SOLID TUMORS
WORKSHOP

October 19-23, 2015
Jack Swanson
Brad Heltemes
Cancer is now the leading cause of death in those under the age of 85.
Estimated New Cancer Cases* in the US in 2014

**Men**
- Prostate: 27%
- Lung & bronchus: 14%
- Colon & rectum: 8%
- Urinary bladder: 7%
- Melanoma of skin: 5%
- Kidney & renal pelvis: 5%
- Non-Hodgkin lymphoma: 4%
- Oral cavity & pharynx: 4%
- Leukemia: 4%
- Liver & intrahepatic bile duct: 3%
- All other sites: 20%

**Women**
- Breast: 29%
- Lung & bronchus: 13%
- Colon & rectum: 8%
- Uterine corpus: 6%
- Thyroid: 6%
- Non-Hodgkin lymphoma: 4%
- Melanoma of skin: 4%
- Kidney & renal pelvis: 3%
- Pancreas: 3%
- Leukemia: 3%
- All other sites: 21%

*Excludes basal cell and squamous cell skin cancers and in situ carcinoma except urinary bladder.*
### Estimated Cancer Deaths in the US in 2014

<table>
<thead>
<tr>
<th>Condition</th>
<th>Percentage</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung &amp; bronchus</td>
<td>28%</td>
<td>310,010</td>
<td>26%</td>
</tr>
<tr>
<td>Prostate</td>
<td>10%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>8%</td>
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<td>Pancreas</td>
<td>7%</td>
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<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>5%</td>
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<tr>
<td>Leukemia</td>
<td>5%</td>
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<tr>
<td>Esophagus</td>
<td>4%</td>
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<td></td>
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<tr>
<td>Urinary bladder</td>
<td>4%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>3%</td>
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<tr>
<td>All other sites</td>
<td>24%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breast</td>
<td>15%</td>
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<tr>
<td>Colon &amp; rectum</td>
<td>9%</td>
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<tr>
<td>Pancreas</td>
<td>7%</td>
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<tr>
<td>Ovary</td>
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</tr>
<tr>
<td>Leukemia</td>
<td>4%</td>
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</tr>
<tr>
<td>Uterine corpus</td>
<td>3%</td>
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<td>Non-Hodgkin lymphoma</td>
<td>3%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Liver &amp; intrahepatic bile duct</td>
<td>3%</td>
<td></td>
<td></td>
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<tr>
<td>Brain &amp; other nervous system</td>
<td>2%</td>
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<tr>
<td>All other sites</td>
<td>23%</td>
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</table>
Net survival adjusted for age and sex for each cancer in 2010–11, and absolute change since 1971, all adults (15–99 years), England 10 years after diagnosis
Prostate Cancer

- In the U.S. 2012 estimate -- 242,000 new cases and 28,000 deaths
  - Most common cancer in men
  - Most commonly diagnosed human cancer, excluding skin cancers
  - 2nd leading cause of death from cancer in men
- About 1 in 6 men will be diagnosed with prostate cancer during their lifetime (yet at least 1/2 of men over age 40 will develop prostate cancer)
  - Rates are 10-50 times higher than those reported in many Asian countries (due in part to screening practices)
  - Most men with occult disease die of other diseases
Prostate Cancer – Case #1

- 75 y/o Male (treated and followed by “prostate cancer oncology specialist”).
  - January 2009 – PSA 4.4, 20% free
  - August 2009 – PSA 5.2
  - Sept 2009 – PSA 6.4
  - Dec. 2010 – PSA 6.5
  - January 2010 – PSA 9.0 14% free

- Color Doppler Jan 2010 showed 80cc prostate with “fairly distinct hypoechoic region in left lateral mid gland toward apex, 12x9 mm with increased vascularity”.
  - March 2011 – PSA 7.4, 15% free
  - April 2011 – PSA 7.5, 19% free
  - May 2011 – PSA 6.9

- Biopsy May 2011 – 16 cores
Case #1

- May 2011 biopsies - prostate cancer:
  - Left lateral mid-gland: 31% Gleason score (GS) 3+3=6
  - Left lateral apex: 10% GS 3+3=6
  - Right lateral mid-gland: 12% GS 3+3=6.
  - All other cores benign.

- Outside consultation on these slides:
  - Left lateral mid: 10% GS 3+3=6
  - Left lateral apex: 30% GS 3+4 =7
  - Right lateral mid 10% GS 3+3=6
  - Consultants note no perineural invasion or extra prostate adipose cancer. However, right lateral base – focus small atypical glands suspicious but not diagnostic for cancer (ASAP – atypical small acinar proliferation). They also note HGPIN right apex. All other cores called benign.

- What is the cancer stage and grade here?
- Does the difference of opinion in pathology evaluation of biopsies concern you?
- How much do “atypical” biopsy changes and “ASAP” affect your evaluation of this case?
PROSTATE CANCER STAGING

Clinical (c) & Path (p) staging:

- cT1c – Unapparent, biopsy diagnosis only
- c or p T2a – ½ of one lobe
- c or p T2b – up to one lobe
- c or p T2c – bilateral
- c or p T3a – extends through capsule
- c or p T3b – seminal vesicle invasion
Simplified Schematic of Gleason’s Grading System
PROPOSED NEW PC GRADING

- Gleason score 6: grade group I
- Gleason score 3+4=7: grade group II
- Gleason score 4+3=7: grade group III
- Gleason score 4+4=8: grade group IV
- Gleason score 9-10: grade group V
NEW PC GRADING

Higher the grade- higher risk of recurrence and death. “Reflect prognosis.”

5 year biochemical recurrence-free survival:
- Grade I - 94.6%
- Grade II - 82.7%
- Grade V - 34.5%.

Case #1

- Patient given Finasteride. After 6 months, color Doppler showed reduction in hypoechoic region to 8x8 mm & reduction in prostate volume to 60 cc.
  - Nov 2011 PSA 3.7; Feb 2012 – negative bone scan
  - April 2012 – PSA 3.7
  - May 2012 – PSA 3.7
  - Nov 2012 – PSA 4.8
  - Sept 2013 – PSA 3.4, Color Doppler unchanged
  - Sept 2014 – PSA 6.5, MRI /Ultrasound Fusion: no change from previous Doppler.
  - Insurance lab PSA March 2015 – 5.9, 15% free.

- Do you agree with MD on his active surveillance recommendation? Reasonable at this age.
- What if follow-up PSA has risen to 8.0 or 9.0 in August 2015? Should there then be follow-up biopsies? Yes, greater concern.
- What are follow-up recommendations for active surveillance?
MRI/Ultrasound Fusion

- Guides biopsies detect more PC Gleason score 7 or more, detect less PC Gleason score 6 or less. i.e. increased detection of high-risk PC and decreased detection of low-risk PC.

- Basis- how tightly cells are packed, how blood flows through it, & “chemical makeup. JAMA Jan. 27, 2015, pgs. 390, 367.
ACTIVE SURVEILLANCE CRITERIA

- Clinical stage: cT1c, cT2a(b)
- Gleason score: 6 (3+4=7 if age > 70)
- PSA < 10 (< 15 for age > 70) (Toronto)

JS: age, co-morbidities, # positive cores (of at least 12 cores), % of cores with cancer. Concern if > 2 positive cores or 50% of core w/ cancer or Gleason 4 or 5.
FOLLOW-UP

- PSA q 3 months
- Repeat biopsies first year. Then q 4-5 years to look for progress to GS 4+3=7 or PSA doubling time < 3 years.

* JS: PSA q 6 (or 4 at first) months for several years. Bx after 1 or 2 years, or if rising PSA
Case #1

Outside consultation on these slides:
- Left lateral mid: 10% GS 3+3=6
- Left lateral apex: 30% GS 3+4 =7
- Right lateral mid 10% GS 3+3=6

Patient given Finasteride. Color Doppler showed reduction in hypoechoic region
- Nov 2011 to Sept 2013 – PSA 3.4-4.8
- Feb 2012 – Negative bone scan
- Sept 2013 – Color Doppler unchanged
- Sept 2014 – PSA 6.5, MRI /Ultrasound Fusion: no change from previous Doppler.
- Insurance lab PSA March 2015 – 5.9, 15% free.

- Favorable and unfavorable factors in this case?
- Mortality risk – negligible, low, moderate, or high?
**CONCERNS**

- Upgrade Gleason score after radical prostatectomy – 27-38%.
- Upstage 24-52% after radical prostatectomy.
- Gleason: Up to 2.7 different grades in prostatectomy specimens.
- PC mortality usually 10-15 yrs. post-DX.
- With limited sampling, can miss high grades
MORE CONCERNS

- With PC’s long mortality tail (10-25 years), A.S. for younger men is risky.
- Gleason: Ave. Over 50% - 3 Gleason patterns (Gleason: Ignore 3rd).
- Mayo Clinic’s Bostwick: Gleason grade 3 “particularly difficult to separate from benign acini in biopsies” (CA 1997; 47; 297).
Prostate Cancer – Case #2

- 61 y/o Male. Fam. Hx – 64 y/o brother with recurrent prostate cancer.
  - PSA April 2008 – 1.2
  - Dec. 2008 – 2.36
  - April 2009 – 2.1 (same lab).
- April 2009 12 core biopsy:
  - 3 cores with Gleason score 3+3=6, all on left, 25% of two cores, 5% one core.
- May 2009: Robotic radical prostatectomy.
  - DX – prostatic cancer, Gleason score 3+3=6, in 17% of left lobe.
  - Path diagnosis provided: “Stage pT2b. Microscopic: focal margin affected, left posterior, with perineural invasion. No extraprostatic involvement. Seminal vesicles free of cancer.”

- Do you think the pT stage is accurate? Does the focal margin involvement affect pathology staging? pT2a based on <1/2 of one lobe, but ??pT3a noting the margin.
- Is perineural invasion or any other additional factor significant in your evaluation? Yes, higher risk.
Other Comments

- Need serial sections in prostate biopsies (all cases).
- Use prostatectomy Gleason score & stage, over biopsy score & clinical stage.
- TRUS:
  - Hyperechoic – inflammatory
  - Hypoechoic – suspect cancer (case 1)
- 90% PC now diagnosed local & regional, w/100% 5 yr. survival.
- Past 25 yrs., survival rate for all prostate cancer stages has risen from 68 to 100% in 5 years, 98% in 10 years, & 91% in 15 years. (Siegal. CA.2012. 62; 220).
Immunohistochemistry

“Antibody cocktail” to detect markers for basal cells in prostate biopsies.

The key: basal cell layer is absent in invasive prostate cancer.

Helpful in atypical small acinar proliferation (ASAP), other atypia, & infiltrative single cell patterns. (Arch Pathol Lab Med, Sept 2008)
Case #2

- Follow-up PSA’s:
  - May 2009 – < 0.10
  - Aug 2009 – 0.01
  - April 2010 – 0.01
  - Aug – 0.04
  - Jan 2014 – 0.12
  - Aug 2014 – 0.1 (all same lab)
  - June 2015 – 0.12 (insurance lab)

- List the favorable and unfavorable factors here, including age.
- Risk category – high, low, or medium? Do you need further testing to evaluate?
- What would have been the risk category if this man had been followed with active surveillance? **Unfavorable**
**PCA3**

- RNA-based urine test (Cancer Sept-Oct 2011, p. 319)
- Highly overexpressed in prostate cancer
- Cut-points a problem. Scores range from 4 to 125. 35 (50) or more deemed high risk.
- Some believe age dependent: older the age the higher PCA3.
- Chronic prostatitis does not influence.
Prostate Cancer – Case #3

- 63 y/o Male. First PSA was 1.0 at age 56, then it gradually rose to 2 and then to 3 at age 59.
- TRUS 12 biopsies July 12, 2011: One positive core, Gleason score 3+3=6, in 5% of that core. Other 11 cores negative except scattered HGPIN.
- Applicant chose active surveillance. PSA returned to 1 after biopsies. But, in 2013, PSA again slowly increased from 1 to 2 to 3.
- December 12, 2013 he had another set of TRUS 12 core biopsies: Right base, GS 3+3=6 in 1% of that one core; Right mid, one core 3+3=6 in 20%; Right apex, one core with GS 3+3=6 in 15% of that core. Urine PCA3 – 102.7 (>35 cut-off for suspicious.)
- Patient then elected robotic radical prostatectomy, May 5, 2014. Pathology: Prostate cancer only in right lobe, est. 2.5% of that lobe, GS 3+3=6. Stage pT2a, “with no extension”.
- PSA’s every 2 months ever since, all undetectable (<0.8).
- This case illustrates apparently successful active surveillance resulting in definitive treatment in a relatively young man.

- Is mortality risk low or intermediate?
- Is this an appropriate way to manage active surveillance?
- What is the difference between active surveillance and watchful waiting, or is there a difference?
- Is Gleason 6 always low risk?
- Favorable and unfavorable factors?
Salvage radiotherapy

- Salvage radiation if PSA elevation after prostatectomy. Only hope for cure. Survival studies conflicting – ave. c. 50% (16-64%) (case 3, Q 2). Need RCT – so far only observational studies. (Also risk of rectal & bladder cancer with radiotherapy.)

- Stephenson: tumor in margins of resection (case 3), elevated PSA due to local recurrence, not widespread (JAMA 2004; 291:1325). (Others disagree.) Start salvage radiotherapy w/in 2 years after PSA recurrence, before PSA >2.0 (Trock. JAMA 2008;299:2760). Case 3: 1 yr. after PSA rise but PSA 3.8 when started salvage.

- Regarding last slight PSA elevation in case 3, Q. 4: Amer. Urol. Assn.: Post radiation recurrence diagnosed if PSA 2.0 > nadir, or 3 consecutive rises.

- Freedland studies suggest long survival for case 3 w/ its 14 years from 1st treatment, 5 years from salvage, low PSA levels (JAMA 2005; 294: 433). (next slide)
BIOCHEMICAL RECURRENCE, PROSTATE CANCER

- Not synonymous with death
- Median survival is over 16 years.
- 15 year survival varies from <1% to 94%
- 94% 15 year survival if:
  - Gleason score 6 or less, long PSADT, > 3 yrs post-tx
- High mortality risk:
  - Rapid PSA doubling time (<3 mo.)
  - Gleason score 8-10
  - Years to recurrence < 3
  - Median survival 3 years

Freedland. JAMA 2005; 294:433-439
Malignant Melanoma

- 76,100 new cases of invasive melanoma anticipated in U.S. in 2014 (44,200 in 1999). 58% men.
- From 1982 to 2011, melanoma incidence rates doubled in the United States to 24.6/100,000 in non-Hispanic whites
  - 1/34 (men) and 1/53 (women) lifetime risk in 2009
- Rates increasing in those of European descent worldwide
  - Highest in Australia and New Zealand (~50/100,000/yr), and Southern California
  - Fastest increases in incidence are in central Europe
Cancer mortality rates by state (age-adjusted 2000 US population)

Rates per 100,000 person-years, 1970-2004

<table>
<thead>
<tr>
<th>Mortality rate</th>
<th>Confidence interval</th>
<th>No. of deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>US 2.81</td>
<td>2.79 - 2.82</td>
<td>195,999</td>
</tr>
</tbody>
</table>

Sporadic data (3)
Melanoma Risk Factors

- Hx of sun exposure, particularly blistering sunburns, especially in childhood (est. 65% of the risk)
- Tanning bed use – prior to the age 30 increases risk by 75%.
- Fair skin/freckling/tendency to sunburn
- Light hair/eye coloring – MC1R gene in redheads
- >25 nevi (>50-100 yields a RR of 5 to 17)
- Atypical (dysplastic) nevi
  - Can be a melanoma precursor (25-50% of MM) but most arise de novo
- Family hx of melanoma or of atypical nevi
- Prior hx of melanoma
- History of nonmelanoma skin cancer and prostate cancer
- Parkinson’s, Xeroderma pigmentosum, Immunosuppression
Melanoma Case #1

- 72 year-old male
  - Applied May 2014
  - $2 million UL policy
- History of malignant melanoma 2.5 years prior to application.
- History of HTN, otherwise medical history, paramed exam and lab all unremarkable.

Stage?
- Possibly T1b, but...
Information complete?
- Positive margin, need follow-up since
Primary Tumor (T)

- Tumor Thickness – Continuously increasing risk with increasing thickness
  - T1: ≤ 1.0 mm
  - T2: 1.01 - 2.00 mm
  - T3: 2.01 - 4.00 mm
  - T4: > 4.00 mm

- Ulceration (absence of intact epithelium)
  - No ulceration = “a”
  - Ulceration present = “b”

- Mitotic Rate – Risk increases with increasing mitotic rate, regardless of thickness
  - Affects only T1 for staging though: “b” if ≥ 1/mm²
**Lymphatic Involvement (N)**

- NX: Nodes are not assessable (e.g. previously resected)
- N0: No regional lymphatic metastases
- N1: One involved lymph node
  - N1a - presence of micrometastasis (by sentinel node bx)
  - N1b - presence of macrometastasis (clinically detected nodes or with extracapsular extension)
- N2:
  - N2a - two or three nodes with micrometastases
  - N2b - two or three nodes with macrometastases
  - N2c - without lymph node involvement but with in transit or satellite metastasis.
- N3: Four or more positive nodes, or matted nodes, or in transit metastases/satellites with one or more positive nodes
Distant Metastasis (M)

- **M0**: No detectable evidence of distant metastases
- **M1a**: Metastases to skin, subcutaneous, or distant lymph node, normal serum LDH
- **M1b**: Lung metastases, normal LDH
- **M1c**: Metastasis to other visceral sites with a normal LDH, or any distant metastasis with an elevated LDH

Staging is closely tied to prognosis
Melanoma
Case #1

Subsequent wide excision revealed no residual melanoma and sentinel lymph node biopsy was negative.

- Seen in follow-up every six months – no evidence of recurrence or of additional lesions

- Tumor Stage?
  - T1bN0Mx

- Favorable and unfavorable features?
  - Do tumor location, age, or gender have an impact?
Stage Groupings

- **Stage I:** T1a to T2a, N0 and M0
  - Stage IA – T1a
  - **Stage IB – T1b or T2a**

- **Stage II:** T2b to T4b, N0 and M0
  - Stage IIA – T2b or T3a, N0, M0
  - Stage IIB – T3b or T4a, N0, M0
  - Stage IIC – T4b, N0, M0

- **Stage III:** N1-3, M0
  - Stage IIIA – T1-4a, N1a or N2a
  - Stage IIIB – T1-4b, N1a or N2a; or T1-4a, N1b, N2b, or N2c
  - Stage IIIC – T1-4b, N1b, N2b, or N2c; or Any T, N3

- **Stage IV:** M1
  - Any T, Any N, M1a-M1c

*Isolated metastases arising in lymph nodes, skin, or subcutaneous tissue, without an identifiable primary, are classified as stage III*
Melanoma Prognostic Factors

- Depth of invasion (Breslow thickness)
- Ulceration
- Mitotic rate
  - <1, 1-20, and >20 mitoses/mm²
- Lymph node status
- Anatomic site (scalp/neck > hands, feet > trunk > legs > arms)
- Other histologic features:
  - Microsatellites (unfavorable)
  - Desmoplastic (more favorable for degree of thickness)
  - Lymphocytic infiltration (favorable) and tumor regression (possibly favorable?!?) not a consistent finding
- Gender (F better survival than M, for Stage I & II)
- Age (worsens with age)
- Lymphatic invasion (2-fold increased 10-yr mortality risk)
- Elevated Serum S-100 protein (5-yr survival 51% vs 91%)
- ??Mutations in the MAPK pathway (BRAF and NRAS) and circulating melanoma cells (by RT-PCR)
Melanoma Case #1

- Subsequent wide excision revealed no residual melanoma and sentinel lymph node biopsy was negative.
- Seen in follow-up every six months – no evidence of recurrence or of additional lesions

- Tumor Stage?
  T1b, N0, Mx = (Likely) Stage IB

- Favorable and unfavorable features?
  Favorable: No ulceration, forearm location
  Adverse: Mitoses, age, male, depth 0.73mm within T1b stage(?)

- Mortality risk: Very little, low, moderate, or high?
**Thin Melanomas – T1a**

- Excellent long-term survival after full excision
  - 96% 20-year melanoma specific survival in large Australian database
  - Greater risk though if:
    - Thickness >0.75
    - Age >65
    - Males
    - Head and Neck location
    - Clark’s level IV or V
  - Similar survival rates seen with SEER data
  - 93% 10-year survivals seen with AJCC database
### Survival by Mitotic Count

**Stage I and II**

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<tr>
<th>Mitoses/mm²</th>
<th>5 year survival</th>
<th>10 year survival</th>
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</thead>
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<tr>
<td>0 – &lt;1.0</td>
<td>97</td>
<td>93</td>
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<tr>
<td>1.0 – &lt;2.0</td>
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<tr>
<td>2.0 – &lt;5.0</td>
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<td>5.0 – &lt;11.0</td>
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<tr>
<td>&gt; 20.0</td>
<td>59</td>
<td>48</td>
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**Survival by T Classification**

*AJCC Database*

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<thead>
<tr>
<th>Thickness Class</th>
<th>5 year survival %</th>
<th>10 year survival %</th>
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</thead>
<tbody>
<tr>
<td>T1a</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>T1b</td>
<td>94</td>
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<td>57</td>
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<tr>
<td>T4b</td>
<td>53</td>
<td>39</td>
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</table>
Melanoma – Impact of T Stage

Twenty-year survival rates comparing the different T categories (top) and the stage groupings (bottom) for stages I and II melanoma.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.
Melanoma Case #1 (cont.)

- Mortality risk?

  Relatively low, but not insignificant at this point given the stage and older male
Melanoma Case #2

- 37 yo female applied June 2013 for $350,000 term life insurance
- Application notes melanoma excision Sept 2008, C-section Nov 2010
- Regular dermatology follow-up since; no problem, no recurrence
  - Willing to accept as is, since now nearly 5 years out? Sorry, better get the details!
- What is the melanoma stage?
  T2a, Nx, Mx = ?Stage IB

- Is the assessment complete?
  With thickness >1mm (??>0.75mm), sentinel node biopsy is generally advised

- Other favorable and unfavorable factors?
  Favorable: Age and gender.
  Adverse: Dysplastic nevus. No info on ulceration, lymphatic invasion, mitoses.
Primary Tumor (T)

- Tumor Thickness – Continuously increasing risk with increasing thickness
  - T1: ≤ 1.0 mm
  - T2: 1.01 - 2.00 mm
  - T3: 2.01 - 4.00 mm
  - T4: > 4.00 mm

- Ulceration (absence of intact epithelium)
  - No ulceration = “a”
  - Ulceration present = “b”

- Mitotic Rate – Risk increases with increasing mitotic rate, regardless of thickness
  - Affects only T1 for staging though: “b” if ≥ 1/mm²

- T2a – Possibly Stage IB, but...
  Sentinel node biopsy usually advised for anything other than T1a lesions – possibly understaged without this information
Melanoma Work-up

- For asymptomatic patients stage T1a (and T1b???) melanoma – no additional testing advised, close clinical follow-up only
- If clinically negative nodes but primary melanoma at intermediate or high risk for lymph node metastasis – Sentinel lymph node (SLN) biopsy for staging purposes usually advised, and completion lymph node dissection then if SLN positive
- For Stage IIIB or IIIC disease (and ??Stage IIIA also), or with an initial locoregional recurrence – CBC, serum LDH, and CT imaging of the chest, abdomen, and pelvis
- PET/CT if additional surgery for advance local disease is contemplated, and at follow-up in very high risk patients
9/23/08 path: 1 of 3 sentinel nodes showing rare isolated cells positive for melan A

- Stage now? Does this represent node positive disease? T2a, Nx, Mx = ??Stage IB vs IIIA
- Prognosis?
  More worrisome? Possibly not...
Melanoma Case #2 (cont.)

- The SLN biopsy of 2008 equivocal -- immunohistostain positive cells are generally consistent with node mets, but in this case was just the Melan A and not HMB45, which is more specific for melanoma (S100 not checked??).
- Data have shown also that even those with more definite "submicrometastases" the prognosis is only slightly worse than if was SLN negative. ¹²

- Prognosis?
- Any additional exam findings or history that would be nice to know?
  
  Family history, risk factors, additional lesions (number and atypia), follow-up
## Survival rates for melanoma TNM and staging categories

<table>
<thead>
<tr>
<th>Pathologic stage</th>
<th>TNM</th>
<th>Ulceration</th>
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Melanoma Case #2 (cont.)

- Multiple nevi noted
- Fair skin, history of extensive sun damage
- Melanoma in maternal grandmother and maternal uncle
- Additional moles with atypia in 6/09, 5/10, 2/11, 5/11 (2)
- No derm evaluations from 5/11 until last visit prior to the 6/13 app in 8/12 (no lesions of concern noted then)
- Path: 6/9/09
  - A. RU Back. junctional nevus with architectural disorder and mild cytologic atypia
  - B. L post shoulder: Malignant Melanoma in situ w/in a background of junctional dysplastic nevus; margins free.

- Do these results change the prognosis any? If so, how would you now assess the risk??
  Now a concern for “Dysplastic nevus syndrome” or even FAMMM, though skin exam otherwise not well described
Second Melanoma Risk

- After melanoma diagnosis, risk of second melanoma 2-11% at 5 years.
- Higher risk seen with atypical nevi (RR 2), high nevus counts (RR 3), family history of MM (RR 2), more than one melanoma, if melanoma was nodular (RR 2), or if first melanoma at age <30.
- Familial Atypical Multiple Mole and Melanoma (FAMMM) Syndrome
  - Characterized by a 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

- How would you now assess the risk - Low, moderate, or high?
  Second melanoma risk of 20+%+, possibly 50% or more
  Appears to be less than adequately followed – often an even greater concern.
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)
Melanoma Case #2 -- What if...

What if a sentinel node biopsy was clearly positive for metastatic melanoma:
- Stage then?
  - Still uncertain – completion lymph node dissection indicated
- How about if LND was carried out and just that one node was positive?
  - T2a, N1a, M0 = Stage IIIA
- Prognosis?
  Survival per melanomaprognosis.org:
  - 1-yr 98%
  - 2-yr 95%
  - 5-yr 87%
  - 10-yr 81%
Melanoma Case #2 (What if?)

What if she had received adjuvant treatment (and what should she receive)?

Interferon vs Ipilimumab (CTLA-4 blocker just recently FDA approved).

However, other immune checkpoint inhibitors may be better yet (e.g. PD-1 inhibitors nivolumab or pembrolizumab)

What if it was now 8 years since the original diagnosis and she was well followed with no further atypical lesions?

Improved prognosis, but still significant risk, mostly of second malignancy but also of recurrence, out at least 15-20 years
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 >1mm thickness
  - Not performed for early localized lesions (stage I and carcinoma in situ) unless additional high risk features present
  - If melanoma present, completion lymph node dissection (CLND) is done -- unless only submicrometastases??
- LND performed if clinically evident adenopathy is present
- Adjuvant therapy for stage IIB or IIC or node positive disease
  - See prior slide
- Resection of locoregional or isolated metastatic recurrence
  - Rare cures obtained
- Systemic therapy for metastatic disease -- limited effectiveness but major advances in just the past few years
  - Immunotherapy – usually pembrolizumab or nivolumab
  - For patients with a V600 BRAF mutation, targeted therapy using a BRAF inhibitor/MEK inhibitor (dabrafenib/trametinib) or vemurafenib (+cobimetinib) also an option
- Radiation therapy – mostly a palliative role, +/- nodal bed??
Melanoma-specific 5-year conditional survival estimates stratified by disease stage. Error bars represent the standard error.
Conditional Survival

Prognosis after 5 years disease-free?

- 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
Melanoma Case #2 – Alternative history

What if, after a year, melanoma recurred at the margins of the wide excision, and was then re-excised – does this change the prognosis?

- Equivalent of in-transit metastases – now effectively T2a,N2c; Stage IIIc disease
- 5- and 10-year survival rates of 69% and 52% respectively per AJCC dataset if nodes were negative
Melanoma Specific Survival

Melanoma Survival - SEER Dataset

Years since diagnosis
Melanoma – Impact of Lymph Node Involvement on Prognosis

Twenty-year survival rates comparing the different N categories (top) and the stage groupings (bottom) for stage III melanoma.

Used with the permission of the American Joint Committee on Cancer (AJCC), Chicago, Illinois. The original source for this material is the AJCC Cancer Staging Manual, Seventh Edition (2010) published by Springer New York, Inc.
Head & Neck Melanoma

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

Breast Cancer

- Breast cancer is the most common cancer in women globally with an estimated 1.4 million new cases diagnosed in 2008, and also the leading cause of cancer death in women worldwide.
- Second most common cause of cancer death in women in the U.S. after lung cancer (15% of deaths)
  - Est 235,000 news cases in 2014 and 40,000 deaths
- Leading cause of death in woman aged 45-55
- 1 in 8 women will be diagnosed in their lifetime. If found early, 95% will be cured.
NOTES FOR BREAST CANCER

- IBC = Breast Cancer
- DCIS = Ductal CA in situ
- SLNB = sentinel lymph node biopsy
- ALND = axillary node dissection
- CNB = core needle biopsy
- MOR = margins of resection
- BCT = breast conserving therapy
Breast Cancer Case #1

- 43 year-old female. Suspicious microcalcifications right breast on first mammogram, April 2013 (age 41)
  - Negative family history of breast disease. One full-term pregnancy, age 33. No known risk factors.
- Core needle biopsy, May 2013:
  - Two foci comedo carcinoma-in-situ. 1.0 cm margin of normal tissue, MOR clear. ER/PR positive.

- Does comedo type DCIS influence prognosis? Yes, adverse
- Any other factors influencing risk of recurrence?
- Is recurrence always predictive of increased mortality?
Breast Cancer Case #1

- Post-biopsy mammography – no evidence of residual tumor. Three options presented to patient: mastectomy, post-lumpectomy radiation, or close observation. She chose the last option.
- On tamoxifen since surgery. Bilateral negative mammograms every 9 months, last July 2015.

- Would mortality and recurrence risks be more favorable with mastectomy or irradiation? **Yes, significantly**
- Is her follow-up appropriate?
- If this woman had triple negative breast cancer (ER neg, PR neg, HER 2 neg.), how might your assessment differ?
- Are sentinel lymph node biopsies ever done with in situ cancer? How would one explain a positive node when patient has an in situ cancer? How would that affect prognosis?
- Favorable and unfavorable factors in this case?
- Would you assess as high, low, or medium risk?
Ductal carcinoma in situ

- DCIS in core needle biopsy, 15-20% have invasive cancer on lumpectomy. 10-50% of atypical ductal hyperplasia on CNB ass’d w/ IBC or DCIS. Core needle biopsy is for diagnosis, not definitive treatment.

- Treatment DCIS. DCIS - “very favorable prognosis …diagnosis of DCIS not likely to affect survival”. (Partridge. CA 2012; 62:203.). Lumpectomy w/ radiotherapy – treat most DCIS. Large or multicentric DCIS or + MOR more often invade & require mastectomy. Not all DCIS progresses to invasive cancer, (but can’t predict which). Burstein: “nearly all invasive breast cancers arise from in situ carcinoma” (NEJM 2004; 350:1430). Gene expression profile DCIS - similar to IBC.

- Concern for recurrence: need mammography 6 & 12 months after excision, then annual. 50% of DCIS recurrences invasive. Recurrence more frequent if comedonecrosis, high grade DCIS, narrow margins, larger tumors, < age 45, (Van Nuys), & no radiotx.
Ductal carcinoma in situ

- Sentinel lymph node excision rarely indicated w/ DCIS. < 5% nodes positive (mostly isolated tumor cells). Most positives are associated w/ microinvasive cancer. SLN biopsy indicated if mastectomy or tumor >4 cm.

- Survival data DCIS: 98-99% - mastectomy; 98% lumpectomy w/ radiation. Latest data: DCIS related death: 1.9% in 10 years. NCI: survival poorer if high grade (6/4/15)

- 94-95% lumpectomy alone. Main concern – recurrence or other breast.

- Lobular CIS- no progress to cancer. Marker for invasive ca, either breast (1%/yr. lifetime. 12x relative risk).

- Mammogram underestimates extent/multifocality of DCIS.
Breast Cancer Case #2

- 66 y/o Female. Abnormal mammogram at age 61.
- Family History: Mother had breast cancer, age 57; died of same, age 61.

- Identify the risk factors for breast cancer.
- With her age and risk factors, did she have optimal mammography intervals prior to cancer diagnosis?
- Does she have increased risk now that the biopsy failed to show any breast cancer?
Because of extensive ADH, had lumpectomy in area of suspicious mammogram.

Pathology of lumpectomy:
- Frozen section = infiltrating ductal carcinoma, confirmed by permanent sections.
- Tumor size: 1.1 cm in greatest dimension.
- Histologic grade intermediate (moderately differentiated).
- Comedo DCIS present focally within tumor mass and in two random sections away from tumor mass.
- Lymphovascular invasion not identified.
- Sentinel node biopsy negative (serial sections/special stains).
- Resection margins: tumor in one focus.
- Cancer is ER and PR positive. HER 2 negative. S-Phase elevated at 5.5.
- AJCC/pTN classification: T1cN0

Why was a lumpectomy performed when the core needle biopsy was “only” atypical ductal hyperplasia?

Was her treatment optimal, especially since she also had extensive DCIS?

Why is the sentinel node serially sectioned and given special stains?
ATYPICAL DUCTAL HYPERPLASIA

- Any proliferative breast disease with atypia (esp. atypical ductal hyperplasia) has 4-5 times the usual risk for malignancy.
- Thus case 2 had lumpectomy although biopsy did not show cancer.
- It also explains the distress about atypia missed by pathologists (17%). *(JAMA 3/17/15)*
- Also missed DCIS, esp. w/dense breasts.
Invasive Breast Cancer

- 87% of women w/ IBC alive 5 years; 80% alive at 10 years.
- Rel. survival rates: localized BC – 97% & 93% at 5 & 10 years.
- Regional BC – 80.0% & 67% at 5 & 10 yrs. (Mahoney.CA 2008;58:347).
- Most recur 1st 5 years. Risk of contralateral BC – 1%/year.
- Prognosis IBC – size, grade, histol. of IBC, lymphovascular invasion, lymph node status still important. See later on genomics.
- Pos nodes – require chemotx. Also ER/PR neg., high grade IBC, & < age 50 require chemotx.
**Case #2**

- Treated with external beam radiation and CMF chemotherapy. Subsequently on taxomoxifen until March 2010. Follow-up exams and mammography negative, at first semiannually and annually since. Last mammogram August 2015.

- How long should patients be on tamoxifen? Why? At her age, is there a better alternative?
- Survival statistics for pT1c breast cancer?
- Favorable and unfavorable factors in this case?
Staging – Tumor size

- **T1** — Tumor 2 cm or less in greatest dimension (20 mm)
  - T1mic — Microinvasion, 0.1 cm or less in size (< 1 mm)
  - T1a — Tumor more than 0.1 but not more than 0.5 cm
  - T1b — Tumor more than 0.5 cm but not more than 1 cm
  - T1c — Tumor more than 1 cm but not more than 2 cm
- **T2** — Tumor more than 2 cm but not more than 5 cm in greatest dimension
- **T3** — Tumor more than 5 cm in greatest dimension
- **T4** — Tumor of any size with direct extension to (a) chest wall or (b) skin, only as described below:
  - T4a — Extension to chest wall
  - T4b — Edema (including peau d’orange) or ulceration of the breast skin, or satellite skin nodules in the same breast
  - T4c — Both (T4a and T4b)
  - T4d — Inflammatory carcinoma
TNM Staging

- **Primary Tumor (T)**
  - Tis: Carcinoma in situ
  - T1mic: to 0.1cm. microinvasion (97% survival)
  - T1a: >0.1-0.5 cm. diam. (99% 10 yr. survival)
  - T1b: >0.5-1.0 cm. diam.
  - T1c: >1.0-2.0 cm. diam.
  - T2: T = 2.1 - 5 cm
  - T3: T = > 5 cm
  - T4: T of any size with direct extension to chest wall or skin

- **Regional Nodes (N)**
  - N0: No involved nodes
  - N1: 1-3 ipsilateral axillary nodes
  - N2: 4-9 axillary nodes
  - N3: 10 or more nodes, or regional nodes other than axillary

- **Distant Metastasis (M)**
  - M0: None detected
  - M1: Distant metastasis present (includes ipsilateral supraclavicular nodes)
Breast Cancer TNM Staging

- Stage 0 – TisN0M0
- Stage IA – T1N0M0
- Stage IB - T0N1micM0
- Stage IIA – T0N1M0( !)
  - T1N1M0
  - T1N1micM0
  - T2N0M0
- Stage IIB - T2N1M0
  - T3N0M0
- Stage IIIA – T0N2M0
  - T1 N2M0
Breast Cancer Survival By Node Status
Ages 30-75, 0-2 cm Lesions
SEER Data

Survival (%) vs Years

- Expected
- 0 Nodes
- 1-3 Nodes
- 4 + Nodes

Survival (%)
100% 90% 80% 70% 60% 50% 40% 30%

Years
1 2 3 4 5 6 7 8 9 10 11 12
Invasive Breast Cancer

- Survival w/ lumpectomy + radiation same as mastectomy. Radiation decreases recurrence. Over age 70, radiation optional if on tamoxifen.
- With earlier diagnosis & better treatment, 5 yr. survival has increased from 75% to the 90 percentiles since 1990 (DeSantis CA, 2011; 61:409).
- 5 yr. survival: localized IBC 98%, regional 84%, distant 23% (Siegal.CA 2012; 62:220).
- If + axillary nodes, twice as likely to have spread elsewhere & recur. Positive intramammary lymph nodes worsens prognosis.
BREAST CANCER IMAGING

- Tomosynthesis added to digital mammography: decrease recall rate, increase in cancer detection. JAMA p. 452, 2/3/ 2015. These are 3-D mammograms, with multiple slices to create the 3-D. Esp. helpful if dense breasts.

- Digital mammography still has value when other radiologists not available for second opinion or for “generalist” radiologist.

- Need post-excision mammography 3-5 weeks post-op to assure completeness.
Mammography: BI-RADS

1 Negative: 0 % malignant
2 Benign: 0% malignant
3 Probably benign: <2% malignant
4 (A,B,C) suspicious: 2-95% malignant
5 Highly suggestive: >95% malignant
MAMMOGRAPHY: BI-RADS FOLLOW-UP

- BI-RADS 3 needs repeat mammogram soon (<6 mo.)
- BI-RADS 4A – (2-10% malignant)
- BI-RADS 4B – (10-50% malignant)
- BI-RADS 4C – (50-95% malignant)
- All BI-RADS 4 categories need biopsy
- BI-RADS 5 – needs biopsy
Sentinel lymph node, isolated tumor cells, micromets, microinvasive cancer

- Steve Rigatti’s review includes when no ALND despite + SLN (JIM 2012;43: 18).
- Need caution, esp. if micromets. Some still claim Isolated Tumor Cells (ITC) same as negative nodes (conundrum).

- Serial Sections/ IHC diagnose 10-30% of false negatives on H&E routine on SLN.
DeBoer: Micromets & ITC – better survival w/ endocrine &/or chemo therapy. (NEJM. 2009:361:653)


SLN biopsy 94% sensitive (usually done on T1,2 IBC).

Extensive DCIS more often ass’d w/ IBC.

Impact of family hx on BC -- Relative risk:
- 1.8 RR if 1st degree relative w/ post-menopausal BC
- 3.3 RR if 1st degree premenopausal BC
- 3.6-5.0 w/ two 1st degree BC

BRCA1 or 2: 40-80% lifetime risk. (Mahoney. CA 2008; 58:347)
MINIMALLY INVASIVE BREAST CA

- Microinvasion (T1mic– up to 0.1 cm invasion into stroma)
  - Overall 97-100% survival. Higher risk if there is EDIC (extensive DCIS) or necrotic DCIS.
  - Survival is between DCIS & T1 (< 2 cm) cancer.
  - Very few metastasize.
- T1a (<0.6 cm), grade 1
  - Up to 99% 10-year survival
  - Similar to DCIS treated with mastectomy or lumpectomy with irradiation
- T1a cancers need SNL bx & if ER+: Tamoxifen or aromatase inhibitor.
- (75% of recurrent BC – long-term survivors.)
BREAST CANCER GENOMICS

- 21-Gene Recurrence Score (Oncotype) is among best validated prognostic assay. It may predict who will respond to chemo. Use if node neg. & ER/PR +. (ASCO guidelines). < 18 good, > 18 not good.

- 70-Gene Profile (Amsterdam): determines prognosis regardless of HR receptor status & in HER2 + (MammaPrint).

- Many other tests. (Up-To-Date, 9 Sept. 2015)
BREAST CANCER GENOMICS

- Luminal A & B associated w/ epithelial cells & overlap w/ ER/PR + cells.
- Luminal A most common (40%), best prognosis. HER 2 may be neg.
- Luminal B 20%, prognosis not as good per 21-Gene Recurrence Score. HER2 variable.
- Basal cells more primitive, don’t express hormone receptors. Triple negative breast cancer is basal. Basal are high grade.
Thyroid Cancer

- 59 y/o Female. April 2008, bilateral thyroidectomy because of bilateral nodules.

- Pathology:
  - Right - 7 mm. medullary carcinoma, with 3 of 13 positive nodes.
  - Left - 2 mm papillary carcinoma, with 1 of 13 positive nodes. Microscopic mets in right perithyroid lymph node < 2 mm. in size.

- July 2008, full body scan, no metastases.

- Only follow-up, physical exams – “doing well”. No evidence of calcitonin testing.
Thyroid Cancer

- Thyroid carcinoma subtypes
  - Papillary carcinoma (75-85% of cases) best differentiated, best survival (>97% in 5 years), microinvasive even better.
  - Follicular carcinoma (10-20% of cases) – good survival data
  - Medullary carcinoma (5% of cases) – often younger
  - Anaplastic carcinoma (<5% of cases) – very malignant
Thyroid Cancer

- Genetic patterns (BRAF mutations)
- 9% of people receiving radiation treatment during childhood develop thyroid malignancies later
- Isolated cervical lymph node mets do not dampen good prognosis.
- Age 20-45 – best prognosis
- Higher risk w/ increased size, soft tissue invasion, distant mets, age >45.
AJCC Thyroid Cancer Staging

- **T1** – Tumor 2cm or less. Limited to thyroid
  - **T1a** – Tumor 1 cm or less
  - **T1b** - Tumor >1 to 2 cm
- **T2** – Tumor >2 to 4 cm. Limited thyroid
- **T3** – Tumor > 4 cm or any w/ minimal extrathyroid extension
- **T4** – Advanced disease (a & b)
**QTNM Thyroid Cancer Staging System**

- Based on histopathology, age, node involvement and tumor size.
- QTNM = quantitative tumor/node/metastasis
- Used for differentiated thyroid cancer.
- Some studies – QTNM better at discriminating survival than TNM system.
Thyroid Cancer

- Micro-invasive – 1 cm or less.
- Increased incidence w/ more US & FNA of neck. Early detection – “subclinical”
- Papillary micro-invasive cancer mortality is 1%. w/ Tx- almost 0%.
- Papillary & follicular are usually differentiated, so often with an especially good prognoses.
Thyroid Cancer

- Medullary may be part of Multiple Endocrine Neoplasia (MEN) type 2.
- Genetic testing of RET mutations (underlying defect in MEN2). ?pheochromocytoma also?
- More aggressive cancer, esp. in young
- Parafollicular (C cells) produce calcitonin – level proportionate to tumor size.
- Most already metastasized when diagnosed
- Anaplastic (undifferentiated) – very aggressive w/ high mortality
1% thyroid nodules are malignant.
Thyroid cancer is only 1% of all cancer deaths.
Most thyroid cancer is well differentiated and has good prognosis.
Increased incidence w/ U/S & FNA.
Early detection – often “subclinical”.
Colorectal Cancer (CRC)

- Approximately 133,000 new cases of CRC diagnosed each year in U.S. – this has been decreasing by about 2-3% per year (1)
  - 4th most common cancer diagnosed (prostate, breast, lung)
- Approximately 49,700 deaths each year from CRC
  - 2nd most common cause of death due to cancer
- Globally it is the 3rd most commonly diagnosed cancer in male and the 2nd in females
Global Colorectal Cancer Statistics

[Bar graph showing age-standardized incidence per 100,000 of colorectal cancer by region and gender.]
Trends in mortality from colorectal cancer

Age-standardized rate per 100,000, men

WHO (www.who.int/gho)
Risk Factors for Colorectal Cancer

- FAP (familial adenomatous polyposis)
- MAP (MUTYH-associated polyposis)
- Lynch Syndrome (hereditary non-polyposis colon cancer -- HNPCC)
- Serrated polyposis syndrome

- Advanced age
  - Risk doubles with each decade after 40
  - 90% occur after age 50 (though this is decreasing)

- Country of birth (10x higher in N. America than Africa)

- Inflammatory bowel disease
  - 5-15x risk if pancolitis
  - 3x risk if left-sided only

- Abdominal radiation

- History of CRC (1.5 to 3% new cancers within 5 years)

- Family history of CRC (2x risk if first degree relative)

- History of colon polyps, especially if large, villous component, or high-grade dysplasia

- Obesity (1.5x risk compared to BMI 18-25)
- Alcohol (RR 1.2 if 2-3 drinks/day; 1.5x risk if > 4 drinks/day)
- Diet high in red meat, low in fruits/vegetables/calcium/fiber/fish oil/garlic
- Smoking (1.2x risk)
- Diabetes, Acromegaly, and Renal transplant recipients
- Lack of exercise
- Not on ASA or an NSAID (20-40% reduction with “regular” use)
Colon Polyps and Cancer Risk

- History of villous polyp or adenomatous polyp >1.0 cm (3.5 to 6.5x risk)
- Serrated adenomas
  - Flatter and more difficult to visualize endoscopically
  - Characteristically carry BRAF V600E mutations, microsatellite instability, and greater HNPCC concern
- Patients with proximal hyperplastic polyps may have a similar risk for developing adenomas within 5 years as patients who have baseline adenomas
  - Veterans Affairs Cooperative Study 380
Earlier screening and/or treatment recommended for those considered high risk:

- Familial adenomatous polyposis
  - Total colectomy generally advised
- Hereditary nonpolyposis CRC syndromes
  - Colonoscopy every one to two years beginning at age 20 to 25, or 10 years earlier than the youngest age of colon cancer diagnosis in the family (whichever comes first)
  - Consider screening also for endometrial, ovarian, gastric cancers
Colorectal Cancer Case #1

54 year old male. Colon cancer diagnosed on screening colonoscopy 2 years prior to application.

- No prior medical hx of note, no medications.
- Insurance exam and lab unremarkable.
- Family history positive for colon cancer in father, died age 54; “abdominal tumor” in paternal grandmother, died in her 40’s.

Was the screening appropriate? Usually done starting 10 years prior to onset in youngest relative. Guidelines vary.
USPSTF Draft Statement: Colorectal Cancer Screening

**Draft: Recommended Screening Strategies for Colorectal Cancer, beginning at age 50**

* Applies to persons with negative screening tests (including hyperplastic polyps) and is not intended for those in surveillance programs.

Abbreviations: FIT=fecal immunochemical test; gFOBT=guaiac-based fecal occult blood test.

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<th>Screening Modality</th>
<th>Frequency*</th>
<th>Other Considerations</th>
</tr>
</thead>
<tbody>
<tr>
<td>FIT or high-sensitivity gFOBT</td>
<td>Every year</td>
<td>Requires the fewest lifetime colonoscopies (a proxy for harms). Does not require bowel cleanout, anesthesia, or transportation to and from the screening examination (test is performed at home).</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy with FIT</td>
<td>Flexible sigmoidoscopy every 10 years plus FIT every year</td>
<td>Potentially attractive option for persons who want endoscopic screening but wish to limit exposure to colonoscopy. May also be useful when access to colonoscopy is geographically limited.</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 10 years</td>
<td>Requires less frequent screening. Screening and diagnostic follow-up of positive results can be performed during the same examination.</td>
</tr>
</tbody>
</table>

- CT Colonography and Multitargeted stool DNA (FIT-DNA)??
- Intense screening and genetic counseling advised for those with familial cancer syndromes
CRC Case #1 Path Report

A. RIGHT COLON (RESECTION):

INVASIVE ADENOCARCINOMA OF THE RIGHT COLON.

Histologic type: MUCINOUS ADENOCARCINOMA.

Histologic Grade: LOW GRADE.

Tumor size: 5.0 X 4.0 X 1.2 CM.

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

Macroscopic Tumor Perforation: NEGATIVE.

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

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

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

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

What are the important prognostic factors determined from the path report?
TNM Staging System for Colorectal Cancer

AJCC (American Joint Committee on Cancer) Cancer Staging Manual, 7th edition

- Primary tumor (T)
  - Tis (intramucosal) -- Carcinoma in situ; intraepithelial or invasion of lamina propria
  - T1 -- Tumor invades submucosa
  - T2 -- Tumor invades muscularis propria
  - T3 -- Tumor invades through the muscularis propria into pericolorectal tissues
  - T4a -- Tumor penetrates to the surface of the visceral peritoneum
  - T4b -- Tumor directly invades other organs or structures

- Regional lymph node (N)
  - NX -- Regional nodes cannot be assessed
  - N0 -- No regional nodal metastases
  - N1 -- Metastasis in 1 to 3 regional lymph nodes
    - N1a – Metastasis in one regional lymph node
    - N1b – Metastasis in 2-3 regional lymph nodes
    - N1c – Tumor deposit(s) in the subserosa, mesentery, or nonperitonealized pericolorectal tissues without regional nodal metastasis
  - N2 -- Metastasis in 4 or more regional lymph nodes
    - N2a – Metastasis in 4-6 regional lymph nodes
    - N2b – Metastasis in 7 or more regional lymph nodes

- Distant metastasis (M)
  - MX -- Distant metastasis cannot be assessed
  - M0 -- No distant metastasis
  - M1 -- Distant metastasis
    - M1a – Metastasis confined to one organ site
    - M1b – Metastasis in more than one organ/site or the peritoneum
### AJCC TNM Staging for Colorectal Cancer, 7th edition

**Compared to Modified Astler-Coller (MAC) and Duke's Staging Systems**

<table>
<thead>
<tr>
<th>TNM</th>
<th>AJCC Stage</th>
<th>MAC*</th>
<th>Duke’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tis</td>
<td>N0 M0</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>T1</td>
<td>N0 M0</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>T2</td>
<td>N0 M0</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>T3</td>
<td>N0 M0</td>
<td>II A</td>
<td>B2</td>
</tr>
<tr>
<td>T4a</td>
<td>N0 M0</td>
<td>II B</td>
<td>B</td>
</tr>
<tr>
<td>T4b</td>
<td>N0 M0</td>
<td>IIC</td>
<td>B3</td>
</tr>
<tr>
<td>T1-2</td>
<td>N1/N1c M0</td>
<td>III A</td>
<td>C1</td>
</tr>
<tr>
<td>T1</td>
<td>N2a M0</td>
<td></td>
<td>C1</td>
</tr>
<tr>
<td>T3-4a</td>
<td>N1/N1c M0</td>
<td>IIIB</td>
<td>C2</td>
</tr>
<tr>
<td>T2-3</td>
<td>N2a M0</td>
<td></td>
<td>C1/2</td>
</tr>
<tr>
<td>T1-2</td>
<td>N2b M0</td>
<td></td>
<td>C1</td>
</tr>
<tr>
<td>T4a</td>
<td>N2a M0</td>
<td>IIC</td>
<td>C2</td>
</tr>
<tr>
<td>T3-T4a</td>
<td>N2b M0</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>T4b</td>
<td>N1-2 M0</td>
<td></td>
<td>C3</td>
</tr>
<tr>
<td>Any T Any N M1a</td>
<td>IVa</td>
<td>D</td>
<td></td>
</tr>
<tr>
<td>Any T Any N M1b</td>
<td>IVb</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>
Prognostic Factors for CRC

- **Stage** – Single most important factor
  - Serosal involvement of T4 lesions – now subdivided into T4a (tumor perforates visceral peritoneum) and T4b (direct invasion or adherence to other structures)
  - However, histologic determination of serosal penetration is difficult, and conservative interpretation may lead to understaging of disease.
    - One study: cytologic exam of serosal scrapings from pT3 specimens found malignant cells in up to 26% \(^{(12)}\)

- **Lymph nodes**
  - Number involved with tumor
    - CRC mortality roughly twice as high for N2 vs N1 status
  - Number in surgical specimen
    - Recommended at least 13 nodes retrieved at surgery
    - Some advocate using “Lymph node ratio” – more predictive than number of positive nodes alone
  - Mesenteric tumor nodules are each considered as a positive node (N1c)
  - Micrometastases/Isolated tumor cells (ITCs): single tumor cells or small clusters of cells measuring <0.2mm in size
    - Appears to have worse outcome per a meta-analysis \(^{(14)}\)
    - However considered only as pN0(i+) if detected by standard histologic techniques or IHC, or pN0 (mol+) if detected only by special molecular techniques such as RT-PCR

- **Clinical**
  - Stage II patients with obstruction or perforation

- **Residual tumor**
  - Based largely on the status of the circumferential resection margin (CRM)
**Additional Prognostic Factors for CRC**

- Lymphovascular invasion
- Grade (well/moderately vs. poorly differentiated)
- Histology
  - Signet cell variant, Adenosquamous carcinomas
- Appendiceal cystadenocarcinoma
  - Often associated with pseudomyxoma peritonei
- CEA >5.0
  - Independent of tumor stage
  - Node (-) disease with increased CEA fares worse than node (+) with normal CEA
- Microsatellite instability (MSI)
  - Seen in HNPCC tumors and in 15-20% of sporadically occurring tumors
  - Despite being poorly differentiated, the prognosis is more favorable
- Tumor regression after neoadjuvant therapy – favorable
- Tumor infiltrating lymphocytes & Crohn’s-like lymphoid response – favorable
- Perineural invasion – adverse
- 18q deletions, KRAS mutation, codon 12 – adverse
- Tumor border — irregular, infiltrating pattern of growth is an independent adverse prognostic factor
  - may predict liver metastasis.
Colorectal Cancer Case #1 Questions:

- What additional prognostic information would you like to see?
  - AST 21, ALT 19, Alk Phos 42 (all U/L)
  - CEA level 0.6 ng/mL
  - CT of chest, abdomen and pelvis for M staging negative
  - MSI testing, any special staining of nodes?

- What is the expected clinical follow-up in this situation?
  - Guidelines vary but for stage II and III CRC most include:
    - H&P and CEA q 3-6 months x 3-5 years
    - Annual abdominal and chest CT x 3 years
    - Repeat colonoscopy after one year, then q 3-5 years
**CRC Case #1**

- **What additional treatment would you expect?**
  - ASA? Adjuvant Tx – base on gene profile??

- **What would you assess his current mortality risk to be?**
  - Recurrence risk low, moderate, or high?
  - 5 year observed survival Stage IIa AJCC 66.5%
  - 5 year disease-free survival 80-95% based on gene-expression profiling database
  
  Considering also grade, age, gender, number of nodes:
  - Per MSK calculator: 95% 5 yr and 93% 10 yr DFS
  - Or 5 year disease-specific conditional survival after 2 years is 93% with few recurrences after that
    - SEER database: MD Anderson Colon Cancer Survival Calculator

- **Any other features to consider in this case?**
  - Family history and MSI results
Risk of colon cancer associated with a family history

The highest risk is in people with multiple first-degree relatives or relatives who have developed colorectal cancer at a relatively young age. Data from Johns, LE, Houlston, RS, Am J Gastroenterol 2001; 96:2992.
CRC Case #1

<table>
<thead>
<tr>
<th>Test Performed</th>
<th>Result</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLH1 sequencing rearrangement analysis</td>
<td>R226X (G76C&gt;T)</td>
<td>Deleterious</td>
</tr>
<tr>
<td></td>
<td>No Mutation Detected</td>
<td>No Mutation Detected</td>
</tr>
</tbody>
</table>

Analysis consists of sequencing of all exons and adjacent intronic regions of the MLH1 gene and large rearrangement (LR) testing of the MLH1 gene by microarray comparative genomic hybridization (microarray CGH). Testing at Myriad found that LR mutations account for ~17% of MLH1 mutations. The classification and interpretation of all variants identified in this assay reflect the current state of scientific understanding at the time this report was issued. The classification and interpretation of such variants may change as new information becomes available.

It is our understanding that this patient was identified for testing due to a personal or family history suggestive of Lynch syndrome (hereditary non-polyposis colorectal cancer, HNPCC). The results of this analysis are consistent with the germline MLH1 mutation R226X, resulting in premature truncation of the MLH1 protein at amino acid position 226. Although the exact risk of cancer conferred by this specific mutation has not been determined, deleterious mutations in MLH1 confer as much as an 82% risk of colorectal cancer and a 60% risk of endometrial cancer by age 70. Other increased cancer risks include as much as a 13% risk of gastric cancer and a 12% risk of ovarian cancer by age 70. (Vasen HFA et al. Gastroenterology 1996;110:1020-1027; Aarnio M et al. International Journal of Cancer 1999;81:214-218). First degree relatives of this individual each have a one-in-two chance of having this mutation. Family members can be tested for this specific mutation with a single site analysis.

➢ What is the significance of this finding and does it alter your assessment or your expectations for follow-up?
Hereditary Colorectal Cancer Syndromes

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

- HNPCC mean age at initial cancer diagnosis is ~45 years
  - But few are before the age of 30, unlike FAP
- Autosomal dominant inheritance
- Lifetime risk of developing CRC is approximately 60%
- Approximately 10% will have synchronous cancers
- Extracolonic cancers are also common, including endometrial carcinoma in ~40% of female gene carriers
- Associated with serrated adenomas
  - Flatter and more difficult to visualize endoscopically
  - Characteristically with BRAF V600E mutations and microsatellite instability
- MMR (mismatch repair) gene testing in the youngest living member of the family with colorectal cancer is advised
- Cumulative cancer risk by age 70 for the three main mutations (95% of cases)\(^9\)
  - 40-50% for MLH1 and MSH2
  - ~12% for MSH6
- Colonoscopy every one to two years beginning at age 20 to 25, or 10 years earlier than the youngest age of colon cancer diagnosis in the family (whichever comes first)
The National Comprehensive Cancer Network\(^1\) and cancer genetics experts recommend the following cancer screening for individuals with a *MLH1* mutation (NCCN Guidelines version 1.2014). Please talk with your physician about the screening that is right for you.

<table>
<thead>
<tr>
<th>Procedure</th>
<th>How Often?</th>
<th>Beginning When?</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Colon</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Every 1-2 years</td>
<td>Age 20-25 (Or 2-5 years before the first diagnosis if diagnosed before 25)</td>
</tr>
<tr>
<td>May consider subtotal colectomy if patient is not a candidate for optimal screening</td>
<td>N/A</td>
<td>Discuss with your physician</td>
</tr>
<tr>
<td><strong>Ovary (women only)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider Pelvic ultrasound + serum CA-125 test</td>
<td>N/A</td>
<td>Discuss with your physician (no clear evidence, so no recommendations made at this time)</td>
</tr>
<tr>
<td>Consider surgery to remove both ovaries (prophylactic oophorectomy)</td>
<td>N/A</td>
<td>Once childbearing is completed; Discuss with your physician</td>
</tr>
<tr>
<td><strong>Uterine/Endometrial (women only)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider Endometrial aspirate + pelvic ultrasound</td>
<td>Every year</td>
<td>Discuss with your physician (no clear evidence, so no recommendations made at this time)</td>
</tr>
<tr>
<td>Consider surgery to remove uterus (prophylactic hysterectomy)</td>
<td>N/A</td>
<td>Once childbearing is completed; Discuss with your physician</td>
</tr>
<tr>
<td><strong>Stomach &amp; Small Bowel</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider upper endoscopy, extending through duodenum or into jejunum (upper sections of small bowel) **</td>
<td>Every 3-5 years</td>
<td>Age 30-35</td>
</tr>
<tr>
<td><strong>Urinary Tract</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Consider urinalysis with cytology</td>
<td>Every year</td>
<td>Age 25-30</td>
</tr>
<tr>
<td><strong>Central Nervous System</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical examination</td>
<td>Every year</td>
<td>Age 25-30</td>
</tr>
</tbody>
</table>

** In selected individuals or families or those of Asian descent
Colorectal Cancer Case #1

- What is his likelihood of developing a second colorectal cancer?
  - New tumors developing at least six months after the initial diagnosis occur in 1.5-3% of patients within five years and roughly 9% after several decades in survivors of the primary cancer.
  - In those with HNPCC, 20-40% will develop metachronous cancer if colectomy not performed.
  - In one report, the standardized incidence ratio (SIR) for a second cancer was 1.5 overall but was significantly greater in younger patients (38.3 and 7.6 for ages 30-39 and 40-49, respectively).
Case #1; what if...

- He instead had positive lymph nodes (and no HNPCC):
  - Stage then?
  - What factors would then be important?
    - T stage remains significant.
    - Number of nodes surveyed also does. If just one node positive in this case (a lymph node ratio of 0.05) it would be a reasonably favorable feature.
## AJCC TNM Staging for Colorectal Cancer, 7th edition

**Compared to Modified Astler-Coller (MAC) and Duke's Staging Systems**

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<tr>
<td>Tis</td>
<td>N0 M0</td>
<td>0</td>
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</tr>
<tr>
<td>T1</td>
<td>N0 M0</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>T2</td>
<td>N0 M0</td>
<td></td>
<td>A</td>
</tr>
<tr>
<td>T3</td>
<td>N0 M0</td>
<td>II A</td>
<td>B2</td>
</tr>
<tr>
<td>T4a</td>
<td>N0 M0</td>
<td>II B</td>
<td>B</td>
</tr>
<tr>
<td>T4b</td>
<td>N0 M0</td>
<td>II C</td>
<td>B3</td>
</tr>
<tr>
<td>T1-2</td>
<td>N1/N1c M0</td>
<td>III A</td>
<td>C1</td>
</tr>
<tr>
<td>T1</td>
<td>N2a M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4a</td>
<td>N1/N1c M0</td>
<td>III B</td>
<td>C2</td>
</tr>
<tr>
<td>T2-3</td>
<td>N2a M0</td>
<td></td>
<td>C1/2</td>
</tr>
<tr>
<td>T1-2</td>
<td>N2b M0</td>
<td></td>
<td>C1</td>
</tr>
<tr>
<td>T4a</td>
<td>N2a M0</td>
<td>IIIC</td>
<td>C2</td>
</tr>
<tr>
<td>T3-T4a</td>
<td>N2b M0</td>
<td></td>
<td>C</td>
</tr>
<tr>
<td>T4b</td>
<td>N1-2 M0</td>
<td></td>
<td>C3</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N M1a</td>
<td>IVa</td>
<td>D</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N M1b</td>
<td>IVb</td>
<td></td>
</tr>
</tbody>
</table>
CRC Caveats

- >90% of CRC are adenocarcinomas arising from epithelial cells of the colorectal mucosa
- ~80% are low grade (well- or moderately differentiated)
  - >50% gland formation
- Invasive implies has invaded into the submucosa
  - Confined to lamina propria or muscularis mucosae is in-situ, due to lack of lymphatics
- High MSI levels are poorly differentiated and often associated with HNPCC but behave like low grade
- Mucinous adenocarcina with MSI-H are often with Lynch and more favorable than if MSS
- Signet ring <1%, usually high grade
Chemotherapy Options

- Survival outcomes for Stage IIIA CRC often better than for Stage II
  - T stage more important than early nodal metastases
- Adjuvant chemo advised if node positive – roughly 30% reduction in mortality
  - Oxaliplatin based regimen – 6 month course initiated within 6-8 weeks after CRC resection
    - FOLFOX - includes also Leukovorin and 5-FU
- Adjuvant chemo for Stage II CRC more controversial
  - Absolute improvement in 5-year survival ~ 5%
  - Probably indicated for higher risk Stage II
    - Fewer than 12 nodes in the surgical specimen
    - T4 or perforated/obstructed lesion
    - Poorly differentiated histology (including signet ring)
    - Lymphovascular or perineural invasion
    - V600E BRAF mutation (for patients with proficient MMR/microsatellite stable tumors)
Treatment of Metastatic CRC

- Surgical resection often indicated for isolated mets
  - ~40% 5-year and 20% 10-year survivals
- Chemotherapy, recent study: FOLFOXIRI (FOLFOX and irinotecan) plus bevacizumab significantly improved progression-free survival of patients with metastatic colorectal cancer compared with FOLFIRI (above, without oxaliplatin) plus bevacizumab
  - Median overall survival was 29.8 months in the FOLFOXIRI plus bevacizumab group compared with 25.8 months in the FOLFIRI plus bevacizumab group.
  - Median overall survival was 37.1 months in the RAS and BRAF wild-type subgroup compared with 25.6 months in the RAS-mutation-positive subgroup and 13.4 months in the BRAF-mutation-positive subgroup
Estimated Five-year Colon Adenocarcinoma Survival Rates by TMN Stage

- **Stage 0**: 100 %
- **Stage I**:
  - T1 — 97%
  - T2 — 90%
- **Stage II**:
  - T3 — 85%
  - T4 — 72%
- **Stage III**:  
  - IIIA (T1-2, N1 = 1-3 (+) regional lymph nodes) — 83%
  - IIIB (T3-4; N1 = 1-3 (+) regional lymph nodes) — 64%
  - IIIC (Any T; N2 = 4 or more (+) regional nodes) — 44%
- **Stage IV**:  
  - Any M1 = presence of distant metastases — 8%
## Relationship Between Number of Lymph Nodes Recovered and 5 year Outcomes in a Meta-analysis

<table>
<thead>
<tr>
<th>Stage</th>
<th>Number of lymph nodes</th>
<th>Cause-specific survival %</th>
<th>Disease-free survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>II</td>
<td>&lt;11</td>
<td>80</td>
<td>72</td>
</tr>
<tr>
<td></td>
<td>11-20</td>
<td>85</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>&gt;20</td>
<td>92</td>
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</tr>
<tr>
<td>IIIA-IIIB</td>
<td>&lt;11</td>
<td>74</td>
<td>65</td>
</tr>
<tr>
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<td>11-40</td>
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<td></td>
<td>&gt;40</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>IIIC</td>
<td>1-35</td>
<td>55</td>
<td>48</td>
</tr>
<tr>
<td></td>
<td>&gt;35</td>
<td>71</td>
<td>69</td>
</tr>
</tbody>
</table>
Stage IIIb, 2 years out

- Prognosis?
  - 64% 5 year survival per AJCC database, however...
  - 85% 3 yr DFS per Mayo model
  - 91% 5 yr and 88% 10 yr DFS per MSKCC calculator

- Prognosis if he were now 8 years out since surgery?
  - Reported recurrence rates of <0.5%/year in those receiving adjuvant chemotherapy
CRC Stage IIIB Survival

Disease-specific survival, 54 year-old male, well-differentiated tumor\textsuperscript{16}
CRC - Excess Death Rate by Stage

Derived from Wesley; J Insurance Med 2009
**CEA**

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


18. ACCENT-Based Web Calculators to Predict Recurrence and Overall Survival in Stage III Colon Cancer" (L.A. Renfro et al., JNCI 106(10), 2014).