Does Early Prostate Specific Antigen Doubling Time after Radical Prostatectomy, Calculated Prior to Prostate Specific Antigen Recurrence, Correlate with Prostate Cancer Outcomes? A Report from the SEARCH Database Group

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Purpose: Short prostate specific antigen doubling time following recurrence after radical prostatectomy portends a poor prognosis. Prostate specific antigen doubling time is traditionally calculated using prostate specific antigen values 0.2 ng/ml or greater. We determined whether early prostate specific antigen doubling time, calculated from the first detectable postoperative prostate specific antigen up to and including the first recurrence value, correlates with prostate cancer outcomes.

Materials and Methods: Cox models were used to examine the association between early prostate specific antigen doubling time and castration resistant prostate cancer, metastases, and all cause and prostate cancer specific mortality in 674 men who underwent radical prostatectomy between 1988 and 2014 and had a biochemical recurrence. Early prostate specific antigen doubling time was examined as a log transformed continuous and a categorical variable.

Results: After adjusting for multiple clinicopathological characteristics, log transformed early prostate specific antigen doubling time was not associated with any outcome. However, when early doubling time was categorized as 15 or greater, 9 to 14.9, 3 to 8.9 and less than 3 months, on multivariable analysis men with early doubling time less than 3 months were at increased risk for castration resistant prostate cancer (HR 6.20, p = 0.004), metastases (HR 5.26, p = 0.001), prostate cancer specific mortality (HR 5.06, p = 0.026) and all cause mortality (HR 1.63, p = 0.065) compared to those with an early doubling time of 15 months

Abbreviations and Acronyms

ACM = all cause mortality
BCR = biochemical recurrence
CRPC = castration resistant prostate cancer
ePSADT = early PSADT
PCSM = prostate cancer specific mortality
PSA = prostate specific antigen
PSADT = PSA doubling time
RP = radical prostatectomy
SEARCH = Shared Equal Access Regional Cancer Hospital

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or greater. However, the association with all cause mortality was not significant. Those with an early prostate specific antigen doubling time of 3 to 8.9 months were at increased risk for castration resistant prostate cancer (HR 3.56, p = 0.015), all cause mortality (HR 1.67, p = 0.006) and prostate cancer specific mortality (HR 3.17, p = 0.044) but not metastases (p = 0.13).

Conclusions: Early prostate specific antigen doubling time less than 9 months, calculated using prostate specific antigen values before and up to biochemical recurrence, is associated with an increased risk of castration resistant prostate cancer, metastases, and prostate cancer specific and all cause mortality among men with biochemical recurrence after radical prostatectomy. Early prostate specific antigen doubling time allows for risk stratification at biochemical recurrence and before prostate specific antigen doubling time is calculable, enabling these men to be referred for early aggressive secondary treatment and/or clinical trials.

Key Words: prostatic neoplasms; prostate-specific antigen; neoplasm recurrence, local; prostatectomy; prognosis

SHORT PSADT following BCR after RP portends a poor prognosis.[1–5] These findings are based on standard PSADT calculated using PSA values after recurrence (ie PSA 0.2 ng/ml or greater). Indeed, guidelines to calculate PSADT recommend starting at 0.2 ng/ml.[6] Therefore, to use PSADT a patient must experience recurrence and be followed for several months with serial PSA testing. Given data that lower PSA leads to improved outcomes after salvage radiation,[7] decisions regarding salvage treatment are often made at BCR when PSADT is not yet calculable. Thus, many men are treated early and will never have a calculable PSADT.

We previously reported that men with the worst disease are treated early after BCR before there are sufficient PSA measurements to calculate PSADT and, thus, noncalculable PSADT is associated with worse prognosis.[8] Ideally tumor growth kinetics could be used for decision making at BCR. Notably many men have multiple detectable PSA measurements before they reach the BCR threshold. While these low but detectable PSAs can be used to calculate ePSADT, the clinical usefulness of these low values is unclear. We also previously found that while ePSADT and standard PSADT correlated, the overall correlation was modest.[9] To our knowledge no study to date has examined whether these low PSA values can be used to predict longer term outcomes.

To address this we examined the correlation between ePSADT and prostate cancer outcomes, including CRPC, metastases, ACM and PCSM, among men in the SEARCH database,[10] a racially diverse cohort treated with RP at multiple Veterans Affairs hospitals nationwide. If ePSADT correlated with any of these outcomes, it would allow men at highest risk to be identified months to years before they could be identified using PSADT, which is essential for appropriate risk stratification.

MATERIALS AND METHODS

Clinical and Pathological Variables

After obtaining institutional review board approval, data on patients who underwent RP at Veterans Affairs hospitals in West Los Angeles, San Diego and Palo Alto, California; Augusta, Georgia; and Asheville and Durham, North Carolina were entered in the SEARCH database.[10] Patients who received neoadjuvant treatment were excluded from study. BCR was defined as a single PSA greater than 0.2 ng/ml or 2 concentrations at 0.2 ng/ml.[11] CRPC was defined as a PSA rise of 2 ng/ml or greater and 25% greater than the post-ADT nadir while being castrate.[12] All imaging tests (bone scan, magnetic resonance imaging, computerized tomography and x-ray) were assessed to determine the development of metastases. Mortality was determined from the medical records. PCSM was defined as metastases showing progression after hormonal therapy without another obvious cause of death.

Doubling Time Calculations

PSA values were obtained postoperatively at the discretion of the treating physician. At different centers different PSA tests were used, although at each center PSA tests were consistent except when changing to an ultrasensitive assay sometime in 2001 to 2005 (the year differed across centers). Starting with the first detectable PSA after RP, ePSADT was calculated, including all PSA values up to and including the first value used to define BCR (ie the first value greater than 0.2 ng/ml or the second consecutive PSA 0.2 ng/ml). Patients needed 2 or more values separated by 3 or more months to have a calculable ePSADT. Men who started salvage hormonal or radiation therapy prior to BCR were excluded from analysis. Thus, all PSA values used for ePSADT calculations were obtained before subsequent treatment. The 31 men with a doubling time of 0 or less (ie no increase or a decline in PSA) or a long doubling time (more than 120 months) were assigned a value of 120 months for ease of analysis.

To calculate ePSADT we used previously described methods, assuming first order kinetics and calculating by dividing the natural log of 2 (0.693) by the slope of the