Surrogate Endpoints in rare cancers

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Surrogate Endpoint - Definition

1. A clinical, instrumental or laboratory variable

2. which can be used in a clinical trial as the primary endpoint (instead of the true endpoint)

3. because it allows to assess/estimate the effect of the test treatment on the ‘true’ (natural) endpoint
Possible uses of a surrogate endpoint

To assess the efficacy of a new treatment:

a) In trials
   • In less time
   • With less patients

b) In the individual patient
Surrogate endpoints in Cancer

- Activity Endpoints
  - % Responders, % pts with “Disease Control”, % pts with ETS, DoR
  - CTC’s, Circulating DNA
  - PET response

- Endpoints “Time to Event”
  - RFS/DFS, PFS
  - Time to “disease control”
Surrogate Endpoints and dilution

The effects of a treatment on a VALID surrogate endpoint, for mathematical reasons, are always larger than those on the true endpoint.
Dilution

Hypothesis:

1. Response doubles the proportion of “cures” (from 20% to 40%)

2. If an experimental treatment doubles the proportion of responses (from 30 to 60%) what is going to be its effect on the proportion of “cures”? 
Dilution

Response doubles % cures (from 20 to 40%)

Exp doubles % response vs St. (from 30 to 60%)

Standard: **26% CURES**

Experimental: **32% CURES**
Dilution & Sample Size

Number of patients that are needed in a trial to assess with power =80% if the effect of the experimental treatment is to raise

- Response Rate from 30% to 60% = 100 pts

- Cure Rate from 26% to 32% = 1860 pz

TIME: 3 months vs several years
MBC

Standard
100 pz

Responder
30 pz

Median OS
2 yrs

Non-resp
70 pz

Median OS
1 yr

Median OS
totale:15 mos

New Th.
100 pz

Responders
60 pz

Median OS
2 yrs

Non Resp
40 pz

Median OS
1 yrs

Median OS
totale:18 mos
If surrogate endpoints are so effective in reducing required sample size and study duration, why don’t we always use them in clinical trials?

Only valid surrogate endpoints can be used!
Validity of a Surrogate Endpoint

‘Surrogacy requires that the effect of the intervention on the ‘candidate’ surrogate predicts its effect on true clinical outcome’

Prentice RL
## Plausible but Invalid Surrogate Endpoints

<table>
<thead>
<tr>
<th>Intervention</th>
<th>Surrogate</th>
<th>True endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Screening</td>
<td>Stage/Survival</td>
<td>Mortality</td>
</tr>
<tr>
<td>Antiaritmins</td>
<td>Arithmias</td>
<td>Sudden Deaths</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>Glycemia</td>
<td>Mortality CVD</td>
</tr>
<tr>
<td>Oral Contr.</td>
<td>BBD</td>
<td>B.C. Risk</td>
</tr>
<tr>
<td>Ormonotherapy in Prostate c.</td>
<td>PSA changes</td>
<td>Survival</td>
</tr>
</tbody>
</table>
‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit looked for by the patient
- Treatment benefit looked for by cancer patient = To live longer and/or better
  - Longer: True endpoint = Overall Survival
  - Better: True Endpoint = Quality of Life
‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit desired by the patient
- Treatment benefit desired by the (cancer) patient = To live longer and/or better
  - Longer: True endpoint = Overall Survival
  - Better: True Endpoint = Quality of Life
- Difficult to study (S.E. major problems)
- PB not an expert
‘True’ (Natural) Endpoint in efficacy (phase III) trials

- Efficacy = treatment benefit desired by the patient
- Treatment benefit desired by the (cancer) patient = To live longer and/or better
- Longer: True endpoint = Overall Survival
Surrogate Endpoints of Survival

Endpoints that, when measured in a clinical trial, allow to predict the effect of a treatment on Survival.
A surrogate endpoint may or may not precede the natural endpoint, and may or may not be involved in the pathway of events leading to treatment effect.
Surrogate Endpoint: Sensitive to the effects of treatment

Disease

Treatment

Natural Endpoint (Treatment aims)

Surrogate Endpoint
Surrogate Endpoint: Correlated with outcome

Disease

Treatment

Surrogate Endpoint

Natural Endpoint (Treatment aims)
Surrogate endpoints vs Prognostic Factors

- **Prognostic Factor:** Predicts the outcome (e.g. Stage): Measured at any time

- **Surrogate Endpoint:** Used to assess the efficacy of the treatment: Assessed AFTER therapy – It is prognostic
Surrogate endpoints vs Predictive Factors

- **Predictive Factor:** Predicts the efficacy of a therapy (e.g. Estrogen Rec. and Tamoxifen): Assessed BEFORE therapy

- **Surrogate Endpoint:** Used to assess the efficacy of the treatment: Assessed AFTER therapy – It is prognostic
Activity Endpoints vs Surrogate endpoints

• Activity Endpoints:
  To assess if the treatment is sufficiently active to warrant efficacy trials
  – Tumor shrinkage
  – PET response
  – Markers
  – Molecular changes (Target)

• Surrogate Endpoint
  To assess if the treatment is effective
Activity Endpoints vs Surrogate endpoints

- Activity Endpoints:
  - Not always prognostic
  - Sensitive to treatment effects on its target
  - Specific
  - Often not surrogate

- Surrogate Endpoint
  - Prognostic
  - Sensitive to treatment effect
  - Often not activity endp.
  - Must adsorb the effect of treatment on the true endpoint
# Activity Endpoints vs Valid Surrogate Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Activity Endpoint</th>
<th>Surrogate Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>SBP, DBP</td>
<td>Yes</td>
<td>(Yes?)</td>
</tr>
<tr>
<td>Blood Sugar</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>Earlier Diagnosis</td>
<td>Yes</td>
<td>NO!</td>
</tr>
<tr>
<td>Disease Incidence</td>
<td>yes</td>
<td>?</td>
</tr>
<tr>
<td>RFS, PFS</td>
<td>NO</td>
<td>Yes?</td>
</tr>
<tr>
<td>Objective response</td>
<td>YES</td>
<td>Yes?</td>
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Theory of surrogate endpoints

Blood Pressure and Cardiovascular Mortality
Blood Pressure and CVD Mortality

The graph shows a positive correlation between blood pressure and CVD mortality. As blood pressure increases, CVD mortality also increases linearly.
Many trials showed that treatments lowering Blood Pressure reduce CVD mortality
Based on this evidence…

• Can we use a new therapy only because it is effective in lowering blood pressure?

• Can we use Blood Pressure to monitor and modify therapy in a patient?
Blood Pressure and CVD Mortality

- Blood Pressure
- CVD Mortality

- Standard t.
- New Therapy
Blood Pressure and CVD Mortality

CVD Mortality

Blood Pressure

Standard t.
New Therapy
The outcome depends only on the surrogate and not on the treatment.
Blood Pressure and CVD Mortality – Alternative possibility

- Standard T.
- New Ther.
Tumor Burden and Mortality

![Graph showing the relationship between tumor burden and mortality. The x-axis represents tumor burden (CM3), and the y-axis represents mortality. Two lines are plotted: one for Standard t. and one for New Therapy. The graph indicates that as tumor burden increases, mortality also increases.](image)
Tumor Burden and Mortality

- Tumor Burden
- Mortality

No Survival Benefit
Response

Standard t.
New Therapy
Responders to the experimental treatment \( \neq \) Responders to standard therapy

![Graph showing the comparison between no survival benefit and response to different therapies based on tumor burden and mortality.](image-url)
Responders to the experimental treatment ≠ Responders to standard therapy

Survival Benefit greater than that predicted by the effect on response (Nonresponders have a benefit)
The correlation between an intermediate endpoint and the true endpoint, is necessary but not sufficient to justify the use of this intermediate endpoint in the assessment of treatment efficacy

Validation of surrogate endpoints
Validation of surrogate endpoints

- Prentice’s Criteria
  (Individual level surrogacy)

- Meta-analytic Approach
  (Trial level surrogacy)
Validation of a surrogate endpoint

- Correlation with outcome
- Sensitivity to treatment effects
- *Individual level surrogacy*
  
  Outcome related to surrogate & independent of therapy

- *Trial level surrogacy*

  Correlation across trials between effect on surrogate and effect on true endpoint
Requirements for validation

- **Individual level**
  - Large database (usually meta-analysis) from RCT(s) where both surrogate and true are recorded

- **Trial level**
  - Meta-Analysis of RCTs in which adequate variation in treatment effects on surrogate and true was observed
**Validated Surrogate Endpoints in cancer**

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<td>Objective response</td>
<td>Survival</td>
</tr>
<tr>
<td>CTX in metastatic CRC (BC)</td>
<td>PFS</td>
<td>Survival</td>
</tr>
<tr>
<td>Adjuvant CTX in Early CRC (BC)</td>
<td>DFS</td>
<td>Survival</td>
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NONE in Rare Cancers (incl. Sarcomas)
Main Limitation of Surrogate Endpoints

1. To validate a Surrogate it takes a large randomised Trial demonstrating the efficacy of the experimental treatment on the true endpoint (or a meta-analysis)

2. Validation is
   - disease-specific
   - treatment-specific
   - natural endpoint-specific
Limitations of Surrogate Endpoints

If there is already a RCT showing efficacy, and it is not possible to extrapolate to other diseases or treatments…..

– Trials of new therapies in the same disease? NO!
– Trials of same therapy on other endpoints? NO!
– Trials of same therapy in other diseases? NO!

what is the use of SURROGATE ENPOINTS?
? 
(to keep biostatisticians busy?)
Possible Uses

- Confirmatory Trials
- Trials of analogues with the same mechanism of action
- Quality of care (Districts, Groups of patients, Hospitals)

- Phase II Trials

- Medical decision and Treatment Modulation in the Individual patient
Phase II trials

Primary Endpoint: A Surrogate Endpoint validated for different therapies/diseases

- When no activity endpoint can be measured (e.g. no biopsies)
- Stronger Plausibility for subsequent phase III trial
- Smaller sample size?
Surrogate endpoints for the individual patient

Experimental treatment vs Standard treatment
Gain in Median survival: From 6 to 12 months

All patients have the same benefit (4 months)

Only responders (30%) have a benefit
- Partial responders (25%) 1 year
- Complete resp.s (5%) 5 years
Note

The requirements to use Surrogate Endpoints
- in rare tumors
- in the individual patient
may be much less strict than those for phase III trials
“Bayesian” validation of a S.E.

- A SE already validated in other types of cancer
- Confirmed to be correlated with true endpoint also in the rare cancer X
- Modified by treatment
- Prognosis seems to be similar between “responders” to different treatments
Example

- Response to an immunotherapeutic agent has been shown to be a VALID surrogate endpoint in lung cancer, colon cancer, and kidney cancer.
- In rare tumor X, the agent doubles the % of responders.
- Responders to the agent have the same OS as responders to standard therapy and live longer than non-responders.
- Do you need more evidence?
Bayesian validation of surrogate endpoints

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<th>New Criteria</th>
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<td>1. SE Correlated with outcome</td>
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</tr>
<tr>
<td>2. SE sensitive to treatment effects</td>
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</tr>
<tr>
<td>3. Treatment affects outcome</td>
<td>3. (- shown to be a valid SE in other cancers)</td>
</tr>
<tr>
<td>4. Treatment effect disappears when SE is adjusted for</td>
<td>4. Test: Outcome SE-specific independent of treatment</td>
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Conclusions

• Surrogate endpoints are a neglected area of methodological research

• They may prove extremely important in rare cancers

• Need to start new studies (prospective data collection)