Surrogate end points in early prostate cancer clinical states: ready for implementation?

Christos E. Kyriakopoulos¹, Emmanuel S. Antonarakis²

¹University of Wisconsin Carbone Cancer Center, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA; ²Johns Hopkins Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, Baltimore, MD, USA

Correspondence to: Emmanuel S. Antonarakis, MD. Associate Professor of Oncology and Urology, Johns Hopkins Sidney Kimmel Cancer Center, Johns Hopkins University, CRB1, Room 1M45, 1650 Orleans St, Baltimore, MD 21287, USA. Email: cantona1@jhmi.edu.

Provenance: This is an invited Editorial commissioned by Section Editor Jianrong Zhang, MD (George Warren Brown School of Social Work, Washington University in St. Louis, St. Louis, MO, USA).


doi: 10.21037/atm.2017.10.25

View this article at: http://dx.doi.org/10.21037/atm.2017.10.25

The prostate cancer disease continuum is best conceptualized as a series of clinical states starting from localized disease (which is curable, in some) and often progressing to biochemically-recurrent disease, to non-metastatic or metastatic castration-resistant disease, and finally to lethal prostate cancer (1). Accordingly, a major decrease in the recurrence rate or death from prostate cancer after primary definitive therapy could potentially be achieved with more effective adjuvant therapies. For patients with localized prostate cancer, treatment options for definitive therapy include surgery or radiation, with approximately one-third of these men experiencing disease recurrence (2). Due to the heterogeneous natural history of recurrent prostate cancer, the survival of these patients can vary widely and often exceeds a decade (3,4). Recently, it has been suggested that metastasis-free survival (MFS) might be associated with overall survival (OS) in patients with biochemically-recurrent disease after local therapy who defer androgen suppression until the development of radiographic metastases (5). Until now, this intriguing observation had not been confirmed.

OS is a clinically meaningful and objectively assessed end point that is often used in phase III trials in advanced prostate cancer and can be used for regulatory approval. However, its use carries significant disadvantages, such as the requirement for large numbers of patients and prolonged follow-up. Especially in prostate cancer patients who generally have longer survival times compared to patients with many other cancer types, all these factors can render the monetary and social cost of conducting an adjuvant trial prohibitive. As a recent example, a cooperative group phase III study that examined the role of high-dose bicalutamide in combination with post-prostatectomy salvage radiotherapy was published 19 years after the trial was initiated (6). In addition, due to the growing number of approved therapies for advanced disease and crossover between treatments, it is becoming increasingly difficult to detect an OS benefit based on an initial treatment that may have been administered a decade earlier. Furthermore, trials with early interventions might even lose their clinical relevance by the time that they are completed and reported. Thus, there is a critical need to generate clinical end points that will serve as surrogates for OS and will assist the conduct of adjuvant clinical trials in early prostate cancer clinical states within a feasible timeframe.

In a very timely meta-analysis just reported by Xie et al. (7), the investigators evaluated whether 5-year MFS and disease-free survival (DFS) endpoints could serve as surrogates for 8-year OS for men with early-stage prostate cancer. To assess their hypothesis, they pooled individual patient-level data from 28 adjuvant (surgery-based or radiation-based) clinical trials encompassing 28,905 total patients. Adjuvant treatment modalities varied between studies, including ADT, bicalutamide, docetaxel and radiation (for patients who underwent surgery as primary treatment). Median follow-up for the overall study
population was 10 years. This analysis provides evidence that in patients with localized prostate cancer who are treated with either radiation or prostatectomy, both DFS and MFS are strong surrogates for OS at the patient level (Kendall’s \( \tau \) correlation with OS, 0.85 and 0.91 for DFS and MFS, respectively) and at the trial level [\( R^2 \) 0.86 (95% CI, 0.78–0.90) for DFS and 0.83 (95% CI, 0.71–0.88) for MFS, respectively]. The study also showed that the treatment effect had a positive correlation with both surrogates (MFS, DFS) as well as OS. Due to the stronger correlation between MFS and OS [\( R^2 \) 0.92 (95% CI, 0.81–0.95) for MFS versus 0.73 (95% CI, 0.53–0.82) for DFS], the authors raised the possibility that MFS could be reasonably used as an intermediate clinical end point (ICE) for the conduct of adjuvant trials in early-stage prostate cancer.

This exemplary study was completed by a collaborative international working group called Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) (8), and truly represents a Herculean effort. To date, it is by far the largest study that aimed to define an ICE for clinical trial design in early prostate cancer. Previous studies have used different variables as predictors of OS or prostate cancer-specific survival, including time to biochemical relapse, PSA doubling time, PSA nadir after therapy initiation, MFS as well as general treatment failure (5,9–13). Most of these variables were suggested to be accurate predictors of OS; however, the heterogeneity of the patient populations and interventions do not allow for firm conclusions when examining each study individually. The current meta-analysis takes a big step forward in the right direction. The large number of trials and patients included and the individual patient-data methodology, provide solid first-in-field evidence that MFS is a strong surrogate for OS in early prostate cancer and can reasonably be used as an ICE, especially in adjuvant clinical trials, in order to complete these studies in a more expeditious manner. As an example, a recently launched phase III study of primary radiation therapy with or without apalutamide in men with localized disease (NCT02531516) has appropriately selected MFS as its primary endpoint.

Although future adjuvant trials in prostate cancer can reasonably use MFS as an ICE, one needs to remain cautious when generalizing these results to all prostate cancer trials. This analysis included patients that received a curative-intent treatment before eventually developing metastatic disease and subsequently death. The investigators did not include trials where the patients continued an active systemic therapy for recurrent or even castration-resistant disease, in which case OS should continue to be the end point of choice. In addition, the clinical trials that were included in this analysis used conventional imaging for the detection of radiographic metastatic disease. Newer imaging techniques have emerged as useful clinical tools in detecting metastases at earlier stages (14,15) and once they become widely available they will lead to earlier detection of metastatic disease (and therefore, cause a stage migration). It is currently unclear what the correlation between MFS and OS will be in that case, and whether DFS and MFS will continue to associate with OS to the same degree. Finally, it is uncertain if these data can be extrapolated to the biochemically-recurrent population (which is presumed to have undetectable micrometastatic disease), in order to evaluate the effect of some systemic therapy on MFS. Nevertheless, an ongoing phase III study that has adopted this approach is the EMBARK trial (NCT02319837), in which MFS has been selected as a primary endpoint to compare leuprolide versus enzalutamide versus the combination of the two agents in men with biochemically-recurrent prostate cancer after local treatment.

In conclusion, Xie et al. provide compelling evidence that DFS and particularly MFS are strong surrogates of OS in patients with localized prostate cancer who receive either primary radiotherapy or radical prostatectomy, culminating in the recommendation (with which we agree) that MFS may be used as a reasonable primary end point in future adjuvant trials in order to expedite their conduct and interpretation. While this meta-analysis provides solid data towards this end, further clinical and molecular stratification would be desirable to further select those early-stage patients who are more likely to hit these intermediate endpoints sooner. Unless our patient selection in adjuvant trials becomes more sophisticated, not only are we less likely to meet even these intermediate endpoints in a timely fashion, but we may also be overtreating a significant proportion of men in whom adjuvant therapy may not be needed at all.

**Acknowledgements**

**Funding:** This work was partially supported by National Institutes of Health Grant P30 CA006973 (ES Antonarakis).

**Footnote**

**Conflicts of Interest:** ES Antonarakis is a paid consultant/advisor to Janssen, Astellas, Sanoí, Dendreon, Medivation,
ESSA, AstraZeneca, Clovis and Merck; he has received research funding to his institution from Janssen, Johnson & Johnson, Sanofi, Dendreon, Genentech, Novartis, Tokai, Bristol Myers-Squibb, AstraZeneca, Clovis and Merck; and he is the co-inventor of a biomarker technology that has been licensed to Tokai and Qiagen. CE Kyriakopoulos has no conflicts of interest to declare.

**References**


**Cite this article as:** Kyriakopoulos CE, Antonarakis ES. Surrogate end points in early prostate cancer clinical states: ready for implementation? Ann Transl Med 2017;5(24):502. doi: 10.21037/atm.2017.10.25