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# Progression-free survival: too much risk, not enough reward?

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Given the increasing number of potential therapies for glioblastoma and the slow rate of progress to date, clinical trials must become more efficient while providing clinically relevant answers. In this context, careful selection of clinical trial endpoints is extremely important. Adoption of new therapies requires trials that demonstrate real, clinically meaningful improvements in outcome attributable to the experimental therapy. While survival is undeniably clinically meaningful, there is interest in using other endpoints such as response rate or progression-free survival as more efficient 'surrogates' that limit non-treatment related variation and confounding by post-progression therapy.

Han et al. conducted a meta-analysis to determine whether PFS and response rate could be used as surrogates for OS in glioblastoma.[1] The most relevant finding was a strong correlation between PFS HR estimates and OS HR estimates ($R^2$ 0.92) in non-bevacizumab containing comparative studies. It is important to note, however, that these analyses examine relationships between parameter *estimates*. If every trial included in the meta-analysis were identical and from the same study population, there would still be variability in summary statistic estimates, which would be strongly correlated but give little information on the value of the proposed surrogate. The analysis should therefore account for the variability and correlation of the study-specific summary statistics and limit comparisons to historical controls to reduce correlations attributable to selection bias. Overall response rate had a poor correlation with OS and point estimates of PFS and OS within groups showed moderate to good correlations. Correlations of PFS and OS estimates within non-comparative groups are less meaningful with respect to the surrogacy question, however.

Ideally, a surrogate captures the entire relationship between treatment and the true endpoint- an idea codified in the Prentice definition.[2] In a comparison of two treatment groups, there may be independent strong correlations between PFS and OS within each group but if these relationships are different, *change* in PFS may not reflect *change* in OS. We expect some degree of correlation within each group because PFS and OS share similar information. Consider a hypothetical therapeutic with no effect on survival that inhibits the ability to assess progression. Improvement in PFS would be accompanied by a strong correlation between PFS and OS (PFS = OS). PFS and OS would correlate in each arm independently but PFS would be an inappropriate surrogate for OS in terms of the *effect* of the hypothetical therapeutic.

With the caveats above, the strong correlation between treatment effects on PFS and OS in non-bevacizumab containing trials reported by Han et al. were also demonstrated by landmark EORTC 26981/NCIC CE.3 study (included in the meta-analysis). Temozolomide effects were entirely on PFS time, with identical median survival post progression (SPP).[3] But the question of whether PFS is *useful* as an endpoint does not entirely depend on the demonstration of surrogacy. On the contrary, strong PFS/OS correlation may negate one of the best arguments for using PFS. Broglio and Berry provide a useful framework, segmenting OS into PFS and SPP.[4] Assuming treatment effect only on PFS and a random distribution of SPP times, translation of a real benefit from PFS to OS is dependent on the length of SPP, with longer SPP diluting positive real effects.[4] For glioblastoma, strong correlation between PFS and OS can therefore be at least partially explained by the short SPP. Additionally, the strong correlation between PFS and OS reported by Han et al. provides evidence that post progression heterogeneity is limited (as in EORTC 26981/NCIC CE.3), thereby refuting one of the strongest arguments to use PFS. Alternatively, a lack of PFS/OS correlation combined with long and variable SPP might be a good argument for using PFS *instead* of OS, but this does not seem to currently be the case for glioblastoma trials.

An argument for PFS as a surrogate is that earlier events lead to more power at any given point in the study, resulting in more efficient trials. While strong correlation of PFS and OS effects might provide the foundation for such an argument, AVAGlio and RTOG 0825 provide examples where improvements in PFS were not associated with an OS benefit.[5, 6] Concerns over pseudoprogression, especially with immunologic-based therapies,[7] extend this idea that all "progressions" are not equal. PFS is therefore therapeutic, imaging, and criteria-specific- we may hypothesize relationships between assessment of progression and real effects, but these relationships each require study and validation. We cannot reliably define PFS/OS relationships *a priori*.

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Given this uncertainty, the decision to use PFS as a surrogate should require significant gains in efficiency. Data reported by Han et al. show lead times of 7.4 months for newly diagnosed and 4.2 months for recurrent tumors. A critical question is to consider the relevance of those gains in terms of decision-making. Hypothetically, an adaptively randomized study might gain efficiencies by using the data in real-time, but would also have the most to lose by erroneous decision-making. In non-adaptive trials, OS data is ultimately collected without the need to make decisions in the intervening few months. Small lead-time gains using PFS are outweighed by the uncertainty of the relationship with OS- we should prioritize getting the right answer over the slightly more expedient one.

Another argument for PFS associates progressing tumor with worse quality of life (QOL) but validated QOL endpoints could more directly address this concern with less potential for confounding. For example, by overvaluing PFS, RTOG 0825 may have been less able to assess potential improvements in QOL by continuing biased measurements in patients that may have had progressing tumor not discovered by imaging on the bevacizumab arm.[5]

PFS may ultimately be more useful as survival times lengthen and more efficacious therapies are developed and used in the post-progression setting. Additionally, the more direct link between treatment and PFS or especially response rate continues to argue for value in early development, where evidence for effect attributable to drug may be sufficient. Continued development and validation of these endpoints using varying therapeutics and criteria for assessment is therefore critical. Currently, however, there is little value in replacing OS with PFS and the role of PFS as a surrogate has more potential for erroneous results than substantial efficiency gains.

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