Surrogate End Points for All-Cause Mortality in Men With Localized Unfavorable-Risk Prostate Cancer Treated With Radiation Therapy vs Radiation Therapy Plus Androgen Deprivation Therapy: A Secondary Analysis of a Randomized Clinical Trial.

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Abstract

IMPORTANCE: Several surrogates for prostate cancer-specific mortality satisfying the Prentice criteria exist, but whether these are surrogates for all-cause mortality, and how their performance compares, is unknown.

OBJECTIVE: To ascertain and compare the performance of 4 candidate surrogates (prostate-specific antigen [PSA] failure, PSA nadir >0.5 ng/mL, PSA doubling time <9 months, and interval to PSA failure <30 months) for all-cause mortality using the proportion of treatment-effect metric.

DESIGN, SETTING, AND PARTICIPANTS: For this randomized clinical trial, 206 men with unfavorable-risk prostate cancer who were seen at a Harvard-affiliated academic hospital or an associated community hospital between December 1, 1995, to April 15, 2001, were identified, randomized to radiation therapy alone or radiation therapy followed by 6 months of androgen deprivation therapy, and followed for a median 16.62 years. This analysis looks at the subgroup of 157 men with minimal comorbidities or no comorbidity (median follow-up, 16.49 months).

INTERVENTIONS: Patients were previously randomized to receive radiation therapy or radiation and 6 months of androgen deprivation therapy.

MAIN OUTCOMES AND MEASURES: Risk of all-cause mortality.

RESULTS: Overall, a cohort of 157 men (median [interquartile range] age, 72.43 [68.75-75.53]) with unfavorable-risk prostate cancer and minimal or no comorbidities were selected for this study. Three tested metrics met all 4 Prentice criteria for surrogacy for the surrogate covariate in the adjusted model for all-cause mortality: PSA nadir greater than 0.5 ng/mL (adjusted hazard ratio [aHR], 1.72; 95% CI, 1.17-2.52; P = .01), PSA doubling time less than 9 months (aHR, 2.06; 95% CI, 1.29-3.28; P = .003), and interval to PSA failure less than 30 months (aHR, 1.76; 95% CI, 1.06-2.92; P = .03); while PSA failure did not. For the 3 successful surrogates, the proportion of treatment effect values were 103.86%, 43.09%, and 41.26%,
CONCLUSIONS AND RELEVANCE: A PSA nadir value of greater than 0.5 ng/mL following radiation and androgen deprivation therapy appears to identify men prior to PSA failure who are at high-risk for death. This could be used to select men for entry at the time of PSA nadir onto randomized trials evaluating the impact on survival of salvage androgen deprivation therapy with or without agents shown to prolong survival in men with castrate-resistant metastatic prostate cancer.

TRIAL REGISTRATION: clinicaltrials.gov Identifier: NCT00116220.