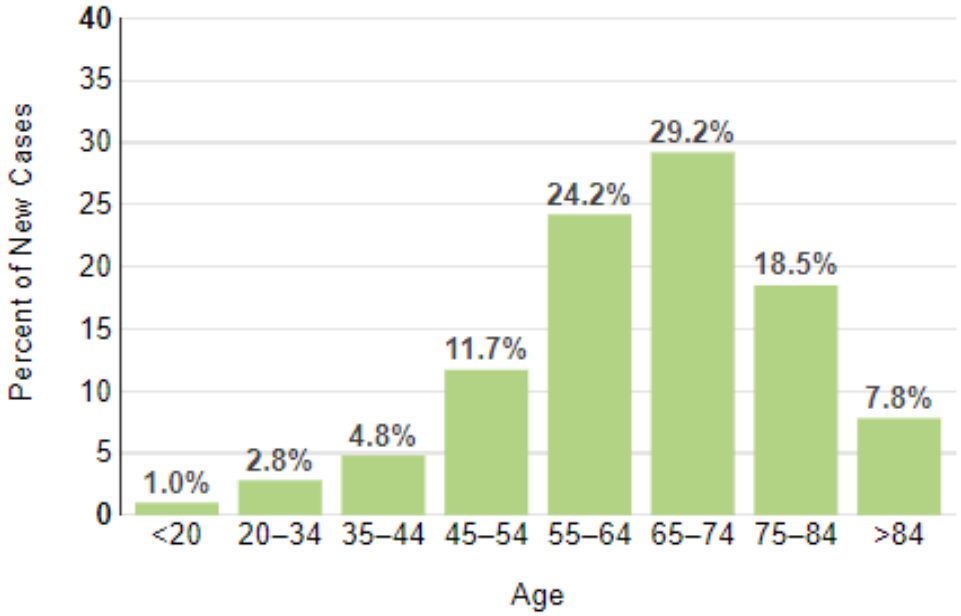


Lifetime risk of being *diagnosed* with cancer
~40% for men
~39% for women

Data sources: DevCan version 6.7.9, National Cancer Institute, 2021

Age at cancer diagnosis

Percent of New Cases by Age Group: Cancer of Any Site



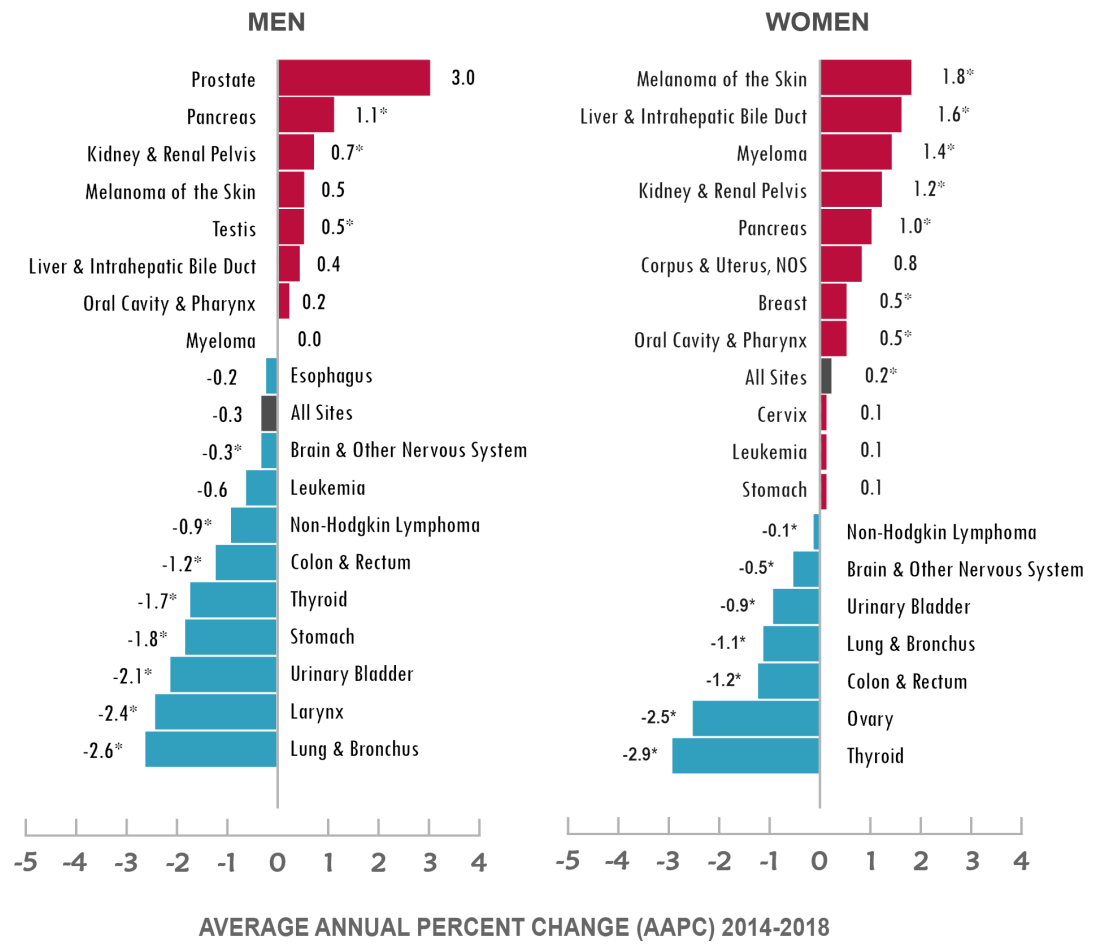
Cancer of any site is most frequently diagnosed among people aged 65–74.

Median Age At Diagnosis
66

SEER 22 2015–2019, All Races, Both Sexes

Cancer case rates

Between 2014-2018, rates of new cancer cases were stable for men and increased slightly—0.2% per year, on average—for women



Cancer death rates

However, overall cancer death rates decreased (on average)

- 2.3% per year for men
- 1.9% per year for women

Prostate Cancer

Photo by Clay Banks on Unsplash

Prostate Cancer – Case #1

- 65 year-old male. $250,000 UL; Sept 2020 application
- Insurance lab 8/20 normal except PSA 10.8

  - Prostate cancer likelihood low, moderate, or high?
  - What are some factors that can help determine that risk?

Underwriting Assessment

- What is the risk of having prostate cancer?
- What is the risk *if has* prostate cancer?

  - Former depends on?

  PSA level and kinetics (eg PSA velocity/doubling time, PSA density, Free% PSA)

  But also:

  - Age, family history, digital rectal exam (DRE), symptoms
  - Transrectal Ultrasound (TRUS), mpMRI
  - Other biomarkers (eg PCA3, proPSA, PHI, 4K score, SelectMDx, ERG)
  - Any prior biopsy results

Prostate Specific Antigen - PSA

- "Normal" range
  - Age 40-49: 0.1- 2.5 ng/mL
  - Age 50-59: 0.1- 3.5 ng/mL
  - Age 60-69: 0.1- 4.5 ng/mL
  - Age 70-79: 0.1- 6.5 ng/mL
- Relatively low sensitivity (35-70%) and specificity (60-90%)
- Elevated levels can be seen with Benign Prostatic Hyperplasia, Advanced age, Prostatitis, Trauma/GU instrumentation, Recent sexual activity
- PSA rises < 0.5 ng/ml/yr (normal PSA velocity)
- A favorable PSA density (PSA/Prostate Volume), consistent with BPH, is $\leq$0.10 ng/ml/ml; values >0.15 are concerning for cancer

Prostate cancer family history

Effect of family history of prostate cancer on lifetime risk of clinical prostate cancer

Family history	Relative risk	Absolute risk
Negative	1.0	8%
1 first-degree relative > 60 years	1.5–2	12–15%
1 first-degree relative < 60 years	2.5–3	20–25%
2 first-degree relatives any age	4–5	30–45%

Bratt, O. Hereditary prostate cancer: clinical aspects. J Urol, 2002; 168: 906-913.

Decision Tools - Biomarkers

- For whom to biopsy
  - PSA/Free PSA/PSA density/PSA velocity
  - mpMRI or TRUS-guided biopsy generally advised where available
  - PCA3 – Gene which is overexpressed with prostate cancer. Obtained from urine after prostatic massage.
    - Positive biopsy probability: From 14% with score <5, to 78% with score >100
  - Prostate Health Index (PHI) – formula combines PSA, free %, and [-2]proPSA
    - Positive biopsy probability: 8.7% PHI 0-23, 20.6% PHI 24-45, 43.8% PHI 46-100
  - 4K Score – 4 prostate specific kallikreins; PSA, free PSA, Intact PSA, beta-Kallikrein 2
    - Predicts aggressive cancer on a scale of 0 to 100% likelihood (usual action cut-off 5 or 7.5%)
- For when to re-biopsy
  - PCA3, PCMT, ConfirmMDX, PTEN, TMPRSS2-ERG
  - Oncotype DX high score, and/or PIRADs score of 4-5 associated with increased risk of biopsy upgrade
- For AS vs Treatment
  - Gene profiles, Circulating tumor cells, PTEN, TMPRSS2-ERG

Prostate Cancer Risk Calculators

- Risk of finding prostate cancer on biopsy:
  - http://riskcalc.org/PCPTRC/
  - http://www.prostatecancer-riskcalculator.com/seven-prostate-cancer-risk-calculators
  - http://riskcalc.org/PBCG/
- Risk following prostate cancer diagnosis:
  - https://umich-biostatistics.shinyapps.io/star-cap/
  - http://urology.jhu.edu/prostate/partin_tables.php
  - https://www.mskcc.org/nomograms/prostate
  - http://riskcalc.org/ProstateCancerPredictingPostRadicalProstatectomy/

Prostate Cancer Prevention Trial Risk Calculator Version 2.0

From SWOP
Prostate Cancer Research Foundation, Reeuwijk

PCPT Risk Calculator | Home | Map

Characteristics

Race
Caucasian

Age
65

PSA [ng/ml]
10.8

Family History of Prostate Cancer
Do not know

Digital rectal examination
Not performed or not sure

Prior biopsy
Not sure

- [ ] Percent free PSA available?
- [ ] PCA3 available?
- [ ] T2:ERG available?

Result | More Information

Risk of prostate cancer if biopsy were to be performed

Based on the provided risk factors a prostate biopsy performed would have a:

- 13% chance of high-grade prostate cancer,
- 21% chance of low-grade cancer,
- 66% chance that the biopsy is negative for cancer.
- About 2 to 4% of men undergoing biopsy will have an infection that may require hospitalization.

Please consult your physician concerning these results.

RISK CALCULATOR

Calculator | About | Language

RESULT

43%
Detectable Cancer Risk

25%
Significant Cancer Risk

Apr-13	2.9
Mar-17	10.2
Mar-17	9.4
May-17	6.2
Sep-17	8.7
Jan-18	10.2
Apr-18	8.2
Jul-18	6.4
Oct-18	7.1
Feb-19	7.5
Apr-19	7.5
Aug-19	7.1
Nov-19	7.2
Feb-20	9.9
May-20	9.1

Case #1 – 65 year-old man

- Previous PSA results
- Percent free PSA
  - 20.2 3/17
  - 19.4 4/18
  - 20.0 4/19
  - 19.1 7/20
- Recall PSA on app 10.8

- Does this alter your opinion?

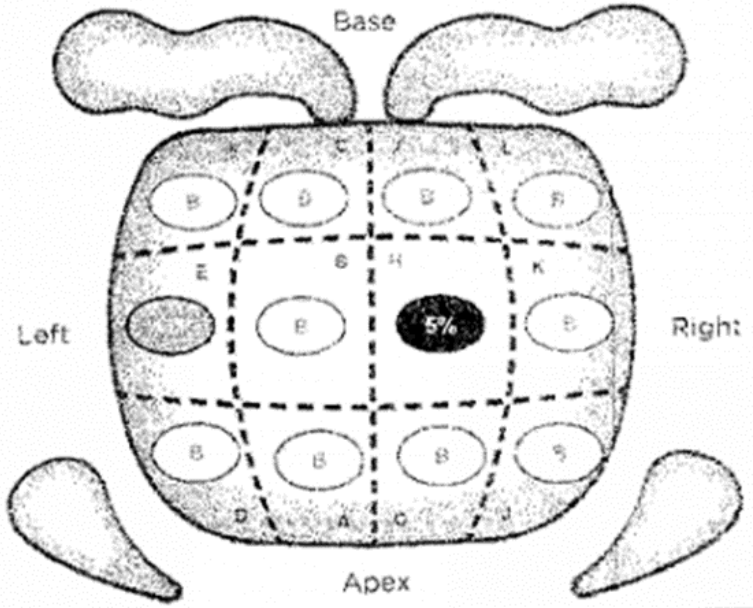
Case #1 – 65 yr-old man
Path report March 2017

- MRI 3/17:
  - BPH, prostate vol 85 cc
  - No discrete suspicious or clinically significant lesion
- Elected to undergo Active Surveillance

- Now, does that alter your opinion?
- Mortality risk minimal, low, moderate, or high?

Diagnosis: Adenocarcinoma , Highest Gleason Score =6(3+3)

PSA, 9.4; ICD: R97.20




Part H IHC Stain

Prostate Map Legend

B = Benign
= High Grade PIN
N% = Carcinoma (% tumor)
= Atypical

Diagnosis Description				Gross Description	
Specimen Site	Diagnosis	Gleason Score	Involvement	Pieces	Length (cm)
A. Left Apex	Benign	-	-	1	1.2
B. Left Mid	Benign	-	-	1	1.3
C. Left Base	Benign	-	-	3	0.2, 0.6, 0.6
D. Left Lateral Apex	Benign	-	-	2	0.4, 0.7
E. Left Lateral Mid	ASAP	-	-	1	1.8
F. Left Lateral Base	Benign	-	-	1	1.1
G. Right Apex	Benign	-	-	2	0.3, 1.2
H. Right Mid	Adenocarcinoma	6(3+3)	5%	2	0.2, 1.1
I. Right Base	Benign	-	-	3	0.2, 0.5, 0.6
J. Right Lateral Apex	Benign	-	-	1	1.0
K. Right Lateral Mid	Benign	-	-	1	1.5
L. Right Lateral Base	Benign	-	-	1	0.8

Underwriting Assessment

- What is the risk of having prostate cancer?
- What is the risk *if has* prostate cancer?
  - Former depends on: Age, PSA factors, family history, DRE/TRUS/MRI, other biomarkers
  - Latter depends on histology and tumor extent, plus –
  - Age, PSA, exam, genetic markers
- Most important factor (assuming no indication of metastases)?
  - Risk for localized cancer is driven by Grade Group

Original Schematic of Gleason's Grading System

Gleason score is derived by adding together the value of the two most prevalent differentiation patterns - a primary grade and a secondary grade (even though there are often more than two different patterns!)

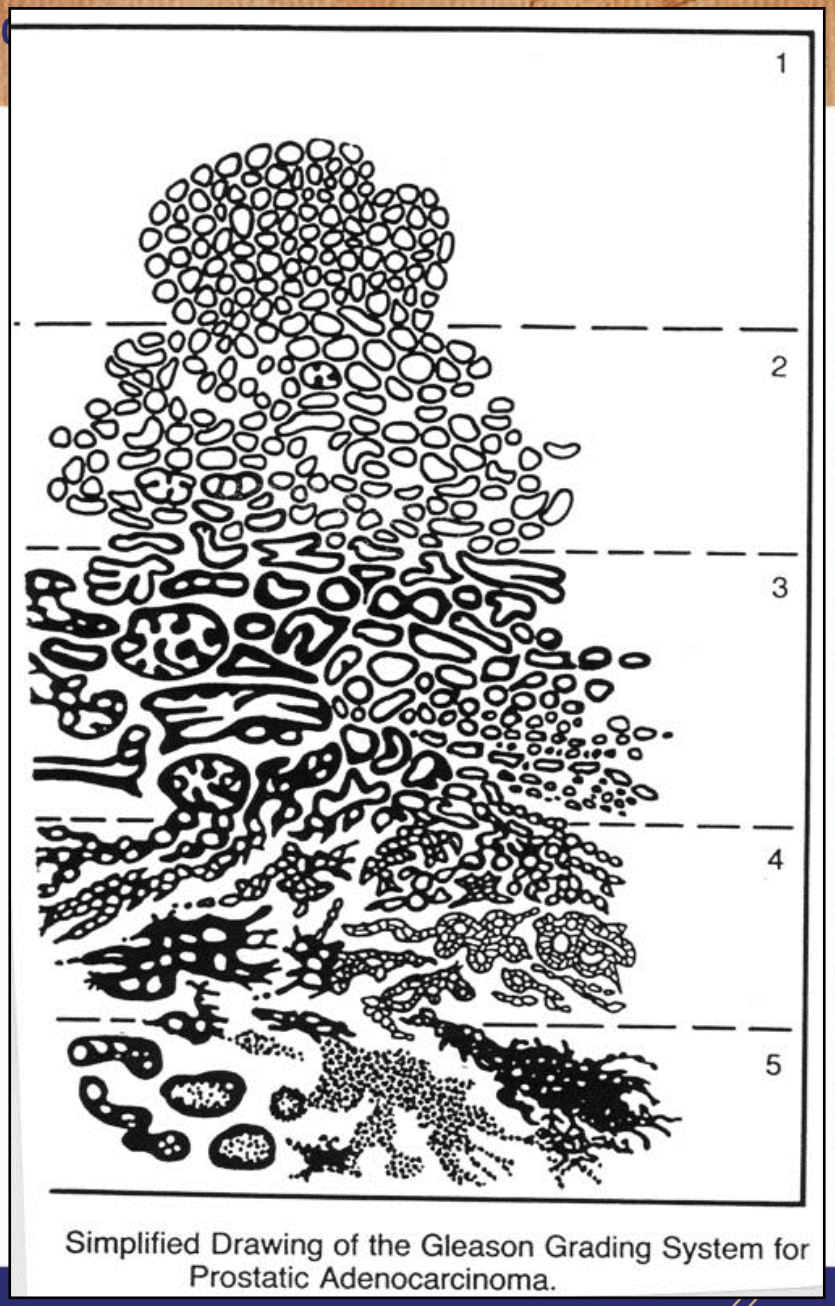
1: Small uniform glands

2: More stroma between glands

3: Distinctly infiltrative margins

4: Irregular masses of neoplastic cells

5: Anaplastic - only occ. gland formation



Simplified Drawing of the Gleason Grading System for Prostatic Adenocarcinoma.

Graphic courtesy Jack Swanson

Prostate Cancer Histologic Grade Groups (GG)

- GG I: Gleason score 3+3=6
- GG II: Gleason score 3+4=7
- GG III: Gleason score 4+3=7
- GG IV: Gleason score 4+4 or 3+5=8
- G V: Gleason score 4+5=9 or 5+5=10

- By separating out a Gleason's score of 3+4 vs 4+3 and of 8 vs 9-10, the GG alone was consistently better at predicting higher risks of T3-4 disease

PROSTATE CANCER STAGING

Clinical (c) staging:

- cT0 – No evidence of primary tumor
- cT1a/b – Incidental finding at TURP
- cT1c – Clinically inapparent, biopsy diagnosis only
- cT2a – Palpable on DRE < ½ of one lobe
- cT2b – Involves up to one lobe
- cT2c – Involves both lobes
- cT3a – Extraprostatic extension (through capsule but not fixed)
- cT3b – Seminal vesicle invasion
- cT4 – Fixed, or invades adjacent structures

Pathological (p) staging:

- pT2 – Organ confined
- pT3a – Extraprostatic extension or microscopic invasion of bladder neck
- pT3b – Seminal vesicle invasion
- pT4 – Fixed or invades adjacent structures other than seminal vesicles

Prostate cancer stage groups – AJCC 8th Edition

Stage	T	N	M	Grade group	PSA
I	cT1a-c, cT2a pT2	N0	M0	1	<10
IIA	As above, or cT2b-c	N0	M0	1	10-20 <20
IIB	T1-2	N0	M0	2	<20
IIC	T1-2	N0	M0	3 or 4	<20
IIIA	T1-2	N0	M0	1-4	≥20
IIIB	T3-4	N0	M0	1-4	Any
IIIC	Any T	N0	M0	5	Any
IVA	Any T	N1	M0	Any	Any
IVB	Any T	Any N	M1	Any	Any

What stage is his prostate cancer?

Is AS appropriate in this case?

Risk Level With Newly Diagnosed Prostate Cancer

National Comprehensive Cancer Network (NCCN)

- Very low risk disease
  - T1c, GGG 1, and PSA <10
  - Fewer than three positive biopsy cores
  - Less than 50% involvement in each core
  - PSA density <0.15 ng/mL/gram
- Low risk disease
  - T1 to T2a, GGG 1, and PSA <10 ng/mL
  - Does not qualify for very low risk
- Favorable intermediate risk disease
  - Low risk disease plus:
  - Percentage of positive biopsies <50
  - One of the following: T2b/c, PSA 10-20, or GGG 2 or 3

Management of localized prostate cancer

- NCCN very low risk
  - Active surveillance (AS) usually recommended
- NCCN low risk
  - Can consider AS, along with Prostatectomy or Radiation
  - Other factors (biomarkers, MRI) often useful
- NCCN favorable intermediate risk
  - Prostatectomy with pelvic lymph node dissection or RT with ADT preferred
  - AS a consideration if patient preferred, but is of higher risk
  - Possibly MRI-guided high-intensity focal ultrasound therapy?
- All others
  - Definitive treatment vs ADT, Chemo, or supportive Tx – depending on extent, health, life expectancy

Additional prognostic factors

Cancer stage, Gleason score, and serum PSA level, are well shown to be important prognostic factors, but still do not fully inform how the tumor will behave.

- PSA dynamics – PSA density and velocity, % free PSA, % proPSA
- Multi-parametric MRI and TRUS findings
- Molecular assays – Oncotype DX, Prolaris, ConfirmMDx, Decipher
- Presence of germline mutations – BRCA, ATM, CHEK2

Case #1 – 65 year-old male

- Stage T1c, GGG 1, 2017 PSAs 6.2-10.2 – *Active* surveillance
- Follow-up PSAs 2018-2020 6.4-10.2; PSA Feb 2020 9.9
- Repeat mpMRI 3/20:
  - 6 x 11mm right medial, base to apex, peripheral zone lesion
  - PIRADS 2
  - BPH, 96 cc

- Insurance app 9/20; PSA 10.8
- Your assessment?

AS Monitoring Protocol

- Protocols differ by institution and have evolved over time
- Typically -
  - Follow-up can vary be level of risk and patient preference
  - PSA measurement every 6 months – possibly going to yearly if with prolonged stability
  - Yearly exam including digital rectal exam (DRE)
  - Follow-up biopsy after 12-18 months often advised
  - mpMRI occasionally used in place of or in addition to repeat biopsy - if no suspicious lesion is detected, imaging can be done every 2-3 years
- A significant rise in serum PSA or a worsening abnormality on DRE or on mpMRI warrants further assessment, typically prostate biopsy
- Definitive treatment usually advised if…
  - Progression to Grade group 3 cancer or
  - Grade group 2 with indications of higher tumor volume (such as by mpMRI progression or a findings of more than half of biopsy cores positive)

Multi-parametric MRI (mpMRI)

- Incorporates T2 signal MRI with magnetic resonance spectroscopic imaging (MRSI), diffusion tensor imaging (DTI), and dynamic contrast enhanced (DCE) imaging
- Provides information on not just anatomy but also tissue characteristics such as prostate volume, cellularity, and vascularity
- Evidence that MP-MRI tends to detect higher risk disease and systematically overlooks low-risk disease
- Common indications:
  - Negative prior biopsy with a continuing elevated or rising PSA
  - Positive DRE with a negative TRUS biopsy
  - Instead of repeated TRUS biopsy for low-risk prostate cancer followed with AS

Prostate Imaging Reporting and Data System Score

- mpMRI provides information on not just anatomy but also tissue characteristics such as prostate volume, cellularity, and vascularity
- MRI-base PIRADS scores correlate with prostate cancer risk

	Cancer detection rate percent by PIRAD score			
Score	1-2	3	4	5
Overall cancer rate	7.7	29.7	42.3	82.4
Clinically significant cancer rate	0	8.9 (3-27)	21.4 (23-65)	62.7 (40-80)

- Prostate cancer of any grade was found in 51.9%, 26.5% and 43.8% of patients of biopsy-naive patients, patients with previous negative TRUS biopsy, and AS patients, respectively

MRI vs repeat biopsy in AS

Korean study of those deemed eligible for Active surveillance (PSA level ≤10 ng/mL, PSA density <0.15 ng/ml/g, Gleason grade group ≤2 within two positive cores, and a clinical stage of cT1–cT2a)

- Those choosing AS were compared to those choosing RP
- AS group followed by mpMRI, and not repeat biopsy unless indicated by MRI
- No difference in 5-year overall and cancer-specific mortality
- However…
  - Only 5-year f/u
  - Over half of AS ended up getting RP; 43% of these because of disease progression

Outcomes in select AS studies

Author/Study	Median follow-up	10-year PCSS	15-year PCSS	Notes
Bokhorst/PRIAS	78 months	99%		By 10 years, 73% had undergone definitive treatment. 10-yr BCR and met-free 94%
Tosoian/Hopkins	68 months	99.9%	99.9%	Select group – 71% very low risk Metastasis-free survival 99.4% at 15 yrs
Klotz/Toronto	77 months	98%	94%	13% of cohort had GGG 2; this group represented 44% of those with mets
Carlsson/MSKCC	77 months	99.4% met-free	98.5% met-free	Median age 62; all GGG 1 2664 pts, 1 death

University of Toronto AS experience

- Toronto group follow-up on 993 patients, median age 67.8 years (range 41-89 yrs)
  - 206 patients have been observed for >10 years
- The 10- and 15-year actuarial cause-specific survival (CSS) rates were 98%, and 94%, respectively. CSS was similar for those age <70 and ≥70 years.
- Mortality analysis (using Canadian Life Table 2005-7), yielded overall MR of 134%
- An age breakdown was not provided, but CSS comparison yields similar results – somewhat higher for age in 60s and lower at 75+

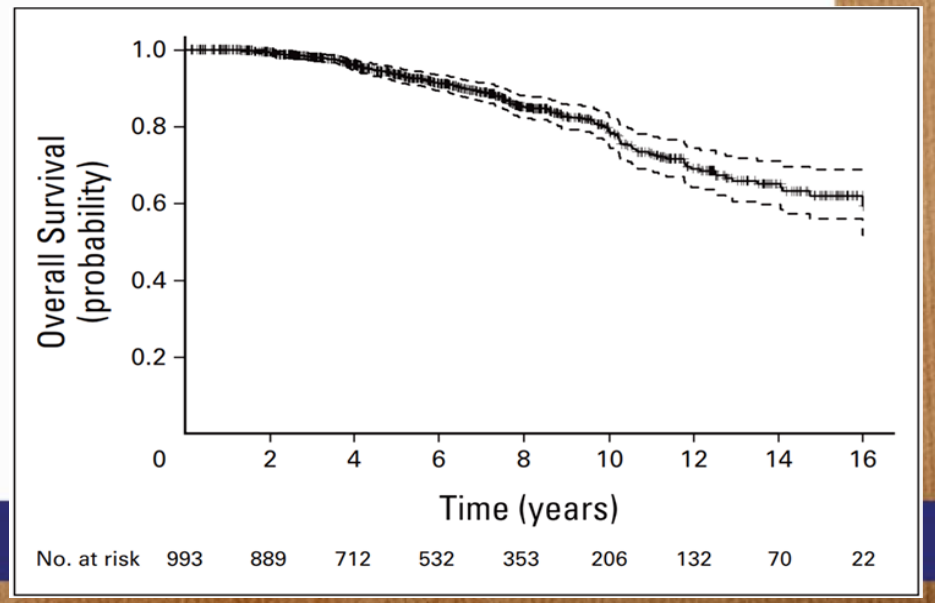


Fig 1. Kaplan-Meier overall survival curve with 95% CIs in all patients.

Klotz. J Clin Oncol 33:272-277. 2014.

Case #1 – 65 year-old male

- Stage T1c, GGG 1, 2017-2020 PSAs 6.2-10.8
- PSAD 3/20: 9.9/96 = 0.103
- Active surveillance
  - Assessment?
- Little to no risk with GG1, small tumor volume
- But critical issue is risk of upgrading (and upstaging)
- Mostly a factor of undersampling (+/- pathologist interpretation)

Prostate Cancer – Case #2

60 year-old male. $350,000 UL; May 2021 application

- 1/19 PSA 4.91 and 4K score of 1%
- 2/19 PSA 3.6, DRE normal. Fam Hx = adopted.
- 4/19 PSA 4.3
- 6/19 MRI = bilat PIRAD grade 2 lesions
- 9/19 PSA 4.07
- 3/20 PSA 5.18, free PSA = 25%
- 7/20 PSA 6.67, free PSA = 18%, DRE no nodules

  - Prostate cancer likelihood low, moderate, or high?
  - Overall risk?

Case #2 – 60 year-old male

- Prostate Ca July 2020
- 7/20 Prostate 12-core biopsy:
  - Gleason 6(3+3) in 8 of 12 cores (5-80% of core) and Gleason 7(3+4) in 30% of one core
  - Tumor is adjacent but not involving periprostatic adipose tissue - suspicious for focal extraprostatic extension
  - Prolaris molecular score 6.2

- AS candidate?

Prostate cancer genomic markers

- Currently 4 commercially available genomic markers
  - Oncotype Dx Genomic Prostate Score
  - Myriads Prolaris risk score
  - Decipher Genomic classifier
  - Metamark's Promark
- Each has evidence as a predictor of prostate cancer outcomes beyond tumor histology
- Clinical utility however is less clear (compared to MRI, PSA kinetics, etc)
- Performed on biopsy tissue -- tumor heterogeneity and multifocality issues may limit proper risk stratification

Cell-cycle progression (CCP) gene panel

- The CCP gene panel (Myriad-Prolaris®) score has been shown to be predictive in prostate cancer outcomes
  - Analyzes 31 cell cycle progression genes plus 15 housekeeper genes
  - Original version CCP score favorable if <-1 and adverse if >1 → now changed to 0-10 score, <3 favorable, >4 adverse
- After prostatectomy, biochemical recurrence risk per 1-unit increase in the CCP score was 1.63 in a multivariate model
- A review study however questioned whether the results led to significant changes in management

Case #2 – 60 year-old male

- RALRP September 2020
- Insurance lab April 2021: PSA 0.04, UA negative
  - Thoughts, now 7 months after surgery?

Case #2 – 60 year-old male

RALRP Sept 2020

- 4/21: PSA 0.04

Final Diagnosis

A. Prostate, anterior prostatic fat, excision:
- Mature fibrofatty tissue, negative for malignancy.

B. Prostate, right base margin, biopsy:
- Fibroconnective tissue, negative for carcinoma.

Note: Frozen section was reviewed and upon comparison with permanent material, original interpretation of atypical glands compatible with inflammatory respond; no evidence of carcinoma is seen.

C. Prostate, mid left, biopsy:
- Fibroconnective tissue, negative for malignancy.

D. Prostate, radical prostatectomy:
- Adenocarcinoma of prostate, Gleason score 6 (3+3), Grade group 1.
- Tumor confined to prostate and present at left posterior lateral margin.
- Perineural invasion is identified.
- Three lymph nodes, negative for malignancy (0/3).

AJCC TNM stage: pT2 pN0

- Thoughts on path, stage, and on difference in GGG?
- Assessment?
  - MSKCC calculator: 10-yr recurrence-free probability 84 vs 93%
  - 15-yr prostate cancer-specific survival 99%

Case #2 – 60 yr old man; alternative history

- What if prostatectomy showed Grade group III (Gleason's 4+3):
  - Stage then?
    - Stage IIC
  - Assessment?
    - MSKCC 10-year recurrence-free…..40%
    - 15-year prostate cancer-specific survival…..97%

- What if GG I but with seminal vesicle involvement?
  - Stage?
    - Stage IIIB
  - Assessment?
    - MSKCC 10-year recurrence-free…..77%
    - 15-year prostate cancer-specific survival…..99% (!)

Prostate cancer specific mortality by risk score

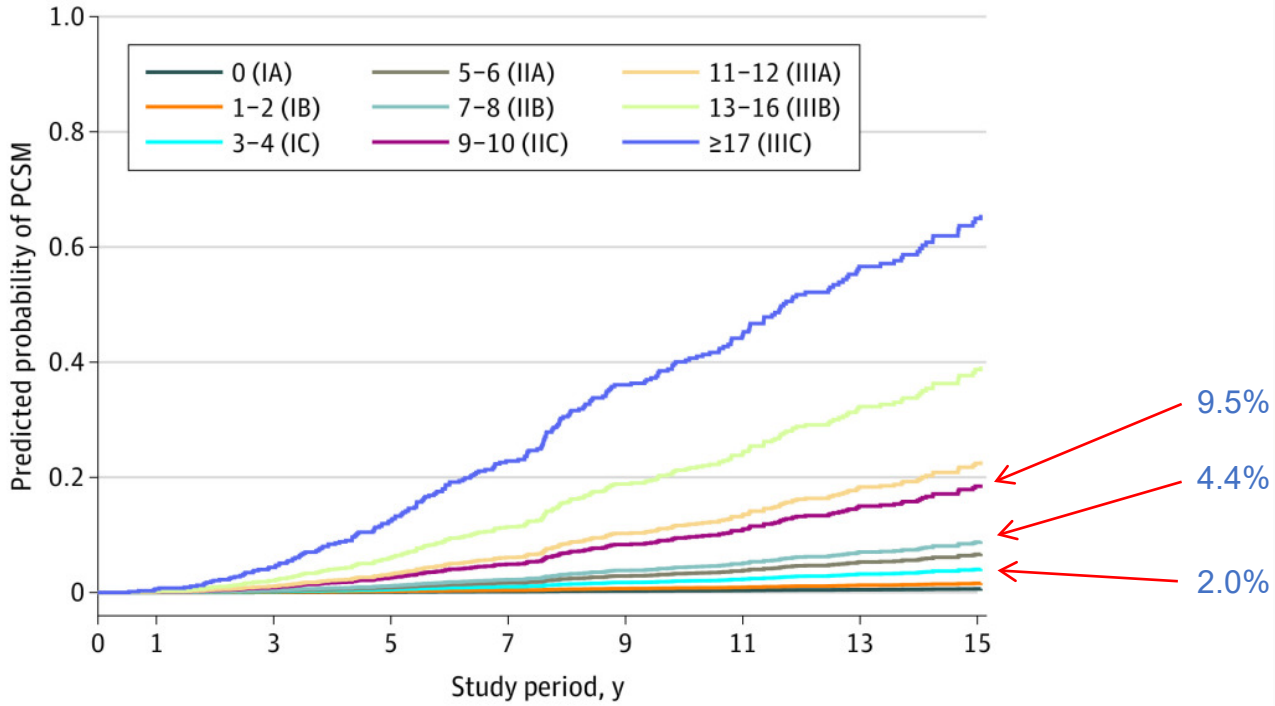
JAMA Oncol. Published online October 22, 2020. doi:10.1001/jamaoncol.2020.4922

Reference 0 =

- Age 51-70
- T1a-c, N0
- GGG 1
- Core biopsy <50%
- PSA < 6

10-year prostate cancer-specific mortality ranges from 0.3 to 40%

Case #2 score = 4 (IC)
Alternative 1 = 9 (IIC)
Alternative 2 = 7 (IIB)



Clinical Prognostic Stage Group Score System for Prostate Cancer–Specific Mortality (PCSM) Prediction in the Validation Cohort

Score stage group IA (0 points) included 1261 patients from the validation cohort (12.9%; 10-year PCSM estimate, 0.3%); Score stage group IB (1-2 points), 2501 patients (25.6%; 10-year PCSM estimate, 0.8%); Score stage group IC (3-4 points), 1901 patients (19.5%; 10-year PCSM estimate, 2.0%); Score stage group IIA (5-6 points), 1554 patients (15.9%; 10-year PCSM estimate, 3.3%); Score stage group IIB (7-8 points), 1208 patients (12.4%; 10-year PCSM estimate, 4.4%); Score stage group IIC (9-10 points), 719 patients (7.4%; 10-year PCSM estimate, 9.5%); Score stage group IIIA (11-12 points), 354 patients (3.6%; 10-year PCSM estimate, 11.7%); Score stage group IIIB (13-16 points), 248 patients (2.5%; 10-year PCSM estimate, 21.2%); and Score stage group IIIC (≥17 points), 23 patients (0.2%; 10-year PCSM estimate, 40.0%).

Case #2 – 60 yr old man; alternative history 2

- What if he underwent prostatectomy as noted, and went two years with an undetectable PSA, but it began to rise over the next year, and he was then treated with radiation:
  - What determines a biochemical recurrence?
    - After prostatectomy, PSA ≥0.2, repeated; however most ≤0.03 and any increasing level is of concern
    - After radiation, PSA increase of 2 ng/mL above nadir
  - Factors to consider at that point?
    - Gleason's score, PSA doubling time, metastases evaluation, PSA post-radiation, +/- Time to PSA recurrence
  - Would he be insurable then, and if not, at what point might he be?

Biochemical Recurrence in Prostate Cancer

- Not synonymous with death
  - Even without additional treatment, median metastasis-free survival was 10 yrs
- But varies significantly (15 yr OS 1-94%)
  - Median survival just 3 years if:
    - Rapid PSA doubing time (<3 mos)
    - Gleason score 8-10
    - Years to recurrence < 3
  - Favorable results if:
    - Gleason score 6 or less
    - Long PSADT (>15 mos)
    - PSA rise >3 yrs post-treatment

Would he be insurable then, or at what point might he be?

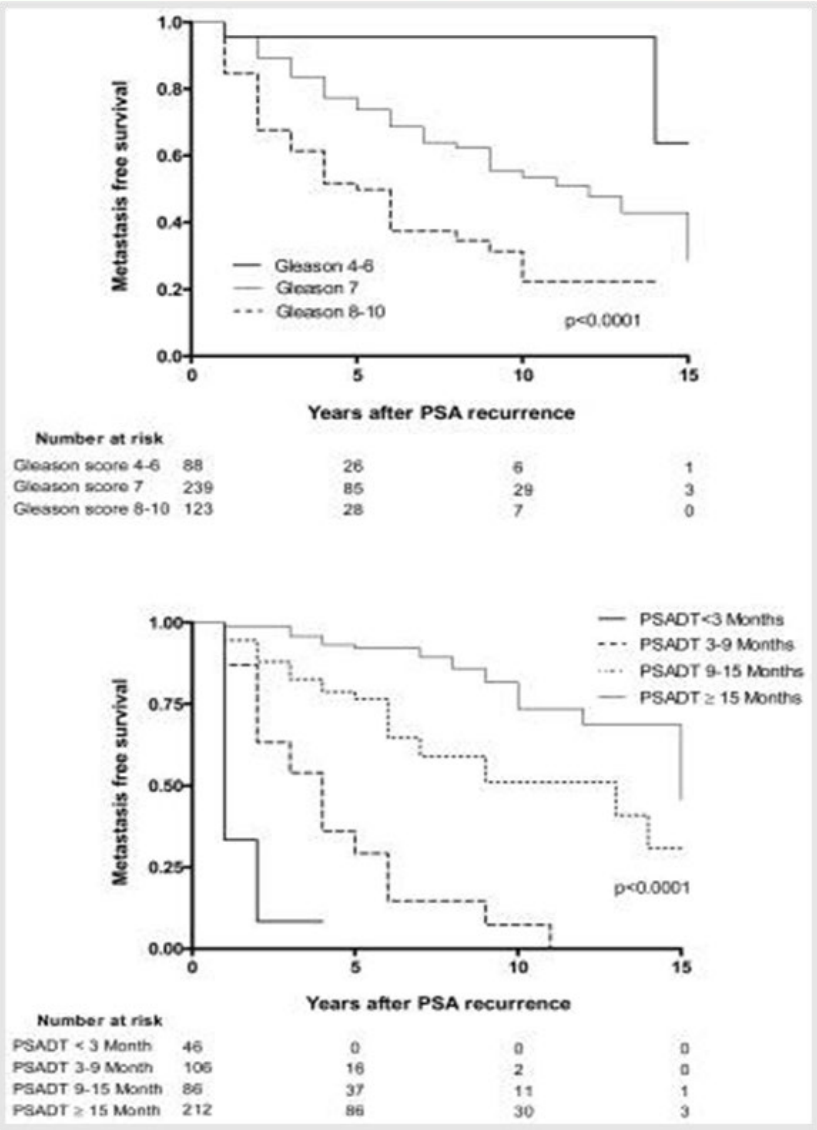
- **If no PSA increase in the first 1.5 years, and then a slow rise, the risk of dying of prostate cancer in 15 yrs is only ~4-8%**

10 and 15-year likelihood of prostate cancer-specific specific survival after biochemical (PSA) recurrence following radical prostatectomy

PSADT, months	Risk estimate, percent (95 percent confidence interval)			
	Recurrence >3 years after surgery		Recurrence ≤3 years after surgery	
	Gleason score <8	Gleason score ≥8	Gleason score <8	Gleason score ≥8
10-year estimate				
≥15.0	98 (96-100)	96 (93-98)	93 (80-98)	86 (61-96)
9.0-14.9	95 (75-99)	90 (58-98)	85 (49-97)	69 (30-92)
3.0-8.9	84 (62-94)	68 (37-89)	55 (25-82)	26 (7-62)
<3.0	59 (29-83)	30 (10-63)	15 (3-53)	1 (<1-55)
15-year estimate				
≥15.0	94 (87-100)	87 (79-92)	81 (57-93)	62 (32-85)
9.0-14.9	86 (57-97)	72 (35-92)	59 (24-87)	31 (7-72)
3.0-8.9	59 (32-81)	30 (10-63)	16 (4-49)	1 (<1-2)
<3.0	19 (5-51)	2 (<1-38)	<1 (<1-26)	<1 (<1-2)

PSADT: prostate specific antigen doubling time.
Data from Freedland, SJ, et al. JAMA 2005; 294:437.

Biochemical Recurrence in Prostate Cancer



Prostate biopsy

- Most prostate biopsies are now done with transrectal ultrasound (TRUS)- or MRI- guidance
  - MRI in particular is better at identifying anterior tumors
- These targeted biopsies are used in addition to 12-core systematic biopsies
  - Systematic biopsies detect an additional 5% to 10% of cancer cases that would be missed with a targeted biopsy
- Transrectal vs perineal
  - The transperineal route leads to lower infectious complications
  - Some studies show comparable cancer detection ability, though others have found a better yield for *clinically significant tumors* by TRUS biopsy

MRI-guided vs Systematic Biopsy

Concordance Between Biopsy and Radical Prostatectomy Pathology in the Era of Targeted Biopsy: Systematic Review &MetaAnalysis_Goel_EAU_1-2020

- 1215 men, median age 65, PSA median 7.2
- 2.47-fold more likely to be upgraded after systematic TR bx compared to MRI-targeted bx
- No difference in down-grading

MRI/Ultrasound Fusion

- Most studies have shown enhanced diagnostic accuracy of multi-parametric MRI and TRUS biopsy in prostate cancer (PRECISION and PROMIS studies)
  - mpMRI had significantly better sensitivity and negative predictive value for clinically important prostate cancer compared with TRUS-biopsy
  - Considering mpMRI as a triage test before first biopsy could allow 25-30% of men at risk to avoid biopsy
  - Targeted biopsy diagnosed 30% more high-risk (GS 7+ and/or extraprostatic extension) cancers vs standard biopsy and 17% fewer low-risk cancers
  - A Cochrane review concluded that MRI had better diagnostic accuracy for clinically significant prostate cancer detection
    - 12% higher detection rate with a pooled sensitivity 0.72 and pooled specificity 0.96

MRI and PIRADS Caveats

- The prostate is divided into four histologic zones:
  - (a) the anterior fibromuscular stroma, contains no glandular tissue
  - (b) the transition zone (TZ), surrounding the urethra, contains 5% of the glandular tissue
  - (c) the central zone (CZ), surrounding the
  - ejaculatory ducts, contains about 20% of the glandular tissue
  - (d) the outer peripheral zone (PZ), contains 70%-80% of the glandular tissue.
- Approximately 70%-75% of prostate cancers originate in the PZ and 20%-30% in the TZ. Cancers originating in the CZ are uncommon, and when found are usually secondary to invasion by PZ tumors.
- A thin, dark rim partially surrounding the prostate on MRI T2W is often referred to as the “prostate capsule” in terms of assessing extraprostatic extension (EPE) of cancer, but the prostate lacks a true capsule; rather it contains an outer band of concentric fibromuscular tissue that is inseparable from prostatic stroma and is incomplete anteriorly and apically.
- Clinically significant cancers in the PZ usually appear as round or ill-defined hypointense focal lesions
- At the apex and base, small nerve branches surround the prostate periphery and penetrate through the capsule, a potential route for EPE.
- When benign prostatic hyperplasia (BPH) develops, the TZ will account for an increasing percentage of the gland volume
- BPH consists of a mixture of stromal and glandular hyperplasia and may appear as band-like areas and/or encapsulated round nodules with circumscribed margins, which exhibit moderate-marked T2 hyperintensity and are distinguished from malignant tumors by their signal and capsule.
- Hemorrhage in the PZ and/or seminal vesicles is common after biopsy, and appears as focal or diffuse hyperintense signal on T1W and iso-hypointense signal onT2W.
- Prostatitis can result in decreased signal in the PZ and the morphology is commonly band-like, wedge-shaped, or diffuse, rather than focal, round, oval, or irregular.
- Lymph nodes over 8mm in short axis dimension are regarded as suspicious, although lymph nodes that harbor metastases are not always enlarged.

Importance of Gleason's grade

- In one study of 7817 patients undergoing radical prostatectomy, only 0.3 percent with Gleason 6 tumors had extraprostatic extension or seminal vesicle invasion (T3)
- As opposed to 9% of Gleasons 3+4 and 20% of Gleasons 4+3

Oncogenetics

- There is a strong familial predisposition for prostate cancer, though only ~5% of cases are linked to specific genetic mutations
- Testing for BRCA1, BRCA2, and HOXB13 gene mutations is advised for those with a significant family history
  - Associated with an increased risk of developing an aggressive prostate cancer
- In a study of 10,120 male participants from the Health Professionals Follow-up cohort, men in the upper quartile of polygenic risk score or who had a family history of prostate or breast cancer accounted for 97.5% of prostate cancer deaths by age 75

Wisdom from Jack Swanson

- Use prostatectomy stage and grade, over biopsy grade & clinical stage
  - Best to have serial sections in prostate biopsies
- TRUS:
  - Hyperechoic – inflammatory
  - Hypoechoic – suspect cancer
- Some argue that Gleason's score is too subjective, there is significant interobserver variability in scoring, and genetic markers or fractal dimensions should prove to be more accurate
- Should a Gleason score of 3+3 no longer be called prostate cancer?
  - Most feel otherwise since Gleason 3+3 has parameters that are associated with cancer, and although there may be a low potential for advanced cancer, there is some risk

Additional caveats…

- With PC's long mortality tail (10-25 years), A.S. for younger men is riskier
- Per Gleason: Ave. Over 50% - 3 Gleason patterns (yet advised to ignore 3rd)
- Patel: importance of tertiary Gleason 5 (JAMA 2007; 298:1533).
- Mayo Clinic's Bostwick: Gleason grade 3 "particularly difficult to separate from benign acini in biopsies" (CA 1997; 47; 297).

And more from Jack: Immunohistochemistry

- "Antibody cocktail" to detect markers for basal cells in prostate biopsies.
- The key: basal cell layer is absent in invasive prostate cancer.
- Helpful in atypical small acinar proliferation (ASAP), other atypia, & infiltrative single cell patterns. (Arch Pathol Lab Med, Sept 2008)

Conditional survival with high-risk prostate cancer

- Korean cohort of 245 NCCN low-risk, 343 NCCN intermediate risk, and 289 NCCN high/very high-risk patients treated with radical prostatectomy
  - Mean age 67, mean f/u 48 months
- 5-year biochemical recurrence(BCR) rates after a 4-year BCR-free period were very low for all groups

  BCR-free survival rates at baseline and after 4 years BCR-free:
  - Low risk group: 92% and 100%
  - Intermediate risk group: 78% and 97%
  - High/VH risk group: 54% and 98%

High risk advanced prostate cancer subtype

- For men with advanced prostate cancer who have defective mismatch repair (dMMR) cancers, overall survival (OS) is roughly half that of those who do not have the genetic anomalies
  - Median OS was 8.5 years in the pMMR group vs 4.1 years in the MMR-proficient group
  - Advanced prostate cancer was defined as metastatic disease that had progressed despite hormone therapy
  - Half of the men with dMMR cancers had high PD-L1 levels compared to fewer than 10% of the men with pMMR cancers, suggesting they may respond to immunotherapy with programmed cell death checkpoint inhibitors.

Outcomes for castration-resistant prostate cancer (CRPC)

- New generation hormone therapies (NGHT) apalutamide and enzalutamide have led to improved outcomes in those with advanced, non-metastatic CRPC
  - Metastasis-free survival: 36-40 months with NGHT versus 15-16 months
- Men with metastatic CRPC have a median survival of 2.5 years, depending on site of metastases

Outcomes and treatment for GS 9-10

- Among patients with Gleason score 9-10 prostate cancer, treatment with Electron Beam Radiotherapy plus Brachytherapy (EBRT+BT) with androgen deprivation therapy was associated with significantly better prostate cancer-specific mortality and longer time to distant metastasis compared with EBRT with androgen deprivation therapy or with Radical prostatectomy (RP) alone
- Adjusted 5-year incidence rates of distant metastasis were RP, 24% (95% CI, 19%-30%); EBRT, 24% (95% CI, 20%-28%); and EBRT+BT, 8%
- Adjusted 7.5-year all-cause mortality rates were RP, 17% (95% CI, 11%-23%); EBRT, 18% (95% CI, 14%-24%); and EBRT+BT, 10% (95% CI, 7%-13%).
- However, there was unknown reason for treatment choice, inadequate dose of definitive EBRT in >50% of patients, inadequate duration of ADT in >50% of EBRT patients, and lack of pelvic nodal radiotherapy in >50% of EBRT patients

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Breast Cancer

Photo by Angiola Harry on Unsplash

Breast Cancer

- Breast cancer is the most common cancer in women globally with an estimated 2.1 million new cases diagnosed in 2018, and the leading cause of cancer death in women worldwide.
- Second most common cause of cancer death in women in the U.S. after lung cancer (15% of deaths)
  - Est 266,000 new cases/year 2018 with ~40,000 deaths
- Leading cause of death in woman aged 45-55
- 1 in 8 women will be diagnosed in their lifetime. If found early, 95% will be cured.

Breast Cancer

- Risks
  - Family History
  - BRCA 1 and 2
  - Early menarche, late menopause
  - Late first pregnancy or nulliparity
  - Higher Estrogen levels
  - Obesity and/or Increased Fat in Diet

NOTES FOR BREAST CANCER

- IBC = Breast Cancer
- DCIS = Ductal CA in situ
- SLNB = sentinel lymph node biopsy
- ALND = axillary node dissection
- CNB = core needle biopsy
- MOR = margins of resection
- BCT = breast conserving therapy
- XRT = External Beam Radiation

Breast Cancer

- Diagnosis
- Treatment
- Surveillance

What would you say is the general trend of treatment for varying stages and grades of breast cancer?

RESOURCE: https://www.nccn.org/

Breast Cancer

- Diagnosis
  - Biopsy, Type, Grade, ER/PR, Her2-neu, Clinical Stage
- Treatment
  - Neoadjuvant, Surgery, Adjuvant
  - Chemotherapy, Radiotherapy, Surgery—To cut is to cure!
- Surveillance
  - Frequency, Labs, Imaging, Goals?

Breast Cancer

- Diagnosis
  - Biopsy, Type, Grade, ER/PR, Her2-neu, Clinical Stage
- Treatment
  - Neoadjuvant, Surgery, Adjuvant
- Surveillance
  - Frequency, Labs, Imaging, Goals?

Diagnosis

- Palpable Mass
- Imaging Abnormality
  - Mass
    - Characteristics?
  - Microcalcifications
    - Characteristics?
  - Other
- Axillary Mass
- Other?

Diagnosis

- Biopsy—MUST HAVE TISSUE
  - What's the appropriate method?
  - Core Needle
  - Needle Localized Open Biopsy
  - Open Excisional Biopsy

Diagnosis

- Type
  - DCIS, LCIS
  - Invasive Ductal, 70-80%
  - Invasive Lobular, 8%
  - Mixed, 7%
  - Others: Paget's, Lymphoma, Metastatic, Phyllodes

Diagnosis

- Grade 1-3
- Receptors ER/PR/HER2
  - Function of luminal and basal cells of origin
- Tumor Genetics
  - OncotypeDx ®:

Diagnosis

- TNM
  - Tumor (size)
  - Node
    - How many?
    - Characteristics?
  - Metastasis
    - Lung, Liver, Bone, Brain
- Classic Staging

Breast carcinoma TNM anatomic stage group AJCC UICC 2017

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	IA
T0	N1mi	M0	IB
T1	N1mi	M0	IB
T0	N1	M0	IIA
T1	N1	M0	IIA
T2	N0	M0	IIA
T2	N1	M0	IIB
T3	N0	M0	IIB
T0	N2	M0	IIIA
T1	N2	M0	IIIA
T2	N2	M0	IIIA
T3	N1	M0	IIIA
T3	N2	M0	IIIA
T4	N0	M0	IIIB
T4	N1	M0	IIIB
T4	N2	M0	IIIB
Any T	N3	M0	IIIC
Any T	Any N	M1	IV

- The anatomic stage group table should only be used in global regions where biomarker tests are not routinely available.
- Cancer registries in the US must use the prognostic stage group table for case reporting.

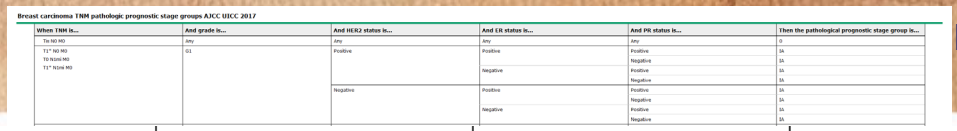
TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Used with permission of the American College of Surgeons, Chicago, Illinois. The original source for this information is the AJCC Cancer Staging Manual, Eighth Edition (2017) published by Springer International Publishing.

UpToDate®

Diagnosis

- Prognostic Staging
  - Why is it important?
    - Includes characteristics of tumor like…
      - Grade
      - HER2 status
      - ER status
      - PR status
      - AND OncotypeDx ®



T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G1	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
T0 N1¶ M0 T1* N1¶ M0 T2 N0 M0	G2	Positive	Positive	Positive	IA
				Negative	IB
			Negative	Positive	IB
				Negative	IIA
		Negative	Positive	Positive	IA
				Negative	IIA
			Negative	Positive	IIA
				Negative	IIA

Genomic profile for pathologic prognostic staging

When OncotypeDx score is less than 11...

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the pathological prognostic stage group is...
T1 N0 M0 T2 N0 M0	Any	Negative	Positive	Any	IA

Treatment--Which should it be?

- Surgery
  - Lumpectomy
  - Mastectomy
  - Sentinel Node
  - Lymphadenectomy
- Radiation
- Chemotherapy
  - Hormonal Therapy
  - Herceptin

Treatment Red Flags

- Red Flags
  - Neoadjuvant
    - MUST CONSIDER the effects on Pathological Staging
  - Adjuvant???
    - What about post-mastectomy radiation?
  - Repeated Operations???
  - Herceptin

Surveillance

- Frequency
- Labs
- Imaging

Goal: Early detection of recurrence or metastasis, and reassurance of cure.

What can any of the above tell you about the disease?

Surveillance

- What's appropriate?

Resource: https://www.nccn.org/

Case 1: JD

- 48 y/o F filed a living benefit (Critical Illness) claim and her history follows:
- Presented with palpable abnormality of the left axilla measuring 1.1cm; US found irregular hypoechoic mass
- Mammography: no distortions or suspicious calcifications in either breast

Concerns? Differential?

She underwent a core needle biopsy of the mass, and this is what it showed…

JD - Slide of Axilla Pathology Report

Surgical Pathology Final Report
Accession #: S18-14258
Collection Date: 5/11/2018 00:00

Diagnosis
1) BREAST, LEFT AXILLARY MASS, CORE BIOPSY: INVASIVE MAMMARY CARCINOMA, NO SPECIAL TYPE, HIGH COMBINED HISTOLOGIC GRADE, HIGH PROLIFERATIVE RATE, 6MM IN EXTENT INVOLVING 3 OF 4 CORES, INVOLVING LYMPH NODE, SEE COMMENT.
Immunohistochemical receptor studies:
Estrogen receptor: No expression in neoplastic nuclei.
Progesterone receptor: No expression in neoplastic nuclei.
HER2 FISH RESULT: AMPLIFIED
HER2/cep 17 ratio = 11.6

Surgical Pathology Final Report
Accession #: S18-16395
Diagnosis
BREAST, LEFT, ULTRASOUND GUIDED CORE NEEDLE BIOPSY: INVASIVE MAMMARY CARCINOMA, NO SPECIAL TYPE, HIGH COMBINED HISTOLOGIC GRADE, HIGH PROLIFERATIVE RATE, PRESENT IN 2 OF 2 CORES, MEASURING AT LEAST 2 MM. SEE COMMENT.
Comments
HER-2 florescence in situ hybridization testing has been performed on the prior biopsy S18-14258 and was not amplified. Thus this test was not performed but can be upon request.
Immunohistochemical receptor studies:
Estrogen receptor: No expression in the neoplastic nuclei.
Progesterone receptor: No expression in the neoplastic nuclei.

JD JD continued…

- MRI of left breast found 9mm mass
- Biopsy found IBC
  - High Grade,
  - High Proliferative Rate,
  - ER/PR Negative
  - HER 2 positive

Anatomic Stage? Pathologic Stage?

Prognostic Stage?

JD continued…

- cT1N1Mx
- pTxNxMx
- Prognostic:
  - IIA

Based on Staging, what is the likely therapy?

JD continued…

- Started on Neoadjuvant treatment
  - Taxotere, Herceptin, Perjeta x 6

What's next?

-Appropriate Treatment?

-Appropriate Surveillance?

-Survival?

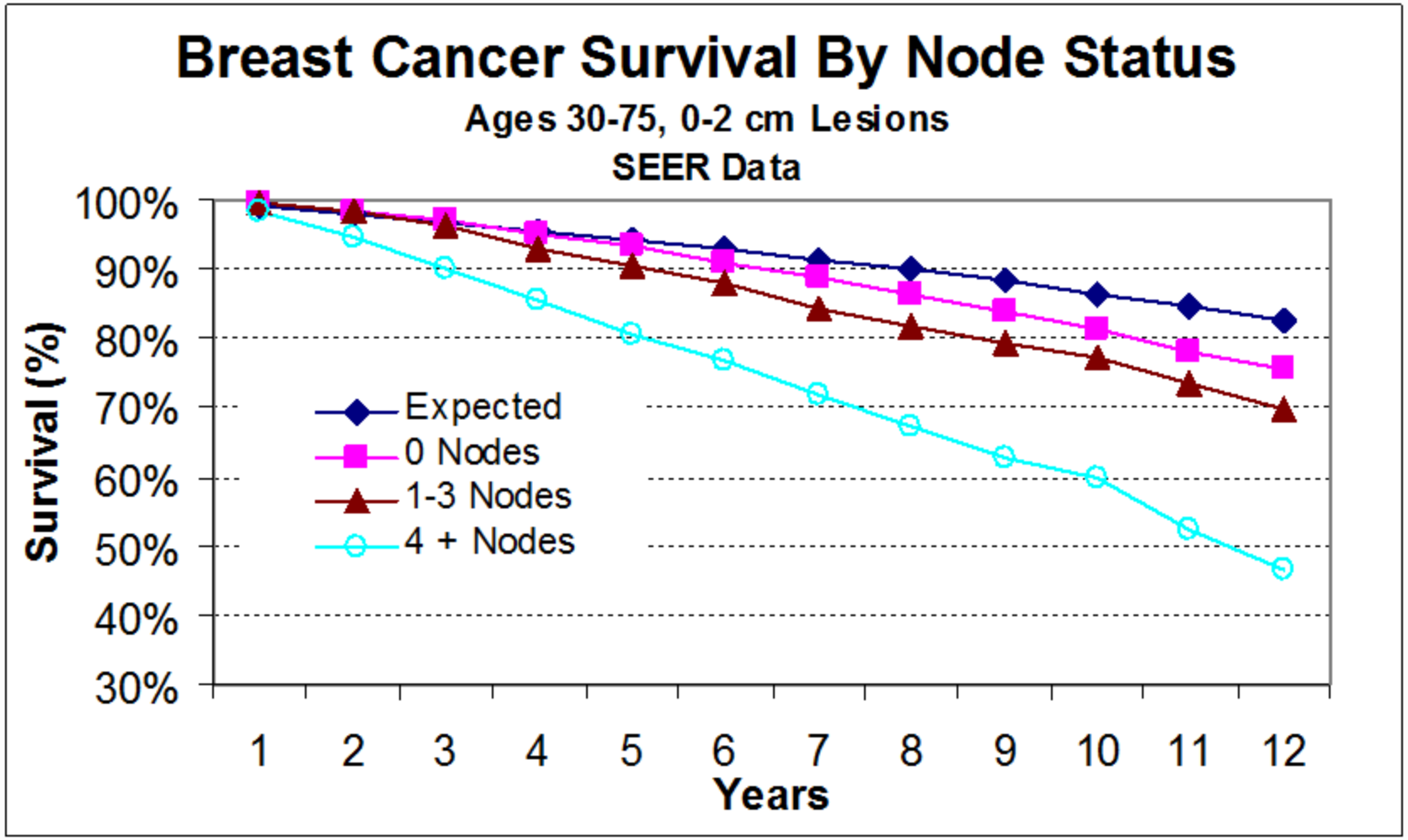
JD

- Treatment
  - Definitive Surgery
  - Adjuvant Chemo
- Surveillance
  - Close Surveillance
- Survival at 5 years: 82.8%
- Resource: https://seer.cancer.gov/

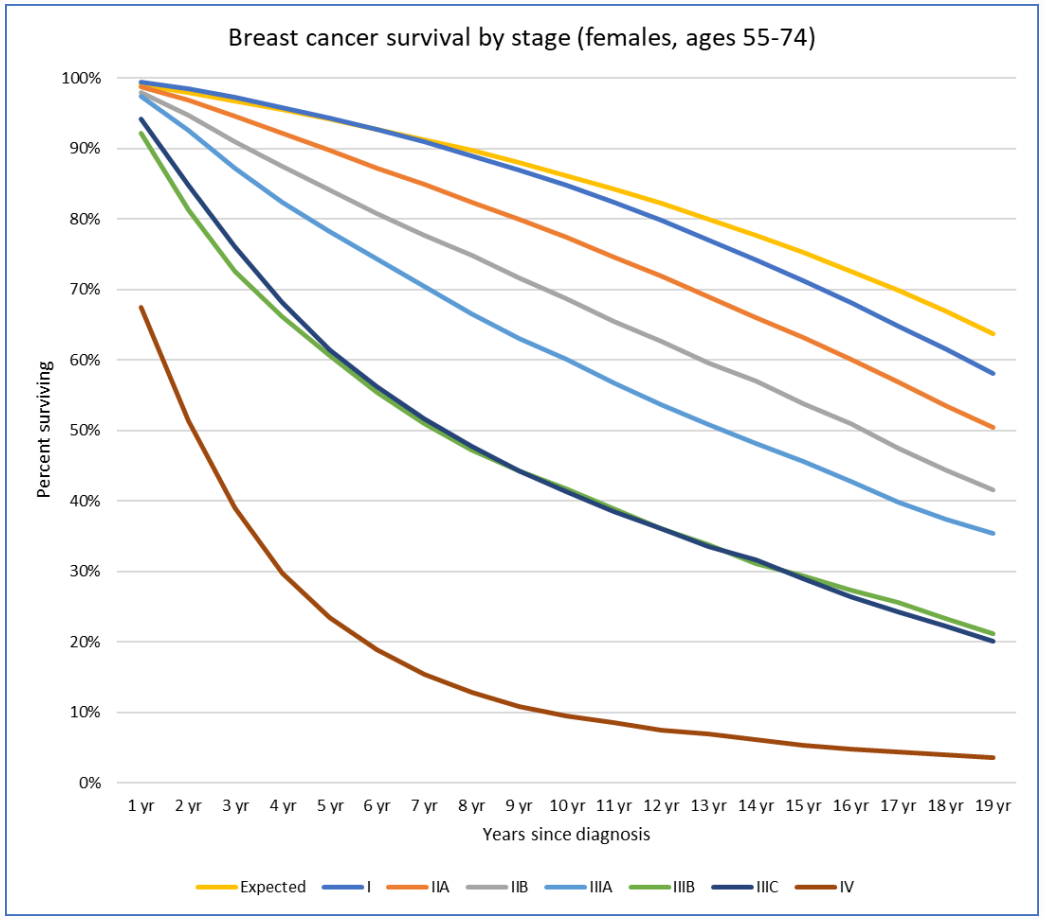
NIH: NCI Surveillance, Epidemiology, and End Results

5-Year Relative Survival Percent, Female Breast Subtypes by SEER Combined Summary Stage

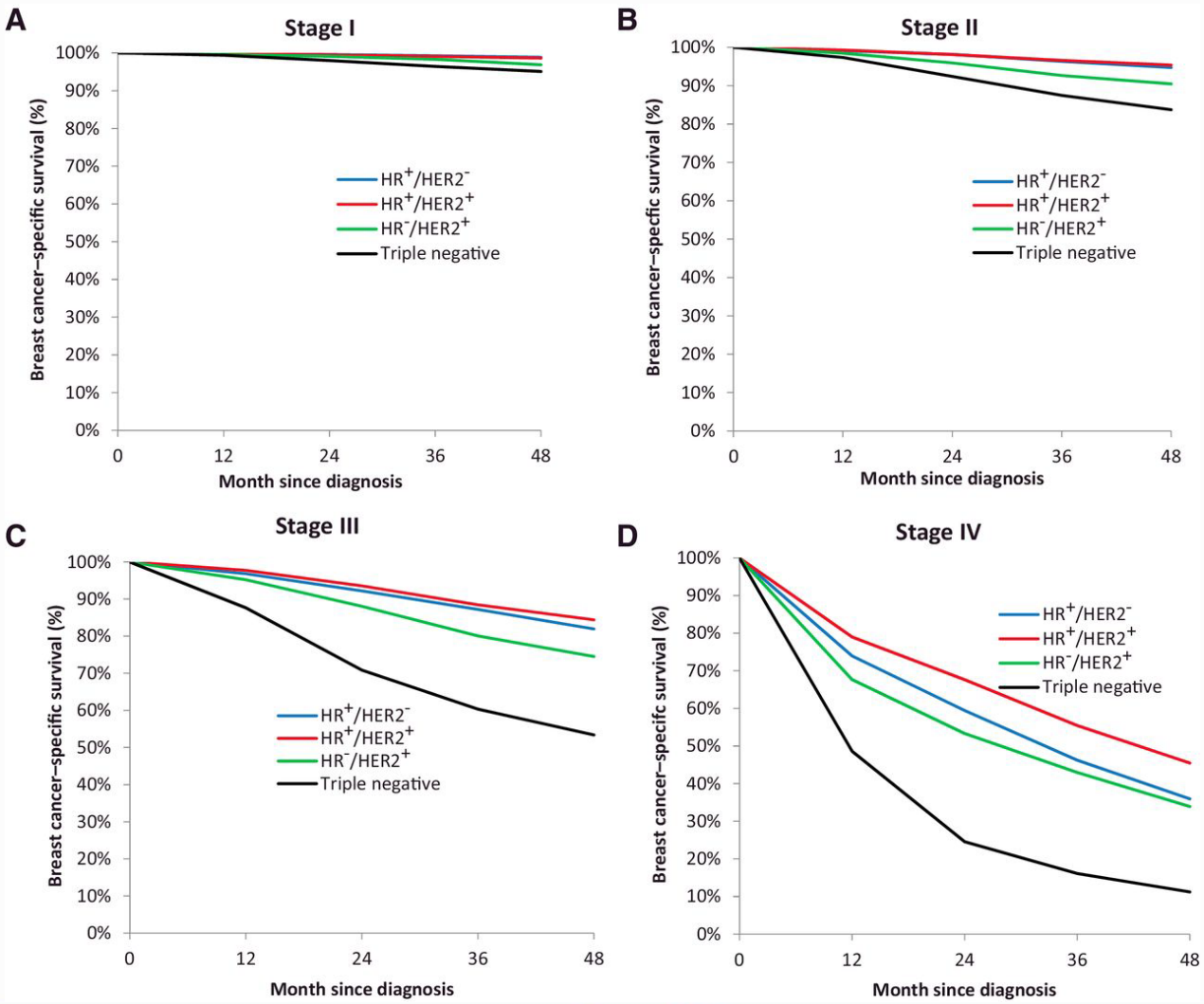
Subtype	Localized	Regional	Distant
HR+/HER2-	100.0%	90.1%	31.9%
HR-/HER2-	91.3%	65.8%	12.0%
HR+/HER2+	98.8%	89.3%	46.0%
HR-/HER2+	97.3%	82.8%	38.8%
Unknown	96.1%	76.4%	15.6%
Total	99.1%	86.1%	30.0%


Breast Cancer Survival By Node Status
Ages 30-75, 0-2 cm Lesions
SEER Data
Survival (%)
100%
90%
80%
70%
60%
50%
40%
30%
Expected
0 Nodes
1-3 Nodes
4 + Nodes
1
2
3
4
5
6
7
8
9
10
11
12
Years

SEER Dataset



From: **Differences in Breast Cancer Survival by Molecular Subtypes in the United States**



Cancer Epidemiol Biomarkers Prev. 2018;27(6):619-626. doi:10.1158/1055-9965.EPI-17-0627

Case 2: JL

- JL is a 70 y/o woman who applied for life insurance with a history of breast cancer. Her wife is the sole beneficiary. The pertinent history follows:
- 5 years ago had an abnormal mammogram—irregular 8mm mass in Upper Outer Quadrant.
- The remainder of the history and physical examination were normal.
- Anything concerning about this history?

JL continued…

- She underwent a core needle biopsy that showed:
- Invasive Ductal Cancer
  - Grade 1
  - ER/PR positive
  - HER2 negative

So far: What is favorable? Unfavorable?

Clinical Stage?

JL continued…

- Stage IA
- Multiple factors
  - Small, Grade 1 (rare), ER/PR and HER2 are as expected for a Grade 1 tumor
- No unfavorable factors that I can see…
- What is appropriate therapy?

JL continued…

- She had a wire-localized partial mastectomy with intraoperative re-excision of medial inferior margin, sentinel node mapping, and biopsy.

Appropriate operation? Is the re-excision concerning? Sentinel node biopsy?

JL – Path report

SYNOPTIC REPORT INVASIVE BREAST CANCER -- RIGHT BREAST, PARTIAL MASTECTOMY WITH MARGIN ADVANCEMENT, AND SENTINEL AND NON-SENTINEL LYMPH NODE BIOPSIES
Specimens A -- E.

MICROSCOPIC FINDINGS
- HISTOLOGIC TYPE AND FOCALITY: Invasive ductal carcinoma, uni-focal.
- SIZE OF INVASIVE COMPONENT: 1.1 x 1.0* x 1.0* cm
- HISTOLOGIC GRADE, NOTTINGHAM SYSTEM
  - Tubule Formation: 1
  - Nuclear Pleomorphism: 2
  - Mitoses: 1 (2 mitoses/10 hpf in a 0.54 mm field diameter).
  - Overall Grade: 1 (4/9 points).
- DUCTAL CARCINOMA IN SITU: Intermediate grade DCIS, solid and cribriform pattern, without necrosis.
- SKIN: Negative.
  - *Dermal lymphatic invasion: Not identified.
- MUSCLE: No skeletal muscle present.
- *PERITUMORAL LYMPH-VASCULAR INVASION: Not identified.

3200 Providence DR
Anchorage AK 99508-4615

MRN: 00768846, DOB: 12/31/1948, Sex: F
Adm: 5/2/2016, D/C: 5/2/2016

- *ADDITIONAL FINDINGS:
  - Biopsy site changes and stromal fibrosis.
- *MICROCALCIFICATIONS
  -- Neoplastic Breast Tissue: Present.
  -- Non-Neoplastic Breast Tissue: Present.
- *TREATMENT EFFECT: No known presurgical therapy.

MARGINS
- Margins are not involved by invasive carcinoma. All margins are clear by greater than 1 cm.
- Margins are not involved by DCIS. All margins are clear by greater than 1 cm.

LYMPH NODES
- Number of sentinel lymph nodes examined: 2
- Total number of lymph nodes examined: 6
- Metastatic carcinoma involves 0 of 2 SENTINEL lymph node(s).
- Metastatic carcinoma involves 0 of 8 TOTAL lymph nodes.
- SUBCATEGORIZATION OF NODES
  -- Number with macrometastasis (>0.2cm): 0
  -- Number with micrometastasis (0.2mm-0.2cm or >200 cells): 0
  -- Number with isolated tumor cells (<0.2mm or <200 cells): 0
  - *Method of Examination: Multiple H/E levels without IHC.

STAGING: - pT1c/pN0/pMX

ANCILLARY STUDIES: Performed at PAMC, *Case S16-3236*
ESTROGEN RECEPTOR (Ventana clone SP1)
Immunoreactive tumor cells: **PRESENT**
Allred Score: 8
PROGESTERONE RECEPTOR (Ventana clone 1E2)
Immunoreactive tumor cells: **PRESENT**
Allred Score: 5
HER2/neu by IHC (Ventana clone 4B5): **NOT OVEREXPRESSED (1+).**

*Data elements with asterisks are not required by the Commission on Cancer.
They may be clinically important, but are not validated.

Electronically signed by Christine D. Clark, MD on 5/3/2016 at 1317

Gross Description -- — — AP

Result:
A. Received labeled "peri-sentinel lymph node fat, right" is a 4.5 x 4.4 x 1.5 cm aggregate of adipose tissue. The tissue is dissected and shows adipose tissue without identifiable lymph nodes. Representative sections are submitted for microscopic evaluation in one cassette.

B. Received labeled "sentinel lymph node right" are 2 lymph nodes with attached adipose tissue. The lymph nodes measure 0.7 x 0.6 x 0.4 cm and 0.6 x 0.5 x 0.5 cm. Both lymph nodes are received with methylene blue. The lymph nodes are bisected per protocol and entirely submitted for evaluation in one cassette, the largest lymph node is inked black.

C. Received labeled "additional lymph nodes, right" are 6 lymph nodes received with a small amount of attached adipose tissue. The lymph nodes range from 0.6-1.1 cm in greatest dimension and 3 of the lymph nodes are received with methylene blue ink. The 2 largest lymph nodes are fibrofatty and all lymph nodes are without evidence of malignancy. All lymph node tissue is submitted for microscopic evaluation.
C1. 3 possible lymph nodes.
C2-4. 1 lymph node in each cassette.

D. Received fresh for intraoperative consultation and directly delivered to the gross room by Dr. Gower labeled "right breast tissue" is an ellipse of skin with a subcutaneous breast tissue that measures 6.5 cm from inferior to superior, 5.5 cm medial to lateral and 3.0 cm anterior to posterior. The ellipse of skin measures 4.5 x 1.4 cm and the specimen weighs 34 g. The specimen is serially cross sectioned and shows a 1.1 x 1 x 1 cm ill-defined, stellate mass with infiltrating borders. The parenchyma is white–speckled yellow with minimal focal hemorrhage. The mass measures 0.3 cm from the medial margin and greater than 0.6 cm from all other margins. Results are discussed with Dr. Gower in the gross room. The remaining specimen shows soft yellow adipose tissue with dense white fibrous breast tissue. No additional lesions are identified. Representative sections are submitted for microscopic evaluation as follows:
D1. Inferior margin, perpendicular.
D2. Tumor with medial margin
D2. Tumor with medial margin.
D3. Tumor with medial and lateral margins.
D4. Deep margin closest to tumor.
D5. Skin overlying tumor, inferior/medial skin tip.
D6. Superior margin, perpendicular.

E. Received labeled "New margin, medial inferior, yellow dye" is a 3 g, semilunar shaped excision of adipose tissue with yellow ink on the new margin. The specimen is cross sectioned and shows dense white fibrous breast tissue surrounded by soft yellow adipose tissue. No fibrocystic disease or evidence of tumor identified. Approximately 50% of the specimen is submitted for microscopic evaluation in 2 cassettes. BA

Microscopic Description – — — AP
Result:
D. Histologic section demonstrates invasive ductal carcinoma characterized by good tubule formation, intermediate nuclear grade, and low mitotic rate. There is associated intermediate grade DCIS, solid and cribriform pattern. There are innumerable microcalcifications. The initial closest surgical margin for invasive and in situ carcinoma is medial at 7 mm; however this margin was advanced (specimen E) and is negative for tumor. Therefore all margins are clear by greater than 1 cm. Benign breast tissue demonstrates stromal fibrosis and microcalcifications.

Allred Score ER/PR = % Staining Score + Intensity Score (ref range 0-8).

ASCO/CAP recommendation: NEGATIVE*: Any tumor with less than 1% staining regardless of intensity (Allred score range 0-4). POSITIVE: any tumor with 1% or greater staining regardless of intensity (Allred score range 3-8).
% staining score range: 0 = none, 1 <1%, 2 = 1-10%, 3 = 10-33%, 4 = 34-67%, 5 > 67%. Intensity score: Weak (1+) = 1, Moderate (2+) = 2, Strong (3+) = 3.

*The Allred recommendation includes as POSITIVE those cases with <1% staining with moderate (2+) or strong (3+) intensity (Allred Score 3-4). The ASCO)/CAP guidelines assert that any case with <1% cells be called NEGATIVE. It is as yet unclear whether patient's in this discrepant range may respond to hormonal therapy. These cases should be managed according to a appropriate clinical considerations.

Fixation time was in compliance with CAP/ASCO guidelines.
ER/PR stained on LSAB system, 10% buffered formalin-fixed paraffin-embedded sections with appropriate positive and negative controls.

Intraoperative Consultation – — — AP
Result: D. RIGHT BREAST, PARTIAL MASTECTOMY, MARGIN EVALUATION: Tumor is 3 mm from the

JL—Path Report Summary

- 1.1 cm Invasive Ductal Carcinoma
- Grade 1
- DCIS Intermediate Grade, solid and cribriform
- Lymph nodes: 2 sentinel, 6 others
  - Metastatic Carcinoma involves 0/8

Pathologic staging?

JL continued…

- Pathologic Anatomic Staging
  - T1N1MX
- Pathologic Prognostic Staging
  - 1A

What is appropriate treatment?

What if OncotypeDx ® were scored highly?

JL continued…

Treatment: Radiation of breast, Tamoxifen

Any additional concerns related to the DCIS or type of DCIS (cribriform and solid pattern)?

Not really—beware of comedo changes, however…

What type of surveillance should she have?

JL continued…

- Surveillance of Stage IA, Grade 1 cancer is pretty straightforward. F/U every 6 months with history and physical and get mammograms yearly.
- Imaging would be driven by symptoms.

Insurable?

Rating?

A word on DCIS…

- DCIS found on core needle biopsy has a rate of invasive cancer of 15-20% at the time of full excision. Must have final Pathology report from excision with negative margins!
- Treatment: excision with margins negative + radiation in most (consider no adjuvant XRT in favorable (ER/PR +) DCIS in postmenopausal women with good follow up)).
- Surveillance: basic history and physical and yearly breast imaging.
- Survival data for DCIS:
  - 98-99% with Mastectomy
  - 98% for Lumpectomy + XRT
  - 94-95% for Lumpectomy alone

More words on DCIS…

- Survival data for DCIS:
  - 98-99% with Mastectomy
  - 98% for Lumpectomy + XRT
  - 94-95% for Lumpectomy alone

And what about breast imaging???

- For screening: standard digital mammography with computer aided detection.
- Tomosynthesis (aka 3D mammography): studies are still out but it appears this modality increases detection of very small tumors and lesions with DCIS
- MRI: indicated at the time of diagnosis of breast cancer. Much more sensitive and slightly more specific.
  - Also indicated for those at high risk with dense breasts

BI-RADS, what the heck?

- 1 Negative, 0%
- 2 Benign, 0%
- 3 Probably Benign, <2%
- 4 Suspicious and need additional imaging or action, 2-95%
- 5 Highly Suggestive, >95%

Those pesky findings in the Sentinel Node…

- ITC (Isolated Tumor Cells): small clusters of tumor cells not greater than 0.2 mm or nonconfluent or nearly confluent clusters of cells not exceeding 200 cells in a single histologic lymph node cross section. Patients seem to do as well as those without nodal involvement.
- Micrometastasis: nodal involvement is defined as a metastatic deposit >0.2 mm but <2.0 mm. Slightly worse prognosis but no additional risk of local recurrence.

AJCC Staging Manual

A word on genomics…

- OncotypeDx ®: 21 gene panel to predict recurrence. Validated and incorporated into prognostic staging. Use on low stage tumors to predict recurrence and therefor need for adjuvant chemotherapy.

Breast Cancer Bibliography

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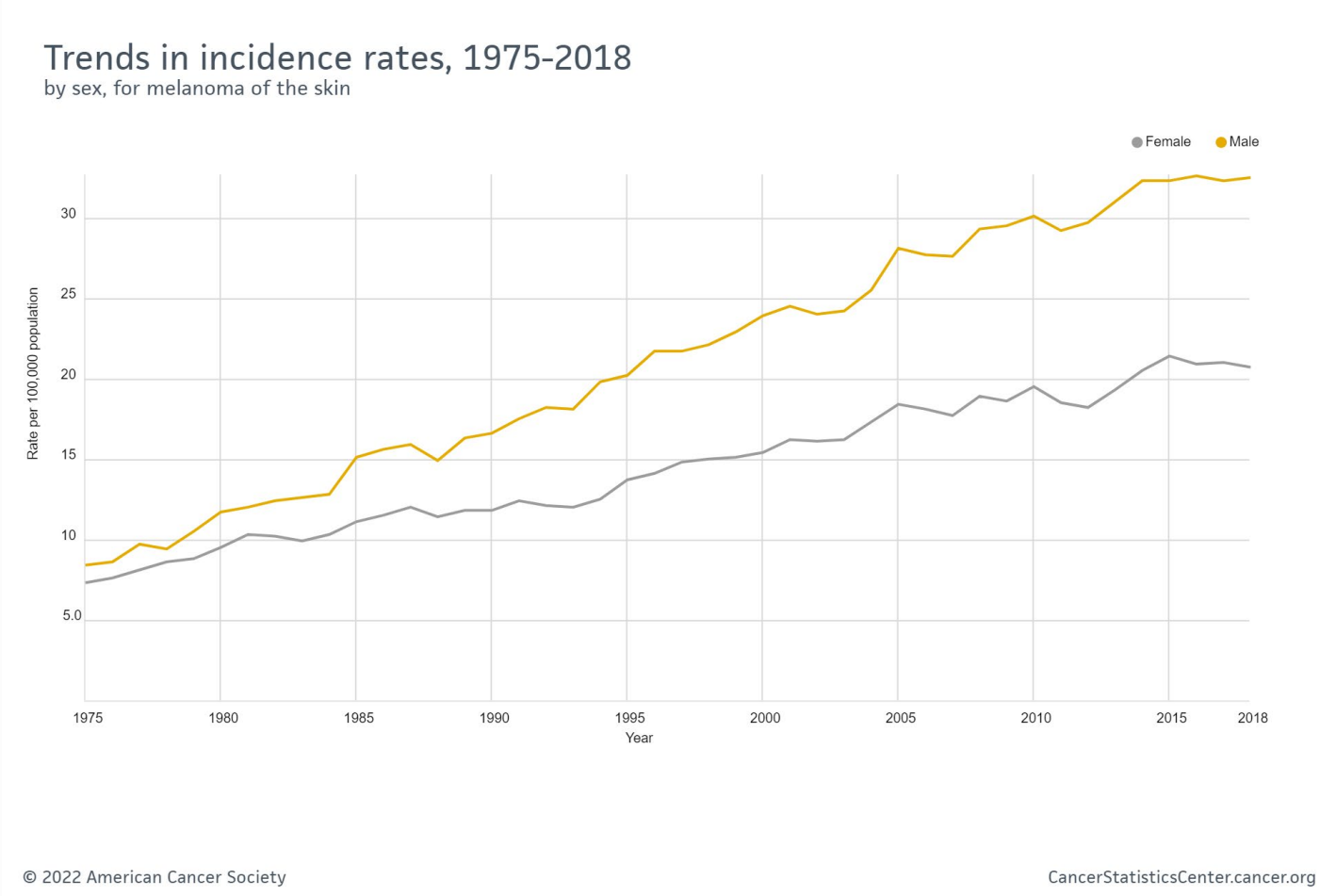
Melanoma

Malignant melanoma

- Rising incidence throughout the past 50 years
- 5th most commonly diagnosed cancer in the U.S.
- Often found at early stages and when the prognosis is very good



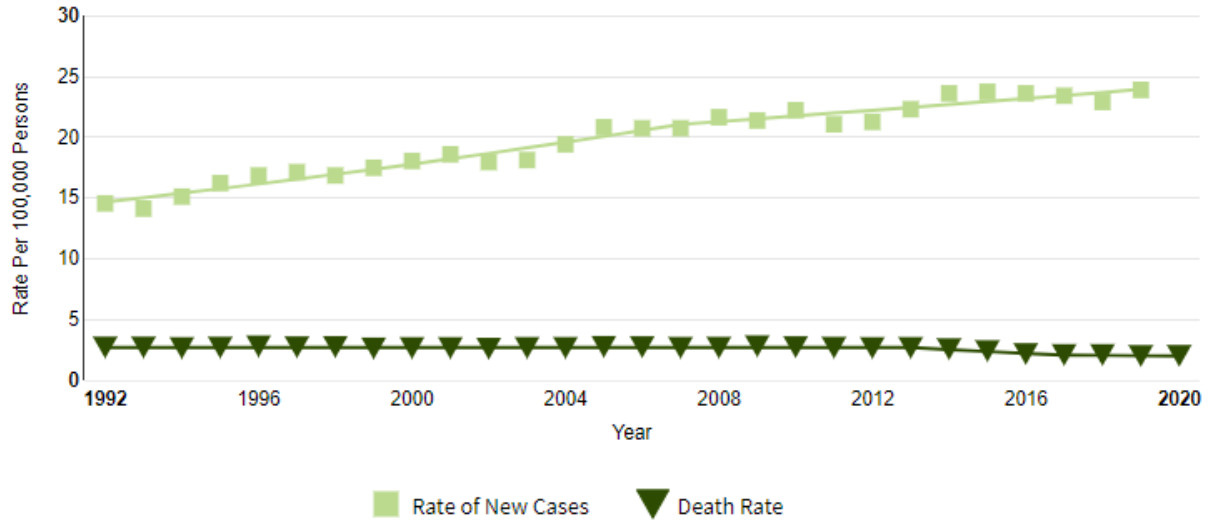
Melanoma basics

Rising incidence, but not mortality

Estimated New Cases in 2022	99,780
% of All New Cancer Cases	5.2%

Estimated Deaths in 2022	7,650
% of All Cancer Deaths	1.3%

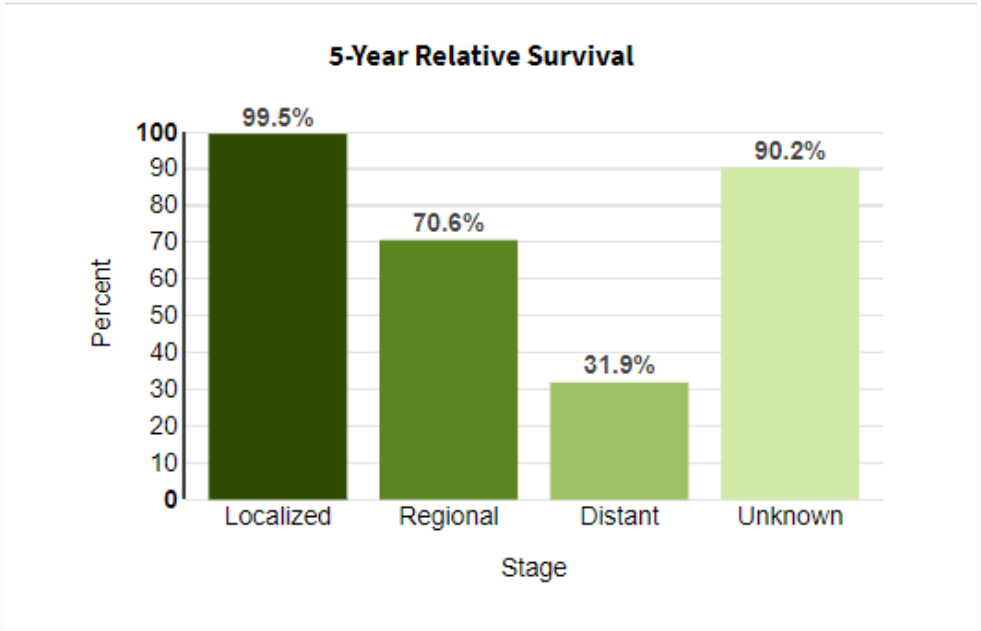
5-Year Relative Survival
93.7%
2012–2018

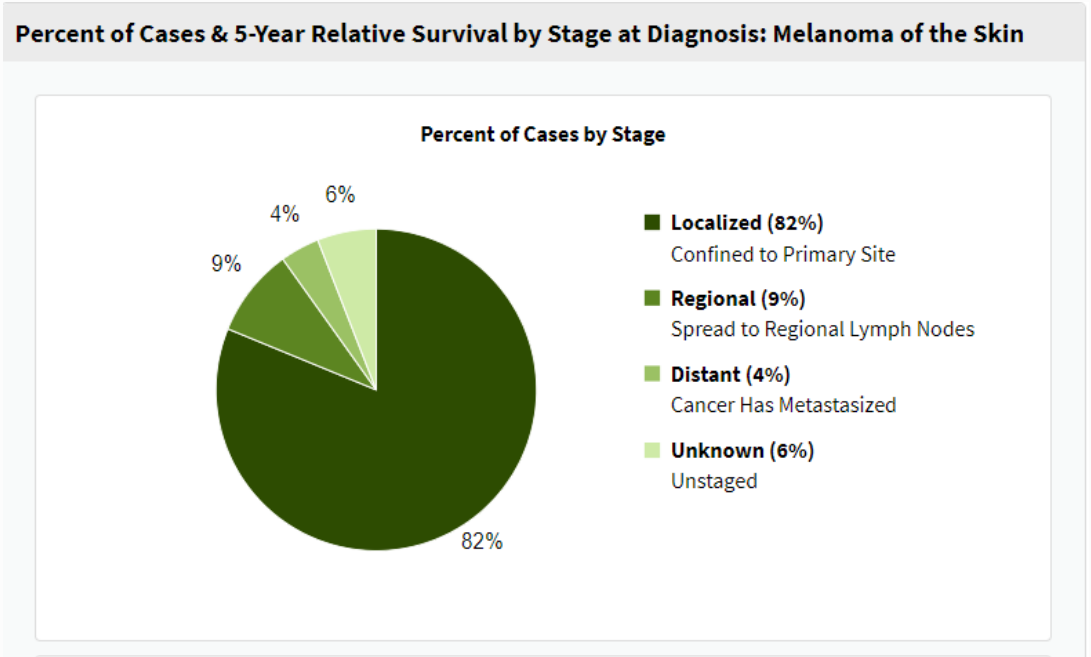


New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.

Melanoma: 5-year survival by stage

- Often found early, and then with a very good prognosis
- Advanced disease however does not fare well – or at least has not in the past





Melanoma Risk Factors

Photo by Jared Rice on Unsplash

- Hx of sun exposure, particularly blistering sunburns, especially in childhood
  - Est. 65% of the risk
- Tanning bed use – prior to the age 30 increases risk by 75%
- Fair skin/freckling/tendency to sunburn
- Light hair/eye coloring – MC1R gene in redheads
- Immunosuppression, Xeroderma pigmentosum
- >25 nevi (>100 yields a RR of 5 to 17)
- Atypical (dysplastic) nevi
  - Can be a melanoma precursor but most arise de novo
- Prior hx of melanoma
- History of nonmelanoma skin cancer
- Family hx of melanoma or of atypical nevi
- Parkinson's, Prostate cancer

Four major melanoma subtypes

- Superficial spreading
  - Most common (~70%)
  - Most often diagnosed as a thin lesion that is highly curable
  - Melanomas arising in dysplastic nevi are usually of this type
- Nodular
  - Accounts for ~15% of all melanomas
  - Enter a vertical invasive growth phase early on
  - Increased risk, even after accounting for thickness
- Lentigo maligna
  - Tends to occur on sun-exposed regions such as the face
  - Usually grow very slowly for many years in a superficial (radial) growth pattern
  - Occurs, on average, at age 70
- Acral lentiginous
  - Located on palms, soles, nail beds, and mucous membranes
  - <5% of melanomas but are the type most often encountered in dark-skinned individuals
  - Often more difficult to recognize and thus present at more advanced stages

Melanoma case #1

- 56 year-old female; $500,000 Term
- Application notes superficial melanoma on leg in September 2020, no recurrence
  - Good to go with that?
  - If need additional information, what would you require?

Likely favorable, but probably best get the path, especially since just 2 years prior

Case #1 – 56 year-old female

Diagnosis:
Left leg - MALIGNANT MELANOMA APPROXIMATELY 0.2 MM IN THICKNESS
Note:
There are nevoid features. There is <1 mitosis/mm squared. There is no evidence of ulceration, regression, intra-vascular involvement, satellite metastasis or an associated melanocytic nevus. The neoplasm extends to near lateral margins.

- Diagnosis?
- Favorable and unfavorable features?

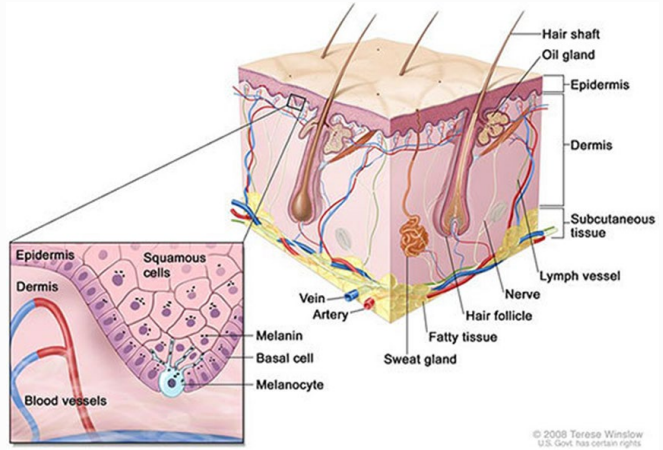
Subsequent excision revealed no additional tumor

- Stage? Assessment now?
- If not, what else would you like to know?

Additional risk factors and subsequent follow-up

Primary Tumor (T) AJCC 8th Edition

- Tumor Thickness – Continuously increasing risk with increasing thickness
  - T1: ≤1.0 mm
  - T2: >1.0 - 2.0 mm
  - T3: >2.01 - 4.0 mm
  - T4: >4.0 mm
- Ulceration (absence of intact epithelium)
  - No ulceration (and for T1 <0.8mm) = “a”
  - Ulceration present OR 0.8-1.0mm = “b”
- Mitotic Rate – no longer part of staging
  - And yet, risk increases with increasing mitotic rate, regardless of thickness



Lymph Node Involvement (N)

- NX: Nodes are not assessable (e.g. no biopsy or previously resected)
- N0: No regional lymphatic metastases
- N1:
  - N1a – one node, clinically occult (detected by sentinel node bx)
  - N1b – one node, clinically detected
  - N1c - no nodes but presence of in-transit, satellite, and/or microsatellite metastases
- N2:
  - N2a - two or three clinically occult nodes
  - N2b - two or three nodes with one or more clinically detected
  - N2c - with one lymph node involvement plus of in-transit, satellite, and/or microsatellite metastases
- N3:
  - N3a - four or more clinically occult nodes
  - N3b - four or more nodes, at least one clinically detected, or presence of matted nodes
  - N3c - any other node pattern

Distant Metastasis (M)

- M0: No detectable evidence of distant metastases
- M1a: Metastases to skin, soft tissue, muscle, or non-regional lymph node
- M1b: Lung metastases
- M1c: Metastasis to other non-CNS visceral sites
- M1d: Metastasis to CNS sites

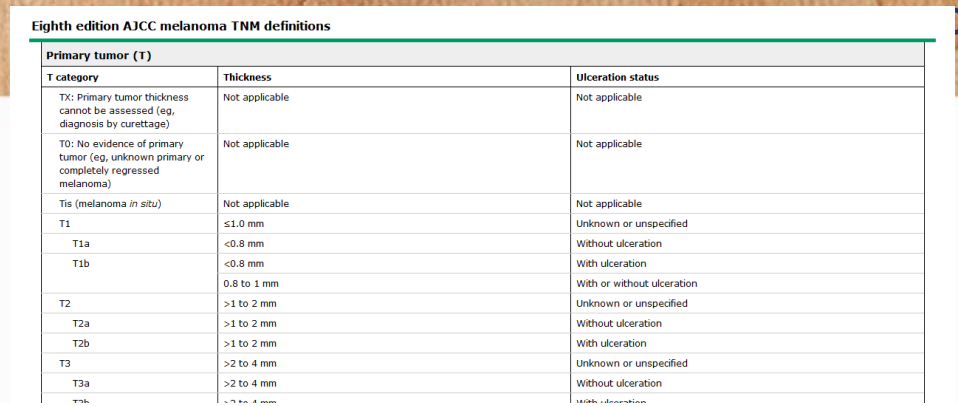
Suffixes for M category: (0) LDH not elevated, (1) LDH elevated. No suffix is used if LDH is not recorded or is unspecified.

Staging is closely tied to prognosis

AJCC Database

- Staging criteria are based on the AJCC melanoma database
- Large dataset of 43,792 patients with stage I to III melanoma followed since 1988
- However, it is more prognostic than predictive –
  - Antedate a number of important advances in treatment that are likely to have an impact on both relapse and mortality outcomes

Melanoma AJCC 8th Edition Staging



Eighth edition AJCC melanoma TNM definitions

Primary tumor (T)		
T category	**Thickness**	**Ulceration status**
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8 to 1 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration

Eighth edition AJCC melanoma TNM definitions

Tumor thickness is recorded to the nearest 0.1 mm rather than 0.01 mm

Primary tumor (T)		
T category	**Thickness**	**Ulceration status**
TX: Primary tumor thickness cannot be assessed (eg, diagnosis by curettage)	Not applicable	Not applicable
T0: No evidence of primary tumor (eg, unknown primary or completely regressed melanoma)	Not applicable	Not applicable
Tis (melanoma *in situ*)	Not applicable	Not applicable
T1	≤1.0 mm	Unknown or unspecified
T1a	<0.8 mm	Without ulceration
T1b	<0.8 mm	With ulceration
	0.8 to 1 mm	With or without ulceration
T2	>1 to 2 mm	Unknown or unspecified
T2a	>1 to 2 mm	Without ulceration
T2b	>1 to 2 mm	With ulceration
T3	>2 to 4 mm	Unknown or unspecified
T3a	>2 to 4 mm	Without ulceration
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; SLN: sentinel lymph node; LDH: lactate dehydrogenase; CNS: central nervous system.

8th Edition AJCC Melanoma Stage Groups

Stage Group	Criteria	% 10 Year Overall Survival Rate
O	Melanoma in situ (Tis N0 M0)	
IA	Localized melanoma < 0.8 mm, no ulceration (T1a N0 M0)	98
IB	Localized melanoma 0.8-1.0 mm, or ≤ 1.0 mm and ulceration present (T1b N0 M0)	96
IB	Localized melanoma 1.1–2.0 mm, no ulceration (T2a N0 M0)	92
IIA	Localized melanoma 1.1–2.0 mm, ulceration present (T2b N0 M0)	88
IIA	Localized melanoma 2.1–4.0 mm, no ulceration (T3a N0 M0)	88
IIB	Localized melanoma 2.1–4.0 mm, ulceration present (T3b N0 M0)	81
IIB	Localized melanoma > 4mm, no ulceration (T4a N0 M0)	83
IIC	Localized melanoma > 4mm, ulceration present (T4b N0 M0)	75
IIIA	T stages T1a, T1b, and T2a, plus one to three clinically occult regional lymph nodes, i.e., detected by SLN biopsy (T1a/b-T2a, N1a or N2a, M0)	88
IIIB/C/D, IV	Advanced regional metastases or any patient with distant metastases	

Important changes:

- Thickness 0.8-1.0mm replaces increased mitotic rate as criteria for T1b (and clinical stage IB)
- Thickness to be rounded to the nearest 0.1mm, so effectively 0.75-1.04mm
- If T1b but sentinel lymph node test is done and negative, then becomes pathologic stage group IA

Thin Melanomas

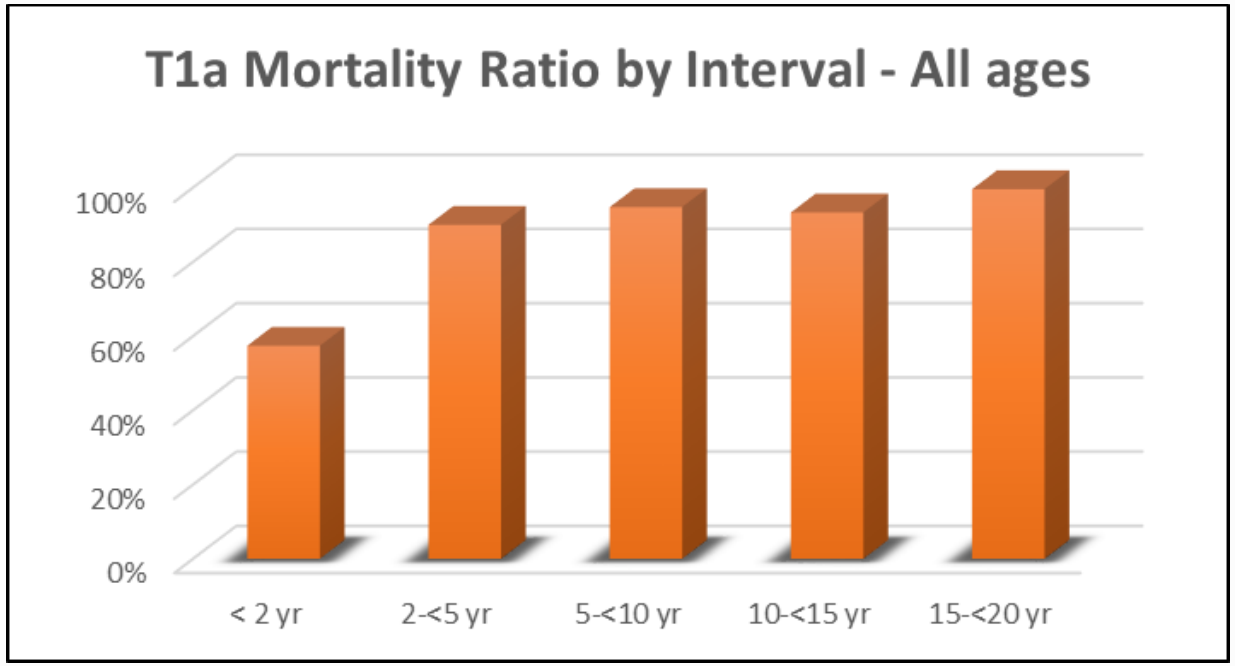
Excellent long-term survival after full excision

- Large Australian database: 96% 20-year melanoma specific survival (MSS)
- SEER data analysis stage IA: 99.5% 15-year MSS
- CancerMath.net: 97.7% 15-year MSS
- T1a Swedish database: 10- and 20-year MSS 97% and 95%
- 99.2% survival with mean 13 yr f/u with thickness ≤0.5mm
- 3 of 428 pts with melanoma ≤0.5mm and followed 5+ years died of melanoma – all due to a second melanoma

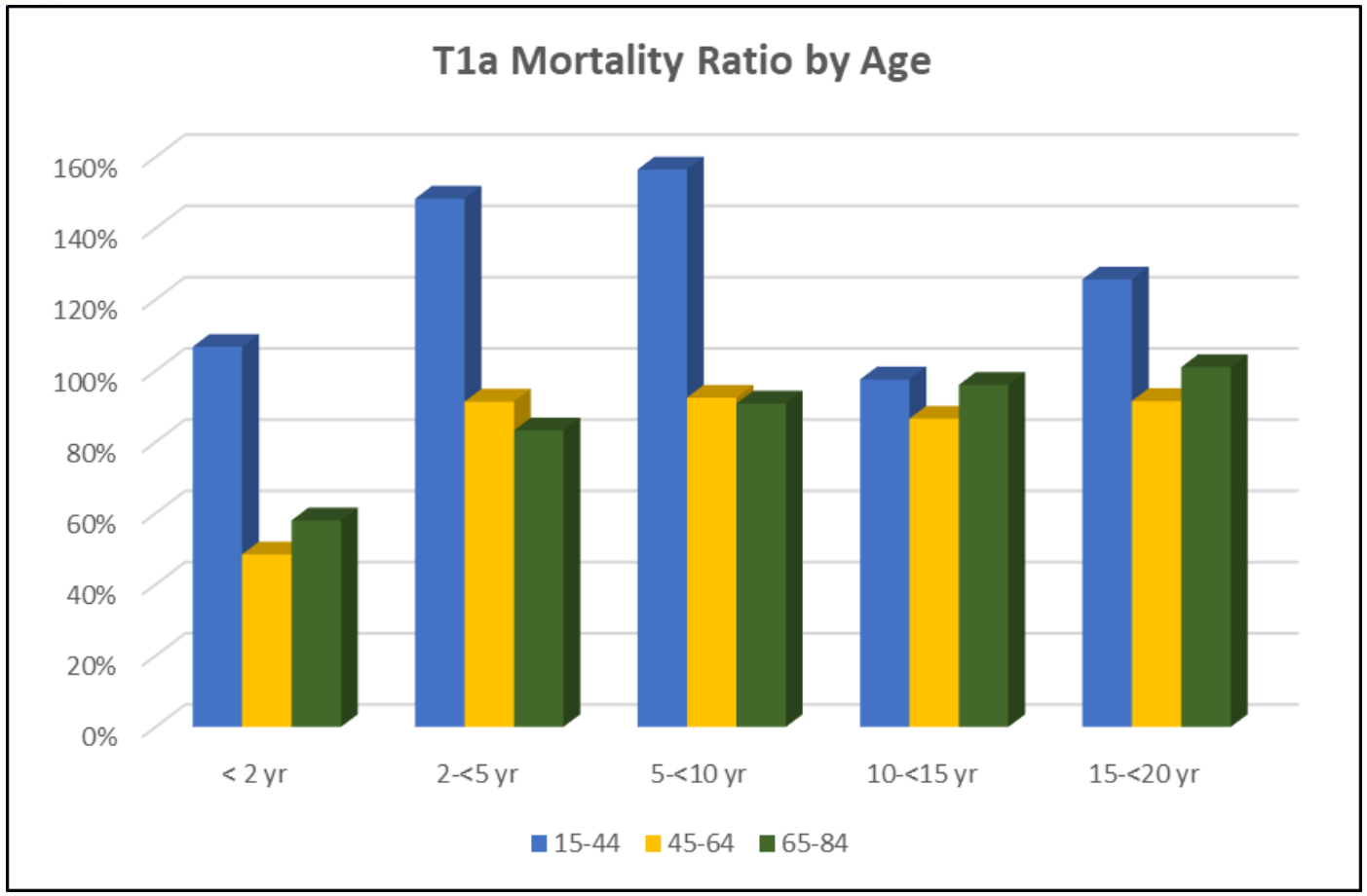
SEER Dataset – Stage 1A

- 6th Edition Stage T1aN0M0 or modeled equivalent 1993-2016
  - Melanoma ≤1 mm in thickness
  - Clark's level II or III
  - No ulceration
- No apparent excess mortality for stage 1A as a whole
- Better than expected survival in first two years likely reflects
  - Selection bias (seeking medical care and healthy enough to undergo surgery)
  - A low recurrence rate

SEER Dataset 50,940 cases



SEER dataset – stage IA



- Tumor ≤1.0 mm, non-ulcerated, no clinical nodes or mets (1988-2016)
- Actual to expected mortality, ages 15-84

Melanoma case #2

- 47 year-old female; $1,000,000 Term
- Melanoma in 2017, no recurrence

  - Stage?
  - Favorable and unfavorable factors?

Stage T2b

Unfavorable LVI, absence of TILs

Favorable location, low mitotic rate, low end of T2 range

Diagnosis:

A. SKIN (LABELED AS "RIGHT THIGH"), BIOPSY:
INVASIVE MALIGNANT MELANOMA
ULCERATION PRESENT
BRESLOW THICKNESS = 1.17 MM
CLARK LEVEL IV
ABSENT HOST RESPONSE OF TUMOR INFILTRATING LYMPHOCYTES
NO EVIDENCE OF REGRESSION
LYMPHOVASCULAR INVASION PRESENT
MARGINS NEGATIVE OF THE PLANE OF SECTIONING
MITOTIC INDEX: FEWER THAN ONE MITOSIS PER MM

8th Edition AJCC Melanoma Staging

- Important changes:
  - Thickness 0.8-1.0mm replaces increased mitotic rate as criteria for T1b (and clinical stage IB)
  - Thickness to be rounded to the nearest 0.1mm, so effectively 0.75-1.04mm
  - If T1b but sentinel lymph node test is done and negative, then becomes pathologic stage group IA

Stage Group	Criteria	% 10 Year Overall Survival Rate
O	Melanoma in situ (Tis N0 M0)	
IA	Localized melanoma < 0.8 mm, no ulceration (T1a N0 M0)	98
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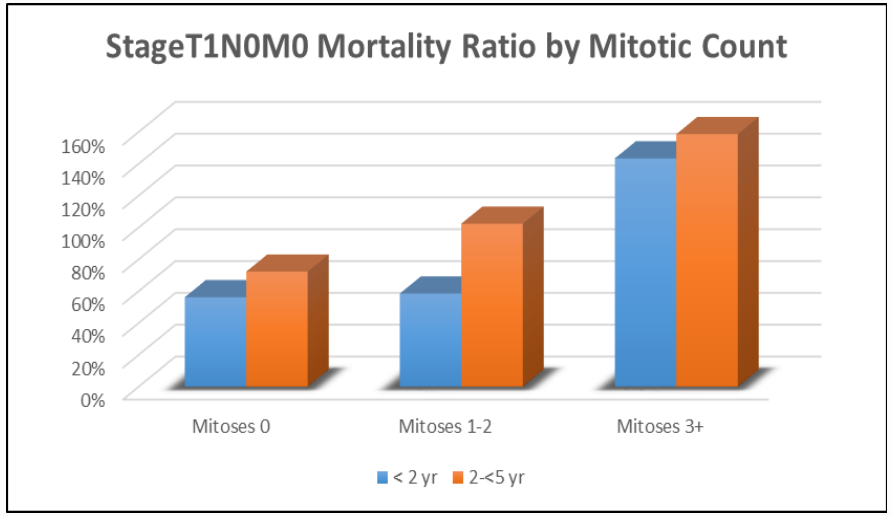
IIIB/C/D, IV	Advanced regional metastases or any patient with distant metastases	

Not all similarly staged melanomas are created equal

Besides thickness and ulceration…

Additional factors associated with higher recurrence risk:

- Increasing mitotic rate
- Lymphovascular invasion
- Older age at diagnosis, males
- Location on scalp, neck, or lip (arm most favorable)
- Nodular growth pattern (independent of thickness)
- Lack of tumor-infiltrating lymphocytes
- Regression of >50%
- ?? Gene expression profiling (DecisionDX-Melanoma, MelaGenix), circulating tumor cells or tumor DNA, proteomics



Each has been shown to increase the melanoma mortality risk by 1.5 to 3-fold

128

Survival by Mitotic Count

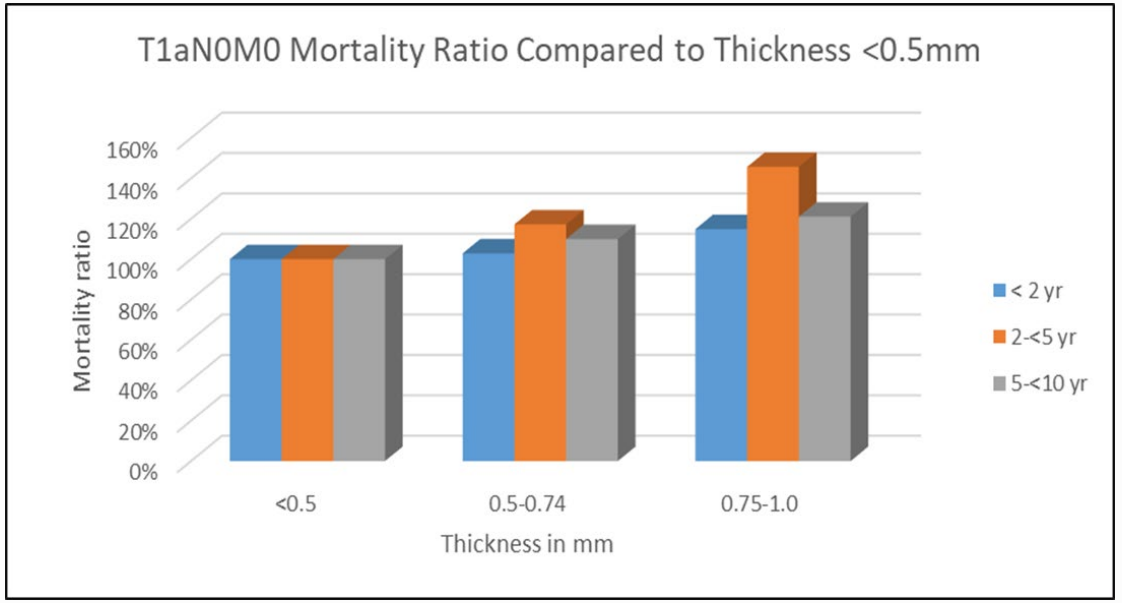
Stage I and II - AJCC 8th edition [6]

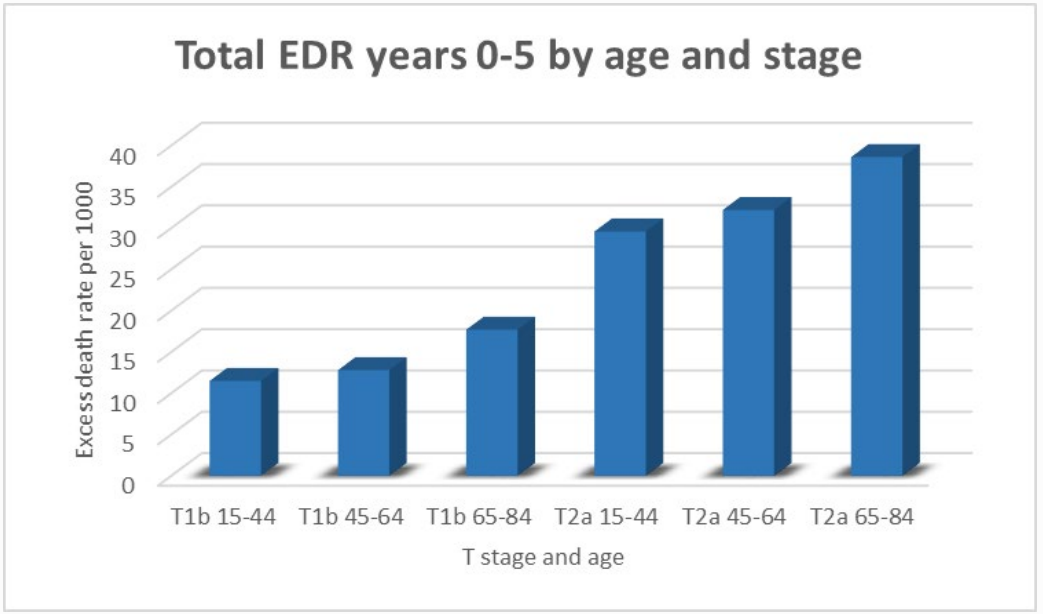
Mitoses/mm2	5 year survival %	10 year survival %
0	99	97
1	98	96
2 – 3	96	91
4 – 10	91	86
11+	84	77

Risk within stage groups

SEER dataset

Mortality ratios within T1a





Or IB: Excess death rate by age, T1b vs T2a

Melanoma case #2; 47 year-old female

- T2b melanoma in 2017
- Wide excision with clear margins, SLN biopsy negative
- No family history melanoma
- Followed every 6 months 2017-2019, yearly since including virtual visit in 2020
  - Stage group?
  - Adequate treatment and follow-up?

Stage IIA. Adjuvant Rx not generally advised for Stage I to IIA.

Melanoma Work-up

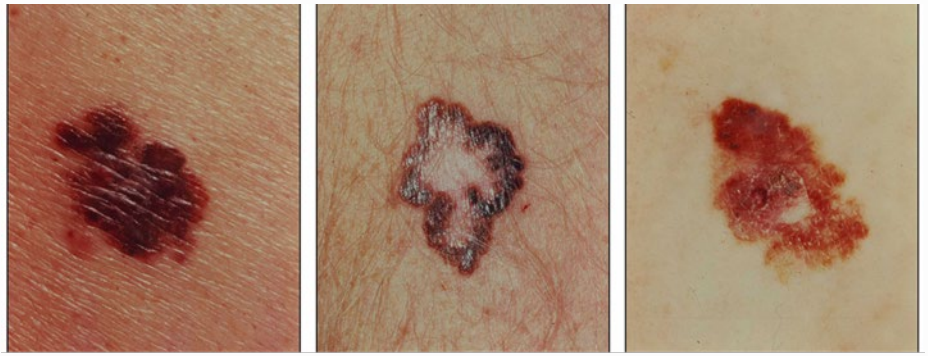
- For asymptomatic patients stage T1a (and T1b???) melanoma – no additional testing advised, close clinical follow-up only
  - Sentinel lymph node (SLN) metastases are very infrequent (<5%) in T1a melanomas but occur in ~5-12% of patients with T1b melanomas
- If clinically negative nodes but intermediate or high risk for lymph node metastasis –> SLN biopsy for staging purposes usually advised
- If SLN (+), observation coupled with ultrasound surveillance rather than completion lymph node dissection is now usually advised
- For Stage IIIB or IIIC disease or with an initial locoregional recurrence – CBC, serum LDH, and possibly whole body CT imaging and brain MRI
- PET/CT if additional surgery for advance local disease is contemplated, and at follow-up in very high-risk patients

Melanoma case #2: 47 year-old female

- Melanoma in 2017, no recurrence
  - Stage T2b, N0, M0 = IIA
  - Unfavorable LVI, absence of TILs
  - Favorable location, low mitotic rate, low end of T2 range

- Prognosis now at 5 years out?

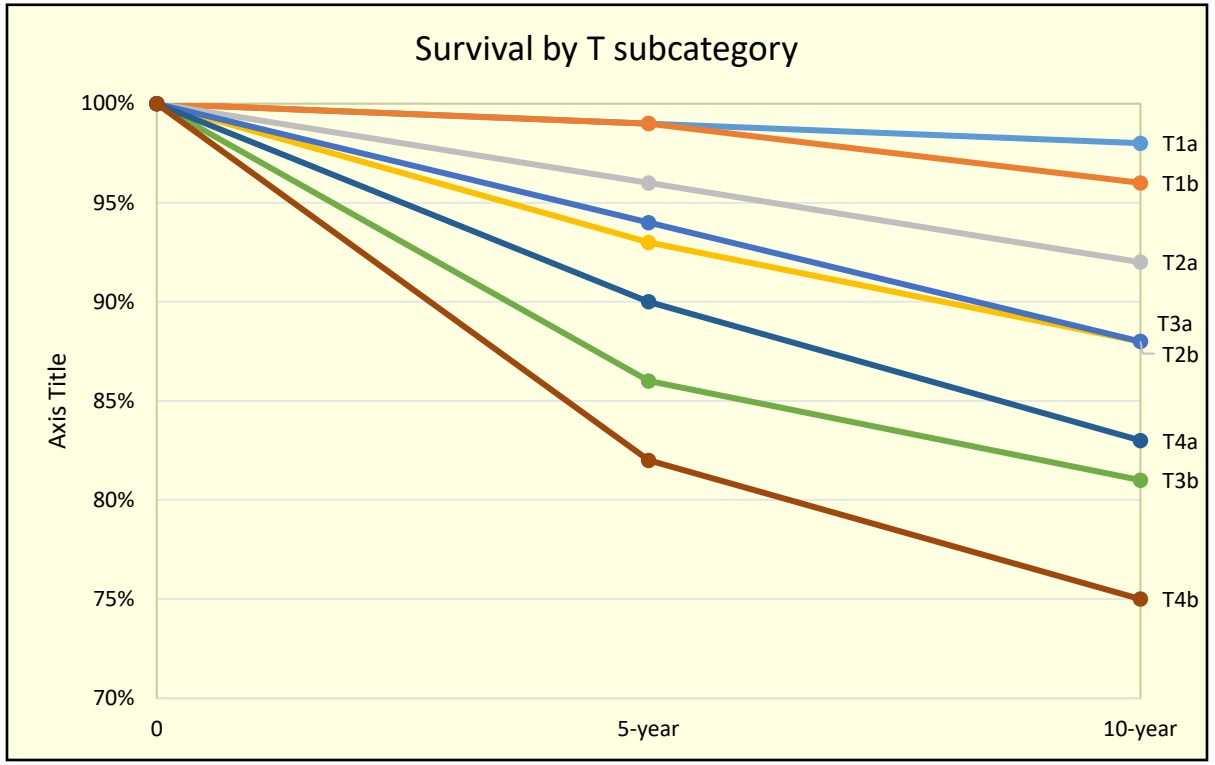
  Minimal, low, moderate, or high risk?



Photos: https://www.cancer.gov/types/skin/hp/melanoma-treatment-pdq

Survival by T Classification

AJCC Database 8th edition [6]

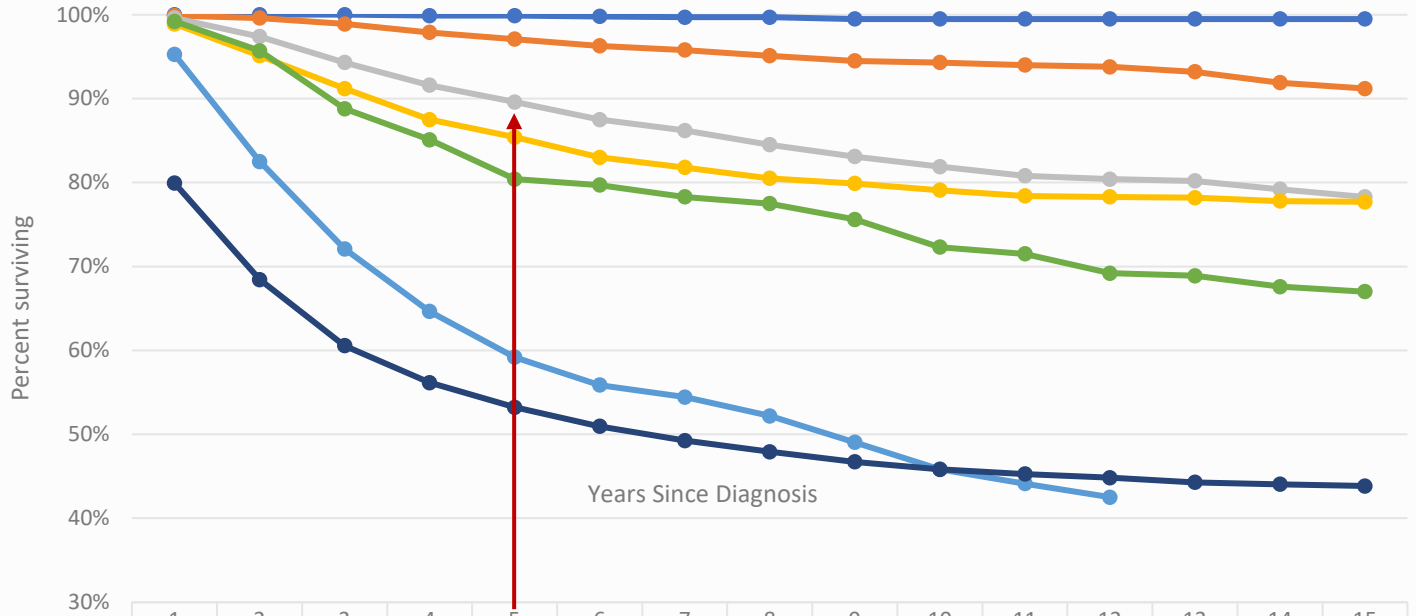


T class	5 year survival %	10 year survival %
T1a	99	98
T1b	99	96
T2a	96	92
T2b	93	88
T3a	94	88
T3b	86	81
T4a	90	83
T4b	82	75

From: Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017; 67(6):472-492.

SEER analysis – Survival by Stage Group

Figure 1. Relative Cumulative Survival by Stage



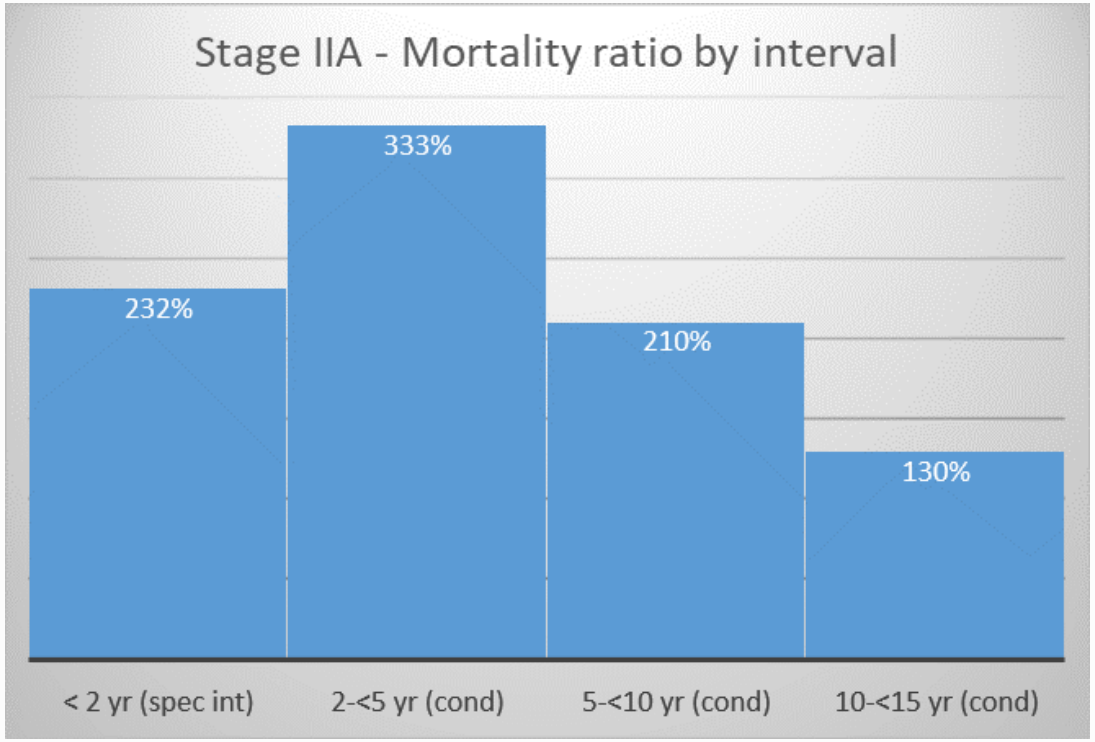
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1A	100.0%	100.0%	100.0%	99.9%	99.9%	99.8%	99.7%	99.7%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%
1B	99.9%	99.6%	98.9%	97.9%	97.1%	96.3%	95.8%	95.1%	94.5%	94.3%	94.0%	93.8%	93.2%	91.9%	91.2%
2A	99.6%	97.4%	94.3%	91.6%	89.6%	87.5%	86.2%	84.5%	83.1%	81.9%	80.8%	80.4%	80.2%	79.2%	78.3%
2B	98.9%	95.1%	91.2%	87.5%	85.4%	83.0%	81.8%	80.5%	79.9%	79.1%	78.4%	78.3%	78.2%	77.8%	77.7%
2C	95.3%	82.5%	72.1%	64.6%	59.2%	55.9%	54.4%	52.2%	49.0%	45.8%	44.1%	42.5%			
3A	99.2%	95.7%	88.8%	85.1%	80.4%	79.7%	78.3%	77.5%	75.6%	72.3%	71.5%	69.2%	68.9%	67.6%	67.0%
3B-4	79.9%	68.4%	60.6%	56.2%	53.2%	51.0%	49.2%	47.9%	46.7%	45.8%	45.3%	44.8%	44.3%	44.0%	43.8%

78.3/89.6 = 87.4% 10-yr survival after 5 years

i.e. 12.6% mortality

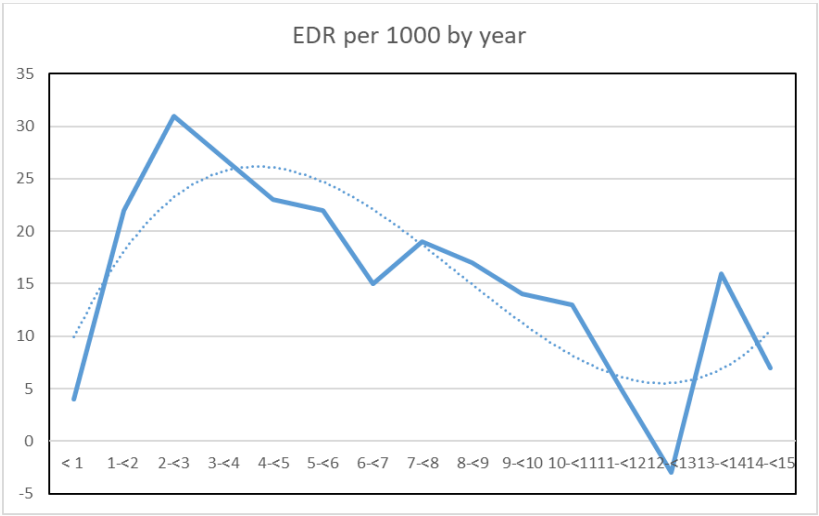
135

SEER dataset – Melanoma Stage IIA



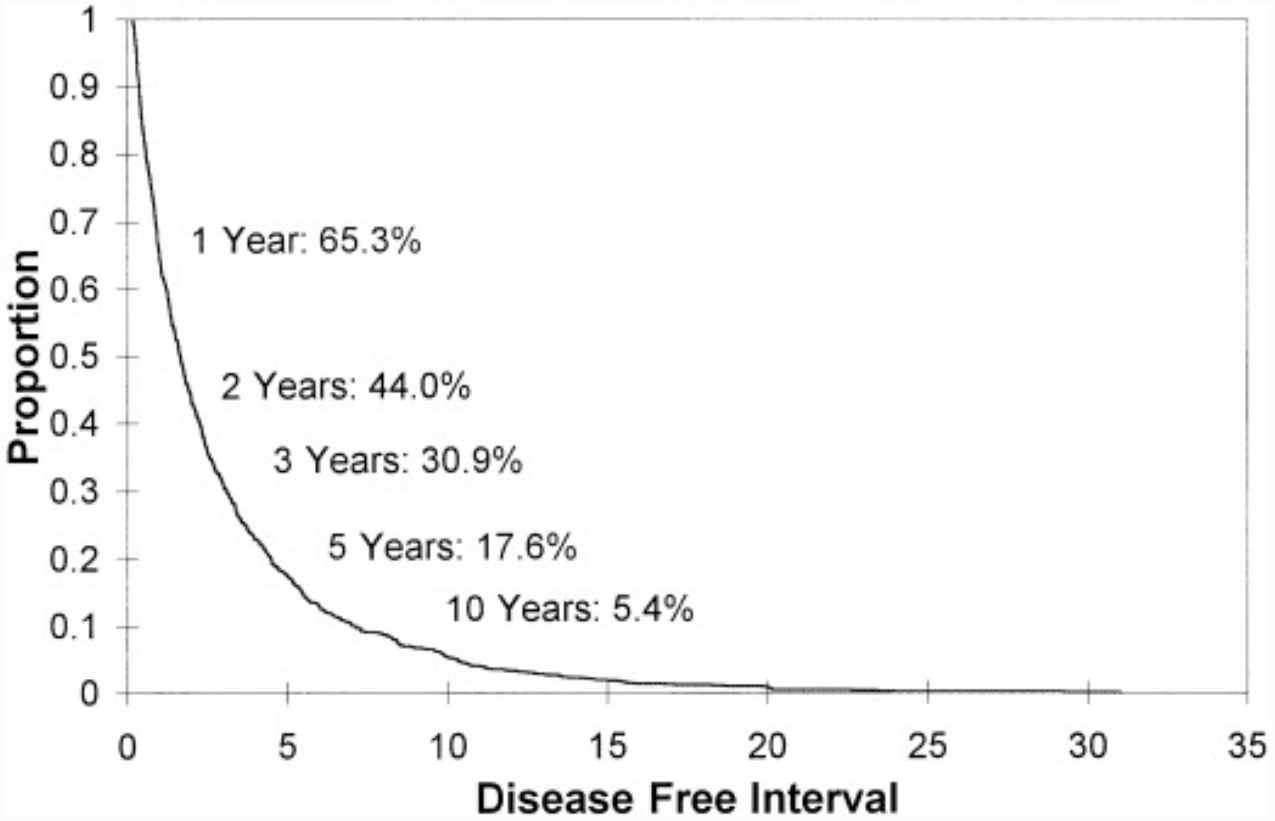
Actual to expected mortality by years since diagnosis, ages 15-84

- Rating approach?



Per CancerMath.net: 15.7% 15-yr mortality at diagnosis; 3.5% at 5 years out

Melanoma time to local recurrence

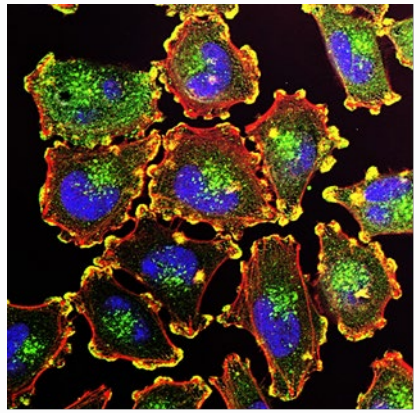


The proportion of patients who developed local recurrence is shown with respect to time
More than 55% of local recurrences occurred by the end of 2 years

Melanoma Case #2 -- What if…

What if sentinel node biopsy revealed a single, clinically unapparent, positive lymph node:

- Stage then?
  - T2b, N1a, M0 = Stage IIIB
- Usual therapy then for stage IIIB disease?
  - Adjuvant PD-1 inhibitors now advised (nivolumab or pembrolizumab)
  - OR
  - Dabrafenib plus trametinib if BRAF-mutant positive



Metastatic melanoma cells_Credit- JC Valencia, NCI Center for Cancer Research

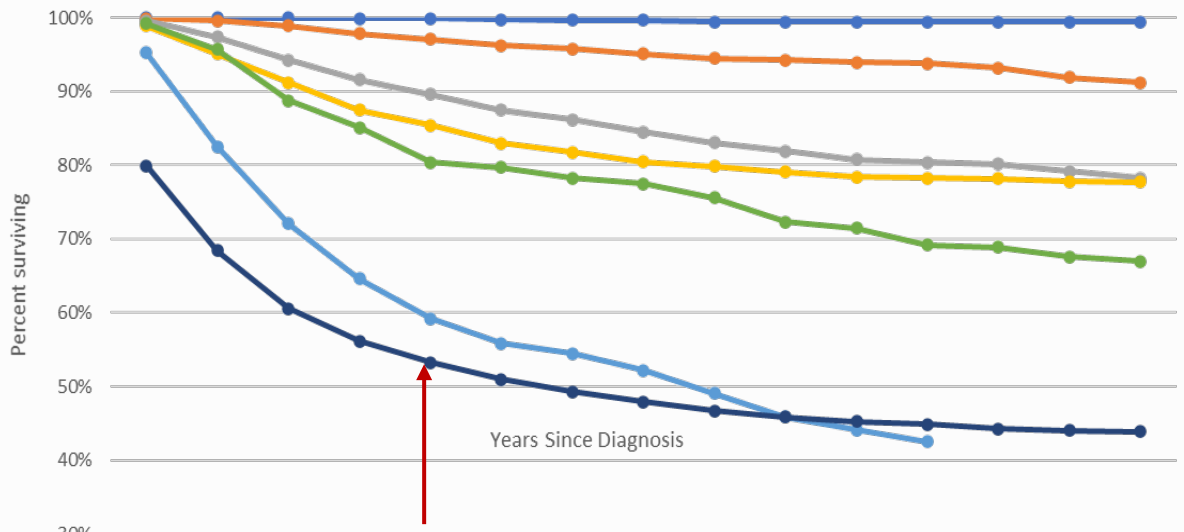
Melanoma Case #2 (What if?)

Prognosis?

Conditional melanoma-specific mortality after 5 years for stage IIIB:

- ACS dataset stage IIIB 7.2% 5-year mortality

Figure 1. Relative Cumulative Survival by Stage



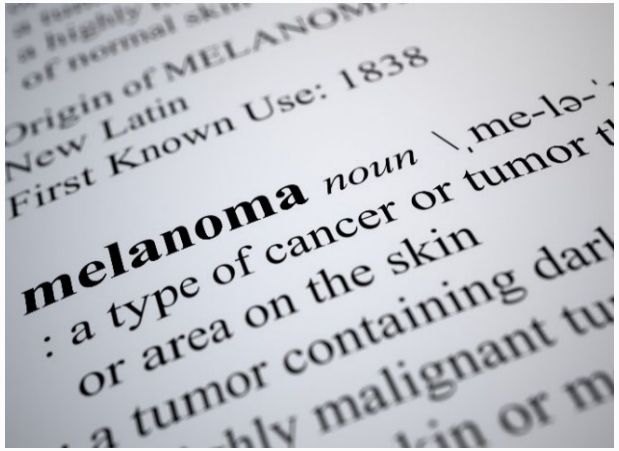
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
1A	100.0%	100.0%	100.0%	99.9%	99.9%	99.8%	99.7%	99.7%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%	99.5%
1B	99.9%	99.6%	98.9%	97.9%	97.1%	96.3%	95.8%	95.1%	94.5%	94.3%	94.0%	93.8%	93.2%	91.9%	91.2%
2A	99.6%	97.4%	94.3%	91.6%	89.6%	87.5%	86.2%	84.5%	83.1%	81.9%	80.8%	80.4%	80.2%	79.2%	78.3%
2B	98.9%	95.1%	91.2%	87.5%	85.4%	83.0%	81.8%	80.5%	79.9%	79.1%	78.4%	78.3%	78.2%	77.8%	77.7%
2C	95.3%	82.5%	72.1%	64.6%	59.2%	55.9%	54.4%	52.2%	49.0%	45.8%	44.1%	42.5%			
3A	99.2%	95.7%	88.8%	85.1%	80.4%	79.7%	78.3%	77.5%	75.6%	72.3%	71.5%	69.2%	68.9%	67.6%	67.0%
3B-4	79.9%	68.4%	60.6%	56.2%	53.2%	51.0%	49.2%	47.9%	46.7%	45.8%	45.3%	44.8%	44.3%	44.0%	43.8%

Melanoma case #3

- 40 year-old male; Dermatologist. $5,000,000 UL.
- Left thigh melanoma 0.25mm 3/2019

For amount, and age – full records

- What might you do if for $100,000?



Melanoma case #3; 40 year-old male

- 2/19 visit:
  - Multiple uniform skin lesions, except slightly atypical left thigh and upper back lesions
  - Mother with ocular melanoma, died of metastatic MM
  - Brother and maternal uncle with MM
- Path reports 3/2019:

Diagnosis: Skin, left thigh, melanoma in-situ, inflamed.

COMMENT: **SOX-10 immunoperoxidase or Melan-A immunoperoxidase with a Red chromogen would be of value to exclude incipient invasion. This will help determine the degree of removal necessary.**

ADDENDUM:

Left thigh - Recut reveals no additional alterations. Melan-A immunoperoxidase with appropriate control is negative. SOX-10 immunoperoxidase, a more sensitive stain, with appropriate control is positive for individual atypical cells extending 0.25 mm into the areas of inflammatory infiltrate. Accordingly, early incipient invasion is not excluded, 0.25 mm tumor thickness, pT1a.

COMMENT: **Complete re-excision with a 1 cm margin is recommended.**

Diagnosis: Skin, upper back, compound nevus (associated architectural disorder and focally severe cytologic atypia).

- Assessment?

Melanoma case #3; 40 year-old male

- Re-excision with wide margins – no residual
- Dermatology follow-up every 6 months
- Path reports 2/2020:

Specimens

A	SKIN, Left lateral superior back
B	SKIN, Right medial superior back

Final Diagnosis

A: SKIN, LEFT LATERAL SUPERIOR BACK, SHAVE BIOPSY:
- MODERATE TO SEVERELY DYSPLASTIC COMPOUND MELANOCYTIC NEVUS WITH ARCHITECTURAL DISORDER AND CYTOLOGIC ATYPIA, PRESENT 1.3 MM FROM THE LATERAL BIOPSY MARGIN AND 0.2 MM FROM THE DEEP MARGIN

B: SKIN, RIGHT MEDIAL SUPERIOR BACK, SHAVE BIOPSY:
- MODERATELY DYSPLASTIC COMPOUND MELANOCYTIC NEVUS WITH ARCHITECTURAL DISORDER AND CYTOLOGIC ATYPIA, PRESENT 0.8 MM FROM THE LATERAL BIOPSY AND 0.15 FROM THE DEEP MARGIN

Photo by ahmad kanbar on Unsplash

- Is re-excision needed?
- Diagnosis?
- Assessment?

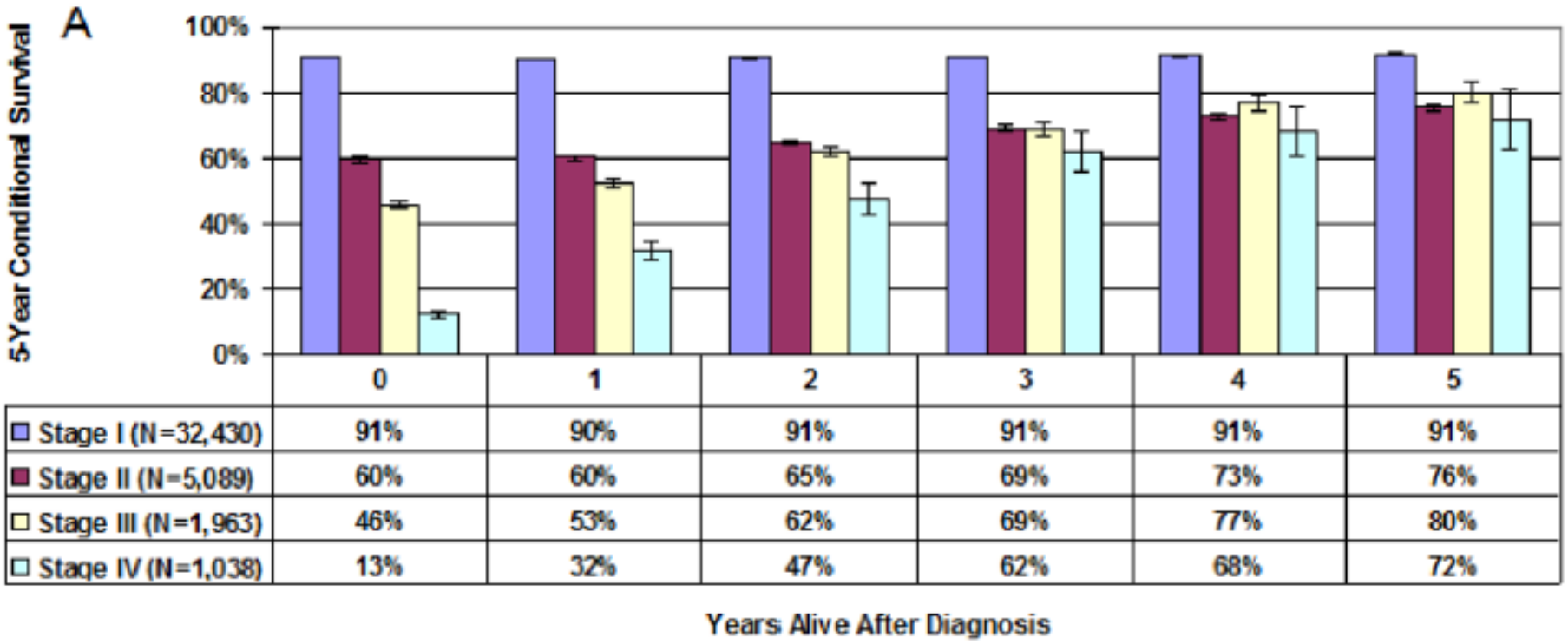
Second Melanoma Risk

- After melanoma diagnosis, risk of second melanoma 2% at 5 years and 5-10% at 20 years
- Higher risk seen with:
  - Atypical nevi (RR 2-6), or high nevus counts (RR 3-5)
  - Family history of melanoma (RR 2-3)
  - If melanoma was nodular (RR 2), or of head and neck location
  - If first melanoma at age <30, or more than one melanoma
- Familial Atypical Multiple Mole and Melanoma (FAMMM) Syndrome
  - High number of common and atypical nevi (>50) and history of melanoma in one or more first- or second-degree relatives
  - Mutations in the CDKN2A gene – autosomal dominant with reduced penetrance and variable expressivity
  - High risk of melanoma – 30% by age 50 and 67% by age 80 in one study
  - Increased risk also of pancreatic and brain cancer

Genetic Screening

- Autosomal dominantly inherited mutations in melanoma susceptibility genes are responsible for probably less than 1 to 2% of cutaneous melanomas
- Mutations in CDKN2A and CDK4 genes, have been identified in melanoma-prone families
  - The major gene resides on chromosome 9p and encodes the tumor suppressor gene CDKN2A, also called p16INK4A or MTS1 (multiple tumor suppressor-1)
- Approximately 20 to 40% of families with three or more affected first-degree relatives have mutations in the CDKN2A gene
- Incidence of melanoma in carriers was estimated to be 14, 24, and 28% at 50, 70, and 80 years of age, respectively
- May be increased risk of pancreatic and brain cancers
- In a cohort of young patients (median age 32 years) with sporadic melanoma, there was no increase in the prevalence of CDKN2A mutations in the absence of a positive family history
- Low to moderately increased melanoma risk:
  - BRCA2 (RR 2.6)
  - Retinoblastoma gene
  - MC1R - Melanocortin-1 receptor - gene leads to red hair and failure to tan (RR 2-4)

Conditional Survival Estimates -- SEER database

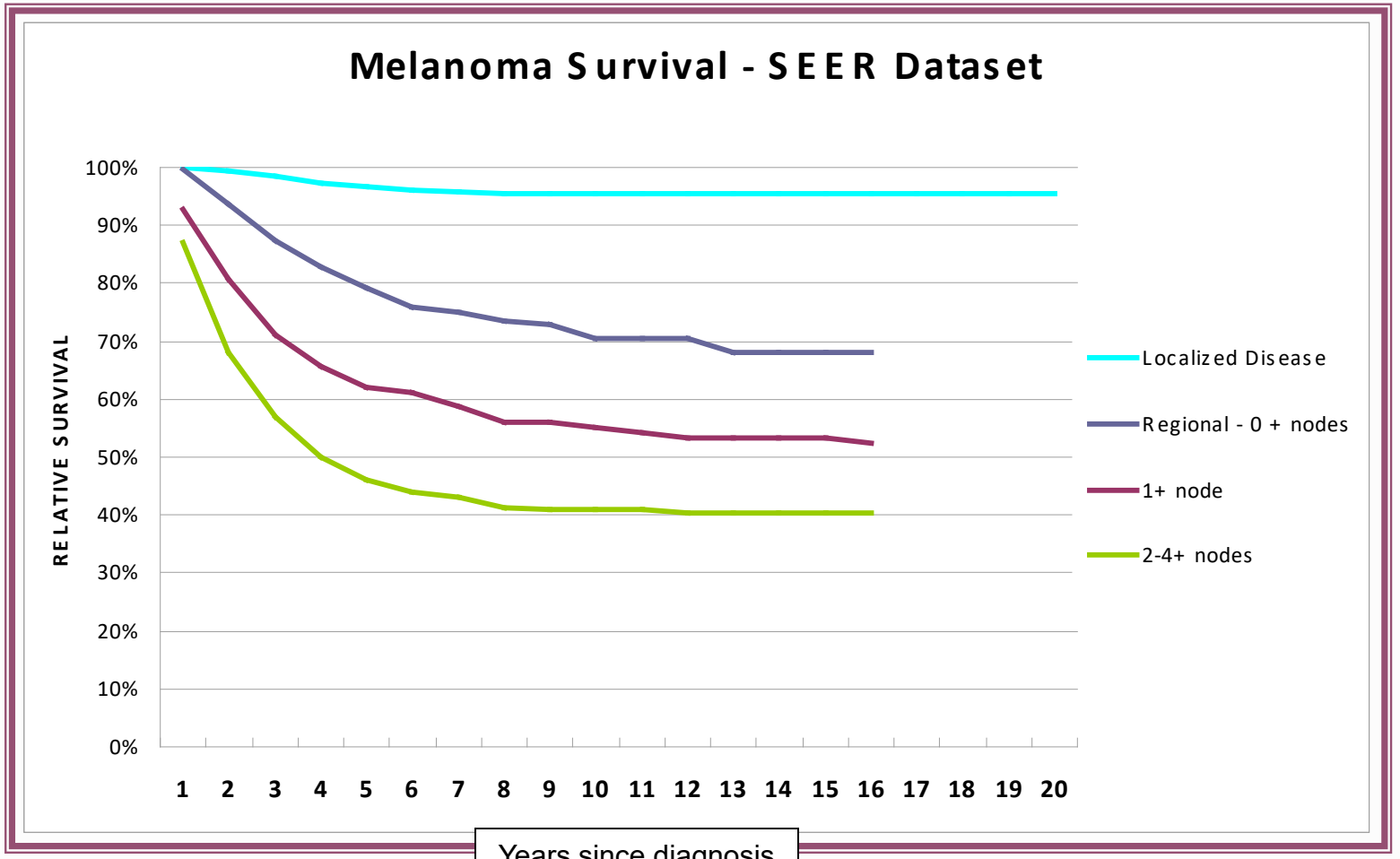


	0	1	2	3	4	5
Stage I (N=32,430)	91%	90%	91%	91%	91%	91%
Stage II (N=5,089)	60%	60%	65%	69%	73%	76%
Stage III (N=1,963)	46%	53%	62%	69%	77%	80%
Stage IV (N=1,038)	13%	32%	47%	62%	68%	72%

Melanoma-specific 5-year conditional survival estimates stratified by disease stage

[Error bars represent the standard error]

Melanoma Specific Survival



Conditional Survival Stage III Melanoma

Prognosis after 5 years disease-free? Additional studies breaking the stage III data down by substage

- Conditional 5 year disease-specific survival:
  - Stage IIIA: 78% at year 0 & 90% at year 5
  - Stage IIIB: 54% at year 0 & 79% at year 5
  - Stage IIIC: 39% at year 0 & 78% at year 5

Stage III and IV Disease - PD-1 Rx

- As adjuvant Rx for stage III disease, at a median follow-up of 15 months, pembrolizumab was associated with significantly longer recurrence-free survival than placebo (75% at 1 year) [25]
- In Stage IV disease, median OS was ~24 months with Pembrolizumab Rx, and 3-year and 4-year survival in treatment-naive patients was 51% and 48%, respectively
  - Of the 1 in 6 with a complete remission, 2-year disease-free survivals of 90% have been seen, even without ongoing Rx
- Cures???

Melanoma Treatment

- Surgical resection of primary tumor with wide local excision
  - 1-2 cm margins (depending on T stage), down to the deep fascia
- Sentinel node biopsy advised for lesions >0.8mm thickness
  - Not performed for early localized lesions (stage I and carcinoma in situ) unless additional high risk features present
- Adjuvant therapy for stage IIB or IIC or node positive disease
  - See prior slide
- Resection of locoregional or isolated metastatic recurrence
  - Rare cures obtained
- Systemic therapy for metastatic disease -- limited effectiveness but major advances in just the past few years and some flattening of the mortality curves after 2-3 years → Cures?!?
  - Immunotherapy – usually pembrolizumab or nivolumab
  - For patients with a V600 BRAF mutation, targeted therapy using a BRAF inhibitor/MEK inhibitor (dabrafenib/trametinib) or vemurafenib (?+cobimetinib) also an option
- Radiation therapy – mostly a palliative role, +/- nodal bed??

Head & Neck Melanoma

- Consistently worse prognosis noted for head and neck location of melanoma, especially scalp location
  - 5 year survivals of 79-83% vs 92-93% for other sites (and 67% for scalp specifically) [8,9]
- Tend to have greater depth, more frequent node involvement however attempts to control for these adverse factors still leaves H&N location as a poor prognostic factor:
  - After adjusting, mortality rates still 60-80% higher for H&N location

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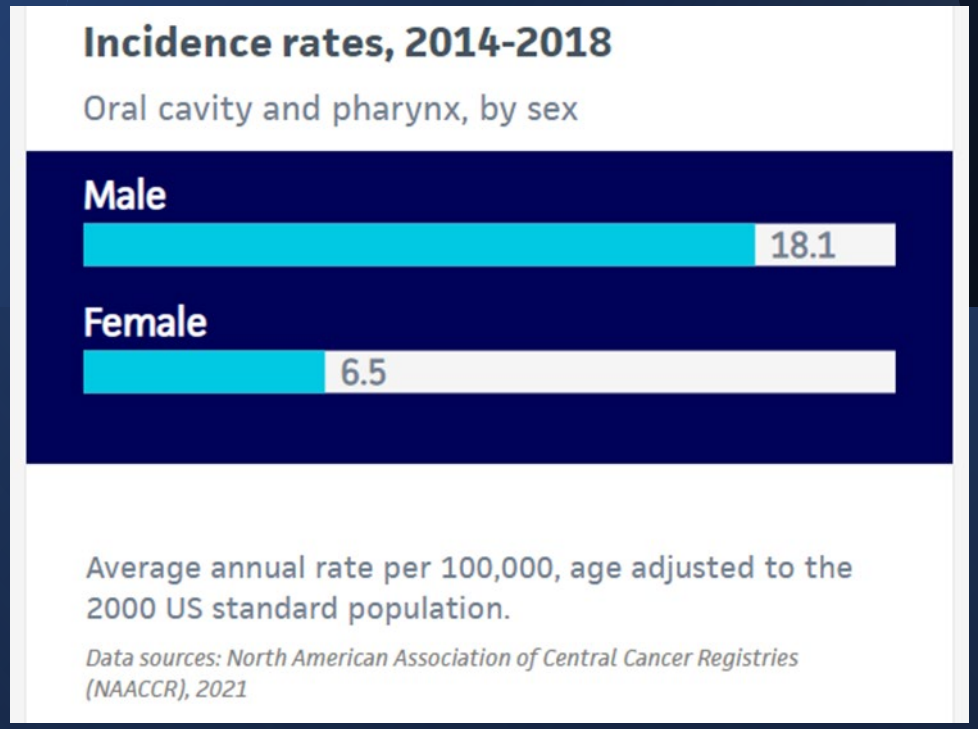
Lagniappe
Head & Neck Cancer



At a Glance

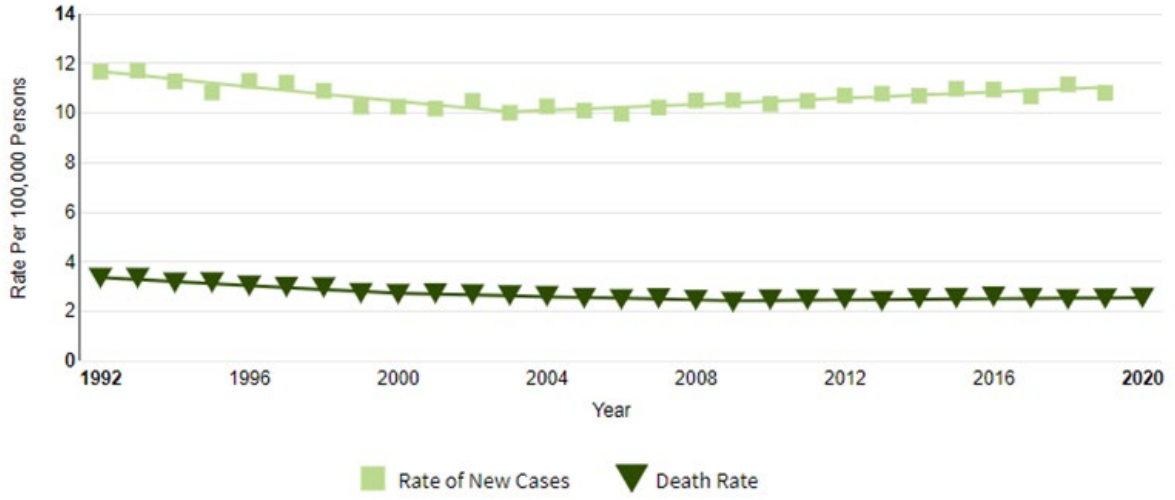
Estimated New Cases in 2022	54,000
% of All New Cancer Cases	2.8%

Estimated Deaths in 2022	11,230
% of All Cancer Deaths	1.8%

5-Year Relative Survival

68.0%

2012–2018



New cases come from SEER 12. Deaths come from U.S. Mortality.
All Races, Both Sexes. Rates are Age-Adjusted.

Head & Neck Cancer Case

- Male age 54 for $2,000,000 IUL “Quick quote”
- Tonsil cancer excised 5 years ago
  - pT1: 1.5 cm right tonsil
  - pN2b: 3 of 41 nodes (+) right neck, largest 5 cm
  - cM0: No evidence of mets
- Followed by 40 days of radiation treatment
- No evident disease since with close follow-up

Stage Group?

Additional information needed?

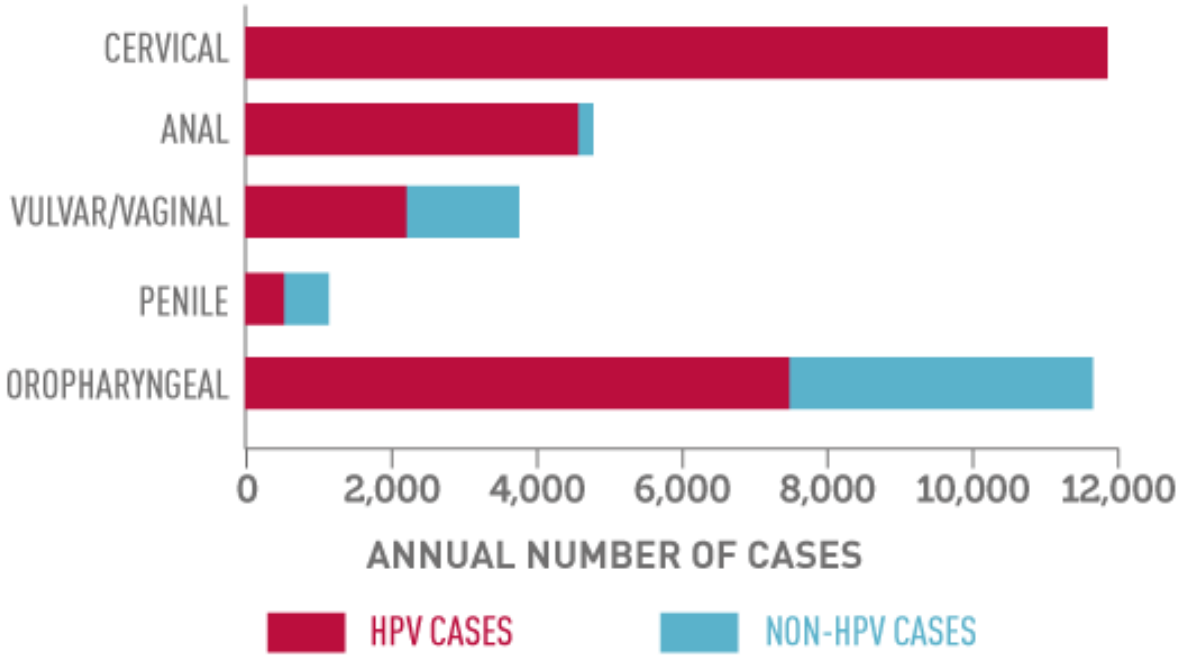
Insurability?

HPV Related Cancer

- HPV has been well known to be the major cause of cervical cancer since the 1990s
- It is also now known to cause anal, vulvar, vaginal, penile, and oropharyngeal cancers
  - A causative factor in ~5% of all new cancer cases
- HPV-associated oropharyngeal cancers are primarily found in the base of the tongue, tonsils, and larynx
- The incidence of oropharyngeal cancer in men is now higher than for cervical cancer in women!

PROPORTION OF CANCERS CAUSED BY HPV IN THE UNITED STATES

HPV infection causes virtually all cases of cervical cancer and a substantial proportion of several other cancers.



www.cancer.gov

Source: Schiller JT and Lowy DR. Understanding and learning from the success of prophylactic human papillomavirus vaccines. *Nat Rev Microbiol* 2012; 10(10): 681-692.

HPV vs Non-HPV Squamous Cell Carcinomas

- Despite an overall decrease in head and neck cancers overall since 1980, corresponding to a decline in tobacco use, the incidence oropharyngeal cancers has been increasing
- Many patients with oropharyngeal cancer do not have the traditional head and neck cancer risks (e.g. smoking, smokeless tobacco, alcohol consumption) [4]
  - Over half of these are positive for high-risk HPV strains [5,6]
  - On average occur at younger ages than non-HPV cancers [7]
- The prognosis for HPV vs non-HPV cancers is quite different

HPV and Non-HPV Cancer Outcomes

- Differences in prognosis and in gene expression suggest that HPV positive and HPV negative head and neck cancers represent distinct entities
  - Two HPV viral oncogenes (E6 and E7) are mainly responsible for malignant transformation
- HPV(+) cancer is more likely to present with an early-stage primary tumor, even though there is an increased risk of more advanced nodal disease
- Despite this, the prognosis tends to be much better than similarly staged HPV (-) tumors and with a lower risk of second malignancy
  - For example, in one study, progression-free survival at 8 yrs was significantly better for HPV+ patients (64 vs 23%)
- The better prognosis is reflected in the latest staging system

Not your parent's TNM staging system

HPV related oropharyngeal carcinoma TNM pathologic staging AJCC UICC 2017

Primary tumor (T)	
T category	**T criteria**
T0	No primary identified
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible or beyond.*
Regional lymph nodes (N) - Pathological N (pN)	
N category	**N criteria**
NX	Regional lymph nodes cannot be assessed
pN0	No regional lymph node metastasis
pN1	Metastasis in four or fewer lymph nodes
pN2	Metastasis in more than four lymph nodes
Distant metastasis (M)	
M category	**M criteria**
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups - Pathological			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
T0, T1, or T2	N0, N1	M0	I
T0, T1, or T2	N2	M0	II
T3 or T4	N0, N1	M0	II
T3 or T4	N2	M0	III
Any T	Any N	M1	IV

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Oropharyngeal cancer
P16 negative
TNM pathological staging
AJCC UICC 2017

Oropharyngeal (p16 negative) cancer TNM pathological staging AJCC UICC 2017

Primary tumor (T)

Oropharynx (p16−)

T category	T criteria
TX	Primary tumor cannot be assessed
Tis	Carcinoma *in situ*
T1	Tumor 2 cm or smaller in greatest dimension
T2	Tumor larger than 2 cm but not larger than 4 cm in greatest dimension
T3	Tumor larger than 4 cm in greatest dimension or extension to lingual surface of epiglottis
T4	Moderately advanced or very advanced local disease
T4a	Moderately advanced local disease. Tumor invades the larynx, extrinsic muscle of tongue, medial pterygoid, hard palate, or mandible.*
T4b	Very advanced local disease. Tumor invades lateral pterygoid muscle, pterygoid plates, lateral nasopharynx, or skull base or encases carotid artery.

* *NOTE:* Mucosal extension to lingual surface of epiglottis from primary tumors of the base of the tongue and vallecula does not constitute invasion of the larynx.

Regional lymph nodes (N)

Pathological N (pN) - Oropharynx (p16−) and hypopharynx

N category	N criteria
NX	Regional lymph nodes cannot be assessed
N0	No regional lymph node metastasis
N1	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(−)
N2	Metastasis in a single ipsilateral lymph node, 3 cm or smaller in greatest dimension and ENE(+); **or** larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−); **or** metastases in multiple ipsilateral lymph nodes, none larger than 6 cm in greatest dimension and ENE(−); **or** in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N2a	Metastasis in single ipsilateral node 3 cm or smaller in greatest dimension and ENE(+); **or** a single ipsilateral node larger than 3 cm but not larger than 6 cm in greatest dimension and ENE(−)
N2b	Metastasis in multiple ipsilateral nodes, none larger than 6 cm in greatest dimension and ENE(−)
N2c	Metastasis in bilateral or contralateral lymph node(s), none larger than 6 cm in greatest dimension and ENE(−)
N3	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−); **or** in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); **or** multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); **or** a single contralateral node 3 cm or smaller and ENE(+)
N3a	Metastasis in a lymph node larger than 6 cm in greatest dimension and ENE(−)
N3b	Metastasis in a single ipsilateral node larger than 3 cm in greatest dimension and ENE(+); **or** multiple ipsilateral, contralateral or bilateral nodes, any with ENE(+); **or** a single contralateral node 3 cm or smaller and ENE(+)

NOTE: A designation of "U" or "L" may be used for any N category to indicate metastasis above the lower border of the cricoid (U) or below the lower border of the cricoid (L).
Similarly, clinical and pathological ENE should be recorded as ENE(−) or ENE(+).

Distant metastasis (M)

Oropharynx (p16−) and hypopharynx

M category	M criteria
M0	No distant metastasis
M1	Distant metastasis

Prognostic stage groups

When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, 1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

TNM: tumor, node, metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control; ENE: extranodal extension.

Oropharyngeal p16(-) cancer - TNM stage groups

Prognostic stage groups			
When T is...	**And N is...**	**And M is...**	**Then the stage group is...**
Tis	N0	M0	0
T1	N0	M0	I
T2	N0	M0	II
T3	N0	M0	III
T1, T2, T3	N1	M0	III
T4a	N0, 1	M0	IVA
T1, T2, T3, T4a	N2	M0	IVA
Any T	N3	M0	IVB
T4b	Any N	M0	IVB
Any T	Any N	M1	IVC

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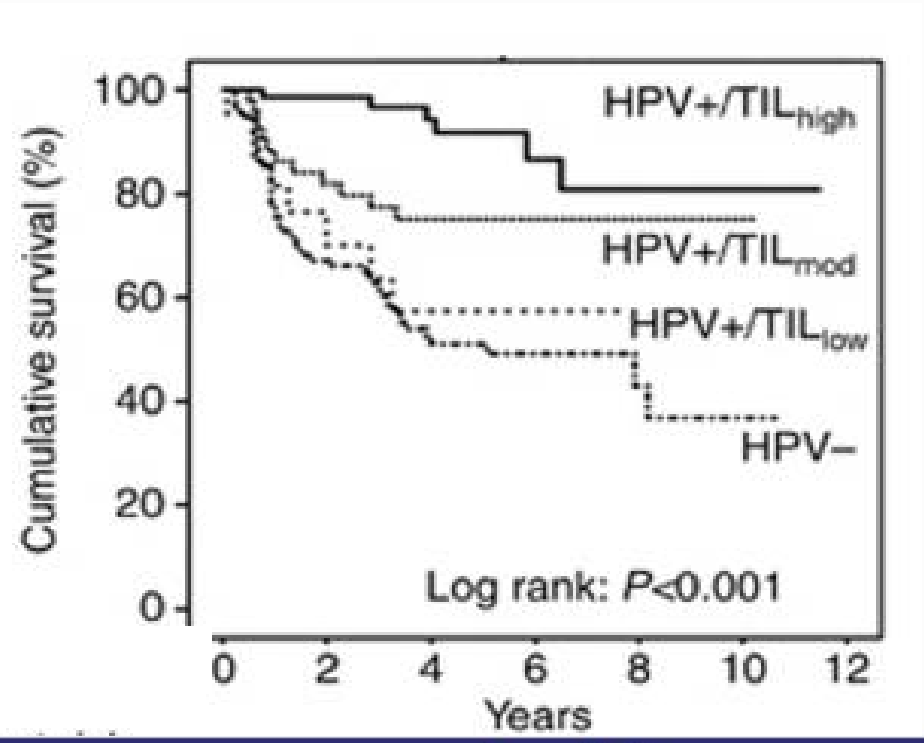
Oropharngeal Ca outcomes

- HPV(+) Stage I: [1 or T2 primary tumor, either N0 or N1 nodal disease, M0]
  - The five-year survival rate was 85-88%
- HPV(+) Stage II: [T3 primary, N0 to N2 nodal involvement, or T1/T2 primary and N2 lymph node disease]
  - The five-year survival rate was 78-81%
- HPV(+) Stage III: [T4 primary tumor, regardless of nodal status, or N3 nodal involvement, regardless of size of the primary tumor]
  - The five-year survival rate was 53-65%
- For patients with HPV negative disease, prognosis worsened with increasing stage of disease.
  - The five-year overall survival rates for stage I, II, III, IVA, and IVB were 76, 68, 53, 45, and 34 percent

Other Factors in Oropharyngeal Cancer Prognosis

- In those HPV(+), tobacco use and presence of tumor-infiltrating lymphocytes are additional predictors of survival



Oropharyngeal cancer - Male age 54

- Tonsil cancer excised 5 years ago
  - pT1: 1.5 cm right tonsil
  - pN2b: 3 of 41 nodes (+) right neck, largest 5 cm → now N1 if HPV+!
  - cM0: No evidence of mets
- Followed by radiation treatment over 40 days
- No evident disease since with close follow-up

Additional information needed?

- HPV 16(+), never tobacco user, EtOH 2/week

Stage?

- Stage III when diagnosed, but now T1N1M0 = Stage I

Insurability?

- Probably, with a TE to cover the ongoing risk

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COLORECTAL CANCER

Photo by National Cancer Institute

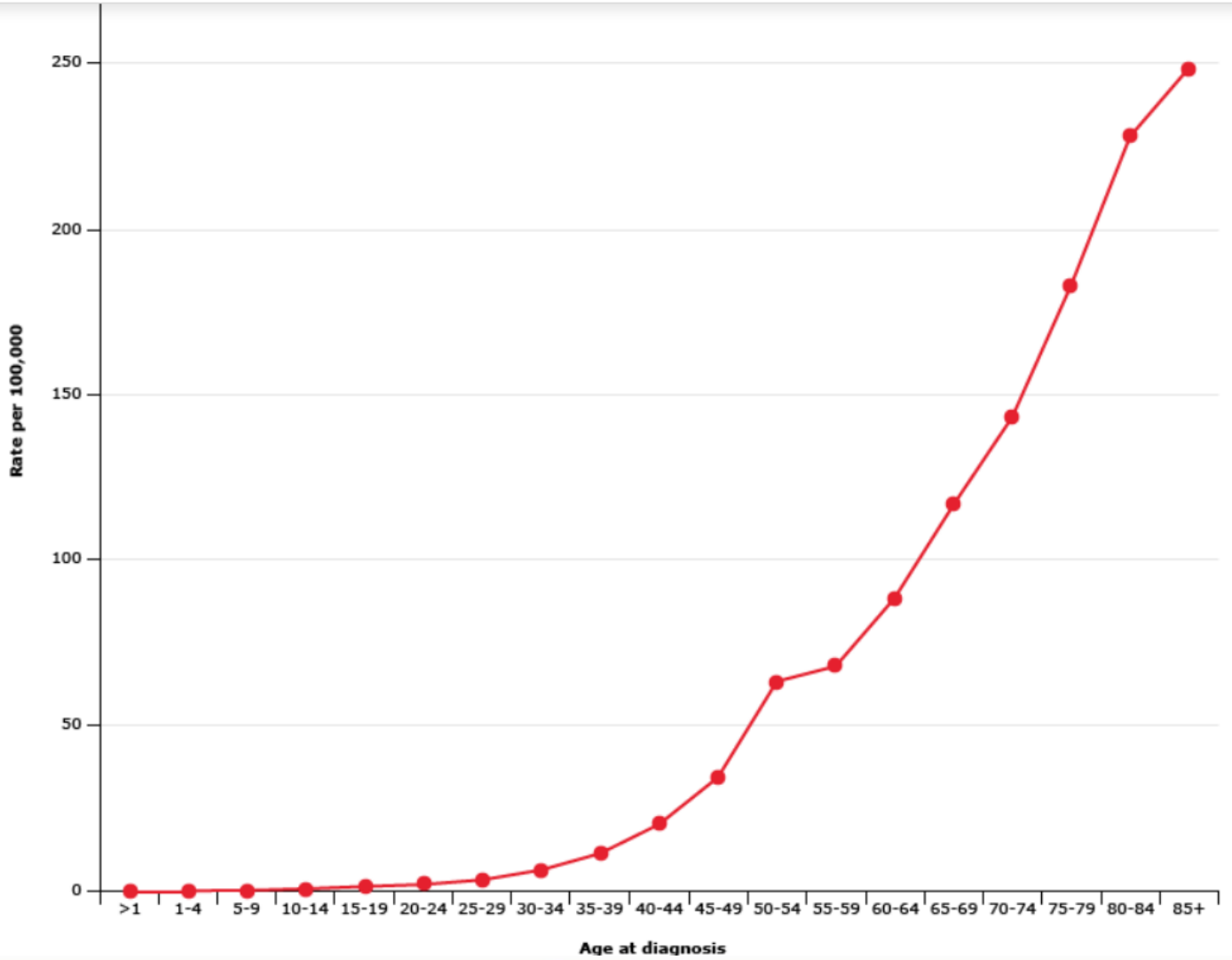
Colorectal Cancer

- Introduction with epidemiology
- The way I approach these cases
- An Actual Case for discussion
- A little lagniappe…
  - something given as a bonus or extra gift

Colorectal Cancer (CRC)

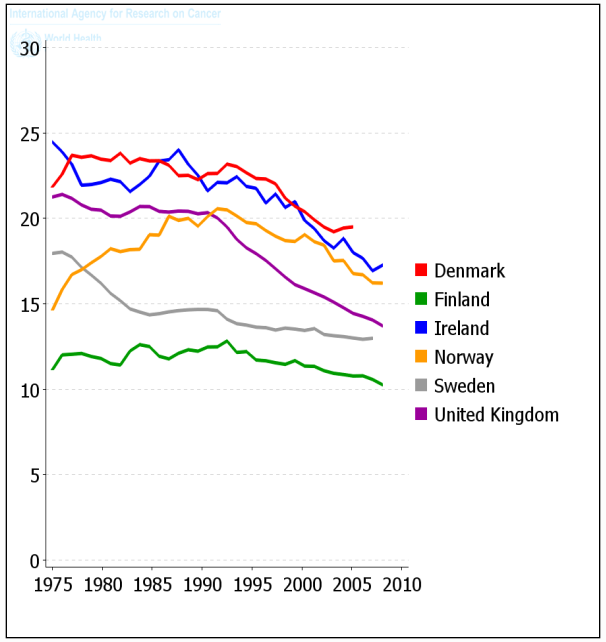
- Approximately 151,000 new cases of CRC diagnosed each year in U.S. – this has been decreasing by about 2-3% per year (1)
  - 4th most common cancer diagnosed (prostate, breast, lung)
- Approximately 52,580 deaths each year from CRC
  - 4th most common cause of death due to cancer per CDC data from 2019
- Globally it is the 3rd most commonly diagnosed cancer in males and the 2nd in females

Increasing incidence of colorectal cancer in the United States with age, SEER 2014 to 2018

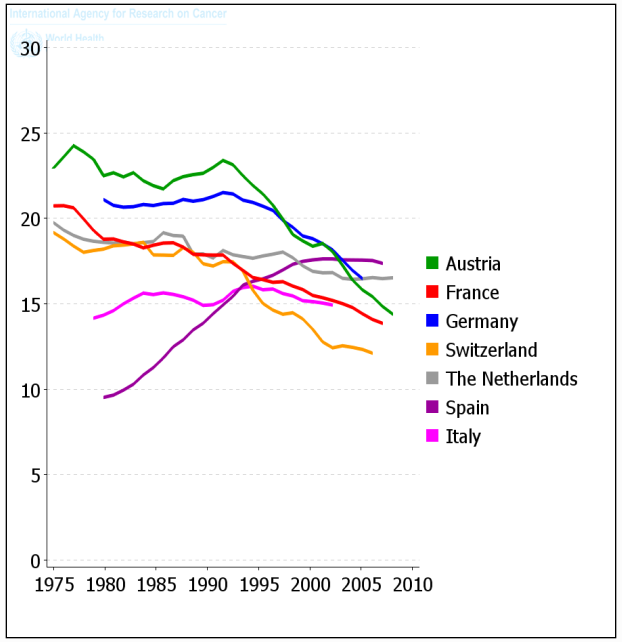


Trends in mortality from colorectal cancer

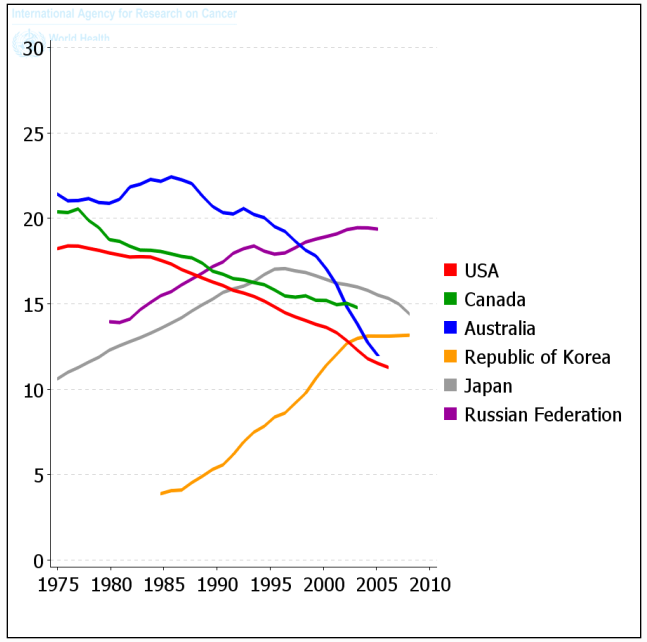
Age-standardized rate per 100,000, men



WHO (www.who.int/gho)

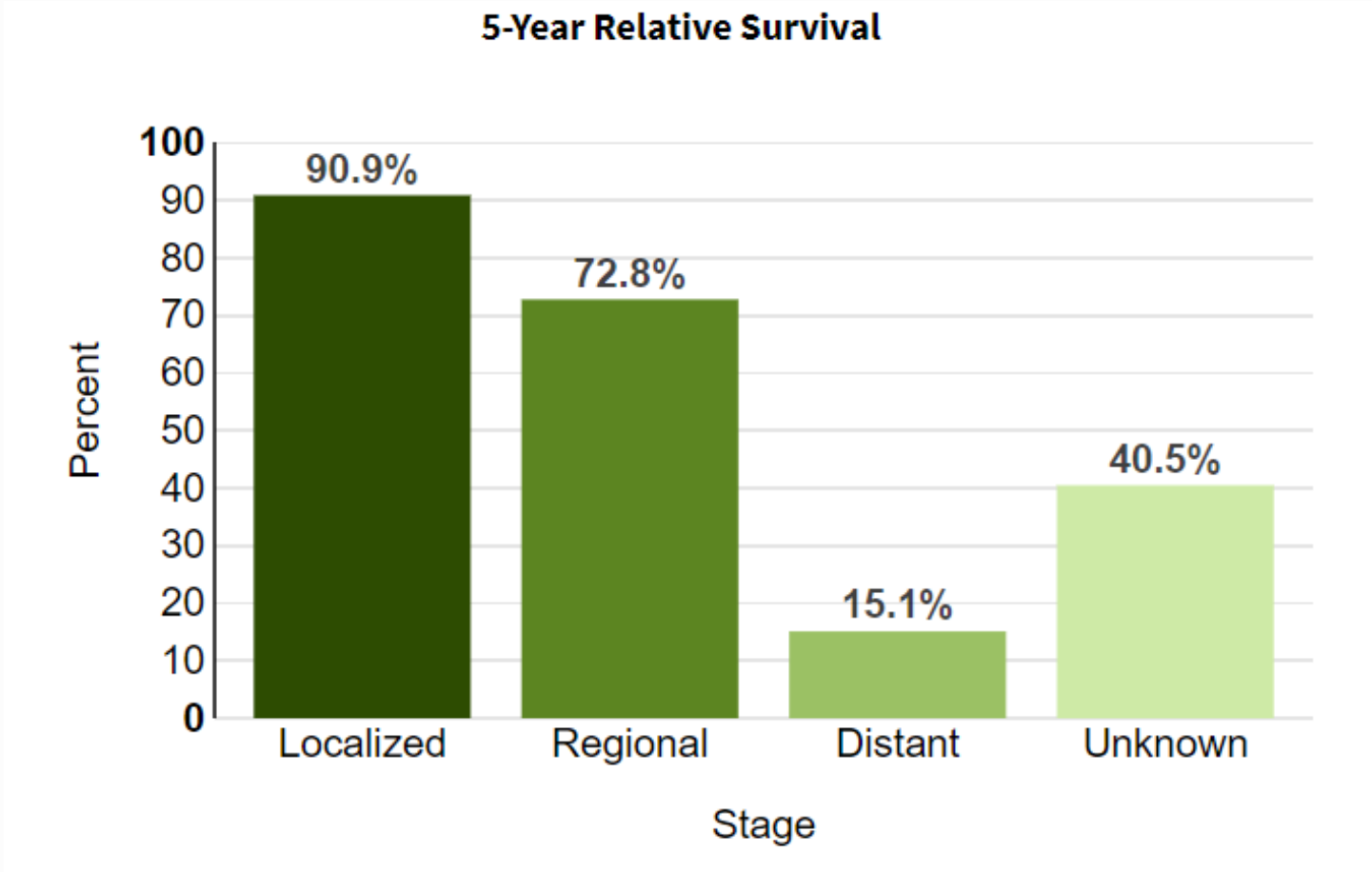


WHO (www.who.int/gho)



WHO (www.who.int/gho)

5 years Survival by Stage, SEER



Nomogram to predict survival

- https://www.mskcc.org/nomograms
- Includes nomograms for multiple cancers—not strictly validate But approved by AJCC

Risk Factors for Colorectal Cancer

- FAP (familial adenomatous polyposis)
- MAP (MUTYH-associated polyposis)
- Lynch Syndrome (hereditary non-polyposis colon cancer -- HNPCC)
- Serrated polyposis syndrome
- Advanced age
  - Risk doubles with each decade after 40
  - 90% occur after age 50 (though this is decreasing)
- Country of birth (10x higher in N. America than Africa)
- Ulcerative Colitis
  - 5-15x risk if pancolitis
  - 3x risk if left-sided only
- Abdominal radiation
- History of CRC (1.5 to 3% new cancers within 5 years)
- Family history of CRC (2x risk if first degree relative)
- History of colon polyps, especially if large, villous component, or high-grade dysplasia
- Obesity (1.5x risk compared to BMI 18-25)
- Alcohol (RR 1.2 if 2-3 drinks/day; 1.5x risk if $\geq$ 4 drinks/day)
- Diet high in red meat, low in fruits/vegetables/calcium/fiber/fish oil/garlic
- Smoking (1.2x risk)
- Diabetes, Acromegaly, and Renal transplant recipients
- Lack of exercise
- Not on ASA or an NSAID (20-40% reduction with “regular” use)

Colon Polyps and Cancer Risk

- History of villous or adenomatous polyp >1cm = 3.5-6.5 x risk
- Serrated Adenomas
  - Flatter and more difficult to visualize endoscopically and likely impossible to see with virtual colonoscopy
  - Carry BRAF mutations and have microsatellite instability and greater concern for HNPCC

Screening recommendations courtesy of USPSTF

Population	Recommendation	Grade
Adults aged 50 to 75 years	The USPSTF recommends screening for colorectal cancer starting at age 50 years and continuing until age 75 years.	A
Adults aged 45 to 49 years	The USPSTF recommends screening for colorectal cancer in adults aged 45 to 49 years.	B
Adults aged 76 to 85 years	The USPSTF recommends that clinicians selectively offer screening for colorectal cancer in adults aged 76 to 85 years. Evidence indicates that the net benefit of screening all persons in this age group is small.	C

How do we screen

- The guidelines support the following screening options:
- Colonoscopy
- Fecal immunochemical testing (FIT) for occult blood
- Sigmoidoscopy plus FIT
- Computed tomography colonography (CTC)
- FIT-DNA multitargeted stool DNA testing (MT-sDNA, also known as fecal immunochemical testing-DNA)
- Guaiac-based fecal occult blood testing (gFOBT)
- Sigmoidoscopy alone

What about those at High Risk?

- Personal history of CRC, Family history of CRC, Syndromic family history of CRC
- Screen earlier and with colonoscopy
- FAP—Proctocolectomy recommended
- HNPCC—every 1-2 years beginning at age 20-25 or 10 years younger than the youngest age at which a family member was diagnosed with CRC
- Endometrial, Ovarian, Gastric cancers—screen earlier

Diagnosis

- Symptoms and signs
  - Change in bowel habits (74%)
  - Rectal bleeding + change in bowel habits (71%)
  - Rectal mass (24.5%) or Abdominal mass (12.5%)
  - Iron Deficient anemia (9.6%)
  - Abdominal pain (3.8%)

Clinical assessment to determine the risk of bowel cancer using Symptoms, Age, Mass and Iron deficiency anaemia (SAMI). Thompson MR, O'Leary DP, Flashman K, Asiimwe A, Ellis BG, Senapati A Br J Surg. 2017;104(10):1393. Epub 2017 Jun 21.

Diagnosis

- Evaluation
  - CT scan of Chest, abdomen, and Pelvis
  - PET scanning in those with isolated Metastases to either liver or lung in whom resection of those lesions is planned
  - CEA
- T 1-4 Depth of Invasion
- N 0-2 Number of nodes
  - 1 1-3 nodes or peri-tumor seeding
  - 2 4+ nodes
- M 0-1
  - 1a one site or organ Without peritoneal
  - 1b two or more sites without peritoneal
  - 1c Peritoneal alone or with organ involvement

Diagnosis

Prognostic stage groups

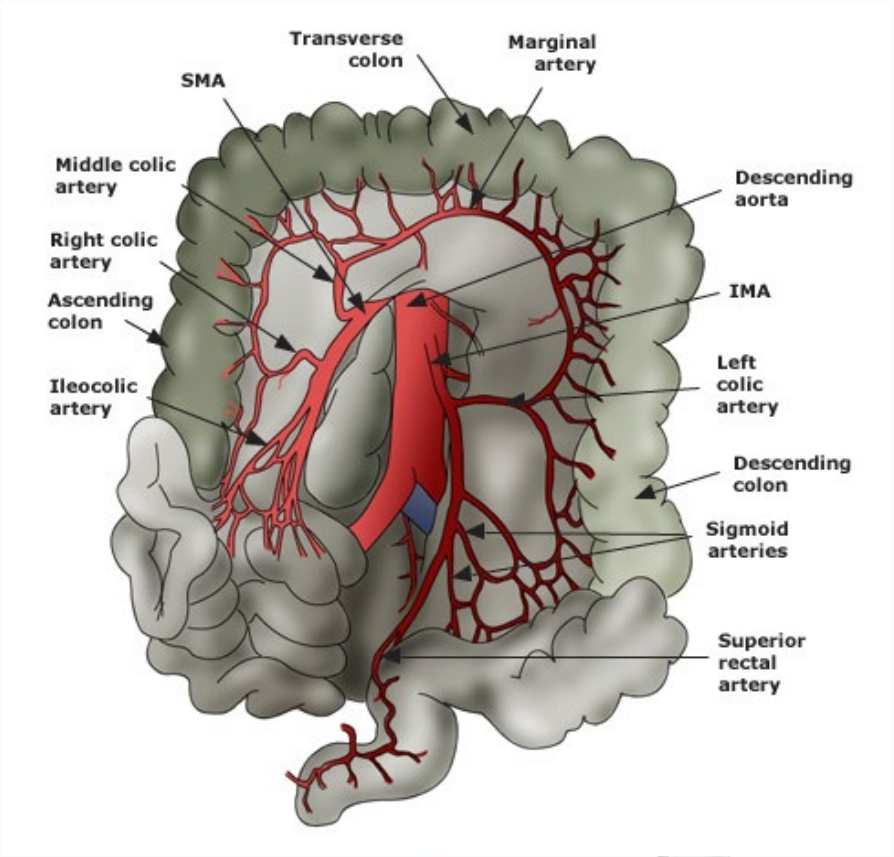
When T is...	And N is...	And M is...	Then the stage group is...
Tis	N0	M0	0
T1, T2	N0	M0	I
T3	N0	M0	IIA
T4a	N0	M0	IIB
T4b	N0	M0	IIC
T1-T2	N1/N1c	M0	IIIA
T1	N2a	M0	IIIA
T3-T4a	N1/N1c	M0	IIIB
T2-T3	N2a	M0	IIIB
T1-T2	N2b	M0	IIIB
T4a	N2a	M0	IIIC
T3-T4a	N2b	M0	IIIC
T4b	N1-N2	M0	IIIC
Any T	Any N	M1a	IVA
Any T	Any N	M1b	IVB
Any T	Any N	M1c	IVC

Diagnosis

- Less favorable tumor characteristics
  - Serosal involvement
  - No significant downstaging after neoadjuvant therapy (denoted yp)
    - Note that survival is more closely linked with post-neoadjuvant stage
  - the most important prognostic determinants for CRC are the Stage, presence of extramural tumor deposits, lymphovascular and perineural invasion, histologic grade of differentiation, the preoperative level of serum carcinoembryonic antigen (CEA), microsatellite instability (MSI), and *RAS* and *BRAF* mutations

Treatment

- To Cut is to Cure! Bring on the bright lights and cold steel…



Treatment

- Localized—Surgery alone
- Neoadjuvant chemotherapy + Radiation is most commonly employed in locally advanced Rectal Cancer
- Multivisceral excision is preferred in locally advanced colon cancer
- Adjuvant Chemotherapy in Stage III (node positive disease) is clearly beneficial with a 22-32% reduction in mortality

Surveillance

- Stage I—debatable whether any is needed
- Stage II-III—History and physical every 6 months with CEA; CT scanning yearly; Colonoscopy to detect metachronous tumors

CRC Case

54 y/o Male. Colon cancer diagnosed on screening colonoscopy 2 years prior to application.

- No Medical history
- Insurance exam and labs OK

Family history: colon cancer in father (deceased at 54); paternal grandmother deceased in her 40's due to an "Abdominal tumor"

Was screening appropriate?

CRC Case

- Screening recommendations with family history=10 years prior to diagnosis in youngest relative. 44 would likely have been better; 30's not unreasonable considering Grandma's "diagnosis"

CRC Case

A. RIGHT COLON (RESECTION):

INVASIVE ADENOCARCINOMA OF THE RIGHT COLON.

Histologic type: MUCINOUS ADENOCARCINOMA.

Histologic Grade: LOW GRADE.

Tumor size: 5.0 X 4.0 X 1.2 CM.

Extent of invasion: THE TUMOR FOCALLY INVADES INTO THE SUBSEROSAL SOFT TISSUE.

Macroscopic Tumor Perforation: NEGATIVE.

Margins:
Proximal NEGATIVE FOR TUMOR.
Distal NEGATIVE FOR TUMOR.
Mesenteric: NEGATIVE FOR TUMOR.
Closest Margin: MESENTERIC, 7.5 CM.

Lymphatic/vascular Invasion: NOT IDENTIFIED.
Perineural Invasion NOT IDENTIFIED.
Tumor Infiltrating Lymphocytes: NOT IDENTIFIED.
Marked Crohn's-like Lymphocytic Response: FOCALLY PRESENT.

Regional Lymph Nodes: TWENTY LYMPH NODES ARE NEGATIVE FOR TUMOR (0/20).
Tumor Deposits (discontinuous extramural extension): NOT IDENTIFIED.

Other Adenomas: NOT IDENTIFIED.
Appendix: NO PATHOLOGIC DIAGNOSIS.
Additional Findings: NONE.

CRC Case

- What are the favorable findings on the Pathology Report?
- Any unfavorable findings?
- Staging?
- What about Duke's stage?

CRC Case

- What are the favorable findings on Pathology Report?
  - Localized, low grade, no nodal metastases, crohn's like lymphocytic response
- What are the unfavorable findings?
  - Invades through serosa
- Staging?
  - T3N0Mx = Stage IIa
- But, what about Duke's staging?
  - FUGGID ABOUT IT!!!!

CRC Case

- Any additional prognostic information you would like to see?
- Any additional therapy needed?
- What type of surveillance would you expect?

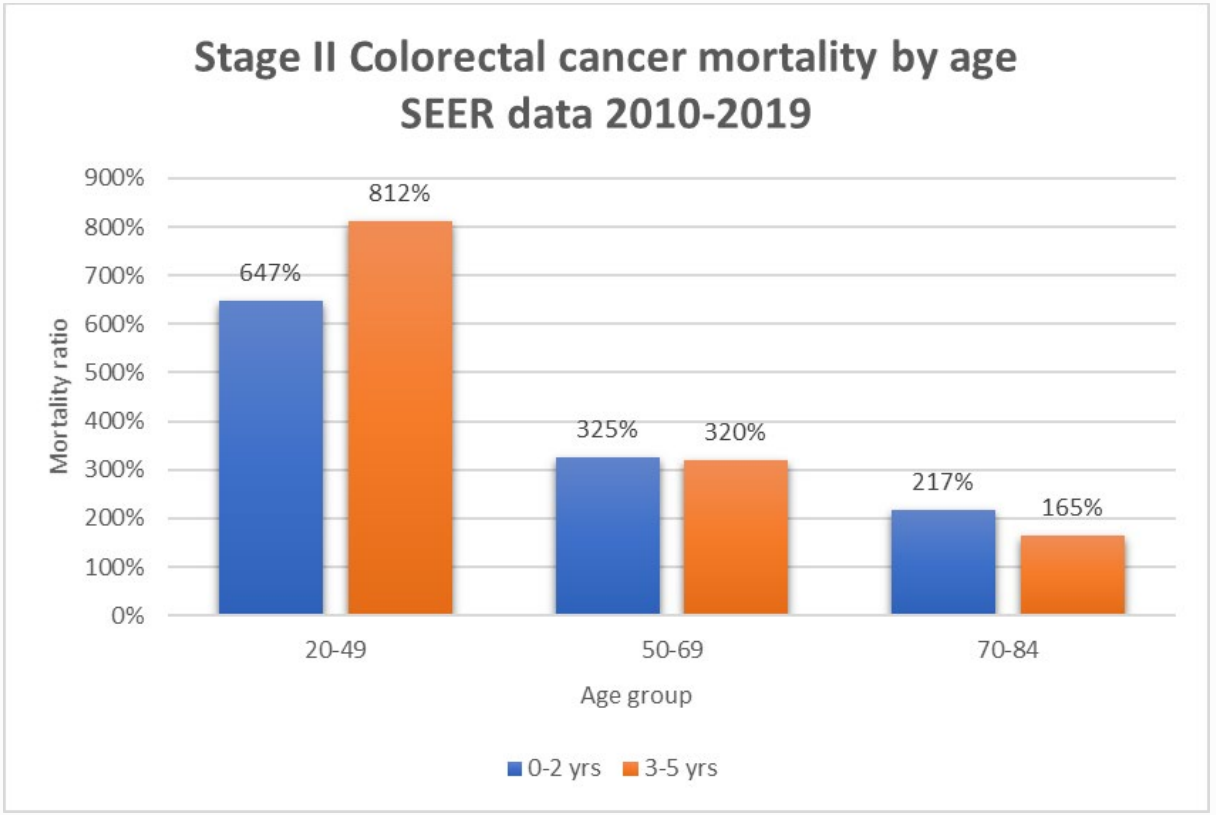
CRC Case

- LFT's normal, CEA 0.6, CT of Chest, Abdomen and Pelvis all normal.
- No chemotherapy is required—generally reserved for high grade tumors that breach the colon wall or metastasize to nodes; Consider ASA, Vitamin D, coffee, high fiber diet and exercise as Adjunctive therapies.
- Has had follow up every 6 months with normal history and physical examinations, CEA's have remained <1, and one repeat CT was normal except for postoperative changes.

CRC Case

- Insurable?
- Preferred? STD? Substandard?
- Concerns?

CRC - Excess Death Rate by Stage



Courtesy of Dr. Heltemes and SEER data

Nomogram to predict survival

- https://www.mskcc.org/nomograms
- Includes nomograms for multiple cancers—not strictly validate But approved by AJCC

Lagniappe: Prognostic factors

- Stage is the single most important factor but there are a few others:
  - Residual tumor after resection
  - Lymphovascular or perineural invasion
  - Poorly differentiated
  - Signet cell, adenosquamous, appendiceal cystadenocarcinoma
  - CEA >5.0 independent of tumor stage
  - Microsatellite instability (MSI)
  - No regression after neoadjuvant therapy
  - KRAS mutation
  - Irregular infiltrating tumor border (may predict liver mets)

Hereditary Colorectal Cancer Syndromes

- **Represent high risk for colorectal cancer when present, however <5% of CRC cases are due to these**
  - But present in approximately 2/3 of those with CRC before age 35
- **Familial adenomatous polyposis (FAP)**
  - Autosomal dominant inheritance, but 25% from de novo mutation
  - Characterized by ≥ 100 adenomas throughout the GI tract
  - Increased risk for desmoid tumors; cancers of the small intestine, thyroid, brain, ampulla, pancreas, and stomach; and hepatoblastoma.
  - Average age of symptom onset ~16 years
  - CRC occurs in 90% of untreated individuals by age 45
  - Attenuated form (20-99 adenomas) has an older average age of cancer diagnosis
- **MUTYH-associated polyposis (MAP)**
  - Autosomal recessive
  - Caused by biallelic mutations in the MUTYH gene
  - Clinical picture similar to attenuated FAP; CRC onset typically age 40s and 50s
- **Serrated polyposis syndrome (SPS)**
  - >2 sessile serrated adenomas/polyps (SSA/Ps) proximal to splenic flexure and ≥1 proximal SSA/P with high-grade dysplasia were independent CRC risk factors (OR=2)
- **Lynch syndrome**

Lynch Syndrome - Hereditary nonpolyposis colorectal cancer

- HNPCC mean age at initial cancer diagnosis is ~45 years
  - But few are before the age of 30, unlike FAP
- Autosomal dominant inheritance
- Lifetime risk of developing CRC is approximately 60%
- Approximately 10% will have synchronous cancers
- Extracolonic cancers are also common, including endometrial carcinoma in ~40% of female gene carriers
- Associated with serrated adenomas
  - Flatter and more difficult to visualize endoscopically
  - Characteristically with BRAF V600E mutations and microsatellite instability
- MMR (mismatch repair) gene testing in the youngest living member of the family with colorectal cancer is advised
- Cumulative cancer risk by age 70 for the three main mutations (95% of cases)[9]
  - 40-50% for MLH1 and MSH2
  - ~12% for MSH6
- Colonoscopy every one to two years beginning at age 20 to 25, or 10 years earlier than the youngest age of colon cancer diagnosis in the family (whichever comes first)

CEA

- Carcinoembryonic Antigen
  - Screening use is very limited as not very sensitive or specific
    - Non-cancer-related causes of an elevated CEA include gastritis, peptic ulcer disease, diverticulitis, liver disease, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammatory state
  - Independent prognostic marker in those with CRC:
    - Pre-op levels >5 portend a worse prognosis, stage for stage, than those with lower levels (HR ~1.6)
    - Node negative CRC with an elevated CEA fare worse than node positive disease with a normal CEA[15]
  - Also for monitoring for recurrence
    - See CRC follow-up

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