



Event-Free Survival, a Prostate-Specific Antigen–Based Composite End Point, Is Not a Surrogate for Overall Survival in Men With Localized Prostate Cancer Treated With Radiation

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PURPOSE Recently, we have shown that metastasis-free survival is a strong surrogate for overall survival (OS) in men with intermediate- and high-risk localized prostate cancer and can accelerate the evaluation of new (neo) adjuvant therapies. Event-free survival (EFS), an earlier prostate-specific antigen (PSA)–based composite end point, may further expedite trial completion.

METHODS EFS was defined as the time from random assignment to the date of first evidence of disease recurrence, including biochemical failure, local or regional recurrence, distant metastasis, or death from any cause, or was censored at the date of last PSA assessment. Individual patient data from trials within the Intermediate Clinical Endpoints in Cancer of the Prostate–ICECaP–database with evaluable PSA and disease follow-up data were analyzed. We evaluated the surrogacy of EFS for OS using a 2-stage meta-analytic validation model by determining the correlation of EFS with OS (patient level) and the correlation of treatment effects (hazard ratios [HRs]) on both EFS and OS (trial level). A clinically relevant surrogacy was defined a priori as an $R^2 \geq 0.7$.

RESULTS Data for 10,350 patients were analyzed from 15 radiation therapy–based trials enrolled from 1987 to 2011 with a median follow-up of 10 years. At the patient level, the correlation of EFS with OS was 0.43 (95% CI, 0.42 to 0.44) as measured by Kendall's tau from a copula model. At the trial level, the R^2 was 0.35 (95% CI, 0.01 to 0.60) from the weighted linear regression of log(HR)–OS on log(HR)–EFS.

CONCLUSION EFS is a weak surrogate for OS and is not suitable for use as an intermediate clinical end point to substitute for OS to accelerate phase III (neo)adjuvant trials of prostate cancer therapies for primary radiation therapy–based trials.

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INTRODUCTION

Despite various strategies for the early detection of prostate cancer, more than one half of all deaths occur in men who initially presented with localized disease.¹ Curing metastatic prostate cancer is still a formidable challenge, and the most likely near-term strategy to substantially decrease the approximately 300,000 prostate cancer deaths that occur worldwide from the 1.1 million newly diagnosed cases is by preventing relapses from intermediate- and high-risk localized disease with more effective (neo)adjuvant systemic therapy.²⁻⁵

Improvements in systemic therapies increase the longevity of some men with metastatic hormone-sensitive prostate cancer and castration-resistant prostate cancer (CRPC).⁶⁻¹⁸ When metastases are occult to conventional computerized tomography and technetium bone-scan imaging, they are more sensitive to testosterone-suppression therapy, resulting in an increase in the chance of cure when systemic therapies are given with local therapy.^{5,19,20} Potential eradication of micrometastases with new therapies may further decrease the number of men who die as a result of prostate cancer. When the

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

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CONTEXT

Key Objectives

To determine whether event-free survival (EFS), an early prostate-specific antigen (PSA)-based composite end point can be used as an intermediate clinical end point and serve as a surrogate for overall survival (OS) in localized prostate cancer. If surrogacy was established, the secondary objective was to detail how to deploy EFS as an end point to expedite completion of randomized phase III clinic trials in this setting.

Knowledge Generated

EFS has very a low correlation with OS in men with localized prostate cancer treated with radiation, and is therefore a weak surrogate for OS.

Relevance

Unlike metastasis-free survival, EFS is not suitable for use as an intermediate clinical end point to substitute for OS to accelerate phase III (neo)adjuvant trials of prostate cancer therapies for primary radiation therapy-based trials. Research is ongoing and needed to quantify other clinical benefits from preventing a PSA relapse in this setting.

quintessential end point of overall survival (OS) is used as the primary end point, (neo)adjuvant prostate cancer clinical trials usually take longer than a decade to be reported.

Recently, the Intermediate Clinical Endpoints in Cancer of the Prostate (ICECaP) working group has shown that metastasis-free survival (MFS: metastasis on conventional imaging or death from any cause) is a strong surrogate for OS in localized prostate cancer trials.²¹ For new treatments with an anticipated treatment effect size that will decrease the rate of metastases by > 33% (ie, hazard ratio [HR] < 0.67), MFS as the primary end point can shorten the time to show an OS benefit.²¹ Disease-free survival (DFS), which is MFS plus local-regional recurrence events, is not as strong a surrogate for OS.

Use of an earlier intermediate clinical end point (ICE) including prostate-specific antigen (PSA) recurrence could result in even more expeditious adjuvant trial conduct than DFS or MFS. However, for an ICE to serve as a good surrogate for OS, there must be no confounding from salvage therapy for relapsed disease that can either cure the disease and/or prolong postrelapse survival to the point that competing risks of death affect the analysis.²²⁻²⁷ Salvage prostate bed radiation after a prostatectomy and the prolonged survival of patients treated with androgen deprivation therapy (ADT) for biochemical recurrence (BCR) are potential confounders for prostate cancer outcomes. Prior studies have shown PSA nadir, end of treatment PSA, time to BCR, and post-BCR PSA doubling time (PSA-DT), are prognostic for OS and have some surrogacy at the patient level.²⁸⁻³¹ However, to our knowledge, no prior studies using individual patient data (IPD) from multiple studies have been conducted to assess trial-level surrogacy, which evaluates whether a treatment effect on the ICE (eg, time to BCR) is correlated with the treatment effect on the ultimate end point (ie, OS) across many trials.

We hypothesized that event-free survival (EFS), which includes all components of DFS plus PSA-only relapse, may be a surrogate for OS at both the patient and the trial level. We also assessed the surrogacy of EFS for MFS, because MFS is a strong surrogate for OS. Given the observation that most patients with intermediate- or high-risk localized prostate cancer are cured, and even if they relapse with a rising PSA, often die as a result of a nonprostate cancer death, we also investigated the surrogacy of ICEs for disease-specific survival (DSS).

METHODS

Trial Selection Criteria

Eligible trials were identified from the established ICECaP data repository, composed of 22,825 IPD from 28 randomized trials conducted in Australia, Canada, Europe, New Zealand, and the United States for localized prostate cancer.¹ For this analysis, eligible trials included radiation therapy as primary therapy that had evaluable PSA and disease follow-up data suitable for EFS analysis (see end point definitions). Prostatectomy-based trials were not included because of a lack of evaluable PSA data.

Definition of End Points

EFS was measured from the date of random assignment to the date of first evidence of disease recurrence, including biochemical failure, local or regional recurrence, distant metastasis, or death from any cause, or was censored at the date of last PSA assessment. Death without prior disease recurrence was also censored at the last PSA assessment if the interval between the last PSA assessment and the date of death was > 15 months. MFS was measured from the date of random assignment to the date of the first evidence of recorded distant metastases or death from any cause, or was censored at the date of last follow-up. OS was measured from the date of random assignment to death from any cause and censored at the date of last follow-up in

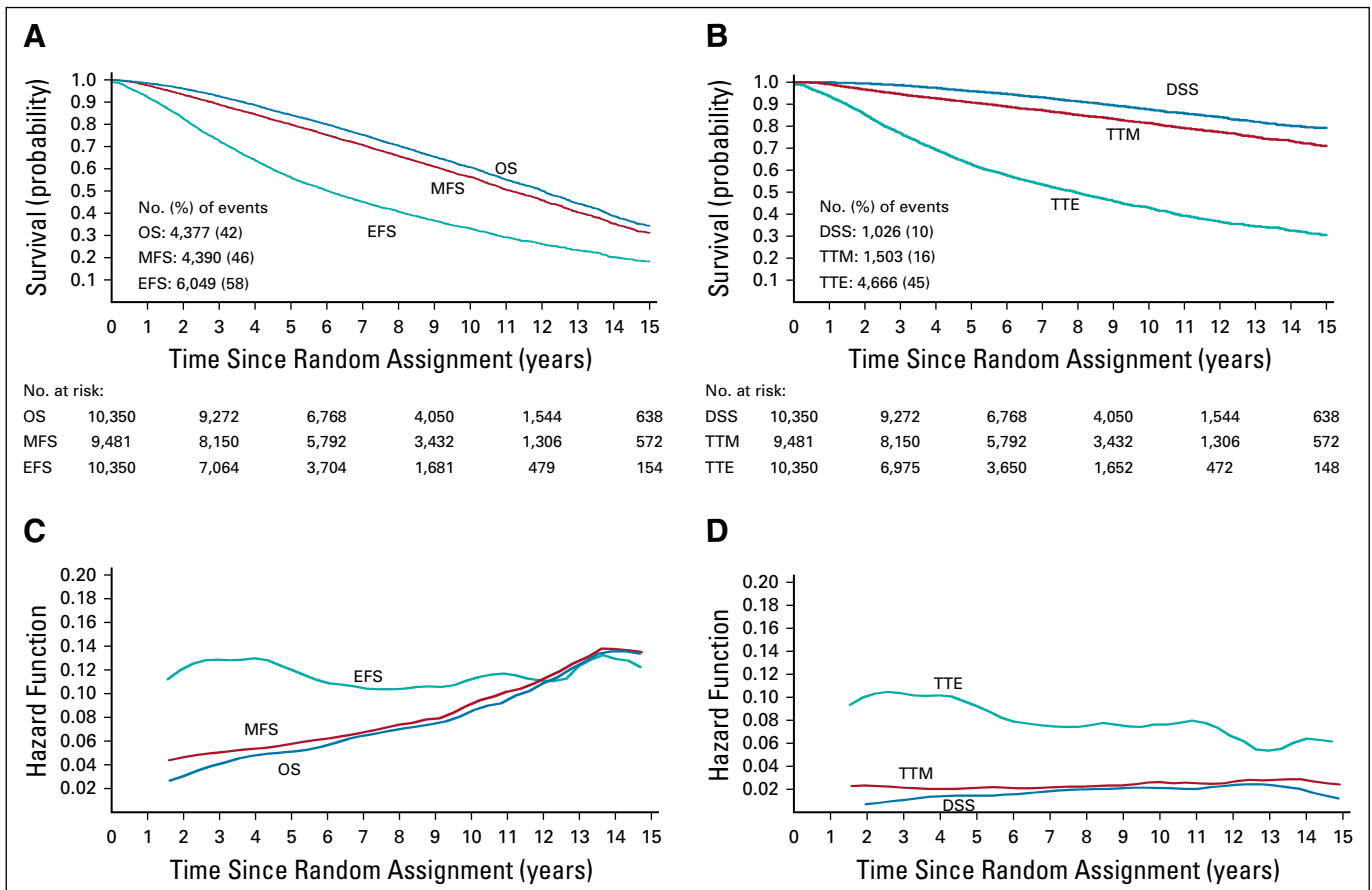


FIG 1. (A) Kaplan-Meier estimates of overall survival (OS), metastasis-free survival (MFS), and event-free survival (EFS) where non-prostate cancer deaths were counted as events. (B) Kaplan-Meier estimates of disease-specific survival (DSS), time to metastasis (TTM), and time to event (TTE) where non-prostate cancer deaths were censored. (C) Estimated hazard functions over time for OS, MFS, and EFS. (D) Estimated hazard functions over time for DSS, TTM, and TTE. Median follow-up was 10 years.

surviving patients. Time to event (TTE), time to metastasis (TTM), and DSS were defined analogously to EFS, MFS, and OS, respectively, but patients with nonprostate deaths had end points censored or considered as competing risk in sensitivity analyses.

Biochemical failure was defined according to the 2006 RTOG-ASTRO Phoenix definition. A PSA rise by ≥ 2 ng/mL above the nadir was considered biochemical failure; patients not fully meeting the PSA criteria for failure who underwent subsequent therapy were also declared to be failures at the time of salvage initiation. Of the 15 included trials, 14 trials were viable for harmonization by the Phoenix definition and 1 trial used the ASTRO definition (Data Supplement, online only). Local or regional recurrence was based on trial-defined events; distant metastasis was confirmed by imaging or histologic evidence as described in our prior MFS analysis.²¹

Statistical Analyses

Surrogacy criteria. We evaluated the surrogacy of EFS with OS using a 2-stage meta-analytic validation model as described previously.³² Two conditions must hold to claim

EFS is a surrogate for OS. Condition 1 requires EFS and OS to be correlated. Condition 2 requires that the treatment effects on both end points be correlated. The validity of the surrogate is reflected by the strength of both correlations. To be consistent with our previous work and other surrogacy assessments in oncology, we defined a priori a clinically relevant surrogacy as $R^2 \geq 0.7$.^{1,21}

Condition 1 was tested at both the patient and the trial level. At the patient level, associations of OS with EFS were evaluated via a bivariate copula model over the entire follow-up of IPD (Data Supplement). Kendall's tau (range, 0-1) quantified the correlation between end points. At the trial level, we first obtained Kaplan-Meier estimates of 5-year EFS and 8-year OS rates for each treatment arm within each trial. We then performed weighted linear regression (WLR) of trial- and arm-specific 8-year OS rates on 5-year EFS rates. Similar analyses were performed at an earlier milestone time: OS rates at 5 years on EFS rates at 3 years. These time points were chosen because they are reported frequently in the literature and reflect the earlier time of biochemical failures. Regressions were weighted by

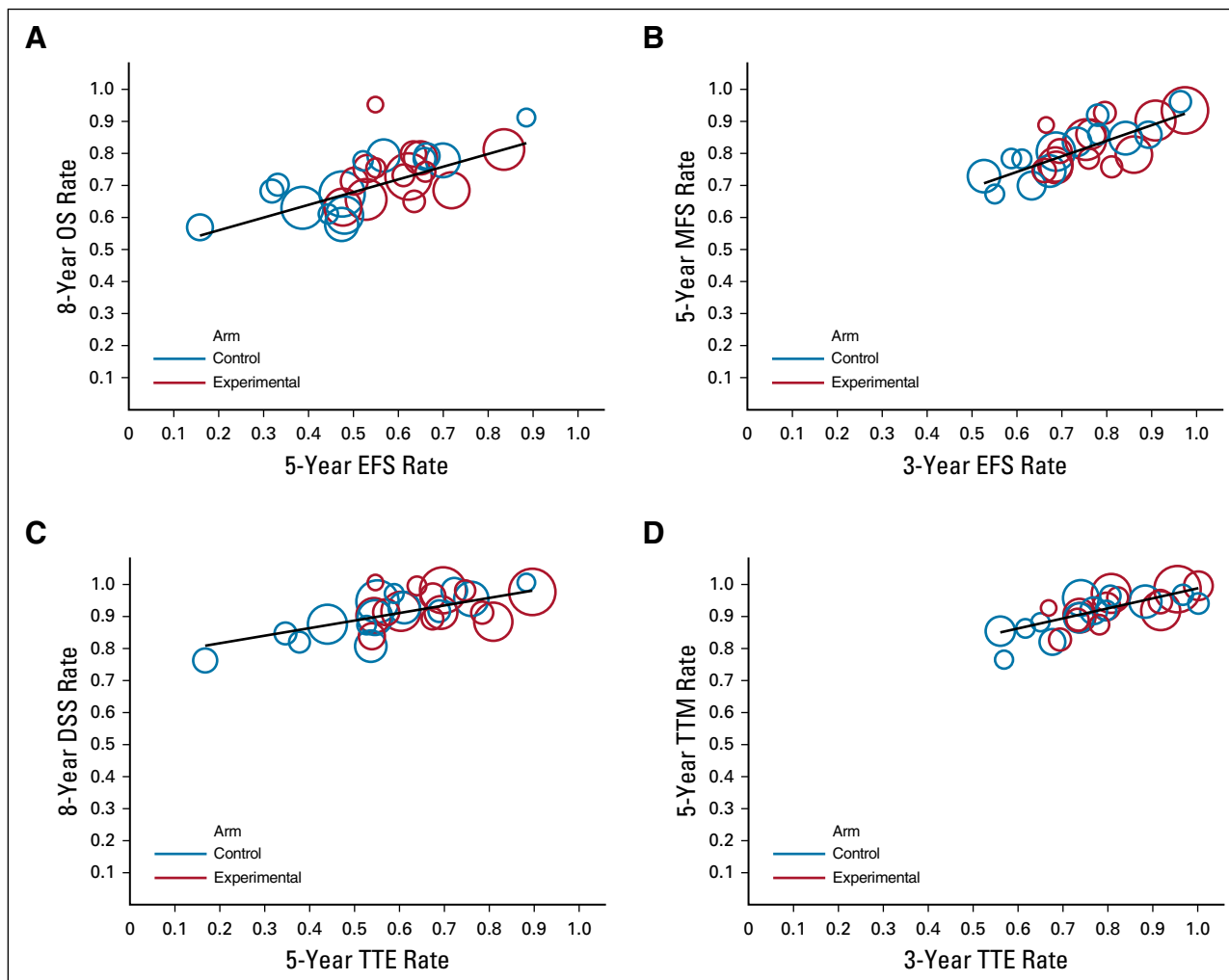


FIG 2. Bubble plot and regression of (A) overall survival (OS) at 8 years on event-free survival (EFS) at 5 years; (B) metastasis-free survival (MFS) at 5 years on EFS at 3 years; (C) disease-specific survival (DSS) at 8 years on time to event (TTE) at 5 years; and (D) time to metastasis (TTM) at 5 years on TTE at 3 years. All rates were Kaplan-Meier estimates by trial and treatment arm. Circle size and regression were weighted by inverse variance of the 5- or 3-year estimate for EFS and TTE.

the inverse of variances of the 5- or 3-year estimates of EFS. R^2 was used to quantify the proportion of variance that was explained by the regressions.

Condition 2 was tested at the trial level. Proportional hazards models estimated the study-specific treatment effects (ie, the natural $\log[\text{HR}]$ of the experimental v the control arm) on the EFS and OS. We then fit a WLR of $\log(\text{HR})$ -OS on $\log(\text{HR})$ -EFS across trials. Regressions were weighted by inverse variances of the $\log(\text{HR})$ -EFS. The same approach was applied to the surrogacy analysis of EFS for MFS, and the surrogacy of TTE for TTM and DSS, where end points of patients with nonprostate cancer deaths were censored.

Subgroup and sensitivity analysis. We conducted pre-planned subgroup analyses by age (< 70 years, \geq 70 years), by duration of ADT (None, 3-8 months, \geq 2 years), by patient risk groups (defined by the National Comprehensive Cancer Network [NCCN] or D'Amico's criteria), and by biochemical

failure criteria (Phoenix definition only). Because a large proportion of OS events were non-prostate cancer deaths, we performed sensitivity analyses to estimate the trial-level correlation between cumulative incidence estimates of TTE and DSS, and between the subdistribution treatment effect HR estimates for TTE and DSS from competing risk models, for which non-prostate cancer deaths were considered to be the competing risk for each end point. Model accuracy was assessed by the leave-one-out cross validation approach (Data Supplement).

Surrogate threshold effect. The surrogate threshold effect (STE) is defined as the minimum treatment effect on the surrogate (HR-EFS) necessary to predict a significant OS benefit, corresponding to the upper 95% prediction limit for OS HR lower than 1 (Data Supplement). All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC) and R packages.³³

TABLE 1. Surrogacy Condition 1: Correlation Between Clinical End Points (correlation using patient-level data)

Correlation Using Patient-Level Data	No. of Trials	No. of Patients	Kendall's Tau (95% CI)
When non-CaP deaths were counted as events			
Correlation of OS and EFS	16	10,350	0.43 (0.42 to 0.44)
Correlation of MFS and EFS	13 ^a	9,481	0.51 (0.49 to 0.52)
When non-CaP deaths were censored			
Correlation of DSS and TTE	14 ^b	9,934	0.52 (0.50 to 0.54)
Correlation of TTM and TTE	13 ^a	9,481	0.53 (0.51 to 0.55)

Abbreviations: CaP, cancer of the prostate; DSS, disease-specific survival; EFS, event-free survival; MFS, metastasis-free survival; OS, overall survival; TTE, time to event; TTM, time to metastasis.

^aExcluding 3 studies that did not collect metastasis data.

^bExcluding 2 studies with < 3 prostate cancer deaths.

RESULTS

Trial and Patient Characteristics

For analysis, 10,350 patients from 15 primary radiation therapy-based trials were included (Data Supplement). One trial was split into 2 experimental arms, which resulted in 16 study units for EFS and OS analysis and 13 study units for MFS analysis (Data Supplement). Most trials compared the duration of ADT (10 trials) or different radiation doses or fields (4 trials). Patients enrolled in the trials from 1987 to 2011, and the median follow-up was 10 years (range, 0.1-22 years). More than 80% of patients were < 75 years of age, and nearly 60% had high-risk disease according to the NCCN or D'Amico criteria (Data Supplement).

For the EFS end point, 6,049 events were reported, 4,666 (77%) from disease recurrence (biochemical failure only 56%; the following were with or without reported biochemical failure: local or regional recurrence, 12%; distant metastasis, 6%; and unknown recurrence site, 3%) and 23% from nonprostate cancer death (Data Supplement). The median duration of EFS from random assignment was

6.0 years (95% CI, 5.9 to 6.2 years). There were 4,390 events for the MFS end point: 29% metastasis, 5% prostate cancer death without recoded metastasis, and 66% non-prostate cancer death. Observed 5-year rates from the Kaplan-Meier curves were 56% (95% CI, 55% to 57%) for EFS, 80% (95% CI, 79% to 81%) for MFS, and 84% (95% CI, 84% to 85%) for OS (Fig 1). Cumulative event rates for disease recurrence, metastasis, and prostate cancer death compared with non-prostate cancer death were delineated for the overall cohort and by the NCCN risk group and age group (Data Supplement). For patients who experienced an EFS disease recurrence event (n = 4,666 of the 6,049 events), median postrecurrence OS was 7.4 years (95% CI, 7.1 to 7.7 years). For patients who were reported to have a metastasis (n = 1,287 of 4,390 MFS events), median postmetastasis survival was 1.9 years (95% CI, 1.8 to 2.1 years).

Surrogacy Condition 1: Correlation Between ICE and OS

At the patient level, the Kendall's tau correlation over the entire follow-up was 0.43 (95% CI, 0.42 to 0.44) for EFS with OS and 0.51 (95% CI, 0.49 to 0.52) for EFS with MFS. When non-prostate cancer deaths were censored, the correlations of TTE

TABLE 2. Surrogacy Condition 1: Correlation Between Clinical End Points (regression using trial level estimates)

Regression Using Trial-Level Estimates	No. of Trials	No. of Arms	R ² (95% CI)
When non-CaP deaths were counted as events			
8-year OS rate on 5-year EFS rate	14 ^b	28	0.55 (0.26 to 0.70)
8-year MFS rate on 5-year EFS rate	11 ^{a,b}	22	0.63 (0.31 to 0.76)
5-year OS rate on 3-year EFS rate	16	32	0.61 (0.35 to 0.73)
5-year MFS rate on 3-year EFS rate	13 ^a	26	0.73 (0.48 to 0.82)
When non-CaP deaths were censored			
8-year DSS on 5-year TTE rate	14 ^b	28	0.45 (0.15 to 0.63)
8-year TTM on 5-year TTE rate	11 ^{a,b}	22	0.49 (0.15 to 0.67)
5-year DSS on 3-year TTE rate	16	32	0.44 (0.17 to 0.62)
5-year TTM on 3-year TTE rate	13 ^a	26	0.57 (0.27 to 0.72)

Abbreviations: CaP, cancer of the prostate; DSS, disease-specific survival; EFS, event-free survival; MFS, metastasis-free survival; OS, overall survival; TTE, time to event; TTM, time to metastasis.

^aExcluding 3 studies that did not collect metastasis data.

^bExcluding 2 studies with median follow-up of < 6 years.

with DSS and with TTM were 0.52 (95% CI, 0.50 to 0.54) and 0.53 (95% CI, 0.51 to 0.55), respectively.

The end point correlation was also tested using trial-level estimates (Fig 2). The R^2 was 0.55 (95% CI, 0.26 to 0.70) from WLR of 8-year OS on 5-year EFS rates and was 0.63 (95% CI, 0.31 to 0.76) of 8-year MFS on 5-year EFS rates across trials and treatment arms. With earlier milestone time points of 5-year OS and MFS rates versus 3-year EFS rates, R^2 was 0.61 (95% CI, 0.35 to 0.73) and 0.73 (95% CI, 0.48 to 0.82), respectively. Tables 1 and 2 also summarize R^2 for these end points when non-prostate cancer deaths were censored.

Surrogacy Condition 2: Correlation Between Treatment Effect on ICE and OS

At the trial level, trial-specific treatment effects, measured by log-HR for each end point, are shown in forest plots in the Data Supplement. The R^2 from the WLR of log(HR)-OS on log(HR)-EFS was 0.35 (95% CI, 0.01 to 0.60) and was 0.55 (95% CI, 0.09 to 0.74) for log(HR)-MFS on log(HR)-EFS (Table 3). When non-prostate cancer deaths were censored, the R^2 of log(HR)-DSS on log(HR)-TTE was 0.39 (95% CI, 0.01 to 0.64) and was 0.68 (95% CI, 0.23 to 0.81) for log(HR)-TTM on log(HR)-TTE (Fig 3).

Subgroup and Sensitivity Analysis

At the patient level, results were consistent when the analysis was restricted to the 14 trials using the Phoenix definition for biochemical failure, or to the populations with high-risk features or above and below the median age of 70 years (Data Supplement). The Kendall's tau correlation between OS and EFS was slightly stronger in those who received ≥ 2 years of ADT compared with those who received short-term or no (neo)adjuvant ADT (0.53, 0.43, and 0.39, respectively). In patients with high-risk features and when non-prostate cancer deaths were censored, the estimated R^2 from the WLR of log(HR)-DSS on log(HR)-TTE across trials was 0.64 (95% CI, 0.21 to 0.79). Results were also consistent in a WLR analysis of trial-level correlations when non-prostate cancer deaths were treated as competing risk

(Data Supplement) and in leave-one-out cross-validation (Data Supplement).

STE

The STE was an HR(EFS) of 0.33 on OS (Fig 3A) and an HR(EFS) of 0.44 on MFS (Fig 3B), which indicates that large risk reductions of at least 67% and 56% on EFS would predict a significant treatment effect on OS and MFS, respectively. The STE was an HR(TTE) of 0.29 on DSS (Fig 3C) and an HR(TTE) of 0.48 on TTM (Fig 3D) when non-prostate cancer deaths were censored.

DISCUSSION

This work clearly shows that EFS is a weak surrogate for both OS and DSS for men with intermediate- and high-risk localized prostate cancer treated with curative-intent radiation with a 10% chance of dying as a result of prostate cancer and approximately a 60% OS at 10 years. Notably, this analysis included only patients treated with primary radiation, and therefore, the findings should not be extrapolated to trials of patients treated with prostatectomy or salvage radiation after prostatectomy²⁶. As the estimated hazard curves over time (Fig 1) depict, there are many early EFS events (mostly PSA relapses) with few MFS and OS events. This indicates that despite 80% of men being younger than 75 years old and fit for a clinical trial, they are still more likely to die a non-prostate cancer death even if they have a PSA relapse. This provides additional evidence that many PSA relapses are indolent and/or are controlled by testosterone suppression.^{34,35}

Prior studies have shown PSA relapse heralding a prostate cancer recurrence is prognostic for OS and DSS, mainly on the basis of single-trial, patient-level data and using landmark analysis at selected time points.²⁹⁻³¹ In particular, the subpopulation of younger men with a rapidly rising PSA at relapse are more likely to die as a result of prostate cancer. However, the new data presented in this manuscript showing the low correlation of EFS with OS at both the patient and the trial level indicate that EFS is not a viable surrogate for OS to replace it as the primary end point in phase III localized prostate cancer trials. This was

TABLE 3. Surrogacy Condition 2: Treatment Effects on End Points are Correlated

Regression Analysis Details	No. of trials	R^2 (95% CI)	Regression Equation
When non-CaP deaths were counted as events			
Regression of Log(HR)-OS on Log(HR)-EFS	16	0.35 (0.01 to 0.60)	$\text{Log(HR)}_{\text{OS}} = 0.0047 + 0.3470 \times \text{Log(HR)}_{\text{EFS}}$
Regression of Log(HR)-MFS on Log(HR)-EFS	13 ^a	0.55 (0.09 to 0.74)	$\text{Log(HR)}_{\text{MFS}} = 0.0449 + 0.4978 \times \text{Log(HR)}_{\text{EFS}}$
When non-CaP deaths were censored			
Regression of Log(HR)-DSS on Log(HR)-TTE	14 ^b	0.39 (0.01 to 0.64)	$\text{Log(HR)}_{\text{DSS}} = -0.0118 + 0.7554 \times \text{Log(HR)}_{\text{TTE}}$
Regression of Log(HR)-TTM on Log(HR)-TTE	13 ^a	0.68 (0.23 to 0.81)	$\text{Log(HR)}_{\text{TTM}} = 0.0443 + 0.7567 \times \text{Log(HR)}_{\text{TTE}}$

Abbreviations: DSS, disease-specific survival; EFS, event-free survival; MFS, metastasis-free survival; OS, overall survival; TTE, time to event; TTM, time to metastasis.

^aExcluding 3 studies that did not collect metastasis data.

^bExcluding 2 studies with < 3 prostate cancer deaths.

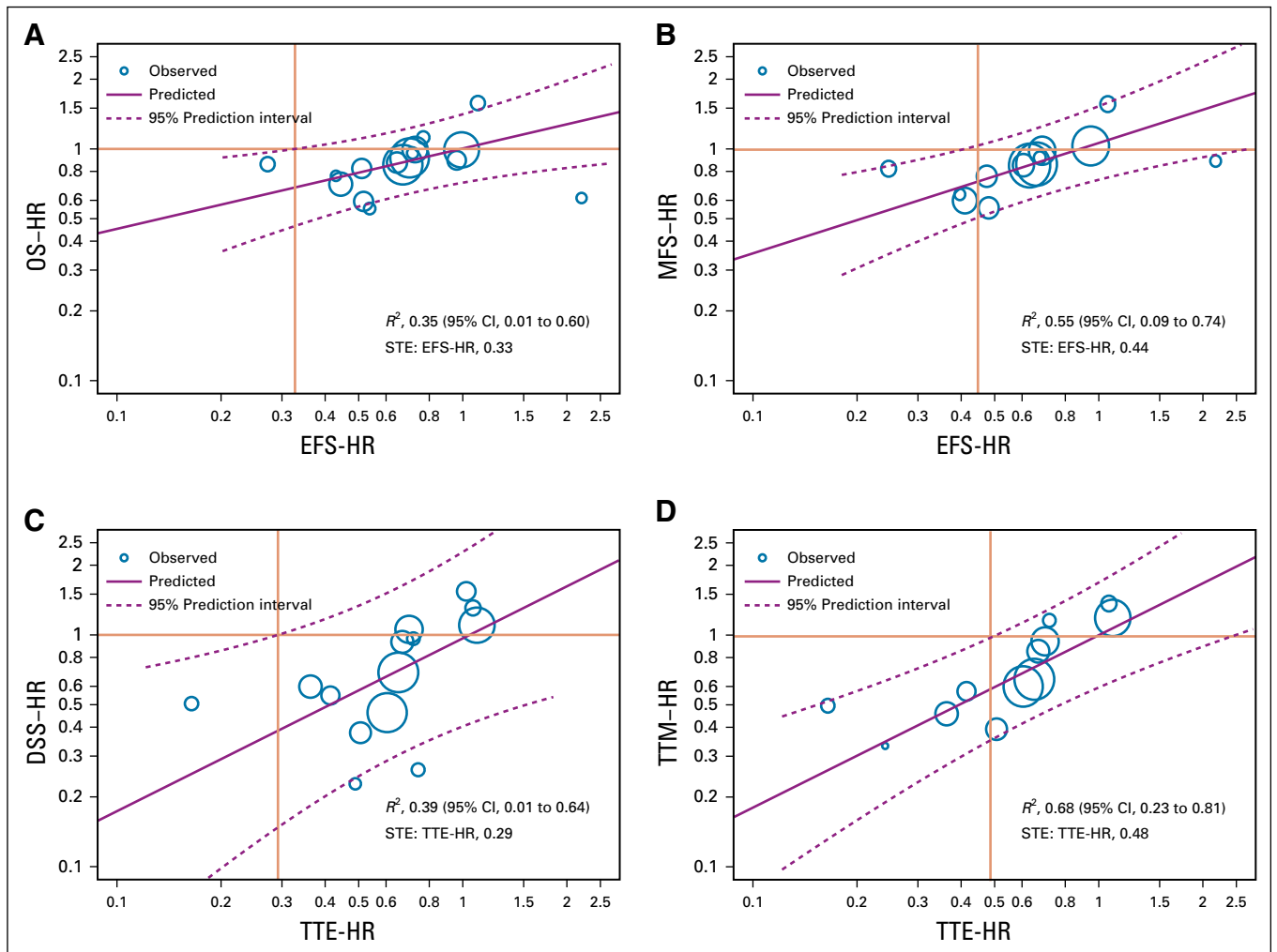


FIG 3. Bubble plot and regression of (A) hazard ratio for overall survival (OS-HR) on hazard ratio for event-free survival (EFS-HR); (B) hazard ratio for metastasis-free survival (MFS-HR) on EFS-HR; (C) hazard ratio for disease-specific survival (DSS-HR) on hazard ratio for time to event (TTE-HR); (D) hazard ratio for time to metastasis (TTM-HR) on TTE-HR. Cox proportional hazards regression estimated HR for each study, and values were natural logarithm transformed. Circle size and regression were weighted by inverse variance of $\log(\text{HR})$ estimates for EFS or TTE. The orange lines display surrogate threshold effect (STE), which is the intersection of the upper 95% prediction limit with the horizontal line representing an HR of 1 for the true end points.

underscored by showing that removal of non-prostate cancer deaths (approximately 20% of EFS events) as part of the TTE analysis did not substantially improve the correlation. By contrast, MFS was a strong surrogate for OS in the same population treated with radiation (with all surrogacy association parameters > 0.8).²¹ EFS may play a role in enriching the analysis or the interim monitoring analysis during phase III clinical trials.³⁶ This finding does not undermine the observation that identification of PSA relapses has other benefits such as identifying men for postprostatectomy salvage radiation and use of PSA-DT for counseling about prognosis. The long-term results of ongoing (neo)adjuvant trials with potent androgen receptor inhibitors will determine whether EFS can serve as a surrogate for OS in this setting. This possibility is further confounded by the fact this class of therapy may directly affect the biomarker (PSA).

It is also recognized that there are other benefits to patients and society from not having a PSA relapse. From the patient perspective, there is the potential impairment in quality of life associated with a PSA relapse, both from the anxiety of the recurrence itself and from the adverse effects of salvage radiation therapy (if treated with a prostatectomy) and protracted testosterone suppression, noting the median post-recurrence survival in this cohort was 7.4 years. In addition, there are the patient and health care impacts from increasing comorbidities associated with prolonged ADT such as glucose intolerance, cardiovascular events, and bone loss. If a patient does progress to having metastatic disease, there are additional impairments from cancer-related events of bone pain and fatigue and the costs and toxicities of more potent hormonal therapy and cytotoxic agents.³⁷ Recent modeling analyses from the STAMPEDE docetaxel results show that preventing progression events with docetaxel was

also a more efficient use of health care resources.³⁸ The ICECaP Working Group has established a health economics team who are using the ICECaP IPD to estimate the health economic impacts on patients and society of preventing metastatic disease and earlier PSA relapse. If these benefits of preventing earlier relapses can be defined at both the patient and the societal level, and they offset the associated costs from the use of the new therapies in the (neo)adjuvant setting, then PSA-based end points could be used to accelerate the conduct of adjuvant prostate cancer trials.

The inherent limitations of this work are as follows. First, the data were generated from an era before the use of the more active therapies shown to prolong OS in the metastatic hormone-sensitive prostate cancer and CRPC settings.^{6-9,17,18} However, a recent analysis indicates that the cumulative use and efficacy of these new therapies have a limited impact on CRPC longevity.³⁹ It is hoped that some of these new therapies will have more impact in the adjuvant setting. Second, because of incomplete PSA or salvage therapies, only a subset of all the trials in the ICECaP database was included in the EFS analysis, and these were

only radiation-based trials. However, the analyzed IPD from 10,000 patients was representative of both the entire ICECaP database (Data Supplement) and the general population of patients with intermediate- or high-risk prostate cancer treated with radiation,¹ which supports the relevance of the results. Another notable limitation is the lack of granular testosterone and PSA data to assess doubling time before subsequent therapies; this highlights the need for a harmonized and strategic data collection plan for future trials to robustly assess other PSA metrics.⁴⁰

In conclusion, EFS is only a weak surrogate for OS in clinically localized prostate cancer in a patient population treated with radiation with approximately a 10% chance of dying of prostate cancer over 10 years despite potentially curative local therapy. As such, EFS cannot be used as a surrogate for OS and replace it as the primary end point to accelerate (neo)adjuvant prostate cancer phase III trials. Health economic analyses are underway to determine if other metrics of benefits to patients and society can be quantified to support the use of EFS as an end point to accelerate (neo)adjuvant prostate cancer trials.

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**Event-Free Survival, a Prostate-Specific Antigen–Based Composite End Point, Is Not a Surrogate for Overall Survival in Men With Localized Prostate Cancer Treated With Radiation**

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