Solid Tumors Workshop

And much, much more

Brad Heltemes
John White III
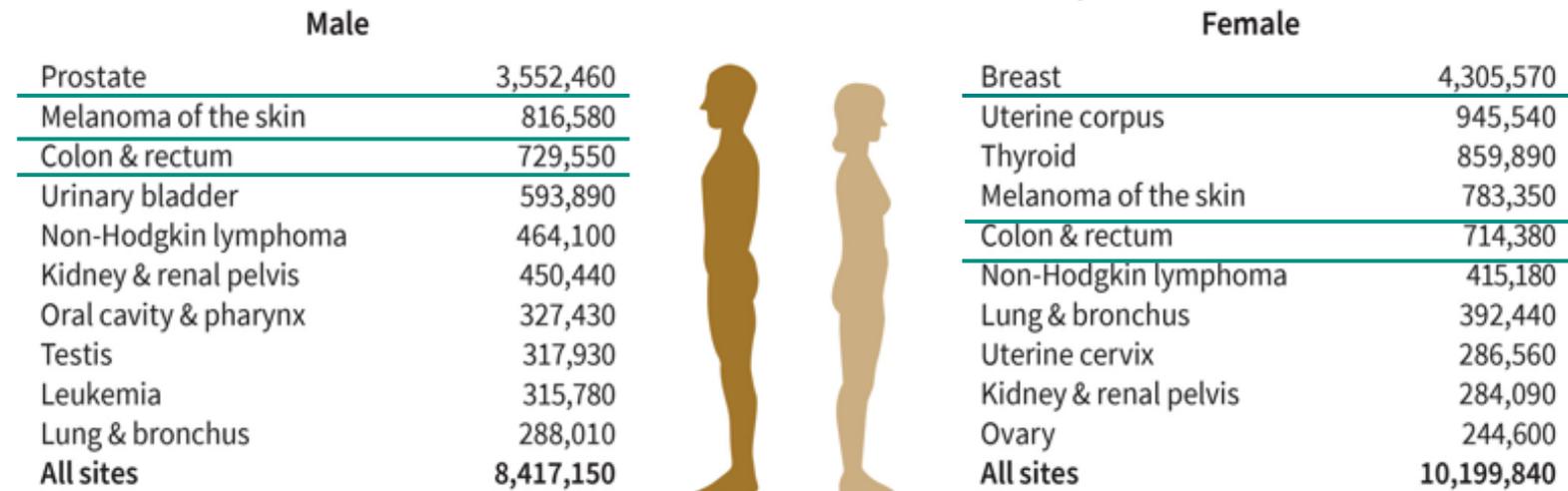
Estimated New Cancer Cases by Site; US 2025

Male

Site	Cases	%
Prostate	313,780	30%
Lung & bronchus	110,680	11%
Colon & rectum	82,460	8%
Urinary bladder	65,080	6%
Melanoma of the skin	60,550	6%
Kidney & renal pelvis	52,410	5%
Non-Hodgkin lymphoma	45,140	4%
Oral cavity & pharynx	42,500	4%
Leukemia	38,720	4%
Pancreas	34,950	3%
All sites	1,053,250	

Female

Site	Cases	%
Breast	316,950	32%
Lung & bronchus	115,970	12%
Colon & rectum	71,810	7%
Uterine corpus	69,120	7%
Melanoma of the skin	44,410	4%
Non-Hodgkin lymphoma	35,210	4%
Pancreas	32,490	3%
Thyroid	31,350	3%
Kidney & renal pelvis	28,570	3%
Leukemia	28,170	3%
All sites	988,660	

Estimated New Cases

Estimated US Cancer Survivors by Site; US 2025

Male

Site	Survivors
Prostate	3,552,460
Melanoma of the skin	816,580
Colon & rectum	729,550
Urinary bladder	593,890
Non-Hodgkin lymphoma	464,100
Kidney & renal pelvis	450,440
Oral cavity & pharynx	327,430
Testis	317,930
Leukemia	315,780
Lung & bronchus	288,010
All sites	8,417,150

Female

Site	Survivors
Breast	4,305,570
Uterine corpus	945,540
Thyroid	859,890
Melanoma of the skin	783,350
Colon & rectum	714,380
Non-Hodgkin lymphoma	415,180
Lung & bronchus	392,440
Uterine cervix	286,560
Kidney & renal pelvis	284,090
Ovary	244,600
All sites	10,199,840

Siegel, RL., et al. "Cancer statistics, 2025." Ca 75.1 (2025): 10. doi.org/10.3322/caac.21871
Wagle, NS, et al. "Cancer treatment and survivorship statistics, 2025." CA: A Cancer Journal for Clinicians (2025).

Figure 3. Leading Sites of New Cancer Cases and Deaths – 2025 Estimates

Estimated New Cases

Male				Female		
Prostate	313,780	30%		Breast	316,950	32%
Lung & bronchus	110,680	11%		Lung & bronchus	115,970	12%
Colon & rectum	82,460	8%		Colon & rectum	71,810	7%
Urinary bladder	65,080	6%		Uterine corpus	69,120	7%
Melanoma of the skin	60,550	6%		Melanoma of the skin	44,410	4%
Kidney & renal pelvis	52,410	5%		Non-Hodgkin lymphoma	35,210	4%
Non-Hodgkin lymphoma	45,140	4%		Pancreas	32,490	3%
Oral cavity & pharynx	42,500	4%		Thyroid	31,350	3%
Leukemia	38,720	4%		Kidney & renal pelvis	28,570	3%
Pancreas	34,950	3%		Leukemia	28,170	3%
All sites	**1,053,250**			**All sites**	**988,660**	

Estimated Deaths

Male				Female		
Lung & bronchus	64,190	20%		Lung & bronchus	60,540	21%
Prostate	35,770	11%		Breast	42,170	14%
Colon & rectum	28,900	9%		Pancreas	24,930	8%
Pancreas	27,050	8%		Colon & rectum	24,000	8%
Liver & intrahepatic bile duct	19,250	6%		Uterine corpus	13,860	5%
Leukemia	13,500	4%		Ovary	12,730	4%
Esophagus	12,940	4%		Liver & intrahepatic bile duct	10,840	4%
Urinary bladder	12,640	4%		Leukemia	10,040	3%
Non-Hodgkin lymphoma	11,060	3%		Non-Hodgkin lymphoma	8,330	3%
Brain & other nervous system	10,170	3%		Brain & other nervous system	8,160	3%
All sites	**323,900**			**All sites**	**294,220**	

Estimates exclude US territories and are rounded to the nearest 10; cases exclude basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder. Ranking is based on modeled projections and may differ from observed data.
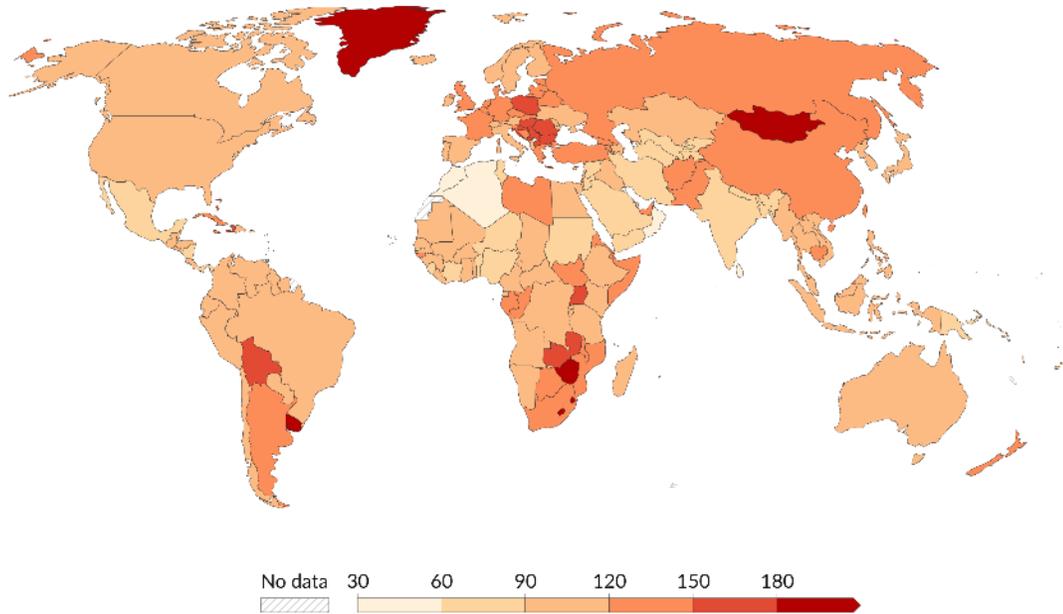
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Cancer: A global phenomenon

Death rate from cancer, 2021
Estimated annual number of deaths from all types of cancer[1] per 100,000 people.

No data | 30 | 60 | 90 | 120 | 150 | 180

Data source: IHME, Global Burden of Disease (2024)

OurWorldinData.org/cancer | CC BY

Note: To allow for comparisons between countries and over time, this metric is age-standardized[2].

1. **Cancer** Cancer describes a group of diseases in which abnormal cells in the body begin to grow and multiply uncontrollably. These cells can form lumps of tissue called tumors, which can interfere with normal bodily functions.
Cancerous cells have the potential to spread to other parts of the body (this process is called "metastasis"), disrupting normal processes and causing serious health problems.

2. **Age standardization** Age standardization is an adjustment that makes it possible to compare populations with different age structures, by standardizing them to a common reference population.
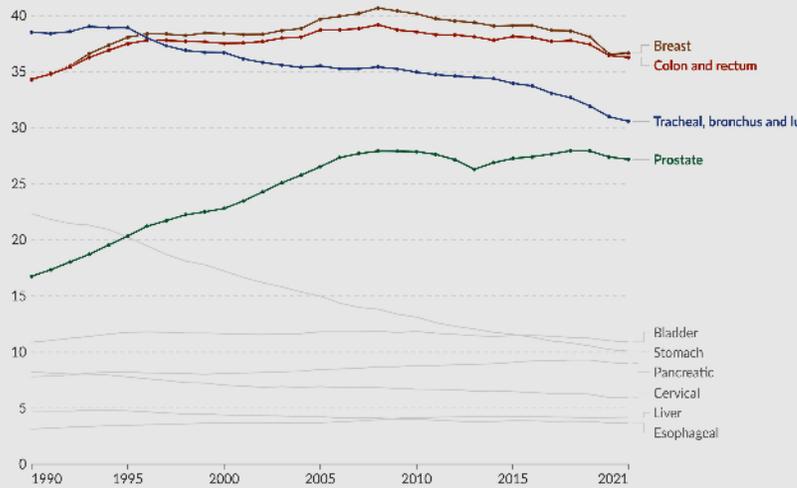Read more: How does age standardization make health metrics comparable?

Death rate from cancer, 1980 to 2021
Estimated annual number of deaths from all types of cancer[1] per 100,000 people.

Mongolia
China
Germany
United States
World
Brazil
India

1980 1985 1990 1995 2000 2005 2010 2015 2021

Data source: IHME, Global Burden of Disease (2024)

OurWorldinData.org/cancer | CC BY

Note: To allow for comparisons between countries and over time, this metric is age-standardized[2].
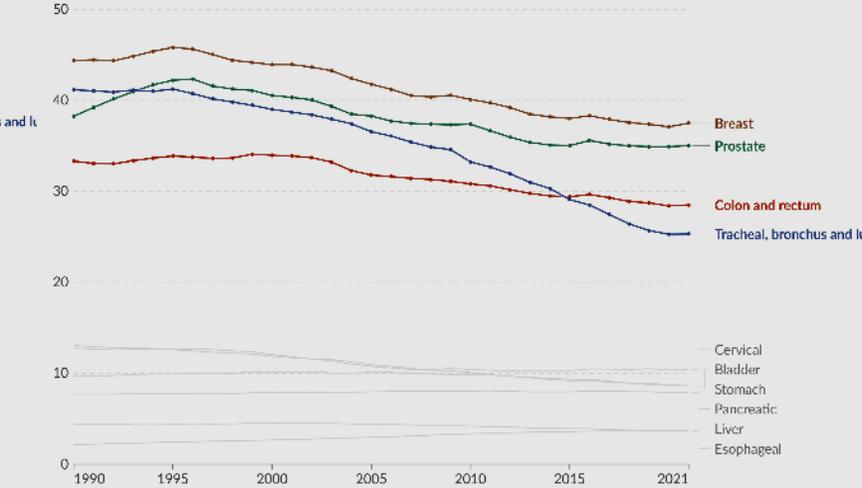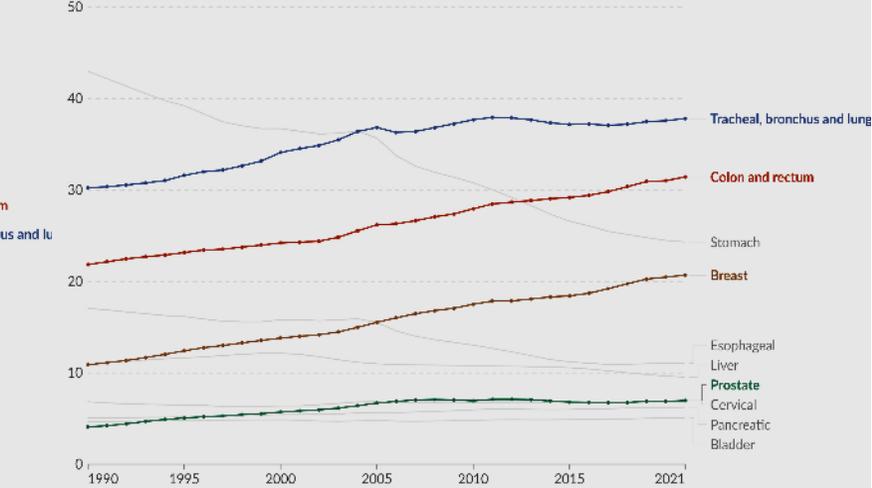
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Read more: How does age standardization make health metrics comparable?

Regional cancer incidence rates (per 100,000 people)

https://ourworldindata.org/cancer#all-charts

Cancer underwriting questions

Diagnosis:

- Accurate and Adequate?

Treatment:

- Appropriate? Completed?
- Anything else needed?

Surveillance:

- Appropriate follow-up for recurrence - imaging, labs including tumor markers, liquid biopsy?
- Assessment of treatment risk and second malignancy?
- Anything else not required, but useful?

These then inform → Conditional survival:

- Impact of age, prognostic factors, treatment, and follow-up?
- Insurable at what point (and with what terms)?

PROSTATE CANCER

Photo by Clay Banks on Unsplash

Prostate Cancer in the U.S.

Prevalence in 2025 - estimated 3,552,460 men living with prostate cancer in the U.S.
- 43% of all male cancer survivors
- ~2% of the entire male population

About 1 in 9 men will be diagnosed with prostate cancer during their lifetime
- Yet at least 1/2 of men over age 40 will <u>develop</u> prostate cancer

The overall prostate cancer specific 5-year survival rate ~99%

Despite these high 5-year survival rates, outcomes are variable

- 100% survival in organ-confined disease

- 34% survival with advanced disease

➢ The challenge:

➢ Identify the high-risk cases and not the indolent cancers

10/29/2025

- Prostate cancer death rate 18.8/100k

- Rates have been improving since 1992

  ➢ Earlier diagnosis

  ➢ Improved management

  ➢ Advances in treatment

Trends in death rates, 1930-2019
by sex, for prostate

● Male

Data sources: National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention, 2021

Diagnosis, not development

- Median age at diagnosis 67

- Median age at death 79

- From 2007-2013, the incidence of early-stage disease decreased in men aged >50

- In 2018 compared with 2011, the incidence of metastatic cancer in men of all ages (and especially for ages ≥75) increased, by ~6.5% annually

Probability of developing cancer, 2016-2018
undefined, for prostate

0–49 years

0.2%

50–59 years

1.8%

60–69 years

5.1%

70+ years

9%

© 2022 American Cancer Society   CancerStatisticsCenter.cancer.org

Preliminary Estimates (Selected Registries 2000-2023): Prostate / Male
Delay: 3 Joinpoints versus Non-Delay: 2 Joinpoints#

Legend:
- ■ Delay
- 2000-2004 APC = -4.1*
- 2004-2007 APC = 3.5
- 2007-2014 APC = -6.1*
- 2014-2023 APC = 3.0*
- • Non-Delay
- 2000-2009 APC = -1.3
- 2009-2014 APC = -6.5*
- 2014-2023 APC = 2.3*

* Indicates that the Annual Percent Change (APC) is significantly different from zero at the alpha = 0.05 level.
# The following Observed Y Value was excluded from the model fitting: 2020
Final Selected Model: Delay - 3 Joinpoints, Non-Delay - 2 Joinpoints.

After years of declining rates, increase in prostate cancer mortality rates in the last 10 years
- Related to declines in screening??

PSA/Prostate Cancer Case #1

59 year-old man; 5'8" 173# $1500k

- Insurance lab PSA 5.4 ng/mL (lab otherwise unremarkable)

  ➢ Rate for lab results?

  ➢ What is the likelihood of having prostate cancer?

  ➢ What is the risk *if has* prostate cancer?

  Clinically significant prostate cancer (csPCa)

  Likelihood of prostate cancer, depending on source, 25-50%

  - ~20% low-grade

  - 5-25% csPCa

Underwriting Assessment

➢ What is the risk *if has* prostate cancer?

Clinically significant prostate cancer (csPCa)

➢ What else can help determine that risk?

Risk depends on:

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

- Age, family history, digital rectal exam (DRE), symptoms

- Other biomarkers (eg PCA3, PHI, 4K score, ExoDx Prostate)

- Transrectal Ultrasound, mpMRI

- Any prior biopsy results

PSA 5.4 ng/mL

APS:

- History of Adult ADHD, Hyperlipidemia. Non-smoker. Father died of heart disease age 80.

- PSA 3 years ago 5.2, repeat was 3.5. Normal DRE.

- PSA one year ago 4.1.

➢ How does that change your assessment?
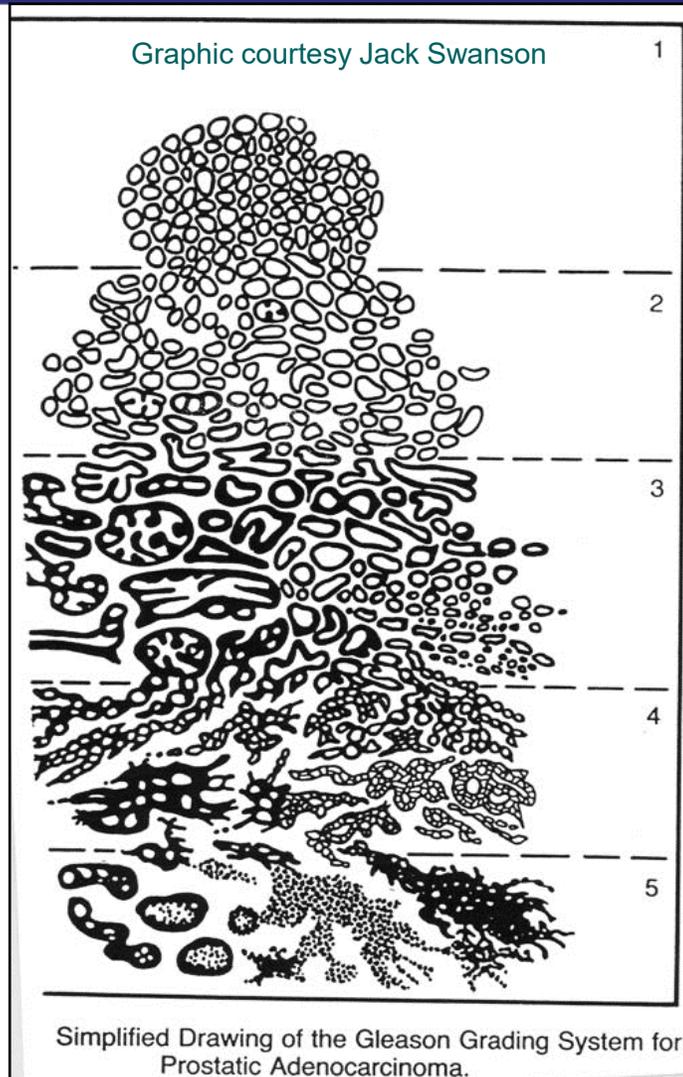
Urology evaluation:

- Normal DRE, no symptoms

- Repeat PSA 5.4, PHI 35

- Biopsy advised

- Plan for Active Surveillance

  ➢ AS appropriate?

  ➢ Cancer stage?

  ➢ Mortality risk with GG 1 PCa?

  ➢ Offer?

DIAGNOSIS:
A. Right Apex Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 10 % of the specimen (1 of 2 core(s) positive).
        Grade Group 1. Ends not involved by the tumor.
B. Right Mid Needle biopsy
C. Right Base Needle biopsy
        Benign prostatic tissue.
D. Right Lateral Apex Needle biopsy
        Benign prostatic tissue.
E. Right Lateral Mid Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 5 % of the specimen (1 of 1 core(s) positive).
        Grade Group 1. Ends not involved by the tumor.
F. Right Lateral Base Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 10 % of the specimen (1 of 1 core(s) positive).
        Grade Group 1. Ends not involved by the tumor.
G. Left Apex Needle biopsy
        Benign prostatic tissue.
H. Left Mid Needle biopsy
        Benign prostatic tissue.
I. Left Base Needle biopsy
        Benign prostatic tissue.
J. Left Lateral Apex Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 40 % of the specimen, discontinuous (1 of 1 core(s) positive).
        Grade Group 1. Ends not involved by the tumor.
K. Left Lateral Mid Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 70 % of the specimen, discontinuous (1 of 1 core(s) positive).
        Grade Group 1. Tumor involves one end.
L. Left Lateral Base Needle biopsy
    ADENOCARCINOMA, GLEASON SCORE 3 + 3 = 6 involving 20 % of the specimen, discontinuous (1 of 1 core(s) positive).
        Grade Group 1. Ends not involved by the tumor.

Graphic courtesy Jack Swanson

Simplified Drawing of the Gleason Grading System for Prostatic Adenocarcinoma.

1: Small uniform glands

2: More stroma between glands

3: Distinctly infiltrative margins

4: Irregular masses of neoplastic cells

5: Anaplastic - only occasional gland formation

Gleason score:
Derived by adding 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!

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
GG V:	Gleason score 4+5=9 or 5+5=10

➤ Prior patterns 1 and 2 no longer considered to be cancer (but may represent increased risk?)

➤ 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

➤ Tertiary grade still matters!

Prostate cancer stage groups – AJCC 8ᵗʰ Edition

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')
- 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

Stage	T	N	M	Grade group	PSA
I	cT1a-c, T2a 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

Risk Level With Newly Diagnosed Prostate Cancer

➢ **Very low risk disease**

- ▪ T1c, GG 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, GG 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 GG 2 or 3

→ Active surveillance (AS) usually recommended

→ Consider AS; or Prostatectomy or Radiation if preferred

→ Prostatectomy or Radiation, but AS can be considered

Risk stratification schema for localized prostate cancer, according to the National Comprehensive Cancer Network (NCCN)

Risk group	Clinical/pathologic features
Very low	- T1c AND - Grade group 1 AND - PSA <10 ng/mL AND - Fewer than 3 prostate biopsy fragments/cores positive, ≤50% cancer in each fragment/core AND - PSA density <0.15 ng/mL/g
Low	- T1 to T2a AND - Grade group 1 AND - PSA <10 ng/mL AND - Does not qualify for very low risk
Favorable intermediate	- No high or very high risk features - No more than one intermediate risk factor: - T2b to T2c OR - Grade group 2 or 3 - PSA 10 to 20 ng/mL AND - Grade group 1 or 2 AND - Percentage of positive biopsy cores <50%
Unfavorable intermediate	- No high or very high risk features - Two or three of the intermediate risk factors: - T2b to T2c - Grade group 2 or 3 - PSA 10 to 20 ng/mL AND/OR - Grade group 3 AND/OR ≥50% of positive biopsy cores
High	- No very high risk features AND - T3a OR - Grade group 4 or 5 OR - PSA >20 ng/mL
Very high	- T3b to T4 OR - Primary Gleason pattern 5 OR - Two or three high-risk features OR >4 cores with Grade group 4 or 5

PSA: prostate-specific antigen.

Adapted from: NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®): Prostate Cancer. Version 1.2023.

UpToDate®

October 18-23, 2025
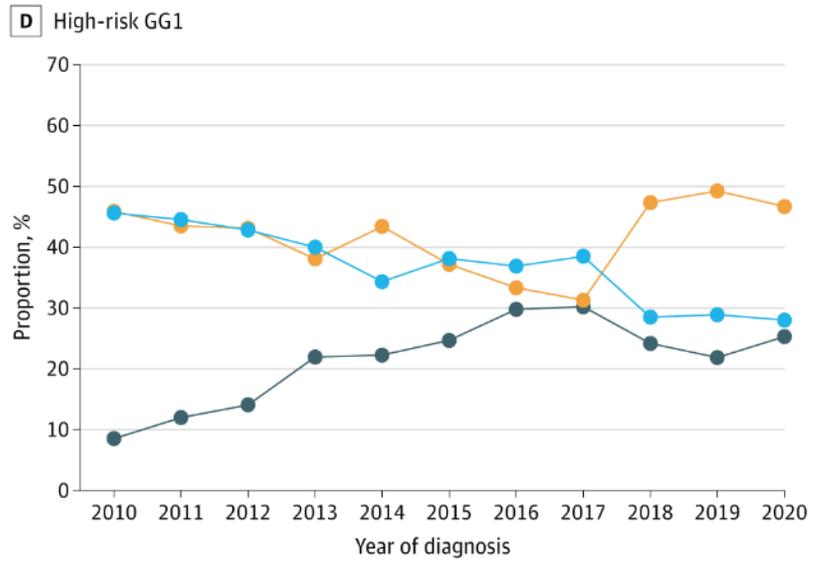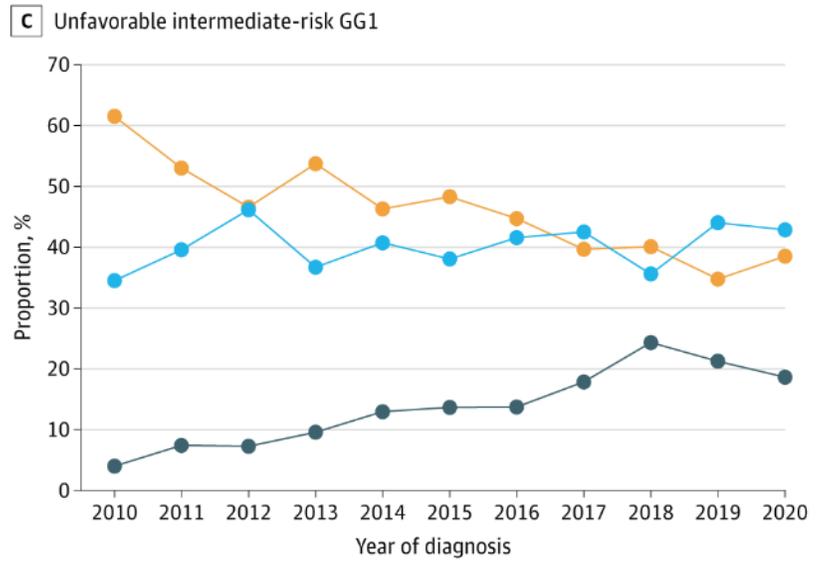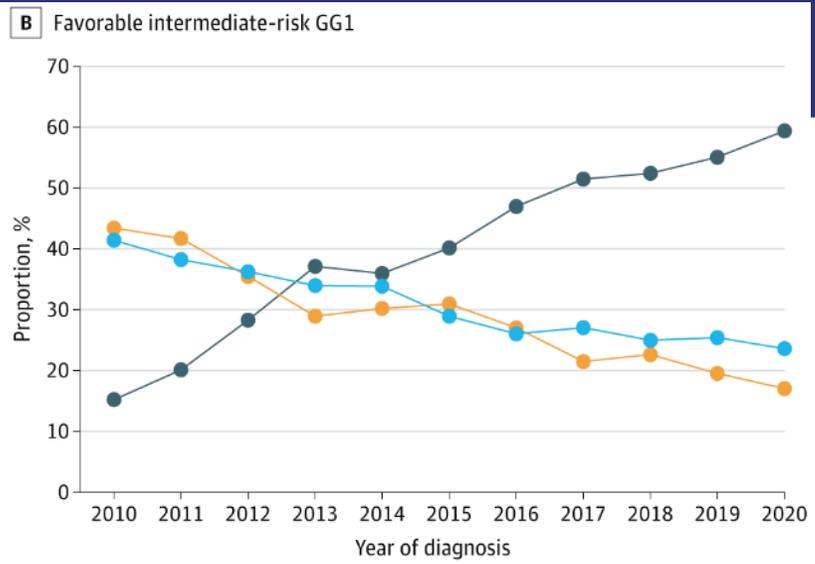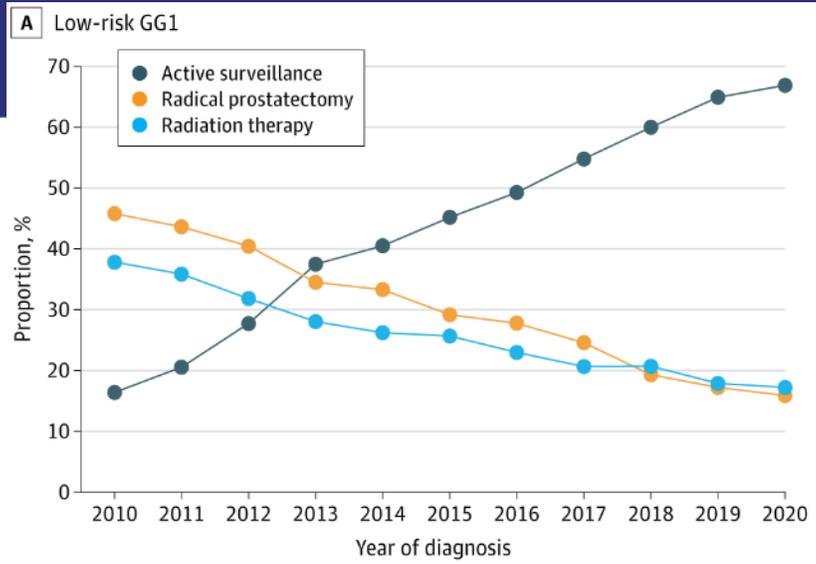
- Trends in use of Active Surveillance for GG1 prostate cancer between 2010 and 2020

Case #1 59 yo man with GG 1 prostate cancer

PSA 5.4, normal DRE, no symptoms

GG 1 Prostate cancer in 6 of 12 biopsy cores

Undergoing Active Surveillance

- ➢ Mortality risk with GG 1 PCa?

- ➢ Offer?

Prostate Cancer Survival Rates by Stage

Relative survival of men with prostate cancer, 5 and 10 years after

Stage	5-Year	10-Year
Localized	100.0	100
Regional	98.6	96.1
Distant	30.7	18.5

Percent of Cases by Stage

- Localized (73%) — Confined to Primary Site
- Regional (14%) — Spread to Regional Lymph Nodes
- Distant (7%) — Cancer Has Metastasized
- Unknown (6%) — Unstaged
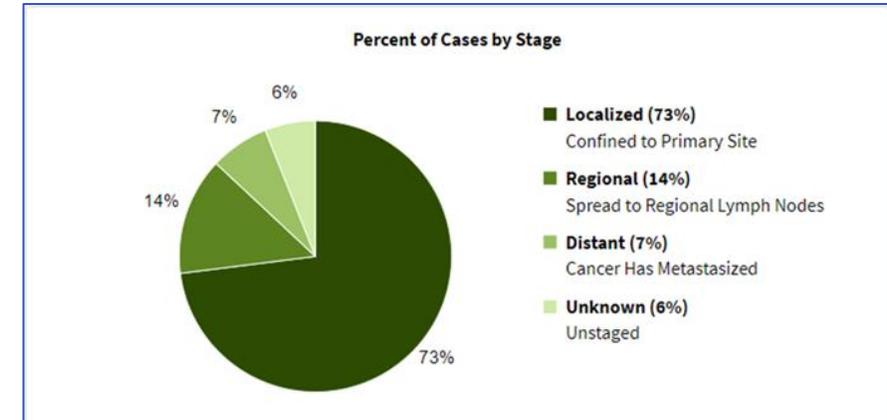
Caveats:
- Most in this era received definitive treatment
- Even 10-year survival rates don't tell the whole story with early-stage prostate cancer!

Survival rates by AJCC Stage Group

AJCC 8th Edition Stage Group	5-Year Survival (%)	15-Year Survival (%)
I	>99	~95–97
II (IIA, IIB, IIC)	>99	~93–96
III (IIIA, IIIB, IIIC)	>99	~85–92
IVA (N1, M0)	~96–99	~75–85
IVB (M1)	~32	<5

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

PASS Cohort
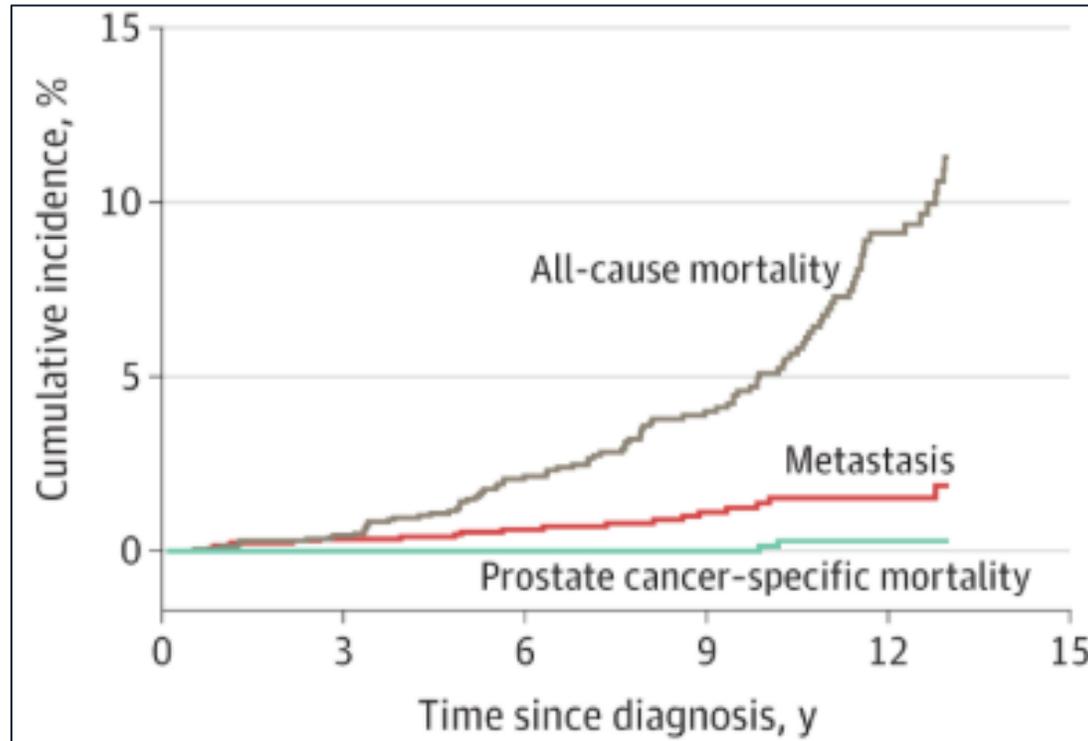
GÖTEBORG-1 screening trial
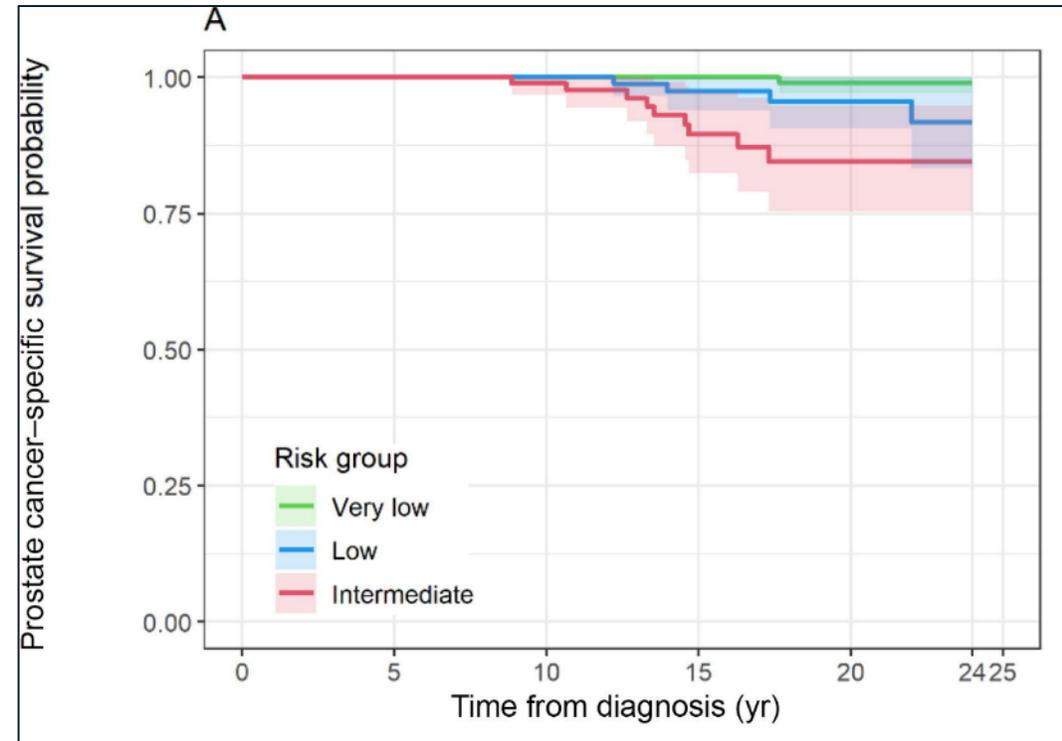
- OK to consider prostate cancer-specific rather than all-cause mortality?

Active Surveillance follow-up strategy

No single widely accepted AS monitoring strategy…

- PSA every 6 months
  - Reassess if PSA doubling time of <3 years or a rise of PSA >10 to 15 ng/mL
- DRE yearly
- Repeat biopsy after 6 to 18 months (MRI-targeted if feasible)
  - Thereafter as needed with changes
  - mpMRI an alternative to repeat biopsy – then biopsy if MRI evidence of growth or a PI-RADs increase
- Definitive treatment usually advised if:
  - Progression to a higher-grade disease
  - New abnormalities on DRE or imaging suggestive of extracapsular extension
  - Serial, confirmed rises in PSA

Issues with Active Surveillance

- Most who progress do so within the first two years (undersampling error??), but the risk continues to accrue with ongoing surveillance

- With limited biopsy sampling, can miss high grades

  - Upgrade Gleason score after radical prostatectomy ~30%

  - In PASS cohort, upgrade rate of 23% at confirmatory biopsy and 43% at 10 years

  - However…

  - Recent data, in the era of MRI targeted biopsies, suggest a 10-15% upgrade rate

Case #1.5 - A now 62 year-old man …

At age 59:

- Urology evaluation normal DRE, volume est. 40cc
- Repeat PSA 5.4, PHI 35. 12-core biopsy obtained.
- GG 1 cancer in 6 cores – Active Surveillance

Now 3+ years later and applying for coverage

- PSA 7/22 (6 months after biopsy) 11.3; repeat PSA 8.5

➢ Any concerns?
➢ I hope so!
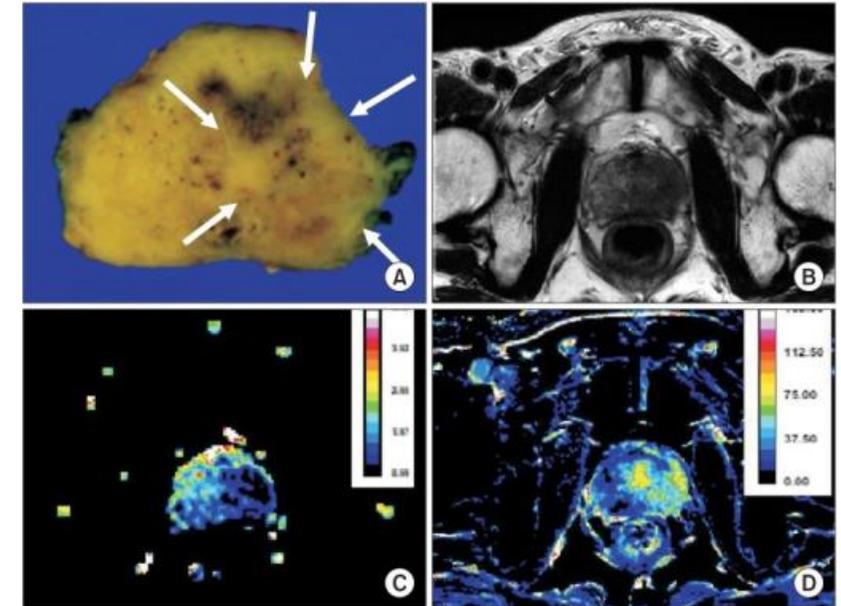
Prostate MRI_Yoo S -Korean journal of urology(2015)

mpMRI: Prostate volume 54.8ml. Lesion 8mm x 7mm left lateral mid peripheral zone; PIRADS 4. Changes of prostatitis right base and mid peripheral.

➢ Likelihood of csPCa?

Prostate Multiparametric MRI (or Biparametric?)

Goal is to recognize *clinically significant* prostate cancer
> And not low grade, prostate confined tumors

- PI-RADS 1 – Clinically significant cancer is highly unlikely to be present.
- PI-RADS 2 – Clinically significant cancer is unlikely to be present.
- PI-RADS 3 – The presence of clinically significant cancer is equivocal.
- PI-RADS 4 – Clinically significant cancer is likely to be present.
- PI-RADS 5 – Clinically significant cancer is highly likely to be present.

MRI also used to "target" the biopsy to the suspicious site
> Identifies more csPCa and more accurate tumor grading

Prostate mpMRI -- For detection of csPCa
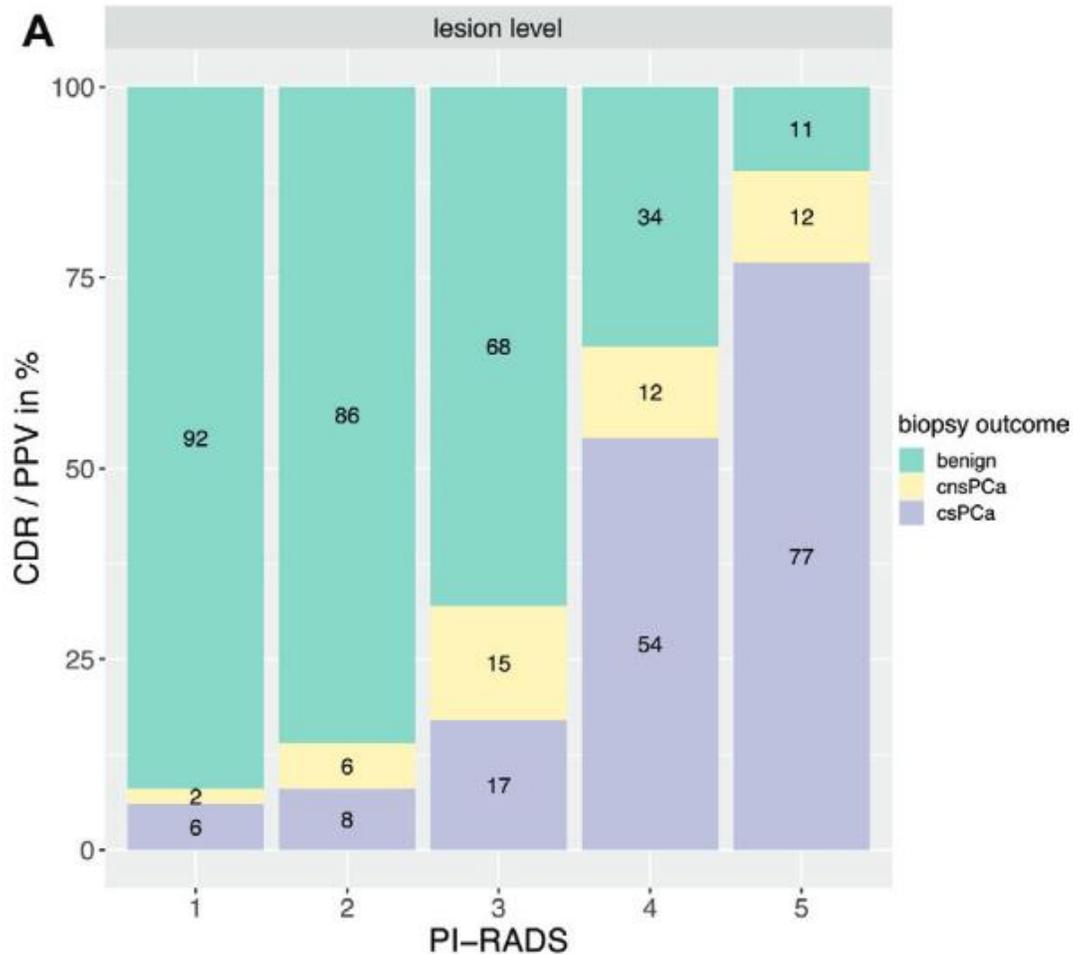
Oerther B. Published Online: August 13, 2024
https://doi.org/10.1148/radiol.233337

Per a 2024 systematic review and meta-analysis

PIRADS 3-5:
- 96% sensitivity; 43% specificity; AUC 0.86

PIRADS 4-5:
- 89% sensitivity; 66% specificity; AUC 0.89

Per a Dutch assessment of AI-assisted MRI
(doi: 10.1001/jamanetworkopen.2025.15672)

PIRADS 3-5, AI-assisted vs unassisted:
- Sens 96.8% vs 94.3%; Spec 50.1% vs 46.7%
- AUC AI assisted 0.916 vs 0.882 unassisted

Case #1.5 - 62 yo man with prostate cancer

- Repeat PSA 8.5

- mpMRI: Prostate volume 54.8ml. Lesion 8mm x 7mm left lateral mid peripheral zone; PIRADS 4. Changes of prostatitis right base and mid peripheral.

- Repeat fusion targeted biopsy – Gleason's score 3+4 in 40% of one core

  ➤ AS still appropriate?
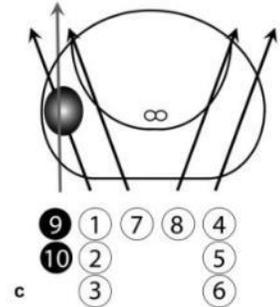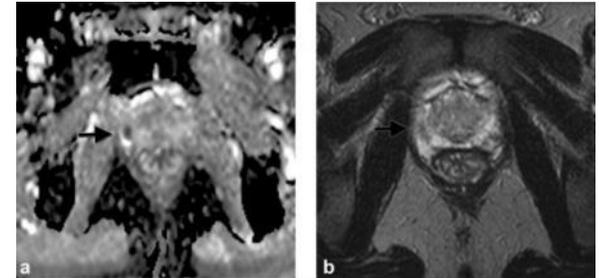
Targeted biopsy_Watanabe Y - JMRI(2012)

Risk Stratification

- Factors that impact prognosis and treatment:

➢ Anatomic staging (TNM) - tumor extent

➢ Gleason grade – tumor differentiation

➢ PSA level

- Most important prognostic factors - but still do not fully inform how the tumor will behave

➢ Other Prognostic Factors:

- PSA dynamics – PSA density and velocity, % free PSA   PSAD 8.5/54.8 = 0.157

- Additional biomarkers – PHI, 4K score, % proPSA   PHI 35 – intermediate risk

- Multi-parametric MRI and TRU/S findings   PIRADs 4

- Molecular assays

- Presence of germline mutations

- Polygenic risk score

Case #1.5 - 62 yo man with prostate cancer

✓ PSA 8.5; PSAD 0.155

✓ mpMRI: Lesion 8mm x 7mm; PIRADS 4.

✓ Gleason's score 3+4 in 40% of one core = GG 2
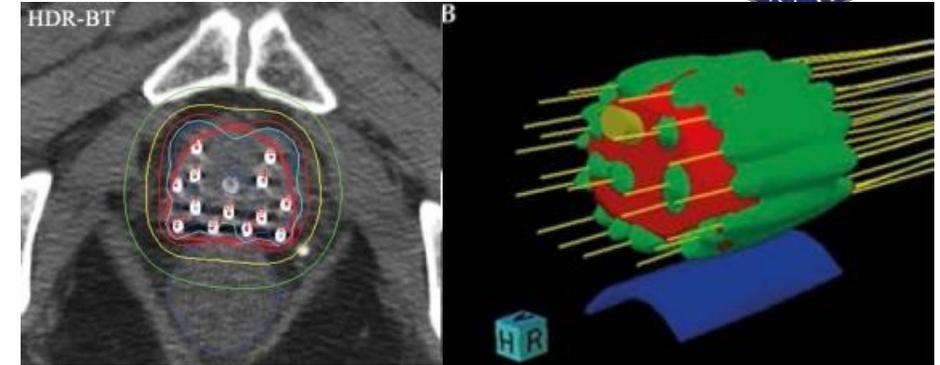
Prostate Brachytherapy_Fukuda -Journal of radiation research(2014)

- Elected to undergo brachytherapy 9/22

- Follow-up since: No issues or findings except increase in urinary urgency and nocturia

- Select subsequent PSAs:

8/22	3.9
1/23	1.8
2/24	0.7
10/24	0.42
8/25	0.12

➤ Stage and grade now?
   cT1c, GG2, PSA <20 = *Clinical* stage group IIB
➤ Time to assess the case!

Prostate cancer specific mortality by risk score

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%).

Reference 0 (IA) =
- Age 51-70
- T1a-c, N0
- GG 1
- Core biopsy <50%
- PSA < 6

10-year PCSM ranges from 0.3 to 40% by stage

IIB equivalent (~8.5% at 15 yrs)

Mostly favorable factors
Ongoing but low risk to at least 15 years out

October 18-23, 2025

What if had robotic assisted radical prostatectomy rather than radiation therapy and subsequent PSAs were all <0.1?

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

Insurance lab PSA 0.02
➤ Offer possible, 7 months after surgery?

Prostate cancer survival following definitive treatment

- pT2N0M0, GG 1, PS <10 = Prognostic Stage Group I

- Outcomes tied mostly to pathologic staging and prognostic stage group
  - ✓ Stage, grade, PSA
  - ✓ Surgical margin status and genomic classifiers also alter RP prognosis
  - ✓ PSA nadir and pretreatment MRI findings impact prognosis after RT

- Very favorable prognosis following RP if organ confined and low grade
  - Mayo: 10-year BCR rate 18% but PCSM of 0.3%
  - U of Chicago: 15-yr Prostate ca specific mortality (PCSM) 0.03%
  - MSKCC calculator: 10-yr recurrence-free probability 79% (91% if margins negative); 15-yr prostate cancer-specific survival 99%
  - German prostate cancer clinic: 20-year PCSM 2.1% for those with negative surgical margins and 4.9% if margins positive

- What if the repeat biopsy 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 most recent PSA, was 2.2, rather than 0.12?

Prostate cancer specific mortality by risk score

Reference 0 =

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

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

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

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%).

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 3 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.

61 year-old man for $500,000 IUL. 6' 231lbs, BP 120/80.

- 5/23 PSA 6.98

   What else would we like to know?

- History of LUTS, increased PSA, HTN

- DRE ??

- Never smoker, moderate alcohol use

- Twin brother diagnosed with Prostate Cancer 2021

- 6/23 MRI:

Heltemes, B. (2025). Man wishing to avoid a prostate biopsy [AI-generated image]. Microsoft Copilot.

FINDINGS:

PROSTATE:

Size: 5.7 cm transverse x 4.2 cm AP x 4.4 cm longitudinal

Volume: 54.8 ml (PSA density of 0.13)

PERIPHERAL ZONE: No definable PIRADS 4 or PIRADS 5 lesions.

TRANSITION ZONE: Multiple T2 bright well-circumscribed nodules are present scattered throughout, causing prostate enlargementconsistent with BPH-related changes.

Likelihood of csPCa?

Lesion # 1

Size: 15 x 14 x 19 mm (series 4 image 12, series 5 image 11)

Zone: Transitional zone

Location: Left side anterior and posterior transitional zone at the junction of the base and mid segment of the gland.

T2WI: Slightly lobulated, focal hypointense signal, score of 4.

DWI: Mildly decreased ADC map, and minimally increased diffusion-weighted signal on high b-value sequences, score of 3.

DCE: Positive

This lesion meets criteria for a PIRADS 5 lesion.

CAPSULE: Intact

NEUROVASCULAR BUNDLE INVASION: Absent

SEMINAL VESICLES INVASION: Absent

OTHER ORGAN INVASION: Absent

LYMPH NODES: Negative for suspicious lymph node(s).

IMPRESSION:

1. PIRADS 5 lesion suggested within the left side transitional zone at the junction of the base and mid segment of the gland.
2. No evidence for pelvic lymphadenopathy pathologic by size criteria.
3. No evidence for suspicious bone lesion seen within the visualized segments of the lumbar spine and the bony pelvis.
4. Incidental note of potential bilateral varicoceles.

Tissues

| A. Prostate, NOS - Right prostate |
| B. Prostate, NOS - Left prostate |
| C. Prostate, NOS - Left transitional zone |

Final Diagnosis

A. Prostate, right, core needle biopsy:
   Atypical small acinar proliferation.

B. Prostate, left, core needle biopsy:
   Focal high grade prostatic intraprostatic neoplasia.

C. Prostate, left transition zone, core needle biopsy:
   Benign prostatic tissue with mild acute and chronic inflammation.

Comment: These results were given to Dr. Kellerman on 9/17/21 at 9:25 a.m.

Diagnosed By: ADAM M. BELL, MD
Electronically Signed By: ADAM M. BELL, MD on 09/20/21 at 0917

Gross Description

A. Received in formalin labeled with the patient's name and "right prostate." The specimen consists of six tan-white cores ranging from 1.5-2.1 cm in length and averaging 0.1 cm in diameter. The specimen is inked black. Entirely submitted as A1-A2.

B. Received in formalin labeled with the patient's name and "left prostate." The specimen consists of seven tan-white cores and core fragments ranging from 0.6-2.1 cm in length and averaging 0.1 cm in diameter. The specimen is inked black. Entirely submitted as B1-B2.

C. Received in formalin labeled with the patient's name and "left transitional zone." The specimen consists of three tan-white cores ranging from 1.3-2.1 cm in length and averaging 0.1 cm in diameter. The specimen is inked black. Entirely submitted as C1.

Biopsy specimen adequate?
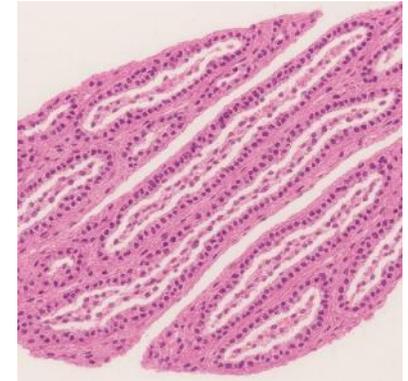
Heltemes, B. (2025). Pathology slide of a prostate needle biopsy [AI-generated image]. Microsoft Copilot.

10/23 follow-up: Significant BPH, LUTS – steam vaporization (REZUM) procedure w/ moderate improvement

12/23 Insurance lab: PSA 3.10, CEA 1.1

3/24 PSA 3.57

4/24 PSA 3.69

1/25 Insurance lab: PSA 4.19

8/25 PSA 4.95, PSA density 0.068; DRE "palpably benign"

Assessment?

9/25 Repeat MRI:

FINDINGS:

The prostate gland measures: 4.2 x 5.5 x 6.0 cm.
Prostate volume 73 mL.
PSA 4.945. PSA density 0.068.

Peripheral zone: No index lesion. Heterogeneous T2 hypertense signal compatible with chronic/remote prostatitis.

Central gland: No index lesion. Moderate BPH with median lobe hypertrophy causing intravesicular protrusion.
Foci of T1 hyperintense signal within the transition zone compatible with blood degradation products.

Prostatic capsule: Normal

Neurovascular bundles: Normal

Seminal vesicles: Normal

Lymph nodes: No lymphadenopathy by size criteria.

Bones: No aggressive osseous lesion.

IMPRESSION:
1. No index lesion.
2. Moderate BPH.

- Favorable and unfavorable features?
- How likely is he to have prostate cancer?
- How likely is he to have csPCa?
- Offer?

- Increased risk with PSA, family hx. PIRADs 5 then high likelihood, but less concern in transitional zone.

  - Per Israël B, et al., 91-97% PCa, 67-83% csPCa

- And with ASAP, he very likely has prostate ca present, though biopsy may have reduced likelihood of cs PCa some (but still 20-30%??).

- Repeat MRI favorable with no lesion – did steam vaporization obliterate the lesion somehow? It did likely lead to the decreased PSA but with PSA then increasing, albeit slowly, there is some added concern.

- Agree with original decline/PP - very high PCa likelihood (and effectively shown with the ASAP) and, more importantly, high csPCa risk - 67-83% likelihood by one meta-analysis).

- But then no need to PP further after f/u:

- Given the prior ASAP and PIRADs 5 (and fam hx), I do suspect he has prostate cancer, but it is more likely <u>not</u> csPCa. Prostatitis per MRI could explain PSA increase.

- Consider low Substd without a f/u biopsy, but plenty of uncertainty here!

Prostate cancer caveats - 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

- Additional biomarkers – PHI, 4K score, % proPSA

- Multi-parametric MRI and TRU/S findings

- Molecular assays – Decipher, Oncotype DX, Prolaris, Promark, ConfirmMDx

- Presence of germline mutations – BRCA, ATM, CHEK2

Prostate cancer caveats

- PSA alone has difficulty distinguishing between benign, low-grade, and csPCa
  - Consider all other factors, especially mpMRI, to determine risk
- Prognosis depends heavily on tumor extent, grade, and PSA
  - But multiple other factors modify this further
- Use prostatectomy stage and grade, over biopsy grade and clinical stage
- With clinical staging, keep in the mind the likelihood of upgrading and/or upstaging
  - Upgrade – PSA and PSAD, MRI, genomic classifiers, pathogenic germline mutations
  - Upstage – Tumor volume on biopsy, MRI, PSAD, and age
  - MRI-guided biopsy more accurate
  - Pathologist experience matters (and AI based??)
- Close follow-up is necessary, especially with AS
- A biochemical recurrence is not always adverse if it occurs late and with a slow PSA rise
- Given the often prolonged course of prostate cancer, the relative risk is lower at older ages (when competing causes of death prevail)

GG 1 Prostate Ca on biopsy

True GG1 cancer, confined to the prostate, presents very little risk

However, some with cT1c or cT2 GG1 PC on biopsy will actually have higher grade and/or tumor extent

In a SEER data study of 299,746 men (median age, 64 years; IQR, 58-69), of whom 117,162 (39%) had biopsy GG1 PC:

- In men undergoing radical prostatectomy, adverse pathology was found in 4170 of 26,452 men (16%) with low-risk GG1 PC, 555 of 2478 men (22%) with favorable intermediate-risk GG1 PC, 389 of 1246 men (31%) with unfavorable intermediate-risk GG1 PC, and 867 of 1455 men (60%) with high-risk GG1 PC.

- The cumulative incidence of PCSM at 10 years was 1.3% for low-risk GG1 PC, 2.0% and 2.1% for favorable intermediate-risk GG1 and GG2 PC respectively, 2.4% for unfavorable intermediate-risk GG1 PC, and 4.7% for high-risk GG1 PC.

- The proportion of men with high-risk GG1 PC increased from 3.2% (478 of 14,957) in 2010 to 4.3% (310 of 7258) in 2020

Table. Adjusted Risk of Prostate Cancer–Specific Mortality and Adverse Pathology at Radical Prostatectomy

Risk type	Adverse pathology, adjusted OR (95% CI)[a]	Prostate cancer–specific mortality, adjusted HR (95% CI)[b]
Low-risk GG1	1 [Reference]	1 [Reference]
Favorable intermediate-risk GG1	1.42 (1.29-1.57)	1.60 (1.30-1.96)
Unfavorable intermediate-risk GG1	2.31 (2.03-2.62)	2.10 (1.53-2.89)
High-risk GG1	7.15 (6.40-7.99)	3.58 (2.93-4.38)
Favorable intermediate-risk GG2	2.13 (2.03-2.25)	1.55 (1.33-1.80)
Unfavorable-risk ≥GG2	6.06 (5.82-6.31)	3.06 (2.76-3.38)
High-risk ≥GG2	32.8 (31.1-34.5)	9.82 (8.93-10.8)

Abbreviations: GG, grade group; HR, hazard ratio; OR, odds ratio.

[a] Adjusted for age, race and ethnicity, income, year of diagnosis, census region, and rurality.

[b] Adjusted for treatment, age, race and ethnicity, income, year of diagnosis, census region, and rurality.

Date of download: 8/4/2025

Additional screening options

- Prostate Health Index (PHI) – combines PSA, free PSA, and proPSA

- 4Kscore test – combines PSA, free PSA, intact PSA, and human kallikrein 2 (hK2), along with some other factors

- Prostate cancer antigen 3 (PCA3) – urine test after a DRE

- TMPRSS2:ERG – urine gene test

- ExoDx Prostate IntelliScore (EPI) – based on 3 biomarkers in urine

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 TRU/S findings

- Molecular assays – Oncotype DX, Prolaris, ConfirmMDx, Decipher

- Presence of germline mutations – BRCA, ATM, CHEK2

Prostate cancer genomic markers

- Currently 4 commercially available genomic markers

  - Decipher Genomic Classifier (GC)

  - Oncotype Dx Genomic Prostate Score (GPS) assay

  - Myriads Prolaris risk score (CCP) assay

  - Metamark's Promark

- Each has evidence as prognostic factor for prostate cancer outcomes beyond tumor histology

  - Best level of evidence Decipher GC?

- Clinical utility however, e.g. as a predictive factor, is less clear (compared to MRI, PSA kinetics, etc)

- Performed on biopsy tissue -- tumor heterogeneity and multifocality issues may limit proper risk stratification

- Mulitmodal AI Pathology interpretation (ArteraAI) both predictive and prognostic

Treatment approaches for low-risk prostate cancer
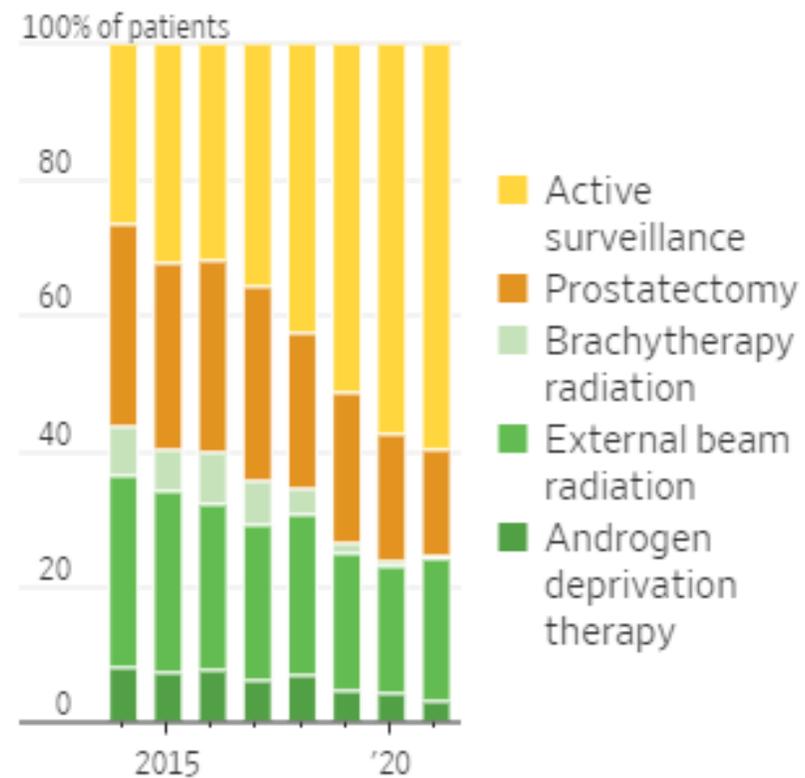
Source: Matthew Cooperberg, University of California, San Francisco

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%

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- **But varies significantly (15 yr OS 1-94%)**
  - Median survival just 3 years if:
    - Rapid PSA doubing time (<3 mos)
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    - Years to recurrence < 3
  - Favorable results if:
    - Gleason score 6 or less
    - Long PSADT (>15 mos)
    - PSA rise >3 yrs post-treatment

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)
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<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.

Outcomes Following Conservative Management

- 15-year outcomes for men age >65
- "Watchful waiting" initial therapy (not AS)
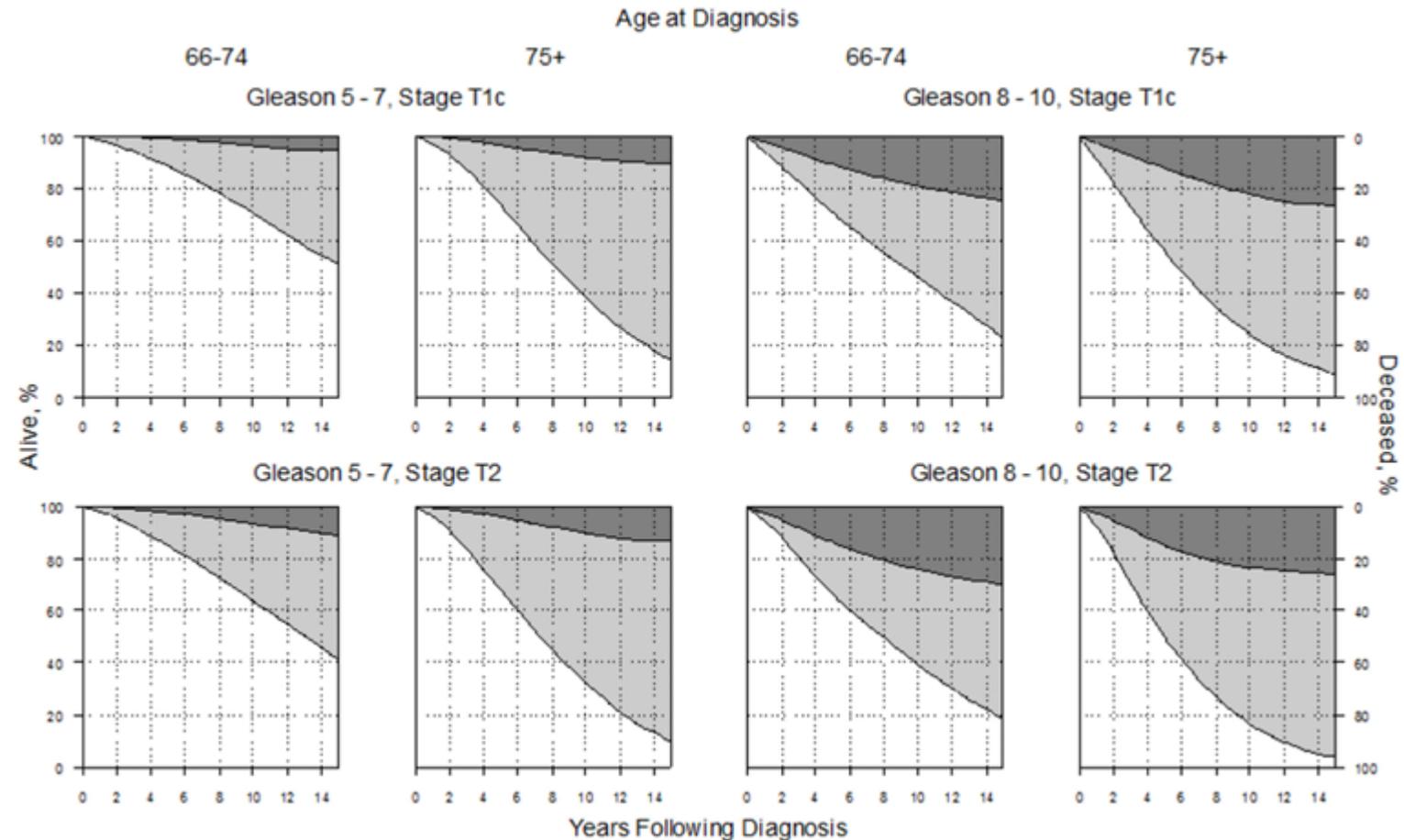
Outcomes in select AS studies

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 GG 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 GG 1 2664 pts, 1 death

TABLE 3. Description of Assays

Test(s)	Company	List Price,* USD	Sample Requirement	Clinical Utility/Intended Use	Comments
Decipher Biopsy and Decipher Postoperative	Decipher Biosciences (formally Genome Dx)	$5,150	FFPE tissue from prostate biopsy, or	Categorize patients into low/high risk to stratify patients to surveillance v treatment (and intensity of treatment)	Evaluates mRNA expression levels of 22 genes from FFPE tissue; generates score from 0 to 1.0
			Prostate tissue after RP	Postprostatectomy for patients with adverse pathologic features to guide whether surveillance, adjuvant, or salvage therapy may be warranted	
Oncotype Dx GPS	Genomic Health	$4,520	Tumor tissue from original biopsy in neutral buffered formalin; prostatectomy specimens not accepted	Biopsy-based likelihood of adverse pathologic features (Grade Group ≥ 3 or extracapsular extension); identify those who may benefit from surveillance v treatment	GPS ranges from 0 to 100 based on mRNA expression of 17 genes across four pathways
Prolaris Biopsy and Prolaris Postprostatectomy	Myriad Genetic Laboratories	$3,900	FFPE tissue from: prostate tumor biopsy, or prostatectomy specimens	Aggressiveness of cancer; provides a 10-year risk of metastasis after definitive therapy, and disease-specific mortality under conservative management	mRNA expression of cell-cycle progression genes are used to calculate the score; clinical factors are subsequently added for risk assessment
ProMark, Proteomic Prognostic test for prostate cancer	MetaMark	$3,900	Requires tissue collected with patented biopsy kit available from MetaMark	Uses automated image recognition technology to determine the likelihood of Grade Group ≥ 2 or stage ≥ T3b	Expression of 8 proteins; uses automated image recognition technology to generate a score from 1 to 100 indicating the aggressiveness of prostate cancer

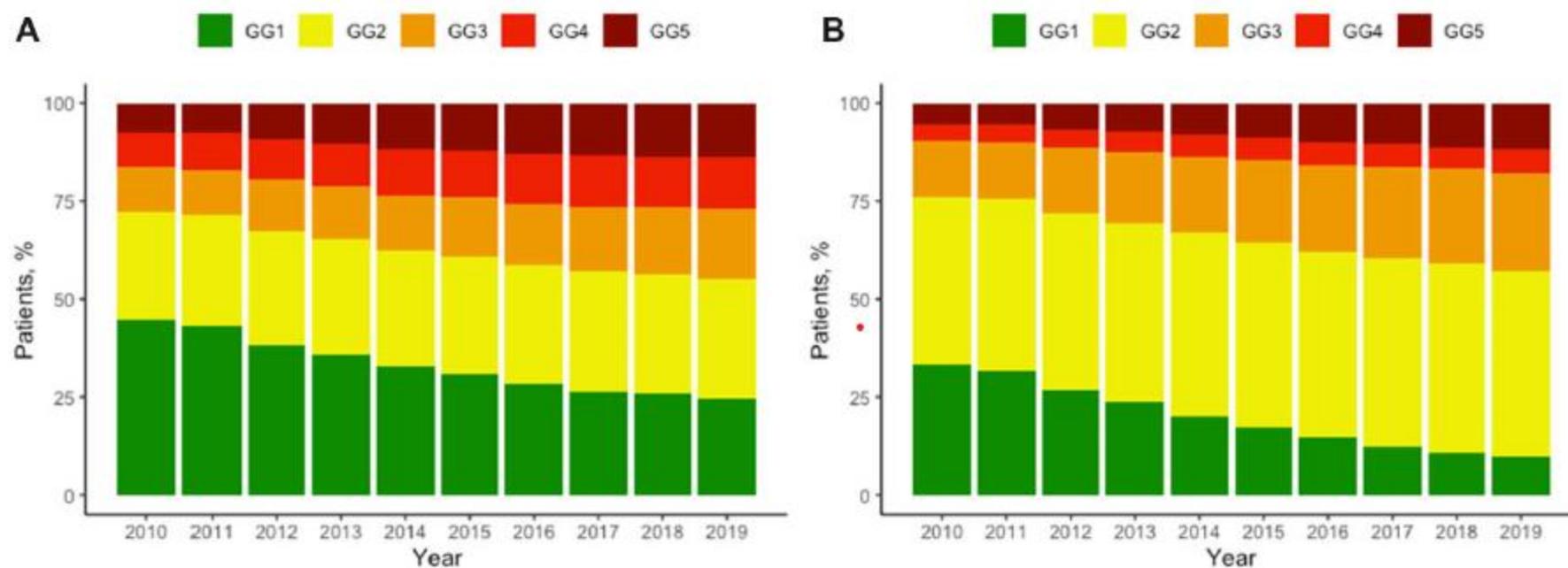Abbreviations: FFPE, formalin fixed, paraffin embedded; GPS, Genomic Prostate Score; RP, radical prostatectomy.

*Cost was not available on the Web site and was therefore obtained by contacting sales team or customer support for each company during the week of April 22, 2019. List prices do not necessarily reflect prices paid by Medicare or out of pocket by patients or other discounted rates.

TABLE 3. Description of Assays

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/

Figure 1. Distribution of Gleason grade group (GG) 1-5 on **A)** biopsy and **B)** radical prostatectomy pathology, National Cancer Database 2010-2019.

AAIM 133rd Annual Meeting

October 18-23, 2025

IPTW-adjusted HRs of initial treatments by D'Amico risk group

Variable	Death from any cause		Death from prostate cancer	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Low-risk				
Observation	-		-	
Radiotherapy	1.09 (1.02–1.17)	0.009	1.68 (1.22–2.31)	0.001
Radical prostatectomy	0.64 (0.60–0.69)	<0.001	0.79 (0.54–1.14)	0.204
Intermediate-risk				
Observation	-		-	
Radiotherapy	0.80 (0.77–0.84)	<0.001	0.90 (0.75–1.07)	0.230
Radical prostatectomy	0.40 (0.38–0.43)	<0.001	0.43 (0.35–0.54)	<0.001
High-risk				
Observation	-		-	
Radiotherapy	0.57 (0.55–0.60)	<0.001	0.68 (0.60–0.77)	<0.001
Radical prostatectomy	0.32 (0.30–0.34)	<0.001	0.36 (0.31–0.42)	<0.001

CI: confidence interval, HR: hazard ratio, IPTW: inverse probability of treatment weighting.

Han JH, et al. "Observation, radiotherapy, or radical prostatectomy for localized prostate cancer: Survival analysis in the United States." The World Journal of Men's Health 41.4 (2023): 940.

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

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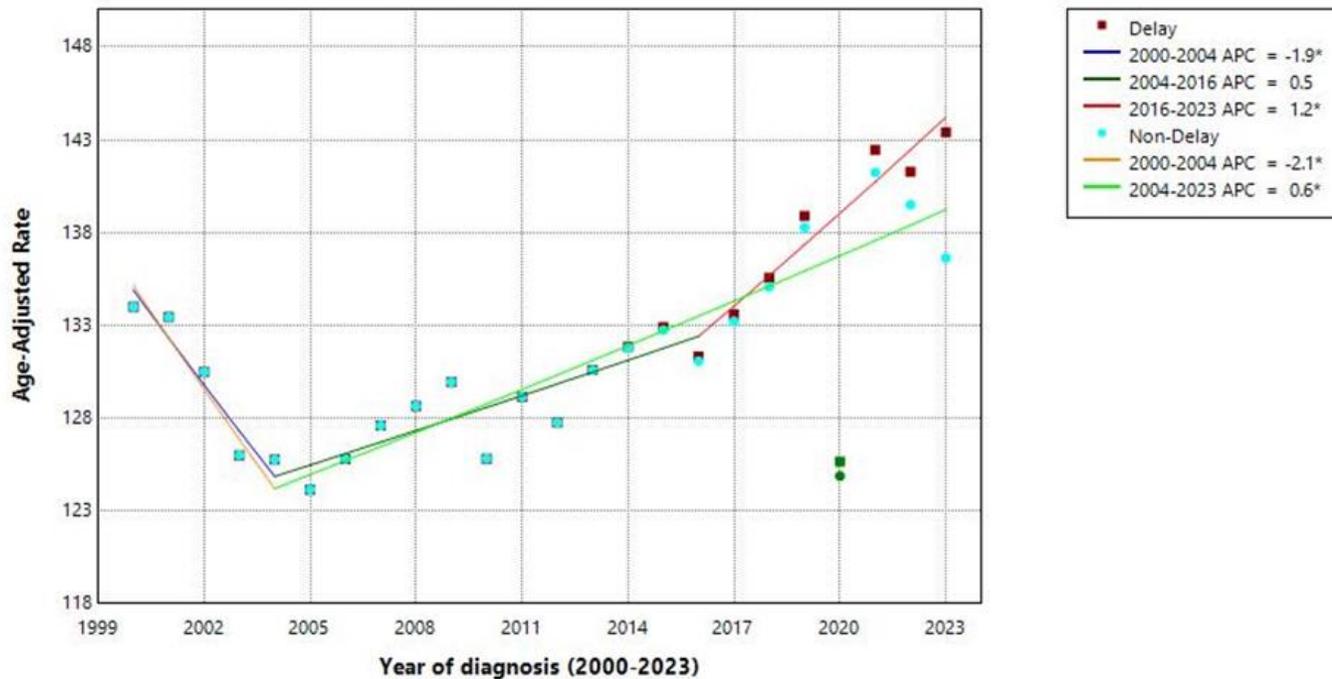
BREAST CANCER

Trends in U.S. Breast Cancer Incidence

Globally, breast cancer is the most frequently diagnosed malignancy and the leading cause of cancer death in women

In the U.S. in 2022, there were an estimated 4,091,000 women living after a breast cancer diagnosis (2.4% of the population), including 1,109,000 ages 50-64, and 269,000 under age 50.

Breast Cancer

- Breast Cancer is the most common cancer in women globally.

- It is the leading cause of cancer death in women, globally; is second only to Lung Cancer as the leading cause of cancer death in US women; and, it is the leading cause of death in women between ages 45-55.

- Individual risk for breast cancer in one's lifetime is ~1:8; Individual risk of dying from breast cancer is ~1:43 or 2%

- Global Disease Burden, 2022 data: 2,296,840 new cases; 666,103 Deaths

- US Disease Burden, 2024 estimates: ~310,720 new cases of invasive breast cancer; ~56,500 new cases of DCIS; ~42,250 will have died

How old are women when they get Breast Cancer?

TABLE 1. Estimated new ductal carcinoma in situ and invasive breast cancer cases and breast cancer deaths among women by age, United States, 2024.

Age, years	DCIS cases		Invasive cases		Deaths	
	No.	%	No.	%	No.	%
<40	1360	2	13,180	4	990	2
40–49	8750	15	37,650	12	2620	6
50–59	13,760	24	67,310	22	6800	16
60–69	17,660	31	89,540	29	10,010	24
70–79	11,890	21	69,130	22	10,140	24
≥80	3080	5	33,910	11	11,690	28
All ages	56,500	100	310,720	100	42,250	100

Note: Estimates are rounded to the nearest 10. Percentages may not sum to 100% because of rounding.

Abbreviation: DCIS, ductal carcinoma in situ.

Breast Cancer Incidence Among US Women Aged 20 to 49 Years by Race, Stage, and Hormone Receptor Status

Shuai Xu, MPH; Sara Murtagh, MD; Yunan Han, MD; Fei Wan, PhD; Adetunji T. Toriola, MD, PhD, MPH

Figure 1. Joinpoint Analysis of Overall Incidence of Primary Invasive Breast Cancer Among US Women Aged 20 to 49 Years, 2000-2019
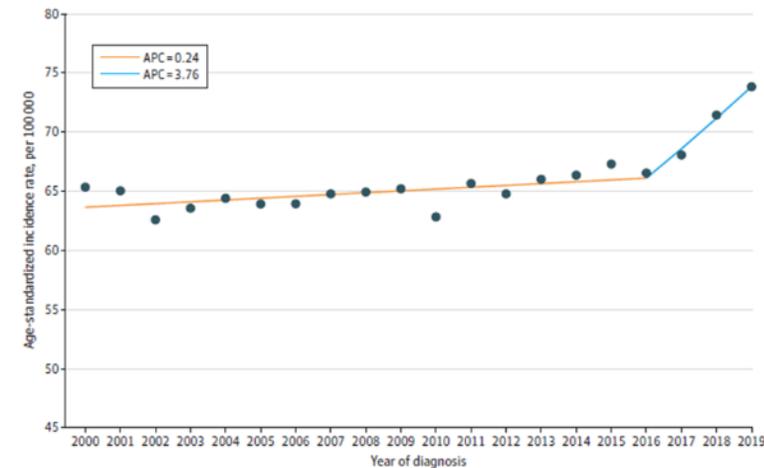
APC indicates annual percent changes.

Female breast cancer incidence rates by subtype and race and ethnicity for ages (A) older than 20 years, (B) 20–49 years, and (C) older than 50 years, United States, 2017–2021. Rates are age adjusted to the 2000 US standard population and adjusted for reporting delays. Breast cancer subtype status was imputed for cases with missing information. Y-axis have different scales. – indicates negative; +, positive; AAPI, Asian American/Pacific Islander; AIAN, American Indian/Alaska Native; HER2, human epidermal growth factor 2; HR, hormone (estrogen and progesterone) receptor.
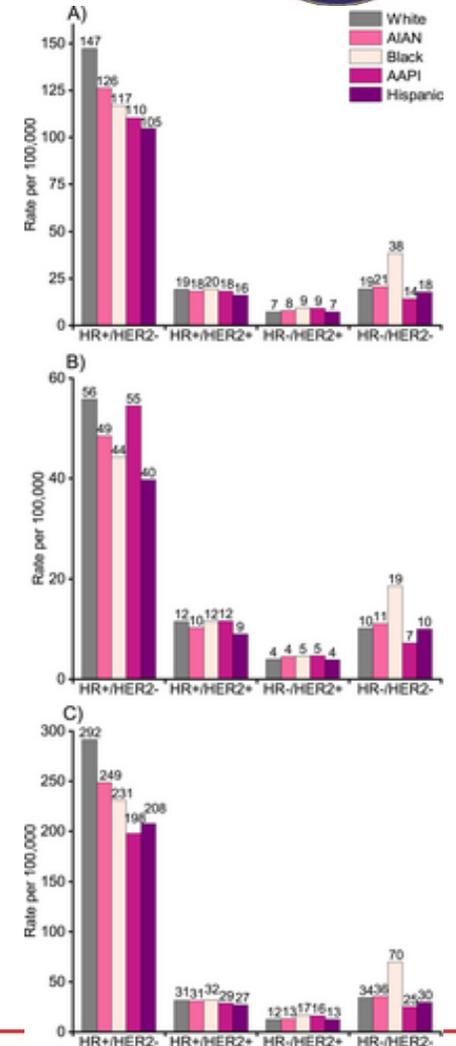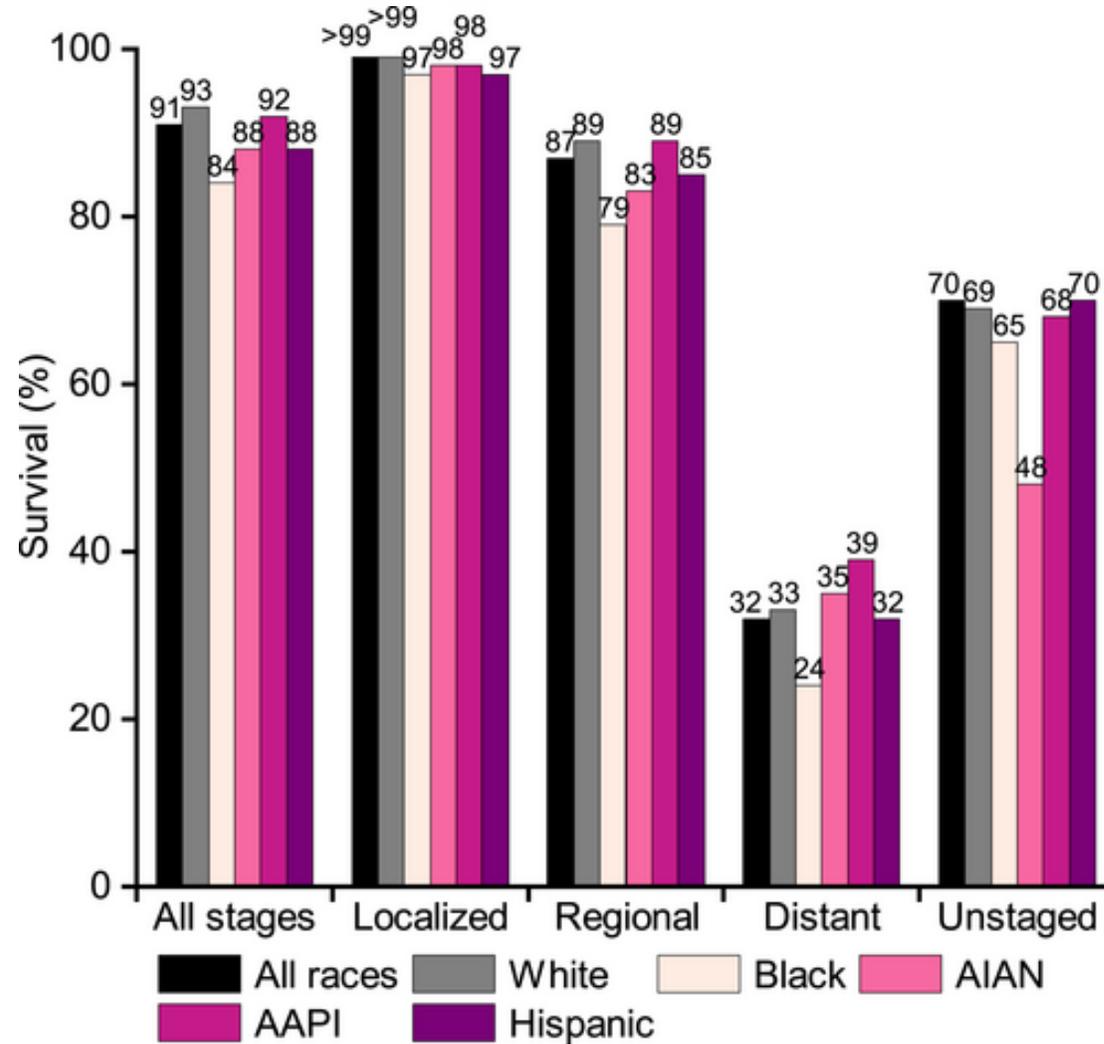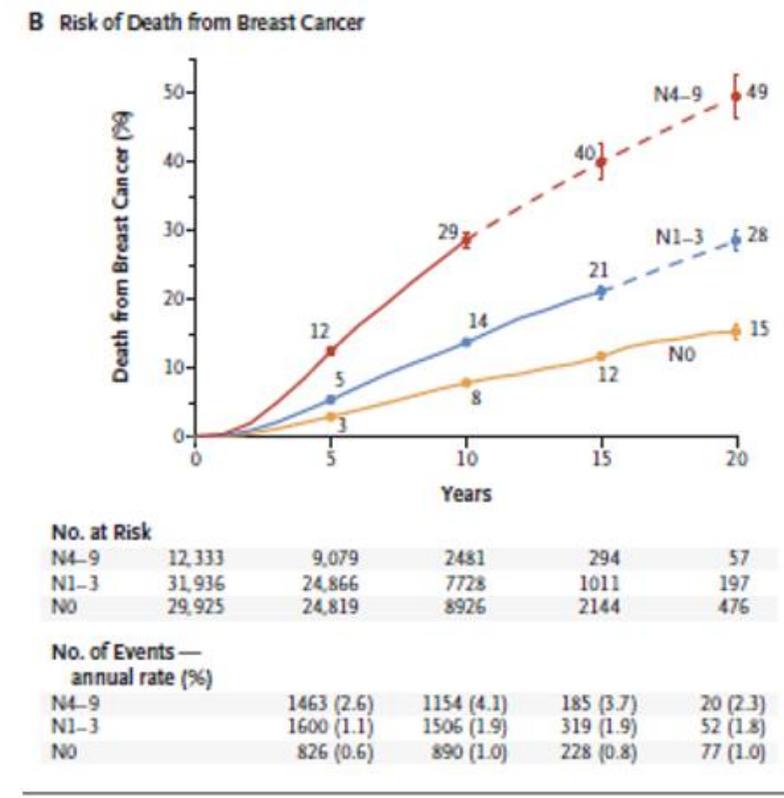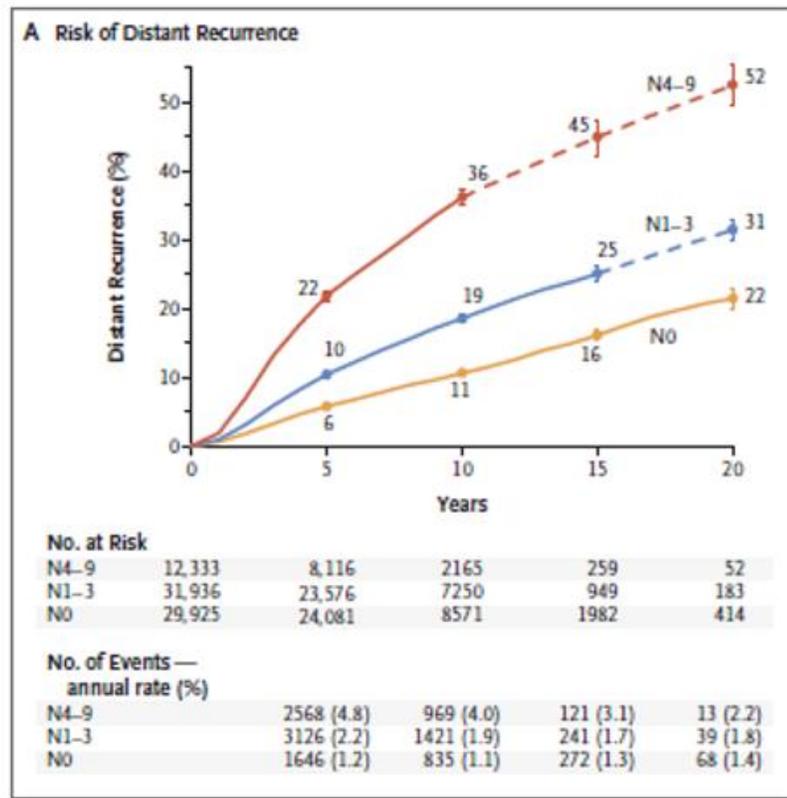
Hongchao Pan, Ph.D. et al; 20-year risks of Breast-Cancer Recurrence after Stopping Endocrine Therapy at 5 years; NEJM2017; 377; 1836-46.

Important Risk Factors For Breast Cancer

- Personal History of IBC (Invasive Breast Cancer) or DCIS (Ductal Carcinoma In Situ)

- Family History of either IBC or DCIS: one first degree relative -> two-fold; two first degree relative -> three-fold increase

- BRCA 1 (72%) and 2 (69%); TP53, PTEN, etc.

- Early Menarche, Late Menopause, Late First Pregnancy, Nulliparity (RR 1.2-1.7): Unopposed Estrogen

- Higher endogenous estrogen levels at all ages; mixed reviews on post-menopausal hormone replacement

- Obesity: RR 1.1 for each 5 BMI unit incremental increase

- Alcohol, +/- smoking and diet

- Increasing Age

- Breast Density by Mammography—more dense ->higher risk

Key Things to Know in Underwriting

- Diagnosis: thorough and reliable?
  - Imaging characteristics (BI-RADS)
  - Biopsy
  - Clinical Stage
- Treatment: appropriate to stage, grade, and molecular type?
  - Pathologic and Prognostic Stage
  - Mastectomy
  - Lumpectomy with Sentinel Node Biopsy and Radiation
  - Hormone Therapy
  - Chemotherapy, Neoadjuvant Chemotherapy!
- Surveillance: appropriate to stage, risk of recurrence, and risk of complications from treatment?

RESOURCE: [National Comprehensive Cancer Network - Home](#)

Diagnosis

- Biopsy—percutaneous unless not feasible >surgical

  - Imaging with MMG, US or both; MRI in higher risk individuals/more dense breasts

  - BI-RADS 4 or 5 -> image guided core needle biopsy

- Type—Infiltrating Ductal Carcinoma (IDC) 70-80%; Infiltrating Lobular Carcinoma (ILC) 8%; Mixed 7%; others…

- Grade 1-3 from less to more aberrant

- ER/PR, Her2-neu (15-20%), Oncotype Dx

- Metastatic evaluation: concerning signs/symptoms

- Oncotype Dx—21 Genes yielding Recurrence Score for T1b-T3 N0 tumors

Assessment	Management	Likelihood of cancer
Category 0: Incomplete – Need additional imaging evaluation and/or prior mammograms for comparison	Recall for additional imaging and/or comparison with prior examination(s)	N/A
Category 1: Negative	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 2: Benign	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 3: Probably benign	Short-interval (6-month) follow-up or continued surveillance mammography	>0 but ≤2% likelihood of malignancy
Category 4: Suspicious	Tissue diagnosis*	>2 but <95% likelihood of malignancy
Category 4A: Low suspicion for malignancy		>2 to ≤10% likelihood of malignancy
Category 4B: Moderate suspicion for malignancy		>10 to ≤50% likelihood of malignancy
Category 4C: High suspicion for malignancy		>50 to <95% likelihood of malignancy
Category 5: Highly suggestive of malignancy	Tissue diagnosis*	≥95% likelihood of malignancy
Category 6: Known biopsy-proven malignancy	Surgical excision when clinically appropriate	N/A

Breast carcinoma TNM clinical prognostic stage groups AJCC UICC 8th edition

When TNM is...	And grade is...	And HER2 status is...	And ER status is...	And PR status is...	Then the clinical prognostic stage group is...
Tis N0 M0	Any	Any	Any	Any	0
T1* N0 M0	G1	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0	G2	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA
				Negative	IA
		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB
T1* N0 M0	G3	Positive	Positive	Positive	IA
T0 N1mi M0				Negative	IA
T1* N1mi M0			Negative	Positive	IA

- T: Size of Tumor
  - T1: <2cm
  - T2: 2-5 cm
  - T3: >5 cm
  - T4: extension to chest wall, ulceration, satellite nodules, peau d'orange, inflammatory carcinoma
- N: Number and Consistency of Nodes—primarily axillary
  - N0: no regional metastases; i+ malignant cells, mol+ molecular findings
  - N1: 1-3 ipsilateral nodes
  - N2: 4-9 ipsilateral nodes, internal mammary, fixed or matted
  - N3: 10+ ipsilateral nodes, supraclavicular, infraclavicular
- M: Distant Metastasis
  - M1: Detectable distant metastases (bone, liver, lung, brain, etc.)

			ER+, PR+, HER2+	ER+, PR+, HER2-	ER+/PR-, HER2+	ER-/PR+, HER2+	ER-, PR-, HER2+	ER+, PR-, HER2-	ER-, PR+, HER2-	ER-, PR-, HER2-	Anatomic stage
TisN0	M0	G1-3	0	0	0	0	0	0	0	0	0
T1N0 T0N1mi T1N1mi		G1	IA	IA	IA	IA	IA	IA	IA	IA	IA
		G2	IA	IA	IA	IA	IA	IA	IA	IB	IA
		G3	IA	IA	IA	IA	IA	IA	IA	IB	IA
T0N1 T1N1 T2N0		G1	IA	IA	IB	IB	IIA	IB	IB	IIA	IIA
		G2	IA	IA	IB	IB	IIA	IIA	IIA	IIA	IIA
		G3	IA	IB	IIA	IIA	IIA	IIA	IIA	IIA	IIA
T2N1 T3N0		G1	IA	IA	IIB	IIB	IIB	IIB	IIB	IIB	IIB
		G2	IB	IB	IIB	IIB	IIB	IIB	IIB	IIB	IIB
		G3	IB	IIA	IIB	IIB	IIB	IIB	IIB	IIIA	IIB
T0N2 T1N2 T2N2 T3N1 T3N2		G1	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA	IIIA
		G2	IB	IB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIB	IIIA
		G3	IIA	IIB	IIIA	IIIA	IIIA	IIIA	IIIA	IIIC	IIIA
T4N0 T4N1 T4N2 AnyN3		G1	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB	IIIB
		G2	IIIA	IIIA	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIB
		G3	IIIB	IIIB	IIIB	IIIB	IIIB	IIIC	IIIC	IIIC	IIIB
Any	M1	Any	IV	IV	IV	IV	IV	IV	IV	IV	IV

Additionally, pT1, pT2, pN0, M0, ER+, and HER2− cancers are assigned as Pathologic Prognostic Stage group IA when Oncotype DX recurrence score is <11

Treatment of IBC

- A chance to cut, in most cases, is a chance to cure!

- Surgery—primary means to deal with localized, low stage breast cancer. In most cases, the entire breast should be treated.
  - Modified Radical Mastectomy
  - Breast Conserving Therapy

- Radiation—used in BCT patients and MRM patients with positive margins
  - WBRT (Whole Breast Radiation Therapy)
  - APBI (Accelerated Partial-Breast Irradiation): Older, T1 tumors, -Margins

- Hormone Therapy: ER/PR positive; Aromatase Inhibitors (AI) preferred

- Chemotherapy: TNBC (Triple Negative), nodes, ^ recurrence score,
  - *Herceptin—all patients with Her2-neu positive tumors
  - Adjuvant: Doxorubicin (heart) + cyclophosphamide (multi-organ) + paclitaxel (neuropathy)
  - Neoadjuvant: similar drugs with some caveats; **REMEMBER the downstaging effects and don't be fooled

Surveillance for IBC

- The more advanced the disease, the closer and longer surveillance must be.

- It is helpful to remember that breast cancer has a very long tail of excess mortality—underwrite surveillance accordingly!

- It is also helpful to remember that one of the main risk factors for breast cancer is a prior history of breast cancer—remember there are two breasts (usually) and underwrite accordingly!

- In general, additional testing outside annual physicals and breast imaging is/should be symptom driven.

- Keep in mind the risks associated with treatment:

  - Heart dysfunction from Adriamycin

  - Accelerated CAD from Left Breast Radiation

  - Increased risk for ovarian cancer in women with breast cancer

  - Increased risk for uterine cancer with Tamoxifen

- 40 y/o F for $10MM Whole Life

- Sister with IDC of the breast undergoing chemotherapy; mother A&W with h/o breast cancer in her 40's

- Medically healthy, normal weight, no unusual exposures; G1P1 at 35 y/o; SBE's and Physical exam normal

- Follow up of initial screening MMG; left breast normal in appearance but noted to be extremely dense

> Rt mammo w/ tomosynthesis, rt breast US
> Ind: screening mammogram 10/11/2023 for right breast calcification. Family history of breast cancer in sister age 45
> Comp: 10/11/2023
> US Finds: -No suspicious sonographic findings at the 9:00-10:00 locations; Oval hypoechoic mass measuring 0.6 x 0.3 x 0.5 cm at 11:00, 6 cm from nipple. Clustered microcysts spanning up to 0.7 x 0.3 x 1.0 cm at 5:00, 4 cm from the nipple which likely correlates to mammographic asymmetry in the lower inner right breast.
> Imp: Right breast: Suspicious. BI-RADS Category 4. Recommend sampling of suspicious calcifications (lower central right breast at mid depth) and hypoechoic mass (11:00, 6 cm from nipple). These would be amenable to stereotactic-guided and ultrasound-guided
> core needle biopsies, respectively

- THOUGHTS?

Risk Factors

- What do you think about her risk factor(s) for breast cancer?

- This is an important case for the agent and company. What is the minimum amount of information you need to make a decision?

- Does she need genetic testing? If so, what genes?

- Her sister was diagnosed at 45 y/o. When should screening have started in this applicant?

- Appropriately, she underwent biopsy of the right breast microcalcifications, and this is what they found:

Path
Dx: A. Right breast, lower central, tomosynthesis-guided core biopsy: Ductal carcinoma in situ, intermediate nuclear grade (cribriform and papillary patterns), with focal necrosis, mucin production, and involvement of sclerosing papilloma; columnar cell change and columnar cell hyperplasia. Calcifications associated with DCIS and columnar cell lesions.
Immunohistochemical studies show the following results for DCIS (block A1): - Estrogen receptor (ER): POSITIVE (>95%, strong)
- Progesterone receptor (PR): POSITIVE (>95%, strong)
B. Right breast, 11:00, 6 cm FN, ultrasound-guided core biopsy: Myxoid fibroadenoma (up to 0.6 cm).

- THOUGHTS?

DCIS

- What is DCIS?

- Is there any mortality risk with DCIS?

- How is it treated?

- Anything about her findings that are

    - Favorable/Unfavorable? Size of Tumor? Histopathology? Hormone Receptors?

- Any concerns with the fibroadenoma?

- Now do you want genetic testing?

- What's next?

- Observational Study of ~108,000 women previously diagnosed with DCIS

Figure 1. Twenty-Year Breast Cancer-Specific Survival After Ductal Carcinoma In Situ (DCIS) by Race/Ethnicity
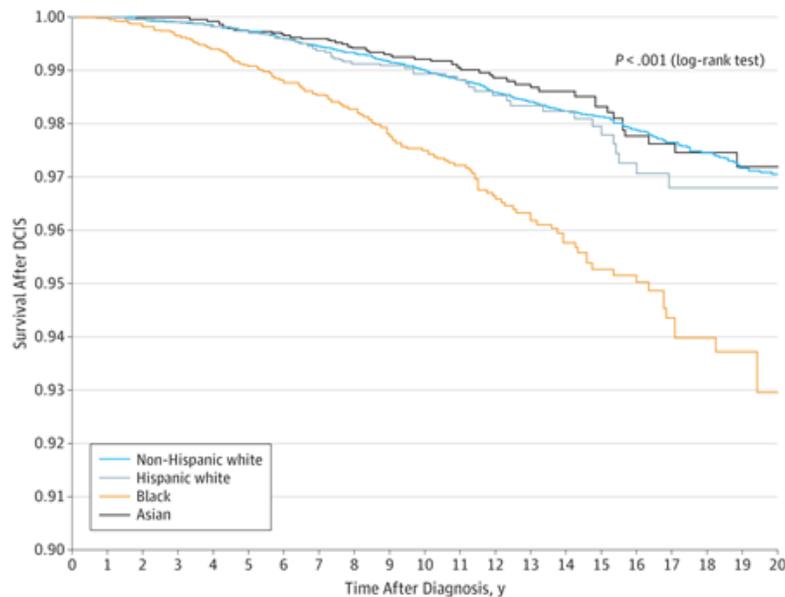
Figure 2. Twenty-Year Breast Cancer-Specific Survival After Ductal Carcinoma In Situ (DCIS) by Estrogen Receptor (ER) Status
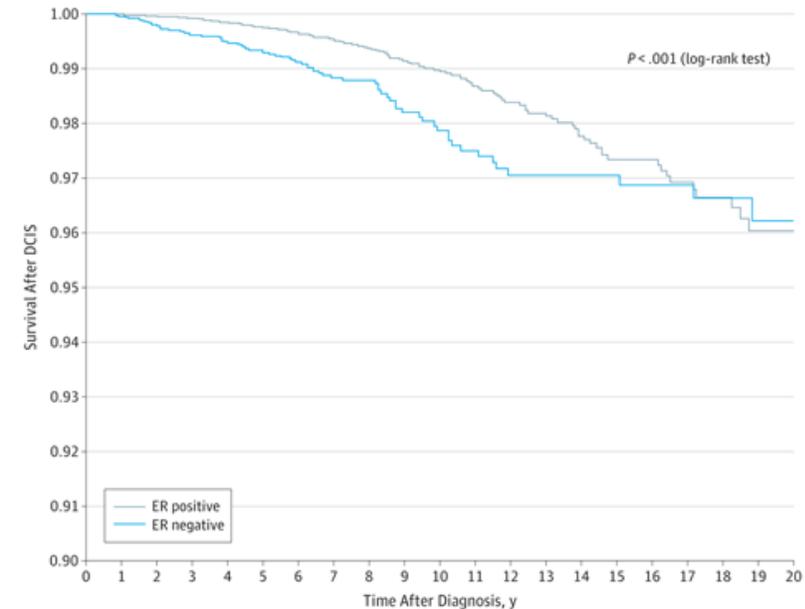
Death occurred by 20 years after a diagnosis of DCIS for 82 of 8908 patients with ER-negative disease and 157 of 46 002 patients with ER-positive disease.

- In light of the family history, dense breasts, and recent diagnosis of DCIS, they opted to do an MRI of the breasts, and this is what was found:

MR Breast
Ind: . Recent diagnosis of right lower central breast ductal carcinoma in situ, intermediate nuclear grade with focal necrosis, mucin production and involvement of sclerosing papilloma; ER/PR positive. Additional right breast biopsy was performed at the 11:00 location with pathology results of myxoid fibroadenoma. Family history of breast cancer in her sister age 45. MRI requested for extent of disease.
Comp: 11/16/2023
Imp: Left breast: Suspicious. BI-RADS Category 4.
1.5 cm spiculated mass within the posterior lower outer left breast. Biopsy is recommended. 0.6 cm round mass within the anterior lower outer left breast. Biopsy is recommended.
Additional non-mass enhancement between and beyond the masses extending 10 cm in greatest dimension. -Possibly focally cortically thickened low left axillary lymph node. Recommend left diagnostic mammogramand MRI directed ultrasound for the masses and lymph node.
Right breast: Known biopsy-proven malignancy.. Non-mass enhancement spanning at least 4.3 cm, possibly more posteriorly up to 10.2 cm surrounding the susceptibility artifact from stereotactic biopsy revealing DCIS. If breast conservation is pursued, consider 2 site MRI guided core needle biopsy to determine extent of disease. Findings and recommendations discussed with the pt by phone on 10 January 2024

- THOUGHTS?

What's next?

- So, now we have a very definitive look at both breasts with MRI. Is MRI more sensitive or specific than MMG and/or US?

- What BI-RADS categories should always be biopsied?

- Remember, this is an important case for the agent and your company? Can we proceed with a rating for this? STD? Substandard? High Substandard?

- If not, then what? Based on what presumptive diagnosis?

BI-RADS assessment categories

Assessment	Management	Likelihood of cancer
Category 0: Incomplete – Need additional imaging evaluation and/or prior mammograms for comparison	Recall for additional imaging and/or comparison with prior examination(s)	N/A
Category 1: Negative	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 2: Benign	Routine mammography screening	Essentially 0% likelihood of malignancy
Category 3: Probably benign	Short-interval (6-month) follow-up or continued surveillance mammography	>0 but ≤2% likelihood of malignancy
Category 4: Suspicious	Tissue diagnosis*	>2 but <95% likelihood of malignancy
Category 4A: Low suspicion for malignancy		>2 to ≤10% likelihood of malignancy
Category 4B: Moderate suspicion for malignancy		>10 to ≤50% likelihood of malignancy
Category 4C: High suspicion for malignancy		>50 to <95% likelihood of malignancy
Category 5: Highly suggestive of malignancy	Tissue diagnosis*	≥95% likelihood of malignancy
Category 6: Known biopsy-proven malignancy	Surgical excision when clinically appropriate	N/A

BI-RADS: Breast Imaging-Reporting and Data System.

* Practice guidelines recommend biopsy for all BI-RADS 4 and 5 lesions. If there are clinical factors (eg, age, comorbidities, etc) for which the patient, in consultation with the clinician, chooses to defer biopsy, the reasoning should be documented in the medical record.

- 40 y/o, sister and mother with breast cancer, DCIS right breast, IDC Left Breast.

- Bilateral Mastectomies

  - Right Simple Mastectomy

  - Left Modified Radical Mastectomy

DUCTAL CARCINOMA IN-SITU OF THE BREAST
Procedure: Mastectomy
Specimen Laterality: Right breast
Tumor Focality: Unifocal
Tumor Site: Central
Size (extent) of DCIS: 0.4 cm
Histologic Type: Ductal carcinoma in situ
Nuclear Grade: Intermediate
Pattern(s): Cribrifrom
Necrosis: Not identified
Estrogen receptor (ER): >95% strong
Progesterone receptor (PR): >95% strong
Surgical Margins (DCIS):
>0.2 cm away from all margins
Additional Findings: myxoid fibroadenoma
Microcalcifications: None
Sentinel Lymph Node Status: No nodes submitted or found
Total Lymph Node Status: No nodes submitted or found
Representative block(s) for ancillary testing: F8
Pathologic Staging (AJCC 8th edition) pT Category: pTis (DCIS) Ductal carcinoma in situ

- 40 y/o, sister and mother with breast cancer, DCIS right breast, IDC Left Breast

Path: A. Breast, left, total mastectomy: Multifocal invasive ductal carcinoma (1.2 cm and 0.4 cm), modified Bloom-Richardson grade 2 of 3, see IDC Template. Multifocal ductal carcinoma in situ.
B. Lymph node, left axilla, sentinel excision #1: One lymph node, negative for carcinoma.
C. Lymph node, left axilla, sentinel excision #2: One lymph node, negative for carcinoma.
D. Lymph node, left axilla, sentinel excision #3: One lymph node, negative for carcinoma.
E. Breast, left additional lateral inferior margin, resection: Negative for carcinoma.
F. Breast, right, total mastectomy: Ductal carcinoma in situ, intermediate nuclear grade. See DCIS Template. Myxoid fibroadenoma.
G. Breast, right additional lateral inferior margin, resection: Negative for carcinoma

Synoptic report
Procedure: Mastectomy
Specimen Laterality: Left breast
Tumor Laterality: Left
Tumor Focality: Multifocal
Tumor Size: 1.2 cm and 0.4 cm
Histologic Type: Invasive carcinoma of no special type (invasive ductal Carcinoma)
Histopathologic Grade (modified Bloom-Richardson): Overall GradE: II; * Tubular differentiation: 3; Nuclear pleomorphism: 2; Mitotic count: 1; Nottingham Score: 6/9
Ductal Carcinoma in Situ: Present
Nuclear Grade: Intermediate
Necrosis: Present, comedo
Biomarker Status:
Estrogen receptor (ER): 95%
Progesterone receptor (PR): 95%
Her2 (IHC): Negative (1+
Pathologic Staging (AJCC 8th Edition): Primary Tumor: pT1c Tumor >10 mm but <20 mm in greatest dimension m (multiple foci of invasive carcinoma)
Regional Lymph Nodes: pN0 No regional lymph node metastasis identified or ITCs only
Distant Metastasis: Not applicable - pM cannot be determined from the submitted specimen(s)

- **STAGE? THOUGHTS?**

512,447 Women, England, Early Breast Ca

- Diagnosis thorough and reliable?
  - Stage and Grade R breast TNM
  - Stage and Grade L breast TNM
- Treatment appropriate to Stage, Grade, Molecular Characteristics? Does she need anything else?
  - Oncotype Dx?
- Surveillance expectations?
  - CXR, Tumor Markers, Other Labs, PET Scans?
- 5 year survival?
- Insurable at what point and with what terms?
- Concerns for mortality?
  - Based on Tumor
  - Based on Treatment?
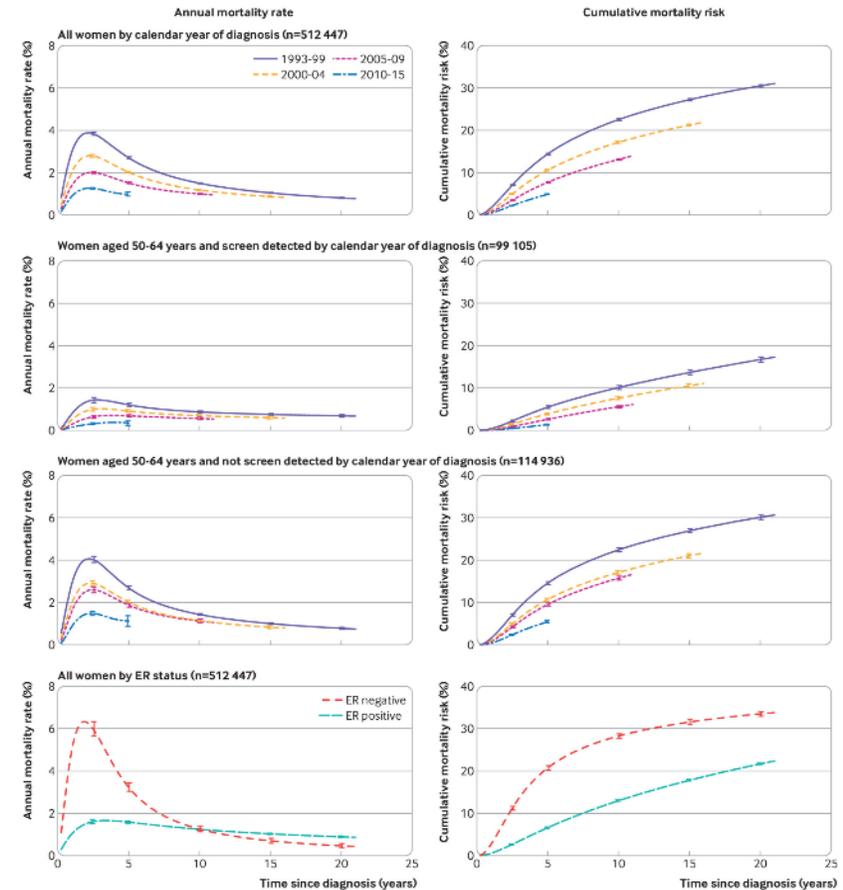
- 68 y/o F, $1.5MM

- H/O IBC 2 years prior to application

- Retired

- Medical History: Metabolic Syndrome X, HTN, Venous Insufficiency Bilateral Lower Extremities

- Medications: Anastrozole, HCTZ, Lisinopril

- Breast Cancer History:

  - Diagnosed on screening mammography in '23, prior mammo 2018

  - Bilateral Lumpectomy with SNB in '23

- Exam and Labs

  - 5'6", 242 lbs, BP and HR normal

  - A1c 6.1

  - Labs otherwise normal

Clinical History

Malignant neoplasm of central portion of left breast in female, estrogen receptor positive and malignant neoplasm of lower outer quadrant of right breast of female, estrogen receptor positive. Medical History: Has the two same preop diagnoses in addition to trigger finger of left hand. Hypertension. Family history of breast cancer. Palpitations.

Pathologic Diagnosis

A. Right axillary sentinel lymph node #1, count 5, excision:
- 1 lymph node with isolated tumor cells by H&E and AE 1/3

B. Right axillary sentinel lymph node #2, count 29, excision:
- 1 lymph node with macrometastatic carcinoma by H&E, 11 mm deposit

C. Right axillary sentinel lymph node #3, count 101, excision:
- 2 lymph nodes, negative for carcinoma by H&E, AE 1/3 and LMWK

D. Left axillary sentinel lymph node #1, count 213, excision:
- 2 lymph nodes with isolated tumor cells by H&E, AE 1/3, and LWMK

E. Breast, left, bilateral needle localized lumpectomies:
- Invasive ductal carcinoma, grade 2, measuring 1.5 cm, see synoptic report #1
- Invasive carcinoma is 4 mm from the closest margin (posterior)
- Ductal carcinoma in situ (DCIS), intermediate nuclear grade
- DCIS is 0.5 mm from the closest margin (posterior), and within <1 mm from the posterior margin along a span of 3 mm

L. Breast, right, bilateral needle localized lumpectomies:
- Invasive ductal carcinoma, grade 2, measuring 1.3 cm, see synoptic report #2
- Invasive carcinoma is 6 mm from the closest margin (posterior)
- Ductal carcinoma in situ (DCIS), intermediate nuclear grade
- DCIS is 5 mm from the closest margin (posterior)

Estrogen receptor: Positive (100%, strong intensity)
Progesterone receptor: Positive (100%, strong intensity)
HER2 IHC: Not performed
HER2 FISH: Negative (ratio: 1.0, avg. HER2/cell: 2.2) per outside report
Specimen in which ER/PR/HER2 performed: Previous outside biopsy S22-002420
pTNM: pT1c pN0(sn)(i+)
Additional findings: Biopsy site changes
Comments: Immunohistochemical statins (on block E9) support the diagnosis. SMMS and p40 highlight myoepithelial cells surrounding foci of DCIS. ERG, and CD31 highlight endothelial cells.

Breast Case 2—Some Questions

1. Diagnosis?
2. Stage?
   - L
   - R
3. Grade?
4. Receptor Status?
5. Does ITC make a difference?
6. What about micro metastasis?
7. What is next for her?
8. Any more studies needed?

- **Right Breast**

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

- **Left Breast**

T1* N0 M0	G2	Positive	Positive	Positive	IA
				Negative	IA
T0 N1mi M0			Negative	Positive	IA
				Negative	IA
T1* N1mi M0		Negative	Positive	Positive	IA
				Negative	IA
			Negative	Positive	IA
				Negative	IB

- ITC
  - Definition: Individual tumor cells identified in nodes
  - Mortality Concerns: Formally, no, but…
  - Staging difference: None (yet?)
- Micrometastasis
  - Definition: ~200 cells but no deposit >2mm; clumps of tumor cells generally between 0.2-2mm
  - Mortality Concerns <0.2mm likely more close to ITC; Nmic has excess risk for recurrence, distant recurrence, and decreased Overall Survival
  - Staging Difference: it depends on the other factors of importance, like hormone receptors, Her2neu,and Grade

- What is the purpose of Oncotype Dx?

- Does a specific score change treatment?

- To this point, are we comfortable with the Diagnosis? Staging? Treatment?

- Ready to offer? And, at roughly what terms (STD, Preferred, Rated)?

- If not, what more do we need to know?

- After lumpectomy and a metastatic workup (neg whole body PET CT), she underwent radiation of both breasts and axillae.

- She was offered cytotoxic chemo but opted not to have it.

- She has been on anastrozole since radiation finished.

- Now, can we offer on this case that is important to the agent and company? Or, are you going to persist in your role of the insurance prevention division?

- What more would you like to know?

- Since completing radiation, she has followed every 6 months with Oncology.

- She suffered some burns of the skin of the breast and axillae and was followed until resolution of those burns by Rad Onc (~4 months).

- Her last mammogram was 6 months prior to application, and it was normal except for post-surgical changes.

- Now, can we offer?

- What things would you consider as risks for excess mortality in this woman?

  - Based on the history of cancer

  - Based on the treatment rendered

  - Based on her underlying risk factors

- Angela N. Giaquinto MSPH, Hyna Sung PhD et al. Breast Cancer Statistics 2024; CA:A Cancer Journal for Clinicians; Vol 74, Iss 6; pp477-495.

- World Cancer Research Fund, www.wcrf.org

- Chlebowski, RT et al. Factors that modify breast cancer risk in females; UpToDate, Mar 07, 2025.

- Joe, BN, Esserman, LJ. Breast Biopsy; UpToDate; Jul 2025.

- Joe, BN. Clinical features, diagnosis, and staging of newly diagnosed breast cancer; UpToDate; Jun 20, 2025.

- Taghian, A. Overview of the treatment of new diagnosed, invasive, non-metastatic breast cancer; UpToDate; Jul 22, 2025.

- Taghian, A. Adjuvant radiation therapy for women with newly diagnosed, non-metastatic breast cancer; UpToDate, Jul 18, 2025.

- Pritchard, KI. Adjuvant endocrine and targeted therapy for postmenopausal women with hormone receptor-positive breast cancer. UpToDate, Jul 18, 2025.

- Collins, LC, Laronga, C, Wong, JS: Breast ductal carcinoma in situ: Epidemiology, clinical manifestations, and diagnosis. UpToDate, Feb 8, 2024.

- Collins, LC et al. Ductal carcinoma in situ: Treatment and prognosis. UpToDate, Jul 30,2025.

- Tylor, Carolyn et al. Breast cancer mortality in 500 000 women with early invasive breast cancer diagnosed in England, 1993-2015: population based observational cohort study. BMJ; 381; 13 June 2023.

- Narod, SA et al. Breast cancer mortality after a diagnosis of Ductal Carcinoma In Situ. JAMA Oncology, Vol. 1, No. 7; October 2015
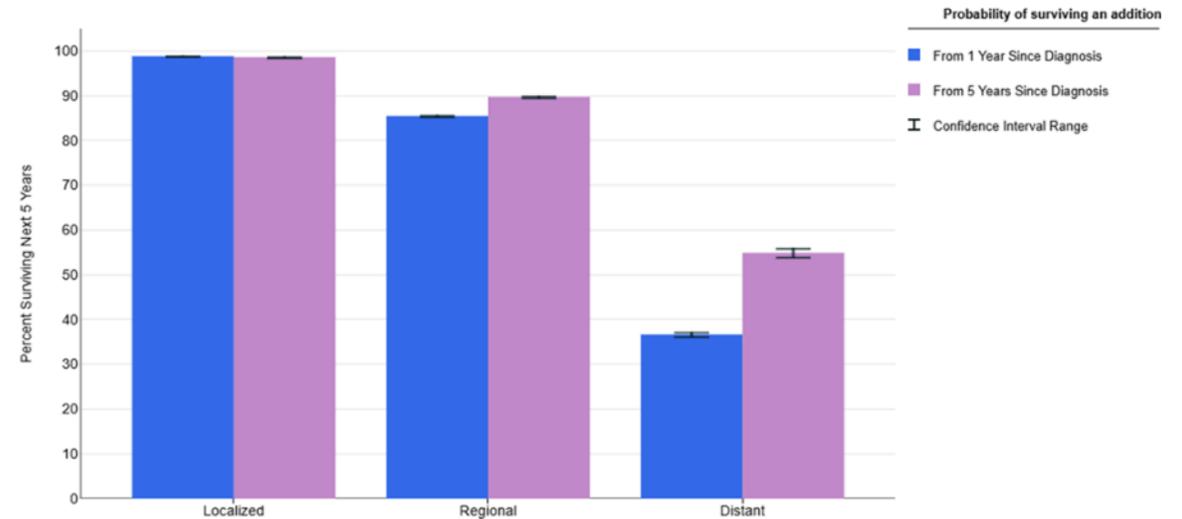
Breast Cancer

Breast
Stage Distribution of SEER Incidence Cases, 2013-2022
By Age, Female, All Races / Ethnicities
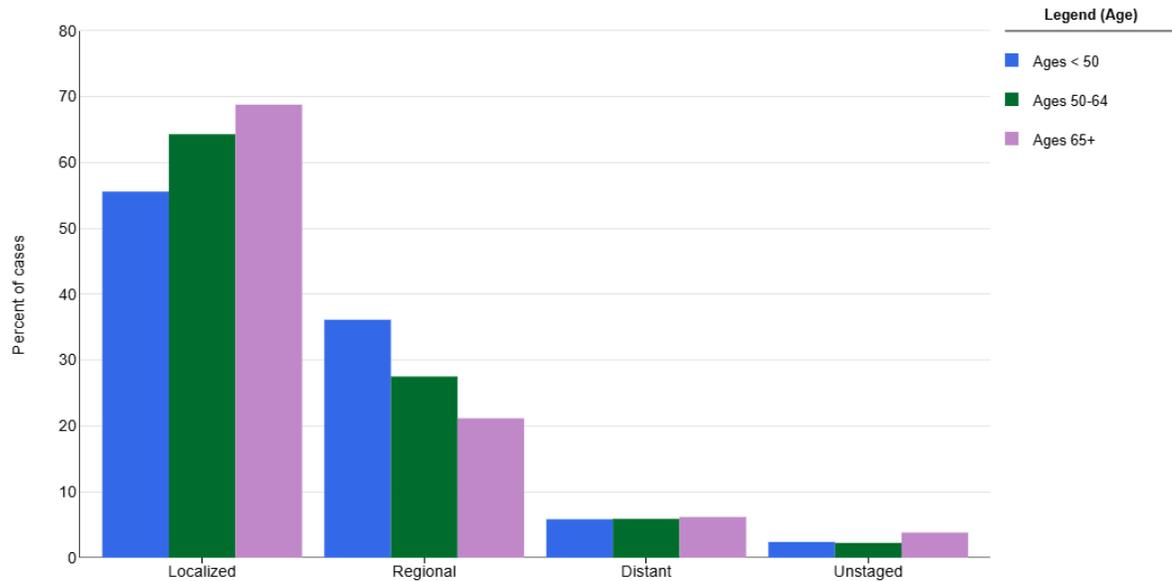
Breast
SEER 5-Year Conditional Relative Survival Rates, 2000-2021
By Stage at Diagnosis and Surviving 5 More Years, Female, All Races / Ethnicities, All Ages

Disease-Specific Survival (DSS) -- California Cancer Registry prognostic stage

Log-rank *P* < .001
C index, 0.8426
AIC, 80661.68

NLM Image ID A026044

MALGNANT MELANOMA

Malignant melanoma -trends

- 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

Incidence and Mortality Rates for Melanoma of the skin Cancer Over Time

Incidence Rates

Female • Male • Sexes combined
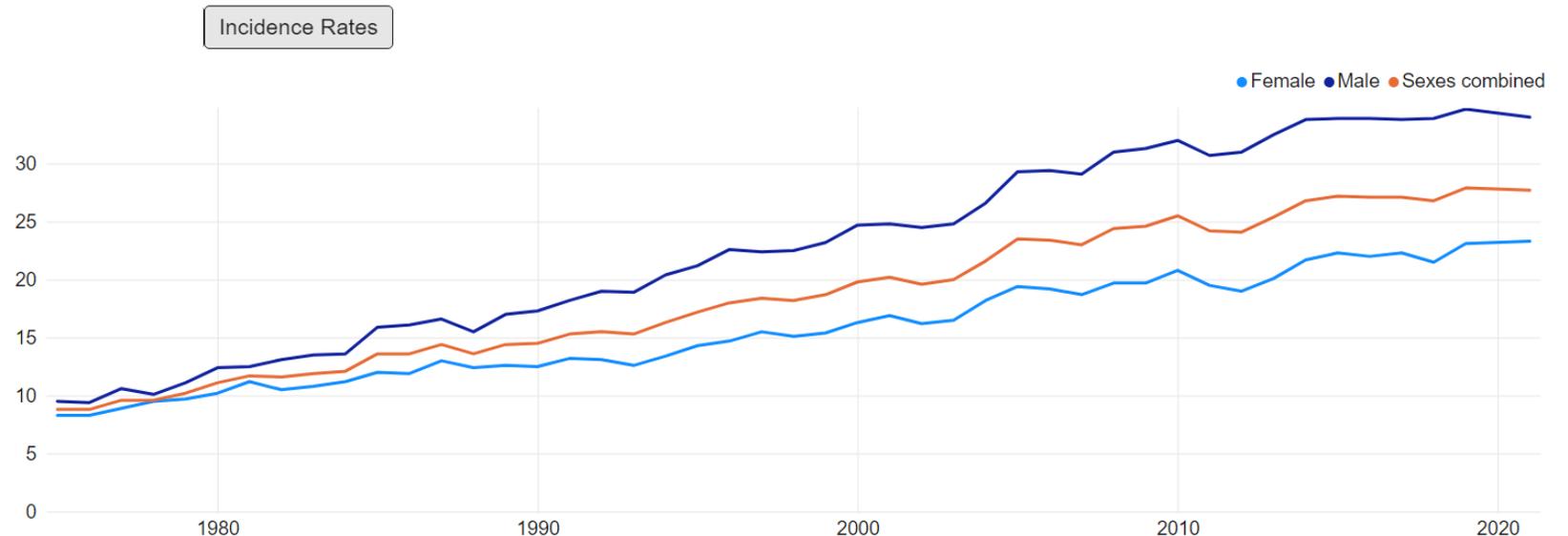
©American Cancer Society, 2025
Data Sources: Surveillance, Epidemiology, and End Results 8 registries, National Cancer Institute, 2022
Average annual rate per 100,000, age-adjusted to the 2000 US standard population. Incidence is adjusted for delays when possible.

Malignant melanoma -trends

Incidence and Mortality Rates for Melanoma of the skin Cancer Over Time
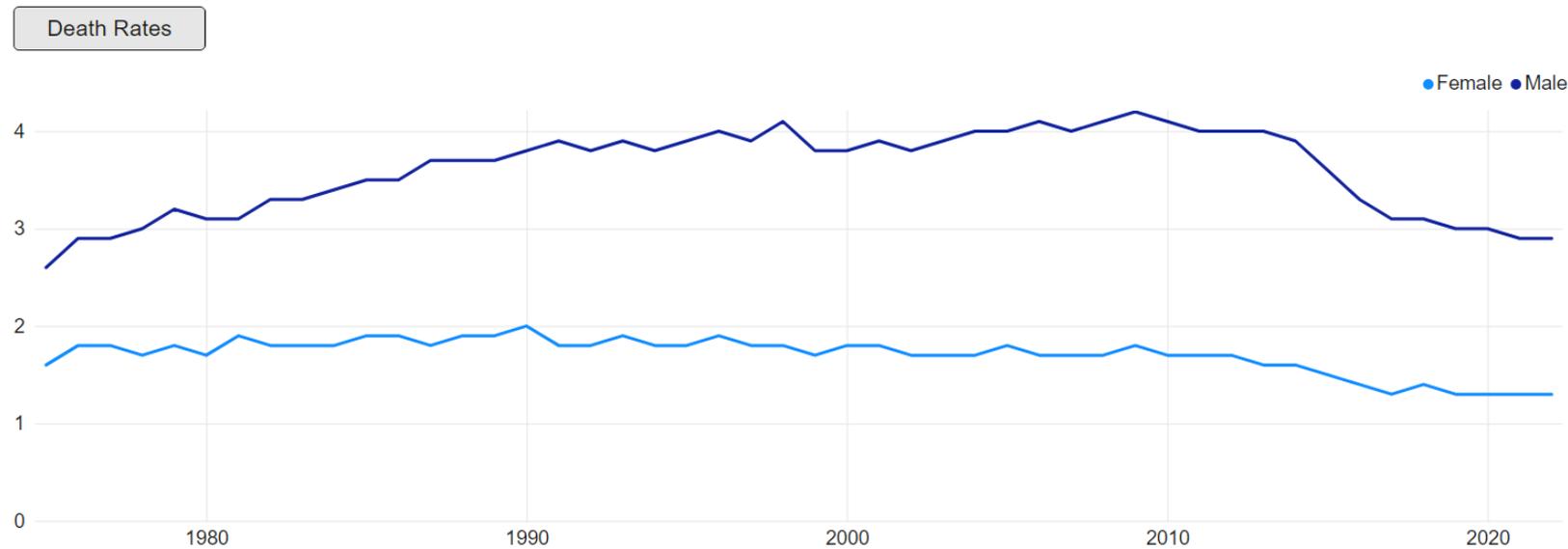
But declining death rates

©American Cancer Society, 2025
Data Sources: National Center for Health Statistics, Centers for Disease Control and Prevention, 2022
Average annual rate per 100,000, age-adjusted to the 2000 US standard population. Incidence is adjusted for delays when possible.

Melanoma Basics

Estimated New Cases in 2025	104,960
% of All New Cancer Cases	5.1%

Estimated Deaths in 2025	8,430
% of All Cancer Deaths	1.4%
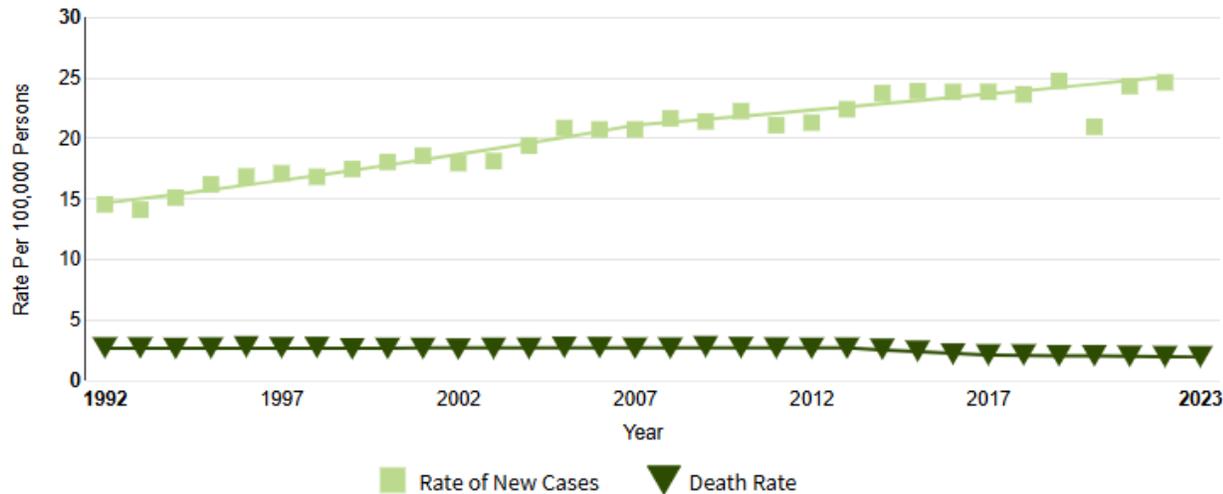
5-Year Relative Survival

94.7%

2015–2021

➤ Rising incidence, but not mortality

➤ Lifetime risk ~ 2.2% in the U.S.

➤ Estimated 1.6 million people living with melanoma in U.S.

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

5-Year Relative Survival

Stage	Percent
Localized	99.5%
Regional	70.6%
Distant	31.9%
Unknown	90.2%
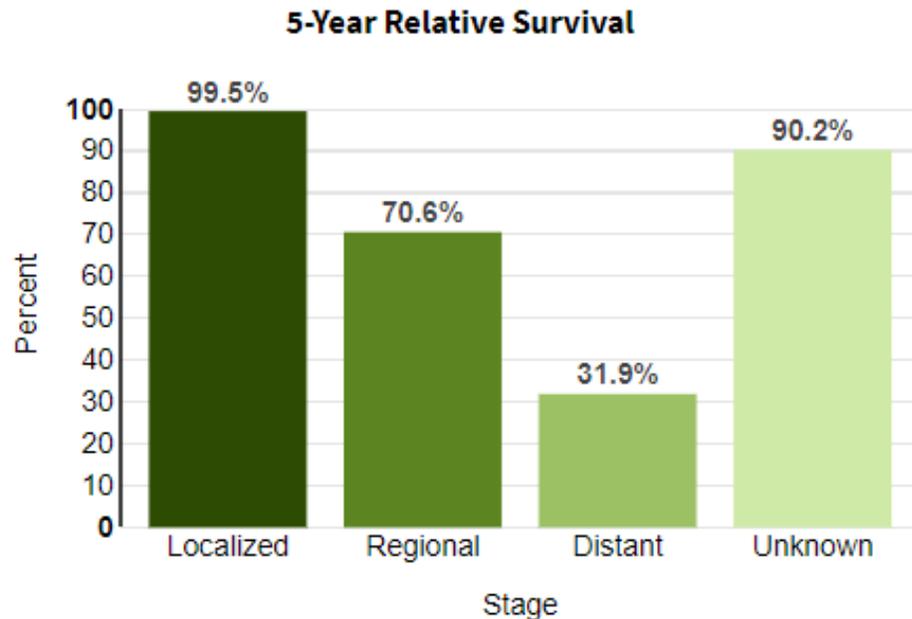
Percent of Cases & 5-Year Relative Survival by Stage at Diagnosis: Melanoma of the Skin

Percent of Cases by Stage

- **Localized (82%)** Confined to Primary Site
- **Regional (9%)** Spread to Regional Lymph Nodes
- **Distant (4%)** Cancer Has Metastasized
- **Unknown (6%)** Unstaged
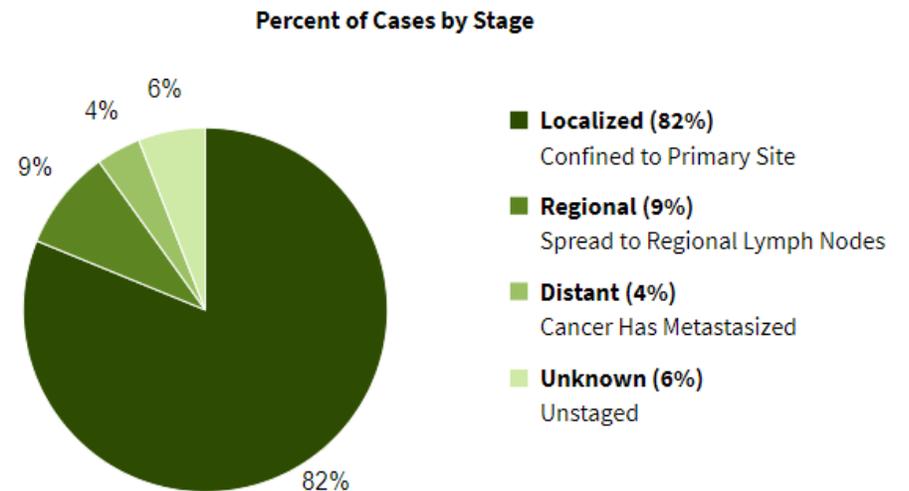
Improving melanoma survival at all stages

Melanoma of the Skin
Recent Trends in SEER Relative Survival Rates, 2004-2022
By Stage at Diagnosis, 10-year Relative Survival, Both Sexes, All Races / Ethnicities, All Ages

Melanoma Case #1

- 34 year-old male, ER resident. $2,000,000 Term. Bene spouse.
- Application:
  - Melanoma – July 2021, R knee, stage 1, surgically removed September 2021, no recurrence
  - Annual follow-up with dermatologist
  - Family history – Mother with DM
  - No PCP
- Insurance lab April 2025:
  - 6.1.260. 131/80.
  - Gluc 97, a1c 5.47, Chol 225, HDL 39, Triglycerides 120
  - UA - cotinine positive
    - Offer?

Melanoma SEER Survival Rate by Age and Stage

Melanoma of the Skin
SEER 5-Year Relative Survival Rates, 2015-2021
By Stage at Diagnosis and Age, Both Sexes, All Races / Ethnicities

Legend (Age)
- Ages < 50
- Ages 50-64
- Ages 65+
- Confidence Interval Range

Created by https://seer.cancer.gov/statistics-network/explorer/ on Wed Jul 30 2025.
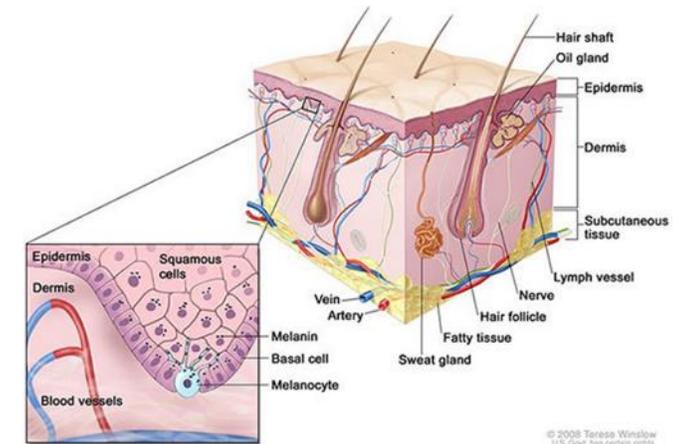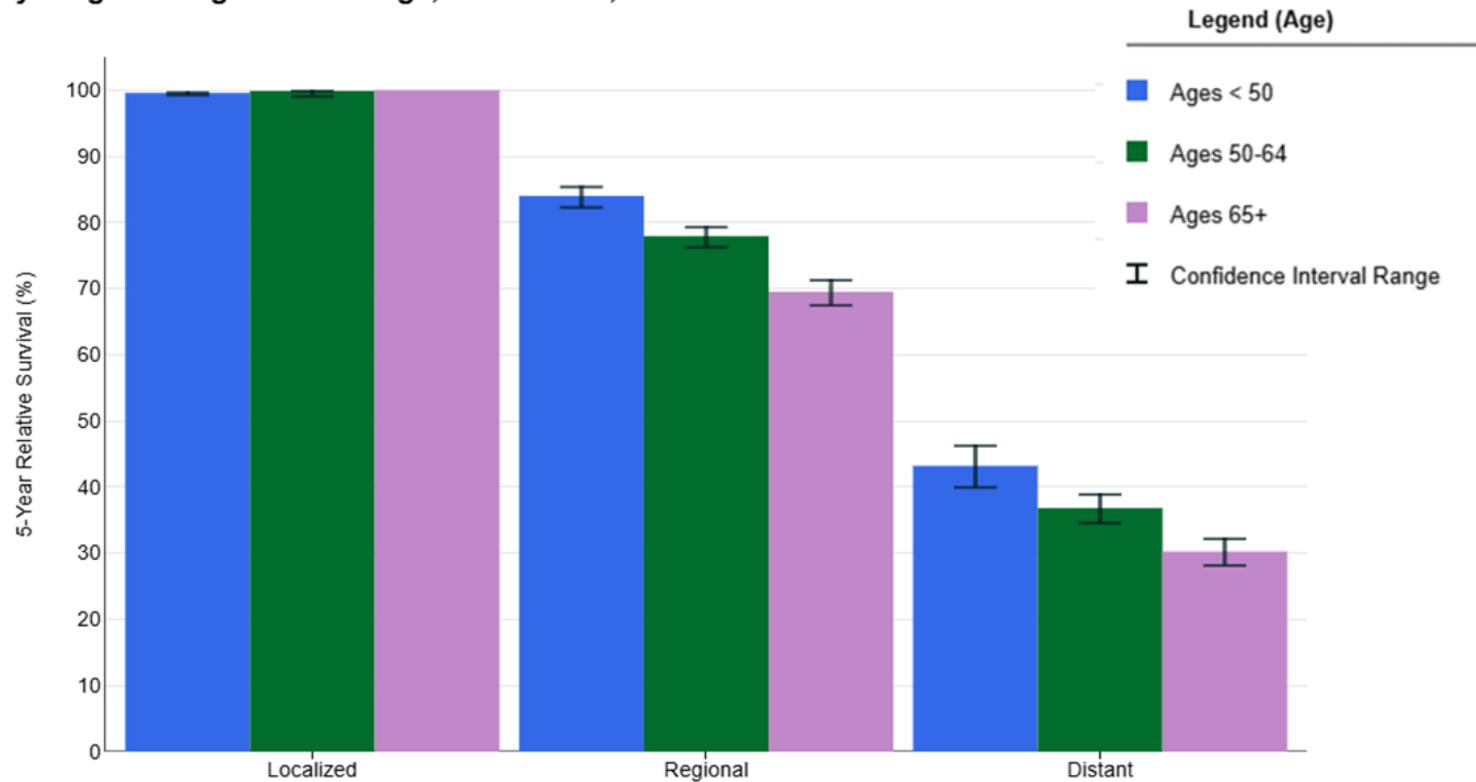
Dermatology APS:

- Aug 2021:

  - MM right knee; invasive per outside path. No medical history, no medications.

  - Exam: Multiple scattered benign appearing nevi. Fitzpatrick II skin. No inguinal adenopathy evident.

  - Frequent sunburns as child. Fam hx melanoma paternal uncle.

  - Plan WLE.

    - What now?

| Asymmery | Border | Color | Diameter (>6mm) | Evolution or Elevation |
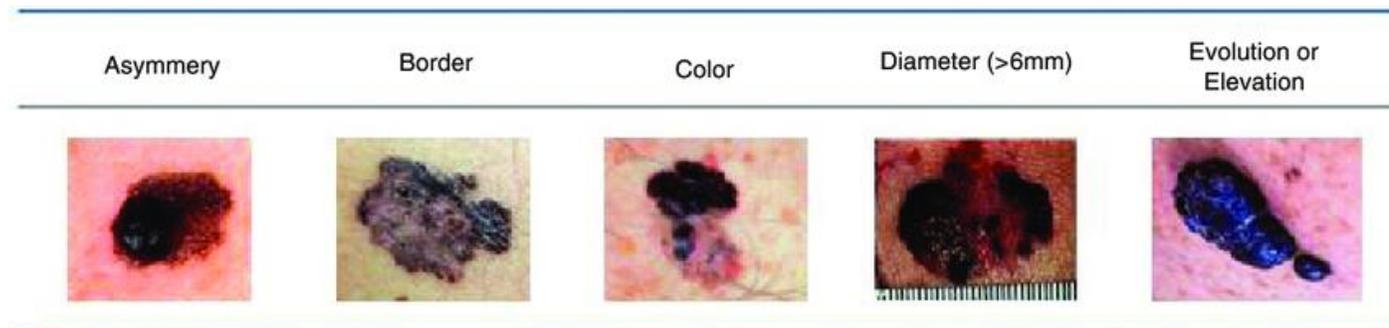
https://www.researchgate.net/figure/ABCDE-System-for-Diagnosis-of-Melanoma_fig1_321583297

Right leg pathology report:

Diagnosis
DIAGNOSTIC SUMMARY:
MALIGNANT MELANOMA, INVASIVE (PER OUTSIDE PATHOLOGY REPORT
P19-12147/DL19-78910) [NO RESIDUAL MELANOMA IN CURRENT SPECIMEN]
MAXIMUM TUMOR (BRESLOW) THICKNESS: 1.05 MM
ULCERATION: NOT IDENTIFIED
MITOTIC RATE: 2-3 PER SQUARE MILLIMETER
FINAL MARGINS: NEGATIVE FOR INVASIVE MELANOMA
SATELLITE / IN-TRANSIT METASTASIS: NOT IDENTIFIED
LYMPH NODES: TWO BENIGN SENTINAL LYMPH NODES (0/2)

➢ Anatomic stage?

➢ Grade?

➢ Favorable and unfavorable factors?
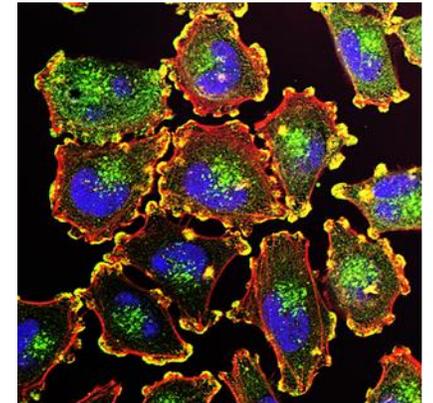
Metastatic melanoma cells_Credit- JC
Valencia, NCI Center for Cancer Research

- Tumor Thickness – Continuously increasing risk with increasing thickness
  - T1: $\leq$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
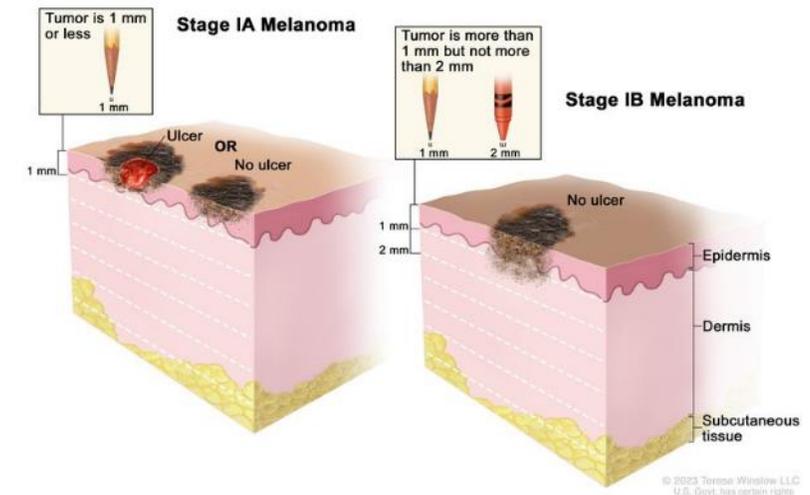
Not all similarly staged melanomas are created equal

Besides thickness, ulceration, and metastases…

Additional factors associated with higher recurrence risk:

- Older age at diagnosis, males
- Location on scalp, neck, or lip (extremities most favorable)
- Increasing mitotic rate
- Lymphovascular invasion
- Nodular growth pattern (independent of thickness)
- Lack of tumor-infiltrating lymphocytes
- De novo origin (non-nevus associated)
- Regression of >50%
- Circulating tumor cells or cell-free tumor DNA
- ? Gene expression profiling (DecisionDX-Melanoma, MelaGenix), proteomics

Nodular melanoma. Up-to-date
Courtesy of James C Shaw, MD.

Each has been shown to increase the melanoma mortality risk by 1.3 to 3-fold

34 year-old male – Melanoma

➢ Favorable and unfavorable factors?

➢ Offer?

- Subsequent dermatology visits:
  - Dec 2021: Excision site healed and without residual. Multiple nevi, no change.
  - June 2022, February 2023: N.E.D.
  - February 2024: Irregular nevus; biopsy moderate atypia
  - August 2024, March 2025: N.E.D.

➢ Treatment and follow-up adequate?

➢ Mortality risks?

Diagnosis
DIAGNOSTIC SUMMARY:
MALIGNANT MELANOMA, INVASIVE (PER OUTSIDE PATHOLOGY REPORT
P19-12147/DL19-78910) [NO RESIDUAL MELANOMA IN CURRENT SPECIMEN]
MAXIMUM TUMOR (BRESLOW) THICKNESS: 1.05 MM
ULCERATION: NOT IDENTIFIED
MITOTIC RATE: 2-3 PER SQUARE MILLIMETER
FINAL MARGINS: NEGATIVE FOR INVASIVE MELANOMA
SATELLITE / IN-TRANSIT METASTASIS: NOT IDENTIFIED
LYMPH NODES: TWO BENIGN SENTINAL LYMPH NODES (0/2)

C. SKIN, LABELED AS "RIGHT LEG MELANOMA", EXCISION:
· BENIGN SKIN WITH BIOPSY SITE REACTION
· NO RESIDUAL MELANOMA IDENTIFIED
· BENIGN SURGICAL MARGINS

PATHOLOGIC STAGING (pTNM): pT2a pN0 (sn)(i-)
NUMBER OF LYMPH NODES EXAMINED: TWO (2)
NUMBER OF LYMPH NODES INVOLVED: ZERO (0/2)

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 $\geq$0.8mm thickness

  ▪ Not performed for T1 lesions or carcinoma-in-situ unless additional high risk features present

➤ Adjuvant therapy for stage IIB or IIC or node positive disease

  ▪ One year of adjuvant immunotherapy with a PD-1 inhibitor

  ▪ BRAF inhibitor/MEK inhibitor if V600 BRAF mutation

➤ Metastatic disease

  ▪ Major recent advances and some flattening of the mortality curves after 2-3 years

    ✓ Possible cures?

  ▪ Immunotherapy with a PD-1 inhibitor or BRAF inhibitor/MEK inhibitor if V600 BRAF mutation

  ▪ Surgical metastasectomy, stereotactic radiation therapy, cytotoxic chemotherapy, and/or intralesional therapy with talimogene laherparepvec (T-VEC) in select situations

Figure 1. Relative Cumulative Survival by Stage
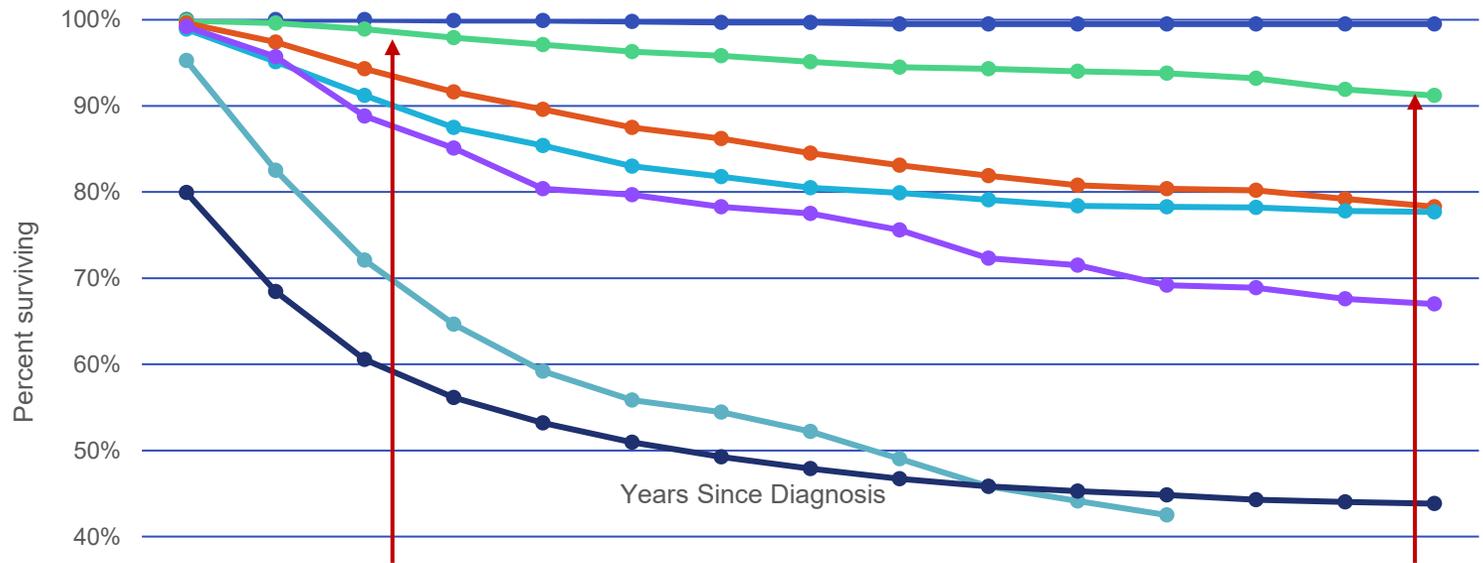
- 15 yr survival

	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%

Overall survival by melanoma stage

10-year melanoma-specific survival (AJCC database) for T2 lesion by mitotic rate:

- <1: 90.9%
- 1-1.99: 83.1%
- 2-4.99: 79.4%
- 5-9.99: 76.5%

Thompson. J Clin Oncol. 2011;29(16):2199-2205. doi:10.1200/JCO.2010.31.5812

Adjusted HR melanoma-specific mortality, T1-2, by mitotic rate:

0	1.0	0.65
1	1.55	1.0
2-3	2.89	1.86
4-10	4.10	2.65
>10	7.69	4.96

Patuzzo. Cancer. 2023;129(15):2331-2340. doi:10.1002/cncr.34824

Offer?
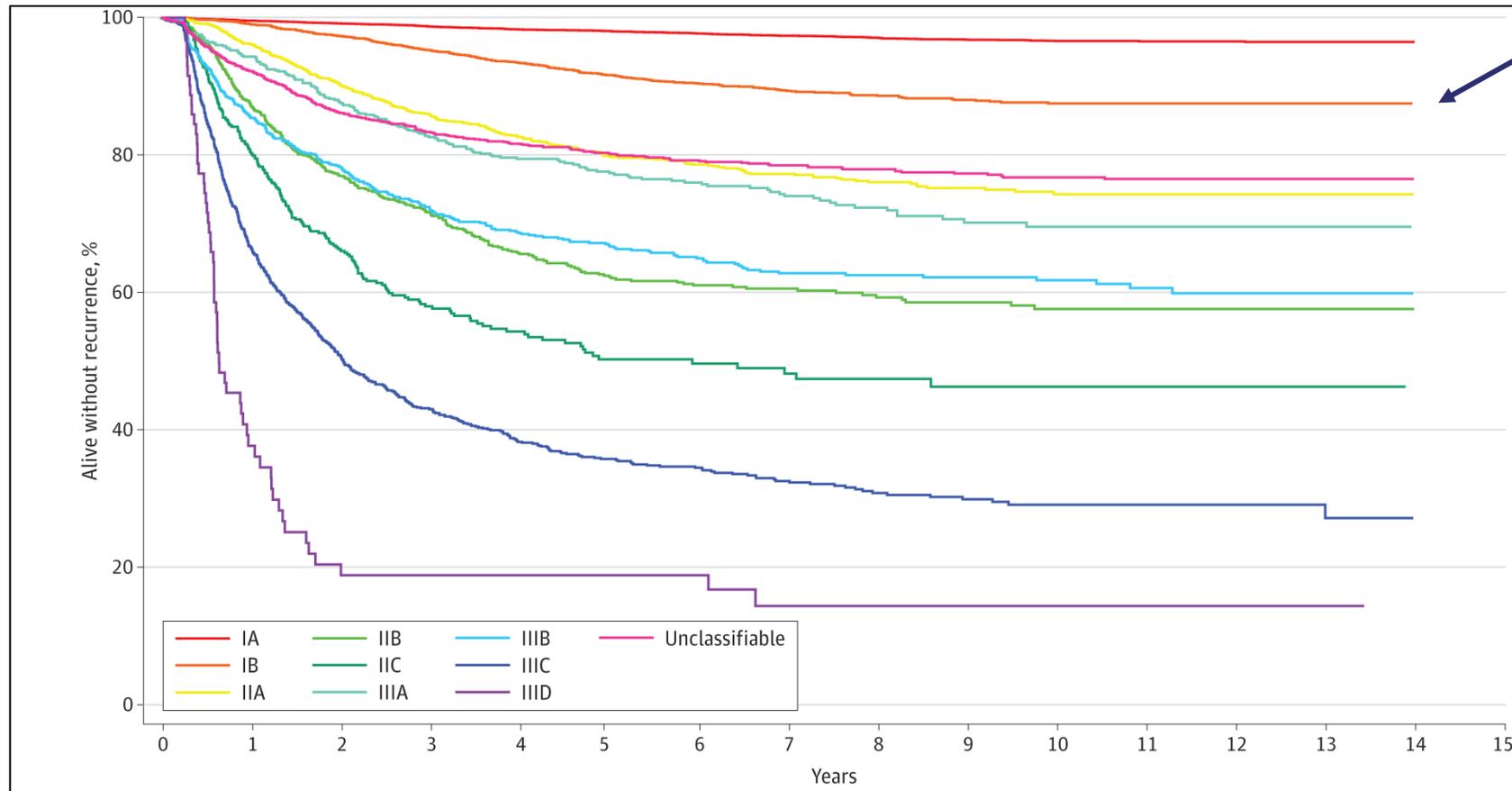
Stage IB

Recurrence rates
Overall
- 10.6% by 10 years
- A majority (60-70%) as distant metastases

Stage IB
- 8.2% at 10 years
- 38% of these within 3 yrs
- 68% within 5 yrs

Other sources found ~5% recurrence rate after 5 years

Melanoma-Specific Recurrence-Free Survival per American Joint Committee on Cancer Eighth Edition Stage

Data are from 25 310 Danish patients with stage IA to IIID melanoma.

JAMA Dermatol. 2023;159(11):1213-1222. doi:10.1001/jamadermatol.2023.3256

AAIM 133rd Annual Meeting

October 18-23, 2025

Melanoma risk factors (and risk of 2nd melanoma!)

Risk Factor	Estimated Relative Risk
Numerous melanocytic nevi (vs <15)	1.5 (16-40); 4.7 (80-100)
Dysplastic nevi	2.3 (1.5-6.4 for 1 vs 5+ DNs)
History of intense sun exposure/sunburns	1.7-5.4
Indoor tanning >10 times/year	2.5 in women age <40
Fair skin	2.1
Red hair / MC1R genotype	3.1-3.6 (10-25 if also >20 nevi)
Inability to tan	3.4
Personal history of melanoma	4.3
Family history of melanoma	1.7-3.7
Parkison disease	2.0
Organ transplant	3.6

Photo by Jared Rice on Unsplash

Melanoma Case #1 -- What if…

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

- Stage then?

  T2a, N1a, M0 = Stage IIIA

- Usual therapy then for stage IIIA disease?

  Adjuvant PD-1 inhibitors now advised (nivolumab or pembrolizumab)

  OR

  Dabrafenib plus trametinib if BRAF-mutant positive

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

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

Staging is closely tied to prognosis

SEER analysis – Survival by Stage Group

Figure 1. Relative Cumulative Survival by Stage
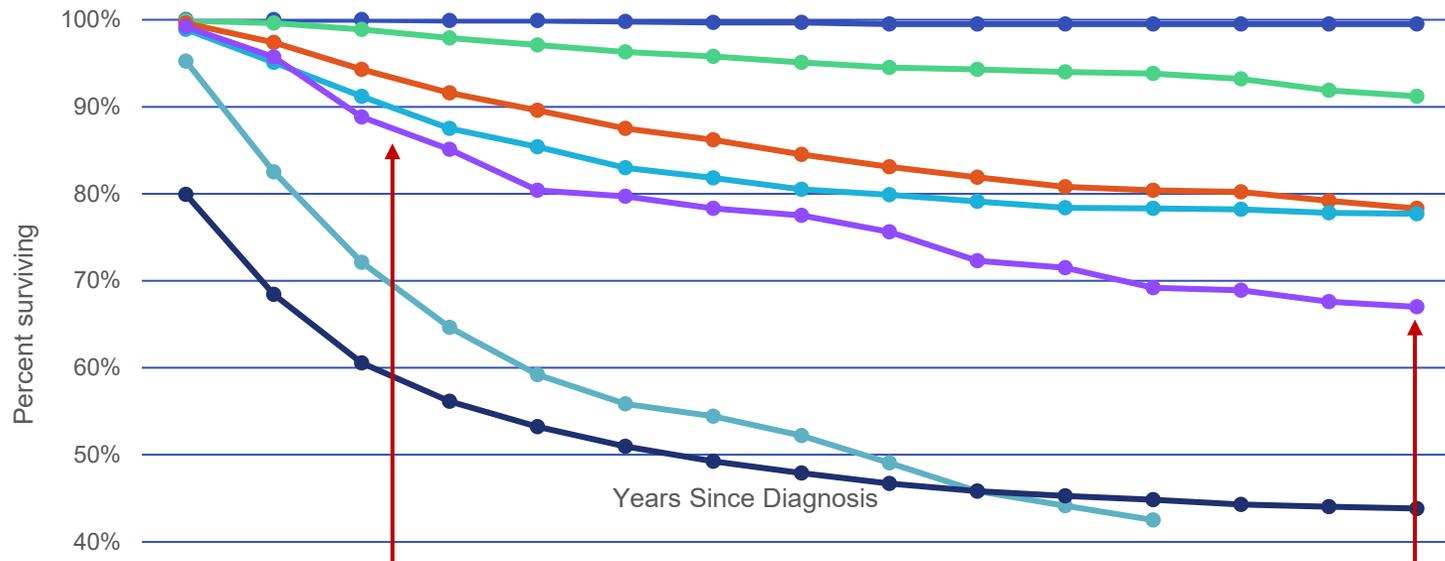
Overall survival stage IIIA per AJCC database:
- 94% at 5 years
- 88% at 10 years
- 83% at 15 years

	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%

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	

- T2a, N1a = Stage group IIIA

- Overall fares better than thicker melanomas with negative SLN!
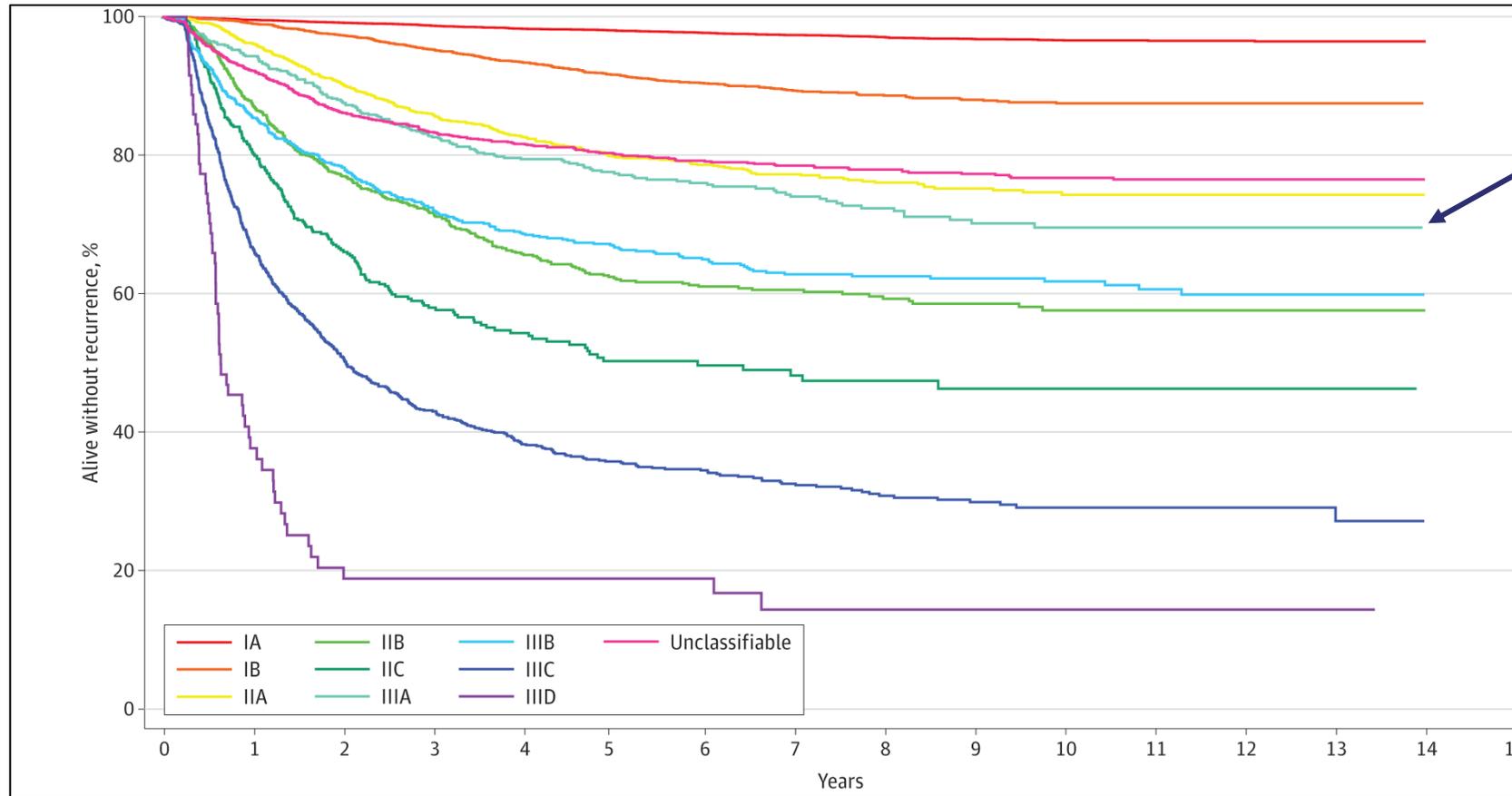
Stage IIIA (but just 2.5% of 25,720 cohort)

Recurrence rates
Stage IIIA
- 24.8% at 10 years
- 58% of these within 3 yrs
- 74% within 5 yrs

Other sources found ~5-8% recurrence rate from 5-10 years out (similar to lower staged lesions?)

Melanoma-Specific Recurrence-Free Survival per American Joint Committee on Cancer Eighth Edition Stage

Data are from 25 310 Danish patients with stage IA to IIID melanoma.

JAMA Dermatol. 2023;159(11):1213-1222. doi:10.1001/jamadermatol.2023.3256

AAIM 133rd Annual Meeting

October 18-23, 2025

Melanoma Survival by Age and Stage
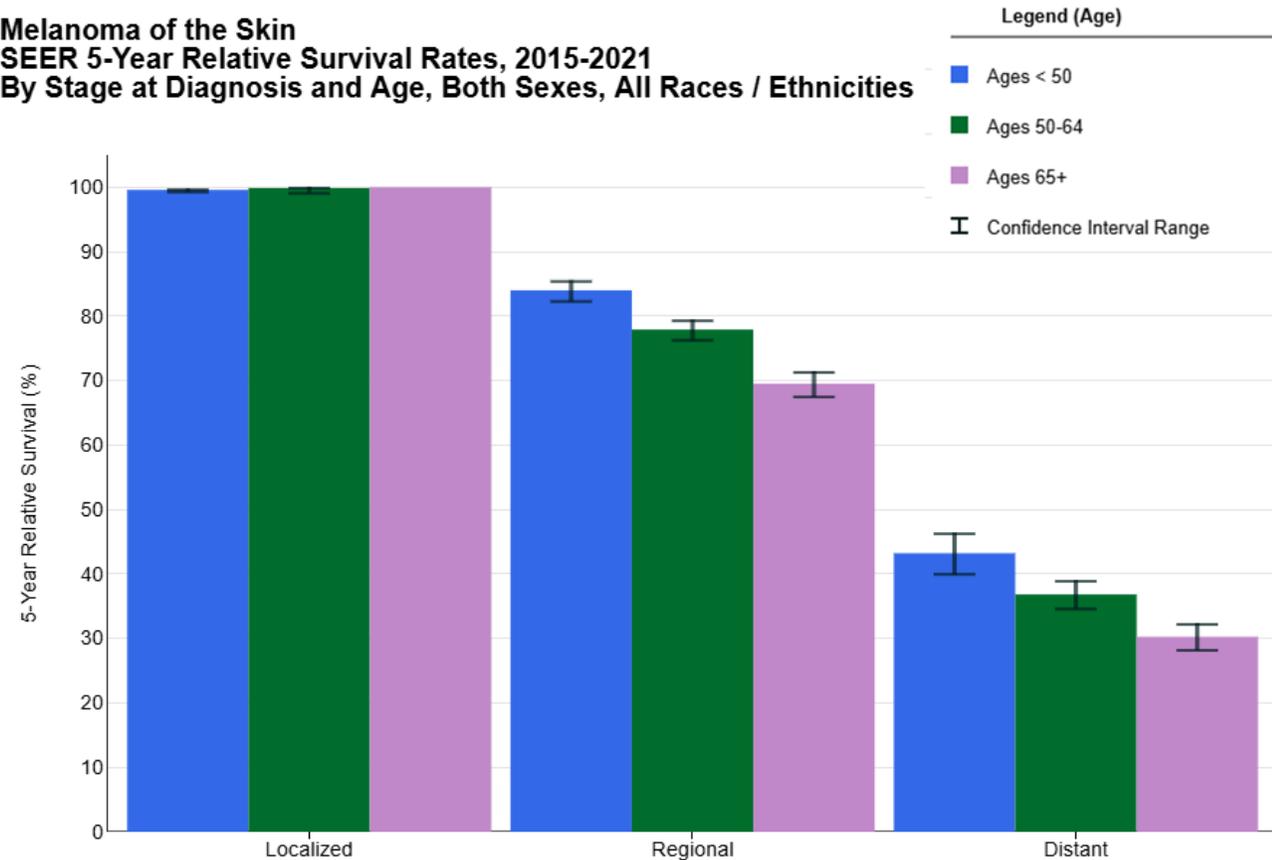
Conditional survival by stage

Melanoma of the Skin
SEER 5-Year Conditional Relative Survival Rates, 2000-2021
By Stage at Diagnosis and Surviving 5 More Years, Both Sexes, All Races / Ethnicities, All Ages

Four major melanoma subtypes

1. 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

2. Nodular
   - Accounts for ~15% of all melanomas
   - Enter a vertical invasive growth phase early on
   - Increased risk, even after accounting for thickness

3. 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

4. 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

8Oct2020

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

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
T3b	>2 to 4 mm	With ulceration
T4	>4 mm	Unknown or unspecified
T4a	>4 mm	Without ulceration
T4b	>4 mm	With ulceration

Regional lymph nodes (N)

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
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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 $\leq$0.5mm

- 3 of 428 pts with melanoma $\leq$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 $\leq$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

T1a Mortality Ratio by Interval - All ages

T1a Mortality Ratio by Age
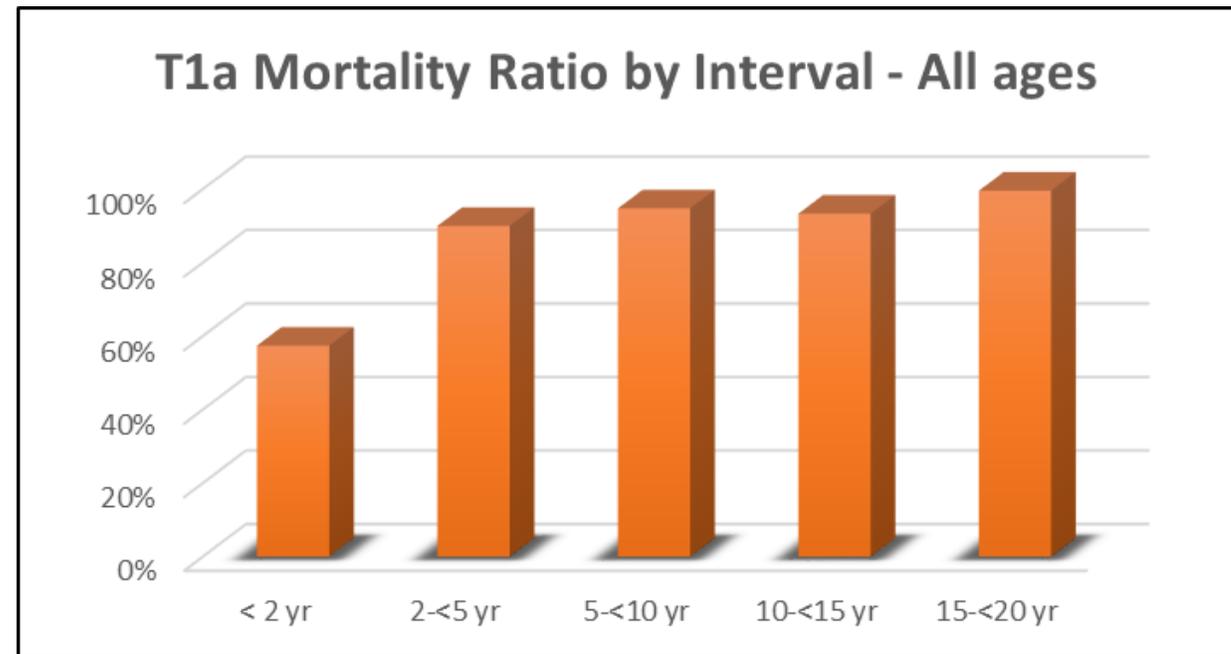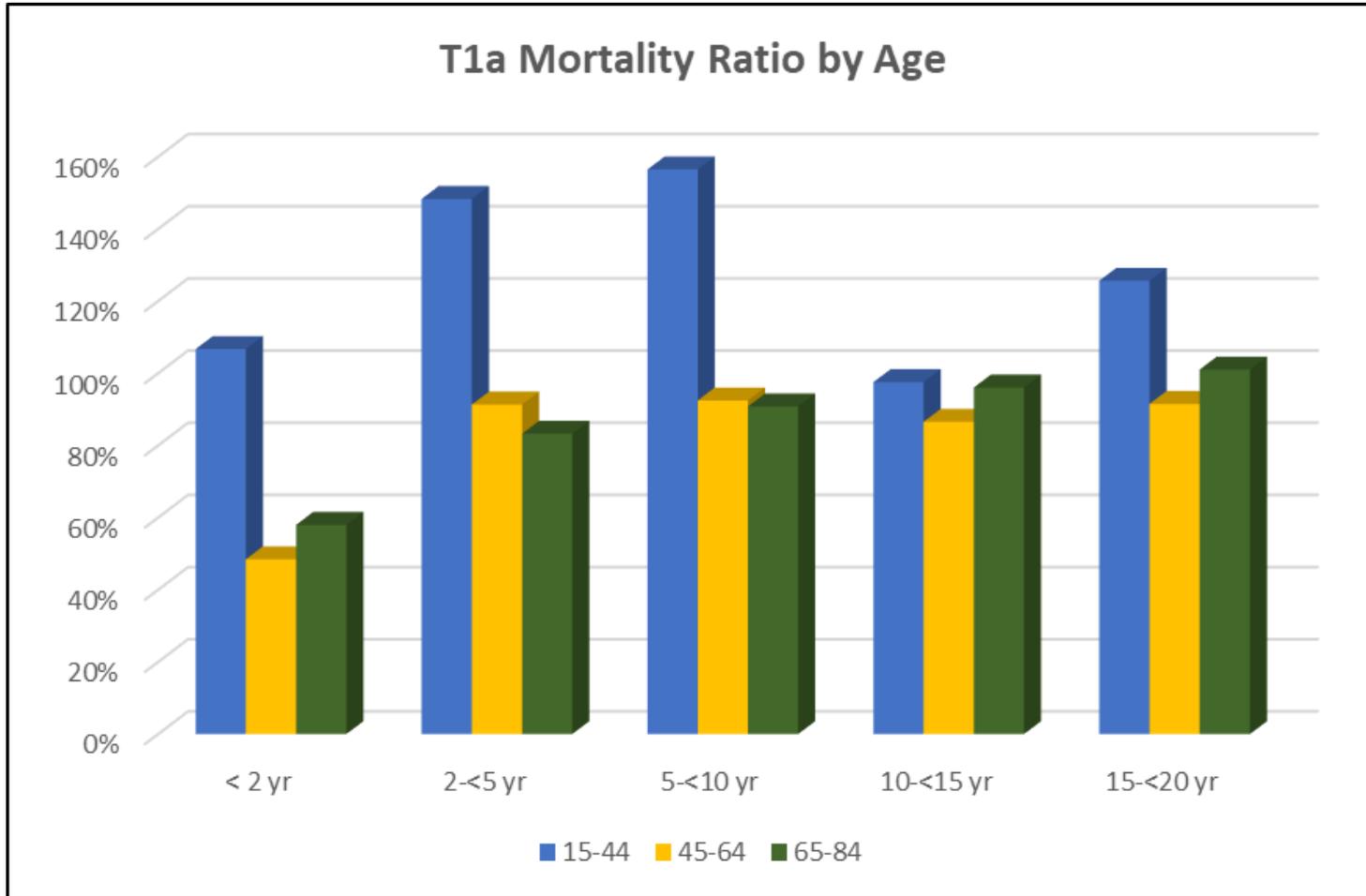
- Tumor ≤1.0 mm, non-ulcerated, no clinical nodes or mets (1988-2016)
- Actual to expected mortality, ages 15-84

- 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 N1a and N2a
- 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

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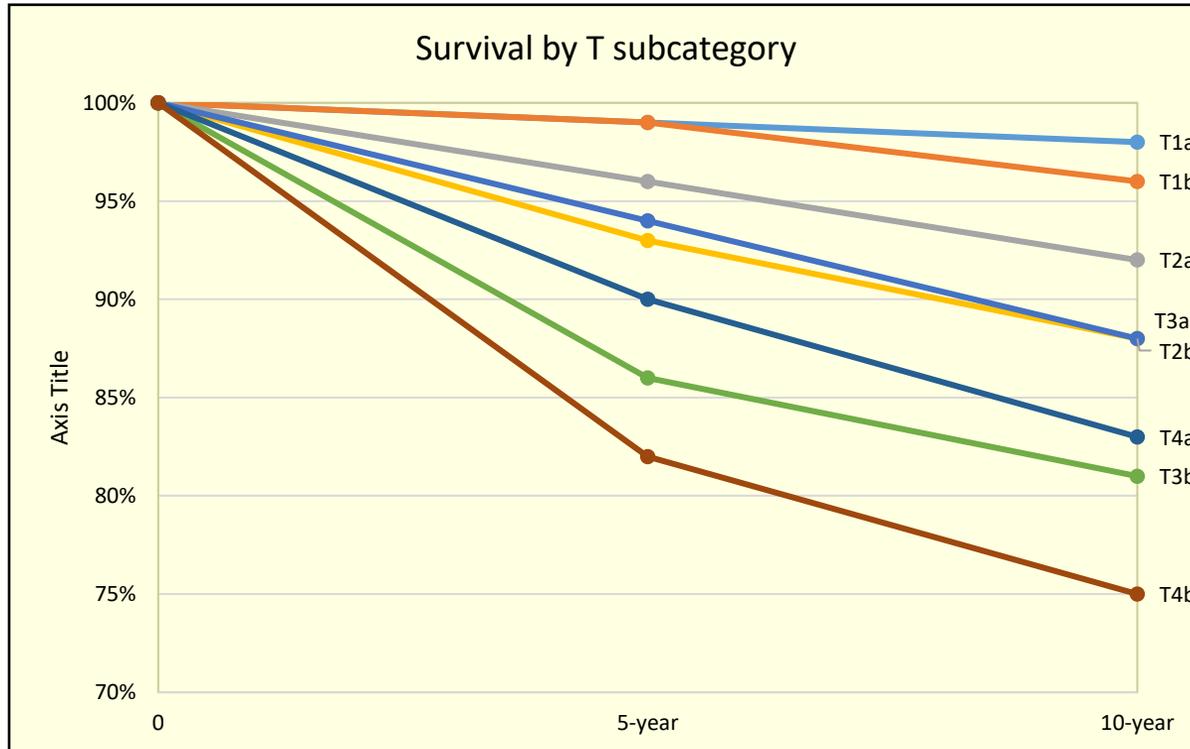
T class	5 year survival %	10 year survival %
T1a	99	98
T1b	99	96
T2a	96	92
T2b	93	88
T3a	94	88
T3b	86	81
T4a	90	83
T4b	82	75

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.

Figure 1. Relative Cumulative Survival by Stage

Percent surviving

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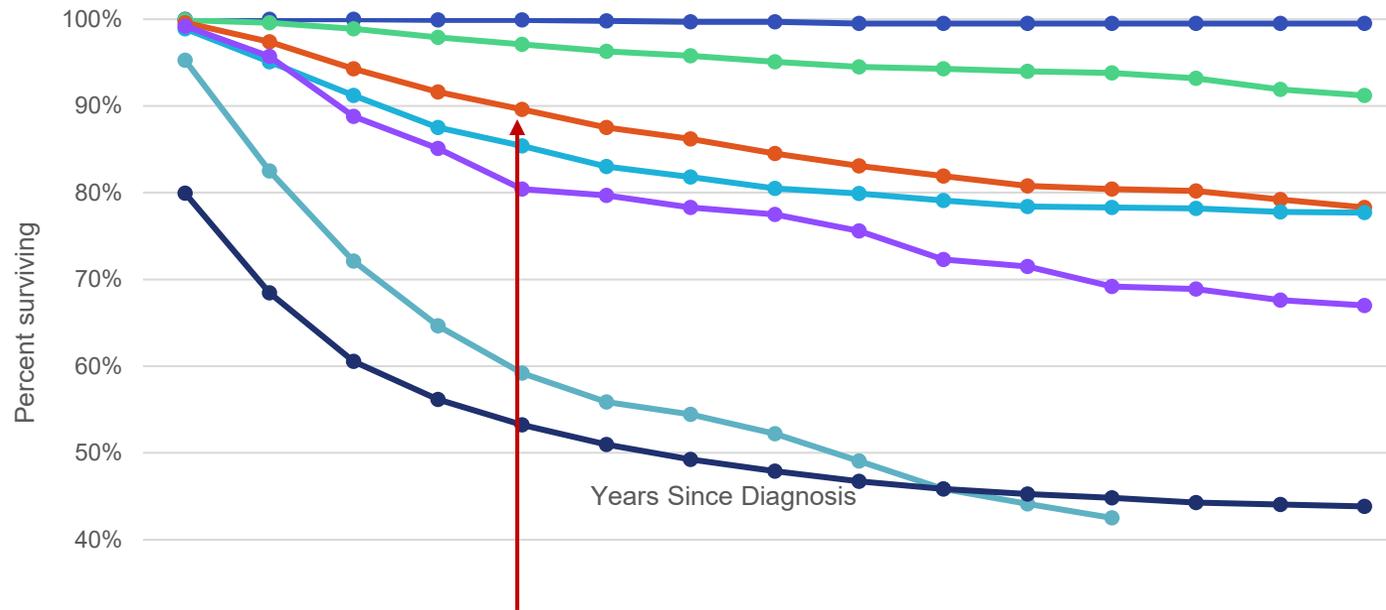
78.3/89.6 = 87.4% 10-yr survival after 5 years

i.e. 12.6% mortality

	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%

Stage IIA - Mortality ratio by interval

Interval	Ratio
< 2 yr (spec int)	232%
2-<5 yr (cond)	333%
5-<10 yr (cond)	210%
10-<15 yr (cond)	130%

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

EDR per 1000 by year
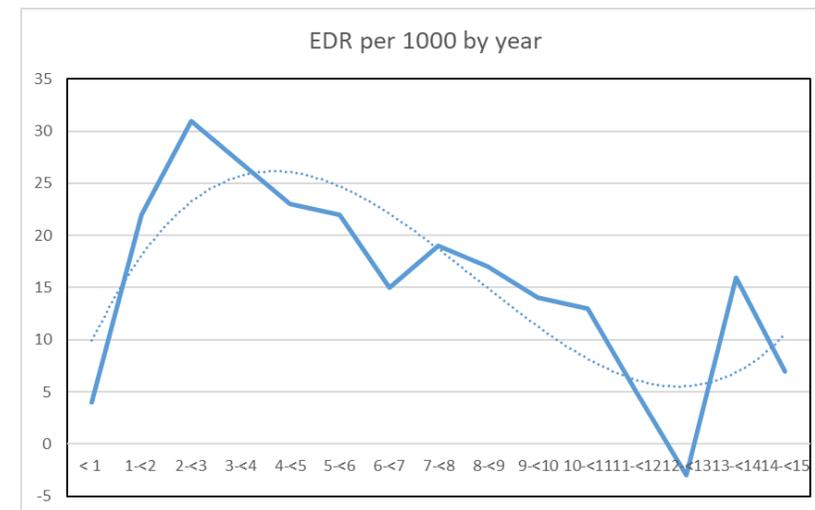
Per CancerMath.net: 15.7% 15-yr mortality at diagnosis; 3.5% at 5 years out

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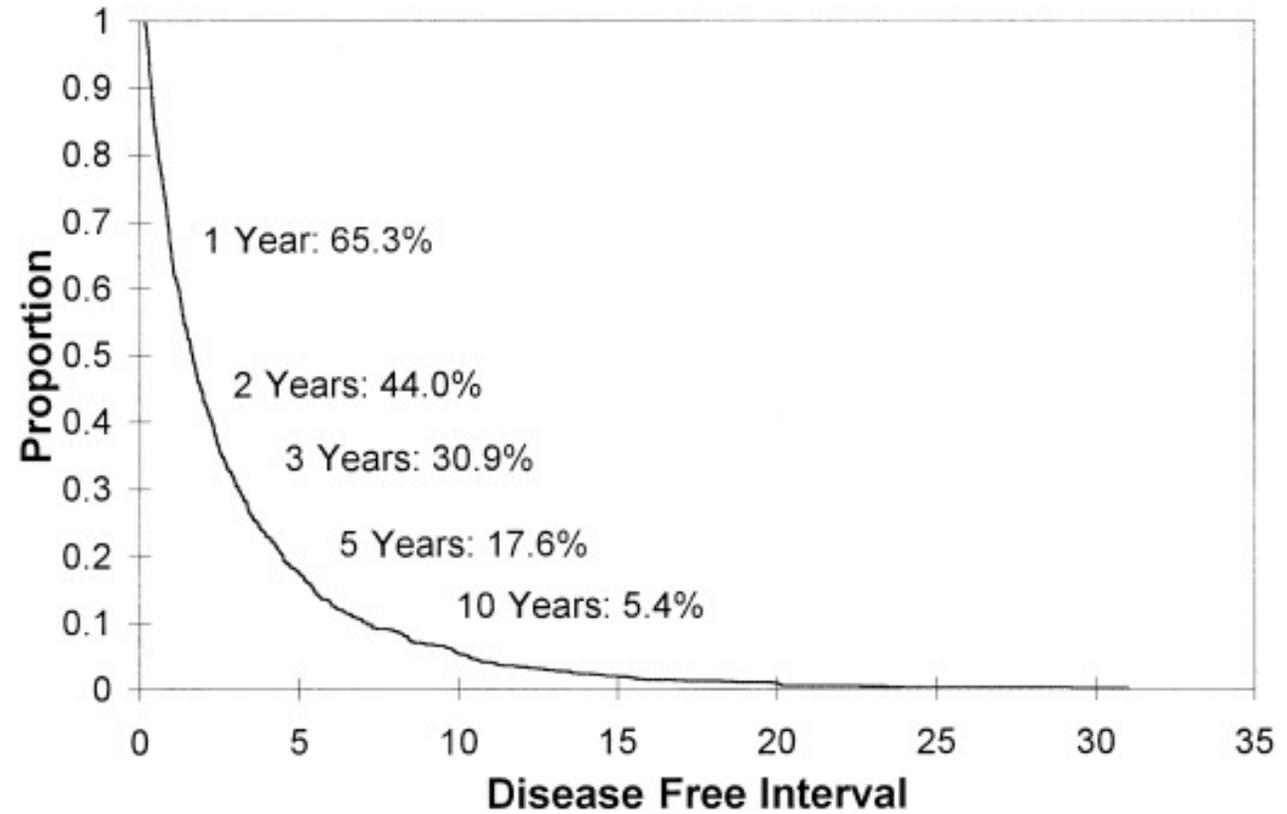
The proportion of patients who developed local recurrence is shown with respect to time
More than 55% of local recurrences occurred by the end of 2 years

SPECIMEN INFORMATION	
Collected: 02/08/24	Accession #: **D24-28628**
Received: 02/08/24	
Reported: 02/15/24	

DERMATOPATHOLOGY REPORT
PHOTOMICROGRAPH(S)

RESULTS

DIAGNOSIS:
SKIN AND SUBCUTANEOUS TISSUE EXCISION, LEFT ANTERIOR SHOULDER -
> WIDE EXCISION FOR PREVIOUSLY DIAGNOSED MELANOMA (0.2 MM IN THICKNESS); NEGATIVE FOR
> RESIDUAL MELANOMA.
> LENTIGINOUS MELANOCYTIC HYPERPLASIA WITH MILD TO MODERATE ATYPIA (ADJACENT TO
> PREVIOUS OPERATIVE SITE); HISTOLOGIC MARGINS FREE.
> DERMAL CICATRIX CONSISTENT WITH PREVIOUS OPERATIVE SITE.

SPECIMEN INFORMATION

Collected: 03/07/25 Accession #: **D25-54863**
Received: 03/07/25
Reported: 03/14/25

DERMATOPATHOLOGY REPORT
PHOTOMICROGRAPH(S)

RESULTS

DIAGNOSIS:

A. SKIN BIOPSY, RIGHT DISTAL LATERAL POSTERIOR UPPER ARM -
   LENTIGINOUS DYSPLASTIC COMPOUND NEVUS WITH MILD TO MODERATE ATYPIA; NOT INVOLVING
   HISTOLOGIC MARGINS OF SECTIONS EXAMINED.
   Note: Because of the close proximity to the margins, clinical follow-up is recommended.

B. SKIN BIOPSY, RIGHT PROXIMAL POSTERIOR UPPER ARM -
   LENTIGINOUS DYSPLASTIC COMPOUND NEVUS WITH MILD TO MODERATE ATYPIA FOCALLY
   INVOLVING PERIPHERAL MARGIN.
   Note: Conservative complete removal is recommended for further evaluation and therapy.

C. SKIN BIOPSY, RIGHT MEDIAL UPPER BACK -
   LENTIGINOUS DYSPLASTIC JUNCTIONAL NEVUS WITH MODERATE ATYPIA AND FOCAL DERMAL
   REGRESSIVE CHANGES; NOT INVOLVING HISTOLOGIC MARGINS OF SECTIONS EXAMINED.
   Note: Because of the close proximity to the margins, clinical follow-up is recommended.

D. SKIN BIOPSY, LEFT DISTAL POSTERIOR THIGH -
   LENTIGINOUS DYSPLASTIC COMPOUND NEVUS WITH MILD TO MODERATE ATYPIA; NOT INVOLVING
   INKED HISTOLOGIC MARGINS OF SECTIONS EXAMINED.
   Note: Because of the close proximity to the margins, clinical follow-up is recommended.

E. SKIN BIOPSY, RIGHT PROXIMAL POSTERIOR THIGH -
   LENTIGINOUS DYSPLASTIC JUNCTIONAL NEVUS WITH MODERATE ATYPIA; NOT INVOLVING INKED
   HISTOLOGIC MARGINS OF SECTIONS EXAMINED.
   Note: Because of the close proximity to the margins, clinical follow-up is recommended.

F. SKIN BIOPSY, LEFT ANTERIOR PROXIMAL THIGH -
   LENTIGINOUS DYSPLASTIC COMPOUND NEVUS WITH MILD TO MODERATE ATYPIA INVOLVING
   PERIPHERAL MARGIN.
   Note: Complete removal is recommended for further evaluation and therapy.

G. SKIN BIOPSY, RIGHT RIB CAGE -
   LENTIGINOUS DYSPLASTIC COMPOUND NEVUS WITH MILD ATYPIA; NOT INVOLVING INKED
   HISTOLOGIC MARGINS OF SECTIONS EXAMINED.
   Note: Because of the close proximity to the margins, clinical follow-up is recommended.

Collected: 06
Received: 06
Reported: 06

DER

DIAGNOSIS:

A. SKIN BIOPSY, LEFT SUPERIOR UPPER B
   LENTIGINOUS MELANOCYTIC PROL
   COMPOUND MELANOCYTIC NEVUS;
   Note: Adequate complete excision is
   atypical process.

B. SKIN BIOPSY, LEFT MID UPPER BACK -
   COMPOUND MELANOCYTIC NEVUS.

C. SKIN BIOPSY, RIGHT SUPERIOR MEDIAL
   MILDLY TO MODERATELY DYSPLAS
   Note: Complete removal is recomme

D. SKIN BIOPSY, LEFT DISTAL CALF -
   LENTIGINOUS DYSPLASTIC COMPO
   INVOLVING HISTOLOGIC MARGINS (
   Note: Because of the close proximity

E. SKIN BIOPSY, LEFT LATERAL ABDOMEN
   MILDLY TO MODERATELY DYSPLAS
   OF SECTIONS EXAMINED.

SPECIMEN INFORMATION

24 Accession #: **D24-218306**
24
24

TOPATHOLOGY REPORT
OTOMICROGRAPH(S)

RESULTS

N, LEFT MID-UPPER BACK -
H MODERATE ATYPIA IDENTIFIED.
PREVIOUS OPERATIVE SITE.

N, RIGHT SUPERIOR MEDIAL LOWER BACK -
H MODERATE ATYPIA IDENTIFIED.
PREVIOUS OPERATIVE SITE.

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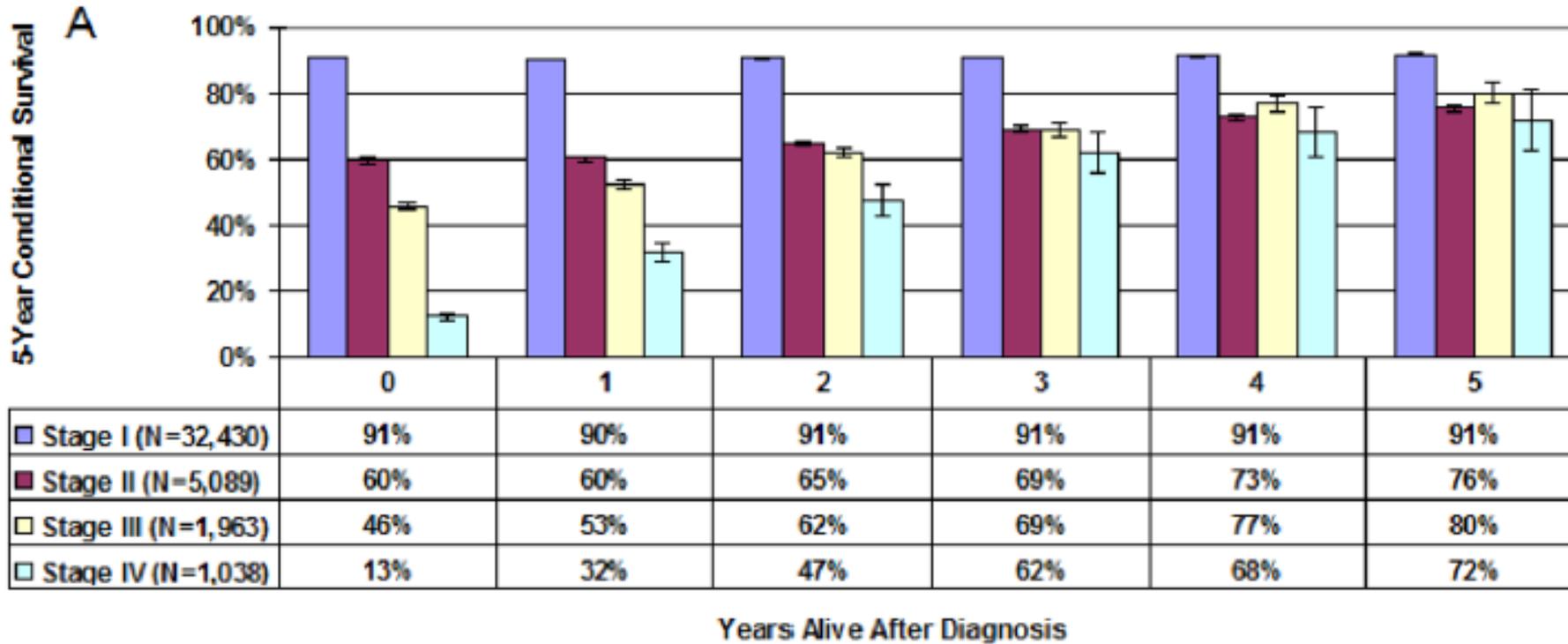
Melanoma-specific 5-year conditional survival estimates stratified by disease stage

[Error bars represent the standard error]

Melanoma-specific survival

- **Melanoma mortality for stage IIA**

- At 5 years: 7.4%

- At 10 years: 16.9%

- Between 5 and 10 years: 10.3%

- However, 25% had a recurrence by 5 years out

Per CancerMath.net: 13.7% 15-yr mortality at diagnosis; 3.0% at 5 years out
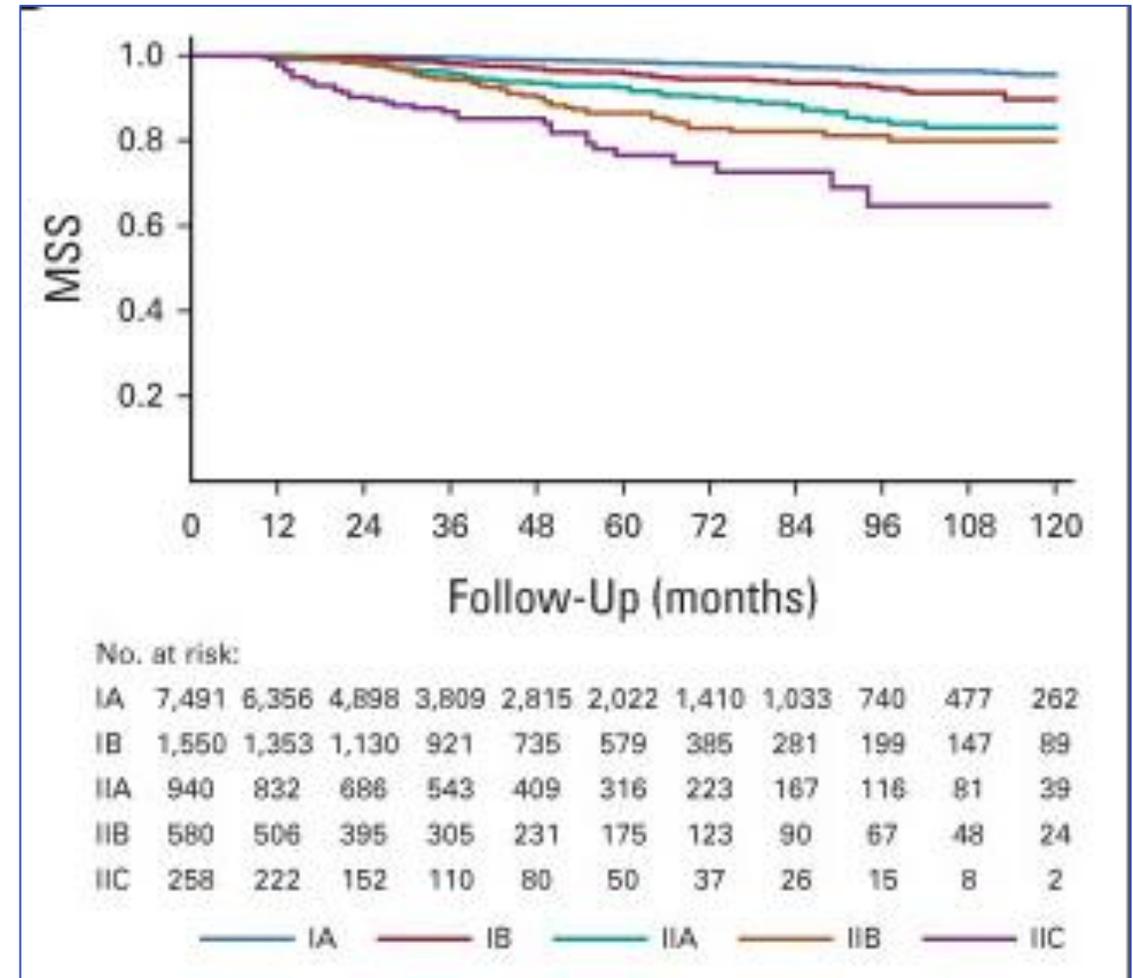
Conditional Survival Stage III Melanoma

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)

- 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???

Head & Neck Melanoma

- Consistently worse prognosis noted for head and neck location of melanoma, especially scalp location

  - 5 yr survivals of 79-83% vs 92-93% for other sites (and 67% for scalp specifically)

- 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 [13-15]

  - After adjusting, mortality rates still 60-80% higher for H&N location

- Before FDA approval of checkpoint inhibitor immunotherapy for stage IV melanoma, surgical resection conferred a 5-year overall survival (OS) of 16% compared to a 5-year OS of 7% with systemic therapies.

- Currently, resection with immunotherapy has been associated with a 5-year OS of 52%.

- In a study of 11,414 patients with stage IV melanoma[1]:

  - On multivariable analysis, resection with immunotherapy and immunotherapy alone were associated with improved OS compared with resection alone in single-site metastasis, except for non-regional lymph node and in-transit metastasis, where resection alone was associated with improved survival.

  - 5-year OS ranged from 70% (lung met) to (51% brain met) for surgery and ICI tx, and 80% for distant LN with surgery alone.

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COLORECTAL CANCER

COLORECTAL CANCER

Colon and Rectum (excluding Appendix)
Stage Distribution of SEER Incidence Cases, 2013-2022
By Age, Both Sexes, All Races / Ethnicities
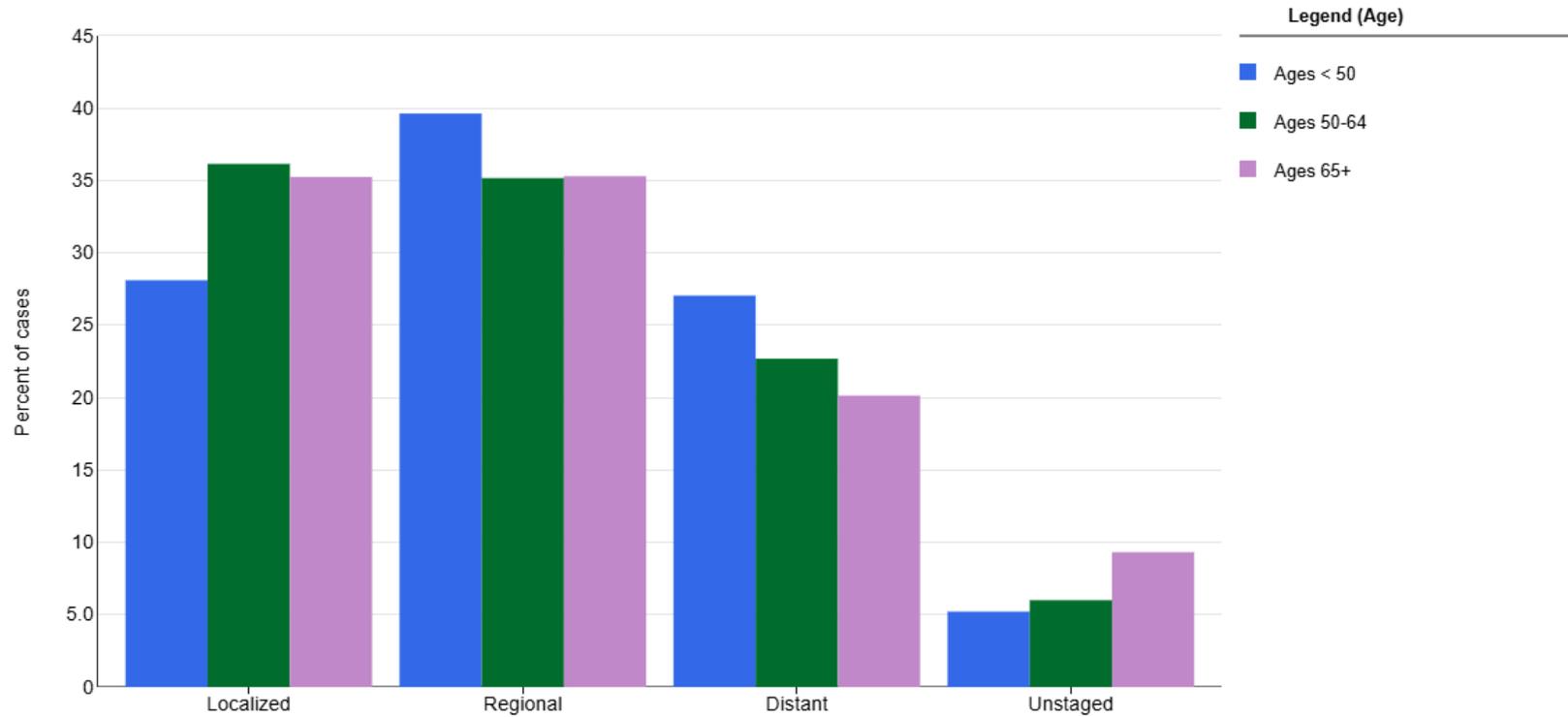
Trends in colorectal cancer diagnosis, age <50

Colon and Rectum (excluding Appendix)
Recent Trends in SEER Age-Adjusted Incidence Rates, 2004-2022
Observed SEER Incidence Rate By Stage at Diagnosis, Both Sexes, All Races / Ethnicities, Ages < 50
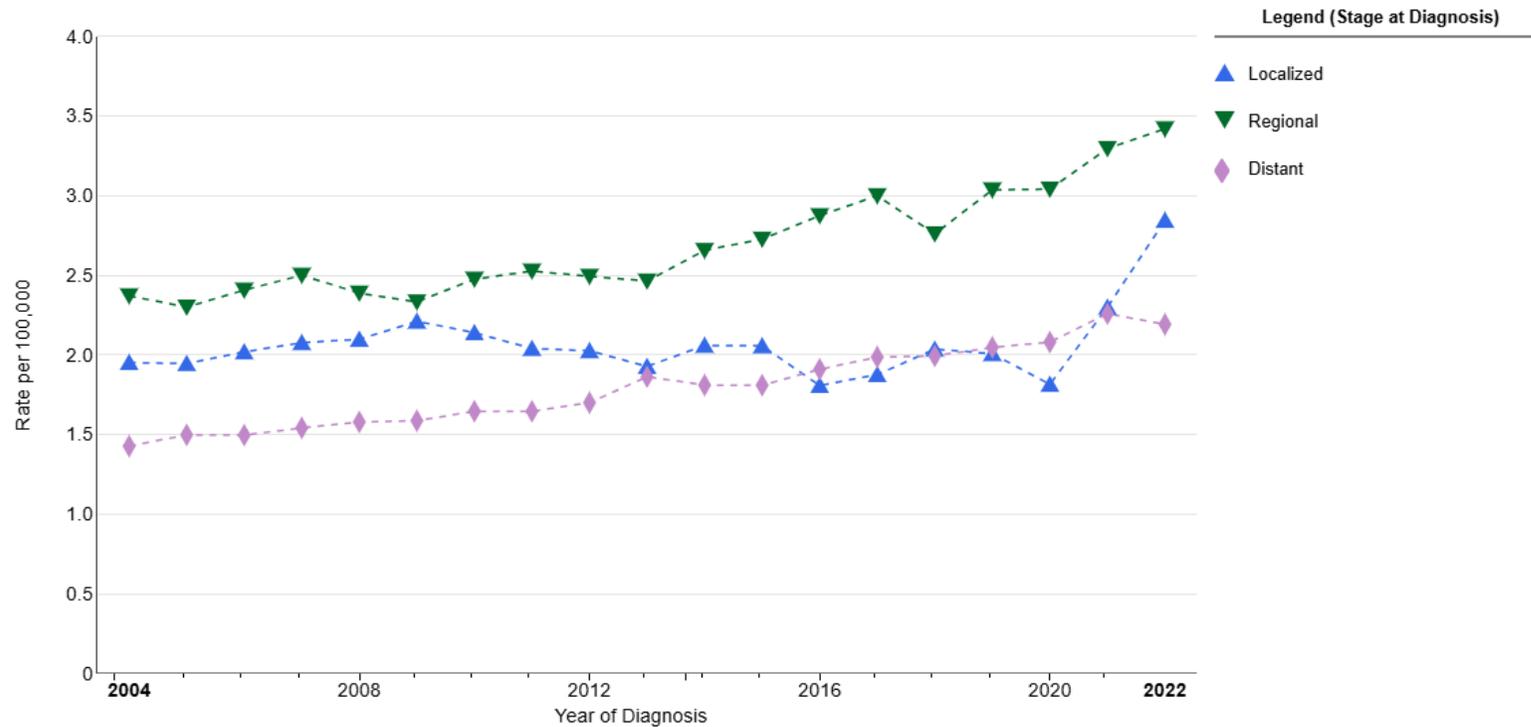
From: **Colorectal Cancer Incidence in US Adults After Recommendations for Earlier Screening**

Figure Legend:

Trends in Colorectal Cancer Incidence Rates by Age and Stage at Diagnosis, 2004-2022Dots are observed rates (light gray, observed rates in 2020); lines, modeled rates; numbers in parentheses, 95% CIs. Data for 2020 were excluded from trend analysis.

Stage was classified according to SEER Combined Summary Stage With Expanded Regional Codes (2004+) (localized only; regional: regional by direct extension only, regional lymph nodes involved only, regional by direct extension and lymph node involvement; distant sites and nodes involved).

aAnnual percentage change (APC) statistically significantly different from 0 (P < .05).

CRC Conditional Survival by Stage and Age

Colon and Rectum (excluding Appendix)
SEER 5-Year Conditional Relative Survival Rates, 2000-2021
By Stage at Diagnosis and Surviving 5 More Years, Both Sexes, All Races / Ethnicities, All Ages
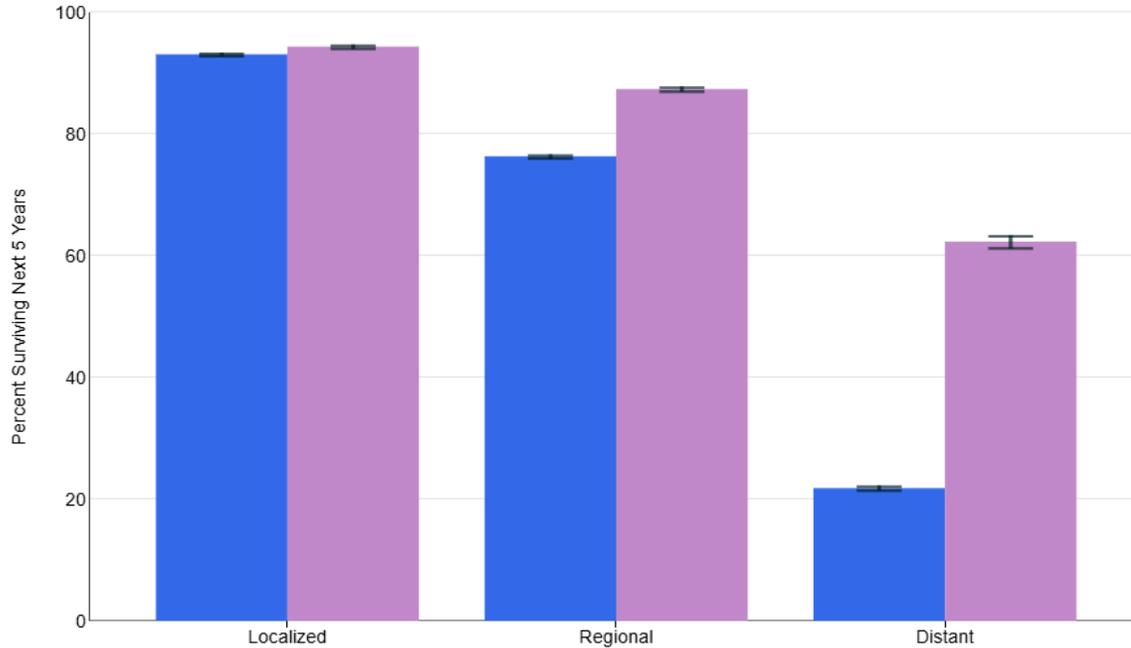
Colon and Rectum (excluding Appendix)
SEER 5-Year Conditional Relative Survival Rates, 2000-2021
By Age and Surviving 5 More Years, Both Sexes, All Races / Ethnicities, Localized

Created by https://seer.cancer.gov/statistics-network/explorer/ on Wed Jul 30 2025.
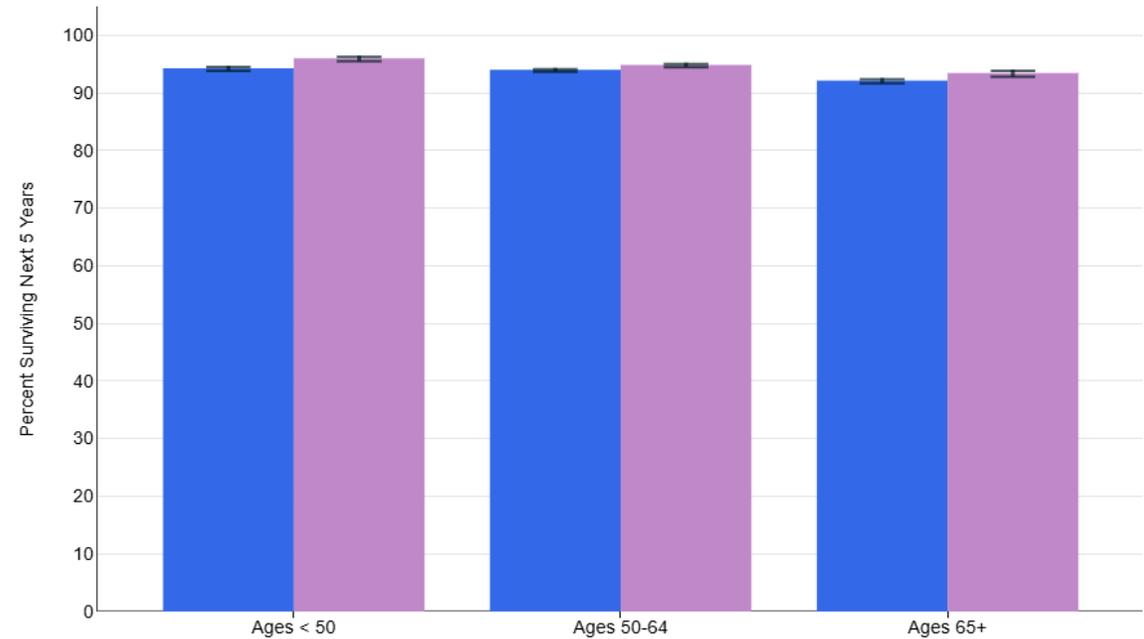
Legend:
- From 1 Year Since Diagnosis
- From 5 Years Since Diagnosis
- Confidence Interval Range

COLORECTAL CANCER

CRC Epidemiology

mOS = median months of survival
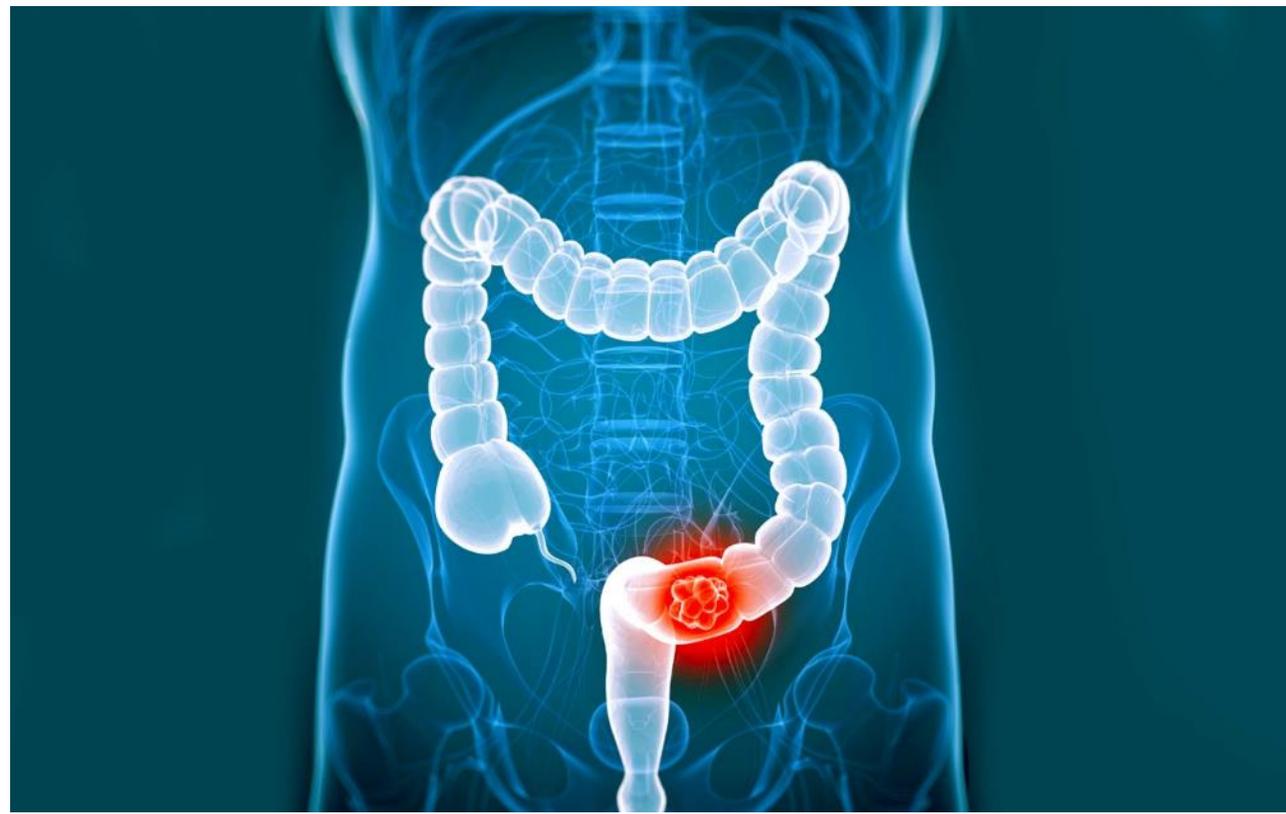
- Colorectal Cancer (CRC) is the third most commonly diagnosed malignancy worldwide accounting for 10.7% of cases

- CRC is the second leading cause of cancer death globally (Lung, CRC, Liver, Stomach, and Breast) accounting for 9.5% of cancer deaths.

- In the US, it is the 4th most diagnosed cancer (Breast, Lung, Prostate, CRC, Melanoma) and the 2nd leading cause of cancer death (Lung, CRC, Pancreas, Breast, Prostate).

- 2025 US estimates: 154,270 new cases with 52,900 deaths

	Lung	CRC	Pancreas	Breast	Prostate
Total cases (2000-2020)	1,006,919	761,332	220,496	1,228,461	1,120,295
Males	52.82%	51.86%	50.48%	0.75%	100%
Females	47.17%	48.13%	49.51%	99.25%	N/A
Most affected race	White	Black	White	White	White
Median age of diagnosis	65	67	70	63	67
mOS males	8	61	5	96	172
mOS females	12	64	5	191	N/A

- 54% are estimated to occur in those with modifiable risk factors (ACS)

  - Excess body weight

  - Physical inactivity

  - Long-term cigarette smoking

  - High consumption of red and/or processed meats

  - Heavy EtOH consumption

  - Low intake of Calcium, Whole grains, and/or fiber-rich foods

- Remainder genetic or sporadic

  - Personal or family history of CRC

  - Inherited Genetic Disorders (e.g. Lynch syndrome)

  - UC or Crohn's (RR ~2.75)

  - Type 2 DM

What about screening?

- Standard Risk

  - Begin at 45 y/o, end at 75 y/o assuming there is still a 10-year life expectancy

  - Preferred: Colonoscopy q 10 years or FIT (Fecal Immunochemical Testing) q 1 year

  - Alternatives:

    - Ms-sDNA aka FIT-DNA ("Cologuard") q 1-3 years

    - Computed Tomography Colonography (CTC), formerly "virtual colonoscopy" q 5 years

    - Sigmoidoscopy with fecal testing (FIT, Guaiac): timing varies for each

    - Sigmoidoscopy alone—only 60cm of colon, which is problematic for those at risk for more proximal lesions (women and older folks); q 5 years is better than nothing

    - g(FOBT)—less sensitive and specific but better than nothing; q 1 year on three stool samples

- High Risk (Family history, Syndromes pre-disposing to CRC, Personal history of concerning polyp)

  - Begin at 40 or 10 years before the age of diagnosis in first degree relative

  - Colonoscopy at least q 5 years is the preferred screening method

  - There is guidance by syndrome of concern in UpToDate®
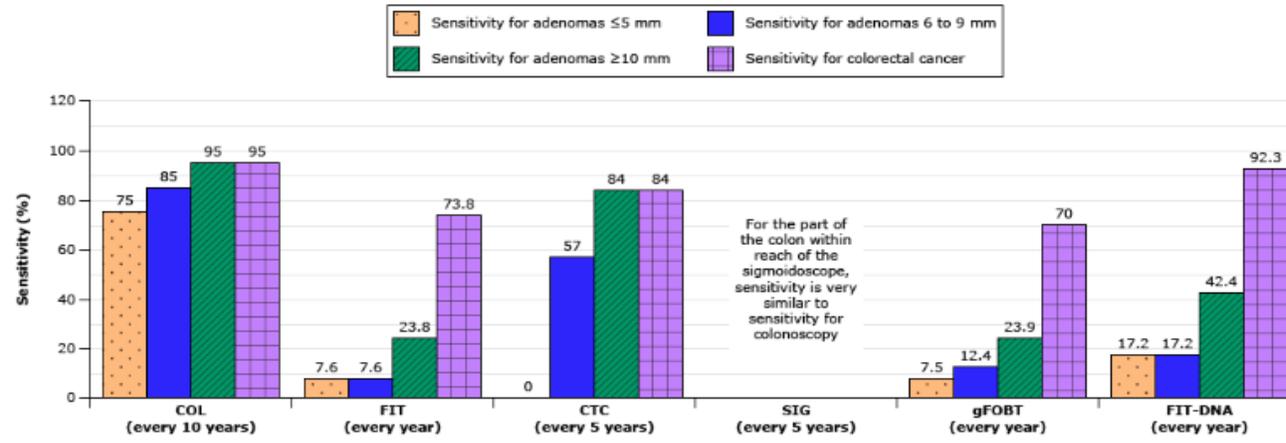
Sensitivity, specificity, and cancer-specific deaths averted for each screening strategy.

COL: colonoscopy; CTC: computed tomography colonography; FIT: fecal immunochemical test; FIT-DNA: multitargeted stool deoxyribonucleic acid test; gFOBT: guaiac-based fecal occult blood test; SIG: sigmoidoscopy.

* Assumes screening from ages 50 to 75 years, including 100% adherence, complete follow-up without delay, and appropriate surveillance. Ranges reflect results from 3 models.

Data from:
1. Zauber A, Knudsen A, Rutter CM, et al. Evaluating the Benefits and Harms of Colorectal Cancer Screening Strategies: A Collaborative Modeling Approach. AHRQ Publication No. 14-05203-EF-2. Rockville, MD: Agency for Healthcare Research and Quality; October 2015.
2. Knudsen AB, Zauber AG, Rutter CM, et al. Estimation of Benefits, Burden, and Harms of Colorectal Cancer Screening Strategies: Modeling Study for the US Preventive Services Task Force. JAMA 2016; 315:2595.

Important things to know with respect to underwriting:

- Diagnosis that is thorough and reliable
  - Location
  - Stage
- Treatment that is appropriate to Stage and Location
  - To Cut Is To CURE!
  - Chemotherapy
  - Role of radiation
- Surveillance that is appropriate to Stage, risk of metachronous disease, and risk of complications from treatment
  - How frequently?
  - What testing?
  - When is the next colonoscopy due?

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%)
- Tissue Sample/Biopsy is the only way to make a definitive diagnosis
- Evaluation once diagnosed should include:
  - CEA
  - CT with Contrast of Chest, Abdomen, and Pelvis
  - PET scanning reserved for those with Isolated Metastasis to liver or lung in whom resection is planned

Staging TNM (AJCC UICC 8th edition)

- Be aware of the "y" indicating Pathological Staging AFTER Neoadjuvant Therapy

- T: Depth of Invasion

  - Tis no invasion across muscularis mucosa

  - T1 invades submucosa

  - T2 invades muscularis propria

  - T3 invades through muscularis propriate into peri colorectal tissues

  - T4 invades through visceral peritoneum, including perforation) or invades/adheres to adjacent organs/structures

- N: Number of nodes

  - N0: None

  - N1: 1-3 nodes or no nodes but tumor deposits in subserosa, mesentery, or peri colorectal tissues

  - N2: 4+ nodes

- M: Distant Metastasis (Liver, Lung, Peritoneum, Brain)

  - M0: None

  - M1: present

- **Fare thee well, Duke's! No longer used.**

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

TNM: Tumor, Node, Metastasis; AJCC: American Joint Committee on Cancer; UICC: Union for International Cancer Control.

Treatment

- To cut is to cure—bring on the bright lights and cold steel…

Treatment
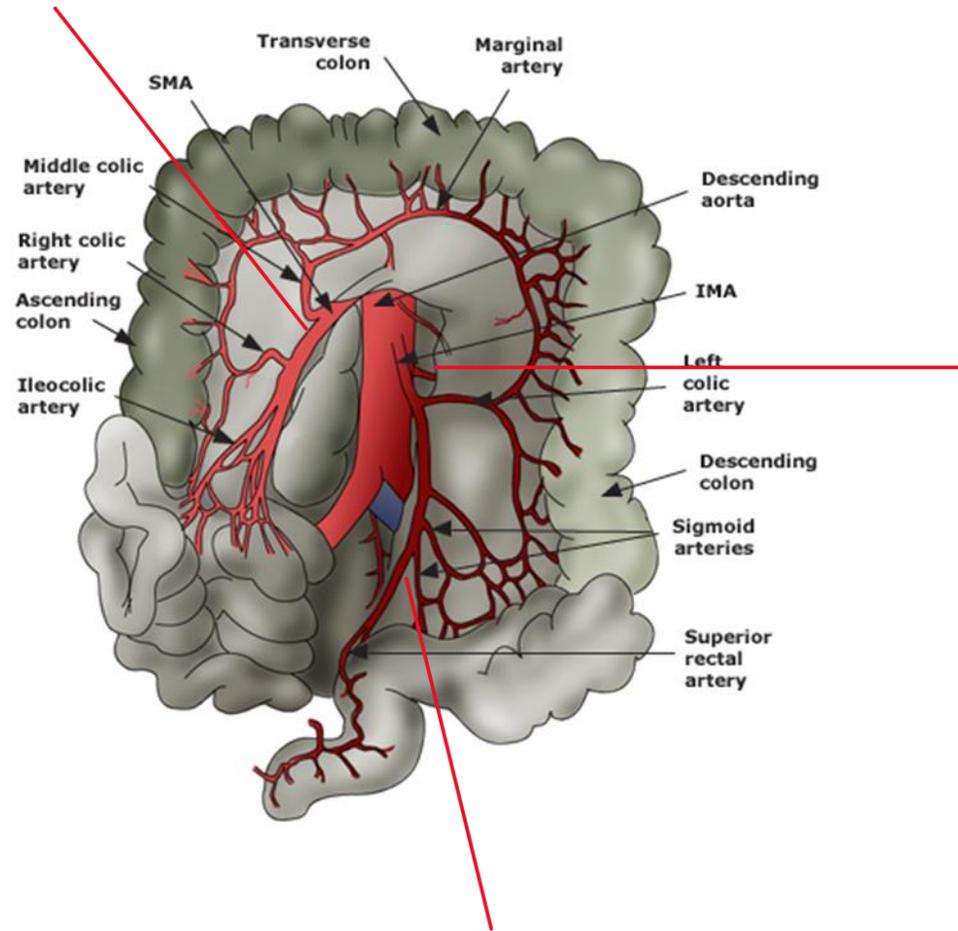
- Localized—Surgery alone

    - Removal of tumor, major vascular pedicle, and lymphatic drainage basin of the affected segment

    - Endoscopic resection of tumor-laden polyps is acceptable UNLESS tumor is poorly differentiated, invades nerves or vessels, cancer is present at resection margin, or there is submucosal invasion (T1 or greater)

- Locally "advanced" based on depth of invasion, unfavorable histology, MMR positivity

    - Colon: multi-visceral excision

        - Consider adjuvant chemotherapy in those at high risk with good life expectancy

    - Rectum: Neoadjuvant +/- Surgery

        - Chemo

        - Chemo + Radiation

        - Query the necessity of an operation: "Total Neoadjuvant Therapy"

            - *See: Loria, A, Tejani, MA, and Temple, LK. Practice patterns for organ preservation in US patients with Rectal Cancer, 2006-2020. Jama Oncology Vol. 10, No. 1; Nov 9 2023.

- Stage III (N1-2): Surgery + Adjuvant Chemotherapy

- Stage IV with isolated metastasis to liver: Surgery + Chemotherapy (to cut is still a possibility for cure)
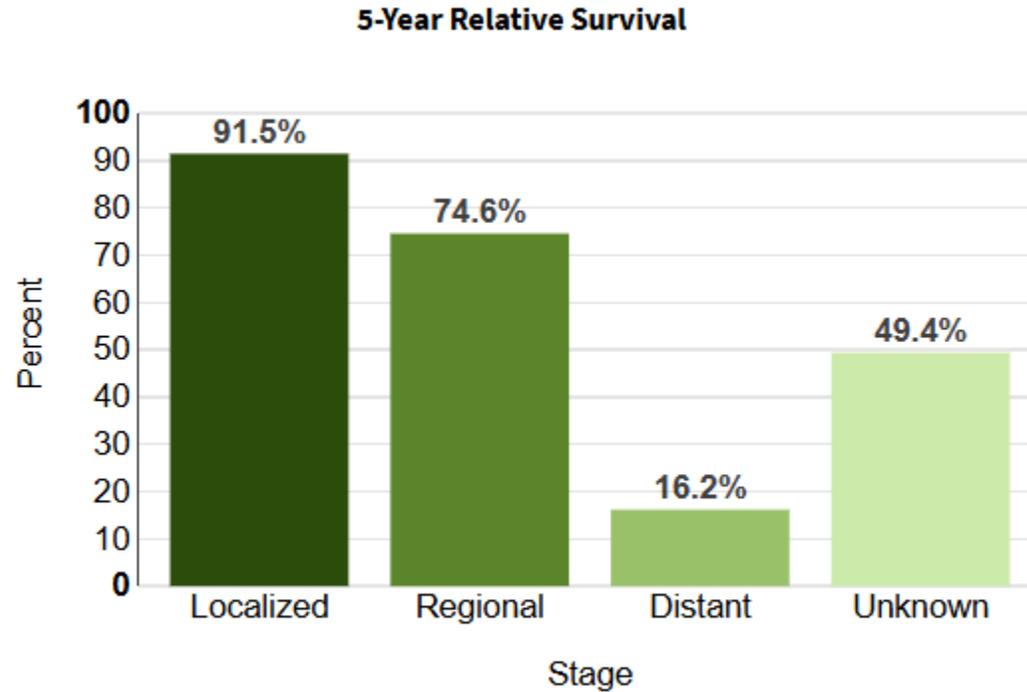
Figure 2. Time From Surgery to Colorectal Cancer Recurrence by Union for International Cancer Control (UICC) Stage
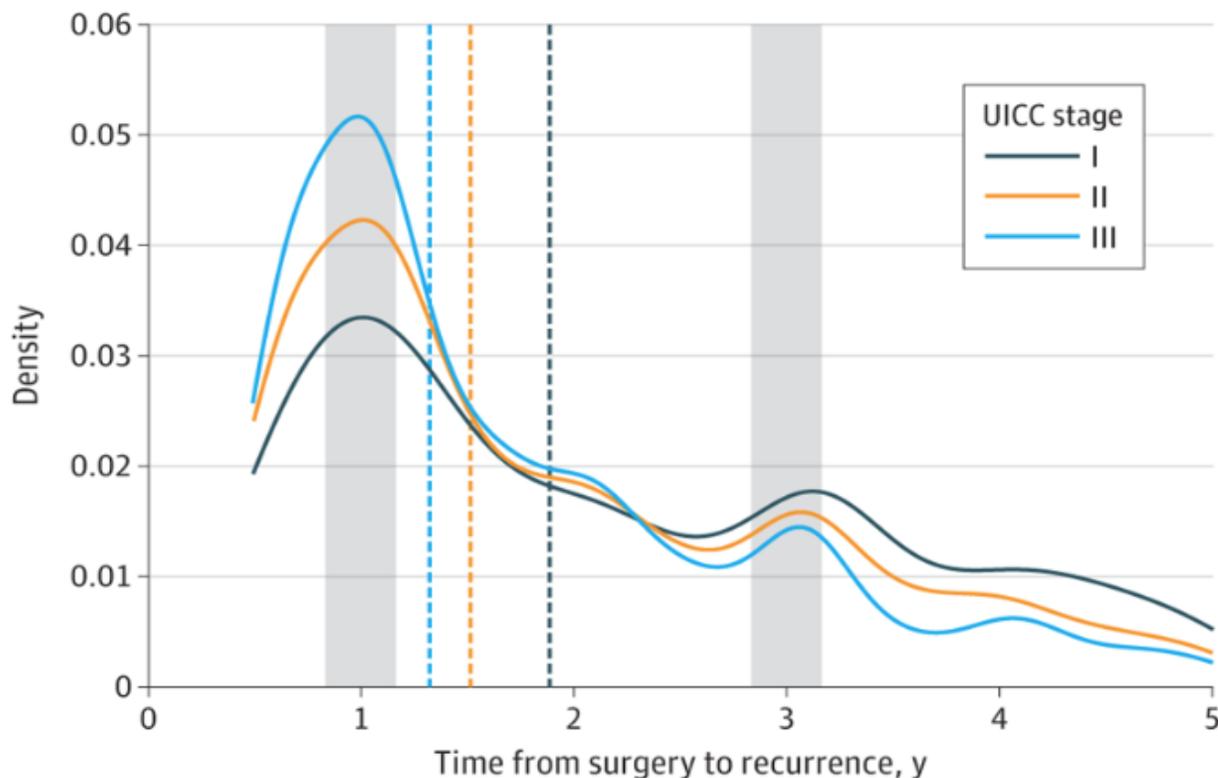
Vertical dashed lines represent median time from curative surgery to recurrence. Shaded areas represent time points of surveillance imaging at 12 and 36 months after surgery (as per Danish guidelines since 2009).

Figure 3. Cumulative Incidence Function Curves for Colorectal Cancer Recurrence According to Cancer Detection Method (Screening or Not Screening) Stratified by Union for International Cancer Control (UICC) Stage

Screening vs nonscreening
Stage I: sHR, 0.76; 95% CI, 0.61-0.96
Stage II: sHR, 0.65; 95% CI, 0.53-0.81
Stage III: sHR, 0.74; 95% CI, 0.65-0.86

No. at risk

Stage I, nonscreening	2694	2607	2453	2324	1876	1459
Stage II, nonscreening	4272	4068	3673	3422	2721	2141
Stage III, nonscreening	3953	3520	2945	2648	2015	1525
Stage I, screening	2083	2046	1951	1888	1552	1229
Stage II, screening	1102	1077	1002	960	759	588
Stage III, screening	1147	1075	963	911	695	535

Surveillance

- Stage I—debatable as to whether any is needed???

  - My practice—want to see yearly History and Physical for any cancer patient at a minimum

  - Prefer a CEA but may be able to live without it if being followed by a knowledgeable doc

  - 5-year colonoscopy, then return to normal screening

- Stage II-III

  - History and Physical q 6 months x at least five years, then yearly

  - CEA with each H&P

  - CT scanning yearly for at least 5 years

  - Interval Colonoscopy to detect metachronous tumors

  - Follow up of long-term complications of adjuvant therapy (e.g. Neuropathy with Oxaliplatin)

- Stage IV: frequent follow up dependent on treatment considered and rendered

CRC Case 1

- 49 M, $300K 30 year, Term

- No admitted history; Denies Tobacco; Admitted Build: 5'8", 120 lbs (BMI 18.2)

- MIB (Same year, different company): underweight with BMI <18.5

- Rx check with COVID Vaccines only

- Visit History with PCP 2 years prior for vaccination

- MVR Clear

- Simplified Application and UW with IRIX

- Issued at STD 4/7/2023

- Preliminary thoughts or concerns?

Clinical History 10 days after policy issued:

- 49 y/o M, nonsmoker presents with worsening RUQ pain and diarrhea without hematochezia or melena; no h/o screening colonoscopy, no other complaints

- FMHx: breast (40 y/o) and colon cancer (55 y/o) in mother

- Exam: 5'8", 116 lbs. (BMI 17.6), Dehydration, o/w normal

- CONCERNS?

- Differential Diagnosis?

- What are the symptoms of colorectal cancer?

- What are the common signs of colorectal cancer?

- What's next?

Labs

WBC	9.0	8.7
RBC	4.42*	3.94*
HGBAU	10.6*	9.4*
HCT	34.1*	31.3*
MCV	77.1*	79.4*
MCHC	31.1*	30.0*
PLT	625*	552*
MPV	8.0*	8.3*

TBIL	0.6	0.4
ALKP	443*	371*
SGOT	172*	142*
SGPT	74*	58
TPRO	7.5	6.2*
ALB	3.0*	2.4*

Symptoms and Signs of Colorectal Cancer

Symptoms

- NONE for ~30%

- Symptoms indicative of more advanced cases

- ●Hematochezia (45 percent)

- ●Abdominal pain (40 percent)

- ●Change in bowel habits (27 percent)

- ●Weight loss (17 percent)

- ●Loss of appetite (15 percent)

- ●Constipation (14 percent)

- ●Abdominal distension (14 percent)

- ●Diarrhea (12 percent)

- ●Anemia (11 percent)

Signs

- Elevated CEA (what the heck is this and should it be used for screening?)

- Anemia with melena, hematochezia, or more advanced disease

- Low Albumin and Total Protein

- Palpable mass(es)

- Sister Mary Joseph's Node (what the heck is this and who is she???)

- CEA (CarcinoEmbryonic Antigen): neither specific (<<50%) or sensitive (50% at best with cut-off >5) for colorectal cancer, **BUT levels >5ng/ml are independently associated with adverse impact on survival in CRC.**

Cancer Therapy Advisor

Eponyms in Oncology

Sister Mary Joseph
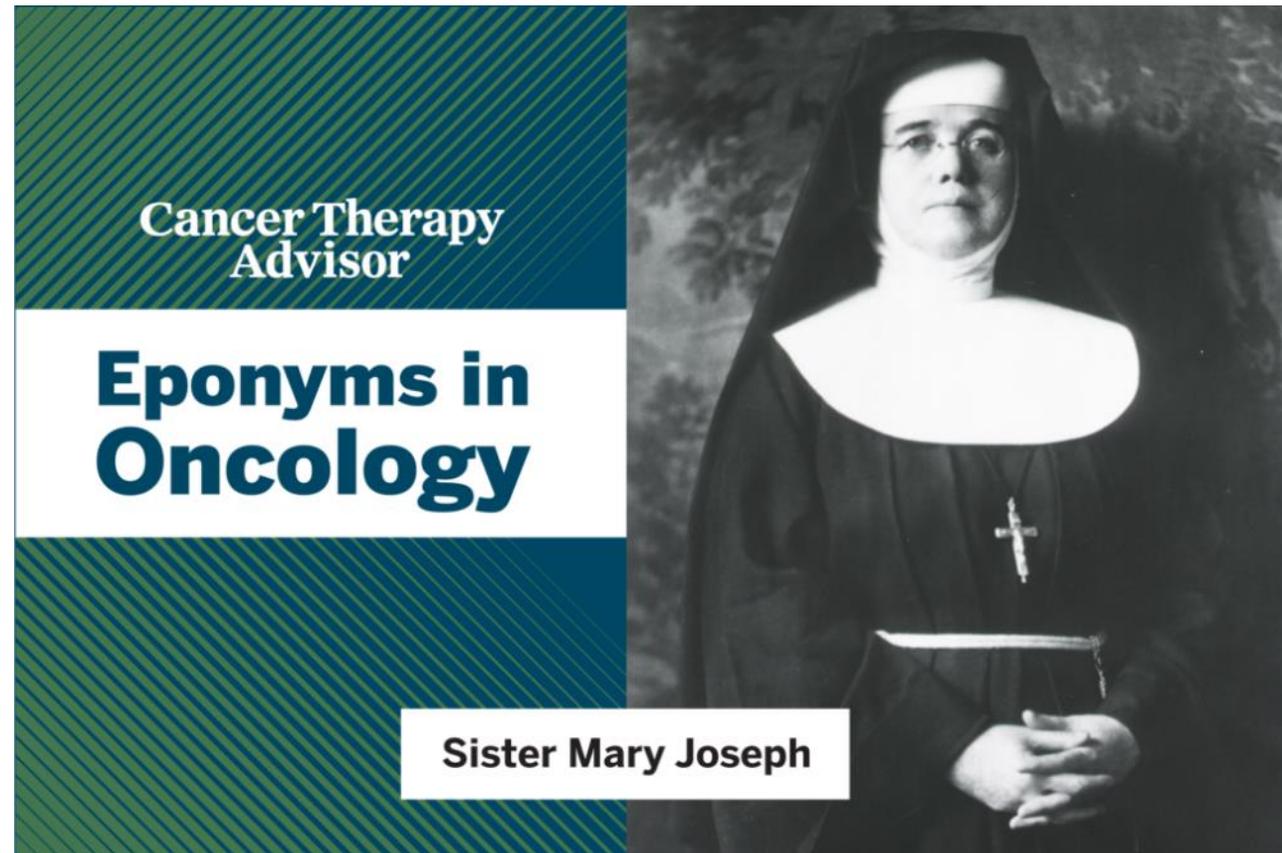
Family History of CRC

- How significant is it?

- When should CRC screening begin in those with a family history?

Findings: A fungating, infiltrative, polypoid and submucosal completely obstructing large mass was found in the distal sigmoid colon with polypoid component and indurated infiltrated component. The mass measured five cm in length from 13 - 18 cm at obstruction, additional 8 - 13 cm appear edematous and infiltrated as well. Oozing was present from mass. Biopsies were taken with a cold forceps for histology. Area was tattooed with an injection of 0.4 mL of Spot (carbon black) (0.2 x 2) at the distal margin of apparent infiltration.

A 11 mm polyp was found in the proximal rectum. The polyp was semi-pedunculated. The polyp was removed with a hot snare. Resection and retrieval were complete.

PROXIMAL RECTAL POLYP, POLYPECTOMY:
   TUBULOVILLOUS ADENOMA.
   NO HIGH GRADE DYSPLASIA OR CARCINOMA.

SIGMOID COLON MASS, BIOPSIES:
   ADENOCARCINOMA IN-SITU.
   DEFINITIVE INVASION IS NOT SEEN.

Procedures/Addenda
Mismatch Repair
Interpretation

There is <u>no loss</u> of nuclear expression of **MMR** proteins. The likelihood of this patient having a form of inherited colon cancer due to mismatch repair defects is low. However, these tests do not rule out the possibility of other genes being affected in DNA mismatch repair, or an inherited defect in other genes not involved in mismatch repair, or that there is a genetic defect in the mismatch repair genes rendering them nonfunctional but still detectable by IHC. This test is only a screen test.

PCR to detect microsatellite instability to further exclude MSI- High phenotype is available upon request.

Addendum Comment

This addendum is being issued to report the results of molecular studies, performed at PathGroup, Nashville, TN. The report (specimen 23-44-006022) is summarized below.

RESULTS
KRAS Mutation: NOT DETECTED
BRAF Mutation: NOT DETECTED
NRAS Mutation: NOT DETECTED

INTERPRETATION

KRAS Mutation Analysis: NOT DETECTED

Interpretation:

This specimen showed no evidence of a mutation in the KRAS gene. If clinically appropriate, consideration may be given to broader genomic profiling.

- What is adenocarcinoma in situ?

- Are the findings on Colonoscopy Report and Pathology Report concordant? Should they be?

- If you only saw the Path report at the time of application, what would your course of action be?

- What is an MMR protein? KRAS? NRAS? BRAF?

- Is he insurable at this time?

- If not, what's next?
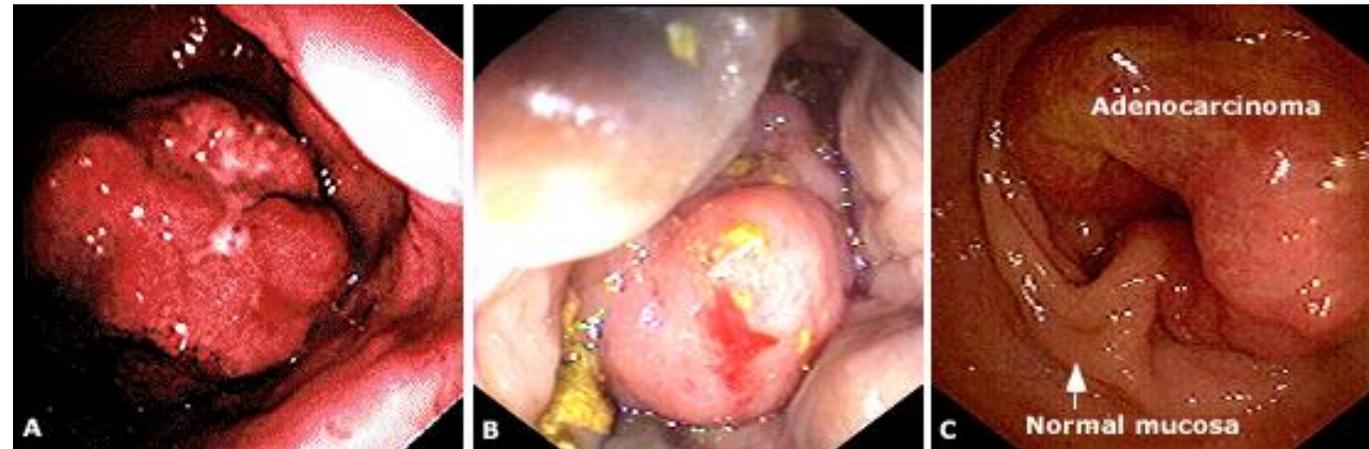
Case 1, some answers…

- In solid tumors we must be confident of the diagnosis, as that drives treatment and surveillance, AND long-term morbidity and mortality assessment.

- If the biopsy and operative reports don't seem to jibe, there is more work for you to do.

- MMR genetic mutations -> Lynch Syndrome; MSI (microsatellite instability)
  - Favorable finding in localized tumors but indeterminate in more advanced tumors
  - Not as sensitive to Fluorouracil-based chemo and may be an indication for immunotherapy

- BRAF V600E—associated with smoking and worse prognosis

- KRAS—worse prognosis

- NRAS—worse prognosis

- Oncotype DS Colon Cancer Assay ® is in trials to better validate its use in recurrence scores and treatment protocols.

- Next Steps in treatment assuming we only have the colonoscopy and Pathology reports?

PATHOLOGY REPORT

DIAGNOSIS:

Colon, subtotal resection to include proximal colon and

separately submitted sigmoid colon:

Adenocarcinoma, moderately differentiated to poorly differentiated.

Located in sigmoid colon.

Full thickness tumor with associated rupture / perforation through bowel wall.

Extensive subserosal tumor within sigmoid colon.

Focal subserosal tumor extending into proximal colon and appendix.

Associated severe acute exudative serositis consistent with peritonitis.

Focal cauterized tumor at sigmoid margin.

Sixteen benign regional lymph nodes (0/16).

Right colon shows prominent mucosal inflammatory changes and atrophy.

Unremarkable terminal ileum.

Lab Results	09/11/2023	08/29/2023	08/14/2023	08/02/2023	07/31/2023	07/17/2023
Tumor Markers						
CEA ng/mL	325.5 Corrected Report*See Comment* (H)		282.4 (H)		315.6 (H)	254.8 (H)

Staging (so far...):

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

- Based on staging, what type of treatment would be expected?

- What is the expected mortality?

- Anything else we need to know?

- Clinical Staging Workup for CRC?

Abdominal pain, nonlocalized TECHNIQUE: Multiple axial CT images of the abdomen and pelvis were obtained without IV or PO contrast. CT scan performed according to ALARA (As low as reasonably achievable) principles. COMPARISON: Abdominal ultrasound 4/16/2023 FINDINGS: Small right-sided pleural effusion is identified. Heart size is normal. Lower lungs are clear. Liver is markedly heterogeneous, with multiple ill-defined lesions identified. Findings are suspicious for metastatic disease. Trace ascites is identified. The spleen, adrenals, and left kidney are unremarkable. There is a 3 mm nonobstructive stone in the midpole of the right kidney. There are no dilated loops of bowel or bowel wall thickening. The bladder is unremarkable. There is wall thickening of the mid sigmoid colon identified.

Heterogeneous liver with multiple liver masses identified, suspicious for metastatic disease. Small right-sided pleural effusion No free fluid No dilated loops of bowel 4 mm nonobstructive stone in the midpole the right kidney Wall thickening of the mid sigmoid colon, suspicious for colitis. Malignancy is in the differential diagnosis. RL: 5252 ELECTRONICALLY SIGNED By: Brian Miller Date/Time 4/16/2023 1:48 AM

COMPARISON: CT from April 16, 2023.

FINDINGS:

There is a small right pleural effusion. There is a trace left effusion.

The right lower liver is nearly completely replaced by tumor. May represent a dominant lesion with smaller adjacent satellite lesions, single lobulated dominant lesion, or multiple confluent masses. Overall the tumor measures 21.3 x 10.6 x 19.8 cm. The tumor is heterogeneous on T2 with central areas of hyperintensity. The tumor is heterogeneous on T1. There is heterogeneous enhancement. Overall MRI features are most suggestive of fibrolamellar HCC. Multiple confluent metastatic lesions also be considered.

The liver is massively enlarged. There is compression of the central and right hepatic and portal veins. Several subcentimeter hepatic cysts are present.

The liver is normal in size and surface morphology. No focal liver lesions are seen. No fatty liver infiltration. No intrahepatic biliary ductal dilatation. Hepatic veins and portal veins are widely patent.

Gallbladder is normal.

Spleen is borderline enlarged measuring 13.1 cm in craniocaudad dimension..

Pancreas is normal in size and signal intensity. No pancreatic duct dilation.

Adrenal glands normal in size and signal.

Kidneys are normal.

No enlarged abdominal lymph nodes. Mild ascites..

Final Pathologic Diagnosis

LIVER MASS, NEEDLE CORE BIOPSY:
   EXTENSIVELY NECROTIC TISSUE WITH VERY RARE VIABLE TUMOR CELLS (SEE COMMENT)

Comment

The vast majority of the sampled tissue shows tumor necrosis with only minute (4-5 cells) cluster of viable tumor cells seen on a deeper level. The immunoprofile of these rare cells is compatible with metastatic colon cancer.

There is insufficient viable tumor for any additional studies.

Case 1, The Rest of the Story

- Admitted to hospital 9 days after issue

- Diagnosed with metastatic colon cancer to liver and peritoneum (carcinomatosis)

- Succumbed to his disease 5 months later.

CRC Prognostic Determinants

- Pathologic Stage at presentation is the most important indicator of survival.

- In addition to stage: extramural tumor deposits, lymphovascular and perineural invasion, histologic grade of differentiation, preoperative CEA, MSI (microsatellite instability), and RAS and BRAF mutations.

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Lagniappe: Head & Neck Cancer

Incidence rates, 2014-2018

Oral cavity and pharynx, by sex

Male 18.1

Female 6.5

Average annual rate per 100,000, age adjusted to the 2000 US standard population.

Data sources: North American Association of Central Cancer Registries (NAACCR), 2021

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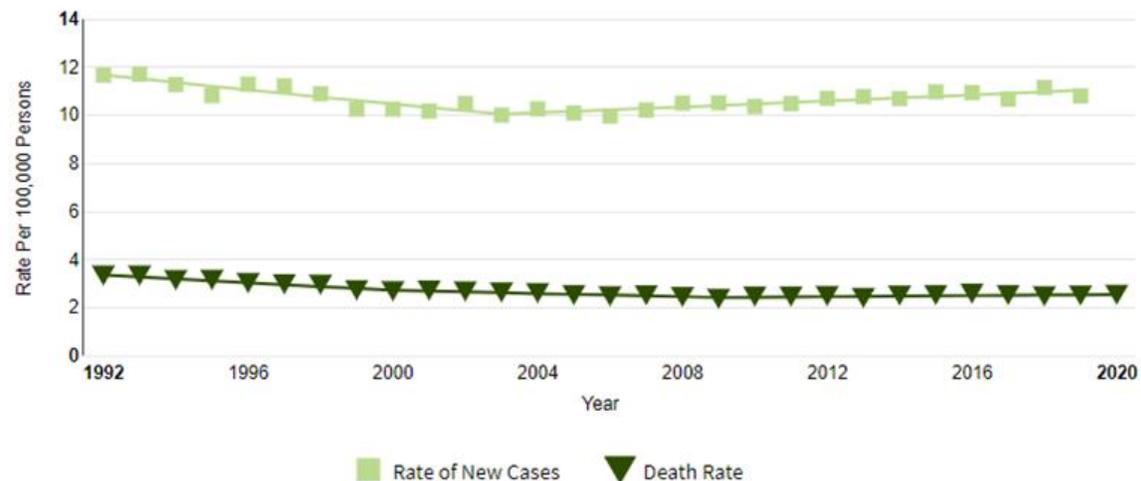
New cases come from SEER 12. Deaths come from U.S. Mortality. All Races, Both Sexes. Rates are Age-Adjusted.

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.
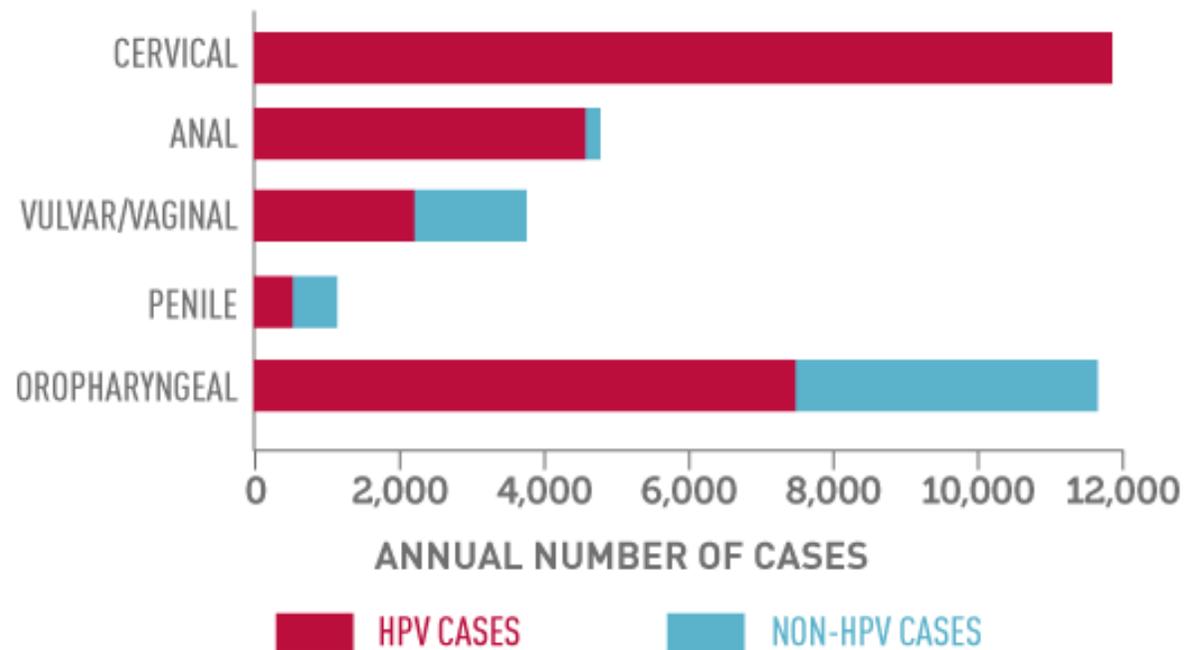
www.cancer.gov

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

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.

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

- 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

- In those HPV(+), tobacco use and presence of tumor-infiltrating lymphocytes are additional predictors of survival
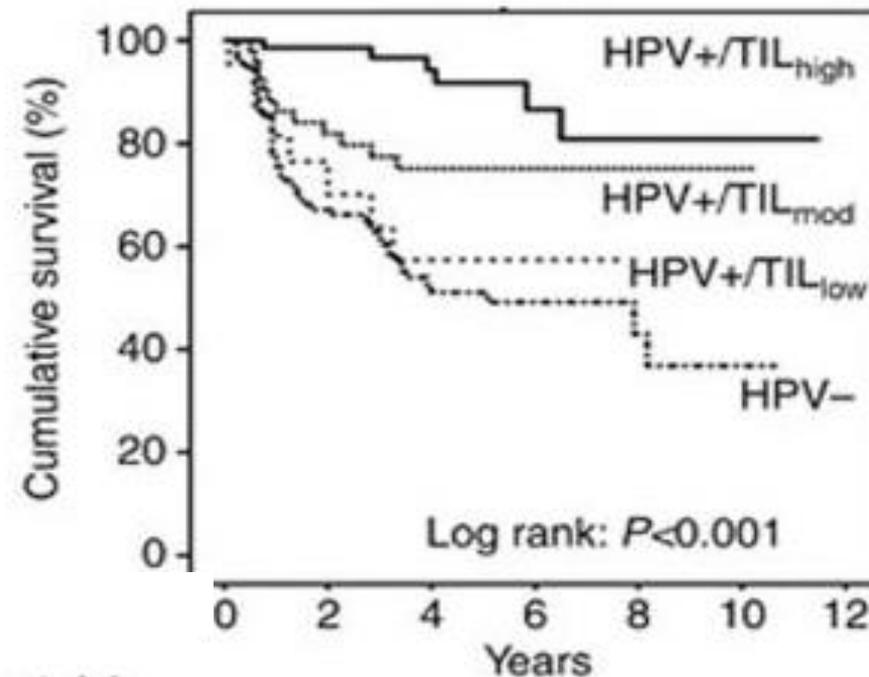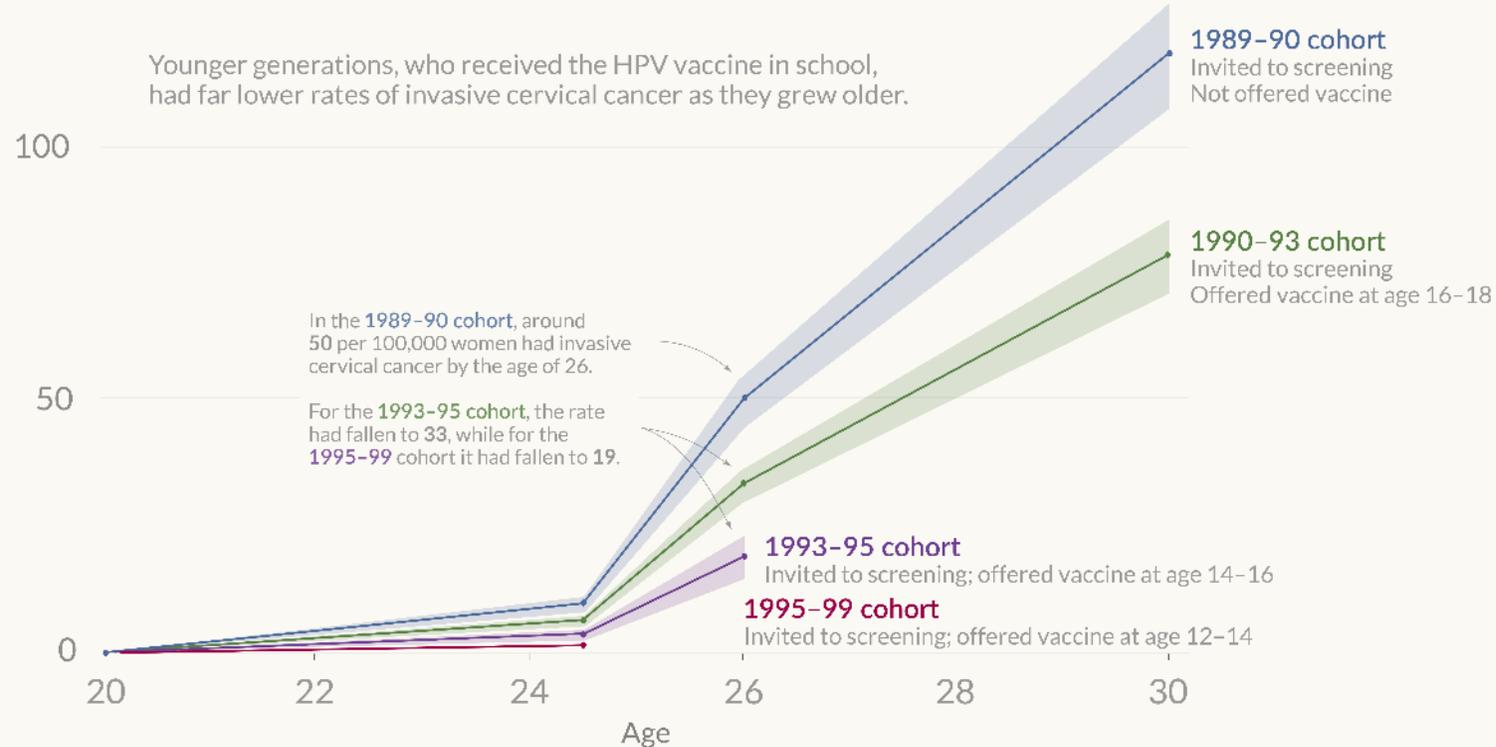
Cervical cancer rates declined in England following national HPV vaccination programs

Our World in Data

Cumulative new cases of invasive cervical cancer per 100,000 women

Younger generations, who received the HPV vaccine in school, had far lower rates of invasive cervical cancer as they grew older.

1989–90 cohort
Invited to screening
Not offered vaccine

1990–93 cohort
Invited to screening
Offered vaccine at age 16–18

In the **1989–90 cohort**, around 50 per 100,000 women had invasive cervical cancer by the age of 26.

For the **1993–95 cohort**, the rate had fallen to **33**, while for the **1995–99** cohort it had fallen to **19**.

1993–95 cohort
Invited to screening; offered vaccine at age 14–16

1995–99 cohort
Invited to screening; offered vaccine at age 12–14

Age

Note: Shaded regions show 95% confidence intervals. Each of the 1989–1999 cohorts was invited to screening at the average age of 24.5.
Source: Milena Falcaro et al. (2021) The effects of the national HPV vaccination programme in England, UK, on cervical cancer and grade 3 cervical intraepithelial neoplasia incidence: a register-based observational study. *The Lancet.*

OurWorldinData.org — Research and data to make progress against the world's largest problems.   Licensed under CC-BY by the author Saloni Dattani
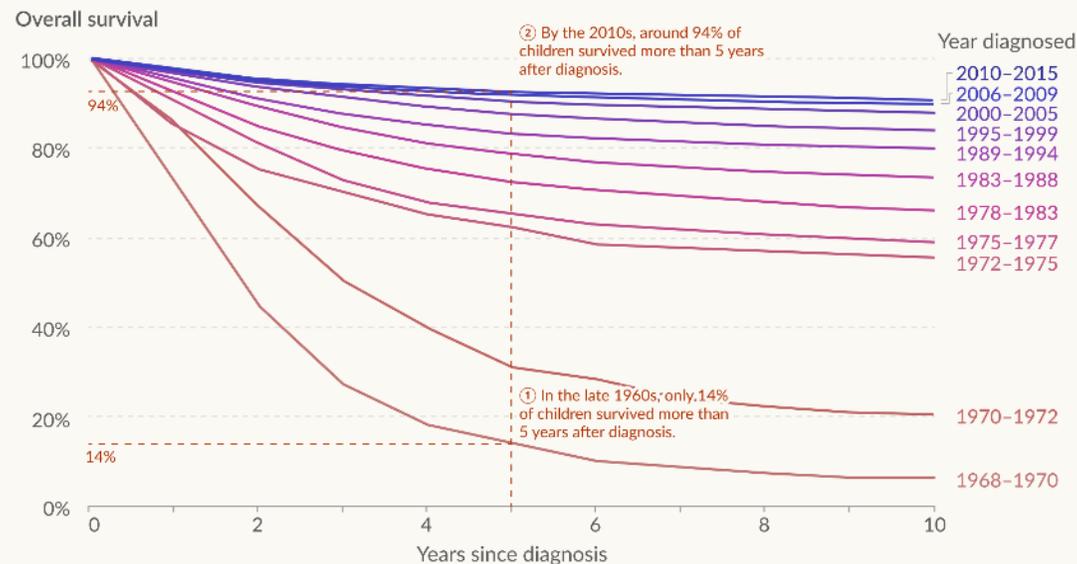
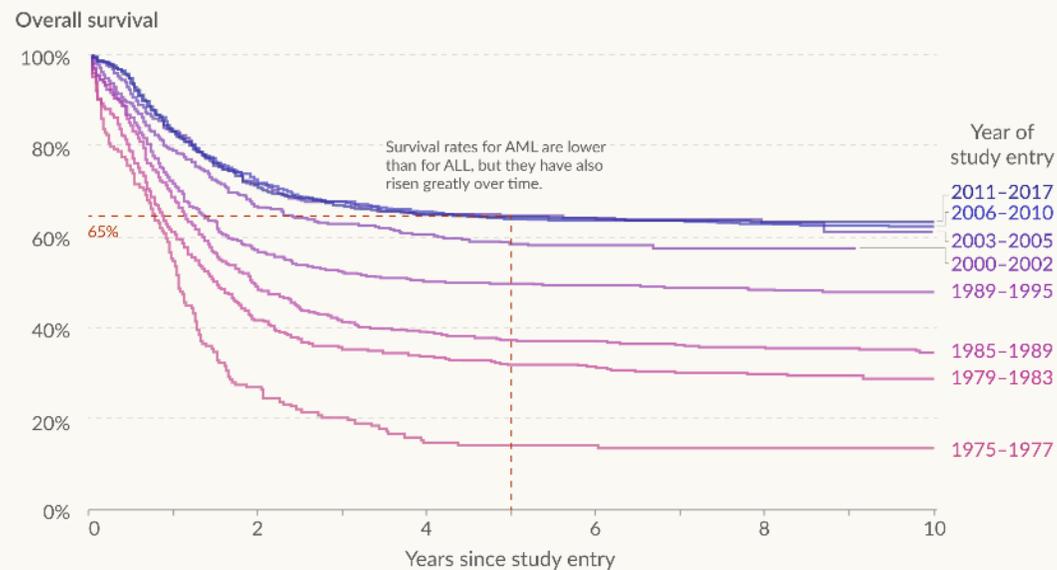# Survival rates for childhood leukemia over time

Survival rates in the Children's Oncology Group trials across the United States, Canada, and other countries.

Our World in Data

Acute lymphoblastic leukemia (ALL)

Overall survival

② By the 2010s, around 94% of children survived more than 5 years after diagnosis.

94%

① In the late 1960s, only 14% of children survived more than 5 years after diagnosis.

14%

Years since diagnosis

Year diagnosed
- 2010–2015
- 2006–2009
- 2000–2005
- 1995–1999
- 1989–1994
- 1983–1988
- 1978–1983
- 1975–1977
- 1972–1975
- 1970–1972
- 1968–1970

Acute myeloid leukemia (AML)

Overall survival

Survival rates for AML are lower than for ALL, but they have also risen greatly over time.

65%

Years since study entry

Year of study entry
- 2011–2017
- 2006–2010
- 2003–2005
- 2000–2002
- 1989–1995
- 1985–1989
- 1979–1983
- 1975–1977

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