Post-Treatment Surveillance in Breast Cancer

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Setting the Cancer CER Agenda

- AHRQ Developing Evidence to Inform Decisions about Effectiveness (DEcIDE) Network
  - 4 major disease areas: cancer, diabetes, cardiovascular, mental health
- One of the first federally-funded initiatives to operationalize stakeholder engagement
  - Coordinating Center for DEcIDE Cancer Consortium
  - Engage the Alliance for Stakeholder Activities
Types of Stakeholders

- Patients and Public
- Providers
- Payers
- Policymakers
- Purchasers
- Product Makers
- Principal Investigators

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Topic Identification Process

- **Brainstorming – Generate Many Topics**
  - Provider Stakeholders
  - Policy/Payer Stakeholders
  - Patient Informants

- **Discuss, Prioritize, Operationalize**
  - All Stakeholders

- **Develop Draft Concepts**
  - DEcIDE Investigators

- **Discuss, Prioritize, Operationalize**
  - All Stakeholders

- **Identify Highest Priority Topic**

- **>15 topics**

- **6-12 topics**

- **6 topics**

- **1-6 topics**

- **1 topic**
Post-Treatment Surveillance

- Cuts across cancer sites
- Lack of data = variations
- Guidelines on expert consensus
- Not tailored to individuals
- Prospective RCT is not feasible at this time
"Compare the effectiveness of imaging technologies in diagnosing, staging and monitoring patients with cancer, including PET, MRI, CT."

"A 48 yo woman has recently completed radiation for a small growth in her breast. Her doctors see no signs of disease, but recommend that she continue to be monitored for potential recurrence. What is her optimal management strategy?"
PCORI Post-Active Treatment Surveillance Projects

1. Post-treatment surveillance in breast cancer: Bringing CER to the Alliance (Greenberg)
2. Patient centered, risk stratified surveillance after curative resection of colorectal cancer (Chang)
3. Improving the effectiveness of routine surveillance following lung cancer resection (Kozower)
4. Optimizing the effectiveness of routine post-treatment surveillance in prostate cancer survivors (Chen)
5. Comparative effectiveness of surveillance imaging modalities in breast cancer survivors (Wernli)
Post-Treatment Surveillance

• Improved screening and survival have led to large survivorship population

• Breast
  – 93% Stage II & 72% Stage III patients survive 5 yrs.
  – 3 million patients requiring ongoing surveillance
Goals of Surveillance Care

- Detection of locoregional recurrence
- Detection of distant metastases
- Monitoring of treatment toxicities
- Management of anxiety and other survivorship issues
- Assure continuation of primary care or other health care
### Surveillance Guidelines-Breast

<table>
<thead>
<tr>
<th>Routine Clinic Visit</th>
<th>Mammogram</th>
<th>Breast MRI</th>
<th>Bone Scans</th>
<th>X-Rays, CT / PET Scans</th>
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</thead>
<tbody>
<tr>
<td><strong>NCCN</strong></td>
<td>Interval hx and physical exam q 4-6m for 5 yrs then q12 m</td>
<td>Annual</td>
<td>Not recommended in asymptomatic patient</td>
<td>Not recommended in asymptomatic patient</td>
</tr>
</tbody>
</table>
| **ASCO** | - 1<sup>st</sup> post-tx mammo 1 yr after initial mammo that leads to dx, but no earlier than 6 m after def rad therapy  
- Subsequent mammos as indicated for surveillance  
- Mammo yearly if findings stable post-therapy | Not recommended for routine surveillance | Not recommended for routine surveillance | Not recommended for routine surveillance |
Evidence Base

• 2005 Cochrane Review
  – 4 well-designed RCTs with 3,055 patients
  – Intensive testing v. annual exam + mammogram
  – No survival advantage or difference in QOL after 10 years of follow up

• 2016 Cochrane Review
  – No significant changes but conclusion includes
    • Caution in interpretation given limitations in data
    • Call for randomized trials
What’s the Problem?

- Included all molecular subtypes without subset analysis based on known variation in risk and pattern of recurrence
- Did not include modern advanced imaging
- Does not account for major advances in ability to treat recurrence
- No evidence re: frequency of clinic visits
Major Practice Variation

- High rates of healthcare utilization
  - 30 episodes per survivor in first year
- Overuse of imaging for metastatic disease
- Underuse of mammograms
- Reflect clinician uncertainty
  - evaluation of strength of scientific evidence?
  - tailoring practice based on patient risk?
Variation in Care - Breast

- **Underuse**
  - Only 60-70% receive mammograms long term

- **Overuse**
  - 50% receive imaging for metastatic disease

Half of women had greater than recommended surveillance imaging for metastatic disease

Grunfield et al, 2010. JCO
Don't perform surveillance testing (biomarkers) or imaging (PET, CT, and radionuclide bone scans) for asymptomatic individuals who have been treated for breast cancer with curative intent.
Gap in Literature

• Previous studies used admin. data
  – Unable to discriminate imaging prompted by patient sign/symptom from asymptomatic surveillance

• Without indication - impossible to distinguish overuse from appropriate, guideline-concordant imaging
Breast Committee Poll
July 2012

- Medium to high levels of uncertainty around post-treatment surveillance
- 60% of providers report never ordering advanced imaging for surveillance

Degree of Provider Perceived Uncertainty regarding Post-Treatment Surveillance

Percentage of Patients for whom a Provider Orders Advanced Imaging for Surveillance
Aim 1

- Determine the risk and patterns of recurrence and treatment toxicities according to tumor characteristics, treatment modalities, and other patient characteristics.

Aim 2

- Evaluate the current utilization and effectiveness of routine surveillance imaging to detect recurrence following active treatment for Stage II or III breast cancer.

Aim 3

- Engage stakeholders to develop a patient-centered, risk-based tailored approach to post-treatment surveillance and identify the highest priority, feasible comparators for prospective randomized trials.
Study Deliverables

- Evidence to inform risk-stratified surveillance strategy
- Evidence-based approach to design of prospective studies
- Reusable de-identified data sources
  - 20,000 participants in prior local-regional trials
  - 12,000 NCDB patients with detailed imaging and recurrence
- Solidify partnership between CoC and Alliance that will enable future CCDR including implementation and other prospective intervention studies
Aim 1

Treatment Modality

Surveillance Start

Tumor Characteristics & Treatment Modality

Competing Risks (Comorbidity & Age)

Recurrence

Loco-regional recur

Distant recur

Treatment Toxicity

Pneumonitis

Cardiac tox

Lymphedema

Resolution/Stable

Treatment & Symptom Management

Progression

Disease Progression

Stage at Detection & Available Treatment Options

Disease Free/Stable

Death

Aim 2

Figure 5. A comprehensive model for disease progression, side effects, and death
CANCER FOLLOW-UP

Clinic Visits - 1-4X/year
- Members of the treatment team
- Assess adherence to medications, side effects of treatment, recurrence

Surveillance Imaging
- annual mammogram
- MRI if high risk/BRCA
- No systemic imaging

Mammo and MRI
- Concordance with guidelines
- Predictors of mammo and MRI use (NCDB, ACS Podium)

Systemic imaging
- Describe current use for surveillance (NCDB, Acad Health*)
- Asymptomatic vs symptomatic recurrence detection & mortality (NCDB, ASCO*)

Substantial variation in follow-up (ASO 2013, SEER-Medicare)

Patient factors
- Tumor characteristics
- Treatment received (ASO 2013, seer-Medicare; ASO 2015 onc qual)

Provider factors
- Who participates in follow-up (ASO 2013, seer-Medicare)
- Who participates is influence by clinical and non-clinical factors (SSO 2013)

Alliance Data (Aim 1- toxicity and recurrence)
- generate “risk” period based on tumor characteristics and treatment received

Suggests tailoring is happening

Opportunity to provide guidance on who

Providers have rationale for who they follow-up
- not concordant with patient view (pt. qual)
- Not concordant with data (NCDB, ASBS 2016*)

Opportunity to provide guidance on who

Deliverable #1: Tool that provider can use to inform tailoring of visit frequency +/- guidance on who should follow

Deliverable #2: Identification of a subgroup for whom there may be benefit to early detection of systemic disease (target for future effectiveness study)

Rationale:
- Increase concordance with current guidelines

Aim 2

Rationale:
- Prior studies describe overuse
- Guidelines based on old RCT using outdated imaging and predating new effective treatment

Aim 2

Aim 3

Lab tests (none)
Aim 1
- Determine the risk and patterns of recurrence and treatment toxicities according to tumor characteristics, treatment modalities, and other patient characteristics.

Aim 2
- Evaluate the current utilization and effectiveness of routine surveillance imaging to detect recurrence following active treatment for Stage II or III breast cancer.

Aim 3
- Engage stakeholders to develop a patient-centered, risk-based tailored approach to post-treatment surveillance and identify the highest priority, feasible comparators for prospective randomized trials.
Alliance Study

• 17 trials of loco-regional breast cancer conducted from 1984-2012 (n~23,000)

• Histological diagnosis of adenocarcinoma regardless of phenotypic characteristics (Stage I-III)

• Evaluate risk & patterns of local and distant recurrence as well as treatment toxicities (lymphedema; pneumonitis; cardiotoxicity)
  – According to tumor characteristics, treatment modalities, other patient characteristics
Patient Factors

• Patient Demographics
  – Age; BMI; ECOG status

• Tumor Factors
  – Tumor size
  – Nodal status
  – ER/PR
  – HER2neu

• First Course Treatment
  – Surgery type
  – Radiation
  – Chemotherapy
  – Herceptin
  – Endocrine therapy
## Alliance Power Calculation

<table>
<thead>
<tr>
<th>Analysis</th>
<th>N</th>
<th>5 year event rate</th>
<th># of expected events</th>
<th>95% CI Total Width</th>
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<tbody>
<tr>
<td>Alliance Local Recurrence</td>
<td>22,881</td>
<td>7 – 13%</td>
<td>1281 – 2379</td>
<td>2.7 – 2.8%</td>
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<tr>
<td>Alliance Toxicity (Cardiac)</td>
<td>20,957</td>
<td>2 – 6%</td>
<td>335 – 1006</td>
<td>2.9 – 3.0%</td>
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<tr>
<td>Alliance Toxicity (Pneumonitis)</td>
<td>10,373</td>
<td>1 - 15%</td>
<td>74 - 1245</td>
<td>4.0 – 4.3%</td>
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<tr>
<td>Alliance Toxicity (Lymphedema)</td>
<td>13,480</td>
<td>2 – 21%</td>
<td>248 - 2242</td>
<td>3.4 – 3.7%</td>
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Patients with HER2 status available and received modern standard of care

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<th>%</th>
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<td>ER/PR-, HER2-</td>
<td>2370</td>
<td>19.47</td>
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<tr>
<td>ER/PR+, HER2+</td>
<td>1971</td>
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<tr>
<td>ER/PR-, HER2+</td>
<td>1508</td>
<td>12.39</td>
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<td>Condition</td>
<td>Observed Percent</td>
<td>Anticipated Percent on Which Power Calculation Based</td>
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<tr>
<td><strong>Local Recurrence (n=12,173)</strong></td>
<td>Stage I: 2.8%</td>
<td>7-13%*</td>
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<tr>
<td></td>
<td>Stage II: 3.8%</td>
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<td>Stage III: 7.6%</td>
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<tr>
<td><strong>Distant Recurrence (n=12,173)</strong></td>
<td>Stage I: 1.9%</td>
<td>12%</td>
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<td>Stage II: 6.4%</td>
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<td>Stage III: 21.5%</td>
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<td><strong>Cardiac (n=8,736)</strong></td>
<td>Broad</td>
<td>2.0%-6.0%</td>
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<td>Narrow</td>
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<td>5.8%</td>
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<td>2.1%</td>
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<td><strong>Pneumonitis (n=12,173)</strong></td>
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<td>&lt;0.5%</td>
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<tr>
<td><strong>Lymphedema (n=12,173)</strong></td>
<td>Broad</td>
<td>2.3%-20.8%</td>
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<td>14.4%</td>
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<td>11.2%</td>
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* Lower recurrence rate observed in the current investigation is consistent with recent literature (Cossetti 2016, JCO), that suggests targeted treatment of women with HER2 positive cancers has reduced the rate of local recurrence. Event rates exclude events recorded within 3 weeks of trial registration to ensure new onset. Pneumonitis rates restricted to patients who received adjuvant radiation.
Figure 1. Annual hazards of locoregional breast cancer first recurrence by molecular subtype and stage (n=10,357)

* Only one Stage I patient with ER/PR+, HER2+ cancer had a recurrence within 5 years of trial registration, the timing of which was unknown.
<table>
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<tr>
<th></th>
<th>Coefficient (coef)</th>
<th>Standard Error</th>
<th>Hazard Ratio</th>
<th>Z</th>
<th>p-value</th>
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<td>Positive Node</td>
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<td>2-5 cm</td>
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<td>45-64</td>
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<td>0.63</td>
<td>-4.11</td>
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</table>
Study Finding #1

- Local & distant recurrence lower than anticipated
  - 5-year recurrence <5% for Stage I and <11% for Stage II
- Likelihood and timing of recurrence vary by molecular subtype for stage III
  - ER+/HER2+ have best outcomes at 5 years
  - Triple negative 40% recurrence (35% by year 3)
  - ER+/HER2- and ER-/HER2+ have similar rates
  - ER+ risk remains after 5 years
- Can inform surveillance strategy and discussions on prognosis
Aim 1
- Determine the risk and patterns of recurrence and treatment toxicities according to tumor characteristics, treatment modalities, and other patient characteristics.

Aim 2
- Evaluate the current utilization and effectiveness of routine surveillance imaging to detect recurrence following active treatment for Stage II or III breast cancer.

Aim 3
- Engage stakeholders to develop a patient-centered, risk-based tailored approach to post-treatment surveillance and identify the highest priority, feasible comparators for prospective randomized trials.
Study Aim

• Evaluate the current utilization of surveillance imaging considering intent of scan
• Assess the effectiveness of routine surveillance versus symptom-based imaging on the improved detection of distant recurrence and survival considering subtypes
• Evaluate whether sufficient preliminary evidence to warrant a pragmatic trial
NCDB Special Study

• Commission on Cancer National Cancer Data Base
  – National oncology outcomes database for accredited facilities
  – 70% of diagnosed cancer cases in U.S.
  – Participation in Special Studies required for accreditation

• NCDB Special Study
  – Primary data collection using secure web platform
  – Registrars abstract non-routine elements (intention of scan; recurrence; comorbidity) for period of 5 years
  – QI project to test the feasibility of improving recurrence capture for FORDS Manual Revision
Figure 3: Geographic distribution of the 1,500 hospitals reporting to the NCDB. Panel 2 presents the proportion of CoC hospitals by census region.
Figure 2: American College of Surgeons Cancer Programs Categories of Accreditation
Identification of Cohort

- Stage II-III breast cancer in 2006-2007
  - Maximizes likelihood of systemic imaging
  - Maximizes likelihood of observing events

- Stage-stratified random sample
  - 10 patients selected at random per facility
    (7 stage II; 3 stage III)
Sample Flow Chart

1,231 eligible facilities; 11,478 sampled patients

Total: Sample:
1,217 facilities
11,360 patients

99% of facilities participated in study

Final Sample
N=10,853

Missing def surgery date; Def surgery >365 days from diagnosis; Recurrence or new primary or death < start of follow-up period, abstraction start date within 180 days of diagnosis (n=507)
Data Collection

• Trained registrars supplemented NCDB data elements with imaging study, biopsy & recurrence information
  – Also updated vital status, comorbidities, and first course treatment fields as needed

• Secure, web-based data collection portal

• Quality assurance
  – Detailed abstraction instructions
  – Pilot in 18 facilities
  – Weekly webinars
  – Validation sample
Recurrence Abstraction

- Recurrence defined as: identification of recurrent tumor >90 days after first surgery
- Suggested high yield locations in medical records
  - Pathology reports
  - Radiology/imaging reports
  - Notes from clinic/consult visits (PCP, medical oncologist, radiation oncologist, surgical oncologist, other provider)
- Hierarchy for determining date of recurrence
  1. Pathology date
  2. Date of imaging study used to confirm suspected recurrence
  3. Date of clinical diagnosis
Predictor Variables

• Sociodemographic & Health
  – Age, Race, Hispanic Ethnicity, Insurance, Urban/Rural, % in zip with < HS degree
  – Comorbidity Count (Charlson/Deyo)

• Tumor-related & Treatment
  – Tumor Size, Nodal Status, Grade, Histology
  – ER/PR, HER2 status group
  – Surgery Type, Radiation, Chemotherapy
Imaging Data Elements

• Date, type, intent, and result of scans
• Type: Chest CT; Abdomen/Pelvis CT/MRI; Head CT/MRI; PET or PET/CT (any location); Bone Scan
• Intent:
  – Surveillance imaging in absence of new sign/symptom
  – Follow-up for new sign/symptom
  – Follow-up for suspicious finding on other imaging
  – Imaging performed as part of staging work up
Advanced Imaging for Surveillance

• Imaging during 4 year follow-up period
  – Includes bone scans, “body” imaging (PET/CT; Abd/Pelvis CT/MRI), brain CT/MRI
  – Cancer-related imaging (1+ scans)
  – Surveillance imaging (1+ or 2+ scans)

• Determining Intent of Imaging:

<table>
<thead>
<tr>
<th>Scan Indication</th>
<th>Cancer-Related</th>
<th>Surveillance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surveillance imaging in absence of new sign or symptom</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Follow-up for new sign/symptom</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Follow-up for suspicious finding on other imaging</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Imaging performed as part of staging work-up for newly detected malignancy</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Not cancer related</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Primary Explanatory Variable

- Asymptomatic Detection of Distant Recurrence (yes/no)

<table>
<thead>
<tr>
<th>How Recurrences First Detected</th>
<th>Signs/ Symptoms</th>
<th>Asymptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient detected sign or symptom</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Physician detected during scheduled, routine visit</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Asymptomatic imaging study for routine cancer follow-up</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Distant recurrence detected as part of work-up for a local-regional recurrence or new primary</td>
<td>X</td>
<td></td>
</tr>
<tr>
<td>Incidental finding on unrelated other imaging</td>
<td></td>
<td>X</td>
</tr>
<tr>
<td>Unable to determine</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Data Quality

• Demonstrating availability of medical records at outside facilities
  – Mammography use in study consistent with national estimates

• Reliability of abstraction
  – Distant Recurrence: (95% agreement: Gwet AC2: 0.94)
  – How distant recurrences first detected (88% agreement; Gwet’s AC2: 0.74)
Data Quality

• 91% ER/PR + received endocrine therapy

• Patients receiving XRT
  – BCT: 89%
  – Mastectomy: 47%

• Tumor Size
  – Stage II: (0-2cm=31%; 2-5cm=64%, >5cm=4%)
  – Stage III: (0-2cm=22%; 2-5cm=47%, >5cm=31%)
Statistical Analysis

- Propensity score weights constructed based on patients likelihood of getting advanced imaging for surveillance in first 3 years
  - Separate propensity models estimated for each of the 3 molecular subtype risk groups (ER/PR+, HER2-; Triple Negative; HER2+)

- Multivariable cox proportional hazards model
  - Models estimated separately for each molecular subtype group
Descriptive Characteristics

- Age ≥ 70: 70
- Medicaid: 10
- 1+ Chronic Cond: 20
- BCS + Radiation: 30
- Chemo: 40
- Comm Cancer Prg: 50
- ER or PR +, Her2-: 60
- ER and PR -, Her2+: 70
- ER or PR +, Her2+: 80
- ER and PR -, Her2+: 0
- Unknown ER/PR/HER2: 0
Results

Sociodemographic Factors

• After adjustment, no significant relation between age, race, Hispanic ethnicity, percent in zip code < HS degree, insurance status, or comorbidities on surv imaging

• Patients in urban areas more likely to receive one or more surveillance scans (OR=1.50, 95% CI: 1.11=2.04)
Results

Tumor Characteristics

<2 cm
2-5 cm
≥5 cm

Negative
1-3 Positive
4+ Positive
Uncertain, Unsampled

ER or PR Pos, Her2neu Neg
ER and PR Pos, Her2neu Neg
ER or PR Pos, Her2neu Pos
ER and PR Pos, Her2neu Pos
Results
Treatment Characteristics

No Chemo
Chemo
BCS + Radiation
BCS Only
Mastectomy + Radiation
Mastectomy Only

Odds Ratio
Advanced Imaging by Intent of Scan (n=10,853)

- No scan: 52.3%
- Scanned for non-surveillance reasons only: 18.0%
- Received 1 or more scans: 47.7%
  - Received at least 1 surveillance scan: 29.0%
  - Received 2 or more surveillance scans: 12.0%
  - Received 1 surveillance scan: 17.7%
  - Received 2 or more surveillance scans: 12.0%
Advanced Imaging by Intent of Scan

Percent of patients with advanced imaging by intent of scan (n=10,948)

<table>
<thead>
<tr>
<th></th>
<th>Percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>1+ Cancer-Related Scans</td>
<td>47.7</td>
</tr>
<tr>
<td>1+ Surveillance Scans</td>
<td>29.7</td>
</tr>
<tr>
<td>2+ Surveillance Scans</td>
<td>12.0</td>
</tr>
<tr>
<td>Intent of Scan</td>
<td>Percent (N=10,853)</td>
</tr>
<tr>
<td>-----------------------------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1+ Cancer-Related Scans</td>
<td>47.7</td>
</tr>
<tr>
<td>1+ Surveillance Scans</td>
<td>29.7</td>
</tr>
<tr>
<td>2+ Surveillance Scans</td>
<td>12.0</td>
</tr>
</tbody>
</table>
Imaging Study Type Combinations

N=3,067 with at least one surveillance bone, body, or brain imaging study
Study Findings #2

- Consistent with prior administrative data studies, half of women with stage II-III breast cancer have cancer-related scans during 5-years surveillance window

- Minority undergo regular asymptomatic surveillance
  - Contrasts with reports of overutilization using administrative data
  - Utilization highest in patients at highest risk of recurrence
  - Choosing Wisely Campaign may not have as much of a direct impact on reducing imaging use as was previously thought
5 Year Recurrence Rates

<table>
<thead>
<tr>
<th></th>
<th>Any Recurrence</th>
<th>New Breast Event †</th>
<th>Distant Recurrence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NCDB</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>10.3%</td>
<td>2.7%</td>
<td>7.6%</td>
</tr>
<tr>
<td>Stage II</td>
<td>7.6%</td>
<td>2.5%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Stage III</td>
<td>16.9%</td>
<td>3.3%</td>
<td>13.6%</td>
</tr>
<tr>
<td><strong>PCORI</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>17.6%</td>
<td>6.3%</td>
<td>13.9%</td>
</tr>
<tr>
<td>Stage II</td>
<td>12.9%</td>
<td>5.3%</td>
<td>9.2%</td>
</tr>
<tr>
<td>Stage III</td>
<td>29.0%</td>
<td>8.7%</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

† New breast events include diagnoses of a locoregional recurrence or new breast primary. In PCORI study both new breast events and distant recurrences were recorded. NCDB includes first recurrence only.

- Published national recurrence estimates: 11-13% for new breast events and distant recurrence for Stage II. (1985-2001)

Brewster 2008, JNCI
Cosetti 2015, JCO
## Local Recurrence after BCS

<table>
<thead>
<tr>
<th></th>
<th>Ipsilateral Breast Event</th>
<th>Contralateral Breast Event</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>% with breast event</strong></td>
<td>4.1% (n=202)</td>
<td>1.7% (n=83)</td>
</tr>
<tr>
<td><strong>Median time to detection</strong></td>
<td>2.6 yr</td>
<td>3.2 yr</td>
</tr>
<tr>
<td><strong>How breast event detected</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Detected by physician</td>
<td>11% (n=22)</td>
<td>10% (n=8)</td>
</tr>
<tr>
<td>Detected by pt</td>
<td>32% (n=64)</td>
<td>22% (n=18)</td>
</tr>
<tr>
<td>Detected on breast imaging (asymptomatic)</td>
<td>43% (n=86)</td>
<td>55% (n=46)</td>
</tr>
<tr>
<td>Incidental on other imaging</td>
<td>2% (n=4)</td>
<td>2% (n=2)</td>
</tr>
<tr>
<td>Other</td>
<td>13% (n=26)</td>
<td>11% (n=9)</td>
</tr>
</tbody>
</table>

- 30/4,988 (0.6%) local recurrences = physician detected
- 132/4,988 (2.3%) local recurrence detected on mammography in absence of symptoms
# Distant Recurrence

<table>
<thead>
<tr>
<th>% with distant recurrence</th>
<th>13.9% (n=1,539)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median time to detection</td>
<td>2.3 yr</td>
</tr>
<tr>
<td>How breast event detected</td>
<td></td>
</tr>
<tr>
<td>Detected by physician</td>
<td>8% (n=131)</td>
</tr>
<tr>
<td>Detected by pt</td>
<td>48% (n=745)</td>
</tr>
<tr>
<td>Detected on surveillance imaging (asymptomatic)</td>
<td>18% (n=273)</td>
</tr>
<tr>
<td>Detected on work-up for local/regional recurrence</td>
<td>11% (n=172)</td>
</tr>
<tr>
<td>Incidental on other imaging</td>
<td>4% (n=65)</td>
</tr>
<tr>
<td>Unable to determine</td>
<td>10% (n=153)</td>
</tr>
</tbody>
</table>

- 131/11,062 (1.1%) physician detected
- 745/11,062 (6.7%) detected by patient
- 273/11,062 (2.5%) detected on asymptomatic imaging
Study Finding #3

- Most recurrences are distant
  - Location determined by receptor status
  - Nearly 20% found on asymptomatic imaging

- Second breast events are rare
  - Risk determined by tumor size, nodal status and ER status
  - Half are detected on mammography and one-third are detected by the patient on BSE
  - Less than 10% of second breast events are detected by the physician = 0.6% of all patients undergoing BCT

- Data to support streamlining follow-up with surgeon and radiation oncologist??
Cohort n=10,853

Surveillance Imaging

- Distant Recurrence
  - No DR

No Surveillance Imaging

- Distant Recurrence
  - No DR

Death
Cohort

- Surveillance Imaging
  - Distant Recurrence
    - No DR
  - Asymptomatic
  - Signs / Symptoms
- No Surveillance Imaging
  - Distant Recurrence
    - No DR

Time 0  Calculation of survival  Death
**Cohort**
- ER/PR+ (n=6370)
- Triple Negative (n=1635)
- HER2 Positive (n=2071)

**Surveillance Imaging**
- No Surveillance Imaging

**Asymptomatic**
- ER/PR+, n=141
- Triple Neg, n=84
- Her2+, n=59

**Signs / Symptoms**
- ER/PR+, n=469
- Triple Neg, n=254
- Her2+, n=213

**Distant Recurrence**
- No DR

**Calculation of survival**

**Time 0**

**Death**

**N=1,220**
Survival Benefit by Method of Detection (n=1,220)

Unadjusted
- ER/PR+ HER2 -
- Triple Negative
- HER2 +

Adjusted/Weighted
- ER/PR+ HER2 -
- Triple Negative
- HER2 +

Hazard Ratio

63%
16%
21%
## Proportion of Patients Surviving by Years from Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>Years from Original Diagnosis</th>
<th></th>
<th></th>
<th>Median Survival (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N</td>
<td>Year 3</td>
<td>Year 4</td>
<td></td>
</tr>
<tr>
<td><strong>Triple Negative Distant Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>84</td>
<td>54% ± 6%</td>
<td>36% ± 6%</td>
<td>39 ± 6</td>
</tr>
<tr>
<td>Signs/Symptoms</td>
<td>254</td>
<td>45% ± 3%</td>
<td>27% ± 3%</td>
<td>34 ± 4</td>
</tr>
<tr>
<td><strong>Her2Neu Positive Distant Recurrence</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>59</td>
<td>85% ± 5%</td>
<td>68% ± 7%</td>
<td>64 ± 14</td>
</tr>
<tr>
<td>Signs/Symptoms</td>
<td>213</td>
<td>68% ± 4%</td>
<td>53% ± 4%</td>
<td>51 ± 7</td>
</tr>
</tbody>
</table>

* Estimates weighted by propensity to receive imaging during first 3 years of follow-up
Study Findings #4

- Women with ER/PR +, HER2neu - tumors, representing 2/3 of women with breast cancer have no potential to benefit from advanced imaging surveillance for metastatic disease.

- The remaining subgroups of patients may benefit from surveillance imaging and a prospective randomized trial is warranted.
Limitations

• Facilities limited to those accredited by CoC
• Not able to directly validate abstraction of scan intent
  – Though assessed reliability – could be function of providers failing to consistently document indication
• 2006-2007 diagnoses (Herceptin not routinely administered)
Sensitivity Analysis

- Removed 360 patients in sign/symptom detected recurrence group who had ever had advanced imaging for surveillance during follow-up
- Triple negative patients: Removed 38 patients from analysis where we could not confirm registrar determination of how recurrences detected with abstracted imaging

- Findings consistent
Aim 1
- Determine the risk and patterns of recurrence and treatment toxicities according to tumor characteristics, treatment modalities, and other patient characteristics.

Aim 2
- Evaluate the current utilization and effectiveness of routine surveillance imaging to detect recurrence following active treatment for Stage II or III breast cancer.

Aim 3
- Engage stakeholders to develop a patient-centered, risk-based tailored approach to post-treatment surveillance and identify the highest priority, feasible comparators for prospective randomized trials.
Stakeholder Engagement

• Engage cancer survivors, providers, and health outcomes researchers in interpreting the results of Aim 1 and 2 to
  1) Develop a patient-centered, risk-based tailored approach to post-treatment surveillance
  2) Identify the highest priority, feasible comparators for prospective randomized trials
Analytic Plan

- Loss functions to model optimal approach to surveillance based on individual risk
  - Incorporate models into decision support tool to facilitate shared decision making
  - Potential to inform more individualized guideline creation

- Value of information analysis will prioritize future prospective trials
Stakeholder Engagement

- **Patient Partners**
  - Patient Advocacy Committee (PAC) of the Alliance
    - Patient advocates as co-investigators
    - Engagement of Committee at Alliance meetings
  - Patient involvement in focus groups and surveys through:
    - Komen Advocates in Science (150 members)
    - Broader group of diverse cancer survivors

- **Providers from Alliance Disease Committees**

- **Formation of Multi-Stakeholder Panel**
  - Patients
  - Surgical, medical, radiation oncologists
  - Academic and community settings
Deliverable #1

DECISION SUPPORT TOOL
Base Inputs

Tumor Characteristics
- ER/PR Status
- HER2 Status
- Tumor Size
- Nodal Status
- Number of nodes
- Grade
- Histology (?)
- Laterality

Treatment
- Surgery
- Chemotherapy
- Radiation
- Biologic Therapy
- Endocrine Therapy

Base Outputs

Risk over time of:
- Toxicity/Adverse events
- Recurrence risk and site
- Mortality

Additional risks of surveillance (routine) imaging
- Additional imaging
- Additional biopsies

Patient-Reported Inputs (Future)
- Preferences for decision-making
- Anxiety/Concern for Recurrence
- Risk Taking/Risk Aversion

Patient-Specific Inputs

Patient Characteristics
- Age
- Comorbidity
- BMI/Obesity
- Geography

Personalized Recommended Surveillance Plan
Multi-Stakeholder Group

• Communicating imaging recommendations
  – Metastatic disease risk
    • “These are the areas of highest risk so this is why we are ordering imaging for x & y...” or “these are outcomes we don’t need to worry as much because of x”
    • “Here is where mets are most likely to happen and here is why detecting it on surveillance does/doesn’t make a difference in outcome”
  – No surveillance imaging
    • “We don’t recommend routine advanced imaging, but here are the symptoms to look for”
Multi-Stakeholder Group

• Provider facing tool to facilitate decision-making about follow-up
• Web-based & easy-to-use interface
• Tailored summary display of key outcome information based on patient and tumor characteristics that could be printed out and given to patient
• Provider and patient will review together in clinic
Use of Tool

• Provider goes to website and enters patient information
• Tool delivers patient-specific tailored risks
• Provider reviews risks and develops evidence-based plan for patient follow-up
• Provider chooses patient-facing display of risks to print and review with patient
• Patient keeps printed summary
Use of the Tool

- Similar to nomograms in breast for sentinel lymph node or DCIS recurrence
- Goal of tool is not to create survivorship care plan (SCP)
  - Goal is to inform follow-up component of survivorship care plan (when, what, and eventually who)
  - Outputs can be combined with information from other sources
Decision Support Tool Objectives

• Stakeholder consensus: Create tool that
  – *Describes* risks patients face after active treatment (toxicities, recurrence, death) in a way that can be readily translated (e.g., probabilities vs. hazards)
  – *Informs* how often should be seen after active treatment?
    • Timing of visits
    • Specialty that may make most sense for patients to continue to see
RoToR
Risks of treatment Toxicities, Recurrence, and mortality following the diagnosis and treatment of stage I-III breast cancer

Age

Comorbidity

Treatments

Surgery

Biologic Therapy

Chemotherapy

Endocrine Therapy

Radiation


ER Status

- Negative
- Positive

PR Status

- Negative
- Positive

HER2 Status

- Negative
- Positive

Tumor Size

Nodal Status

Histology

Grade

Ductal
Lobular
Other

Calculate
Outputs

Adverse Events
- Cardiac toxicity
- Pneumonitis
- Lymphedema

Recurrence
- New breast event (new primary/locoregional)
- Distant (overall)
- Metastasis at specific site (e.g., brain, liver, lung, bone, distant nodal, pleural/peritoneal)

Mortality
- All cause
- Cancer-specific

Additional Tests
- Imaging
- Biopsies
RISK OF RECURRENT AND MORTALITY WITHIN 5 YEARS OF DIAGNOSIS


Highest annual probability of Distant Recurrence is 5% at year 2
Cumulative probability of Distant Recurrence by year 5 = 15%

Highest annual probability of Local Recurrence is 3% at year 2
Cumulative probability of Local Recurrence by year 5 = 9%

Highest annual probability of Mortality is 6% at year 3
Cumulative probability of Mortality by year 5 = 20%
## Prepare for Printing

Select which items you would like to include in the printable report.

### Properties
- Age
- Body Mass Index
- Comorbidity
- Tumor Size
- Nodes Examined
- Positive Nodes
- Histology
- Grade
- Estrogen Receptor Status
- HER2 Neu Status
- Progesterone Receptor Status
- Surgery Type
- Chemotherapy
- Radiation
- Biologic Therapy
- Endocrine Therapy

### Graphs
- Local Recurrence
- Distant Recurrence
- Death
- Pneumonitis
- Cardiac Toxicity
- Lymphedema

[Print Preview]
RISK OF RECURRENCE AND MORTALITY WITHIN 5 YEARS OF DIAGNOSIS


Highest annual probability of Distant Recurrence is 5% at year 2
Cumulative probability of Distant Recurrence by year 5 = 15%

Highest annual probability of Local Recurrence is 3% at year 2
Cumulative probability of Local Recurrence by year 5 = 9%
Possible Uses in Practice

- Summarize individualized patient priorities for care team
- Inform and be included in survivorship care plan
- Integration into medical record
- Send to primary care physician
Patient preferences for intensity of follow-up

• Cultural aspects are important – beliefs about the meaning of the visits ("going back to die")
• Social support availability
• Life focus (family/community vs individual)
• How well they feel their care is being coordinated by providers, relationship with providers
Future Project Directions

• Passive dissemination with data collection around use
• Explore integration into survivorship care plans in EMR
• Potential implementation study with medical oncology home
• Explore dissemination & implementation opportunities with CoC
Deliverable #2

DESIGN PROSPECTIVE RANDOMIZED TRIAL
Support for Highest Priority Comparators

- Breast Committee Survey (n=27)
  - 23% surg, 65% med, 4% rad, 8% other
  - 30% community; 85% reported over half of practice is breast cancer

- Results
  - 81% - pragmatic trial immediate-high priority
  - 2/3 supported enrolling triple negative and HER2neu + patients
Breast Committee Willingness to Enroll Patients (n=27)

- 64% said meaningful survival difference was 6-8 months
- 12% said 9-11 months
Support for Highest Priority Comparators

• Patient Advocate Committee (Audience Response Units)
  – Consensus that results meaningful
  – 84%: Further research possibly or definitely justified
  – 61%: Willing to enroll in trial where randomized to standard or care vs. standard of care + imaging
Pragmatic Trial Design

• Patient Population
  – Triple negative cancer, +/- Her2neu +
  – Stage III +/- Stage II

• Study Outcomes
  – Effectiveness (change in survival)
  – Early initiation of treatment
  – System consequences (NNT, cost)
  – Impact of routine imaging on patients
    • Additional imaging, biopsies
    • Patient reported outcomes
Challenges for Trial Design

• HER2neu + :
  – Survival longer with modern era targeted therapy (>5 years from diagnosis)
  – Not all patients received targeted therapy in 2006-7

• Triple negative: Findings robust in sensitivity analyses, but not 100% possible to rule out bad biology contribution to survival advantage

• Numbers needed to enroll high
Additional support for sub-group selection

3-year follow up is reasonable for 5-year grant

Fig 3. Hazard rate of relapse according to tumor subtype in (A) cohort 1 and (B) cohort 2. ER, estrogen receptor; HER2, human epidermal growth factor receptor 2.

Cossetti, JCO, 2015.
Enthusiasm for CTC’s/Tumor Markers

- Comes up during EVERY presentation
- Stakeholders interested in early detection with “liquid biopsy”
  - Advocates want to know early who is going to recur
  - Oncologists
    - Imaging could provide an answer to pair with CTC’s for the “what do with this” component of CTC’s
    - To guide follow-up
Enroll 2,100 stage 2/3 Triple negative women

1. Surveillance imaging every 6 months for 2 years (CT chest/ab/pelvis)
   2. Tumor markers/CTC’s at baseline (or sequentially?)

Aim 1. Patient reported outcomes around surveillance- anxiety, imaging, false positives, etc.
Aim 2. Tumor markers/CTC’s and association with DR (prospectively collected)
Aim 3. Long-term survival outcomes collected from NCDB

Accomplish during 4 years of PCORI funding
   - Follow-up until DR or until 3 years
PCORI funds: accrual, imaging, blood work for CTC’s, patient surveys, CTC analysis at time of recurrence

Accomplish after PCORI funding ends
Study Specifics

- **Study Design** - prospective pragmatic trial with stratified cluster randomization at the institutional level and nested case-control study
- **Study Population** - patients who present with Stage II and III triple negative or hormone negative, Her2 amplified breast cancer
- **Comparators** -
  1. intervention - surveillance CT scans to detect distant metastases every 6 months for 3 years
  2. control - the current symptom-based monitoring
- **Primary Outcome** – breast cancer specific 3-year mortality rate
- **Secondary Outcomes** –
  1. time from initial diagnosis to detection of distant recurrence
  2. treatment received for distant recurrence
  3. healthcare utilization (biopsy rates, number of imaging studies, total healthcare cost)
  4. patient-reported outcomes (anxiety, fear of recurrence, symptoms)
  5. long-term outcomes (5- and 10- year recurrence)
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