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


<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 cribriform 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

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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 $\leq 1.0$ 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.
  - Microscopic: “Mixed mucinous (colloid) carcinoma predominant pattern plus infiltrating ductal carcinoma within mucoid carcinoma. Extensive lymphatic invasion, extension to margins of resection by intralymphatic carcinoma. Multicentricity due to intralymphatic spread.”
  - Deep margin of resection free of tumor.
  - Two of 16 axillary lymph nodes: metastatic ductal (not colloid) carcinoma. One + node level I, the other level III.
- Four series of chemotx first. Estrogen receptor positive.
- 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 0.1cm. 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; 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. T1mic.
  - 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

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
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: ≤ 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
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 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 may be on the horizon 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?
- Information complete?

Melanoma Case #1

- Dermatology follow-up every 4 months
- Extensive solar damage, multiple basal cell carcinomas, no additional nevi of concern noted
**Additional Dermatology Records**

**MICROSCOPIC EXAMINATION:**
A. No residual melanoma is seen. There is an area of dermal collagen with a focal area of adjacent atypical melanocytic hyperplasia that does not extend to the margins of resection.
B. Sections of skin show no melanocytic lesion.

**DIAGNOSIS:**
A. **MELANOMA SITE, RIGHT CHEEK** (WIDE LOCAL EXCISION OF SKIN AND SUBCUTANEOUS TISSUE):
   NO RESIDUAL MALIGNANT MELANOMA.
   SKIN WITH DERMAL SCAR.

- Tumor Stage?
- Favorable and unfavorable features?
- Mortality risk?
- What if this was just 4 months ago?
- What if it was 4 years later?

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**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.

Can we make an offer as is?
Melanoma Case Study

- 47 year old female. 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 axillary lymph nodes
  - Treated with wide-excision, no residual melanoma
  - Lab and chest X-ray normal

Now are you happy?

Case #2
Path Report

Pathology
05/09/2007 3:12pm
DERM PATH FINAL REPORT

Report Date: 5/9/2007 4:13pm
Status: Final

Acc. Number: 004000DC/200700085/19350385

Diagnosis:
- SKIN (LABELLED AS “RIGHT THIGH”), BIOPSY:
  INVASIVE MALIGNANT MELANOMA
  ULCERATION PRESENT
  BRESLOW THICKNESS < 1.17 MM
  CLARK LEVEL IV
  AIDENTIY OF HOST RESPONSIVE TO TUMOR INFILTRATING LYMPHOCYTES
  NO EVIDENCE OF REGRESSION
  LYMPHOVASCULAR INVASION PRESENT
  MARGINS NEGATIVE OF THE PLANE OF SECTIONING
  MITOTIC INDEX: FEWER THAN ONE MITOSIS PER MM

- Melanoma stage?
- Favorable and unfavorable prognostic features present?
- What else would be useful information?
Melanoma Case #2

- 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?
Prognosis?

Melanoma Case #2 – What if…

What if she was subsequently found to have two atypical nevi excised?
And/or if she also had a family history of melanoma in her mother?
Melanoma Case #2 -- What if…

- What if a sentinel node biopsy was positive for metastatic melanoma: 
  Stage then?
- How about if axillary node dissection was carried out and two nodes were positive:
  Stage then?
  Prognosis?
  And what if we were now 10 years out since the diagnosis?

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?
**Bibliography - Melanoma**


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**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**

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**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.**
- **Latest PSA, April 2012: 2.5. No bx since 2007.**

### 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 focally 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?
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

NORDCAN (www.amc.ru)
France: INVS
Ireland: www.ncri.ie
The Netherlands: www.ikcnet.nl
UK: www.cancerresearchuk.org
Australia: www.aihw.gov.au
Canada: www.statcan.gc.ca
India: Chennai cancer registry
Japan: Miyagi, Osaka and Yamagata cancer registries
Republic of Korea: www.ncc.re.kr
USA: SEER program: seer.cancer.gov

GLOBOCAN 2008 (IARC), Section of Cancer Information (4/9/2012)
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?

- Developed rectal bleeding 2.5 years prior to application, colonoscopy revealed large mass at 10-15 cm from the anal verge
Partial colectomy – pathology as follows:

<table>
<thead>
<tr>
<th>TUMOR CHARACTERISTICS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histologic grade^1</td>
</tr>
<tr>
<td>Depth of mural invasion (pT)</td>
</tr>
<tr>
<td>Lymphatic invasion</td>
</tr>
<tr>
<td>Extramural venous invasion</td>
</tr>
<tr>
<td>Lymph nodes (pN)</td>
</tr>
<tr>
<td>Extrarectal extension</td>
</tr>
<tr>
<td>TNM stage grouping</td>
</tr>
<tr>
<td>Margins of resection, closest</td>
</tr>
<tr>
<td>Proximal and distal</td>
</tr>
<tr>
<td>Radial</td>
</tr>
<tr>
<td>Additional Comments</td>
</tr>
</tbody>
</table>

Colorectal Cancer Case #1 Questions:

- Pathologic stage?
- Favorable and unfavorable prognostic features present?
- What additional prognostic information would you like to see?
- What is the expected clinical follow-up in this situation?
- Assuming she has had good follow-up and no clinical evidence of disease, what is her likelihood of recurrence at this point?
  - And her mortality risk?
- What is her likelihood of developing a second colorectal cancer?
  - What if she had the family history of colorectal cancer last noted (brother and aunt)?
Colorectal Cancer Case #1 – What if…

- What if she were found to have 2 of the 9 nodes positive for malignancy:
  - TNM stage?
  - Any additional prognostic factors or treatment then?
  - Prognosis?
  - Prognosis if she were now 8 years out since surgery?

Anatomy of the Colon – CRC Location

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

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
  - Average age of symptom onset ~16 years
  - CRC occurs in 90% of untreated individuals by age 45
  - Attenuated form has an older average age of cancer diagnosis of 54 years
- 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) if any
- 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
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

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.
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%
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)
Prognostic Factors for CRC

- **Stage** – Single most important factor
  - Serosal involvement of T4 lesions – now subdivided into T4a (tumor perforates the visceral peritoneum) and T4b (direct invasion or histologic adherence to other organs and/or structures)
  - However, histologic determination of serosal penetration is difficult, and conservative interpretation may lead to understaging of disease. For example, cytologic examination of serosal scrapings from pT3 specimens found malignant cells in up to 26 percent (12)

- **Lymph nodes**
  - Number involved w/ tumor
  - 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
  - See table
  - Mesenteric tumor nodules are each considered as a positive node (N1c)
  - Micrometastases/Isolated tumor cells (ITCs): single tumor cells or small clusters of tumor cells measuring <0.2mm in size
    - Appears to have worse outcome per a meta-analysis14
    - 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

- **Rectal vs colon cancer**
- **Residual tumor**
  - Based largely on the status of the circumferential resection margin

Additional Prognostic Factors for CRC

- **Lymphovascular invasion**
- **Grade (well/moderately vs. poorly differentiated)**
- **Signet cell variant**
- **Adenosquamous carcinomas**
- **Appendiceal cystadenomacarcinoma**
  - Often associated with pseudomyxoma peritonei
- **CEA >5.0**
  - Independent of tumor stage
- **Tumor regression after neoadjuvant therapy**
- **Microsatellite instability**
  - Seen in HNPCC tumors and in 15-20% of sporadically occurring tumors
  - Despite being poorly differentiated, the prognosis is more favorable
  - Similarly, mismatch repair deficiency and tumor infiltrating lymphocytes
- **18q deletions**
  - Loss of heterozygosity at 18q portends a worse prognosis
- **Tumor border — irregular, infiltrating pattern of growth is an independent adverse prognostic**
  - May predict liver metastasis.
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?

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, 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
<table>
<thead>
<tr>
<th>TNM</th>
<th>AJCC Stage</th>
<th>MAC*</th>
<th>Duke’s</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 N0 M0</td>
<td>0</td>
<td>A</td>
<td>A</td>
</tr>
<tr>
<td>T2 N0 M0</td>
<td>I</td>
<td>B1</td>
<td>A</td>
</tr>
<tr>
<td>T3 N0 M0</td>
<td>IIA</td>
<td>B2</td>
<td>B</td>
</tr>
<tr>
<td>T4a N0 M0</td>
<td>IIB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T4b N0 M0</td>
<td>IIC</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2 N1/N1c M0</td>
<td>IIIA</td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>T1 N2a M0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3-4a N1/N1c M0</td>
<td>IIIB</td>
<td>C2</td>
<td></td>
</tr>
<tr>
<td>T2-3 N2a M0</td>
<td></td>
<td>C1/2</td>
<td></td>
</tr>
<tr>
<td>T1-2 N2b M0</td>
<td></td>
<td>C1</td>
<td></td>
</tr>
<tr>
<td>T4a N2a M0</td>
<td>IIIC</td>
<td>C2</td>
<td>C</td>
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<tr>
<td>T3-T4a N2b M0</td>
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<tr>
<td>T4b N1-2 M0</td>
<td></td>
<td>C3</td>
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<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></td>
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</tbody>
</table>

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).
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**

CEA

- **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
16) https://www.adjuvantonline.com/online.jsp