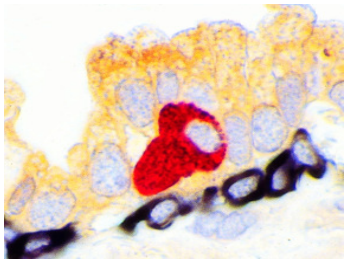

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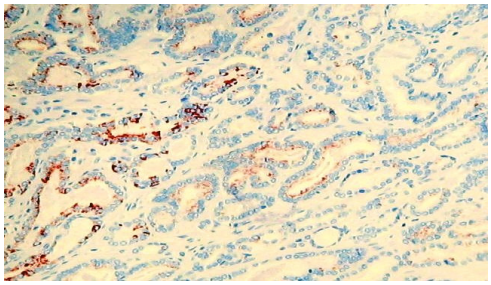
Patient Information

Update: 11/2006

Dear Patient

In addition to the Gleason Grade, tumor volume and PSA there are a series of markers predicting relapse and tumor progression (prognostic factors), and other markers predicting response or resistance to a specific therapy (predictive factors). The following panel of markers is currently available for study in prostate cancer tissue:

- **AMACR** is an enzyme involved in fatty acid synthesis. A recent study has shown that decreased AMACR expression is associated with worse PC outcome, independent of clinical variables in patients being observed. Among those with both low AMACR expression and high Gleason score, the risk of PC death was 18 fold higher. In the same study, the authors show that low AMACR expression predicts PSA recurrence after RP independent of Gleason score, PSA and margin status. **A favorable result for AMACR is high tissue expression.**



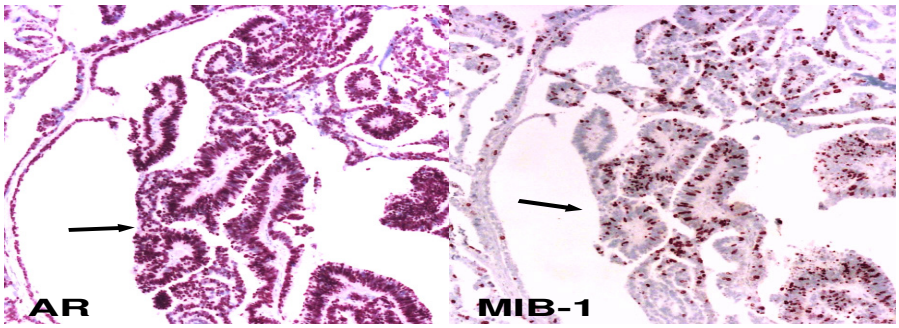
PC (GS 3+3=6) with partial loss of AMACR

- **Androgen receptor (AR)** mediates cell proliferation and plays a pivotal role in tumor growth and progression in PC. The mere presence of AR in PC cells does not imply androgen- dependence or provides any information on its biological activity. A more functional approach to AR biology is feasible by evaluating the AR status in relation to the proliferation activity of PC cells. There are several factors implicated into the prognostic and predictive significance of AR status in PC tissue :

  - **Staining intensity (high/low)**
  - **AR distribution (homogeneity vs heterogeneity)**
  - **Proliferation activity** determined by the proliferation marker MIB-1 (see below)

  In recent studies, high level of AR expression (3+) was found to correlate with clinical stage, lymph node status, extracapsular extension, seminal vesicle invasion, and Gleason score. By multivariate analysis, high level of AR expression was an independent prognostic indicator of biochemical recurrence-free survival after RP. AR expressed at high level (hypersensitive AR) can use residual and small amounts of androgens to mediate prostate cancer growth. Its identification in PC tissue

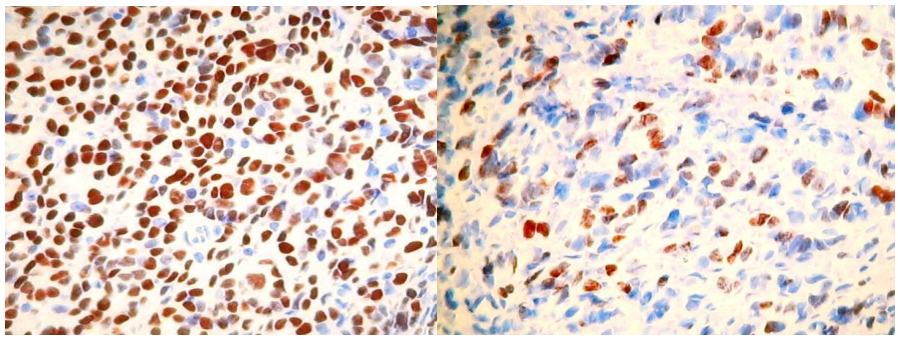
warrants total androgen blockade, especially when AR expression is associated with high proliferation activity (MIB-1).



High levels of AR (→) in PC (GS 4+4=8) associated with high proliferation activity (MIB-1) indicate the presence of an hyperactive receptor pathway

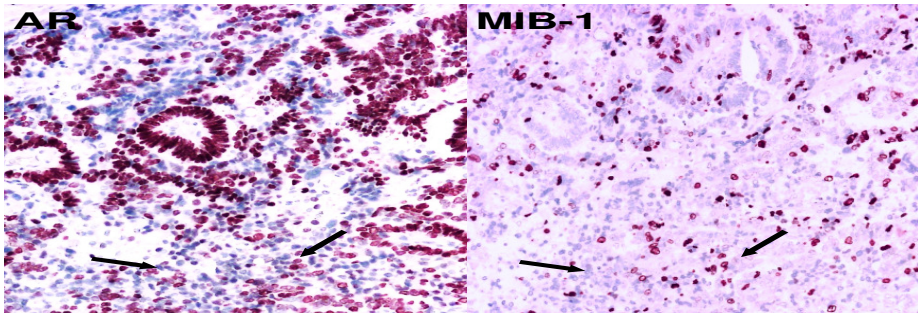
AR upregulation has been found as one of the most consisting events associated with the development of androgen resistance in prostate cancer xenografts. In addition, increasing levels of AR expression cause AR antagonists (biculatimide, flutamide) to function as agonists and confer responsiveness to promiscuous ligands such as estrogens. These results suggest that therapies able to lower AR expression may be effective in patients with high levels of AR expression. Several experimental approaches are currently available to lower AR. These include: (1) geldanamycin analogs to downregulate AR protein in prostate cancer cells, (2) antisense oligonucleotides (ASOs) and small interference RNA inhibiting AR expression. Alternatively, alpha-tocopheryl succinate (Vitamin E) and selenium has been found to be effective in lowering AR expression in LNCaP.

Another pathway associated with the development of androgen residence in prostate cancer refers to the loss of AR expression. Immunohistochemical studies demonstrate that heterogeneous staining or partial loss of AR is associated with hormonal therapy failure, while homogenous staining predicts good response to androgen deprivation therapy.



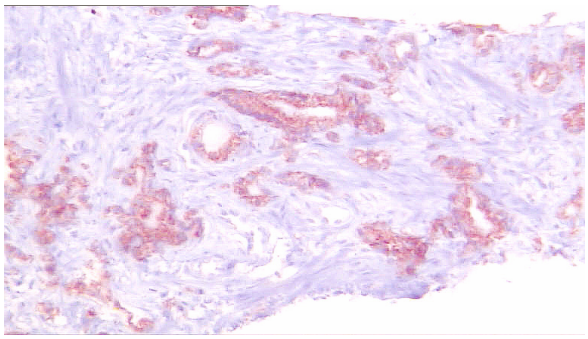
PC (GS 5+5=10) with homogeneous (left) and heterogeneous (right) expression of the AR

When prostate cancer cells lack AR expression, it is important to evaluate their proliferation status. High proliferation activity (MIB-1) in absence of detectable levels of AR invariably identifies androgen- insensitive prostate cancer cells in tissue specimens. **A favorable result for AR is homogeneous expression at low or moderate (1+, 2+) levels.**



Androgen- insensitive PC cells with high proliferation activity (MIB-1) in absence of AR (→)

- **AZGP1** is a glycoprotein (zinc-alpha2 glycoprotein) expressed in normal and neoplastic prostate tissue. Its prognostic significance has been recognised first in gene profiling studies which identified clinically relevant subtypes of prostate cancer. It has been shown that strong AZGP1 staining was associated with a decreased risk of recurrence independent of tumor grade, stage, and preoperative PSA levels. To validate this data AZPG1 expression was analysed in malignant prostate epithelium in prostatectomy specimens from 228 prostate cancer patients. Low (i.e., absent or weak) AZGP1 expression was associated with clinical recurrence (defined as confirmed localized recurrence, metastasis, or death from prostate cancer; hazard ratio [HR] = 4.8, 95% confidence interval [CI] = 2.2 to 10.7, P<.001) and with bony metastases or death from prostate cancer (HR = 8.0, 95% CI = 2.6 to 24.3, P<.001). The most striking feature of AZPG1 as biomarker is that its prognostic significance is independent of Gleason grade, pathological stage, and preoperative PSA levels. **A favorable result for AZGP1 immunostaining is high tissue expression**



Prostate biopsy with strong AZGP1 expression in prostate cancer (Gleason 3+4=7)

- **Basal cell markers (34βE12)** identify intraductal spread of prostate cancer. Depending on tumor volume 10- 45% of prostatic adenocarcinoma spread through pre-existing ducts. Current evidence suggests that intraductal spread of prostate cancer (IDPca) is associated with high Gleason Grade, extraprostatic extension, seminal vesicle involvement, positive surgical margins, high tumor volume, lymph node metastasis and PSA recurrence. Intraductal spread of prostate cancer is a major risk factor for androgen- insensitivity, drug and radiation resistance. **A favorable result for 34βE12 is absence of intraductal spread**

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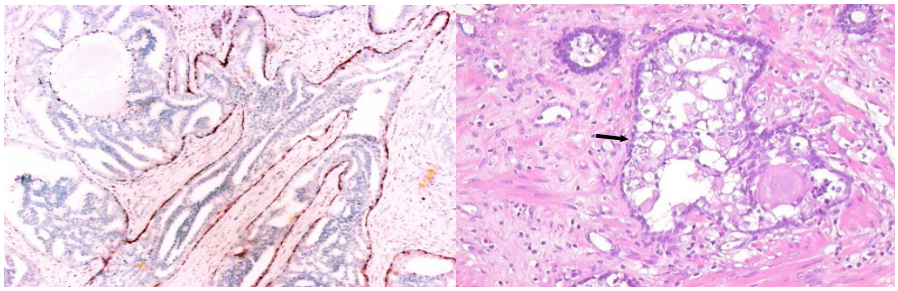
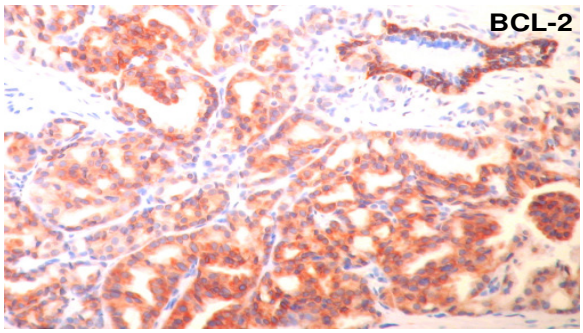


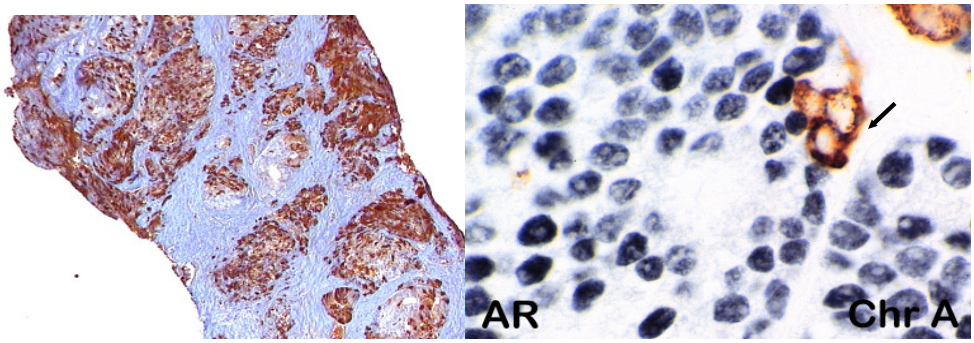
PC with cribriform growth pattern. 34βE12 identifies extensive intraductal spread	*PC 18 month after ADT3. The intraductal parts of the tumor show little regressive changes*

- **BCL-2** is an oncogene that acts as an anti-apoptosis regulator and independently predicts PSA recurrence and outcome after RP. Detectable levels in biopsy tissue would signal concern for possible radiation resistance, the need to use synergistic drugs with RT (such as Vitamin D), or the need to use agents that downregulate BCL-2 such as Taxanes and Aspirin and to avoid argents that upregulate BCL-2 such as Curcumin. Recent clinical studies demonstrated a survival benefit in prostate cancer patients treated with taxane-based chemotherapy when BCL-2 was detectable in tumor specimens.
  A favorable result for BCL-2 is negative (0%).



PC (GS 4+4=8) with high levels of BCL-2 expression

- **Chromogranin A (CGA)** reveals multifocal or extensive neuroendocrine differentiation (NE) in at least 10% of prostate malignancies. Chromogranin A positive prostate cancer cells are androgen-insensitive, escape programmed cell death and are resistant to radiotherapy and androgen deprivation. NE tumor cells are involved in angiogenesis by producing high levels of vascular endothelial growth factor (VEGF). The presence of NE cells would signal concern for the need to use chemotherapy , a somatostatin analogue such as Lanreotide® or long-acting Sandostatin® as well as agents targeting angiogenesis (Thalidomide, Avastin®). **A favorable result for CGA is negative.**



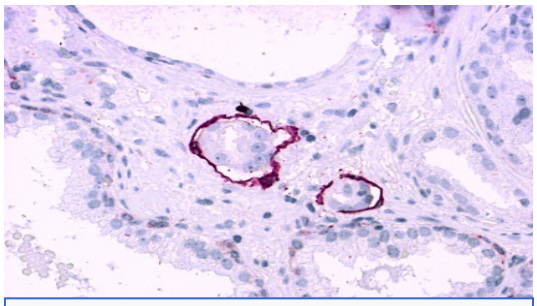
PC (GS 4+4=8) with extensive neuroendocrine differentiation (CGA). Neuroendocrine tumor cells (→) lack the nuclear androgen receptor and are androgen- insensitive

- **COX-2** (cyclooxygenase-2) is a proinflammatory enzyme implicated in prostate carcinogenesis and tumor progression. Clinical studies show that COX-2 expression is an independent predictor of prostate cancer progression following radical prostatectomy. At 62-months follow-up, COX-2 staining predicted progression with 82.4% sensitivity and 81.3% specificity. In multivariate analysis, preoperative PSA (hazard ratio/unit PSA change 1.080; $p = 0.0036$) and COX-2 expression (hazard ratio 16.442; $p < 0.0001$) were independent prognostic indicators. Patients with PSA > 7 ng/ml and high COX-2 expression had the highest probability of recurrence (Kaplan-Meier analysis). The COX-2 inhibitor etodolac exhibits an antitumor effect on prostate cancer cell lines in vitro and in vivo. Dietary supplementation of Celecoxib at different doses provides evidence for the suppression of prostate adenocarcinoma tumor growth in a dose-dependent manner. Suppression of adenocarcinoma by Celecoxib further limits the growth of metastatic prostate cancer. Phase II trial of Celecoxib in PSA recurrent prostate cancer after definitive radiation therapy or radical prostatectomy show that COX-2 inhibitors may help delay or prevent disease progression. **A favorable result for COX-2 is negative or low staining. When COX-2 is expressed at high level, treatment with Celecoxib may be considered. Alternatively, fish oil supplementation has been found to decrease COX-2 expression in prostate cancer tissue.**

- **DNA Ploidy** determination identifies three prognostic categories, i.e. diploid, tetraploid and aneuploid tumors. Aneuploid DNA content predicts a poorer prognosis and would signal concern for the need of more aggressive therapy. DNA determination is feasible in needle biopsy specimens only when a sufficient amount of PC is present. As high-grade PIN (HGPIN), a precursor of PC is often aneuploid, it is important that such lesions are not submitted for study to avoid false positive results. **A favorable result for DNA Ploidy is diploid.**

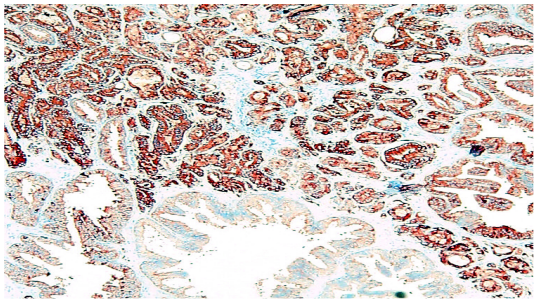
- **Disseminated tumor cells (occult metastases)** may be detected by immunohistochemistry (**Keratins, PSA**) in lymph nodes qualified as negative (pN0) upon histological examination. In a recent study of 180 patients with pathological stage pT3, pN0, occult lymph node metastases (OLN+) were found in 13.3%. The presence of OLN+ was significantly associated with increased recurrence and decreased survival compared with OLN- patients ($P < .001$ and $P = .019$, respectively; relative risk of recurrence, 2.27; relative risk of death 2.07, respectively). The presence of occult lymph node metastases was an independent predictor of recurrence and death in a multivariable analysis. The outcome for patients with OLN+ disease was similar to that for patients with histological evidence of lymph node metastases (pN1). **A favorable result is absence of disseminated tumor cells (occult metastases)**

- **Endothelial markers (CD34, D2-40)** are required for unequivocal detection of lympho-vascular invasion. The first step of the metastatic spread to lymph nodes is the presence of lymphatic vessel invasion (LVI). Detection of LVI by D2-40 in RP is significantly associated with a higher percentage of cases with lymph node metastasis (9/14, 62.3%), as compared to those without lymph node metastasis (1/12, 8.3%, $P<0.01$) and is considered a pathological feature of biologically aggressive disease in patients treated with RP. Patients treated with radiation therapy after RP have a higher risk of PSA recurrence and distant metastases when LVI is detected in RP specimens as compared to patients without evidence of LVI. It is important to differentiate between LVI and blood vessel invasion (BVI). Tumor cells invading blood vessels do not metastasise to lymph nodes but may spread to bone or other distant sites. Using immunohistochemistry distinction between LVI (D2-40+, CD 34 -) and BVI (CD34+, D2-40 + or -) is feasible. **A favorable result for D2-40 and CD34 is absence of lymphatic and blood vessel invasion**



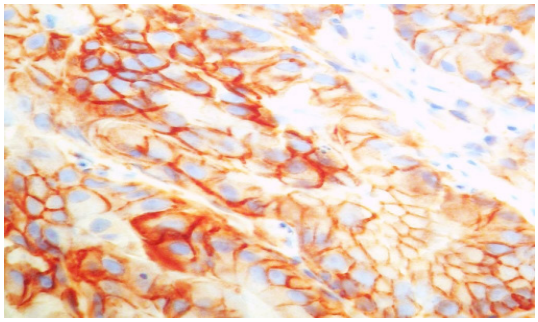
Peritumoral lymphatic invasion. Presence of neoplastic glands between benign prostate tissue. D2-40 identifies these tumor cells within lymphatic vessels

- **Fatty acid synthase (FAS)** is an enzyme involved in fatty acid synthesis. FAS play a role in early development and progression of PC. High FAS levels independently predict pathologic stage and tumor progression. FAS is associated with the development to androgen-independent disease. The biological function of FAS can be inhibited by Orlistat®. **A favorable result for FAS is negative or low staining.**



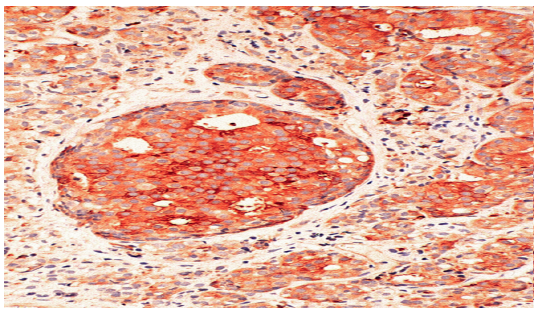
PC (GS 3+4=7) with high levels of FAS expression. Low levels of FAS are found in HGPIN

HER-1 (ErbB-1) and **HER2/neu** (ErbB-2) belong to the epidermal growth factor receptor (EGFR) family of receptor tyrosine kinases that increase activity of the androgen receptor (AR) even in absence of androgens and play an important role in the development of hormone refractory disease. Distinct membranous HER2/neu expression in ≥ 10% of tumor cells (score 2) predicts disease recurrence after androgen deprivation and is associated with an adverse outcome. Treatment with the novel dual EGFR/ HER-2 kinase inhibitor Lapatinib decreases tumor growth and PSA production in LNCaP cells and may provide a novel strategy to disrupt AR function in prostate cancer. **A favorable result for HER1 and HER2/neu is negative or < 10%.**



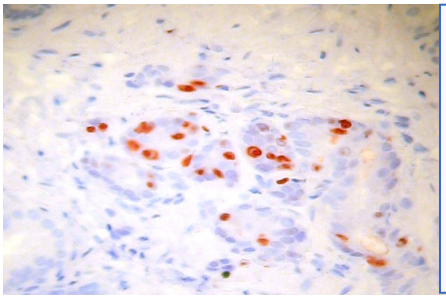
PC (GS 4+4=8) with distinct membranous expression of HER2/neu.

- **HSP-27** is a heat shock protein that function mainly as molecular chaperone, allowing cells to adapt to heat and a variety of other stressful stimuli and to survive in otherwise lethal conditions such as chemotherapy, radiation and androgen withdrawal. HSP-27 is overexpressed in a wide range of human cancers, including breast and prostate cancer, and is implicated in tumor cell proliferation, apoptosis and drug resistence. HSP-27 was found to be one of the most overexpressed genes in hormone-refractory prostate cancer xenografts. Several clinical studies have identified HSP-27 as an independent survival factor in prostate cancer. In fact, high HSP-27 expression was invariably associated with poor clinical outcome. Novel Hsp27-silencing strategies are aimed to downregulate Hsp27 expression. HSP-27 antisense oligonucleotides (ASOs) and small interference RNA potently inhibit HSP-27 expression, with increased apoptosis, decreased tumor cell growth, enhanced paclitaxel chemosensitivity and increased sensitivity to radiation. **A favorable result for HSP-27 is negative staining.**



Androgen- insensitive PC with high levels of HSP27

- **MIB-1** assesses proliferation activity of the tumor cell population. MIB-1 index (at the cut-off level ≥ 10% of proliferating tumor cells) is independently predictive of outcome in patients with clinically localized disease treated with RP, with radiotherapy and patients being observed (watchful waiting or active objectified surveillance). High proliferation activity is a risk factor for systemic disease. **A favorable result for MIB-1 is less than 10%.**

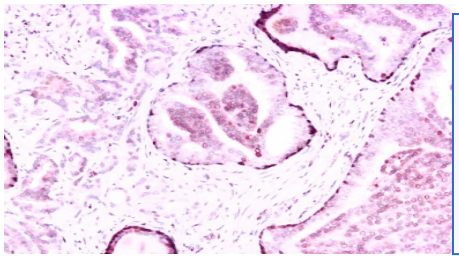


Prostate biopsy with Gleason 3 + 3 = 6 cancer. The therapeutic options include watchful waiting and low dose brachytherapy. MIB-1 immunostain reveals high proliferative activities up to 20% ruling out watchful waiting and low dose brachytherapy.

- **MUC-1** is a glycoprotein that independently predicts PSA recurrence and outcome after RP. It has been shown that 90% of lymph node metastasis expresses MUC-1 indicating that MUC-1 is associated with metastatic disease. It is mandatory to show positive immunostaining for MUC-1 in men being considered for MVA-MUC-1- IL2 vaccine. **A favorable result for MUC-1 is negative.**

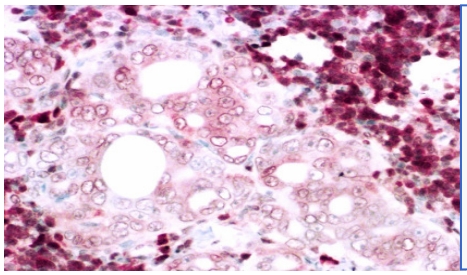
- **PSA and PAP** are androgen- regulated genes expressed in the normal prostate and in PC cells. Its presence at high levels requires a functional AR mechanism. Markedly decreased levels or loss of PSA and PAP in PC cells document a defective AR mechanism and predicts hormone therapy failure. It is mandatory to show positive tissue immunostaining for PAP in men being considered for Provenge® vaccine directed against PAP-expressing cells. **A favorable result for PSA and PAP immunostaining is high tissue expression.**

- **p27** is an important cell cycle regulator inhibiting active cell proliferation. Loss of DNA at the chromosomal region of p27 is detectable in 23% of localized PC and in 47% of patients dying of metastatic disease. Irrespective of the occurrence of mutation, reduced p27 expression predicts a shorter disease- free survival in all patients with PC.
  Preoperative p27 status is an independent predictor of PSA failure following RP. Patients with less than 45% p27 positive cells in the needle biopsy have almost a 2.5 fold increase risk of biochemical recurrence. Among patients with organ-confined disease, p27 expression was the only significant independent predictor for the time to PSA recurrence after RP.



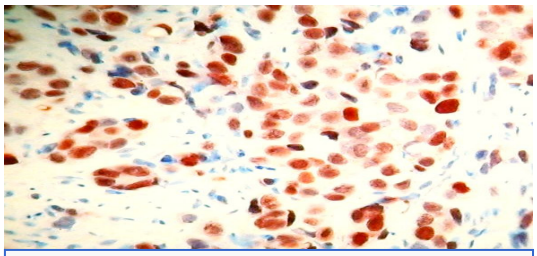
PC with severe loss of p27. Strong nuclear expression of p27 is identified in pre- existing (non- neoplastic) basal cells. The aberrant cytoplasmic presence of p27 was found to be an independent indicator for predicting the probability of biochemical recurrence in PC

There is increasing evidence that the p27 status in prostate cancer is an important factor for predicting response to hormonal therapy. Androgen deprivation therapy results in an increase in p27 expression with concurrent cell cycle arrest. High levels of p27 expression prevent PC cells from proliferation and thus predict good response to androgen deprivation therapy. During development of androgen independence p27 is down regulated as documented in androgen responsive LNCaP cells becoming androgen- independent. Tumor specimens from patients with hormone refractory disease show markedly reduced levels of p27 expression. **A favorable result for p27 is over 45% of positive cells.**



Lymph node metastasis of a patient who developed androgen- independent disease. Complete loss of nuclear p27 expression in PC cells. Strong p27 expression is noted in the adjacent lymph node tissue.

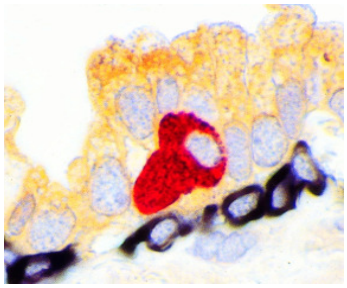
- **p53** is an oncogene usually mutated and upregulated in high-grade and metastatic disease. Nuclear p53 accumulation in $\geq$ 20% of tumor cells independently predicts distant metastases in patients treated with radiotherapy + androgen deprivation therapy. In patients treated with RP, p53 accumulation in > 0% of tumor cells independently predicts PSA recurrence. **A favorable result for p53 is negative (0%).**



PC (GS 4+4=8) with nuclear expression of p53

- **Somatostatin receptors** are activated by somatostatin and blocked by somatostatin analogues. It is suggested that positive immunostaining for somatostatin receptors be confirmed in men being considered for treatment with somatostatin analogues such as Sandostatin LAR® or Lanreotide®. **A favorable result for somatostatin receptors is its presence in tumor tissue in patients being considered for treatment with somatostatin analogues.**

- **Thymosin Beta-15** regulates cell motility and invasiveness. High Thymosin Beta-15 levels identify high-risk patients with "apparent" clinically localized PC. In one clinical study, 62% of patients with tissue specimens which stained 3+ (strongest staining) developed bone metastases compared to 13% of those patients whose specimens stained 1+ (weakest staining). The 5-year freedom from PSA failure was only 25% for those patients with 3+ staining compared with 83% for those with 1+ staining (P = 0.02). **A favorable result for Thymosin Beta-15 is 1+ staining or negative.**



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Order Form

The following prognostic and predictive markers should be performed, if applicable. Please check off.

Immunostain Study	Requested: ☑	Patient Results	Favorable Result Definition
AMACR			High expression (2+, 3+)
AR			Homogeneous expression (1+, 2+)
AZGP1			High expression (2+, 3+)
Basal cell markers			No intraductal spread
BCL-2			Negative (0%)
ChromograninA (CGA)			Negative
COX-2			Low expression (≤1+)
D2-40/ CD34			No lympho- vascular invasion
Disseminated tumor cells			No evidence of occult metastases
DNA Ploidy			Diploid
FAS			Low expression (≤1+)
HER1 (EGF-R)			< 10%
HER2/neu			< 10%
HSP-27			Negative
MIB-1			< 10%, better <5%
MUC-1			Negative (0%)
PAP/ PSA			High expression (2+, 3+)
p27			>45%
p53			Negative (0%) up to <20%
Somatostatin- R			Positive
Thymosin beta-15			≤1+

Molecular signature of aggressive prostate cancer with risk of systemic disease

Marker Profile
High proliferation activity (MIB-1)
Severe loss of p27
p53 up- regulation/mutation
HER1 and HER-2/ neu up- regulation
BCL-2
MUC-1
HSP-27
Loss of AZGP1
Loss of PSA, PAP, AMACR
Lympho- vascular invasion (CD34, D2-40)
Occult metastases (Keratins. PSA)
DNA aneuploidy

Molecular targeting of prostate cancer

Marker/ Target	Marker Profile	Therapeutic Options
Androgen receptor	hypersensitive AR	ADT3 AR lowering therapies
BCL-2	Positive	Taxane, Vitamin E, Aspirin
Chromogranin A (CGA)	Positive	RP better than RT Intermittent AB, Somatostatin-Analoga Anti-Angiogenetic drugs (Thalidomid)
COX-2	High expression (2+,3+)	Celecoxib
FAS	High expression (2+,3+)	Orlistat
HER1 and HER2/neu	>10%	ADT3, Lapatinib
MUC-1	Positive	MVA-MUC-1-IL2
PAP	Positive	Provenge
Somatostatin- receptor	Positive	Somatostatin-Analoga
Occult metastases	Disseminated tumor cells	Systemic therapy

Date:

Name:

Signature:

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AMACR

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