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Review – Prostate Cancer

Prostate-Specific Antigen Kinetics in Clinical Decision-Making During Active Surveillance for Early Prostate Cancer—A Review

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Abstract

Context: The kinetics of prostate specific antigen (PSA) are generally assumed to be indicative of tumour progression and are therefore used in clinical decision-making in men on active surveillance for early prostate cancer.
Objective: This review aims to provide support for exploiting PSA kinetics in an active surveillance setting.
Evidence acquisition: We searched the Medline database and reviewed the evidence on both the relation between PSA kinetics before radical treatment for prostate cancer and outcome, as well as the role of PSA kinetics during active surveillance. Furthermore, the benefits and setbacks of different derivatives of PSA kinetics, minimum required time interval and number of measurements, practical recommendations, and pitfalls of their use in clinical practice are discussed.
Evidence synthesis: The evidence concerning the prognostic value of the PSA velocity (PSA-V) and PSA doubling time (PSA-DT) is sparse, especially in active surveillance. PSA kinetics should therefore be combined with other diagnostic measures as the trigger for deferred radical treatment or repeat prostate biopsies. There seems to be consensus among several reports on the unfavourable outcome relating to a PSA-DT <3–4 yr and on the favourable prognostic value of a PSA-DT >10 yr or a decreasing PSA level. Online tools provide help with calculations and insight on disease development. The best method of calculation, number of measurements, and time interval between measurements is unknown for now.
Conclusions: Despite the current deficits in our understanding of the natural behaviour of early prostate cancer and its relation to serum PSA levels, and despite several secondary factors playing a role in PSA kinetics, PSA kinetics are a practical parameter we can offer men on active surveillance to assess the status of their disease.

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1. Introduction

Active surveillance is presently a frequently practiced strategy to decrease the current overtreatment of early prostate cancer, specifically in Europe. It is, as such, besides surgery and radiation therapy, part of guidelines for the treatment of early prostate cancer. Overdiagnosis and the resulting overtreatment are determined by tumour characteristics on one side and life expectancy of a patient on the other side. Because the greater part of men with a small, localized, and well-differentiated prostate tumour will die with and not of their disease, active surveillance saves men with an insignificant form of prostate cancer from the chance of serious side effects of surgery or radiation therapy. Furthermore, ethical and economic issues are associated with this strategy. An important setback of active surveillance may be the psychological burden of living with ''untreated'' prostate cancer in some men.

Active surveillance consists of an initial selection of tumours with apparently favourable features and of subsequent monitoring of these malignancies. Criteria for insignificant disease used in prospective active surveillance studies are presented in Table 1. Radical treatment with curative intent is preferably only chosen when the prostate cancer seems to progress, but before the tumour becomes incurable; however, it is currently not clear which trigger points are most suitable [1]. Delaying radical treatment in these patients does not appear to alter natural history [2].

The serum level of prostate-specific antigen (PSA) is indicative of prostate size and cancer growth. In different phases before and after treatment of prostate cancer the change over time of PSA level is considered to be an important parameter for assessing the relatively favourable or unfavourable development of a prostate tumour. PSA kinetics measured 10–15 yr before diagnosis, when the effect of benign prostate hyperplasia is small, are even associated with cancer-specific survival 25 yr later [3]. On the other hand, it was found that PSA velocity (PSA-V) has no additional value as a screening protocol for prostate cancer [4].

PSA kinetics are also easy to apply and are a logical tool in clinical decision-making during active surveillance [5]. A high PSA-V (absolute PSA increase per time interval) or short PSA doubling time (PSA-DT; time interval for doubling of initial PSA level) are related with an unfavourable outcome and should lead to performing an additional prostate biopsy or to deferred radical treatment during follow-up of active surveillance. A low PSA-V or a long PSA-DT is associated with a nonaggressive course of the disease and may justify a more conservative attitude. (It should be noted that the use of PSA in this setting is different from the use of PSA as a diagnostic test, as the diagnosis prostate cancer has already been made.)

Different retrospective studies have confirmed that men who have a rapidly rising PSA level during active surveillance choose deferred radical treatment more often, especially younger patients [6,7]. The triggers to be used in a prospective manner to select men with a medical indication for radical treatment are, however, subject to investigation.

In this article we first review the different available derivates of PSA kinetics, the literature on the relation between PSA kinetics before treatment for prostate cancer and outcome, and furthermore, the literature on the role of PSA kinetics during active surveillance. Because the aim of active surveillance is to make a timely switch to deferred radical treatment during follow-up when necessary, retrospective studies on the relation between PSA kinetics before surgery or radiation therapy and outcome provide valuable information in this setting. Finally, we aim to provide directions and cutoff values to make the most of PSA kinetics in clinical practice by discussing the differences between PSA-V and PSA-DT, the minimal requirements for obtaining objective calculations, practical recommendations, and pitfalls of the use of this parameter.

Table 1 – Criteria for eligibility used in prospective active surveillance studies to select insignificant prostate cancer

	Van den Bergh [31]	Klotz [30]	Carter [23]
PSA (ng/ml)	≤10.0	≤10.0 (patients >70 yr: ≤15.0)	–
PSA density (ng/ml/ml)	<0.20	–	<0.15
Clinical stage	T1c or T2, N0, M0	T1C or T2A, N0, M0	T1C, N0, M0
Number of positive biopsy cores	<3	–	<3
Gleason score	≤3 + 3 = 6	≤3 + 3 = 6 (patients >70 yr: ≤3 + 4 = 7)	≤3 + 3 = 6
% Core invasion	–	–	<50%

PSA: prostate-specific antigen.