Time to Prostate-Specific Antigen Nadir After Radical Prostatectomy – a new potential predictive prognostic parameter and its impact on clinical outcomes

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Abstract

Background

To investigate and validate previously published associations between time to prostate-specific antigen nadir and the time-to-nadir after radical prostatectomy with biochemical recurrence and to extend this analysis to overall survival and prostate cancer-specific mortality risk.

Methods

This is a retrospective analysis of 1796 men from the South Australian Prostate Cancer Clinical Outcomes Collaborative database treated with radical prostatectomy between 1998-2018 with available prostate-specific antigen nadir data within 1-6 months after surgery. Uni- and multivariable analyses of prostate-specific antigen nadir, time-to-nadir, biochemical recurrence and death were performed with Cox and competing risks models (adjusted for age, surgery year, tumour features and preoperative prostate-specific antigen).

Results

The univariable analysis demonstrated those with shorter time-to-nadir <3 months had a decreased risk of biochemical recurrence (log-rank, p=0.0098) compared to those with longer time-to-nadir 3-6 months. For men with a time-to-nadir <3 months, a Log-rank test showed a decreased risk of prostate cancer-specific mortality (p=0.026) compared to time-to-nadir 3-6 months, without a difference in overall survival. Multivariable competing risk analyses indicated that biochemical recurrence was more likely when time-to-nadir was 3-6 months compared to <3 months (sHR=1.43, CI 1.01-2.02, p=0.04).

Conclusions

Among men undergoing radical prostatectomy, a shorter post-operative time-to-nadir <3 months is associated with decreased risk of biochemical recurrence compared to time-to-nadir 3-6 months. Following adjustment for confounders and competing risks, there was no significant difference in time-to-nadir for mortality outcomes.

Background

Prostate Cancer (PCa) is Australia's second most diagnosed cancer in males and the third most common cause of cancer-related death.(1) Predicting the course and appropriately treating PCa can be difficult due to the typical indolent natural history of the disease and similarly with treated PCa. A widely used, surgical treatment option of early-stage localised PCa is radical prostatectomy (RP). After RP, approximately a third of men will experience biochemical recurrence (BCR) within 10 years.(2) A proportion of men with BCR have rapid and aggressive cancer leading to death, while others may have a slower progression.(3–5) Thus, the need to find surrogate markers to identify those more at risk of aggressive cancer and death to better target adjuvant treatment.

A common and readily available surrogate marker routinely used for surveillance and early detection of cancer recurrence is serum Prostate-specific antigen (PSA). Pre-operative PSA levels have been shown to correlate with adverse pathological features at RP and BCR as evidenced by its inclusion in numerous pre-op predictive nomograms.(6) Pre-op PSA density, pre-op PSA velocity (PSAV) and pre and post-op PSA doubling time (PSADT) have also been shown to have prognostic value, however, none of these PSA metrics has reported a strong and consistent association with prostate cancer-specific mortality (PCSM).(7–9)

Post-op PSAV and PSADT have not found widespread clinical favour as it is often necessary to wait for > 12 months for results which are problematic in view of the need to determine an (early) adjuvant therapy in recurrent disease. Previous studies have observed the lowest PSA level after RP (PSA nadir) is strongly associated with BCR and overall mortality and furthermore, emerging research suggests that the time after RP that men achieve PSA nadir may have a bearing on their prognosis.(10–14) The wait to calculate the time to PSA nadir is at maximum 6 months and hence may prove to be a more judicious and convenient metric.

At least five studies correlate the post-treatment time patients achieve PSA nadir with an impact on prognosis. For example, after androgen deprivation therapy (ADT), longer time-to-nadir (TTN) is associated with higher overall mortality.(10, 11) Conversely, after radiotherapy (RTx), shorter TTN is associated with greater risk of BCR, distant metastases and death.(12, 13, 15)

A recent retrospective cohort analysis by Skove et al. from the Shared Equal-Access Research Cancer Hospital (SEARCH) database concluded men with both a detectable PSA nadir (> 0.01 ng/mL) and shorter TTN (< 3 months) after RP had an increased risk of BCR.(16) A limitation of the study was the lack of more definitive clinical endpoints such as death and although BCR is a clinically relevant determinate, it is largely considered a “surrogate” endpoint as only a small proportion of BCR patients will develop metastatic disease and/or die of prostate cancer.(2, 17) Moreover, though that study did adjust for confounders through multivariable analysis, there was no further survival analysis of competing risks for BCR, such as death from another cause. We are unaware of any other studies which corroborate the work by Skove and we sought to validate these findings in an Australian population by querying the South Australian Prostate Cancer Clinical Outcomes Collaborative (SA-PCCOC) registry database.

Additionally, no study has assessed the prognostic utility of PSA TTN after RP with more distant clinical endpoints. Whether the TTN is associated with overall survival (OS) or PCSM after RP is unknown and we include a mortality analysis in our investigation. For men with localised prostate cancer, treated with RP, we hypothesise a shorter time to PSA nadir in the first six months after surgery may be correlated with poorer OS and PCSM risk.

Methods

Study Population

SA-PCCOC is a third-party collated, disease-specific, prospective, longitudinal, observational PCa registry and database established in the state of South Australia. The database presently collects approximately 93% of all new histologically confirmed diagnoses of prostate cancer in the state. Men are followed until death or withdrawal from the registry. Commencing in 1998, SA-PCCOC is the longest-running PCa database in Australia and the Southern Hemisphere and at the time of writing has collected approximately 15,000 participants.

Inclusion and Exclusion Criteria

We defined BCR as a post-operative PSA reading of > 0.2 ng/ml which is the most widely accepted consensus definition in the literature.(18)

Men from the SA-PCCOC database were included in this analysis if they had undergone RP between 1998–2018 inclusive. Our study's censor date was 30th June 2018, to allow at least six months of available follow-up data to the end of 2018.

Of 5157 patients in SA-PCCOC treated with RP during this period, patients were excluded if they: had their surgery after the censor date of 30th of June 2018 (n = 206), did not have a PSA value within three months of surgery (n = 1528), had preoperative treatment with ADT/RTx (n = 50), received secondary treatment with ADT/RTx within six months of surgery (n = 200), had recurrence within six months (n = 62), had a PSA nadir > 0.2 ng/mL (i.e. these patients already had a BCR and thus were not at risk of future BCR) (n = 390), only had one PSA level within the 6 months after surgery (which meant a PSA nadir could not be determined) (n = 810) and had TTN of > 6 months (n = 115). This resulted in a study population of 1796 patients (Fig. S1). Additionally, all selected patients had available data for year of RP, pathological staging, Gleason score, margin status and cause of death.

As SA-PCCOC is a population-based observational registry, there was no standardisation for the timing of post-operative PSA tests which were determined by individual clinician discretion. The PSA nadir was defined as the lowest PSA post-RP where there were at least two PSA results. Time to BCR was defined as time from the date of surgery to the first PSA reading > 0.02 ng/ml.

The definition of undetectable PSA differed slightly in our study. The SA-PCCOC database derives its PSA data from several different pathology laboratories so there were considerable variations in the use of ultrasensitive PSA assays and the level each laboratory defined as an undetectable PSA. PSA assay non-uniformity across different laboratories is a recognised issue when comparing studies involving PSA nadirs.(19) As such, our study defined an undetectable PSA as a range of 0.01–0.1 ng/mL, which was representative of the span of various definitions of undetectable PSA levels across the different pathology companies during the period of observation. Skove defined undetectable PSA nadirs as assays < 0.01 ng/ml.

The SA-PCCOC database does not have complete data on ethnicity or body mass index (BMI). This study also did not analyse clinical staging data, as pathological staging was deemed to be more objective for

the evaluation and clinical stage has been reported as having minimal impact on localized prostate cancer treated by RP.

The SA-PCCOC database sources patient death data from the SA Government Births, Deaths and Marriages Registry. If multiple reasons were listed for the cause of death, men were flagged as dying from prostate cancer only if it was recorded as a significant contributing cause of death and not a secondary diagnosis.

Ethics

Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee. Access was granted to the SA-PCCOC database by the SA-PCCOC research committee.

Statistical Analysis

The variable of interest was TTN which dichotomised the cohort into two groups: TTN < 3 months and TTN 3–6 months, as described by Skove.(16) Patient characteristics between these groups were compared using chi-square tests for categorical data and rank-sum tests for continuous variables.

Univariable analysis of time to BCR, OS and PCSM was assessed with Kaplan-Meier plots and log-rank tests. Multivariable analysis of TTN and time to BCR, OS and PCSM was performed using a Cox proportional hazards model. The analysis was adjusted for the following potential confounders: age at surgery (continuous), year of surgery (continuous), pre-operative PSA (continuous) and pathological Gleason score (low-risk ≤ 6, intermediate risk 3 + 4, high-risk 4 + 3 to 10). Proportional hazards assumption of the Cox regressions were assessed using the test described by P. Grambsch and T. Therneau (1994).

Associations between time to BCR and PCSM with TTN were also assessed using Fine and Gray competing risk models, which are reported as sub-distribution hazard ratios (sHR) and presented as cumulative incidence curves. In the models where BCR was the outcome, death from any cause was considered a competing risk. Where PCSM was the outcome, death from non-prostate causes was considered a competing risk. The analysis was adjusted for the same covariates used in the Cox model.

A p-value of < 0.05 was considered statistically significant for all analyses. All statistical analyses were performed using RStudio (v1.1.463) with R (version 3.5.2), with the survival survival analysis, survminer drawing survival curves and cmprsk competing risk packages.(20)

Results

Men with a TTN of <3 months, compared with a TTN of 3-6 months were likely to be older (65 vs 64 years, p=0.044) and have a marginally lower pathological stage (T1 0.4% vs 0.0%; T2-T3 99.6% vs 99.7%; T4 0.0% vs 0.3%, overall p=0.029). There were no statistically significant differences in pathological Gleason score, preoperative PSA, margin status or cause of death (all p>0.05; Table 1).

After differentiating the cohort by TTN (<3 months vs 3-6 months), univariable analyses demonstrated a TTN <3 months has a decreased risk of BCR (log-rank, *p*=0.0098; Fig. S2). After further stratification by PSA nadir level (detectable vs undetectable), we observed no significant difference between PSA nadir level and TTN (Fig. 1). Men with an undetectable PSA nadir, regardless of TTN, had the greatest BCR-free survival. There was no observed difference between men with an undetectable nadir and PSA TTN, however, the number-at-risk at the 100-month mark for the detectable stratification was small. In the multivariable analysis of BCR, men with a TTN of 3-6 months had a progressively higher risk of BCR (hazard ratio [HR] = 1.61, 95% compatibility interval [CI] 1.18-2.20; Table 2) compared to TTN of <3 months.

The univariable analysis of PCSM showed a similar trend to BCR in that men with TTN <3 months had a decreased risk of PCSM (log-rank, *p*=0.026, Fig. S3) compared to TTN 3-6 months. There was no statistically significant difference between OS and TTN <3 months and TTN 3-6 months (log-rank, *p*=0.25; Fig. S4). Proportional hazards assumption of the Cox regressions was met for OS and PCSM Cox proportional hazard analyses using the test described by P. Grambsch and T. Therneau (1994). It was noted that the proportional hazards assumption was not met for BCR. This could be due to a lack of a key confounder. Two potential candidates were identified, BMI and race, however, they were unable to be included in our analyses as the data was not available.

In multivariable analysis, despite men with a TTN 3-6 months having a higher HR for OS (HR=1.39, CI 0.84-2.31) and PCSM (HR=1.99, CI 0.75-5.27) compared to TTN <3 months, the results were not statistically significant (Table 2).

Competing risk analyses indicated that risk of BCR after RP in men with a TTN 3-6 months was still greater than those with a TTN <3 months (sHR=1.43, CI 1.01-2.02, *p*=0.04, Table 3), though clinical risk stratification was a stronger determinate of BCR. Risk of PCSM after RP was not significantly higher in men with a TTN 3-6 months (sHR = 1.97, CI 0.79-4.94, *p*=0.15). Figure S5 and S6 presents the cumulative incidence of BCR and PCSM respectively, stratified by TTN <3 months and 3-6 months. The cumulative incidence univariable *p*-value was 0.07 and 0.36 for BCR and PCSM respectively.

Discussion

This study examined PSA TTN among nearly 1800 men who underwent RP. The data was derived from the Australian SA-PCCOC database. We found, like the SEARCH data, that a PSA TTN of < 3 months compared to 3–6 months was associated with a decreased risk of biochemical recurrence (Fig. S2).(16) After further stratification by PSA nadir level (detectable vs undetectable) TTN was not an independent predictor of BCR (Fig. 1), which was contrary to the SEARCH findings. The reasons for this discrepancy are not clear. The baseline characteristics in terms of patient numbers in each TTN group were comparable to those of the SEARCH database experience; (our study TTN < 3 months, 1551 men [86%]; TTN 3–6 months, 245 men [14%] vs SEARCH TTN < 3 months, 1723 men [89%]; TTN 3–6 months, 216 men [11%]), though some differences exist. Our cohort had an older median age at surgery (SEARCH

62 years vs this study 64–65 years) and higher pre-operative PSA (SEARCH TTN < 3 months, 6.0 ng/mL; TTN 3–6 months, 6.6 ng/mL vs this study TTN < 3 months, 7.1 ng/mL; TTN 3–6 months, 7.3 ng/mL). The SEARCH data also showed a statistically significant difference between their TTN groups regarding pathological Gleason score and margin status, that was not observed in our study, and our study did not have ethnic group or BMI data.

Additionally, univariate analysis of PCSM showed men having a TTN < 3months after RP also had a decreased risk of BCR compared to a TTN 3–6 months, while there was no difference with OS. Multivariable analyses adjusting for confounders showed higher risk of BCR for men undergoing RP with a TTN 3–6 months compared to < 3 months but showed no difference with regard to OS or PCSM. Competing risk regression confirmed a statistically significant decreased risk of BCR for men undergoing RP with a TTN < 3 months (TTN 3–6 months sHR = 1.43, CI 1.01–2.02; Table 3), while there was no significant risk demonstrated for PCSM.

Although we confirmed PSA TTN is a predictor of BCR, like BCR, it is unable to predict more robust endpoints such as PCSM.

Prostate cancer research is embattled by the typical indolent natural history of the disease. Survival endpoints such as OS and PCSM, although relevant, routinely demand large cohorts with long follow-up to achieve sufficient statistical power. This hinders the development of the evidence-base to inform practice considerably and hence there is the need to identify surrogate endpoints. PSA kinetics both pre and post PCa treatment have been studied extensively. Time-to-PSA nadir post-surgery is a PSA kinetic which is easy to assess and requires a short time frame (< 6 months). Given the emerging evidence of post-operative PSA TTN as a potential surrogate marker for clinical outcomes, our study validates the only other previous publication in this area, and we believe we are the first to use TTN in considering the more distant and clinically relevant endpoints, of OS and PCSM, with more robust survival analyses.(20) BCR after RP is a surrogate follow-up endpoint which overall correlates poorly with progression to metastases and PCSM.(19, 21, 22) It is based upon PSA, which is expected to reach undetectable levels 1–3 months after RP.(19)

The European Association of Urology and the American Urological Association have recommended defining BCR as a PSA ≥ 0.2 ng/mL, followed by a subsequent confirmatory level.(19) However, over 50 BCR definitions can be found in the literature.(23) BCR has been used as a “trigger point” to commence adjuvant treatment (e.g. RTx/ADT), which ultimately may be unnecessary. Competing risks analysis is particularly needed for prostate cancer because it more often occurs later in life (63% of prostate cancer is diagnosed in men over 65 years of age in Australia) and progresses slowly.(1) Hence the likelihood of these men, especially those with severe comorbidities, dying before BCR or from another cause prior to BCR progressing to symptomatic or clinically detectable disease, should be considered.

Limitations of the study includes sample size which precluded analysis of PSA nadir stratified by detectable and undetectable in addition to time-to-nadir. Additionally, we were unable to include the effects of ethnicity and BMI in our covariate analysis and this may have biased our results. However,

studies have shown that race has not been an independent predictor of oncologic outcome following radical prostatectomy.(24, 25) Conversely, BMI has often been shown to have an association with BCR after RP and is an independent predictor of BCR survival.(26–28)

Conclusions

A short PSA TTN after RP of < 3 months versus a longer TTN of 3–6 months appears to predict risk of BCR, but not more robust oncologic endpoints such as OS or PCSM. The PSA nadir post-surgery (detectable vs undetectable) is a stronger predictor of BCR than is TTN.

Declarations

Ethics approval and consent to participate

Ethics approval was obtained from the Southern Adelaide Clinical Human Research Ethics Committee (approval number 307.14). Access was granted to the South Australian Prostate Cancer Clinical Outcomes Collaborative Database (SA-PCCOC) database by the SA-PCCOC research committee.

Consent for publication

No individual person's data was included in the manuscript.

Availability of data and materials

The datasets generated and/or analysed during the current study are not publicly available due to patient confidentiality but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

MT and MC were involved in the conception and design, data acquisition, data analysis and interpretation, drafting of the manuscript, critical revision of the manuscript for scientific and factual content and statistical analysis. KM was involved in the conception and design, data analysis and interpretation, drafting of the manuscript and critical revision of the manuscript for scientific and factual content. MC and KM also both contributed in a supervisory role.

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Supplementary Files Legend

Supplemental Material

Figure S1. Exclusion criteria displayed via the STrengthening the Reporting of OBservational studies in Epidemiology Diagram

Figure S2. BCR-free survival after radical prostatectomy by TTN. BCR, biochemical recurrence; PSA, prostate specific antigen; TTN, time-to-nadir

Figure S3. PCSM-free survival after radical prostatectomy by TTN. PCSM, prostate cancer-specific mortality; PSA, prostate specific antigen; TTN, time-to-nadir

Figure S4. Overall survival after radical prostatectomy by TTN. OS, overall survival; PSA, prostate specific antigen; TTN, time-to-nadir

Figure S5. BCR and competing risk all-cause mortality after radical prostatectomy by TTN. BCR, biochemical recurrence; ACM, all-cause mortality; TTN, time-to-nadir

Figure S6. PCSM and competing risk all-cause mortality after radical prostatectomy by TTN. PCSM, prostate cancer-specific mortality; ACM, all-cause mortality; TTN, time-to-nadir

Tables

Due to technical limitations, Tables 1 - 3 are only available for download from the Supplementary Files section.

Figures

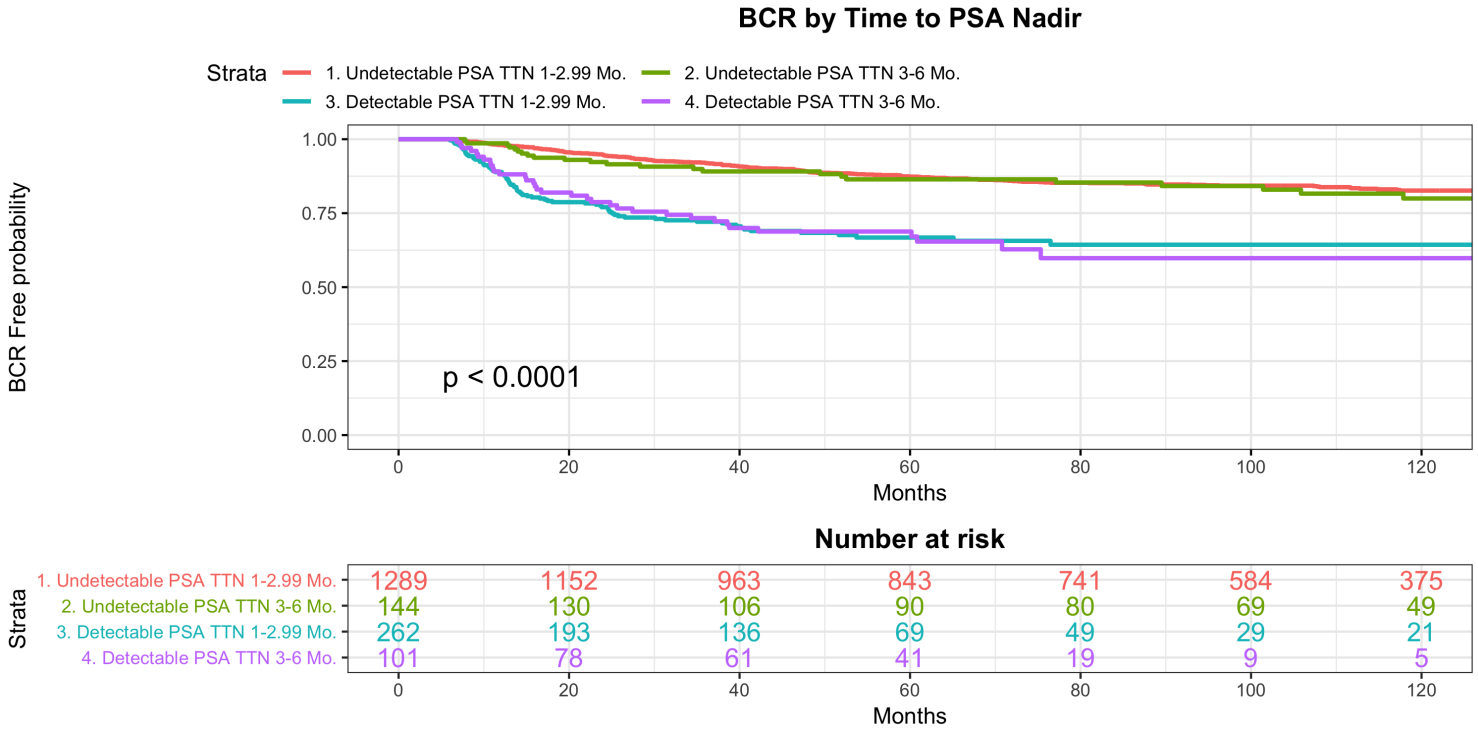

Figure 1

BCR-free survival after radical prostatectomy by TTN stratified by undetectable and detectable PSA nadir. BCR, biochemical recurrence; PSA, prostate specific antigen; TTN, time-to-nadir

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- FigureS6.tif
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