Reviewer's report

Title: Analysis and design of randomised clinical trials involving competing risks endpoints

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Reviewer: Val Gebski

Reviewer's report:

This manuscript describes the need to consider aspects of competing risks when considering time to event problems, particularly in the analysis and interpretation of oncology studies. This is an interesting paper and helps to raise awareness about the need to consider the issue of competing risks when planning analyses.

Major comments (Compulsory Revisions):

1) It would be useful to provide a precise definition of a competing risk (CR). My understanding is that a competing event (risk) censors the event of interest (i.e. once a competing event has occurred, then the event of interest is unobservable). This is the fundamental distinction between CR and recurrent/multiple events. I would think that the example p3 illustrates a multiple event problem rather than CR. For patients who refuse XRT after progression we can still observe their survival – they simply change their risk of death. Similarly for patients who receive prophylactic XRT. This is more a time-dependent/multiple risk scenario rather than CR.

2) The main outcome of interest in the study SQNP01, was all cause survival with the time to development of distant disease (M) a important secondary outcome. My understanding of the disease history of head & neck cancers is that patients who only relapse locally (i.e. loco-regional recurrence) are usually salvageable by local therapy (either further XRT, surgery or both) and as such their treatment is still with curative intent and they do not censor the patient from distant relapse. The local failure does not appreciably alter the course of the disease (local failure followed by distant failure is of clinical interest when considering time to distant metastasis). Indeed, in these patients, one could model time to distant metastasis with loco-regional recurrence first as a time covariate. In this problem, surely the competing risk would be patients who died prior to observing distant metastases (although I would suspect that in this study this number would be small and not appreciably altering the logrank/proportional hazards results). On the other hand if loco-regional failure is the event of interest, then distant failure does considerably alter management in that on distant failure treatment is considered palliative and no longer curative. Distant disease followed by local failure is not generally of major clinical interest except perhaps in palliative care settings and one would well consider distant metastases as a competing risk for loco-regional control.

3) The illustration of incorporating CR when calculating sample sizes is confusing
in that the authors use the results of the current study to plan an (almost) identical study. This can be confused with post-study power, and, not surprising, that the sample size match the current study i.e. they’re rather self-fulfilling.

I would suggest a different example altogether, especially when the modelling of distant failure after local relapse as a CR is potentially clinically contentious.

Minor comments (minor essential revisions):

a) p4 If D occurs surely the other events are not competing risks – they don’t censor D which is always observable. D will be a CR for M, R, & S!

b) How were cases who failed synchronously considered?

b) P5 do you mean that the supraclavicular lymph nodes are large &/or are involved at diagnosis?

c) p6 Cumulative not CuMulative’

d) p 13 – last paragraph - this example is confusing as death is the only competing event and, unless there are many intercurrent events, for all practical purposes a CR analysis would not add much to the analysis’

e) Th graphs should have the numbers at risk shown below the x-axis (see recommendations of Pocock et al in the Lancet)

Level of interest: An article whose findings are important to those with closely related research interests

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.