Oncology
Take Home Messages

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Disclosures:
No relevant conflicts of interest to declare

The Leukemias

Chronic Lymphocytic Leukemia
• Most common form of leukemia
• median age at diagnosis is 65
• involves the bone marrow, lymph nodes and spleen at diagnosis
• malignant cell is a B lymphocyte
• common complications include autoimmune hemolytic anemia and hypogammaglobulinemia
• increased risk of secondary malignancies

Does therapy for Early Stage CLL change survival?

CLL - Indications for Therapy
• Progressive adenopathy
• Anemia
• Thrombocytopenia
• Autoimmune complications

Genetic Aberrations and Survival
Therapy for Early Stage CLL Does Not Change Survival

Infectious Complications in CLL

- Hypogammaglobulinemia common
- Infections with encapsulated organisms
- Replacement therapy indicated for patients with recurrent infections
- Progressive granulocytopenia
- Severe T cell immune suppression
  - Infections with listeria, PCP, etc.
  - Fludarabine leads to reduction in CD4+ T cell counts
  - Consider PCP prophylaxis

Risk Adapted Therapy for AML

1st complete remission

- Favorable cytogenetics - t(8;21), t(15;17), and inv16
  - Chemotherapy
- Unfavorable cytogenetics - t(9;22), -7, -5, 11q23
  - Allogeneic BMT
- Intermediate risk - normal cytogenetics
  - Chemotherapy or BMT

Chronic Myelogenous Leukemia

A myeloproliferative disease characterized by:

- t(9;22) - bcr-abl Philadelphia Chromosome
  - Median age at diagnosis of 53
  - Sex ratio of 1:1
  - Increased risk associated with prior radiation exposure
  - Median survival is approximately 5 years

The Lymphomas
Diffuse large B-cell lymphoma

- 1970’s - CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone)
- 1980’s – 2nd and 3rd generation regimens (addition of other active agents, modification of doses and schedules) with improved CR rates and survivals in pilot studies
- 1990’s – prospective randomized trials demonstrate 2nd and 3rd generation regimens are no better than CHOP

Monoclonal Antibody for NHL: Rituximab

- Chimeric molecule with a murine antigen binding domain and human constant region
- Binds to CD20+ expressed on malignant B-cells
- Indolent B-cell lymphoma response rate 50%
- Relapsed large cell lymphoma response rate 37%

GELA Study

- 399 newly diagnosed patients with DLBCL
- age between 60 and 80
- Randomized to:
  • standard dose CHOP X 8
  • standard dose CHOP + rituximab X 8
Hodgkin Lymphoma - Epidemiology

- 8000 cases and 1500 deaths per year in US
- Bi-modal age distribution
  - 20-30’s
  - > 50’s
- Increased incidence in industrialized countries
- NS subtype associated with high standard of living
- MC/LD in economically disadvantaged countries (EBV+)

Hodgkin lymphoma complications of therapy

- Fertility
  - ABVD low risk of infertility
  - BEACOPP high risk
- Pulmonary Toxicity
  - Bleomycin
  - Mediastinal RT
- Cardiac toxicity
  - Mediastinal RT – pericardial, valvular and CAD
  - Doxorubicin - cardiomyopathy
- Second malignancies
  - solid tumors from radiation - breast, lung, etc
  - leukemia with BEACOPP

Long Term Survival and Competing Causes of Death in HL

On-going research in early HL

- Early stage disease:
  - Given excellent prognosis, focus on preventing long-term complications
  - Less chemotherapy
  - Less radiation
  - Chemotherapy only
- Advanced stage disease:
  - Intensified regimens for patients with poor prognosis
  - Risk adapted therapy using PET scans

Pancreatic Cancer: Survival

Overall survival for all patients admitted to Memorial Sloan Kettering Cancer Center with adenocarcinomas of the pancreas between October 15, 1983 and October 15, 1985 (N = 684, median survival = 6 months)

GI Cancers
Metastatic Pancreatic Cancer: FOLFIRINOX

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response Rate</th>
<th>Median OS</th>
<th>Median PFS</th>
<th>1 year OS</th>
<th>Grade 3/4 WBC</th>
<th>Grade 3/4 Emesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gemcitabine</td>
<td>9%</td>
<td>3.3 m</td>
<td>6.8 m</td>
<td>21%</td>
<td>19%</td>
<td>5%</td>
</tr>
<tr>
<td>FOLFIRINOX</td>
<td>31%</td>
<td>6.4 m</td>
<td>11.1 m</td>
<td>48%</td>
<td>46%</td>
<td>15%</td>
</tr>
</tbody>
</table>

P value: 0.0001, <0.0001, <0.0001, 0.0001, 0.002

Thierry Conroy et al ASCO 2010

Take Home Points of Pancreatic Cancer

- Only 15% of patients diagnosed are eligible for surgery and only 15% of those patients will be cured (cure rate 2-3%)
- Locally advanced disease → chemoRT
- Metastatic disease treated with chemotherapy and median survival ~ 8 months

Take Home Points of Gastric Cancer

- Gastric cancer decreasing incidence in past few decades
- ~50% of patients diagnosed will die from gastric cancer
- Standard of care for localized disease is surgery and often chemo/RT postoperatively
- Metastatic disease median survival < 1 yr

Colorectal Cancer: Screening

- Despite evidence, screening rates still low
  - National Health Interview Surveys of subjects 50 and older and no history of colorectal cancer
    - 32% of men and 30% of women reported having a colonoscopy
    - 16% of men and 15% of women reported FOBT
    - 8% men and 6% of women had sigmoidoscopy
  - Age dependence
    - Age greater than 65 ~ 50% had any screening
    - Age 50-64 ~ 30-40% had any screening
  - Increased use since 2000 due to colonoscopy

Colorectal Cancer: 5 yr Survival by Stage

<table>
<thead>
<tr>
<th>Stage</th>
<th>Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&gt; 90%</td>
</tr>
<tr>
<td>II</td>
<td>70-85%</td>
</tr>
<tr>
<td>III</td>
<td>30-70%</td>
</tr>
<tr>
<td>IV</td>
<td>5-8%</td>
</tr>
</tbody>
</table>

Colorectal Cancer: Chemotherapy

5 yr overall survival for stage III colon cancer

<table>
<thead>
<tr>
<th>Stage</th>
<th>surgery only</th>
<th>surgery w/chemo</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>52%</td>
<td>71%</td>
</tr>
<tr>
<td>IIIB</td>
<td>37%</td>
<td>51%</td>
</tr>
<tr>
<td>IIIC</td>
<td>21%</td>
<td>32%</td>
</tr>
</tbody>
</table>

Take Home Points of Colorectal Cancer
• Disease common – various risk factors that are reversible
• 80% patients without detectable mets at diagnosis
• Treatment depends on stage of disease – surgery is considered in all patients
• Stage III colon cancer → adjuvant chemo
  Stage II and III rectal → neoadj chemoRT or post op chemoRT and chemo adjuvant either way
  Stage II colon → ? Chemo adjuvant ?

Lung Cancer

Lung Cancer Rates - 2008
• 85% of Patients Developing Lung Cancer Will Die from Their Disease
• 71,030 Women and 90,810 Men Projected to Die from Lung Cancer in 2008
• The Number of Men Dying from Lung Cancer is Declining While the Number of Women is Stabilizing
• 29% of all cancer deaths, more than colon, breast and prostate combined
• More than 400,000 Americans with lung cancer diagnosis are still alive

National Lung Screening Trial
• Randomization and Screening

<table>
<thead>
<tr>
<th></th>
<th>LD-CT</th>
<th>CXR</th>
<th>Stats</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Cancer cases per 100,000 person-years</td>
<td>645</td>
<td>572</td>
<td>RR 1.13, 95% CI 1.03-1.23</td>
</tr>
<tr>
<td>Lung cancer deaths per 100,000 person years</td>
<td>247</td>
<td>309</td>
<td>Relative reduction of 20% (95% CI 6.8 - 26.7, p = 0.004)</td>
</tr>
<tr>
<td>Deaths from any cause, N</td>
<td>1877</td>
<td>2000</td>
<td>Relative reduction of 8.7% (95% CI 1.2-13.6, p = 0.02)</td>
</tr>
</tbody>
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National Lung Screening Trial

Summary on Screening
• NLST is the first study to show an impact of screening on lung cancer survival
• Benefit was limited to a narrow study population
• The extent of benefit is reasonably similar to other approved cancer screening studies (e.g., mammography)
• Toxicity, costs, and logistics of implementation need to be addressed
NSCLC: Diagnosis by Stage

Approximately 138,000 New NSCLC cases/year
- 34,000 Stage I
- 12,000 Stage II
- 38,000 Stage III
- 54,000 Stage IV

Source: Plan A Cancer Populations

Survival of Pts with Surgically Treated NSLC

Four Different Combinations for Advanced NSCLC

- Likelihood of response related to mutation in the EGFR kinase region
- Likelihood of mutation related to being:
  - A non-smoker
  - A woman
  - Oriental

Tyrosine Kinase Inhibitors

Gefitinib or Carboplatin-Paclitaxel in Advanced Adenocarcinoma of the Lung

- 1200 patients who were non-smokers or former light smokers with advanced adenocarcinoma of the lung randomized to:
  - Gefitinib 250 mg/day
  - Carboplatin/Paclitaxel

- Primary end point progression-free survival
- Performed in Asia

Mok, NEJM 2009:361:1
Alk Inhibition in NSCLC

- 1500 pts screened by FISH, and 82 found to have Alk mutations (5%)

- Pt characteristics
  - 96% adenocarcinomas
  - 76% non-smokers, and 18% light smokers
  - 35% Asian

- Crizotinib is an oral ATP-selective competitive inhibitor of Alk and MET tyrosine kinases


Response to ALK Inhibition with Crizotinib

Prostate Cancer

PLCO ERSPC

<table>
<thead>
<tr>
<th></th>
<th>PLCO</th>
<th>ERSPC</th>
</tr>
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<tbody>
<tr>
<td>N</td>
<td>76,693</td>
<td>182,000</td>
</tr>
<tr>
<td>Age</td>
<td>55-74 yrs</td>
<td>50-74 yrs</td>
</tr>
<tr>
<td>Sites</td>
<td>10 US sites</td>
<td>7 Euro nations</td>
</tr>
<tr>
<td>% Screened</td>
<td>85% (52% controls)</td>
<td>82%</td>
</tr>
<tr>
<td>Median f/u</td>
<td>7 yrs</td>
<td>9 yrs</td>
</tr>
<tr>
<td>Cancer detection rates</td>
<td>7.4 vs 6.0%</td>
<td>8.2% vs 4.8%</td>
</tr>
<tr>
<td>Rate ratio death</td>
<td>1.13 (p=NS)</td>
<td>0.80 (p=0.04)</td>
</tr>
</tbody>
</table>


PLCO Screening Study

Cancer Incidence Cancer Death


European Randomized Screening for Prostate Cancer (ERSPC)

• In order to prevent a single prostate cancer death over 10 yrs:
  • You need to screen 1410 men
  • Of those, you need to treat 48 patients who are diagnosed with prostate cancer
  • Is this worth the morbidity and cost?

Conclusions of Randomized Screening Studies in 2009

• 2 large randomized trials
• Relatively short follow up
• Significant contamination in control arm
• Modest survival benefit to screening
• Need to consider patient age, relative risks and benefits of screening
• Consider active surveillance more often once diagnosis is made

Screening Recommendations: ACS, AUA

• DRE and PSA in men > 50 years old
• High risk men (AA and +FH)
  • > 40-45 years old
• Frequency? Annually
• End screening? <10 year life expectancy
  • Very difficult for patients to accept
  • Recent USPHS Task Force recommended stopping screening age > 75 yrs

Summary

• PSA and DRE are standard screening tools, though randomized data are lacking for definite evidence of benefit
• PSA screening results in earlier diagnosis
• Tools such as % free PSA and PSA velocity can improve accuracy of diagnosing cancer
• However, there may be no true “PSA cutoff” separating cancer from no cancer

Treatment Options

• Watchful waiting
• Radical prostatectomy
  • Open vs laparoscopic vs robotic
  • Retropubic vs perineal
• External beam radiotherapy
  • 3D conformal
  • IMRT
• Seed implants (brachytherapy)
• Cryosurgery
• Androgen deprivation therapy (ADT)

Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer

Anna Bill-Arnes, M.D., Lars H"{o}glund, M.D., Ph.D., Per Karlstrom, M.D., Ph.D., Hans Fl"{o}tting, M.D., Ph.D., J"{o}rn R"{o}nstedt, M.D., Ph.D., Anders J"{o}f"{o}r, M.D., Ph.D., and on behalf of the Scandinavian Prostate Cancer Group Study No. 4

Breast Cancer is More than 1 Disease

**Old System**
- Pre and Post-menopausal
- Node negative and node positive
- ER positive and negative

**New System**
- Estrogen receptor positive – HER2 negative
- Estrogen receptor positive – HER2 positive
- Estrogen receptor negative - HER2 positive
- Triple negative (basaloid)

**Breast Cancer**

**Cancer Specific Survival**

Cancer-specific survival graph with RR = 0.56, p=0.01

**Metastatic Breast Cancer**

**Treatment Decision Tree**

- **ER +, HER2 -**
  - Hormonal Rx
  - Chemotherapy +

- **ER +, HER2 +**
  - Hormonal Rx +
  - Trastuzumab
  - Chemotherapy +

- **ER -, HER2 +**
  - Chemotherapy +

- **ER -, HER2 -**
  - Chemotherapy +

**Standard Chemotherapy for Patients with Metastatic Breast Cancer - CALGB Trials**

Median Survival = 22 mo

**Trastuzumab and Chemotherapy**

- Metastatic Disease
  - Chemotherapy Alone
  - Chemotherapy + H*

**Berry, JCO 2002;20:743**

**Slamon, NEJM 2001;344:783**
Trastuzumab and Chemotherapy

Slamon, NEJM 2001;344:783

NA Intergroup Adjuvant Trial N9831

AC x 4 q 3 wks
2700 pts

Pacitaxel q wk x 12
Pacitaxel q wk x 12
Pacitaxel q wk x 12
Trastuzumab x 52
Trastuzumab x 40

Perez, NEJM, 2005

Adjuvant AC-T With and Without Trastuzumab: Combined Analysis of NASBP B-31 and N9831

Perez, NEJM, 2005

50% Reduction in Recurrence

Lapatinib is an oral small molecule inhibitor of HER2 and Epidermal Growth Factor Receptor (EGFR)

Lapatinib plus Capecitabine for HER2 Positive Metastatic Breast Cancer

Pts previous treated with Chemotherapy and Trastuzumab

Capecitabine + Lapatinib

Geyer, NEJM 2006;355:2733

Geyer, NEJM 2006;355:2733
**Bevacizumab** is a humanized monoclonal antibody directed against Vascular Endothelial Growth Factor Receptor (VEGF)

- Primary toxicities include
  - Hypertension
  - Proteinuria
  - Wound healing

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The Addition of Bevacizumab (anti-VEGF Antibody) to Paclitaxel Improves Progression-Free but not Overall Survival

Pts with previously untreated Metastatic breast Cancer Randomized to:

- Paclitaxel
- Paclitaxel + Bevacizumab

Miller, ECOG, NEJM 2007;357:2666

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The Addition of Bevacizumab to Paclitaxel Improves Progression-Free but not Overall Survival

Miller, ECOG, NEJM 2007;357:2666

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Thank You