

# What is the possible role of PSA doubling time (PSADT) and PSA velocity (PSAV) in the decision-making process to initiate salvage radiotherapy following radical prostatectomy in patients with prostate cancer?

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## KEY WORDS

prostate cancer ▶ prognostic factors ▶ PSA doubling time ▶ PSA velocity ▶ salvage radiotherapy

## ABSTRACT

This article is an attempt to present a contemporary view on the role of the kinetics of PSA levels as defined by PSA doubling time (PSADT) and PSA velocity (PSAV) in the decision-making process to initiate salvage radiotherapy in patients with prostate cancer after radical prostatectomy (RP).

The dynamics of the rise of PSA levels may be an early endpoint parameter, preceding the diagnosis of distant metastasis or death due to prostate cancer based on a single PSA determination. Thus, it seems reasonable to include the kinetics of PSA levels, apart from single PSA determination, in the decision-making algorithm.

In a group of patients after RP, PSADT might be an early endpoint that could replace cause-specific survival rate as a late endpoint. PSADT allows distinguishing subgroups of patients at high risk of distant metastases and death, which in turn may lead to a change in the further treatment strategy. Therefore, patients with short PSA doubling time should become a subgroup, in which hormonal therapy should be considered. To date, there is no unanimous consent to accept the criteria of assessment of the dynamics of PSA levels as determinants of treatment in case of recurrences following RP. However, a number of non-randomized clinical trials in patients after RP suggest it would be useful to include these parameters in the decision-making process. For instance, a relationship was found between increased PSA velocity (>2 ng/mL/year) before initiation of oncological treatment and increased (12-fold) risk of death. A number of well-documented retrospective analyses show that PSADT is one of the most important parameters to describe the disease aggressiveness. It has to be stressed that single determination of PSA levels is much less precise in terms of describing the biological aggressiveness of prostate cancer than PSADT. Of course, the question regarding the need to include the PSA levels kinetic parameters as crucial elements of patient management algorithms can be answered in a definitive manner only by randomized clinical trials.

## INTRODUCTION

One possible option for radical prostate cancer treatment is the highly efficacious radical prostatectomy (RP). However, treatment failures still occur in a significant percentage of patients [1, 2]. Therefore, methods to improve the treatment results continue to be sought; one of these methods is adjuvant radiotherapy (RT) [3, 4]. The initiation of RT in the prostate cancer treatment is based on the assessment of a number of prognostic factors, such as pT, pN, or post-operative margin status, all included in the histopathology protocol following the RP, and in addition on the determination of PSA levels [5]. In the group of patients after RP with high risk of prostate cancer progression, there is a possibility to initiate early RT without signs of biochemical progression, delayed RT initiated upon detection of biochemical progression, or hormonal therapy in case of systemic progression [6, 7]. In case when recurrence risk factors are present (positive post-operative margin, infiltration outside the prostatic capsule – pT3a, infiltration of seminal vesicles – pT3b), the preferred treatment method is early RT [8, 9]. The use of salvage RT, reserved for cases of biochemical progression, is a less efficacious method [10, 11]. However, one must assume that the number of patients, in whom early RT was abandoned despite the presence of the disease progression risk factors defined in the pathology report, could be significant. At the same time, it must be stressed that this group is highly heterogeneous as regards the biological aggressiveness of the neoplastic process. One of the subgroups of these patients consists of patients in whom tumor microdissemination – undetectable by available diagnostic methods – had occurred before the surgery. Another subgroup of patients after RP may consist of patients at very high risk of systemic progression and, at the same time, at very low risk of local progression. And the last group, include patients with biochemical progression after RP with very high risk of local and at the same time very low risk of systemic progression. Therefore, RT in this subgroup (high risk of cell presence in the surgery site) is likely to be associated with therapeutic benefit. However, in clinical practice, it is very difficult to assign a patient to one of these groups, and therefore, additional tools, which would allow to do it in the best possible way, are being sought.

## A patient after radical prostatectomy: diagnostic dilemmas

The goal of the surgical treatment is to remove the entire pool of tumor cells present in the prostate gland, in the seminal vesicles,

and – less commonly – in lymph nodes. However, local efficacy of RP is not always sufficient, leading to biochemical recurrence, preceding or accompanying a simultaneous local recurrence. Postoperative assessment of PSA levels is an early measure of RP efficacy, commonly used in clinical practice [12]. Unfortunately, single determination of PSA levels does not allow defining the failure site (two sequential determinations are used to define the biochemical failure). It must also be stressed that non-lesioned fragments of prostate gland may be retained after the surgery in a group of patients. This may result in the maintenance of PSA level above the accepted cut-off levels, which, when exceeded, suggest biochemical failure. In general, documentation of biochemical failure extorts definition of failure "geography". Firstly, we should define whether the neoplastic process is limited only to post-operative site, or to the site with the accompanying distant metastasis currently beyond the detection capacities of diagnostic methods, or whether it is only a "chip" of non-lesioned prostate? This list shows that basing the therapeutic decision on the pathology report and single determination of post-operative PSA levels suggestive of biochemical failure is still associated with high risk of initiating a suboptimal treatment.

In patients after RP, RT is an established adjuvant treatment method, leading to reduction of biochemical failure incidence by ca. 50% [13]. Unfortunately, most randomized clinical trials conducted to date did not bring evidence of a statistically significant effect of early RT on the improvement in total survival rates [14–18]. An exception is the analysis of survival rates of patients in the SWOG study, presented at the ASCO conference in 2008 [19]. Despite an overwhelming number of publications suggesting that early RT is more efficacious than salvage RT, many urology centers hold to the belief that since there are no clinical trial results explicitly suggesting an increase in total survival rates thanks to early RT, it should be used only in case of biochemical progression. Unfortunately, diagnostic tools helping to define the source of biochemical failure, and thus helpful in qualifying patients for RT, are imprecise due to their low sensitivity and specificity. The role of the simplest of these tools, i.e. the digital rectal examination (DRE), in the diagnosis of local recurrence in patients after RP is very limited; in case of lack of biochemical recurrence this examination provides no useful information at all. [20]. Also, the usefulness of imaging examinations in defining local recurrences is low, even in cases of significant increase in PSA levels exceeding 0.2 ng/mL. Despite the diagnosed biochemical recurrence, the sensitivity and specificity of TRUS procedures and, in case of determining dissemination or isolated local recurrence, examinations such as bone scan, CT, or MRI with surface or anal coils are of limited importance [21, 22]. Hope for more sensitive and specific detection of micrometastases or minute local recurrences lies upon molecular imaging methods, namely [(11C)choline PET/CT [23, 24] Recent reports support its use, showing good pathologic correlation with imaging data [25]. Distinguishing of failure source (isolated local recurrence versus distant metastasis ± local recurrence) is important to the extent that it allows to initiate efficacious treatment in the form of salvage RT on one hand and, on the other hand, to avoid unnecessary RT in case of patients with a distant metastasis and to refer such patient to a clinical trial assessing novel systemic treatments.

One of the parameters most commonly used in clinical practice due to its availability and low acquisition costs is determination of the dynamics of PSA levels, expressed by PSA doubling time (PSADT) and PSA velocity (PSAV). Therefore, a number of articles were published in recent years with regard to the usefulness of these parameters in the therapeutic decision-making process in patients after RP. One of the most important research teams is the D'Amico team, which assessed the usefulness of measuring the kinetics of

PSA levels prior to RP for the assessment of patients' fates after prostatectomy in a group of 1,095 prostate cancer patients [26]. The authors pointed that in 28% of patients, in whom the PSA velocity (PSAV) exceeded 2 ng/mL/year, a 10-fold increase in the risk of death due to prostate cancer than in the group of patients with PSAV <2 ng/mL/year. What's interesting, this risk was practically independent of other clinical and pathological parameters describing the prostate cancer. According to the authors, adjuvant RT in cases when PSAV exceeds 2 ng/mL/year brings little benefit due to large risk of disease dissemination. Therefore, authors think it would be advisable to consider initiation of systemic treatment in this group of patients (PSAV >2 ng/mL/year).

The next study by D'Amico et al. was very important in terms of defining the role of prognostic factors in patients after RP and RT [27]. In this study, clinical parameters associated with the risk of death due to prostate cancer in case of biochemical recurrence after radical treatment were singled out. With this purpose, an analysis of 8,669 patients (5,918 patients after RP, 2,751 patients after radical RP) was conducted, with mean observation time of 7.1 years after RT and 6.9 years after RP. The results of the statistical analysis showed that PSADT <3 months (found in 12% of patients in the operative treatment group and in 20% of patients in radiotherapy group) was an independent prognostic factor of the risk of death due to prostate cancer (HR = 19.6, CI 95%; 12.5–30.9). Therefore, the authors claim that documentation of PSADT <3 months indicates advisability of considering initiation of systemic treatment. In addition, the authors stress the potential usefulness of PSADT as an early endpoint, which might replace the assessment of prostate cancer-specific survival rates in clinical trials. The use of this parameter might lead to significant reduction in the waiting time with respect to the summaries of the results of clinical trials evaluating novel treatments. However, it must be highlighted that the most important premise stemming from this study is the fact that patients with short PSADT should constitute a group in which hormonal therapy or participation in clinical trials evaluating novel treatments should be considered. This is especially important since the probable cause of treatment failure is associated with micrometastases, present even before the radical treatment (RP).

Also the study by Zhou et al. assessed the usefulness of PSADT as a prognostic factor in patients after RP and radical RT. Based on observation of 1,159 patients with prostate cancer (498 patients after RP, 661 patients after radical RT), the PSA doubling time shorter than 3 months was associated with relative risk of death due to prostate cancer of 54.9 (16.7–180.0) in RP patients, and 12.8 (7.0–23.1) in radical RT patients [28].

Tollefson of Mayo Clinic analyzed the treatment results of 1,064 patients after RP. For analytic purposes, the author differentiated three disease progression risk subgroups: a high risk subgroup, when PSADT was shorter than 12 months; a medium risk subgroup, when PSADT was between 1 and 10 years; and low risk subgroup, when PSADT was longer than 10 years [29]. The relative risk of distant metastases was 21.7 (8.0–58.6) and 6.8 (2.3–19.8) in the high and low risk groups, respectively. The author suggests that patients from the high risk group should firstly be the potential candidates for initiation of systemic therapies, while patients at medium risk (PSADT between 12 and 120 months) should be qualified for adjuvant RT, and patients at low risk remain under observation.

Freedland et al. analyzed the relationship between PSADT and the risk of death due to prostate cancer in a group of 5,096 patients after RP [3]. The statistical analysis performed by the authors allowed differentiating patients with PSADT of less than 3 months, in whom the relative risk of death due to prostate cancer was 27.48 (10.66–70.85). In the subgroup of patients with

PSADT ranging from 3.0 to 8.9 months, the risk of death was 8.76 (3.74–20.50), while in the subgroup of patients with PSADT between 9.0 and 14.9 months, the risk of death was 2.44 (0.88–6.81). Thus, a question arises, whether early hormonal therapy may improve the survival of patients in the high failure risk subgroup? Experience gathered to date suggest a potential possibility of such an effect, but the lack of results of randomized clinical trials assessing this aspect of hormonal therapy does not allow routine recommendation of this treatment in clinical practice. Thus, probably future RCTs would evaluate all aspects of early HT in patients at high risk of prostate cancer progression determined on the basis of the PSADT.

PSADT and PSAV seem to be attractive parameters that might significantly improve the optimization of treatment selection process in patients after RP. However, it must be kept in mind that calculation of these parameters requires observation of patients in whom biochemical progression was observed. On the other hand, it is a commonly held belief that early initiation of salvage RT, i.e. at the lowest possible PSA levels, is most efficient. Thus, based on the available clinical data it is impossible to assess how the length of the waiting period required for PSA measurements for PSADT or PSAV calculation might negatively affect the results of salvage RT. It is possible that in the future, the use of determination of PSA dynamics based on PSA determinations in the range of 0 ng/mL to 0.2 ng/mL would allow early determination of the "geography" of the biochemical failure.

## CONCLUSIONS

To sum up, it must be stated that PSADT is a very useful tool for defining subpopulations of patients after RP in case of biochemical failure. This endpoint may be used as a potential tool for proposing local or systemic therapy in a subgroup of patients at high risk of distant metastases. Such differentiation would allow abandoning systemic therapy in patients at low risk of systemic progression while proposing salvage RT as highly efficacious treatment method.

Based on the review of studies assessing the kinetics of PSA level changes, it can be stated that in patients with the presence of biochemical recurrence, PSADT may be an early treatment efficacy endpoint, which might potentially replace the assessment of cause-specific survival rates, especially in the clinical trials [27, 29, 30]. The most important premise stemming from this bibliographical review is that patients with short PSADT should constitute a group in which hormonal therapy should be considered, while patients with long PSADT should be destined for salvage RT.

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