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# The Role of Prostate-Specific Antigen (PSA) and PSA Kinetics in the Management of Advanced Prostate Cancer

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## Abstract

Prostate-specific antigen (PSA) plays an important role in the diagnosis and management of prostate cancer. The utility of PSA has been extended to a number of parameters which may guide clinical decision-making in subsequent treatment. This book chapter systematically reviewed the current evidence of PSA and PSA kinetics in the management of advanced prostate cancer. Results showed that the prognostic significance of pre-treatment PSA level is uncertain. PSA nadir predicts survival outcomes but may be confounded by the pre-treatment PSA level, and the PSA nadir may only be known after there is a PSA rise in subsequent follow-up. Time to PSA nadir has some prognostic significance but is limited by the potential immortal bias. Evidence on the use of PSA doubling time is limited and the different calculation methodologies render difficulties in generalization of such parameter. PSA progression is the best surrogate marker of survival and can be considered as the primary endpoint in future clinical trials. PSA response predicts survival but has not been shown prospectively to be a surrogate of clinical benefit. PSA and its kinetics should play an important role in the management of advanced prostate cancer and should be utilized in a more standardized manner.

**Keywords:** prostate cancer, prostate-specific antigen, prostate-specific antigen nadir, time to prostate-specific antigen nadir, prostatic-specific antigen doubling time, prostate-specific antigen progression, prostate-specific antigen response

## 1. Introduction

The first study investigating tissue-specific antibodies in the human prostate can be traced back to 1969 by Ablin et al. [1]. Nadji et al. [2] later characterized prostate-specific antigen (PSA) as a potential immunohistologic marker for prostatic neoplasms. The landmark article by Stamey et al. [3] showed that serum PSA has a much better performance than prostatic acid phosphatase in the detection of prostate cancer, and appeared to be useful in detecting residual or early recurrence of tumour, and in monitoring response to primary treatment. It has led to extensive researches in this area, and the discovery of PSA has revolutionized the management of prostate cancer, from early detection to definitive treatment and monitoring of the disease. The utility of PSA has been extended to a number of parameters that may have prognostic significance in prostate cancer and hence has gained wide interest in the past two decades.

## 2. Objectives

In this chapter, we systemically reviewed and appraised the current role of PSA and PSA kinetics in the management of advanced prostate cancer. We further discussed the potential benefits and controversies of the different PSA-related parameters.

## 3. Methods

A systematic search was conducted in the PubMed database through November 2015 using the following terms: 'prostate cancer', 'prostate-specific antigen', 'prostate-specific antigen nadir', 'time to prostate-specific antigen nadir', 'prostatic-specific antigen doubling time', 'prostate-specific antigen progression' and 'prostate-specific antigen response'. Only original full research articles published in English with full-length text available were reviewed. A manual search using the Web-based search engine Google Scholar was also performed. Reference lists of the retrieved articles were reviewed for other relevant studies.

## 4. Results

### 4.1. Pre-treatment PSA level

To a certain extent, the pre-treatment PSA level may reflect the volume of cancer cells, and hence, it is a parameter of interest in predicting disease prognosis. However, it does not reflect the sensitivity of cancer cells in response to subsequent therapy, in particular hormonal therapy in the context of metastatic disease. The prognostic significance of pre-treatment PSA level is uncertain. Some studies showed that higher pre-treatment PSA level was associated with disease progression, cancer-specific mortality and all-cause mortality [4–14], while other

studies either showed no association or failed to demonstrate statistical significance upon multivariate analyses [15–32]. The wide range of pre-treatment PSA level in metastatic disease also limited its clinical application.

#### 4.2. PSA nadir

PSA nadir was defined as the lowest PSA level achieved after the initiation of treatment. An undetectable PSA nadir level reflects that most if not all of the prostate cancer cells are androgen-sensitive, while any detectable PSA level reflects the presence of androgen-insensitive prostate cancer cells. This was supported by a study which showed that patients who had biochemical relapse following 3 months of neoadjuvant androgen deprivation therapy and radical prostatectomy had greater PSA mRNA levels and more intense PSA immunostaining despite castrate levels of testosterone, than patients who did not relapse, yet they had similar levels of androgen receptor gene expression and protein staining [33]. The majority of the literature showed that PSA nadir is consistent in predicting disease prognosis. A higher PSA nadir level has been shown to be associated with biochemical or disease progression [4, 15, 19, 25, 31, 32, 34–37], prostate cancer-specific mortality [6, 7, 16, 22, 25, 38–40] and all-cause mortality [6, 15, 16, 24, 26, 29, 30, 41–44]. However, there is no absolute threshold level for PSA nadir being recognized by any regulatory agency, and cut-off values at 0.2 ng/mL, 1.0 ng/mL and 4.0 ng/mL have been proposed in various studies. In particular, the drop of PSA to < 4.0 ng/mL has commonly been recognized as PSA normalization, and similar to PSA nadir, PSA normalization was associated with better progression-free survival, cancer-specific survival and overall survival [35, 39, 43, 44]. However, PSA nadir may be affected by the pre-treatment PSA level, rendering difficulty in clinical application, and the PSA nadir may only be known after there is a PSA rise in subsequent follow-up.

#### 4.3. Time to PSA nadir

Time to PSA nadir was defined as the duration needed for the PSA level to reach its nadir after the initiation of treatment. Upon hormonal therapy, one may expect the PSA level to drop to its nadir within a shorter period of time in case of hormone-sensitive prostate cancer, but the ability to have sustained continuous suppression over a longer period of time may be as important. The majority of the studies showed that a longer time to PSA nadir was associated with better outcomes including biochemical or disease progression, cancer-specific survival and overall survival [15, 16, 26, 29, 34, 36]. The other studies either showed the contrary or did not detect any associations between them [6, 22, 23, 31]. Due to the potential immortal time bias, the relationship between time to PSA nadir and survival has to be interpreted with caution [45]. For example, one must have survived 12 months in order to have a time to PSA nadir of 12 months. Hence, this immortal time bias favours a positive correlation between time to PSA nadir and survival outcomes. In order to minimize this potential bias, one study attempted to investigate the prognostic significance of time to PSA nadir using survival beyond time to PSA nadir as an alternative outcome measurement. It has been shown that a longer time to PSA nadir was associated with better survival beyond time to PSA nadir [45]. A longer time to PSA

nadir was also shown to be associated with a lower PSA velocity after progression, but whether PSA velocity after progression can be a surrogate for survival is doubtful [46].

#### 4.4. PSA doubling time

PSA doubling time can generally be interpreted as the time needed for the PSA level to double itself. It assumes an exponential increase in serum PSA and first-order kinetics and can be calculated by natural logarithm of 2 divided by the slope of the relationship between the logarithm of PSA and time of PSA measurement [47]. However, several other calculation models have been proposed, and there is no standardization in the calculation of PSA doubling time. A shorter PSA doubling time has been shown to predict metastasis after prior radical prostatectomy [27, 28, 47], disease progression [32, 48], prostate cancer-specific mortality [6, 7, 22, 23, 25, 40, 49–51] and all-cause mortality [6, 9, 24, 27, 38, 52–54]. The utility of PSA doubling time has been widespread, yet the inconsistencies in the methodologies in calculating PSA doubling time [55] and the complicated logarithm calculations involved limited its use in clinical practice. Small deviations from the different methods of calculations may also lead to wide variations in the calculated PSA doubling time [55]. In 2008, the Prostate Cancer Clinical Trials Working Group (PCWG2) discourages the use of PSA doubling time as the primary endpoint in clinical trials because its significance is uncertain [56]. A subsequent systematic review also concluded that the evidence on PSA doubling time is limited and there is no justification for the use of PSA doubling time to guide decision-making in subsequent treatment [57].

#### 4.5. PSA progression

PSA progression is commonly used as an endpoint in clinical trials, and it was generally thought to represent disease progression and hence reflect the survival outcomes. However, in particular for metastatic disease, multiple definitions of PSA progression have been proposed; they rendered difficulties comparing the results between different studies and limited the generalization of the utility of PSA progression. In 1999, Prostate-specific Antigen Working Group (PCWG1) made consensus recommendations for different outcome measures in clinical trials in prostate cancer [58]. PCWG1 defined PSA progression as a >50% increase from nadir and an increase of at least 5 ng/mL, or back to baseline, whichever was lowest. In 2008, PCWG2 proposed another definition for PSA progression, recognizing that early changes in PSA should not be used for clinical decision-making [56]. For those with PSA decline from baseline, PSA progression was defined as an increase in PSA by  $\geq 25\%$  and  $\geq 2$  ng/mL above the nadir, which should be confirmed by a second value 3 or more weeks later; for those with no PSA decline, PSA progression was defined as an increase in PSA  $\geq 25\%$  and  $\geq 2$  ng/mL after 12 weeks. Hussain et al. [44] reviewed the data from two large-scale clinical trials, namely the Southwest Oncology Group (SWOG) 9346 trial on intermittent ADT and the SWOG 9916 trial on docetaxel. It was shown that both PCWG1 and PCWG2 definitions of PSA progression predicted a 2.4-fold increase in risk of death and a more than 4-fold increase in the risk of death if PSA progression occurred in the first 7 months. This important study demonstrated that PSA progression is a significant predictor of survival in patients who have newly diagnosed

metastatic hormone-sensitive prostate cancer as well as in those with castration resistant prostate cancer treated with chemotherapy. The authors suggested that the PCWG2 definition might be more appealing as patients are identified with progression relatively earlier on. Pooling data from 9 cancer and leukaemia Group B trials [11], both PCWG1 and PCWG2 definitions of PSA progression were shown to be significant predictors of overall survival with hazard ratios of 1.44 (95% CI 1.28–1.62,  $P < 0.001$ ) and 1.43 (95% CI 1.27–1.61,  $P < 0.001$ ), respectively. The above evidence formed the basis of using PSA progression as the primary endpoint in various clinical trials.

#### 4.6. PSA response

PSA response was determined by the degree of decline from its pre-treatment level. The PCWG1 [58] defined PSA response as a decline of  $>50\%$  from baseline, measured twice 3–4 weeks apart. Several studies have shown that a PSA decline of  $>50\%$  was associated with better cancer-specific survival [39, 59] and overall survival [17, 18, 60–62]. However, post hoc analyses in both SWOG 9916 [63] and TAX 327 [43] trials on the use of docetaxel showed that a PSA decline of  $>30\%$  might be a better surrogate marker for survival than a PSA decline of  $>50\%$  based on the proportion of treatment effect and the proportion of variation. A subsequent combined analysis on the SWOG 9346 and SWOG 9916 trials [44] showed that a PSA decline of  $>30\%$  was associated with better overall survival. However, PCWG2 [56] advised against reporting PSA response rates in clinical trials. Concerns were raised about the strength of association between PSA decline and survival, and no criterion, be it  $>50\%$  or  $>30\%$  decline in PSA, has been shown prospectively to be a surrogate of clinical benefit [64]. Instead, PCWG2 recommended the use of waterfall plot to provide a broader and more sensitive display of data. On the other hand, following the discovery of AR-V7 splice variant [65], it was proposed that the lack of PSA response after initial hormonal manipulation might represent primary resistance to hormonal therapy. This is particularly important, as other non-hormonal treatment such as chemotherapy should be considered early on, based on the prediction of poor response to further hormonal manipulation.

## 5. Conclusions

PSA and PSA kinetics may provide additional information about the biological behaviour of prostate cancer and may aid the treatment decision in an individualized approach. One should be aware of the pros and cons of the different PSA-related parameters and should be cautious when interpreting the results from different studies. PSA and its kinetics should play an important role in the management of advanced prostate cancer, and generalization can only be achieved if definitions of the different parameters can be utilized in a more standardized manner. Among the different parameters discussed, PSA progression appeared to be the most consistent and reliable surrogate marker of survival and can serve as the primary endpoint in future clinical trials.



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