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TROG 96.01: TTBF and PSA_{dt} as surrogates for disease specific mortality

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INTRODUCTION

Prostate cancer is a common disease in men and the incidence is increasing due to the aging male population. While the majority of patients with localized prostate cancer can be cured with surgery or radiotherapy, patients with localized prostate cancer with poor risk features have an increased risk of recurrence and succumbing to their disease. In these patients, the time from diagnosis to disease progression and ultimate death from the prostate cancer can span a decade. Thus, our progress to develop better therapies and integrating novel drugs into this population has been severely hindered since prostate cancer-specific mortality has been held as the primary and only acceptable trial endpoint. The development of a valid surrogate marker (s) for prostate cancer specific mortality in this population would significantly improve the efficiency of clinical trials by shortening the follow-up time and ultimately reducing sample size, decreasing costs, and providing results to patients sooner.

Prostate specific antigen (PSA) is an extensively studied biomarker in prostate cancer¹, and has been instrumental in improving early detection and in predicting pathologic stage². As a biologic marker of prostate cancer, PSA drives many treatment decisions in the hope that it would reflect benefit on prostate cancer specific mortality (PCSM). However, PSA has fallen short in its value as a surrogate for PCSM in several trials and in a meta-analysis by Collette *et al*³ who applied the tools of “meta-analytic validation”⁴ in the metastatic, non-metastatic, and castrate resistant settings. Interest turned to PSA elevation as a potential surrogate when the natural history of biochemical failure post-prostatectomy was described⁵, although an elevated PSA alone was not sufficient to guide therapy⁶.

The use of PSA doubling time (PSA_{dt}) and the time to biochemical failure (TTBF) has been explored as a possible surrogate marker by many investigators. D’Amico *et al.* performed a retrospective review of nearly 8700 patients treated for prostate cancer and hypothesized that PSA_{dt} of 3 months could be a surrogate endpoint⁷. They found that TTBF and PSA_{dt} do correlate with true clinical outcome, however it is not clear if the net effect of intervention is fully reflected in these biomarkers. Before PSA can be a surrogate endpoint and replace PCSM,

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it must be formally validated in a trial. The process of validating a surrogate marker in cancer has caused many controversies amongst clinicians and statisticians. The four Prentice criteria has been traditionally been used for data from a single randomized trial that measures both the true endpoint (PCSM) and the potential surrogates prospectively⁸. This is the challenge the authors of the TROG 96.01 trial took on quite successfully.

THE TROG 96.01 TRIAL

Results of the TROG 96.01 trial were first reported in 2005 and showed that short term neoadjuvant androgen deprivation therapy improved outcomes for conventional radiation therapy (66Gy), however this did not translate to a significant difference in overall survival at that time⁹. The trial included 802 men with locally advanced prostate cancer randomized to receive prostate external beam radiation alone or with three or six months of short-term androgen deprivation therapy that was started before radiation. Their primary endpoints were local failure or PCSM; and the secondary endpoints included TTBF as defined by the Houston method¹⁰. The TROG investigators more recently followed this up with their findings of TTBF and PSAdt as potential surrogates for prostate cancer-specific survival¹¹.

The TROG investigators evaluated whether or not TTBF and PSAdt could serve as surrogate markers for prostate cancer-specific-mortality (PCSM). For validation, TTBF and PSAdt should meet the Prentice criteria and show that⁸ treatment (radiation therapy with or without androgen deprivation therapy) should significantly affect 1) TTBF and/or PSAdt and 2) PCSM; 3) that TTBF and/or PSAdt are prognostic for PCSM; and 4) treatment effect on PCSM should disappear when TTBF and/or PSAdt are variables in a multivariate analysis. As criterion 4 is difficult to verify as it attempts to prove the null hypothesis, the investigators rather attempt to show that TTBF and/or PSAdt mediates the effect of primary treatment on PCSM by showing the treatment effect to be statistically not significant when adjusted for the surrogate endpoint. Proportion of treatment effect (PTE) is evaluated with each criterion. Meeting all four criteria is often very challenging, though the TROG authors had ample detailed data to work with, including data on time from randomization to failure, primary therapy, and secondary therapies to achieve meaningful results.

Of 802 patients randomized in the TROG 96.01 trial, 436 (54.4%) had biochemical failure and of these, 119 (27.2%) achieved the true endpoint of PCSM. There were 2 (<1%) patients that died of prostate cancer that were not found to have clinical or biochemical failure. They found that TTBF between 1.5 and 2.5 years predicted all three treatment arms of the trial with PTE of 0.45 to 0.64. Similarly, PSAdt above concentrations of 2ng/mL similarly predicted the three treatment arm's PCSM at cut points of <12months and <15months with PTE of 0.36 to 0.56. These correlations satisfied the four Prentice criteria and were true for both at the time from randomization and end of radiotherapy. The authors correctly conclude that there is sufficient evidence and call to action for a meta-analysis to further assess validity of the markers.

SUPPORT FOR A META-ANALYSIS

Based on these data, we still do not have an adequate surrogate to use as a primary endpoint in prostate cancer clinical trials. The authors are to be commended for a detailed and thorough evaluation. They showed that TTBF and PSAdt are surrogates for their clinical scenario and population in the trial. They make a humble and insightful conclusion that asks the community to pool data across trials to appropriately answer the question. When it comes to surrogacy, it is at best errant and at worst censurable to incorporate results from one trial's surrogate predictability into the next trial's primary endpoint. There is a considerable leap of faith required to assume that a new treatment's effects on the surrogate and true endpoints will reflect

the data and patient setting (castrate resistance status, Gleason score, age, metastatic profile, etc) in the same way as in the TROG trial.

The Prentice Criteria approach can identify a surrogate in one clinical trial, though its relevance in other clinical settings remains in question. While Prentice is known to have added quantifiable validity to the application of surrogate endpoints, he did note their limitations⁸. Based on his approach of validation by testing the null hypothesis, a surrogate can be validated in a clinical trial only if the survival endpoint is also evaluated; that is, the effect of the intervention should be evaluated on the surrogate in addition to the survival endpoint in each trial conducted. So, applying results from a surrogacy trial to a new trial where the surrogate is intended to be the endpoint requires an extrapolation that may not be acceptable as it is a new clinical setting. Additionally, Fleming and DeMets point out that sole surrogate endpoints should be used carefully as results can be misleading¹². This would nearly negate the benefits of the surrogate as it would need to be tested in many trials and clinical settings. Begg and Leung addressed this issue by validating a surrogate endpoint by using a probability method in a surrogate-only trial setting¹³. This allows for validating surrogates across heterogeneous clinical settings, conducive to a systematic meta-analysis. Buyse et al take the probability application in a meta-analysis setting one step further and apply a linear best fit line of treatment effect on true endpoint versus effect on surrogate endpoint, and calculate the squared correlation coefficient (R^2); where 1 is the optimal predictive value for a surrogate⁴. As did Begg and Leung, so does Buyse et al, argue with sophisticated mathematics that many large randomized trials with heterogeneity can improve precision and credibility of a surrogate⁴.

Though the detailed data and analysis of the TROG 96.01 cannot be readily translated to a valid surrogate, it will likely be an integral part of a larger meta-analysis for surrogacy. As we better understand genetics, signalling targets, inflammatory mediators, and as our nanoscale technologies mature, we anticipate synergies that will likely yield more surrogate candidates, and an understanding of the validation tools will be invaluable to have productive and efficient trial platforms.

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