Appropriate Endpoints in Clinical Trials and Markers for Long-Term Clinical Outcome

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Alternative Title

“How to Upset Statisticians and Methodologists in Less Than 20 Minutes”
Goals of Preoperative Systemic Therapy in Operable Breast Cancer

- To improve odds of breast conservation surgery
  → YES, BCS rates improved by 5-10%

- To allow early assessment of treatment effect
  → YES, but what does it truly mean in the long run?
  What are the optimal markers for various phenotypes?
  What is the true outcome of interest?

- To allow therapy adjustments to improve outcome
  → NOT THERE YET...
  When to do it, how to determine the need, and change to what?

What Is The Clinical Utility of PST?
Goals of Preoperative Systemic Therapy in Operable Breast Cancer

• PST may allow trials that target various breast cancer subtypes and that rely on robust surrogate markers for the outcome of interest
  
  → Smaller, faster, and more informative trials
  More efficient use of resources ...

That’s What Ultimately Brought Us Here Today!
What is a Surrogate Outcome?

- A surrogate outcome should be in the causal pathway of true outcome
  - Replaces a distal endpoint (e.g., survival) by a proxy endpoint (e.g., clinical or pathologic response, imaging, gene expression, ...)

- Surrogate marker
  - A measure of the surrogate outcome
What is a Reliable (Robust) Measure?

Basic Assumptions

• A method or assay used to measure a surrogate marker has been standardized
  - Including pre-analytical variables

• A method or assay is reproducible whenever/wherever used
  - Central site → gene expression profiles
  - Locally → pathology assessment
    ER/PR and HER2
What is a Surrogate Marker?

• Defining Characteristic:
  - A marker must predict clinical outcome, in addition to predicting the effect of treatment on clinical outcome

Adapted from E. Garrett-Mayer, PhD
What is a Surrogate Marker?

- **Operational Definition:**
  - Establish an association between marker and clinical outcome
  - Establish an association between marker, treatment, and clinical outcome, in which marker mediates relationship between clinical outcome and treatment

Adapted from E. Garrett-Mayer, PhD
Is a Correlate Marker Also a Surrogate Marker?
Not all Markers Are Appropriate for This Role ...

Response

Alopecia

NO!

Treatment

Marker

Clinical Outcome
Surrogate Markers and PST

Treatment → Marker → Clinical Outcome
during/after Rx

Treatment: CHEMO, ENDOCRINE, ANTI-HER2, ...

Marker:
- RESPONSE
  - clinical or path
  - MOLECULAR
    - proliferation, cell death, gene expression, epigenetics, circulating tumor cells, etc ...
- IMAGING
  - US, PET, MRI

Clinical Outcome:
- LOCAL CONTROL
- SURVIVAL
Surrogate Markers and PST

Treatment -> Marker (during/after Rx) -> Clinical Outcome

CHEMO
ENDOCRINE
ANTI-HER2, ...

RESPONSE
- clinical or path

MOLECULAR
- proliferation, cell death, gene expression, epigenetics, circulating tumor cell, etc ...

IMAGING
- US, PET, MRI

LOCAL CONTROL
SURVIVAL
Is pCR a Surrogate for Survival?

Kaplan-Meier survival curves according to pathologic response in the breast at surgery

**NSABP B-27**

Is pCR a Surrogate for Survival?

**Anthracycline ± taxane PST**

- pCR
- Survival

**DFS**

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>Events</th>
<th>HR</th>
<th>P</th>
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<tbody>
<tr>
<td>Non-pCR</td>
<td>1,899</td>
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<tr>
<td>pCR</td>
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<td>76</td>
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**OS**

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<th>Group</th>
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<tr>
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*Bear et al. J Clin Oncol; 24:2019, 2006*
PST, pCR, and Survival

• Doubling of pCR with addition of docetaxel in NSABP B-27 did not result in improved survival
  - At least, not until this morning!

• Improved survival not limited to a pCR subset
  - Path response is a continuous variable, not “all or none”
  - The role of pathology response as a surrogate for survival can be refined by the use of standardized pathology measures after PST
    - E.g., Residual Cancer Burden (Symmans, ASCO 2006)
    - AJCC TNM after PST (Carey, JNCI 2005)
How to Determine if a Marker is Useful as a Surrogate?

- Treatment
- Marker during/after Rx
- Clinical Outcome

- Treatment
- Marker during/after Rx
- Clinical Outcome

frequency?
predictive ability?
Is pCR a Useful Surrogate in Invasive Lobular Cancer After Chemo?

Anthracycline ± taxane PST

Survival

Absence of pCR - ok
Presence of pCR - ?

<table>
<thead>
<tr>
<th>Cristofanilli, JCO 2005</th>
<th>Inv Ductal (n = 770)</th>
<th>Inv Lobular (n = 118)</th>
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<tbody>
<tr>
<td>pCR</td>
<td>15%</td>
<td>3%</td>
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<tr>
<td>5y OS</td>
<td>70%</td>
<td>93%</td>
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Is pCR a Useful Surrogate in ER-Positive Disease After Chemo?

<table>
<thead>
<tr>
<th>Guarneri, JCO 2006</th>
<th>ER-neg</th>
<th>ER-pos</th>
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<tbody>
<tr>
<td>pCR</td>
<td>24%</td>
<td>8%</td>
</tr>
<tr>
<td>5y OS</td>
<td>84%</td>
<td>96%</td>
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</table>

Anthracycline ± taxane PST → Survival

No

Absence of pCR - truly ok?
Presence of pCR - helps more?

Yes
### Is pCR a Surrogate for Survival in ER-pos Versus ER-neg Disease?

<table>
<thead>
<tr>
<th>n = 1731 Stage I-III Anthracycline-based PST (66% had taxane)</th>
<th>ER neg</th>
<th>ER pos</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No pCR</td>
<td>pCR</td>
</tr>
<tr>
<td></td>
<td>76%</td>
<td>24%</td>
</tr>
<tr>
<td>5y PFS</td>
<td>50%</td>
<td>83%</td>
</tr>
<tr>
<td>5y OS (HR 0.36)</td>
<td>67%</td>
<td>84%</td>
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</table>

Surrogate Markers and PST

Treatment

SURROGATE MARKER

RESPONSE - clinical or path

MOLECULAR - proliferation, cell death, gene expression, epigenetics, circulating tumor cells ...

IMAGING - US, PET, MRI

Clinical Outcome

LOCAL CONTROL

SURVIVAL
Lessons from the Adjuvant Setting?

Treatment  | Surrogate Marker | Clinical Outcome  
---|---|---
.CHEMO  | .RESPONSE  | .LOCAL CONTROL  
.ENDOCRINE  | - clinical or path  | .SURVIVAL  
.ANTI-HER2, ...  | .MOLECULAR  |  
- proliferation, cell  
death, gene expression,  
epigenetics, circulating  
tumor cells ...  
.IMAGING  
- US, PET, MRI
Breast Cancer is a Mosaic!

**Predictive Marker**
- baseline

**TUMOR FEATURES**
- gene expression
- ER, PR, HER2
- pharmacogenetics
- various nomograms

**Treatment**
- CHEMO
- ENDOCRINE
- ANTI-HER2, ...

**Clinical Outcome**
- LOCAL CONTROL
- SURVIVAL
Identification of Tumor Subtypes

Selection of Patient Population for Various Therapy Options is Key!
Marker for Therapy Selection

- Predictive Marker (baseline)
  - Treatment
  - Surrogate Marker (same or 2nd marker)
  - OR
  - Treatment
  - Surrogate Marker (same or 2nd marker)
  - OR
  - Treatment
  - Clinical Outcome
Timing of Observation Matters!

- If ER positive:
  - Endocrine Rx
  - Survival
  - Are we looking too soon?
  - pCR rate high (and early)
  - Will it correlate with survival?

- If HER2 positive:
  - Trastuzumab
  - Survival
  - pCR
  - ?
Timing of Observation Matters!

ER pos → Endocrine Rx → Survival

.pCR rate high (and early)
.Will it correlate with survival? It may ....

HER2 pos → Trastuzumab → pCR → Survival

.Are we looking too soon?

pCR → ?

What if Surrogate Outcome Truly Correlates with True Outcome?
Surrogate Itself Then Becomes the “Endpoint” ...

Marker → Treatment → Survival

Marker → Treatment → pCR
... And The Search Then Begins for a “Surrogate” for the Surrogate!
Marker Utility Trial Design

Marker at Baseline

START THERAPY

Marker at Mid-Point

Good Result

Bad Result

TREATMENT DECISION

Outcome Assessment

Assumes that you have a good marker
Assumes that you have a good 2nd therapy!
For Post-Operative Decisions ...

Marker at Baseline

START THERAPY

Surgical Assessment

Good Result

SAME Rx?

DIFFERENT Rx?

Bad Result

No More Rx?

Survival
For Preoperative Decisions ...

Marker at Baseline
START THERAPY

Marker at Mid-Point
Good Result
SAME Rx?
DIFFERENT Rx?
STOP Rx?

Bad Result

Surgical Assessment

Is the prognostic utility of pCR different if achieved after therapy x, 2x, or x+y therapy?
Take Home Messages

- Surrogate markers are affected by:
  - Population (tumor subtypes)
  - Intervention (therapy of interest)
  - Timing of assessment (depends on therapy and on tumor subtype)
  - Endpoint (survival is the gold standard)
Take Home Messages

• Surrogate markers are affected by:
  - Population (tumor subtypes)
  - Intervention (therapy of interest)
  - Timing of assessment (depends on therapy and on tumor subtype)
  - Endpoint (survival is the gold standard)

• Predictive markers at baseline are more critical than intermediate surrogate markers ... at least right now
Is pCR a Useful Surrogate Marker?

Unequivocally Yes!

But, it depends ...
Thank you!

I think ...