HETEROGENEITY OF BREAST CANCER
KUWAIT 2016

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Outline

• Genomics revolution  
  – How it relates to breast cancer
• Heterogeneity of breast cancer
• Radiomics/Radiogenomics
• Theories of metastatic disease
• Future of screening?
Cancer 1880’s

- Cancer thought to be contagious
- Many hospitals did not want to treat cancer patients
- Round rooms to combat infection
1893 – William B. Coley appointed attending surgeon at MSKCC
- Developed early form of **immunotherapy**
- Treated sarcomas with toxins of bacterial skin infection (Coley’s toxin)
  - induce body’s immune system to target and destroy tumors
“Tonight, I’m launching a new Precision Medicine Initiative to bring us closer to curing diseases like cancer and diabetes – and to give all of us access to the personalized information we need to keep ourselves and families healthier”
**Precision Medicine**

- Every person has a unique genome
- Customize care based on genotype/phenotype
- No more trial and error / one size fits all / average patient

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**Percentage of the Patient Population for Which a Particular Drug is Ineffective, on Average**

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anti-Depressants (SSRIs)</td>
<td>38%</td>
</tr>
<tr>
<td>Asthma Drugs</td>
<td>40%</td>
</tr>
<tr>
<td>Diabetes Drugs</td>
<td>43%</td>
</tr>
<tr>
<td>Arthritis Drugs</td>
<td>50%</td>
</tr>
<tr>
<td>Alzheimer’s Drugs</td>
<td>70%</td>
</tr>
<tr>
<td>Cancer Drugs</td>
<td>75%</td>
</tr>
</tbody>
</table>
Human Genome Project

- Complete DNA sequence 2003
  - $0.5 - 1 billion
  - “Reference Genome”
- Current pricing 2016
  - < $1000
Tyrosine Kinase inhibitors

- Tyrosine kinase (TK) - proteins and enzymes that are involved with cell growth and proliferation
- In cancer cells TK activity is greatly increased – uncontrolled growth
- Imatinib (Gleevec) 2005
  - Chronic myelogenous leukemia (CML) was one of the more fatal cancers
  - after 60 months of Gleevec 98% of patients had complete hematologic response
EGFR-based Therapy for Metastatic Colorectal Cancer

- Responders (15%)
- KRAS (35%-45%)
- BRAF (5%-10%)
- PIK3CA and/or PTEN (15%-20%)
- KRAS/PIK3CA/PTEN
- BRAF/PIK3CA/PTEN
- Nonresponders (20%-25%)
Multiple actionable genomic alterations in breast cancer

Therapy targeting gene or pathway in development or approved by FDA
ctDNA in blood highly correlates with tumor tissue genetic abnormalities

- ctDNA panel
  - 504 solid tumor relevant genes
ctDNA for early detection

ctDNA from tumor tissue is released through secretion, necrosis and mostly apoptosis
Cell-free DNA (cf-DNA)
Circulating tumor DNA (ctDNA)
Circulating tumor cells (CTCs)
Exosomes
Micro-RNA

**Standard Biopsy**
- Time-Intensive Procedure
- Localized Sampling of Tissue
- Not Easily Obtained
- Some Pain/Risk
- Invasive

**Liquid Biopsy**
- Quick
- Comprehensive Tissue Profile
- Easily Obtained
- Minimal Pain/Risk
- Minimally Invasive

**Molecular assays:**
- Early detection
- Monitoring
- Detection of resistance mutations
Breast Cancer is heterogeneous
Every breast cancer is different

- Basal-like
- HER-2
- “Normal”
- Luminal B
- Luminal A

Sorlie T, PNAS 2001;98:10869
Comprehensive molecular portraits of human breast tumours

The Cancer Genome Atlas Network*

Takeaway:

1. Confirmed 3 basic subtypes ER+, HER 2+, TN
2. Mutations more in luminal A and luminal B tumors
3. Mutation lowest luminal A & highest in basal-like &HER2E subtypes
4. Most common driver mutations TP53, PIK3CA, GATA3
5. Basal subtype similar to Serous Ovarian Cancer
Breast cancer - multiple diseases with different outcomes & imaging appearance

- **ER + (70%)**
  - 2 types
    - Luminal A – good prognosis, chemoresistant, endocrine sensitive
    - Luminal B – poor prognosis, relatively chemoresistant, endocrine less sensitive
  - Older patients, grade III/III
  - Least likely to recur

- **HER 2 + (15%)**
  - More likely multifocal or multicentric

- **Triple Negative (15%)**
  - Least likely to have nodal involvement
  - Respond well to PARP inhibitors and platinum Cx
Most breast cancers have multiple driver mutations

Intra-tumor Heterogeneity (ITH)

WGS & targeted sequencing

- 40 different cancer genes potential driver mutations
  - 28% had a single driver mutation
  - 72% had multiple (some as many as 6)

- PIK3CA, TP53, PTEN, BRCA2 and MYC

Yates LR et al Nat Med 2015
ITH contributes to resistance & heterogeneous metastases

- Resistance to treatment
  - Tumor sampled before NAC & after NAC
  - Tumor evolution 2° continuous acquisition of mutations and clonal expansion
  - Making treatment decisions based on inadequate information
    - Subclones
    - 24% HER2 + primary tumor has HER2 – metastases

Niikura N et al. JCO 2012
Yates LR et al Nat Med 2015
**89Zr trastuzumab - unsuspected HER2-positive metastases HER2-negative primary**

**Primary breast CA**  
HER2 1+ (negative)

**Zr-trastuzumab PET/CT demonstrates avid Supraclavicular and thoracic nodes**

**Metastasis - Supraclavicular node**  
HER2 3+ (positive)

**Following HER2-targeted therapy, nodes resolve.**

Courtesy Gary Ulaner MD PhD
Emergence of Radiomics

- Recognition of Intratumoral genetic heterogeneity
  - major cause of therapy resistance & recurrence
- Explosion of cancer genetics

Advancing Precision & Patient Centered Medicine
Images aren’t pictures – they’re data

• High-throughput extraction of large amounts of data from images
• Radiologists identify the volumes & areas of interest to be segmented
• Computers then extract hundreds of descriptive & quantitative features
• Features combined with medical & genomic data to create a comprehensive database
How do we do Radiogenomics?

- Combine morphologic/functional information from imaging (imaging biomarkers) with genomic/proteomic data
  - Look for statistically significant correlations
- MRI/CT/PET mostly used
- Imaging features on MRI/CT/PET
- Genomics of disease
  - Gene expression DNA microarrays
  - miRNA sequencing
  - DNA methylation arrays
  - Single-nucleotide polymorphism (SNP) arrays
  - Exome sequencing
  - Reverse phase protein arrays
How will we use Radiogenomics

Five fields to propel global economy next 20 years
1. Genomics
2. Methods of analyzing massive amounts of information
3. Robotics
4. Digital currencies
5. Cybersecurity and big data

Alec Ross 2016
Metastatic disease

• ~10% metastatic at initial diagnosis
• 25% early stage develops metastatic
  – Early detection does not guarantee a cure
• Metastases occurs up to 20 years after original diagnosis
• Metastatic breast cancer - 40,000 deaths annually in U.S.
Cost of Treatment by stage

Table 5: Average 12-Month per-Patient Allowed Costs, by Stage

<table>
<thead>
<tr>
<th>Disease stage</th>
<th>Patients at index diagnosis date, N</th>
<th>Average per-patient costs in initial 12 months, $</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2300</td>
<td>60,637</td>
</tr>
<tr>
<td>I/II</td>
<td>4425</td>
<td>82,121</td>
</tr>
<tr>
<td>III</td>
<td>1134</td>
<td>129,387</td>
</tr>
<tr>
<td>IV</td>
<td>501</td>
<td>134,682</td>
</tr>
<tr>
<td>All patients</td>
<td>8360</td>
<td>85,772</td>
</tr>
</tbody>
</table>

Source: Milliman’s Analysis of Truven MarketScan commercial claims database for

Moral and economic imperative to try to find early stage disease
Mammography works for most women
But not all

- Extreme dense tissue
  - 17X more likely interval cancer than fatty
  - Cancer in extremely dense breasts
    - Larger, higher stage (node positive)
    - More aggressive (ER-)

DBT and US incrementally improve diagnosis
May not be enough to reduce deaths

- 10% deaths - interval cancers metastatic at diagnosis
- 20% deaths – screen detected cancers already metastatic at diagnosis

Bertrand KA et al Breast Cancer Res 2013
Chiu SY et al Cancer Epid Biomark & Prev 2010
Arora et al Ann Surg Oncol 2010
Boyd NF et al NEJM 2007
Gierach GL et al JNCI 2012
Kerlikowsk K et al Ann Intern Med 2015
Theories of metastases

Halsted paradigm

- Cancers arise at single location & grow
  - **Sequential unidirectional process**
- When large enough metastasize to lymph nodes then body
- Cancer cells always pass through the lymph nodes prior to metastatic spread
  - Radical surgery required to remove the entire breast, underlying chest muscle & LN’s to halt metastasis
Bernie Fisher paradigm
Ended 75 y of Halsted mastectomy

• **Breast cancer is systemic disease** where malignant cells disseminate through the body before diagnosis
  – radical mastectomies unlikely to improve overall survival
• Metastases not determined by anatomy
  – influenced by biologic activity of both tumor & host
• Breast conserving therapy replaced mastectomy
Biology trumps anatomy

- Metastatic risk predicted by gene expression of primary tumor
- Metastatic disease can occur at any time regardless of size

De Snoo F et al Gene expression profiling: Decoding breast cancer
Sam Hellman paradigm

Fast & slow cancers are the cancers we need to detect on screening
In order to save ALL lives at what point would optimal detection be?

Adapted from Naviscan

- Molecular imaging
- ctDNA
- MRI
- CEDM
- Mammography
- DBT
MRI is the most sensitive test for breast cancer screening
Can CEDM achieve results of MRI for screening?
100 years later.... Immunotherapy recognized as breakout therapy

Immunotherapy recognizes the systemic nature of cancer
Single-Dose Ipilimumab, Nivolumab and Cryoablation

McArthur H et al MSKCC
Immune stimulation with cryoablation protects from tumor re-challenge

Tumor Free Survival

- No Treatment
- Anti-CTLA-4 Only
- Cryo+IgG
- Cryo+Anti-CTLA-4

Rethinking breast cancer screening for the future

Will this be the future?
Liquid biopsy first test for screening
Positive results followed by imaging

Once cancer diagnosed
Radiogenomic profiling for predictive/prognostic markers
Treatment by perc ablation + immune boosting

CEDM—not enough data on screening yet

**Imaging will play an essential role in screening/diagnosis/treatment**
Precision Medicine at work

Patient

Pathology Image Features

Diagnostic Image Features

Genomic Data

Statistical Model

Outcome Variables

Answer
Thanks to