BARRIERS TO THE META-ANALYSIS OF TIME-TO-EVENT DATA: A CASE STUDY

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ABSTRACT

Background
Methods for the meta-analysis of time-to-event data using summary statistics have been available since the late 1990's and their use is becoming more common in systematic reviews. However, several facets of time-to-event data present problems to the reviewer, particularly in older, more poorly reported controlled trials.

Objectives
To summarize in lay terms: (1) the different categories of analysis and reporting errors identified by the Breast Cancer Group's statisticians in a Cochrane review; and (2) the pragmatic solutions on which reviewers and peer-reviewers agreed.

Methods
Peer review and discussion between reviewers, peer reviewers and other statisticians took place between May 2004 and October 2005. Errors in the review were identified and solutions negotiated.

Results
A wide variety of errors in analysis and presentation were made by reviewers. Most were easily understood and corrected. Others were less easy to address and, in the main, fell into three categories: (1) 'competing risks' in outcomes where death was not an event; (2) 'informative censoring' where censoring is related to the outcome; and, (3) heterogeneity in the definitions of composite outcomes. The first and second are specific to time-to-event analysis; the third is a wider problem but prevalent in cancer studies.

Conclusions
There are limits to the use of summary data in the analysis of time-to-event outcomes. The support of a biostatistician with an interest in time-to-event analysis is invaluable.

INTRODUCTION

Time-to-event outcomes measure not only whether but also when an event happens. They are commonly used to evaluate cancer therapies, where the events of interest include disease recurrence, progression or death.

Meta-analyses of published time-to-event outcomes are most appropriately measured by **hazard ratios**. Cochrane reviewers sometimes use Parmar, Torri and Stewart's method for deriving hazard ratios from meta-analyses using only **published summary statistics**.[1]

We conducted a Cochrane review comparing surgery (+/- tamoxifen) with tamoxifen alone for the adjuvant treatment of operable breast cancer in older women.[2] Our peer reviewers noted a number of **methodological problems** with the published primary research and the **barriers to meta-analysis** they presented.

METHODS

Our Cochrane review, which used published summary statistics and curve data to meta-analyse trial outcomes. In May 2005, statisticians from the University of Sydney (Rachel O'Connell and Val Gebski) identified problems in our use of the primary research data. Pragmatic solutions were identified by discussion and consensus during a teleconference (June 2005) and subsequent correspondence (until November 2005). Key problems and solutions are presented in the remainder of the presentation.

COMPOSITE OUTCOMES: WHAT IS BEING COUNTED?

Composite outcomes, in which **multiple end points are combined**, are often a source of confusion, especially when inadequately reported.[4] We initially and inappropriately meta-analysed a trial with a disease progression outcome, which also counted death without disease as an event, with another study where only disease progression was counted. The table below shows different names for some superficially similar outcomes from included studies.

Outcomes such as disease or progression-***free survival*** usually incorporate death as an event, although there are exceptions: one recent study presented an outcome called 'event-free survival' which did not count death as an event.[5] Similarly, outcomes such as ***time-to***-recurrence or progression usually 'censor' (ignore) death as an event, but it's always best to check in the methods section what was counted.

Study name	What was it called?	What did it count?
CRC	'progression-free interval'	local and distant disease (not death)
Nottingham 1	'disease-free interval'	local and distant disease (not death)
Nottingham 2	'time to progression'	local and distant disease (not death)
St Georges	'time to recurrence'	local and distant disease (not death)
GRETA	'event-free survival'	local and distant disease or death
EORTC 10851	'progression-free survival'	local and distant disease or death

FIRST AND SUBSEQUENT EVENTS: WHEN IS IT BEING COUNTED?

We wanted to meta-analyse the distant recurrence data from two studies. One trial stated that it counted only **distant failure as a first event** Comparing the numbers in tables and curves showed that the other trial counted distant recurrence as a first event and **subsequent to local recurrence**

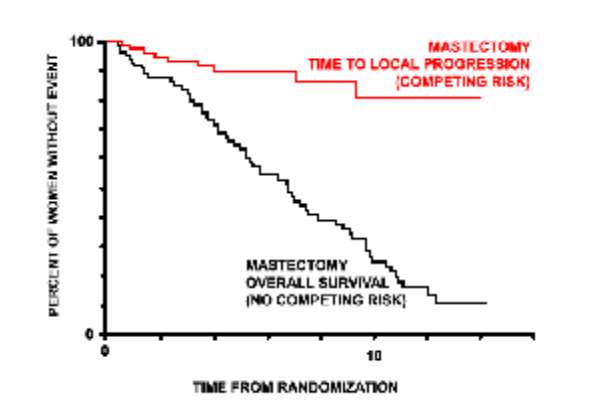
Most studies report distant recurrence only as a first event, as women are treated quite differently once they have had a local recurrence: that point marks the "**treatment failure**".

ACTION: We presented only a narrative summary of the two trials, alerting readers to the difference between the way each study had measured distant recurrence.

COMPETING RISKS: SOME EVENTS PREVENT THE EVENT YOU'RE LOOKING FOR

The graph below, synthesized from a trial report, shows over 80% of women who received mastectomy to be free of cancer in the breast or axilla (local recurrence) at 10 years. At the same time-point, less than 25% of the women randomized are actually alive.

Overall survival and local recurrence rates for the mastectomy arm of EORTC 10851[3]



The calculation of Kaplan-Meier probabilities assumes that **treatment failure** from local recurrence is still possible beyond the time of censoring. When patients fail from other causes (for instance, 'death without recurrence of the cancer'), this is called the "**competing risk**". Censoring patients who fail from competing risks treats women who died without local recurrence the same as those who are still alive and free of disease.

ACTION: Where trial analyses did not adjust for competing risks, we were advised to neither report (because of **bias**) nor meta-analyse outcomes, unless we could tell that:

(a) the rate of deaths without breast cancer recurrence (not necessarily the same as non-breast cancer-related death) was similar and accounted for a small percentage of the deaths in both arms (maybe less than 10%); and,

(b) the duration over which deaths without recurrence occurred was roughly the same (the competing risk deaths are uniform over the two arms across the follow-up period).

INFORMATIVE CENSORING: DOES ASSESSMENT AFFECT OUTCOME?

One analysis of recurrence **censored** women at the time of their **last clinical examination**. Those whose **disease recurs** might be **more likely to attend** follow-up clinics than those who are disease-free: those who are disease-free would then be censored earlier, and stop contributing information to the study.

Kaplan-Meier analyses assume that what causes an individual to be censored is independent of what would cause her to have an event: "**non-informative censoring**".

But, if censoring could be dependent on the likelihood of disease recurrence, then it is related to the outcome: it is, "**informative**". The rate of censoring does not leave a representative sample of those at risk (a source of **bias**).

ACTION: Where informative censoring was present we were advised to neither report nor meta-analyse summary statistics from trials.

REFERENCES

(1) Parmar MKB et al. Extracting summary statistics to perform meta-analyses of the published literature for survival endpoints. Statistics in Medicine 1998; 17:2815-2834.
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(5) Jakesz R, et al. Switching of postmenopausal women with endocrine-responsive early breast cancer to anastrozole after 2 years' adjuvant tamoxifen: combined results of ABCSG trial 8 and ARNO 95 trial. Lancet. 2005; 366(9484):455-62.