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# Biomarker discovery in urogenital cancer

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**Abstract**
Novel approaches for the early detection of urogenital cancers are urgently needed. Metastatic renal cell carcinoma (RCC) has a poor prognosis and unpredictable course and to date there are no molecular markers that reliably protect RCC outcome. A novel kidney cancer marker, carbonic anhydrase IX (CA IX), was investigated as an independent prognostic factor for survival for patients with metastatic RCC. In patients with non-metastatic RCC low CAIX predicted a worse outcome similar to patients with metastatic disease and overall CAIX expression decreased with development of metastasis. CAIX reflects significant changes in tumour biology, which may be used to predict clinical outcome and identify high-risk patients for adjuvant-targeted therapies. With regard to prostate cancer there are a number of putative biomarkers, although there are limited studies providing clinical correlations in humans. Potential biomarkers include caveolin-1, p-Akt, p27, the met oncogene, Ki67 (MIB-1), 8q24 over-expression, polycomb protein EZH2, plasma TGF-B1 and IL-6 among others. The laboratory has concentrated on the Prostate Stem Cell Antigen (PSCA) which is increased in patients with more aggressive features, that is higher Gleason grade and higher stage. Highest expression is seen in metastatic lesions to bone and staining for PSCA may predict for disease progression or recurrence. Also promising is the finding reported by the group that expression of p27 in radical prostatectomy specimens correlates with biochemical recurrence. Loss of p27 (defined as absent expression in more than 70% of the specimen) is an independent predictor of recurrence among all patients and among the sub-set with organ confined and extra-capsular disease. The data also shows that p27 can predict outcome among patients with positive surgical resection margins. As with other biomarkers, major questions still to be addressed is the requirement for universal application with uniform scoring and the need for prospective studies in randomized clinical trials.

**Keywords:** *Kidney cancer, prostate cancer, CAIX, p27, prostate stem cell antibody, PSCA*



## P27: A potential prognostic marker in prostate cancer

This group was among the first to report that loss of p27 expression in radical prostatectomy specimens correlates with recurrence (Yang et al. 1998). This study evaluated 86 patients with clinical stage T1–T2 prostate cancer, none of whom received neoadjuvant or adjuvant therapy. This study showed that loss of p27 (defined as absent expression in more than 70% of the specimen) was an independent predictor of recurrence among all patients and among the sub-set with organ confined and

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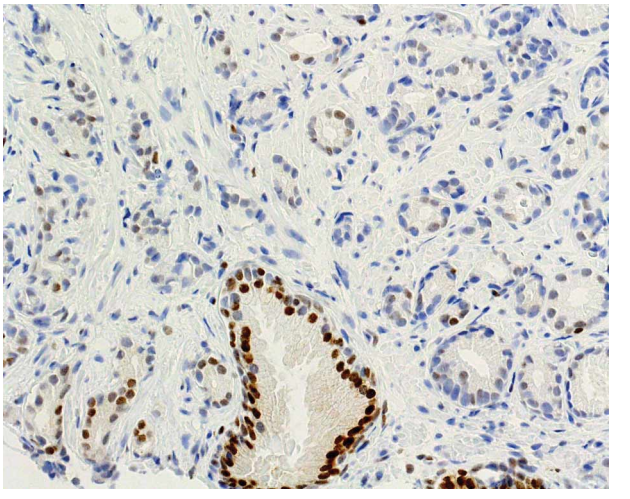

Figure 1. Prostate cancer stains for p27 reveals staining restricted to nuclei of normal prostate glands with loss of p27 expression in the neoplastic glands. Haematoxylin counterstain, original magnification ×120.

extra-capsular disease (Figure 1). It has also been shown that p27 can predict outcome in patients with positive surgical excision margins, loss of p27 correlating once again with prognosis. Retention of p27 expression may even be protective in patients with more advanced stage disease and involvement of the seminal vesicles. This study also compared p27 expression in biopsies and radical prostatectomy specimens and found a high degree of correlation (high sensitivity and specificity) of the p27 score in the biopsy predicting for prostatectomy p27 score (Thomas et al. 2000).

## Prostate stem cell antigen (PSCA): A promising tumour marker and therapeutic target for patients with metastatic prostate cancer

Prostate stem cell antigen (PSCA) is a homologue of the Ly-6/Thy-1 family of cell surface antigens. PSCA was first identified in the LAPC-4 prostate xenograft model of human prostate cancer and is expressed in the majority of prostate cancers as well as bone and soft tissue metastases (Reiter et al. 1998). Although PSCA is highly prostate-specific, it is also found in the transitional epithelium of the bladder and the stomach and is expressed by the majority of bladder and pancreatic cancers. PSCA expression in the serum correlates with increased tumour grade and stage (Gu et al. 2000). Highest expression is found in bone metastases, making PSCA a promising therapeutic target (Figure 2). Monoclonal antibodies against PSCA have been shown to inhibit tumour growth and metastasis and prolong survival in mice with human prostate cancer xenografts (Saffran et al. 2001).

Although p27 is among the most promising biomarkers for prostate cancer, questions remain to be answered before it can be widely utilized. The issue of standardization of the assay and cut-off levels of expression need to be analysed in large clinical trials. For example, in the biopsy study alluded to above a cut-off value of 40% was found to be predictive of outcome, whereas in the studies on prostatectomy specimens the cut-off was set at 30%. Common to most predictive biomarkers under

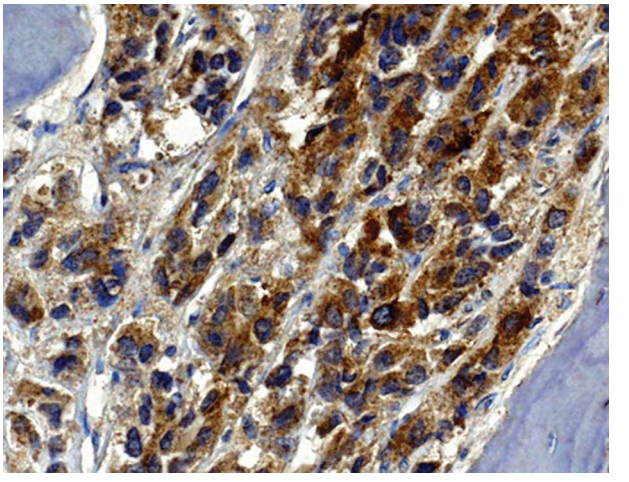

Figure 2. Prostate cancer bone metastasis with strong staining for PSCA in malignant cells. Haematoxylin counterstain, original magnification ×180.

evaluation there is a need for multi-institutional prospective studies which are currently in progress for p27.

## Carbonic anhydrase IX (CAIX)

Renal cell carcinoma is a relatively common malignancy with a poor prognosis and unpredictable choice. Markers currently used as predictors of outcome include tumour stage and grade. Unfortunately, there are few biomarkers which can predict outcome response to therapy. CAIX protein is a member of the carbonic anhydrase family which plays a role in the regulation of cell proliferation in response to hypoxia (Pastorek et al. 1994). CAIX is a transmembrane glycoprotein with an active extracellular enzyme site and is implicated in cell proliferation and oncogenesis.

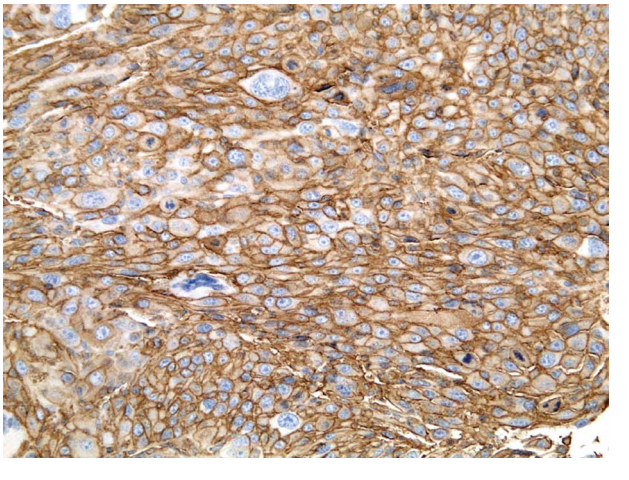

Figure 3. Clear cell carcinoma of the kidney with strong membrane staining for CAIX. Haematoxylin counterstain, original magnification ×120.

In the case of renal cell carcinoma, upregulation of CAIX HIF-1 and VEGF may be a biological consequence of alterations in the VHL gene in clear cell carcinomas. CAIX can be identified by immunohistochemical staining in 94% of clear cell renal cell carcinomas (Figure 3). The UCLA group has shown that, at a cut-off value of 85%, CAIX is an independent poor prognostic factor for survival for patients with metastatic renal cell carcinoma (Bui et al. 2003). CAIX immunostaining may also be predictive of response to IL-2 immunotherapy, a standard method of treatment for renal cell carcinoma. In a study at UCLA all complete responses to IL-2 immunotherapy included patients with high CAIX staining. Overall response to IL-2 was also greater in patients whose tumours highly expressed CAIX (Bui et al. 2003).

CAIX status can be used to identify a sub-set of patients with localized renal cell carcinoma who have a clinical course similar to patients with metastatic disease. This patient cohort is clearly candidates for adjuvant immunotherapy trials which are currently in progress. CAIX is also potentially useful as a molecular target for therapy of clear cell renal cell carcinoma using antibodies to CAIX or immunotherapy using dendritic cells modified with a GM-CSF-CA9 fusion gene. CAIX is an excellent example of a biomarker with potential not only to aid diagnosis and predict outcome, but also for development of specific therapeutic targets for intervention.

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