PROSTATE TUMOURS – HISTOLOGICAL CLASSIFICATION AND MOLECULAR ASPECTS OF PROSTATE TUMORIGENESIS

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In Europe and United States, prostate cancer (CaP) is the most commonly diagnosed malignancy in elderly men and the second leading cause of cancer-related deaths in the male population (DIEFENBACH et al. 2002). Its frequency increases with age and hormonal factors also play a role in its development. CaP and benign prostatic hyperplasia are the two principal causes involving the prostate impairment and they account of 90 % of all prostatic diseases. Most of benign lesions mimicking cancer occur in the same age group as prostatic carcinoma and they may be divided into epithelial and stromal lesions (RO et al. 2001).

Benign lesions mimicking cancer

Nodular hyperplasia (benign prostatic hypertrophia) is a common benign disorder of prostate. It represents nodular enlargement of prostate caused by hyperplasia of both glandular and stromal components (ROSAI et al. 2004). *Postoperative spindle cell nodules* are resembling sarcomas in their deep areas. The temporal relationship with a surgical procedure and their benign evolution support a reactive pathogenesis (PROPPE et al. 1984). *Inflammatory pseudotumor* (pseudosarcomatous fibromyxoid tumor) is characterized with proliferation of spindle cells of myofibroblastic appearance. *Urethral polyps* are composed of tall columnar cells of prostatic origin. They may be occasionally the site of carcinoma (WALKER et al. 1982).

Basal cell hyperplasia, relatively common lesion in hyperplastic prostate is characterized by nodular growth of filled with proliferating darkly staining basal cells mostly palisading toward the periphery. *Clear cell cribriform hyperplasia* is rare form of hyperplasia characterized by a papillary-cribriform hyperplasia of clear cells involving acini of benign prostatic hyperplasia (RO et al. 2001). *Melanosis* of the prostate refers to the presence of melanin containing elongated cells in stromal part.

Other congenital and acquired non-neoplastic abnormalities include hyperplasia and hypertrophy, atrophy and postatrophic hyperplasia, sclerosing addenosis, inflammation, cysts, squamous metaplasia, hyperplasia of mesonephric remnants and nephrogenic adenoma.

Stromal hyperplasia is considered the most common stromal lesion. RO et al. (2001) distinguish *two putative premalignant lesions of the prostate*: prostatic intraepithelial neoplasia and atypical adenomatous hyperplasia.

Acinar adenocarcinoma of prostate

Tumours usually extend microscopically beyond their macroscopic border. In general, grossly recognizable tumours tend to be larger, of higher grade and stage, compared with grossly inapparent often non palpable tumours, which are low grade and low stage. Some large tumors are diffusely infiltrative, and may not be evident grossly (EPSTEIN 1990). Microscopically, prostatic adenocarcinomas (Fig. 1) are ranging from anaplastic to highly differentiated neoplasms. Prostate specific

antigen (PSA) and prostate specific acid phosphatase (PAP) are useful imunohistochemical markers of prostatic differentiation. Poorly differentiated tumors are mostly associated with higher PSA concentrations. It represents over 90 % of the epithelial malignancies in this organ, the majority of cases exhibiting an acinar or acinar/ductal growth pattern.

CaP can be divided into two major categories: 1. adenocarcinoma of peripheral ducts and acini, 2. carcinoma of large ducts. Majority of tumors belong to the first category and most of prostatic carcinomas arise in the peripheral zone. Aproximately 68 % of CaP arise in the peripheral zone (PZ), 24 % in the transitional zone (TZ), and 8% in the central zone (CZ) (Mostofi et al. 1980). Sakai et al. (2006) concluded that TZ cancers, despite high PSA level, had similar biochemical cure rates folloving radical prostatectomy, suggesting a less aggressive phenotype of TZ cancers than that of PZ cancers.

The PZ carcinomas often grow into periprostatic tissue by invading along nerves or by direct penetration out of the prostate. The presence of prostate glands within perineural spaces is characteristic in these tumors (Fig. 2) and it is also indicator of malignancy. Metastatic spread of prostatic carcinoma begins into lymphovascular spaces (Fig. 3). The most common site of metastatic spread are the regional lymph nodes and bones of the pelvis and axial skeleton. Visceral metastatic deposits in the lung and liver are not often clinically apparent, but are common in end-stage disease (Eble et al. 2004).

Common feature of all CaP is the presence of only a single cell type without a basal layer. Benign prostate glands contain a basal cell layer beneath the secretory cells. The complete absence of the basal cell layer is supportive of invasive carcinoma in acinar proliferations in the case of suspicious cytologic or architectural features on HE staining. Some early invasive CaP arising in association with or independent of high grade prostatic intraepithelial neoplasia may have residual basal cells (Oliai et al. 2002). The distinction of prostatic cancer from benign glands rests on architectural, nuclear, cytoplasmic and intraluminal features. Glands in prostate cancers are more crowded than in benign tissue. Glands in CaP typically grow in a haphazard fashion.

The tumors consisting of solid sheets, cords of cells, or isolated individual cells characterize undifferentiated prostate cancer. These patterns are key components to the grading of prostate cancer. The extent of nuclear atypia correlates in most cases with the architectural degree of differentiation. Mitotic figures may be relatively common in high-grade cancer, yet are infrequent in lower grade tumors. One of the important specific features for prostatic cancer is known as either mucinous fibroplasia or colagenous micronodules. It is characterized by very delicate loose fibrous tissue with an ingrowth of fibroblasts, sometimes reflecting organisation of intraluminal mucin. Ordinary adenocarcinoma lacks a desmoplastic stromal reaction, typically adenocarcinoma of the prostate does not elicit a stromal inflammatory response (Eble et al. 2004).

The presence of corpora amylacea is not necessarily a sign of benignancy, as formerly believed. The cytoplasm of the carcinoma cells may be occasionally clear or foamy because of the massive accumulation of lipids. The behavior of these tumors is often aggressive despite the deceptively innocuous microscopic features (Trann et al. 2001). In small number of prostatic biopsies there is not possible to distinguishe the malignancy from benignancy (Epstein 1999), in such cases a second biopsy is needed (Eble et al. 2004).

The main controversies in numerous grading systems have been whether the grading should be based on glandular differentiation alone or a combination with nuclear atypia or whether prostate cancer should be grading according to its least differentiated or dominant pattern.

In 1993 the Gleason grading system (as called after Donald F. Gleason) was recommended by a WHO consensus conference (Murphy 1993). This system is based on glandular architecture, nuclear atypia being not evaluated (Gleason 1977). Five histological patterns or grades with decreasing differentiation are defined. In patterns 1 to 3 epithelial polarity with luminal polarity is present in all glands. In pattern 4, there is reduction of polarity with only occasional luminal differentiation.

Morphologicaly heterogenous CaP contains more than one histological pattern. The most prevalent and the second prevalent pattern are identified, each is graded 1 to 5 and added to obtain Gleason score (Fig. 4) . In tumor of one histological pattern, the primary and secondary scores are the same. Tumor grade is usually higher in larger tumors. This may by due to more rapid growth of high grade cancers. This system also warrants interobserver worldwide reproducibility. Gleason score is also an effective prognostic factor on all prostatic samples. This includes the prediction of the natural history of prostate cancer (Egevad et al. 2002) and

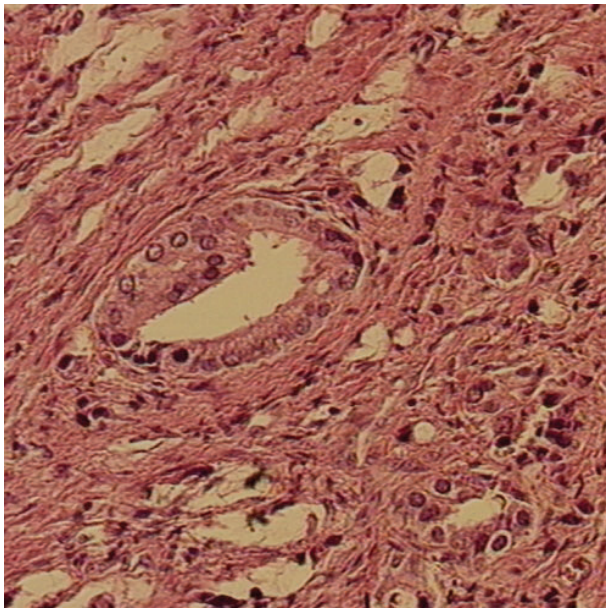

Fig 1 Acinar adenocarcinoma of prostate stained with hematoxylin and eosin (HE)

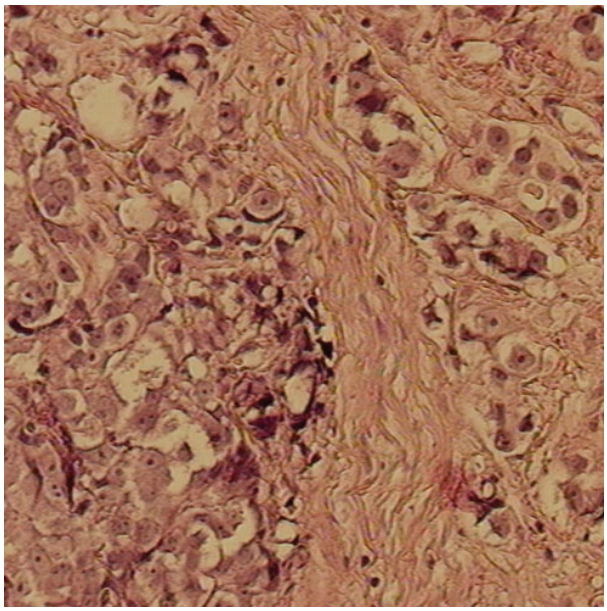

Fig. 2 Perineural spreeding of carcinoma

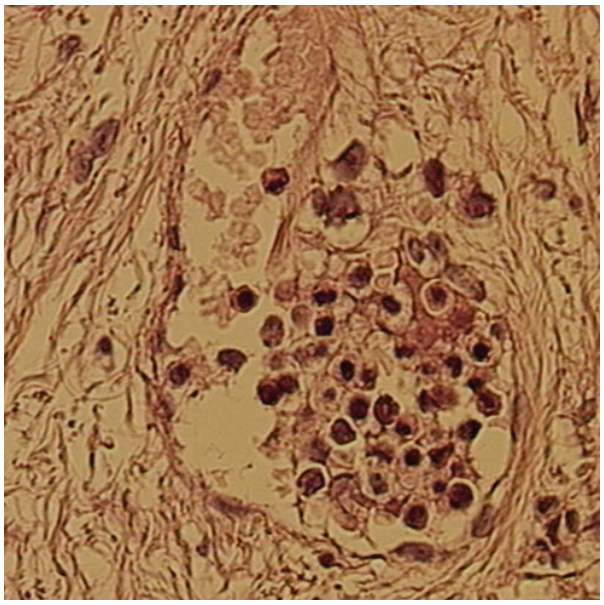

Fig. 3 Metastatic carcinoma cells in vessel

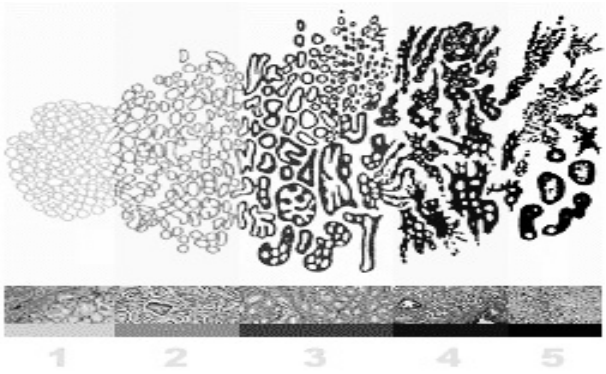

Fig. 4 Gleason score : 2-4 well differentiated carcinoma; 5-7 medium differentiated carcinoma; 8-10 pure differentiated carcinoma

the assessment of risk of recurrence after prostatectomy (GREEN et al. 1998).

Four major patterns described by TOTTEN et al. (1953) have been used up to these days in CaP classification: 1. medium sized glands, 2. small glands, 3. diffuse individual cell infiltration, 4. cribriform. Glands of irregular outline and smooth inner surphace are closely spaced in the first pattern. Glands in tumors of small

glands have regular round configuration and small size. Both of these patterns have enlarged irregular hyperchromatic nuclei and prominent nucleoli often multiple. Cribriform pattern characterized with secondary lumina is marked as intraductal carcinoma. An additional pattern of growth that has recently been described is referred to as glomeruloid and characterized by the presence of intraluminal ball-like clusters of tumor cells (Rosai et al. 2004).

Two opposing morphologic variations of adenocarcinoma are described. The first designated as CaP with atrophic features in which the tumor simulates an atrophic process but the cells have infiltrative patern of growth, enlarged nuclei and nucleoli. Another variation mimics a benign hyperplastic change but it has also just mentioned malignant features (Rosai et al. 2004). Minimal criteria for diagnosis of malignanci in foci of small atypical glands that are suspicious but not diagnostic of carcinoma are well described by Grignon (1998).

For the less obvious cases, diagnoses such as typical gland suspicious of malignancy or atypical acinar proliferation (ASAP) suspicious of malignancy have been recommended (Epstein 1999, Kambham et al. 1999)

Numerically less significant type of CaP originates from the large ducts localised periurethraly. The following types have been recognized (Rosai et al. 2004).

1. Large duct adenocarcinoma characterized by malignant changes in large dilated ducts, often accompanied by papillary foci and occasionally by a cleer cell look. The tumors tend to have a more advanced stage and a higher short term survival rate than peripheral duct-acinar carcinomas. Endometrial-type adenocarcinoma originally described as arising from the prostatic urticle (müllerian remnant) but is regarded as a variant of large duct adenocarcinoma

2. Primary transitional cell (urothelial) carcinoma of prostate comprises less than 2% of all prostatic carcinomas. Outer portion of prostatic ducts is lined by transitional epithelium. Before a diagnosis is made, the possibility of prostatic extension from a bladder or urethral carcinoma should be excluded.

3. Mixed adenocarcinoma-transitional cell carcinoma represents combination of types 1 and 2.

Atypical hyperplasia and carcinoma in situ of periurethral glands, presumably representing the precursors of large duct carcinomas, have been observed.

Histologic variants of acinar CaPe according WHO classification (Eble et al. 2004)

Atrophic variant resembles benign atrophy, but prostate cancer is usually characterised with presence of cytologic atypia. Atrophic cancer may be infiltrative, in benign atrophic glands are not signs of infiltration between larger glands. Some forms of atrophy are assotiated with fibrosis, adenocarcinoma of prostate is not connected with desmoplastic reaction.

Pseudohyperplastic variant resembles benign prostate glands. In pseudohyperplastic variant the neoplastic glands are large with branching and papillary infolding (Humphrey et al. 1998) with cytologic atypia in some of these glands and it can exhibit aggressive bahaviour.

Foamy gland variant is characterized by having abundant foamy appearing cytoplasm with a low nuclear/cytoplasmic ratio. It is recognized as carcinoma by its architecture of crawded and infiltrative glands and frequently dense pink acellular secretion (Nelson and Epstein 1996). Foamy gland variant recommended to classify as intermediate grade carcinoma.

Coloid and signet ring variant is one of the least common morphologic variants of prostatic carcinoma. This variant behaves aggressively. The diagnosis of this mucinous carcinoma like variant should be made when at least 25 % of tumour resected contains lakes of extracellular mucin. A cribriform pattern tends to predominate in mucinous areas. Some carcinomas of prostate will have a signet ring cell appearance (Fig. 5), yet the vacuoles do not contain intracytoplasmic mucin (Ro et al. 1998). Only a few cases have been reported with mucin positive signet cells (Uchijima et al. 1990). Other mucinous tumors of non-prostatic origin must be excluded.

Oncocytic variant is a rare variant composed of large cells with granular eosinofilic cytoplasm and ovoid hyperchromatic nuclei. Metastases are of similar morphology (Ordonez et al. 1992).

Lymphoepithelioma like variant. Undifferentiated carcinoma characterized by a syncytial pattern of malignant cells associated with a heavy lymphocytic infiltrate. Clinical significance is uncertain.

Sarcomatoid variant (carcinosarcoma). Rare neoplasm composed of both malignant epithelial and malignant mesenchymal or spindle cell elements. The gross appearance often resembles sarcomas. Microscopically is the tumor composed of a glandular component of variable Gleasson score. Amongst the specific mesen-

chymal elements are osteosarcoma, chondrosarcoma, rhabdomyosarcoma, leomyosarcoma, liposarcoma, angiosarcoma or multiple types of heterologous differentiation (Dundore et al. 1995).

Prostatic intrepithelial neoplasia

High grade prostatic intrepithelial neoplasia (HGPIN) has been defined relatively recently with respect to diagnostic criteria and terminology. This neoplasia consists of architecturally benign prostatic acini lined by cells (Fig. 6) that seem to be malignant (Demarzo et al. 2003). Total volume of HGPIN increases with a significant correlation between volume of HGPIN and the number of lymph node metastases (Qian et al. 1997a). HGPIN shows strong assotiation with cancer in terms of coincidence in the same gland and in its spatial distribution. Demarzo et al. (2003) state that HGPIN seems to be a precursor lesion to many peripheral intermediate to high-grade adenocarcinomas of the prostate, but the lesion is not a necessary precursor because many early cancers do not have adjacent HGPIN. Androgen deprivation decreases the prevalence and extent of PIN (Montironi et al. 2000).

Relationship of HGPIN to prostate carcinoma (Montironi et al. 2002): 1. The incidence and extent of both lesions increase with patient age; 2. There is an increased frequency, severity and extent in prostate with cancer; 3. Both lesions are multifocal with a predominant peripheral zone distribution; 4. Histological transition from HGPIN to cancer has been reported; 5. High-grade PIN shares moleculargenetics features with cancer (Qian et al. 1997); 6. HGPIN is more strongly assotiated with intermediate-high grade prostatic carcinoma (Epstein et al. 1990, Erbersdobler et al. 1996, Qian et al. 1997).

PIN was originally divided into three grades based on architectural and cytologic features. Subsequently, it has been recommended that the classification should be simplified into a two-tier system: low and high grade lesions (Drago et al. 1992). The distinction between these two grades is based on the degree of architectural complexity and on the extent of cytologic abnormalities.

It is difficult to distinguish low grade PIN from normal and hyperplastic epithelium (Epstein et al. 1995). The basal cell layer normally rimming ducts and acini is intact in low grade PIN. Basal cell layer is retained also in high grade PIN. HGPIN is characterized by

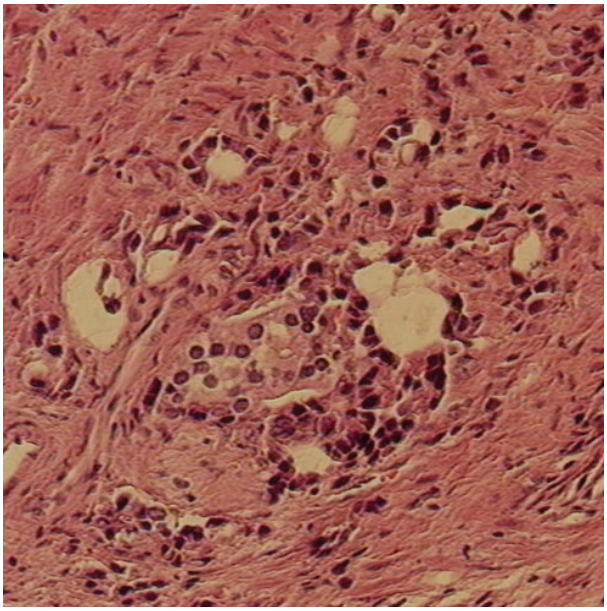

Fig. 5 Acinar adenocarcinoma mixed with signet ring carcinoma

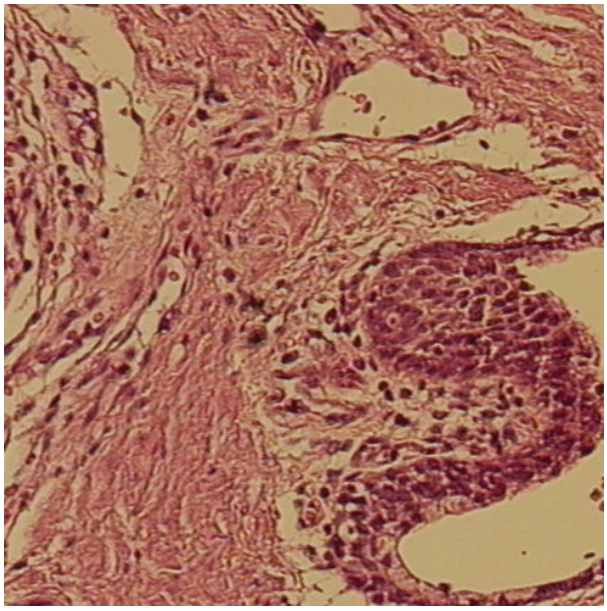

Fig. 6 High grade prostatic intrepithelial neoplasia

a more uniform morphologic alteration. The individual cells are almost uniformly enlarged with increased nuclear/cytoplasmic ratio and mostly prominent nucleoli. HGPIN is characterized also by marked increase in cellularity and nuclear pseudostratification.

Four architectural patterns of HGPIN have been described: 1. Flat pattern – nuclear atypia without significant architectural changes; 2. Tufting pattern – nuclei more piled resulting in undulating mounds of cells; 3. Micropapillary pattern – columns of atypical epithelium with lacking fibrovascular cores; 4. cribriform pattern – cribriform formation with controversial distinction from ductal carcinoma in-situ. These patterns appear to have no prognostic significance but familiarity with the morphologic spectrum may facilitate histologic recognition (Bostwick et al. 1993).

The grade of PIN is based on assessment of the nuclei located up against the basement membrane.

Uncommmon histologic patterns include signet-ring variant, mucinous variant, inverted variant, small cell neuroendocrine variant and high grade cribriform PIN.

Ductal adenocarcinoma

This subtype of adenocarcinoma is composed of large glands lined by tall pseudotsratified columnar cells. This tumor may be located around the prostatic urethra or more frequently located peripherally admixed with typical acinar adenocarcinoma, or both localisations may appear together. Both forms may spread with invasion to extraprostatic tissues and metastasis. Tall pseudostratified columnar cells are similar to the epitehelium in endometrial carcinoma. Metastases appear up to 40 % of cases (Eble et al. 2004).

Large duct adenocarcinoma characterized by malignant changes in large dilated ducts, often accompanied by papillary foci and occasionally by a cleer cell look. The tumors tend to have a more advanced stage and a higher short term survival rate than peripheral duct-acinar carcinomas. Endometrial-type adenocarcinoma originally described as arising from the prostatic urticle (müllerian remnant) but is regarded as a variant of large duct adenocarcinoma.

Ductal adenocarcinoma displays a variety of architectural patterns (papillary, cribriform, individual gland and solid patterns), which may be variously mixed (Epstein and Yang, 2002). In contrast to ordinary acinar adenocarcinoma, some cases of ductal adenocarcinoma are associated with fibrotic response.

Urothelial carcinoma (primary transitional cell carcinoma)

This variant comprises less than 2 % of all prostatic carcinomas. In patients with invasive bladder carcinoma, there is involvement of the prostate in up to 45 % of cases (Nixon et al. 2002, Wood et al. 1989). Before a diagnosis is made, the possibility of prostatic extension from a bladder or urethral carcinoma should be excluded. Primary urothelial carcinoma is usually located within the proximal prostatic ducts. Outer portion of prostatic ducts is lined by transitional epithelium. The full range of histologic types and grades of urothelial neoplasia can be seen. The majority are high grade and are assotiated with an *in situ* component (Cheville et al. 1995, Goebbels et al. 1985). Residual basal cells are frequent in the in situ carcinoma. This component has the characteristic histologic features of urothelial carcinoma in situ with marked nuclear pleomorfism and frequent mitoses. Urothelial carcinomas of prostate usually have glassy eosinophilic cytoplasm or more prominent squamous differentiation, in contrast to foamy, pale cytoplasm of the adenocarcinoma.

Tumor expands the ducts and often develops central comedo necrosis. Stromal invasion is assotiated with a prominent desmoplastic stromal response with poor prognosis for the patient. Metastases are to regional lymph nodes and bone (Takashi et al. 1990).

Basal cell carcinoma

This tumor consists of prostatic basal cells, which can give rise to a spectrum of proliferative lesions ranging from basal cell hyperplasia to basal cell carcinoma (Signoreti et al. 2000). Some patterns comprise large basaloid nests with palisading and necrosis. Other patterns show histologic similarity to florid basal cell hyperplasia or the adenoid basal cell pattern of hyperplasia (adenoid cystic carcinoma). Malignant features of these tumors include: inifiltrativity, extraprostatic extension, perineural invasion, necrosis and stromal desmoplasia.

Neuroendocrine tumors

There exist three forms of these types of tumors of prostate: 1. Focal neuroendocrine tumors in prostatic carcinoma; 2. Carcinoid tumor (new WHO classification well differentiated neuroendocrine tumor); 3. Small

cell neuroendocrine carcinoma (new WHO classification poorly differentiated neuroendocrine carcinoma).

Focal neuroendocrine tumors in prostatic carcinoma - all cancers show focal neuroendocrine differentiation, although the majority shows only rare or sparse single neuroendocrine cells . Prognosis in untreated carcinomas is controversial (EBLE et al. 2004).

Very rare carcinoid tumors represent variety of miscalenous entities, mostly refer to ordinary acinar adenocarcinoma with focal neuroendocrine immunoreactivity. These group of tumors shows cytologic features of carcinoid tumor and neuroendocrine differentiation and they are PSA negative.

Small cell neuroendocrine carcinoma. In approximately a half of cases the tumors are mixed small cell carcinoma and adenocarcinoma of the prostate. While most small cells carcinomas of prostate lack clinicaly evident hormone production, they account for the prostatic tumors with evident ACTH or antidiuretic hormone production. Survival is usually less than one year (EBLE et al. 2004).

Mesenchymal tumors

Lesions have been classified into prostatic stromal proliferations (STUMP) and prostatic sarcomas based on the stromal cellularity, presence of stromal over growth, mitotic figures and necrosis (GAUDIN et al. 1998). Both STUMP and stromal sarcomas express progesterone receptors and they involve hormonally responsive prostatic mesenchymal cells. Sarcomas and related lesions of specialized prostatic stroma are rare.

Leiomyosarcomas are the most common sarcomas in adults (CHEVILLE et al. 1995). They range from smooth muscle tumors with moderate atypia to highly pleomorfic sarcomas. They are clinicaly characterised by multiple recurrences. Metastases are found in the lung.

Rhabdomyosarcomas are the most frequent prostatic mesenchymal tumors in childhood (LOBE et al. 1996). Some patients exhibit distant metastases. Most patients with metastatic tumors (stage IV) have been dying.

Miscalenous sarcomas represent rare cases of malignant fibrous histiocytoma, angiosarcoma, osteosarcoma, chondrosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumors (EBLE et al. 2004).

Leiomyoma is a very rare well-circumscribed proliferation of smooth muscle.

Various described benign soft tissue tumors have been assignet to miscalenous benign mesenchymal tumors.

*Haematolymphoid tumor*s appear in prostate rarely.

Heterogenous group of miscalenous tumors is composed of rare tumors such as cystadenoma, nephroblastoma, malignant rhabdoid tumor, germ cells tumors, clear cell adnocarcinoma, melanoma and paraganglioma (EBLE et al. 2004).

Secondary tumors involving the prostate are metastatic tumors arised outside of the prostate and spreading to the gland by vascular channels.

Prostate cancer classification is not unique, WHO classification is recommended et present. Advance in classification is expected in prognostic factors interposed with molecular biology help.

Molecular mechanisms of prostate tumorigenesis

Despite the high frequency, little is known about the molecular mechanisms involved in prostate tumorigenesis. Currently, the serum PSA level is used for monitoring the course of disease after RP (LEAK et al. 2002). A more effective is detection of micrometastases in the peripheral blood of patients with prostate cancer. The circulating tumor cells are originally epithelial prostatic cells that are characterized by the very specific expression of genes for PSA (prostate-specific antigen) and PSM (prostate-specific membrane antigen). Their presence in the circulation could be one of the steps in the cascade of metastasing process (GHOSSEIN et al. 1995). The micrometastases are detectable also by RT-PCR (reverse transcriptase–polymerase chain reaction), which is extremely sensitive method. Experimental data indicate that RT-PCR can detect a single PSA expressing prostate cancer cell in up to 100 million background cells in vitro (IGNATOFF et al. 1996).

PSA is a monomeric 33 kD long glycoprotein and a member of the kallikrein serine protease family. PSA is secreted primarily by epithelial cells that line the prostatic acini and ducts. Further members of the kallikrein gene family are the hGK-1gene, which is also expressed in prostate, and the tissue kallikrein gene KLK I, which is expressed in pancreas and kidney (Fig. 7). The PSA gene is located on the chromosome 19q13 (STEPHAN et al. 2002, DAVID et al. 2002, ITO, 2004). The gene for PSA has been sequenced and now it is known that the complete gene is 6153 bp long, and that it consists of

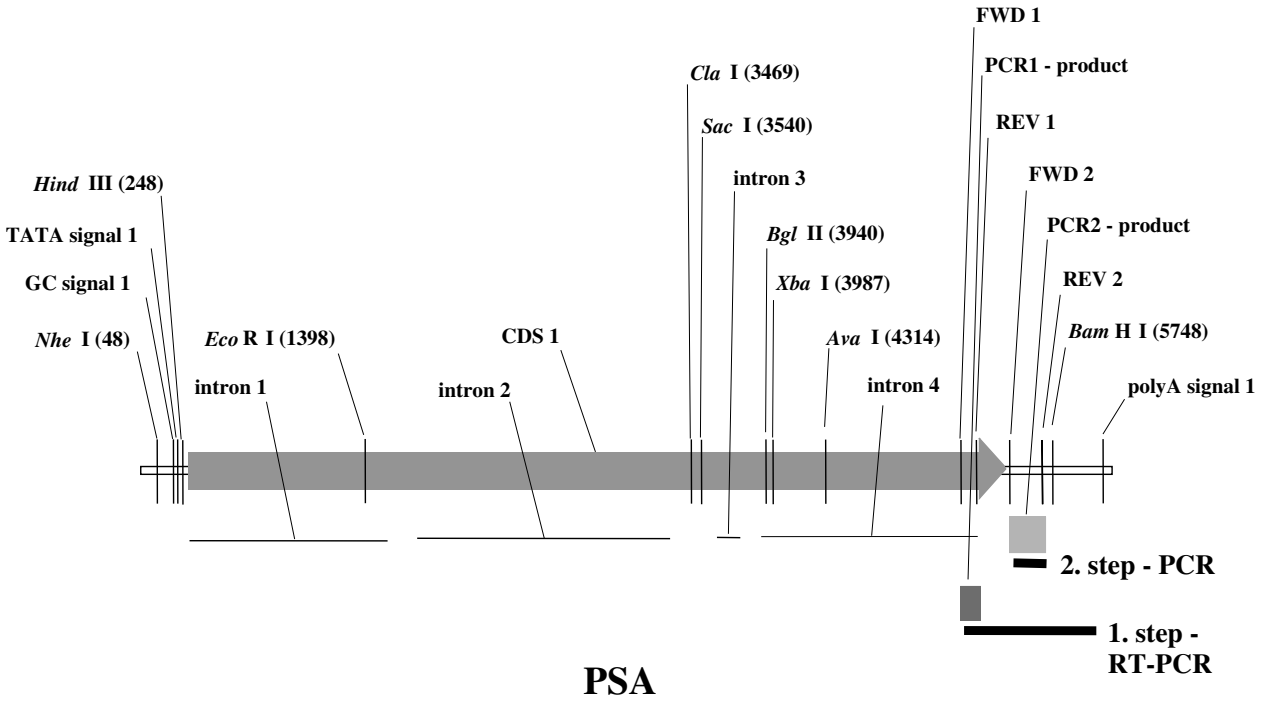

Fig. 7. The PCR primers for PSA gene

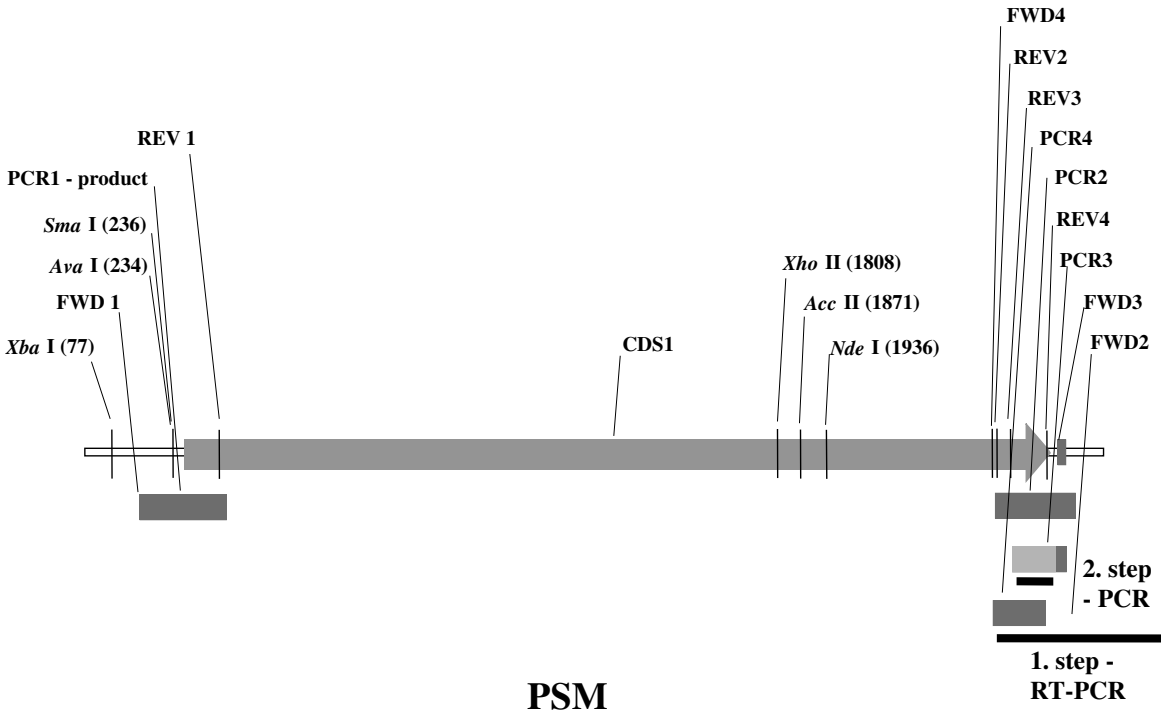

Fig. 8 The PCR primers for PSM gene

4 introns and 5 exons. PSA expression show cell-specificity and is tightly regulated by androgens through the androgen receptor (CLEUTJENS et al. 1996, HERNANDEZ et al. 2004).

PSM is a type II transmembrane protein with folate hydrolase and N-acetylated-alpha-linked-acidic dipeptidase (NAALAdase) activity. The PSM gene encodes for a 750-amino acid protein that has an apparent molecular weight of 100 kD (due to post-translational modification) and is expressed by normal and neoplastic prostate cells. The PSM gene consists of 19 exons spanning approximately 60 kb of genomic DNA (Fig. 8). By radiation hybrid analysis, the gene encoding PSM was mapped to 11p11-p12. On 11q14 there is homolo-

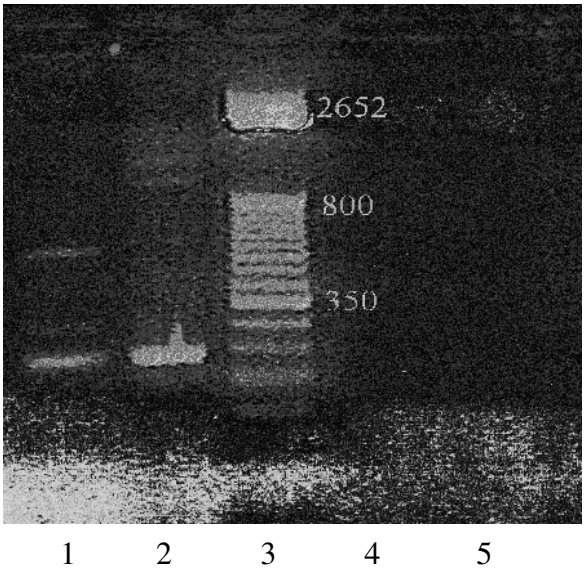

Fig. 9 The products of the nested RT PCR procedure for PSA gene detected by using separation by gel electrophoresis. 1-2 PSA positive, 3 marker, 4-5 PSA negative

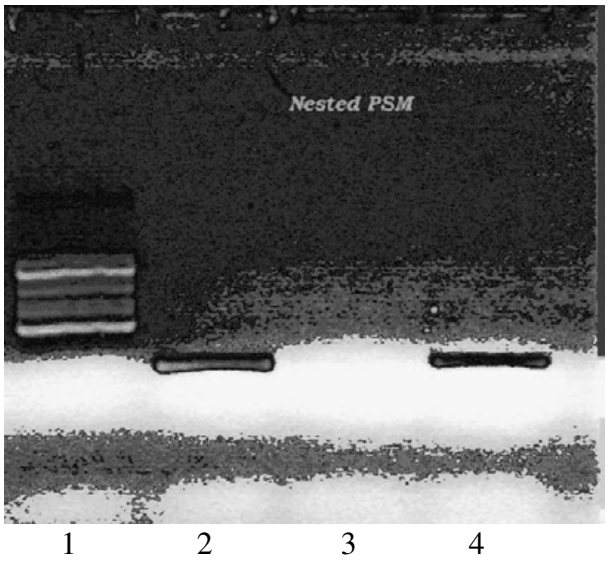

Fig.10 The products of the nested RT PCR procedure for PSM gene detected by using separation by gel electrophoresis. 1 marker, 2 and 4 PSM positive, 3 PSM negative. Genes amplification of protooncogene c-myc and androgene receptor correlate with the progression.

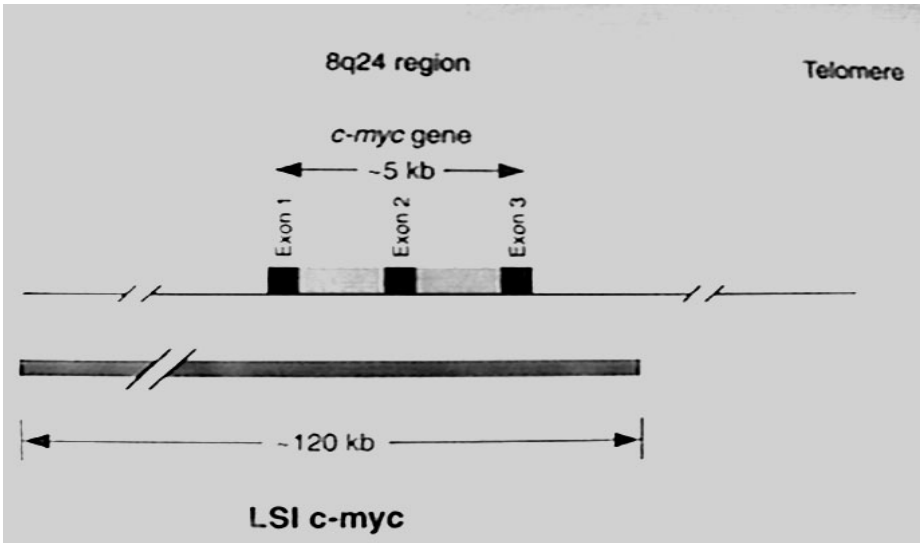

Fig. 11 Probe for c-myc gene.

gous gene, but not identical to PSM (Tasch et al. 2001, Xiao et al. 2001).

Genes amplification of protooncogene c-myc and androgene receptor correlate with progression of disease (Burmester et al. 2004).

Protooncogene c-myc (Fig. 11) serves as nuclear transcription factor, it participates on growth regulation, cell division and appoptosis and also participates in initiation complex in regulation of cell cycle and allowes transition into S phase.

Gene for androgen receptor has essential biological role in patients with advanced prostate carcinoma. Amplification of AR gene of recurent prostate tumors may be the consequence of androgene deprivation therapy.

PSA and PSM are described as good prognostic markers for metastasing process monitoring in prostate cancer (Ghossein et al. 1995, Ito 2004). In positive RT-PCR of both PSA and PSM (Fig. 9 and 10), progression of the disease in the meaning of metastasis formation is observed. The patients with positive PSA and negative PSM RT-PCR are usually without any progression and detected metastases (Moreno et al. 1992, Israeli et al. 1994, Schmittgen et al. 2003). The situation is similar when PSA and PSM are negative. PSM is more sensitive marker than PSA. The patients with positive PSA and negative PSM are in relatively good health condition without a diseases progression. That naturally means higher relevance of RT-PCR for PSM. Israeli et al. (1993) reported that the level of detection of tumor cells with the PSM-PCR assay was significantly higher than with PSA-PCR assay, because PSM, but not PSA, appeared to be highly expressed in anaplastic cells, hormone refractory cells and bone metastases.

The RT-PCR method for the positivity or negativity of PSA and PSM correlates better with health condition of patients than monitoring of the serum level of PSA (Noguchi et al. 1997). It appears that the presence of the RT-PCR can be used as a predictor of early mortality. Piñeiro et al. (2003) published, that the lymph node PSA RT-PCR correlates better than blood PSA RT-PCR with standard prognostic factors such as the Gleason score, pathological T category, lymph node status and preoperative serum PSA. The relatively high positivity rate of blood RT-PCR and its lack of correlation with pathological risk factors indicates that most of the PSA expressing cells detected in peripheral blood do not have metastatic potential and are ultimately cleared from the body without establishing a metastatic site. This capability indicates a malignant characteristic and may partly explain the better correlation of lymph node RT-PCR with established prognostic factors. Moreover, the extraordinary specificity of PSA gene expression and the lack of detection in control population strongly suggest that the lymph node RT-PCR assay actually detects prostate tumor cells.

The suggestion that genetic analysis of lymph nodes is superior to histologic analysis and blood RT-PCR remains to be proved and further clinical follow-up is required to allow validation of lymph node RT-PCR as a predictor of distant disease recurrence.

Searching for a new parameters allowing better prediction of biological behaviour of tumors is the only way to improve the treatement of patients, also with the carcinoma of prostate.

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