

Summary and Conclusions:

- Cytokeratin 18 is frequently expressed in breast cancer.
- TPS® is the only serum marker measuring cytokeratin 18.
- TPS® reflects tumor cell activity.
- TPS® provides the clinician with an early signal about the course of the disease.
- TPS® is an independent marker of survival.
- The combination of TPS® and CA 15-3 is the most efficient and cost-effective for therapy monitoring in comparison to imaging techniques.

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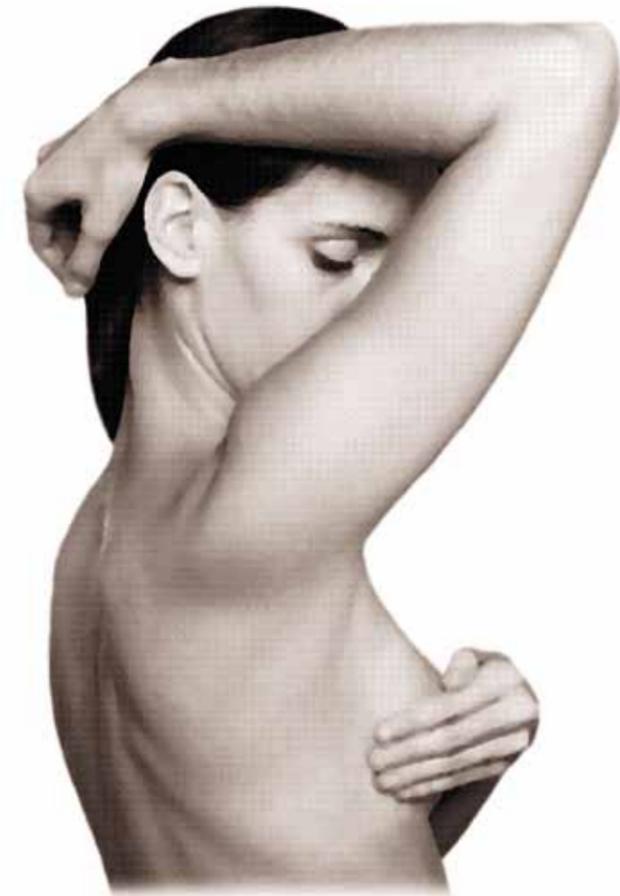


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TPS® in Breast Cancer



For prognosis, monitoring of treatment efficacy
and prediction of recurrence.

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

Breast Cancer

Breast cancer is the most common type of cancer diagnosed in women and accounts for about 32 percent of all cancer diagnosed in women. Prognosis for breast cancer is in general rather good, with estimated average survival rates being 73%. A decline in breast cancer mortality has been reported, as a result of earlier detection and improved treatment. However, despite improved survival rates in recent years, women with a history of breast cancer are at risk of recurrence for the rest of their lives and need to be regularly followed.

Diagnosing breast cancer

Prior to introduction of mammography screening breast cancer was diagnosed as a lump in the breast. Introduction of mammography has significantly changed the sense of awareness to women and this has resulted in earlier detection of breast cancer. No single serum marker is sensitive enough to be recommended for diagnosis of breast cancer. However for monitoring and follow-up tumor markers are an established part of the clinical routine management. The most commonly used markers are CA 15-3 and CEA. However, the clinical sensitivity of these markers is low in early stage disease and there is a need for additional or complimentary products.

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. 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. Cytokeratin 18 is the most frequently found cytokeratin in breast cancer.

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 it is not related to tumor burden

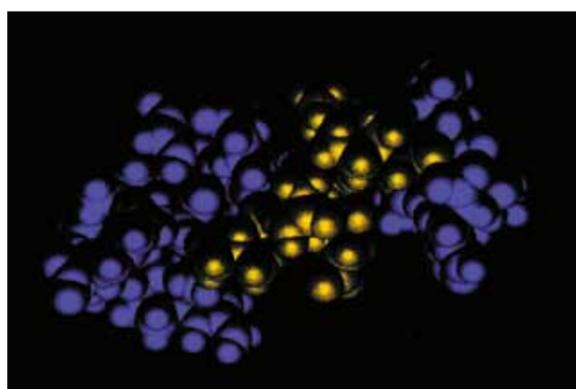


Fig 1: The M3 epitope is localized to amino acid residues 322-342 on human cytokeratin 18

TPS® for monitoring and follow-up

According to several studies published during the last 15 years TPS® have been shown to have the strongest association with clinical response. In total, studies of more than 3000 patients have been reported. TPS® has been found to be a better indicator of disease progression than CA 15-3. In a study by van Dalen et al the sensitivity of TPS to detect progressive disease (PD) was found to be 83% compared to 30% for CA15-3 (Fig 2).

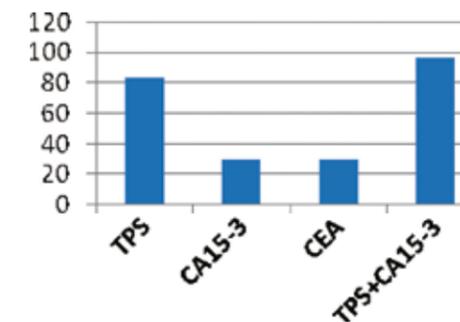
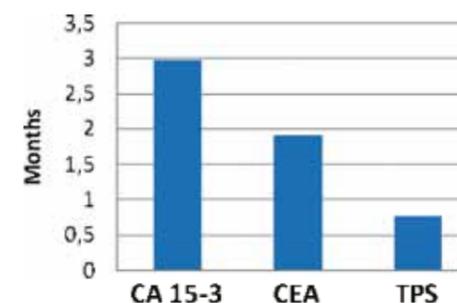


Fig 2: Percentage of patients with an increase in marker level of 25% outside the reference range in a group of totally 46 patients of whom 30 showed clinical progression.

TPS has also been shown to be the marker that exhibits the most frequent and rapid decrease when the applied therapy is effective. CEA and CA15-3 remain elevated during longer time due to continuing presence of tumor mass (Fig 3).

Fig 3: Medium time in months at which 50% decrease in tumor marker level is reached in patients with partial remission or stable disease 3 months after start of treatment and partial remission or complete remission after 6 months.

In another study the sensitivity of TPS and CA 15-3 for detection of clinical response to treatment was evaluated in 69 patients with metastatic or locally advanced breast cancer. The results showed a higher sensitivity for TPS than CA 15-3.

Tumor Marker	Sensitivity (%)	
	CR,PR	PD
TPS	84	82
CA 15-3	68	66

Table: Correlation between clinical response according to UICC (CR, PR,PD) and tumor marker changes (more than 50% decrease or 25% increase in marker signal) during follow-up.

TPS® for Prognosis

TPS has consistently been found to be a good marker for prediction of prognosis and response to therapy. Low baseline levels of TPS indicate a better prognosis. Furthermore TPS is the only independent parameter in the multivariate Cox's regression analysis, showing a relative risk of death of 2.3 for patients with high TPS level versus 1.0 for low level. Patients with low TPS levels (<100 U/L) show a median survival of 815 days compared to 332 days for patients with high TPS levels (>100 U/L). Such a difference in survival according to baseline levels was not found for CA15-3 and CEA.