

Surrogate Endpoint Definition and Application: Aspects of the Observational Study and Clinical Trial Interface

Ross Prentice
Fred Hutchinson Cancer Research Center

- Surrogate outcome definition and concepts
- Role of intermediate outcome trials in hypothesis generation and development
- A lesson from observational studies and clinical trials of postmenopausal hormone therapy and cardiovascular disease

Surrogate Endpoint Definition and Concepts

T – time to response ‘true’ endpoint

$\{S(t); t > 0\}$ – S(t) is history prior to follow-up time t
of surrogate outcome process

x – treatment indicator vector

When can S replace T for evaluation of effects of x
on T?

Define S to be a surrogate for T in respect to x if:

T independent of x \Leftrightarrow S independent of x

(Prentice, 1989, Statist in Med)

$\lambda_T(t; x)$ – hazard rate for T at follow-up time t; given treatment assignment x

$$\begin{aligned}\lambda_T(t; x) &= E[\lambda_T\{t; S(t), x\}] \\ &= \int \lambda_T\{t; S(t), x\} \text{pr}\{S(t); x, F(t)\}\end{aligned}$$

Criteria to ‘operationalize’ this definition:

(i) $\lambda_T\{t; S(t), x\} \equiv \lambda_T\{t; S(t)\}$

S captures (or mediates) relationship between x and T

(ii) $\lambda_T\{t; S(t)\} \neq \lambda_T(t)$

S associated with T

(iii) $E[\lambda_T\{t; S(t)\} | x, F(t)] \neq E[\lambda_T\{t; S(t)\} | F(t)]$

Relationship between S and x not allowed to ‘average out’.

- Principal point of developing these criteria is to document the very restrictive conditions under which study of the relationship between S and x provides valid information on association between T and x.
- Criterion 1 is highly restrictive, and may require S to be of high dimension to be plausible.
- Criterion 1 can never be fully established empirically, but rather requires justification on biological or mechanistic grounds.
- Even if one argues that (i) – (iii) are plausible, a short-term study with S as principal outcome variable may be poorly suited to this assessment of the overall benefits versus risks of x.

Meta-Analytic Approach

Another approach to the use of a short-term S in place of a 'true' outcome T involves exploiting a correlation between T versus x treatment effect parameters with S versus x treatment effect parameters in prior studies of similar treatments in similar populations.

- Doesn't require the strong condition (i) above to hold
- Involves joint modeling of the joint distribution of T and S, given x
- Involves decisions about similarity of treatment and study populations
- May be few situations where prior studies meeting reasonable criteria exist, while relationship between T and x is in doubt?

Role of 'Intermediate' Outcome Trials in Hypothesis Generation and Development

- Even though intermediate outcomes S may rarely be able to replace a study of T in assessing the effects of a treatment or intervention, trials of well-selected outcomes S in relation to X are fundamental to the development and screening of preventive interventions.
- Preventive hypotheses mainly arise from observational studies (specificity? bias?); or from therapeutic trials (timing? relevance?)
- New technologies (e.g., genomics, proteomics) have potential to allow intermediate outcome trials (e.g., human feeding trials, exercise intervention trials) to be increasingly comprehensive and informative.
- Need for trans-NIH forum to encourage such trials and to identify/prioritize interventions that may be appropriate for full-scale trial evaluations.

A Lesson from Combined Postmenopausal Hormone Therapy and Cardiovascular Disease

Women's Health Initiative study of estrogen plus progestin among postmenopausal women in the age range 50-79 at baseline

	CT			OS		
	Placebo	E+P	Age-adj HR	Control	E+P	Age-adj HR
Number of women	8102	8506		35,551	17,503	
Number of events:						
CHD	147	188	1.21	615	158	0.71
Stroke	107	151	1.33	490	123	0.77
VT	76	167	2.10	336	153	1.06

Summary

- Surrogate outcomes rarely available that can provide definitive information about 'true' endpoints of interest in respect to treatment effects
- Intermediate outcome trials becoming practical that can greatly invigorate preventive intervention research agenda
- Situations where both RCT and observational data are available provide excellent opportunities to identify and address study design and analysis issues, and avoid the promulgation of inaccurate public health information.