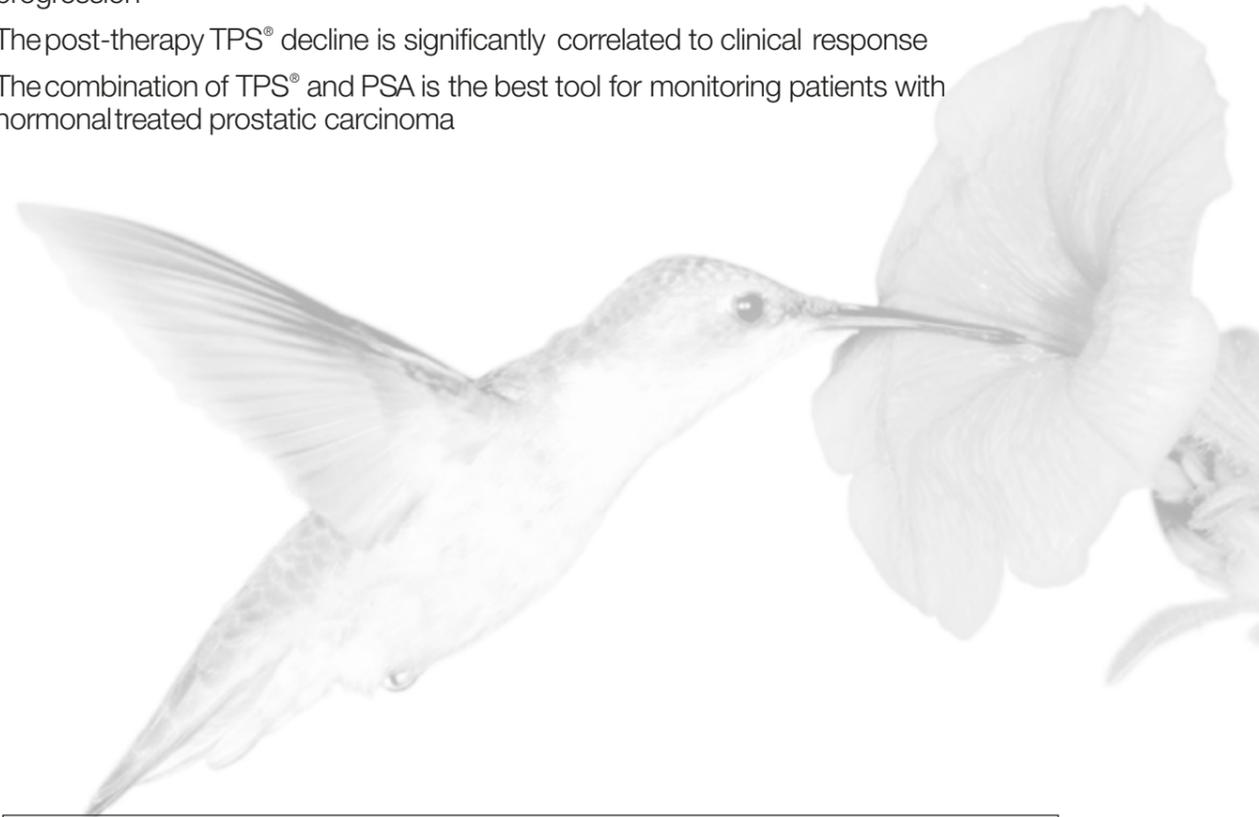


Summary and Conclusions :

- TPS® is the serum marker measuring cytokeratin 18
- TPS® is an androgen independent marker for metastatic prostate cancer
- Pretreatment TPS® is an independent prognostic factor reflecting rapid disease progression
- The post-therapy TPS® decline is significantly correlated to clinical response
- The combination of TPS® and PSA is the best tool for monitoring patients with hormonal treated prostatic carcinoma

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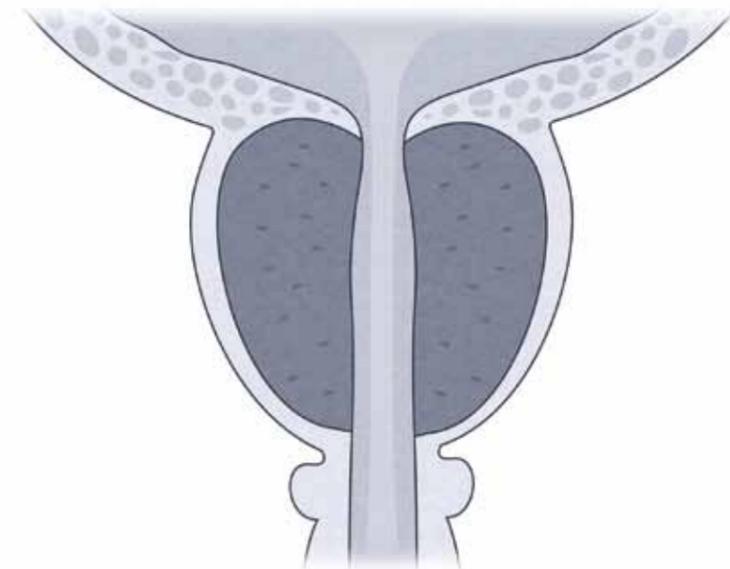
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TPS® in Prostate Cancer

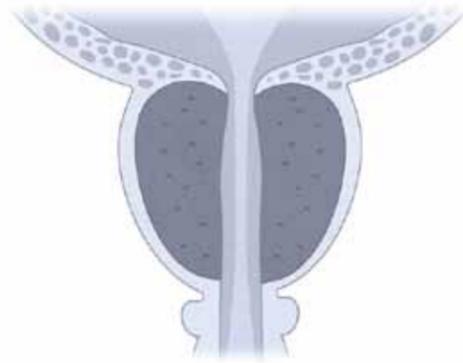


An androgen-independent marker for reliable monitoring of patients on anti-androgen therapy.

The cytokeratin marker TPS® is an indicator of tumor cell activity, which enables the clinician to predict disease status earlier than with conventional methods.

Clinical Background

Prostate cancer is one of the most common types of cancer in men worldwide. However, the incidence rates varies and it is much more common in Europe and USA than in Asian countries. In the United States and Europe, prostate cancer is the most common type of cancer in men and the annual incidence rate is 110-120 per 100 000 men. The prognosis for prostate cancer is good. The 10-year survival rate is 93%, given early detection and accurate monitoring of the disease.



Diagnosing Prostate Cancer

The main diagnostic tools used to look for evidence of prostate cancer include digital rectal examination (DRE), transrectal ultrasonography (TRUS) and serum prostate specific antigen (PSA). PSA is the most common tumor marker for prostate cancer, for screening, diagnosis, following therapy and for early detection of relapse. However, the PSA levels can also be affected by various benign conditions like certain medical procedures, an enlarged prostate and a prostate infection. PSA is an organ specific volume marker and does not reveal any information about the aggressiveness of the disease. A positive test only indicates that further evaluation of the patient is necessary.

Treatment of Prostate Cancer

Depending on the stage of the disease prostate cancer patients are offered different alternatives. The main options include surgery, hormonal therapy, chemotherapy, and watchful waiting. For patients with an already metastatic cancer hormonal therapy is the preferred treatment. The goal of hormonal therapy for prostate cancer is to block the effect of male hormones such as testosterone, which can slow the growth of the hormone-dependent prostate cancer cells.

There are different kinds of hormonal therapies. The most common are:

- *Drugs that reduce testosterone production by the testicles—such as Luteinizing Hormone-Releasing Hormone (LH-RH) agonists*
- *Surgical removal of the testicles, which produce the testosterone*
- *Anti-androgen therapy to block the effects of androgens like testosterone*

PSA is an established marker for monitoring of prostate carcinoma after therapy. However, since production of PSA is androgen dependent, in patients on anti-androgen treatment, the PSA level does not always reflect the efficacy of the treatment. The cytokeratin marker TPS[®] has in several studies shown to be a valuable complement to PSA, by enhancing early detection of recurrence.

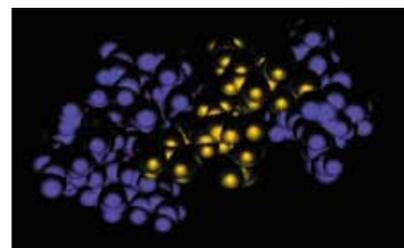
Cytokeratin Proteins

All eucaryotic cells have cytoplasmic cytoskeletal structures known as intermediate filaments. The cytoskeletal network is responsible for the mechanical integrity of the cell and it is critical during cellular processes like cell division, motility and cell to cell contacts. The cytokeratins belong to the intermediate protein family. At present more than 20 different cytokeratins have been identified, of which cytokeratin 8, 18 and 19 are the most abundant in simple epithelial cells. The cytokeratins are epithelial cell specific and the cytokeratin pattern is usually preserved during the transformation of normal cells into malignant cells.

Tissue Polypeptide Specific Antigen (TPS[®])

TPS[®] is the only test that specifically measures cytokeratin 18. It is a monoclonal assay measuring the reactivity against a well defined epitope structure on cytokeratin 18, the M3 epitope. TPS[®] is a marker of tumor cell activity and is not related to tumor burden.

The M3 epitope is localized to amino acid residues 322-342 on human cytokeratin 18



Clinical Value of TPS[®] for Prognosis and Monitoring of Prostate Cancer

PSA and TPS[®] express two different aspects of the cancer disease. TPS[®] is considered to be a marker of cellular activity, which is supported by the direct correlation between TPS[®] values and the Gleason score (scoring system based on the microscopic tumor pattern), whereas PSA is considered to be a marker of tumor mass. PSA is the preferred marker in untreated prostate cancer. However, the expression of PSA is androgen dependent. Therefore, in patients treated with androgen deprivation therapy, a decrease in the level of PSA can be observed even for patients with clinical progression. One explanation for declining and low PSA levels in spite of disease progression could be an outgrowth of dedifferentiated tumor clones that have lost the ability to synthesize PSA (Figure 1). The TPS[®] values, however, are not androgen dependent and correlate therefore with the clinical course of the disease, also for patients who lost the ability to produce PSA. These results were confirmed in an EORTC (European Organisation for Research and Treatment of Cancer) side study. The PSA level remained normal in 5 of 68 patients with progressive disease, whereas TPS[®] increased in a way that coincided with or preceded clinical progression.

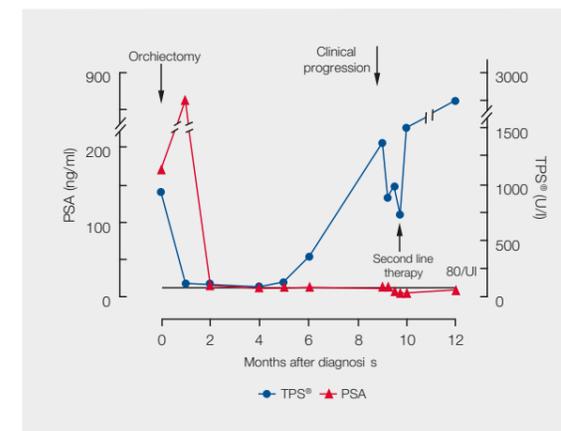


Figure 1: Example of out growth of PSA-negative tumor cells after first line hormonal treatment. PSA remained at a low level although the patient died four weeks later. (Kramer et al)

Furthermore it has been shown that the post-therapy decline rate of TPS[®] following hormone refractory therapy is, in contrary to PSA, significantly correlated to the clinical response and the progression free survival time ($p < 0.00005$ for TPS[®], $p < 0.036$ for PSA). A TPS[®] decrease of more than 50% coincided with palliation in 90% of patients and for PSA the corresponding value was 64%.

The Prognostic Value of TPS[®]

The pretreatment TPS[®] values have been shown to be significantly higher in patients with clinically progressive disease than in patients with stable disease ($p = 0.004$, table 1). In the same patient group pretreatment PSA values, however, did not show any statistical significance ($p = 0.0659$, table 1).

Mean value	TPS [®] -pre (U/L)	TPS [®] -end (U/L)	PSA-pre (µg/L)	PSA-end (µg/L)
Progressive disease (n=18)	201.3 ±40.8	504.1±181.2	305.9±72.9	183.0±53.2
Stable disease (n=33)	82.2±13.7	60.6±14.5	264.4±49.1	14.3±3.7
Statistical significance	P=0.0041		P=0.0659	

Table 1: TPS[®] and PSA values before treatment and at the end of follow-up (Kil et al.)

Conclusion:

The combined use of PSA and TPS[®] has been evaluated in more than 600 patients. The results clearly demonstrate that TPS[®] is an early indicator of treatment response and furthermore identifies patients with clinical progression even when PSA remains normal.