Reviewer's report

Title: A Perfect Correlate Does Not A Surrogate Make

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Reviewer: Stephen Duffy

Level of interest: not specified

Advice on publication: Other (see below)

This paper is a useful demonstration of the continuing relevance of the Prentice criterion for surrogate endpoints, and a very interesting restatement of the criterion in terms of relationship between true and surrogate endpoints. I wish I had thought of it. Essentially the authors demonstrate that for a surrogate endpoint to be valid, the intervention should not distort the relationship between surrogate and true (although we hope it will affect both for the better). I have only two comments.

1. Another interesting development of the idea of an inverse relationship between adenomas and colorectal cancer might be a screening trial in which, for example, a single screen with colonoscopy was compared to one using a less radical technique. The number of adenomas detected at that single screen would probably not be related to the number of future colon cancers in the same way in the two arms, and would be in inverse proportion to future cancers. If however, there were a second screen in which both arms received colonoscopy five years later, the number of adenomas at the second screen might be a reasonable surrogate for future colorectal cancer.

2. The authors' findings contradict the position of Begg and Leung (JRSS A, 2000; 163:15) who feel that a surrogate endpoint should not depend on the treatment comparison but should in some sense be 'universal' (I hope I am not misstating their position). The graphical demonstration in my view clearly shows that the position of the authors (and of Prentice) is correct, and that of Begg and Leung is wrong. A universal surrogate is too much to ask for. It is inevitable that the validity of a surrogate is will be specific to the treatment contrast as well as to the true outcome. For example, advanced stage disease might be a valid surrogate in a trial of early detection of cancer but would be useless in a trial of post-surgical treatment. Despite the fact that I believe the authors position to be the correct one, it may nevertheless be worthwhile referring to Begg and Leung.

Competing interests:

None declared.