# SOLID TUMORS WORKSHOP

October 13-19, 2012  
Jack Swanson  
Brad Heltemes

---

## 2006 Estimated US Cancer Cases*

<table>
<thead>
<tr>
<th></th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>720,280</td>
<td>679,510</td>
</tr>
<tr>
<td>Prostate</td>
<td>33%</td>
<td>31%</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>13%</td>
<td>12%</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>10%</td>
<td>11%</td>
</tr>
<tr>
<td>Urinary bladder</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td>Melanoma of skin</td>
<td>5%</td>
<td>4%</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>4%</td>
<td>4%</td>
</tr>
<tr>
<td>Kidney</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Oral cavity</td>
<td>3%</td>
<td>3%</td>
</tr>
<tr>
<td>Leukemia</td>
<td>3%</td>
<td>2%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>2%</td>
<td>22%</td>
</tr>
<tr>
<td>All Other Sites</td>
<td>18%</td>
<td>All Other Sites</td>
</tr>
</tbody>
</table>

*Excludes basal and squamous cell skin cancers and in situ carcinomas except urinary bladder  
Source: American Cancer Society, 2006.
### Lifetime Probability of Developing Cancer, by Site, Men, 2006-2008

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 2</td>
</tr>
<tr>
<td>Prostate</td>
<td>1 in 6</td>
</tr>
<tr>
<td>Lung and bronchus</td>
<td>1 in 13</td>
</tr>
<tr>
<td>Colon and rectum</td>
<td>1 in 19</td>
</tr>
<tr>
<td>Urinary bladder †</td>
<td>1 in 26</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 in 41</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 43</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 in 51</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 64</td>
</tr>
<tr>
<td>Oral Cavity</td>
<td>1 in 69</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 69</td>
</tr>
</tbody>
</table>

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

### Lifetime Probability of Developing Cancer, by Site, Women, US, 2006-2008

<table>
<thead>
<tr>
<th>Site</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td>1 in 8</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 16</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 20</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td>1 in 38</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Melanoma</td>
<td>1 in 64</td>
</tr>
<tr>
<td>Pancreas</td>
<td>1 in 69</td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 in 69</td>
</tr>
<tr>
<td>Ovary</td>
<td>1 in 71</td>
</tr>
<tr>
<td>Kidney</td>
<td>1 in 84</td>
</tr>
</tbody>
</table>

† All Sites exclude basal and squamous cell skin cancers and in situ cancers except urinary bladder.

---

Breast Cancer

- Diagnosed in about 210,000 individuals/year
  - 1 in 8 women will be diagnosed in their lifetime. If found early, 95% will be cured.
  - 1,600 men

- Over 40,000 deaths per year
  - Second most common cause of death due to cancer in women (lung cancer is #1)
  - Leading cause of death in woman aged 45-55
  - 400 breast cancer deaths in men
Breast Cancer Case #1

  Core needle biopsy:
  - Ductal carcinoma in situ, 11 mm. Cribriform pattern, grade 1-2.
- Lumpectomy - no residual cancer. Followed by radiation.
- Regular follow-ups, mammography normal until……
- 2008: Suspicious MRI, same area previous DCIS.
  Core needle biopsy, lumpectomy; 2 cm tumor:
  - Grade 2-3 cribriform DCIS + areas of grade 3 comedonecrosis. No invasive cancer.
  - Tumor in superior margins of resection.

Breast Cancer Case #1

- Mastectomy, early 2009. Pathology on mastectomy:
  - NO evidence of residual in situ or invasive breast cancer.
- Close follow-ups since, w/ left mammography. All negative.
- Questions:
  - Survival statistics - treatments for ductal CIS?
  - After mastectomy, main concern?
  - After 4 years, mortality risk (low, intermediate, high)?
  - Can pathologists miss invasive foci in DCIS?
  - Compare prognosis cribiform vs. comedonecrosis
  - Is sentinel node biopsy indicated in DCIS?
  - Compare MRI with mammography.
  - Compare prognosis - Ductal CIS vs. Lobular CIS.
Staging – Tumor size

- **T1** — Tumor 2 cm or less in greatest dimension
  - T1mic — Microinvasion, 0.1 cm or less in size
  - 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

10 and 20 year relapse-free survival rates (node negative)

Although the majority of relapses occur within the first five years after treatment, the risk persists up to 30 years

- Tumors ≤1.0 cm — 91 and 88 percent, respectively
- Tumors 1.1 to 2.0 cm — 77 and 72 percent
- Tumors 2.1 to 3.0 cm — 75 and 71 percent
- Tumors 3.1 to 5.0 cm — 62 and 59 percent
Breast Cancer Case #2

- 59 y/o female. Hysterectomy age 35 - endometriosis, 1988, then prescribed HRT.
- Mastectomy, right, age 42, May 1996, after removal of 3 masses, largest measuring 2.3 x 1.6 x 1.6 cm.
  - Two of 16 axillary lymph nodes: metastatic ductal (not colloid) carcinoma. One + node level I, the other level III.
- Regular follow-up w/ mammography of left breast & reconstructed rt. breast. Blood chems, physicals all WNL.

Breast Cancer Case #2 - Questions

- Cancer not staged in records. TNM categories & stage?
- How long risk of recurrence? Does histology influence risk?
- Do positive lymph node levels affect your assessment?
- Mortality risk: low, intermediate, high? Favorable/ unfavorable factors?
TNM Staging

- **Primary Tumor (T)**
  - Tis: Carcinoma in situ
  - T1mic – to 0.1 cm. 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; N0 (i+) - (ITC - <0.2mm)
  - N1mi: Micrometastases – 0.2 to 2.0 mm
  - 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 1** – T1N0M0
- **Stage IIA** – T0N1M0(+) (0-4%; case 1 Q4)
  - T1N1M0
  - T2N0M0
- **Stage IIB** – T2N1M0
  - T3N0M0
- **Stage IIIA** – T0-2,N2
  - T3, N1-2
- **Stage IIIB** – T4, N0-2
- **Stage IIIC** – AnyTN3
- **Stage IV** – AnyT, AnyN, M1
Breast Cancer Case #3

- 50 year old woman: mammogram BI-RAD 4a at age 46.
  - Core needle biopsy: Ductal carcinoma in situ.
- Lumpectomy: Tumor mass 1.8x1.4x1.2 cm.
  - Microscopic: Extensive ductal carcinoma in situ plus two foci microinvasive ductal carcinoma, each <0.1 cm.
  - Sentinel lymph node – neg. for cancer (H&E). W/ serial sections & IHC, positive for small # isolated tumor cells, no micromets. pN0(i+). No axillary lymph node dissection. ER & PR pos., HER2 neg.
- Tamoxifen & radiation therapy. No chemotherapy.
- Family Hx pos. for breast cancer. Mother, sister, both < 45.
- BRCA 1 & 2 testing, negative.

Breast Cancer Case #3 - Questions

- Does extensive DCIS affect prognosis?
- How would you consider isolated tumor cells in regional lymph nodes?
- How would you consider micrometastases when evaluating?
- Should she have been treated with chemotherapy?
- Mortality risk: Low, intermediate, high? Favorable/unfavorable factors.
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

Ductal carcinoma in situ (Case 1)

- 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.) (case 1, Q 1.) Lumpectomy w/ radiotherapy – to 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) (case 1, Q3). 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)(case 1, Q. 4,5).
Ductal carcinoma in situ (Case 1)

- Sentinel lymph node excision rarely indicated w/ DCIS (case 1, Q.6). < 5% nodes positive (mostly isolated tumor cells) (Case 3 also). Most positives are associated w/ microinvasive cancer (case 1, Q 4, case 3). SLN biopsy indicated if mastectomy or tumor > 4 cm.
- Survival data DCIS: 98-99% - mastectomy; 98% lumpectomy w/ radiation (but more recurrences);
- 94-95% lumpectomy alone. (case 1, Q 1) Main concern – recurrence or other breast (case 1, Q2).
- Lobular CIS- no progress to cancer. Marker for invasive ca, either breast (1%/yr. lifetime. 12x rel.risk.) (case 1, Q. 8).

Invasive breast cancer (case 2)

- 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. Soon may be replaced by...
  Multigene, molecular classification (case 2, Q. 3,4). New terms: Luminal cells produce ER, PR, HER2. Basal cells primitive –don’t express these.
- Colloid type more favorable but far less frequent than ductal (ductal is 79- 85% of IBC) (case 2, Q. 2)
- Pos nodes – require chemotx. (case 2,Q 3, 4) Also ER/PR neg., high grade IBC, & < age 50 require chemotx.
Invasive breast cancer (case 2)

- 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.

Sentinel lymph node, isolated tumor cells, micromets, microinvasive cancer (Case 3)

- Steve Rigatti’s review includes no ALND despite + SLN (JIM 2012;43: 18). Recommends caution, esp. if micromets. (Case 3, Q 2,3). Some claim ITC same as negative nodes.
- Serial Sections & IHC diagnose 10-30% false negatives on H&E routine.
Sentinel lymph node, isolated tumor cells, micromets, microinvasive cancer (Case 3)

- DeBoer: Micromets & ITC – better survival w/ endocrine &/or chemo therapy (NEJM.2009:361:653) (case 3, Q4,5).
- SLN biopsy 94% sensitive (only done on T1,2 IBC).
- Extensive DCIS more often ass’d w/ IBC(Case 3,Q1)
- Impact of family hx on BC -- Relative risk:
  - 1.8 if 1st degree relative w/ post-MP BC
  - 3.3 RR if 1st degree premenopausal
  - 3.6-5.0 w/ two 1st degree BC
    - (Mahoney. CA 2008; 58:347), (case 3).

MINIMALLY INVASIVE BREAST CA

- Microinvasion (T1mic– 0.1 cm invasion into stroma)
  - Overall 97-100% survival. Higher risk if there is EDIC (extensive 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
- Should have SNL bx & if ER+: Tamoxifen.
- 75% of recurrent BC – long-term survivors
HORMONE RECEPTORS/ HER2

- Estrogen/progesterone receptor status:
  - Endocrine tx reduces recurrence 41% & death 34% & contralateral cancer 39%.
  - Less predictive after 5 years post-op
  - ER/PR negative tumors have worse prognosis 1st 5-10 years, but chemotherapy has improved prognosis so nearly equal to positive ER/PR.
- 20% of BC are HER2 +. TX w/ trastuzumab. Also predicts response to chemotherapy.
  - Poor prognosis if not treated
  - IHC/ FISH preferred tests (Barton.CA2012;62:71)

Other comments

- Recent advances in genomics will change molecular characterization of cancer. (Pasche. JAMA 2011; 305:1596) Near future, molecular classification of BC, - still in infancy; soon to be used more for prognosis & tx. “High-penetrance genes BRCA1 and BRCA2, +several low-penetrance genes affect risk of breast malignancy” (Mahoney. CA 2008; 58: 347) (case 3).
- “Role of molecular markers & gene expression signatures to identify patients at risk of DCIS and IBC evolving, but clinical usefulness at present time uncertain.” (Partridge CA 2012;62:203)
- DNA microarray (70 gene profile) predicts good(95%) vs. poor(55%) prognosis. 21 gene recurrence score predicts outcome for new ER+, neg lymph node patients on tamoxifen.
Other comments (continued)

- Triple negative breast cancer (ER, PR, HER2 – all neg.)
  More aggressive, higher grade, poorer prognosis, earlier recurrence, more mets. Most BRCA1 are triple neg.
- Young, esp. < age 35: BC more aggressive, higher grade, lymphovascular invasion.
- Case 1, Q. 7. MRI more sensitive, more false pos.
  Mammograms miss 15-20%. Post-menopausal breast mass – cancer until proven otherwise. In presence of lump, mammogram is to identify a second cancer before tx.
- Add ultra sound or MRI to mammogram if dense breasts (Berg.JAMA 2012;307:1394).
- All BC patients need post-excision mammogram 3-5 weeks post-op.
- If core needle bx benign & mammogram suspicious – need another bx.

Malignant Melanoma

- 76,250 new cases of invasive melanoma anticipated in U.S. in 2012 (44,200 in 1999)
  - Plus 54,000 cases of melanoma-in-situ
  - Fastest growing incidence of all cancers
- Estimated deaths 2012: 9180 (7300 in 1999)
- Fifth most common cancer in Americans (was sixth in 2009) and the most common fatal malignancy among young adults
- Incidence of melanoma is increasing
  - 1/1500 lifetime risk in 1935
  - 1/250 lifetime risk in 1980
  - 1/50 lifetime risk in 2009 (whites)
- Median age of onset 53
- Incidence of melanoma estimated to be 0.6, 1.6, and 2.6% at 50, 70, and 80 years of age, respectively
- Rates increasing in those of European descent worldwide
  - Highest in Australia and New Zealand (50/100,000/yr)
  - Rates have tripled in Croatia in the past 40 years
**Melanoma Risk Factors**

- Hx of sun exposure, particularly blistering sunburns, especially in childhood (est. 65% of the risk)
- Fair skin/freckling/tendency to sunburn
- Light hair/eye coloring – MC1R gene in redheads
- Multiple nevi (>50-100 yields a RR of 5 to 17)
- Dysplastic nevi (atypical moles)
  - Precursor of melanoma
- Family hx of melanoma or of atypical nevi
- Prior hx of melanoma
  - Risk 2-11% at 5 yrs, and twice that if also dysplastic nevi or family history of melanoma
  - With history of two melanomas, risk of a 3rd is 30% within 5 yrs
- Parkinson’s, Xeroderma pigmentosum, Immunosuppression

**Atypical (“dysplastic”) Nevi**

- Typically, people have 10-40 nevi, mostly on sun-exposed areas
- Atypical nevi however:
  - Clinically appear similar to melanoma
  - A risk for developing melanoma:
    - 10% risk of transforming into melanoma
    - Risk increased 12 to 20-fold if >10 atypical nevi
- More important if also with personal or family hx of melanoma
- One study found 39% of patients with melanoma have clinically atypical nevi, compared with 7% of a nonmelanoma control group 15
Melanoma and Family History

- Approximately 10% of patients with melanoma have a family history of the disease, but not all of these individuals have hereditary melanoma
  - Apparent familial inheritance pattern may be due to clustering of sporadic cases in families with common heavy sun exposure and a susceptible skin type
- Familial Atypical Multiple Mole and Melanoma (FAMMM) syndrome
  - Clinically affected subjects have multiple (over 100) dysplastic (atypical) nevi, and their lifetime cumulative incidence of melanoma approaches 100%
  - Median age at diagnosis of 33
  - Mutations in certain genes, most commonly CDKN2A and CDK4, have been identified in melanoma-prone families

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)
Staging of Melanoma

- TNM staging system
  - Tumor, Node, Metastasis
- AJCC seventh edition came out in January 2010
  - Staging system is based upon an analysis of over 38,900 patients with cutaneous melanoma from the AJCC Melanoma Staging Database
- Staging is closely tied to prognosis

Factors Affecting Staging:

- Primary Tumor (T)
  - Tumor Thickness – Continuously increasing risk with increasing thickness
    - T1: \( \leq 1.0 \) 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 \( \geq 1/\text{mm}^2 \)
**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
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 II A – T2b or T3a, N0, M0
  - Stage II B – T3b or T4a, N0, M0
  - Stage II C – T4b, N0, M0
- **Stage III**: N1-3, M0
  - Stage III A – T1-4a, N1a or N2a
  - Stage III B – T1-4b, N1a or N2a; or T1-4a, N1b, N2b, or N2c
  - Stage III C – 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 Treatment

- Surgical resection of primary tumor with adequate margins
- Sentinel node biopsy now done for lesions >1mm thickness
  - Not performed for early localized lesions (stage I and carcinoma in situ) unless additional high risk features present
  - Generally recommended for all others
  - If melanoma present, full lymph node dissection (“LND”) is done
- LND performed if clinically evident adenopathy is present
- Adjuvant interferon if node positive disease
- Resection of locoregional or isolated metastatic recurrence
  - Rare cures obtained
- Systemic therapy for metastatic disease
  - Limited effectiveness but major advances in just the past year with new immunotherapies
  - High dose interleukin-2, ipilimumab (a monoclonal antibody) and vemurafenib (a BRAF-inhibitor) have shown promise
Melanoma Case #1

- 51 year-old male $500,000 of Term Life, July 2011
  - 5'9" (175cm), 185 lbs (84kg), BP 128/84, Lab all normal
  - Melanoma of neck 2008
  - Family history of bladder cancer, no melanoma

- Stage? Possibly Tis, but...
- Information complete?
  - Positive margin, need follow-up since

Dermatology follow-up every 4 months

Extensive solar damage, multiple basal cell carcinomas, no additional nevi of concern noted
Additional Dermatology Records

- Tumor Stage?
  T1a, Nx, Mx = Likely Stage IA

- Favorable and unfavorable features?
  Favorable: Depth 0.15mm, no ulceration, no regression, no lymphatic invasion, level II
  Adverse: Location on scalp, male

- Mortality risk?

---

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
Melanoma-specific survival by Tumor Thickness

Table 12.5: Melanoma (Among Whites): Number and Distribution of Cases and 1-, 2-, 3-, 5-, 8-, & 10-Year Relative Survival Rates (%) by Sex and Tumor Thickness, Ages 20+, SEER 1988-2001

<table>
<thead>
<tr>
<th>Sex/Tumor Thickness</th>
<th>Cases</th>
<th>Percent</th>
<th>1-Year</th>
<th>2-Year</th>
<th>3-Year</th>
<th>5-Year</th>
<th>8-Year</th>
<th>10-Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td>29,785</td>
<td>100.0</td>
<td>96.8</td>
<td>93.5</td>
<td>91.0</td>
<td>88.4</td>
<td>86.5</td>
<td>86.3</td>
</tr>
<tr>
<td>&lt; 0.75 mm</td>
<td>12,588</td>
<td>43.5</td>
<td>100.0</td>
<td>98.7</td>
<td>97.2</td>
<td>94.8</td>
<td>92.8</td>
<td>92.8</td>
</tr>
<tr>
<td>0.75 - 1.49 mm</td>
<td>5,545</td>
<td>18.6</td>
<td>100.0</td>
<td>95.8</td>
<td>93.2</td>
<td>91.6</td>
<td>89.5</td>
<td>87.4</td>
</tr>
<tr>
<td>1.50 - 2.49 mm</td>
<td>2,270</td>
<td>7.7</td>
<td>99.0</td>
<td>95.0</td>
<td>93.1</td>
<td>91.2</td>
<td>89.1</td>
<td>87.1</td>
</tr>
<tr>
<td>2.50 - 4.99 mm</td>
<td>1,556</td>
<td>5.3</td>
<td>96.4</td>
<td>92.5</td>
<td>90.2</td>
<td>88.1</td>
<td>86.4</td>
<td>85.6</td>
</tr>
<tr>
<td>4.00+ mm</td>
<td>1,232</td>
<td>4.1</td>
<td>90.0</td>
<td>83.9</td>
<td>80.3</td>
<td>77.4</td>
<td>75.4</td>
<td>74.5</td>
</tr>
<tr>
<td>Unknown</td>
<td>5,372</td>
<td>18.0</td>
<td>84.8</td>
<td>78.3</td>
<td>75.0</td>
<td>71.8</td>
<td>69.2</td>
<td>68.2</td>
</tr>
<tr>
<td>Female</td>
<td>24,213</td>
<td>81.4</td>
<td>97.2</td>
<td>95.9</td>
<td>94.4</td>
<td>92.4</td>
<td>90.4</td>
<td>90.4</td>
</tr>
<tr>
<td>&lt; 0.75 mm</td>
<td>12,201</td>
<td>45.0</td>
<td>100.0</td>
<td>99.0</td>
<td>97.8</td>
<td>96.4</td>
<td>94.9</td>
<td>93.9</td>
</tr>
<tr>
<td>0.75 - 1.49 mm</td>
<td>4,408</td>
<td>15.3</td>
<td>99.0</td>
<td>99.0</td>
<td>97.8</td>
<td>95.6</td>
<td>93.4</td>
<td>92.4</td>
</tr>
<tr>
<td>1.50 - 2.49 mm</td>
<td>1,807</td>
<td>6.5</td>
<td>98.3</td>
<td>94.5</td>
<td>92.0</td>
<td>89.4</td>
<td>87.0</td>
<td>85.9</td>
</tr>
<tr>
<td>2.50 - 4.99 mm</td>
<td>1,002</td>
<td>4.1</td>
<td>97.1</td>
<td>95.7</td>
<td>93.3</td>
<td>91.3</td>
<td>89.3</td>
<td>88.1</td>
</tr>
<tr>
<td>4.00+ mm</td>
<td>965</td>
<td>3.6</td>
<td>93.1</td>
<td>89.2</td>
<td>87.0</td>
<td>84.1</td>
<td>82.1</td>
<td>81.1</td>
</tr>
<tr>
<td>Unknown</td>
<td>3,919</td>
<td>14.1</td>
<td>89.2</td>
<td>84.7</td>
<td>82.7</td>
<td>80.7</td>
<td>78.8</td>
<td>77.8</td>
</tr>
</tbody>
</table>

National Cancer Institute 96 SEER Survival Monograph

Survival for Females to 10 years by Tumor Thickness

Figure 12.4: Melanoma (Among Whites): Relative Survival Rates (%) for Females by Tumor Thickness, Ages 20+, 12 SEER Areas, 1988-2001
## Survival by T Classification

<table>
<thead>
<tr>
<th>Thickness Class</th>
<th>5 year survival %</th>
<th>10 year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>T1b</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>T2a</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>T2b</td>
<td>82</td>
<td>67</td>
</tr>
<tr>
<td>T3a</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>T3b</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>T4a</td>
<td>71</td>
<td>57</td>
</tr>
<tr>
<td>T4b</td>
<td>53</td>
<td>39</td>
</tr>
</tbody>
</table>

## Survival by Mitotic Count

<table>
<thead>
<tr>
<th>Mitoses/mm²</th>
<th>5 year survival %</th>
<th>10 year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – &lt;1.0</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>1.0 – &lt;2.0</td>
<td>92</td>
<td>84</td>
</tr>
<tr>
<td>2.0 – &lt;5.0</td>
<td>87</td>
<td>75</td>
</tr>
<tr>
<td>5.0 – &lt;11.0</td>
<td>78</td>
<td>68</td>
</tr>
<tr>
<td>11.0 – &lt;20.0</td>
<td>70</td>
<td>58</td>
</tr>
<tr>
<td>&gt; 20.0</td>
<td>59</td>
<td>48</td>
</tr>
</tbody>
</table>
**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

**Melanoma Case #2**

- 47 year old female; $1,000,000 Universal Life Insurance
  - Height 65 inches (165 cm), weight 134 lbs (61 kg)
  - Non-smoker, BP 118/80, insurance lab results all within normal limits
  - History of skin cancer excised 2.5 years prior to application. No other health history.
- Attending physician report:
  - Abnormal mole noted on right upper thigh, biopsied.
  - Exam otherwise normal, no palpable inguinal lymph nodes
  - Treated with wide-excision, no residual melanoma
  - Lab and chest X-ray normal

Can we make an offer as is?
Case #2

Path Report

- Melanoma stage?
- Favorable and unfavorable prognostic features present?
- What else would be useful information?

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

T2b, N0 ?? – Possibly Stage IIA
Sentinel node biopsy usually advised for anything other than T1a lesions – possibly understaged without this information
Case #2
Path Report

Melanoma stage – T2b?N0 = ?Stage IIA
- Favorable and unfavorable prognostic features present?
- What else would be useful information?

Melanoma Prognostic Factors

- Depth of invasion (Breslow thickness)
- Ulceration
- Anatomic site (scalp and neck > hands, feet > trunk > arms, legs)
- Mitotic rate
  - <1, 1-20, and >20 mitoses/mm²
- Other histologic features:
  - Microsatellites (unfavorable)
  - Desmoplastic (more favorable for degree of thickness)
  - Lymphocytic infiltration (favorable) and tumor regression (unfavorable) 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%)
- Lymph node status
Melanoma Case #2

- What else would be useful information?
  - Sentinel Lymph node biopsy negative
  - Follows up with dermatologist after 6 months and then every year – no recurrence, no other suspicious skin lesions noted
  - No known family history of melanoma

- Was the evaluation and follow-up adequate?
  - With clinically localized disease, no additional evaluation is required -- Chest X-ray and LDH are optional (and mostly as a baseline for future comparison)
  - Yearly follow-up for locoregional recurrence and second melanoma usually felt to suffice unless have multiple atypical moles or a strong family history

- Prognosis now after 2.5 years? Low, moderate, or high mortality risk?
- What if we were now 6 years out?
  - Still significant, and extends out beyond 6 years

Survival by T Classification

<table>
<thead>
<tr>
<th>Thickness Class</th>
<th>5 year survival %</th>
<th>10 year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1a</td>
<td>97</td>
<td>93</td>
</tr>
<tr>
<td>T1b</td>
<td>94</td>
<td>87</td>
</tr>
<tr>
<td>T2a</td>
<td>91</td>
<td>83</td>
</tr>
<tr>
<td>T2b</td>
<td>82</td>
<td>67</td>
</tr>
<tr>
<td>T3a</td>
<td>79</td>
<td>66</td>
</tr>
<tr>
<td>T3b</td>
<td>68</td>
<td>55</td>
</tr>
<tr>
<td>T4a</td>
<td>71</td>
<td>57</td>
</tr>
<tr>
<td>T4b</td>
<td>53</td>
<td>39</td>
</tr>
</tbody>
</table>
Survival rates for melanoma TNM and staging categories

<table>
<thead>
<tr>
<th>Pathologic stage</th>
<th>TNM</th>
<th>Ulceration</th>
<th>Number + nodes</th>
<th>1-year</th>
<th>5-year</th>
<th>10-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>IA</td>
<td>T1a</td>
<td>No</td>
<td>0</td>
<td>100</td>
<td>99</td>
<td>97</td>
</tr>
<tr>
<td>IB</td>
<td>T1b</td>
<td>Yes or level IV, V</td>
<td>0</td>
<td>99</td>
<td>94</td>
<td>90</td>
</tr>
<tr>
<td>IIa</td>
<td>T2a</td>
<td>No</td>
<td>0</td>
<td>100</td>
<td>91</td>
<td>84</td>
</tr>
<tr>
<td>IIIA</td>
<td>T2b</td>
<td>Yes</td>
<td>0</td>
<td>96</td>
<td>77</td>
<td>65</td>
</tr>
<tr>
<td>IVa</td>
<td>T3a</td>
<td>No</td>
<td>0</td>
<td>98</td>
<td>78</td>
<td>67</td>
</tr>
<tr>
<td>IIIB</td>
<td>T3b</td>
<td>Yes</td>
<td>0</td>
<td>95</td>
<td>71</td>
<td>62</td>
</tr>
<tr>
<td>IVb</td>
<td>T4a</td>
<td>No</td>
<td>0</td>
<td>96</td>
<td>67</td>
<td>56</td>
</tr>
<tr>
<td>IIIC</td>
<td>T4b</td>
<td>Yes</td>
<td>0</td>
<td>93</td>
<td>56</td>
<td>48</td>
</tr>
<tr>
<td>IIIf</td>
<td>N1a</td>
<td>No</td>
<td>1</td>
<td>95</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIIBF</td>
<td>N2a</td>
<td>No</td>
<td>2-3</td>
<td>96</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIIF</td>
<td>N1a</td>
<td>Yes</td>
<td>1</td>
<td>91</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>IIIF</td>
<td>N2a</td>
<td>Yes</td>
<td>2-3</td>
<td>94</td>
<td>59</td>
<td>50</td>
</tr>
<tr>
<td>IIIF</td>
<td>N1b</td>
<td>No</td>
<td>1</td>
<td>92</td>
<td>50</td>
<td>44</td>
</tr>
<tr>
<td>IIIF</td>
<td>N2b</td>
<td>No</td>
<td>2-3</td>
<td>93</td>
<td>68</td>
<td>59</td>
</tr>
<tr>
<td>IIIF</td>
<td>N1b</td>
<td>Yes</td>
<td>1</td>
<td>95</td>
<td>52</td>
<td>37</td>
</tr>
<tr>
<td>IIIF</td>
<td>N2b</td>
<td>Yes</td>
<td>2-3</td>
<td>84</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>IIIF</td>
<td>N3</td>
<td>Any</td>
<td>4</td>
<td>74</td>
<td>27</td>
<td>22</td>
</tr>
<tr>
<td>IVa</td>
<td>M1a-c</td>
<td>Any</td>
<td>Any</td>
<td>42</td>
<td>18</td>
<td>14</td>
</tr>
</tbody>
</table>


Melanoma Case #2

- Prognosis now after 2.5 years? Low, moderate, or high mortality risk?
  - 5-yr 77% survival
  - 10-yr 65% survival

Estimated disease-specific survival per melanomapronosis.org*:
  - 1-yr 99%
  - 2-yr 97%
  - 5-yr 89%
  - 10-yr 80%

- What if we were now 6 years out?
**20-year Melanoma Survival Rates AJCC**

Data 2009

*Used with permission, Balch, CM*

Survival curves for stages I and II comparing:

(A) the different T categories and (B) the stage groupings
Melanoma Case #2 – What if…

What if she was subsequently found to have two atypical nevi excised?
- Roughly doubles the already increased risk of a second melanoma (?15-20% at 5 years)
- Close follow-up is therefore very important

And/or if she also had a family history of melanoma in her mother?
- Similar risk to dysplastic nevi risk, but much higher yet if both factors present

Melanoma Case #2 -- What if…

- What if a sentinel node biopsy was positive for metastatic melanoma:

Stage then?
- Still uncertain – LND indicated

- How about if inguinal node dissection was carried out and two nodes were positive?
  - T2b, N2a, Mo = Stage IIIb

Prognosis?

Survival per melanomaprosnosis.org:
- 1-yr 94%
- 2-yr 88%
- 5-yr 73%
- 10-yr 62%
**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 -- What if…**

And what if we were now 10 years out since the diagnosis?

- Extended risk goes out to at least 20 years.
  - Per AJCC data, 10 and 15 year survivals of roughly 40% and 35% respectively
Melanoma Specific Survival
B. Heltemes analysis

Melanoma Survival - SEER Dataset

20-year Melanoma Survival Rates AJCC Data 2009
Used with permission, Bolk, CM

Stage III survival curves comparing:
(C) the different N categories and (D) the stage groupings
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 T2b,N2c; Stage IIIC disease
- 5- and 10-year survival rates of 69% and 52% respectively per AJCC dataset if nodes were negative

Medical Treatment of Melanoma

- No overall survival benefit has been clearly demonstrated for adjuvant chemotherapy, passive immunotherapy, radiation, retinoid, vitamin, or biologic therapies.
- Adjuvant interferon (IFN) alfa-2b is the only adjuvant therapy approved by the US Food and Drug Administration for high-risk melanoma (currently defined as stages IIB, IIC, and III).
  - benefits of interferon treatment are most pronounced in patients with earlier-stage III melanoma (vs patients with later-stage disease), in patients with no more than one positive lymph node, and in patients with ulceration
- The immunotherapy agent, ipilimumab, and biologic response modifiers (eg, granulocyte macrophage colony-stimulating factor [GM-CSF]), are currently being studied in the adjuvant setting for resected stage III and IV melanoma.
- Vaccines are of unclear benefit, however a recent phase III trial of gp100:209-217(210M) peptide vaccine in combination with high-dose IL-2 showed significant improvement in response rate and progression-free survival compared with IL-2 alone
MAPK Inhibitors

- The mitogen-activated protein kinase (MAPK) signaling pathway (RAS/RAF/MEK/ERK) is activated in up to 80-90% of melanomas, with the most common mutations in either NRAS (15-30% of melanomas) or BRAF (50-70% of melanomas).
- Vemurafenib (Zelboraf) was approved by the US FDA in August 2011. It is an inhibitor of some mutated forms of BRAF serine-threonine kinase, including BRAF V600E. The drug is indicated for the treatment of unresectable or metastatic melanoma with BRAF-V600 mutation. \(^{13}\)
- The BRAF Inhibitor in Melanoma (BRIM)-3 study results showed vemurafenib improved progression-free and overall survival compared with standard chemotherapy in patients with advanced melanoma with no previous treatment. Results found vemurafenib had a 74% reduction in the risk for progression (or death) compared with patients receiving dacarbazine chemotherapy (hazard ratio, 0.26; \(P < .001\)). At 6 months, the estimated overall survival rate was 84% in the vemurafenib group and 64% in the dacarbazine group.
- Combination therapy with a BRAF inhibitor and an MEK inhibitor is more effective than monotherapy in metastatic melanoma. Patients who received full dose of trametinib (2 mg daily) plus 150 mg of dabrafenib had progression-free survival of 9.4 months, compared with 5.8 months for those on dabrafenib monotherapy (hazard ratio [HR], 0.39). \(^{14}\)

Bibliography - Melanoma

Prostate Cancer

- Second most common cancer in men worldwide, with an estimated 900,000 cases and 258,000 deaths in 2008.
- 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)
  - Many men with occult disease die of other diseases

Simplified Schematic of Gleason’s Grading System
NOTES ON PROSTATE CANCER

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

Prostate Cancer – Case #1

- 74 yr old man. PSAs 4.5-5.0, 2009-2010
- March 2011, PSA 7.4.
  - Bx: One focus Gleason 3+4 = 7 Prostate Ca. Only 5% in 1 of 6 cores.
  - Active surveillance.
- November 2011: PSA up to 10.1.
  - Twelve core biopsy – all benign.
- Continue active surveillance.
  - June 2012: PSA 6.4 at insurance lab.
**Case #1 – Questions**

- Is this treatment appropriate?
- Mortality risk: low, intermediate, high?
- Explain PSA variation, May-June, 2012
  - May 2012: PSA 9.1
  - June 2012: PSA 6.4

**Prostate Cancer – Case #2**

- 60 year-old man, applied August 2012
- Sept. 2006, age 54, PSA 3.2 (2.0 in 2005)
- Sextant prostate bx.
  - Focus of atypical cells, w/ absent basal cells, right.
  - HGPIN on left.
- Dec. 2006. Slides referred to Dr. Epstein, Johns Hopkins. His Diagnosis:
  - One tiny focus prostate cancer, Gleason 3+3, with absent basal cells, right side.
  - HGPIN on left.
- Feb. 2007. Repeat sextant bx. Dr. Epstein’s diagnosis:
  - Small atypical focus, right, not diagnostic of cancer.
- FU: All PSA’s in 2.0-3.0 range, most around 2.5.
Case #2 – Questions

- Is this “active surveillance” (A.S.)?
- Is active surveillance or watchful waiting usually appropriate < age 65?
- Compare case 2 with case 1
- Mortality risk: low, intermediate, high?
- Do you think he will soon develop clinical prostate cancer?

Prostate Cancer – Case #3

  - Bx, Gleason 3+3, 3 of 12 cores
- Radical prostatectomy
  - Gleason 3+3, Stage pT3a
- Follow-up PSAs all <0.1 for 8 years
  - Salvage radiation therapy
- PSAs since, all <0.2, until May 2012, then 0.3
**Case #3 – Questions**

- Does grade or stage explain recurrence?
- How effective is salvage radiation after RRP?
- Concern about latest PSA?
- Favorable/unfavorable factors?
- Mortality risk: low, intermediate, high?
- What if he chose active surveillance?

**Prostate Cancer – Case #4**

- 53 y/o. Elevated PSA since 2006. (PSA in 2000: 2.7)
  - Father/brother with PC before age 65
- 2006 until Feb 2011: PSA from 6.4 (8% free), 7.0 (6% F), to 15.0, 16.3, 17.4, (then 9.3 & 12.6 after dutasteride), to 23.2, to 28.7 in 2012. % free not done if PSA >10.
- Multiple biopsies from Feb. 2006.
  - First 12 core biopsy: benign w/ small focus HGPIN.
  - Subsequent 10 to 12 core biopsies: BPH, occasional dense chronic or locally acute inflammation w/ comment about atrophy.
- Rare mention of HGPIN, focal.
- In 2008, whole body scan for mets. Also 2 pelvic MRI’s, 1 w/ endorectal coil. All – no evidence of cancer.
**Prostate Cancer – Case #4 (continued)**

- Nov. 2011-Feb. 2012: intense evaluation. After seven rounds of 10-12 core biopsies over the years, had saturation biopsy of 36 cores!
  - Four of 36 cores showed HGPIN. Has never had evidence of cancer.

- 2012 studies - normal pelvic CT & normal bone scan,
- TRUS: hyperechoic nodule, right base, o/w normal.
- UA: 0-3 WBCs/hpf & urine culture w/ 100,000 Streptococci Viridans.
- Unable to obtain recent PCA3 results.
- DREs: small, firm prostate, no nodules

**Case #4 – Questions**

- Possible cause of PSA elevation?
- Other helpful tests, besides PCA3?
- Is there hidden prostate cancer?
- Favorable/ unfavorable factors?
- Significant mortality risk?
Prostate cancer active surveillance guidelines.

- AGE. A.S. better over 70-75 (case 2, Q2). Most prostate cancer mortality 10-15 years after diagnosis. But younger men now electing active surveillance.

- GLEASON SCORE. Preferably Gleason 3+3=6 or less, (not Gleason 7, esp. not 4+3). Not secure in biopsy Gleason scores. Upgrading frequent after radical prostatectomy (27-38% upgraded). High grade cancer missed on biopsy d/t limited sampling. (Freedland. JAMA 2005; 294:2969).

- NUMBER OF CORES. Prefer at least 10-12 cores. If 1-2 cores w/ cancer, & < 25% - 50% involved, better. If > 2 cores involved, or > 50% of core w/ cancer, not A.S. candidates.

- CLINICAL STAGE. Preferably cT2a (or ? T2b) (unilateral). Clinical stages often upstaged after surgery (24-52% upstaged). Gleason 3+3 assoc. w/ stage pT3a case 3.

---

**Survival by Age and Gleason’s Score**

Gleason score and age affect survival in prostate cancer. Survival (white lower band) and cumulative mortality (from conservatively managed, clinically localised prostate cancer (black upper band) and other cases (light gray middle band) up to 15 years after diagnosis stratified by age at diagnosis and Gleason score. Percentage of men alive can be read from the left-hand scale, and percentage of men who have died from prostate cancer or from other causes during this interval can be read from the right-hand scale. Adapted with permission from Albertsen, PC, Harby, JA, Stamey, SR, Barry, PJ. Competing risks analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localised prostate cancer. *JAMA* 1999; 280:975.
Cases 1 and 2 (continued)


- CLOSE FOLLOW-UP critical. PSAs q 4-6 months for years. Biopsy repeat stat. or after 6-12 mo. or first & second years, & always after PSA elevations (case 2) (no bx for 5 years in case 1). Sanda: PSA 2-3 times per year, biopsy annually (JAMA 2009;301:2141).

- Toronto criteria for A.S.: Gleason score 6 or less, stage T1c or T2a, PSA 10 or less (UTD 2012). Less stringent if > age 70 (GS 3+4, PSA 15).

- Current RCT compares A.S. w/ definitive treatment.

ACTIVE SURVEILLANCE STUDY


- Caution in Lu-Yao report:

  - Median age 78. “not our intent to suggest ..benefit for majority...with localized pc”. “Might not apply to younger patients.” (<65)

  - Androgen deprivation TX high – 60-83%

- Gleason Score 5, 6, & 7 called moderately differentiated, which may overestimate GS 7 survival & underestimate GS 5 survival.

- GS 5 to 7 should not be lumped together. “May not apply to more aggressive disease”.

- Need to compare with studies favoring treatment (next slides).
**TREATMENT vs. A.S.**

- Lower 13 yr. mortality with definitive treatment compared to “observation” (48 vs.58%). Fewer with mets & local progression (Bill-Axelson. NEJM 2011; 364:1708). Mainly benefits men <65.

- SEER Medicare data: survival advantage w/ active treatment for low/ intermediate risk PC ages 65-80 after 8.2 years. With treatment, 23% die. Without tx, 37% die. (Wong. JAMA 2006; 296:2683).

- Merglen: treatment slightly improved 5-year PC specific mortality but he found increased long-term mortality w/ watchful waiting if < age 70 & Gleason score 7. (Arch Int. Med. 2007;167:1944).

---

**Active Surveillance (AS)**

- With PC’s long mortality tail (10-25 years), A.S. for younger men is risky. As we age - higher operative risks if need intervention.

- Gleason: Ave. 2.7 Gleason grades in prostatectomy specimens. Over 50% - 3 Gleason patterns.


- Mayo Clinic’s Bostwick: Gleason grade 3 “particularly difficult to separate from benign acini in biopsies” (CA 1997; 47; 297).
Active Surveillance


- With AS, 1/3 to 1/2 still untreated 5 years. “Indiscriminant watchful waiting in moderate cancers - significant risk of mortality” (Sanda. JAMA2009;301:2141). High risk for AS: GG 4 or 5, > 2 positive cores, > 50% cores w/ cancer.

- “Watchful waiting” now means waiting for symptoms of spread. Only recourse then- androgen deprivation. WW is for men w/ short life expectancy &/or substantial co-morbid problem.

Comments - case 2

- “Basal cell layer is absent in adenocarcinoma, important feature difficult to evaluate in routine tissue sections” (Bostwick, CA 1997; 47: 297.) Epstein report in case 1: If tiny focus of PC on one core, 50% chance of very small cancer on prostatectomy (J. Urol. 2003).

- “Suggestive” or “suspicious” for malignancy requires close follow-up (case 2).
Salvage radiotherapy (case 3)

- 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 14 years after PSA recurrence, before PSA >2.0 (Trock. JAMA 2004; 291:1325). (Others disagree.) Start salvage radiotherapy w/in 2 years due to local recurrence, not widespread (JAMA 2004; 291:1325). (Others disagree.)

- 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).

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
**PSA, case 4**


- If only use + DRE to diagnose PC: 2/3 of cancers are not curable when discovered.

- Carroll: young more likely to have curable cancers. PSA more specific in young. (Carroll. JAMA 2009; 301: 2538)


- Searches for tests to differentiate aggressive from indolent prostate cancers: PCA3 (case 4). PCA3 gene over-expressed in PC. Cutpoints a problem. Range from 4 to 125; If PCA3 of 35 (or 50) & up: high risk. Prostatitis does not influence PCA3.

- Molecular assays for PC: sarcosine, GSTP. cDNA microarray to differentiate PC from BPH. Early PC Antigen. (case 4, Q 2)

---

**HGPIN (case 4)**

- Isolated HGPIN: slightly higher risk for PC. (UTD 2012). PIN seen by third decade in many.

- Autopsy studies: PIN precedes PC by 10 years or more (Bostwick).

- Bostwick: If HGPIN or atypical cells: biopsy q 3-6 mo. x 2 yrs., then q year till diagnose cancer (CA 1997;47:297).
**Other comments**

- Fam. Hx.: brother 3.37 RR, father 2.17 RR, if both 5.08
- Recent Gleason Score upgrading in PC (cases 1,2,3).
- PSA results vary per lab, method, person (case 1, Q3).
- 5-alpha reductase inhibitors (finasteride, dutasteride) decrease PSA 50% (case 4). Gleason grade invalid after their use, & after radiation, chemo & hormone tx.
- Case 3, had biopsy PSA 2.6 because age 52 (Catalona.Ann.Int Med.2006; 144;443).
- % free most helpful for PSA 3-10 (case 4). Invalid if specimen frozen.
- Infection & inflammation elevates PSA (case 4, Q. 1).
- Proliferative inflammatory atrophy may lead to PIN, then to PC (case 4).

---

**Other comments (continued)**

- Need serial sections in prostate biopsies (all cases).
- Use prostatectomy Gleason score & stage, over biopsy score & clinical stage.
- “Today...so much at stake...no time to fall in line behind USPSTF’s recommendation” (Kim.JAMA. 2012; 307;1372). Look at declines in PC mortality since PSA testing.
- Main treatment by age: 18-64: prostatectomy; 65-74: radiotherapy; 75-85: AS.
- 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).
Colorectal Cancer (CRC)

- Approximately 143,000 new cases of CRC diagnosed each year in U.S. (1)
  - 4th most common cancer diagnosed (prostate, breast, lung)
- Over 50,000 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

Trends in incidence of colorectal cancer
Age-standardized rate per 100,000, men

GLOBOCAN 2008 (IARC), Section of Cancer Information (4/9/2012)
Trends in mortality from colorectal cancer
Age-standardized rate per 100,000, men

Risk Factors for Colorectal Cancer
- FAP (familial adenomatous polyposis)
- MAP (MUTYH-associated polyposis)
- HNPCC (hereditary non-polyposis colon cancer)
- Advanced age
  - 2x risk with each decade after 40
  - 90% occur after age 50 (but this may be decreasing)
- Inflammatory bowel disease
  - 5-15x risk if pancolitis
  - 3x risk if left-sided only
- Abdominal radiation
- Country of birth (10x higher in N. America than Africa)
- 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
- Obesity (1.5x risk compared to BMI 18-25)
- Alcohol (1.4x risk if ≥ 3 drinks/day)
- Acromegaly
- Diet high in red meat, low in fruits/vegetables/calcium/fiber
- Smoking (1.2x risk)
- Diabetes
Clinical Manifestations of Colon Cancer

- None
- Abdominal pain
  - Partial obstruction -- cramping, change in stool shape
  - Peritonitis
  - Tumor dissemination
- Change in bowel habit (esp. left-sided tumors)
- Hematochezia (BRBPR) (esp. rectal tumors)
- Anemia (esp. right-sided tumors)
- Melena
- Weakness, malaise, anorexia, weight loss
- Palpable abdominal mass, fever of unknown origin, stool in urine or in vaginal secretions
- Unknown primary site

Anatomy of the Colon – CRC Location

- Right-sided 40%
- Left-sided 32%
- Rectal 28%
**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

**Familial adenomatous polyposis (FAP)**

**Hereditary nonpolyposis colorectal cancer (HNPCC)**

- Represent very high risk for colorectal cancer
- However, less than 5% of CRC cases are due to these
- Autosomal dominant inheritance
- **FAP**
  - 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
  - Caused by mutations in the APC gene and 2 different/biallelic mutations in the MUTYH gene
  - Attenuated form (20-99 adenomas) has an older average age of cancer diagnosis of 54 years and fewer extraintestinal manifestations
- **HNPCC (Lynch Syndrome)**
  - Mean age at initial cancer diagnosis is ~45 years
    - But few are before the age of 30, unlike FAP
  - 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
Amsterdam II criteria for HNPCC

- There should be at least three relatives with an HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis)
- One should be a first degree relative of the other two
- At least two successive generations should be affected
- At least one should be diagnosed before age 50
- Familial adenomatous polyposis should be excluded in the colorectal cancer case(s)
- Tumors should be verified by pathological examination
- If criteria are met, then MMR (mismatch repair) gene testing in the youngest living member of the family with colorectal cancer is advised

Limitations to Amsterdam Criteria

- Misses many with deleterious mutations
  - Sensitivity of only 36% in one study
  - Specificity good though at 97%
- Immunohistochemistry of tumor is better
  - Sensitivity 86%
  - Specificity 92%
- Not all gene mutations are similar
  - Cumulative cancer risk by age 70 for the three main mutations (95% of cases)\(^9\)
    - 40-50% for MLH1 and MSH2
    - Just 12% for MSH6
Bethesda Criteria for HNPCC

Tumors from individuals should be tested for MSI:
- Colorectal cancer diagnosed in a patient who is less than 50 years of age
- Presence of synchronous, metachronous colorectal, or other HNPCC-associated tumors, regardless of age
- Colorectal cancer with the MSI-like histology diagnosed in a patient who is less than 60 years of age
- Colorectal cancer diagnosed in a patient with one or more first-degree relatives with an HNPCC-related tumor, with one of the cancers being diagnosed under age 50 years
- Colorectal cancer diagnosed in a patient with two or more first- or second-degree relatives with HNPCC-related tumors, regardless of age

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
Stage at Diagnosis

- The increase in colorectal cancer screening has been associated with an earlier stage at which colorectal cancer is diagnosed. From the SEER database:
  - Localized - confined to the primary site and to the mucosa, submucosa, and muscle layer (TNM stage I or II) — 40%
  - Lymph node involvement (TNM stage III) — 37%
  - Distant metastases (TNM stage IV) — 19%

Colorectal Cancer Case #1

- 64 year old female; for $750,000 Term Life Insurance
- Height 63 inches (160 cm), weight 174 lbs (79 kg)
- Non-smoker, BP 136/80, insurance lab blood and urine tests all within normal limits
- No important medical problems; family history of colon cancer in her father at age 55
  - What would be the recommended colon cancer screening for her?
  - How about if a brother also had colon cancer, and at age 45?
  - And a paternal aunt had endometrial cancer at age 50?
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.

Screening for Colon Cancer*

- For average risk individuals, beginning at age 50:
  - Fecal occult blood testing annually + flexible sigmoidoscopy every 5 years
  - Colonoscopy every 10 years
  - Double contrast barium enema every 5 years
  - Virtual colonoscopy every 5 yrs
- For those with a family history of CRC or adenoma in a first degree relative (FDR) or 2 or more second degree relatives:
  - Screening as above but beginning at age 40 (or 10 years before age at diagnosis in a FDR if was before age 50)
- For those with ulcerative colitis or Crohn’s disease, colonoscopy:
  - Beginning 8-10 years after symptom onset if pancolitis
  - Beginning 15-20 years after symptom onset if left-sided colitis
- Intense screening and genetic counseling advised for those with familial cancer syndromes

*Joint guidelines from the American Cancer Society, the United States Multi-Society Task Force on Colorectal Cancer (ACS-MSTF), and the American College of Radiology; Published 2008.
Suspected Hereditary Nonpolyposis Colorectal Cancer (HNPCC)

- HNPCC (Lynch Syndrome)
  - Mean age at initial cancer diagnosis is ~45 years
    - But few are before the age of 30, unlike FAP
  - Approximately 10% will have synchronous cancers
  - Extracolonic cancers are also common, including endometrial carcinoma in ~40% of female gene carriers
- MMR (mismatch repair) gene testing in the youngest living member of the family with colorectal cancer is advised
- Not all gene mutations are similar
  - Cumulative cancer risk by age 70 for the three main mutations (95% of cases)\(^9\)
    - 40-50% for MLH1 and MSH2
    - Just 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)

Colorectal Cancer Case #1

- 64 year old female; for $750,000 Term Life Insurance
  - Height 63 inches (160 cm), weight 174 lbs (79 kg)
  - Non-smoker, BP 136/80, insurance lab blood and urine tests all within normal limits
  - No important medical problems; family history of colon cancer in her father at age 55
- Developed rectal bleeding 2.5 years prior to application, colonoscopy revealed large mass at 10-15 cm from the anal verge
- Partial colectomy performed
Partial colectomy – pathology as follows:

Pathologic Stage?
Favorable and unfavorable prognostic features present?

<table>
<thead>
<tr>
<th>Final Diagnosis</th>
<th>Part A: &quot;Rectosigmoid&quot;, resection = Adenocarcinoma. (See tumor characteristics)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TUMOR CHARACTERISTICS</td>
<td></td>
</tr>
<tr>
<td>Histologic grade</td>
<td>Invasive moderately to very focally poorly differentiated adenocarcinoma (grade 2-3)</td>
</tr>
<tr>
<td>Depth of mural invasion (pT)</td>
<td>Invasive adenocarcinoma extends into but not through the muscularis propria (pT2). Focally present.</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
<td>Not identified.</td>
</tr>
<tr>
<td>Extravascular venous invasion</td>
<td>Nine pericolic lymph nodes negative for malignancy (0/9). Not applicable</td>
</tr>
<tr>
<td>Lymph nodes (pN)</td>
<td>pT2N0MX</td>
</tr>
<tr>
<td>Number positive/total number</td>
<td>Free of tumor</td>
</tr>
<tr>
<td>Extrarectal extension</td>
<td>Free of tumor</td>
</tr>
<tr>
<td>TNM stage</td>
<td>None</td>
</tr>
<tr>
<td>Margins of resection, closest</td>
<td></td>
</tr>
<tr>
<td>Proximal and distal</td>
<td></td>
</tr>
<tr>
<td>Radial</td>
<td></td>
</tr>
<tr>
<td>Additional Comments</td>
<td></td>
</tr>
</tbody>
</table>

TNM Staging System for Colorectal Cancer

- **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, mesentry, 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>B1</td>
<td>A</td>
</tr>
<tr>
<td>T3</td>
<td>N0 M0</td>
<td>II</td>
<td>B2</td>
</tr>
<tr>
<td>T4a</td>
<td>N0 M0</td>
<td>IIB</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>IIIA</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>IIIB</td>
<td>C2</td>
</tr>
<tr>
<td>T2-3</td>
<td>N2a M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>N2b M0</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>T4a</td>
<td>N2a M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-T4a</td>
<td>N2b M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b</td>
<td>N1-2 M0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any T</td>
<td>Any N M1a</td>
<td>IVa</td>
<td>C</td>
</tr>
<tr>
<td>Any T</td>
<td>Any N M1b</td>
<td>IVb</td>
<td></td>
</tr>
</tbody>
</table>

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

Partial colectomy – pathology as follows:

**SURGICAL PATHOLOGY REPORT**

**Stage I -- T2, N0, M0(?)**

Other favorable and unfavorable prognostic features present?

---

**Final Diagnosis**

Part A: “Rectosigmoid”, resection = Adenocarcinoma. (See tumor characteristics)

**Histologic grade**

Invasive moderately to very poorly differentiated adenocarcinoma (grade 2-3)

**Lymphatic Invasion**

Invasive adenocarcinoma extends into but not through the muscularis propria (pT3)

**Focally present:**

Not identified:

Nine pericolic lymph nodes negative for malignancy (0/9).

**pT2N0MX:**

Free of tumor

Free of tumor

---

**Additional Comments**

None
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%.

- **Lymph nodes**
  - Number involved with tumor
    - CRC mortality roughly twice as high for N2 vs N1 status
  - Number in surgical specimen (See table)
    - 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
    - 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

- **Residual tumor**
  - Based largely on the status of the circumferential resection margin (CRM)

Additional Prognostic Factors for CRC

- Rectal vs colon cancer
- Lymphovascular invasion
- Grade (well/moderately vs. poorly differentiated)
- Histology
  - Signet cell variant, Adenosquamous carcinomas
  - Appendiceal cystadenomacarcinoma
  - Often associated with pseudomyxoma peritonei
- CEA >5.0
  - Independent of tumor stage
  - Node (-) disease with increased CEA fares worse than node (+) with normal CEA
- Tumor regression after neoadjuvant therapy
- 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 infiltrating lymphocytes – favorable
- Perineural invasion – adverse
- 18q deletions – 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?
  - CEA level, MSI testing, any special staining of nodes
  - Imaging of chest, abdomen and pelvis for M staging
- What is the expected clinical follow-up in this situation?

Follow-up After CRC Diagnosis
(National Comprehensive Cancer Network Guidelines)

- History and Physical Exam
  - Every 3-6 months for the first 3 years then every 6 months years 4 and 5, then annually
- Colonoscopy
  - Within three months if exam was incomplete pre-operatively.
  - Otherwise follow-up colonoscopy in one year and if negative for polyps repeat in three years, then every five years
  - Proctosigmoidoscopy every six months for 5 years if rectal cancer
- CEA
  - Every three to six months for the first two years, then every six months for three additional years for T2 or higher stage disease.
- Chest and abdomen CT scans for Stage II-IV
  - Annually for three years usually advised if patient would be a candidate for additional treatment
  - Annual pelvic CT for three years should be considered for rectal cancer surveillance (especially if not treated with pelvic radiation)
- Generally little else is advised for specific follow-up for stage I CRC since the prognosis is so favorable
Colorectal Cancer Case #1

- Assuming she has had good follow-up and no clinical evidence of disease, what is her likelihood of recurrence and overall prognosis at this point?
  - 5 year survival rates 72-90%, with most of the recurrences happening within the first 2-3 years
- What is her likelihood of developing a second colorectal cancer?
  - 3-5% within the next five years
- What if she had the family history of colorectal cancer last noted (brother and aunt)?
  - May be as high as 20-40%; likely much less though if continues with close follow-up and screening

Recurrence Rates

- Large database found recurrence rates as 12% at one year, 14% year 1-2, then 8%, 5%, and 3% over the next three years respectively
- Overall, 80% of recurrences occurred within the first 3 yrs.

  Mayo ACCENT study, J Clin Oncology 2005 Dec 1; 23(34).
**Colon Ca Mortality by Tumor Extent**

![Colon Ca Mortality by Tumor Extent](image)

Derived from Wesley; J Insurance Med 2009

---

**Synchronous CRCs**

- Two or more distinct primary tumors separated by normal bowel and not due to direct extension or metastasis
  - Present in about 2.5 percent of patients with colon cancer (when patients with hereditary nonpolyposis colorectal cancer are excluded)
  - Synchronous primaries have the same prognosis as solitary malignancies when the highest stage of disease is compared
Metachronous cancers

- Nonanastomotic new tumors developing at least six months after the initial diagnosis
  - Develop in 1.5 to 3 percent of patients in the first five years postoperatively and roughly 9 percent 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 of 6579 subjects followed for an average of 4.3 years after CRC resection, the standardized incidence ratio (SIR) for a second cancer was 1.5 overall but was significantly greater in younger patients (38.3, 7.6, 2.2, and 1.2 for patients age 30-39, 40-49, 50-59, and over 60 years old, respectively)

Colorectal Cancer Case #1 – What if…

- What if she were found to have 2 of the 9 nodes positive for malignancy:
  - TNM stage?
    - T2, N1b = Stage IIIA
  - Any additional prognostic factors?
    - Number of nodes surveyed remains important (Lymph node ratio of 0.22) and is thus an adverse feature in this case
  - Additional treatment warranted?
Chemotherapy Options

- Survival outcomes for Stage IIIA CRC often better than for Stage II
- 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 Leukovorin and 5-FU
- Irinotecan, bevacizumab, and cetuximab usually reserved for metastatic disease
- TAS-102 on the horizon?

Colorectal Cancer Case #1 – What if…

- Stage IIIA, 2.5 years out
  - Prognosis?
    - 60-83% 5 year survival if gets advised adjuvant chemotherapy
  - Prognosis if she were now 8 years out since surgery?
    - Excess death rates are now closer to 10/1000/year, with reported recurrence rates of <0.5%/year in those receiving adjuvant chemotherapy
Estimated Five-year Colon Adenocarcinoma Survival Rates by TMN Stage (3)

- **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%

Rectal Cancer – Prognosis (6, 7)

- Five-year survival rates for rectal cancer tend to be somewhat lower:
  - Stage I — 72 percent
  - Stage II — 52 percent
  - Stage III — 37 percent
    - IIIA — 55% (60/39*)
    - IIIB — 35% (41/22*)
    - IIIC — 25% (29/12*)
  - Stage IV — 4 percent

*Outcomes for chemotherapy and/or radiation treated vs surgery alone*
## Prognosis of Stage II/III Rectal Cancer

<table>
<thead>
<tr>
<th>Tumor (T) stage</th>
<th>Node (N) stage</th>
<th>5-year survival %</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1-2</td>
<td>N1</td>
<td>79</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>67</td>
</tr>
<tr>
<td>T3</td>
<td>N0</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>44</td>
</tr>
<tr>
<td>T4</td>
<td>N0</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>35</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>37</td>
</tr>
</tbody>
</table>

## 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>
<td>83</td>
</tr>
<tr>
<td>IIIA-IIIB</td>
<td>&lt;11</td>
<td>74</td>
<td>65</td>
</tr>
<tr>
<td></td>
<td>11-40</td>
<td>78</td>
<td>70</td>
</tr>
<tr>
<td></td>
<td>&gt;40</td>
<td>93</td>
<td>93</td>
</tr>
<tr>
<td>III C</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>
Observed survival rates for 28,491 cases with adenocarcinoma of the colon

Excess Death Rate by Stage

Derived from Wesley; J Insurance Med 2009
Carcinoembryonic Antigen

- Screening use is very limited as not too 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
- Also for monitoring for recurrence
  - See CRC follow-up

![Graph showing observed survival rates for 9,060 cases with adenocarcinoma of the rectum.](chart.png)

**Treatment of Metastatic CRC**

- Surgery for isolated mets is usually advised
  - Long term survival can be obtained in up to 50% with single liver or lung met
- Preferred systemic chemotherapy regimens for non-resectable metastatic disease now oxaliplatin and/or irinotecan-based with or without biologic agents
  - Greater activity as compared to 5-FU and leucovorin alone.
  - Median survival durations in unselected patients with metastatic disease are 22 to 24 months, and approximately 10 percent of patients remain alive at five years

**Hot off the press!**

- In a trial of 760 people with colorectal cancer that progressed after treatment with all other approved drugs, 24 percent of those receiving regorafenib were alive after a year, compared with 17 percent of those getting a placebo
  - Data presented at the European Society of Medical Oncology’s meeting in Vienna, Oct 2012
Bibliography

11) Synchronous colon primaries have the same prognosis as solitary colon cancers. Passama DA; Pommier RF; Vetto JT. Dis Colon Rectum. 1996;39(9):525.
16) https://www.adjuvantonline.com/online.jsp