

# PROSTATE CANCER: EPIDEMIOLOGY, ETIOLOGY, PATHOLOGY, DIAGNOSIS, AND PROGNOSIS

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## REZUMAT

Cancerul de prostată este cea mai frecventă formă de cancer la bărbați și a doua cauză de mortalitate prin cancer. Incidența sa este în continuă creștere, estimându-se că aproximativ 30% din bărbații din țările dezvoltate vor fi diagnosticați cu cancer de prostată pe durata vieții lor. Mortalitatea prin cancer de prostată este în jur de 13% din totalul afecțiunilor maligne, cu variații geografice semnificative. Cei mai importanți factori de risc sunt vârsta, antecedentele familiale, mutațiile genetice specifice, rasa, statusul hormonal, anumite infecții virale și alimentația. Detecția timpurie a cancerului de prostată se bazează pe trei proceduri esențiale: tușeul rectal, dozarea antigenului prostatic specific seric total și biopsia prostatică ecoghidată transrectală. Stadializarea exactă a cancerului de prostată influențează în mod esențial decizia terapeutică; metodele actuale de stadializare includ tușeul rectal, markerii tumorali serici, gradul de diferențiere histopatologic, investigațiile imagistice și limfodiseția ganglionilor pelvini. Cei mai semnificativi factori de prognostic, pe lângă stadiul clinic, sunt nivelul inițial (preterapeutic) al PSA seric total și scorul Gleason. Studii recente au introdus în discuție noi markeri prognostici, în vederea creșterii acurateții prognosticului; dintre aceștia, și-au confirmat deja valoarea markerii genetici, indexul de apoptoză și densitatea microvasculară.

## ABSTRACT

Prostate cancer is the most frequent form of cancer in males and is also the second cause of death by cancer. Its incidence is continuously rising, being estimated that around 30% males from developed countries will be diagnosed with prostate cancer during their lifetime. Prostate cancer death rate is actually around 13% of all cancer deaths, with important geographic variations. The most significant risk factors are represented by age, family history, specific genetic mutations, race, hormonal status, virus infections and dietary habits. Early detection of prostate cancer is based on three main procedures: digital rectal examination, total seric prostate specific antigen (PSA) dosing and ultrasound-guided transrectal biopsy of the prostate. Accurate staging of prostate cancer influences greatly the correct therapeutic decision; currently available staging methods include: digital rectal examination, seric tumor markers, pathological grading, imaging examinations and pelvic lymph node dissection. The most significant prognosis factors, besides the clinical stage, are the initial (pre-therapeutic) level of total seric PSA and the Gleason score. Recent studies have introduced new prognostic markers to increase the accuracy of the prognosis prediction; the most successful so far appear to be the genetic markers, the apoptosis index and microvascular density.

## INTRODUCTION

Prostate cancer is the most frequent form of cancer in males, being also the second cause of death by cancer, after lung cancer; its main risk factors are aging, hormonal changes and genetic mutations.<sup>1</sup>

From a pathological point of view, prostate cancer is a malignant tumor which is affecting initially a number of small glands inside the prostate, progressing slowly,

confined in the prostate; at a specific moment the cancer spreads beyond the prostate capsule, invading the nearby tissues and organs and only in later stages spreads into metastases, usually in the pelvic lymph nodes and the bones.<sup>2</sup>

Early diagnosed, using digital rectal examination, seric prostate specific antigen dosing and prostate biopsy, prostate cancer is curable by radical surgery, with very good survival and cure rates. Other therapy forms, available for different development stages of prostate cancer, include brachytherapy, hormone therapy and chemotherapy and they are selected specifically to the disease's stage, patient's age and/or his personal choices.

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## EPIDEMIOLOGY

Incidence of prostate cancer is continuously rising, the total number of detected cases in the time interval

2000 - 2005 in the world being over one and a half billion.<sup>3</sup> (World Health Organization, 2006)

In order to understand the social significance of this phenomenon, actual estimations count that as many as 30% of males from developed countries will be diagnosed with prostate cancer during their lifetime (at least at a pathological microscopic level).<sup>4</sup> Despite this fact, only 8% of them will be clinically diagnosed with prostate cancer and the mortality due to this disease will represent only 3% of the total deaths, most of the patients being diagnosed at the autopsy with prostate cancer, but not dying because of it (up to 80% of 80 years old males have at least microscopic lesions of prostate cancer).<sup>5-7</sup>

In order to explain this raise of incidence, several hypotheses were proposed. The first one stipulates that frequent seric PSA dosing during the last 15 years as a screening method allowed a much earlier diagnosis in many cases, offering the chance for cure.<sup>8</sup> Another possible explanation is the constant aging of population from developed countries, with a steady increase of elderly persons and a longer life expectation, making easier to diagnose more cases of prostate cancer, clinically manifest only at advanced ages.<sup>9</sup> A global estimation says that the incidence of prostate cancer is increasing with 3% every year.<sup>8</sup>

Another significant phenomenon, observed quite recently, is the significant rise of incidence of prostate cancer in males under 60 years: the debut age is continuously decreasing, even to less than 50 years; these facts will impose in the near future a re-adjustment of the screening strategies, in order to include younger males, especially with significant risk factors.<sup>8</sup>

Geographic variability is great, because prostate cancer is influenced by multiple risk factors, as race, genetic factors, lifestyle and diet. In Asia, prostate cancer has a lower incidence (fewer than 20 new cases in 100,000 inhabitants per year), while in Europe and the United States, this figure is over 100.<sup>4</sup>

In all the countries where the prostate cancer screening is organized, its detection occurs in early phases, which are surgically curable (only 10-15% of the newly detected cases are not localized), while in the rest of the world the forms of locally advanced or metastasized prostate cancer are most frequently diagnosed, leading to higher therapy costs and, finally, to a mortality increase.<sup>10</sup>

Prostate cancer death rate is actually around 13% of all cancer deaths, with significant geographic variations also (global 5-year survival varies from 70-90% in developed countries to as low as 40% in developing countries).<sup>2,11</sup>

## **ETIOLOGY AND RISK FACTORS**

During the last 20 years a large number on studies focusing on the influence of different risk factors on prostate cancer incidence were published. We will present below only the most significant risk factors, already confirmed in meta-analyses.

### **Age**

Age is an essential factor in prostate cancer debut: while in males under 45 years prostate cancer is unusual, as males get older, the prostate cancer incidence is progressively increasing, with a peak around 65 - 70 years.<sup>12,13</sup>

### **Race**

Another very important factor is represented by the race: the highest frequency of prostate cancer is in black population, followed by Caucasian males, while Asiatic population have the lowest rate.<sup>8</sup> This is explained probably by the differences of hormonal status – people with coloured skin have a higher level of testosterone than those of other races.<sup>14,15</sup> Recent studies suggest also that latent, non clinically manifest forms of prostate cancer are present equally in all races, the differences being mainly the consequence tumor aggressivity, influenced by the hormonal status.<sup>16</sup>

### **Family History**

A male person with a father or brother diagnosed with prostate cancer has a two-fold risk of being also diagnosed with prostate cancer during his lifetime.<sup>13</sup> These statistical observations have triggered new investigations regarding the role of specific genetic mutations, produced during two or more generations.

### **Genetic factors**

The current theories consider that prostate cancer has a complex etiopathogeny, being caused by a multitude of factors; genetic factors have a significant role, emphasized during the last fifteen years, during the completion of the human genome mapping project.<sup>17</sup> A number of mutant genes, located on the chromosomes 1, 17 and X, were described in patients with prostate cancer. Hereditary prostate cancer gene (HPC1) and prostate cancer predisposing gene are located on chromosome 1, while human prostate cancer gene is located on chromosome X.<sup>18-20</sup> More studies are now under way, trying to detect other genetic mutations, because just a small proportion of the patients with prostate cancer (around 10%) have the above described genetic mutations.<sup>21</sup>

### **Hormonal factors**

There were reports that in males castrated during their childhood (eunuchs), or in populations with low 5-alpha-reductase excretion, prostate cancer incidence is very low.<sup>22</sup> Taking into account these observations, several studies were done, showing that the seric testosterone (and its active metabolite, dihydrotestosterone) has a significant role in the etiopathogeny of prostate cancer and benign prostatic hyperplasia.<sup>23</sup>

### **Sexual activity**

Males which are beginning their sexual activity earlier, having more sex partners, may have an increased risk of prostate cancer; some possible causes are the sexually transmitted infections, or testosterone excess.<sup>24</sup>

### **Infective agents**

The viral hypothesis was widely accepted as an etiologic agent of prostate cancer during the 1970's, without clear confirmations; actual researches have showed a correlation between the infection with type two herpes virus and clinically manifest prostate cancer, without any suggestions regarding the mechanism.<sup>25</sup>

### **Diet**

From the observations on large population groups, it was established that a diet rich in fats (especially saturated) associated with high calcium and alcohol intake leads to a higher risk of prostate cancer. In vitro studies have also demonstrated that omega-6 fatty acids stimulate growth of the tumors cells, while omega-3 fatty acids inhibit them.<sup>26</sup>

On the other hand, during the last five years the concept of prevention has emerged, including the recommendations to supplement the dietary intake of selenium (which has an important role in the secretion of glutathione-peroxidase), vitamin E (a powerful antioxidant), lycopene (found in tomatoes), or isoflavones (soy-bean derived products), which could reduce the number of clinically manifest prostate cancer cases.<sup>4,27,28</sup>

### **Body mass**

An above average body mass is also considered a risk factor in the pathogenesis of prostate cancer; the mechanism is probably dual, being influenced by the hormonal status and also by the increased intake of fats.<sup>29</sup>

### **Enviromental factors**

Gamma radiation professional exposure, high concentrations of cadmium or aromatic hydro-

carbonates are associated with an increased risk of prostate cancer, although their influence is considered smaller than that of hormones or genetic factors.<sup>30,31</sup> Solar exposure, which is followed by an increase of vitamin D synthesis, has also a role in the etiopathogeny of prostate cancer: populations from Northern Europe have a higher incidence of prostate cancer than the populations from Southern Europe, in the Mediteranean region (a possible explanation for this difference could be also the different diet patterns, as seen above).<sup>32</sup>

## **PATHOLOGY**

The carcinogenesis process is the result of a series of changes at the cell level (caused by genetic mutations), ending with the declining of the cell proliferation control mechanisms, associated with a reduction of the apoptosis process. During this ongoing process, tumor cells gradually lose their differentiation and the tumor becomes more aggressive.

The vast majority (95%) of the malignant prostate tumors are adenocarcinomas, with origin in the epithelial cells covering the prostatic acini and glandular ducts.<sup>33</sup> Most of the malignant prostate tumors have their origin in the peripheral zone of the prostate and only a small proportion in the central and transition zone.<sup>34</sup> Over 50% of diagnosed prostate adenocarcinomas are already multifocal, but the volume of the isolated tumors is small (less than 0.5 mL).<sup>35</sup> Prostate adenocarcinoma is usually a slowly growing tumor, with tumor doubling time over two years; when the tumor volume is significantly increased, the tumor becomes more aggressive and its growth speed increases.<sup>36</sup>

### **Histological grading of prostate cancer**

Histological grading of prostate cancer is very important, allowing to evaluate the tumor aggressivity and, especially, to assess the prognosis of the patients.

The essential criteria of the various grading systems are the modifications of glandular architecture and/or cellular anaplasia. A number of grading systems were considered during the last 40 years (Gleason, Broders & Mostofi, Anderson, Bocking, Gaeta, Helpap) and the Gleason score is the most widely accepted.

### **The Gleason Score**

The Gleason score evaluates the architecture of the prostate glands, the pattern of tumoral growth and the relationship between the tumor cells and the surrounding stromal tissue.<sup>37</sup>

The Gleason grading system has five levels of progressive tumor aggressivity, grade 1 being the least aggressive, while grade 5 is the most anaplastic.

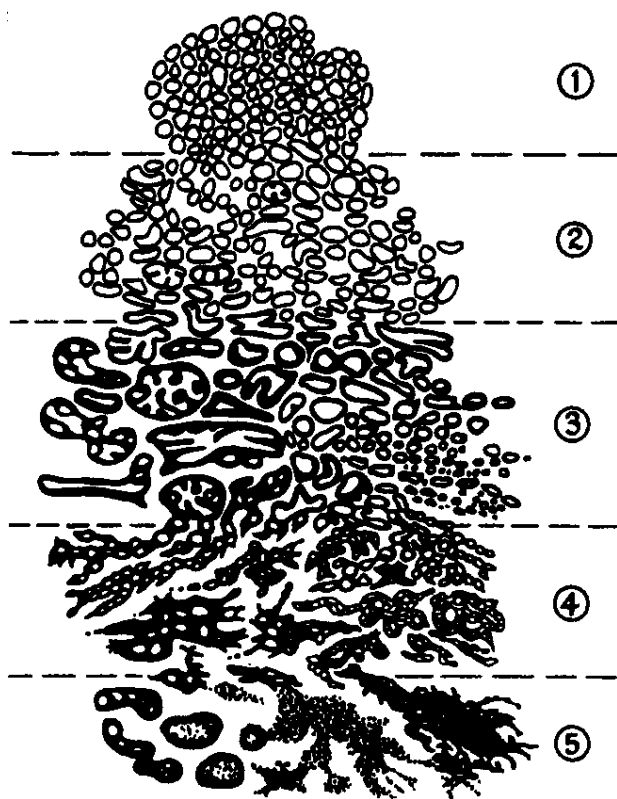
- **Grade 1:** Closely packed, uniform, well formed tumor glands, separated by a reduced quantity of stroma;

- **Grade 2:** Poorly circumscribed nodules of less uniform glands, with more tissue between them;

- **Grade 3:** Marked variations of glands' size and architecture; some of the cells leave the glands and invade the surrounding tissue;

- **Grade 4:** Many fused glands, which have less recognizable structure; many cells invade the surrounding tissue;

- **Grade 5:** Absence of cell differentiation, solid mass of cells or sheets of cells through the surrounding tissue. (Fig. 1)



**Figure 1.** The five Gleason grades (adapted after Ref. 37).

Because the majority of the prostate adenocarcinomas are not homogenous tumors, containing two or more different histological patterns in the tumor mass, Gleason score is established by the addition of the Gleason grades of the two most prominent tumor patterns. This allows for a more precise estimation of cancer prognosis.

The assessment of Gleason score depends on pathologists' experience, having unfortunately a subjective component that gives a degree of inconsistency.<sup>38</sup>

Depending on the Gleason score, we can make the following prognostic stratification:

-  $G_1$ : good differentiation - Gleason score between 2 and 4 - favorable prognosis;

-  $G_2$ : moderate differentiation - Gleason score between 5 and 7 - intermediate prognosis;

-  $G_3$ : poor differentiation - Gleason score  $\geq 8$  - unfavorable prognosis.

### Other histological findings with prognostic implications

Despite the fact that, along the clinical stage, Gleason score is the most significant factor in the prognostic process of the prostate tumors, recent researches have focused on other aggressivity markers: perineural invasion, neuro-endocrine differentiation, neoangiogenesis and proliferation markers.

Perineural invasion is directly correlated with tumor aggressivity, being a rationale for the nerve sparing radical prostatectomy indication.<sup>39,40</sup>

### Evolution forms

The main pathways for prostate cancer metastases are: local invasion, or through the lymphatic and circulatory system. Prostatic capsule works at first as a barrier against the local invasion, so that's why in the initial phases of tumor growth the cancer disseminates widely only inside the prostate (making it a curable cancer, by radical prostatectomy) – this form of cancer, confined within the prostate is considered **localized prostate cancer**.

In a later stage, capsule penetration occurs and the tumor cells invades the neighboring tissues, including the seminal vesicles, bladder neck, ureters and prostatic urethra, defining the **locally advanced prostate cancer**.<sup>41</sup>

### Metastases

Lymph node metastases are frequent, especially in patients with large, poorly differentiated tumors, or in cases of early invasion of the seminal vesicles.<sup>42</sup> The most frequent locations of lymph node metastases are the pelvic, inguinal and lumbar lymph nodes.

Visceral involvement, due to hematogenous metastases, interests mainly the bones, but also the lungs and the liver. Most frequent sites for metastases are the lumbar vertebrae and the pelvic bones.<sup>43</sup>

Clinical evolution of prostate cancer is unpredictable: some tumors are localized for a long period of time and have low malignancy features, while other tumors can give early metastases, even with no significant local prostatic tumor growth.

### **Prostatic Intraepithelial Neoplasia (PIN)**

Prostatic intraepithelial neoplasia is a pre-malignant microscopic lesion, which is isolated, only at the level of several prostatic glands.<sup>44</sup> From the pathological point of view, there are two types of PIN:

- Low grade PIN: mild cell dysplasia;

- High grade PIN: moderate or severe dysplasia, preceding with up to 10 years the invasive prostate adenocarcinoma; this group of patients should be carefully followed-up, due to the high risk of clinically manifest prostate cancer.<sup>45</sup>

The transition between PIN lesions and invasive prostate cancer occurs when the glandular basal layer is broken, finding associated with nuclear atypia, increase of proliferative potential and aneuploidy.<sup>46</sup> A number of studies have shown that 35% of patients with high grade PIN as a single pathological finding in prostate biopsy specimens have developed prostate cancer within two years.<sup>47</sup> A significant proportion of patients with atypical small acinar proliferation (ASAP) will develop also prostate cancer lesions, making their follow-up mandatory, with prostate biopsy repeat.<sup>48</sup>

### **DIAGNOSIS**

Early detection of prostate cancer is based on three main elements: digital rectal examination (DRE), total seric PSA dosing and ultrasound-guided transrectal biopsy of the prostate. The combination between DRE and PSA dosing is the first line testing, while biopsy is not indicated as a routine test, due to its high cost.<sup>49</sup> If the first two tests raise the clinical suspicion of prostate cancer, then the biopsy becomes mandatory.

#### **Symptoms**

Prostate cancer during its early development phase has not specific symptoms, due to the fact that the vast majority of these cancers have their origins in the peripheric zone. Just a small proportion of the prostate cancers have their onset in the transition zone, causing early low urinary tract symptoms, in a similar way with benign prostate hyperplasia.

The majority of the patients with clinically manifest prostate cancer had advanced forms of cancer in the past, just because of this initial scarce symptomatology. The introduction of modern screening methods, combined with the improved patient knowledge about the disease, have led to an increase of early diagnosed curable cancers, so less than 20% of the patients from the developed countries have metastases at the first presentation.<sup>1</sup>

**Localised prostate cancer** does not have specific clinical symptoms, it usually shares its clinical manifestations with benign prostatic hyperplasia. In some cases the tumor is so small that is not palpable in digital rectal examination; in these situations the diagnosis is established usually through prostate biopsy triggered by increased PSA values. In other cases prostate cancer is incidentally diagnosed, on tissue samples obtained by transurethral resection of the prostate, indicated for benign prostatic hyperplasia.

**Locally advanced prostate cancer** may have a variety of symptoms, being seldom non-symptomatic. Usually the patients have obstructive low urinary tract symptoms, similar with those found in benign prostatic hyperplasia. In some situations the patients with locally advanced prostate cancer may present hematuria (urethral or bladder neck invasion), dysuria and/or urinary incontinence (invasion of the sphincter), erectile dysfunction (tumor extension at the neurovascular bundles level), or painful ejaculation (by seminal vesicles invasion).<sup>1</sup>

**Distant metastases**, especially at the bones level, may be the first symptoms of prostate cancer in some situations, convincing the patient to make its first visit to the doctor. Lumbar/ sacral spine and pelvic bones metastasis are associated with intense, sometimes excruciating pain, with rapid onset. Systemic metastasis are associated with general manifestations, like the significant weight loss, secondary anemia and marked asthenia.<sup>50</sup>

#### **Digital rectal examination**

Digital rectal examination (DRE) is the simplest and cheapest prostate cancer diagnosis method, considering that the tumors which are large enough tumors are palpable as indurated nodules on the posterior plan of the prostate.<sup>51</sup>

The predictive value of DRE is directly correlated with age, race and seric PSA values.<sup>52,53</sup> Due to an increased risk of prostate cancer, prostate biopsy is recommended in all males with abnormal DRE, regardless of the PSA value, because up to 25% of the patients with prostate cancer have PSA values smaller than 4 ng/ml. Despite this, the sensitivity of the method is quite low - just a third of the suspect nodules in DRE are confirmed as prostate cancer lesions.

DRE has also a low specificity, missing usually almost a half of the cancer that are currently diagnosed using the PSA testing.<sup>54-56</sup> Additionally, prostate cancer detected by DRE are more advanced, the majority of the patients which are diagnosed only by this method dying later from prostate cancer.<sup>57-59</sup>

As a conclusion, actually we consider that DRE is a valuable test (as a single diagnosis method) only in the hands of experimented clinicians. Despite these, the combination between DRE, PSA and other diagnosis methods could offer valuable information for the clinical staging.

### **Prostate Specific Antigen (PSA)**

PSA is an essential component of the seminal fluid, having an important role in the liquefaction process; PSA is also found (in a very small proportion) in the male serum also, generally being linked by two antiproteases (up to 90%), or in free form (in a small proportion).<sup>60</sup> PSA half-life is 2-3 days and the time for the PSA value to decrease to zero after the radical prostatectomy is up to three weeks.<sup>61,62</sup>

The most studied physiological factors that are influencing the seric PSA level are: the plasmatic level of androgens, age, race and prostate volume.<sup>63-65</sup>

The seric PSA values are also elevated by any prostatic event which is interfering with normal prostatic glandular architecture (breaking the basal membrane) and allows the PSA to pass to the blood stream: benign prostatic hyperplasia, prostate cancer, prostatitis and prostate manipulation (digital rectal examination, prostate biopsy).<sup>61</sup>

The populational studies performed during the last 20 years have shown that PSA dosing has the highest predictive value for prostate cancer.<sup>55,66,67</sup> Despite this, the best way to diagnose prostate cancer is by combining PSA dosing with DRE, because up to one quarter of patients with cancer have PSA values under 4 ng/ml.<sup>52</sup>

According to several multicentric trials, the diagnosis rate for prostate cancer is proportional with the seric PSA level: for PSA values under 4 ng/ml the chance to detect a prostate cancer is 1:50, for values between 4 and 10 ng/ml the chance is between 1:4 and 1:3, while for values over 10 ng/ml the chance is between 1:3 and 1:2.<sup>54,68,69</sup>

The threshold level of seric PSA (actually considered: 4 ng/ml), considered as a starting point for actively looking for prostate cancer is still a subject of controversy. Threshold values lower than 4 ng/ml (even lower than 2,5 ng/ml) could increase the number of detected prostate cancer cases, but they increase also the number of useless prostate biopsies.<sup>57,70</sup>

Taking into account these controversies, several methods were proposed to increase the sensitivity and specificity of the method: the adjustment of the threshold value with race, age and total prostate volume (or transitional zone volume), PSA velocity, or

the free/total PSA ratio.<sup>1</sup>

Ross et al have proposed in 2000 a new screening strategy, which should initially test the seric PSA at 40 years, repeat the testing at 45 and 50 years, and every two years thereafter.<sup>71</sup> This strategy is more cost efficient, while its predictive value is similar with the currently used strategy, which includes yearly PSA testing after 50 years.

### **Transrectal ultrasound**

Transrectal ultrasound is an imaging investigation method, which offers information about the presence of hypoechoic intraprostatic zones, being also able to show prostate capsule deformations or asymmetries.<sup>72</sup> The specificity of the method is relatively low: around 60% of prostatic tumors are hypoechoic, but just a quarter of all hypoechoic lesions are confirmed as prostate cancer after the biopsy.<sup>73</sup> Despite these observations, transrectal ultrasonography is very useful in already diagnosed tumors, during the preoperative evaluation.

### **Transrectal prostate biopsy**

Prostate biopsy is performed under transrectal ultrasound control (when available); the prostatic tissue fragments are harvested by using a special biopsy needle, which is a part of a specially designed biopsy gun.

There are actually a lot of discussions regarding the number of cores from different regions of the prostate which should be examined. The „classical” approach includes six different cores, using the sextant technique, which maps the prostate in six different regions.<sup>74</sup> Newer studies suggest that the standard prostate biopsy should include 12 cores, in order to correctly evaluate the tumor volume and extension.<sup>75,76</sup> If the patients have elevated PSA values before the biopsy, more cores from the lateral regions of the peripheral zone of the prostate are needed.

### **Prostate cancer diagnosis after TURP**

Prostate cancer is sometimes diagnosed incidentally, in prostate tissue fragments after the transurethral resection of the prostate (TURP), performed usually in benign prostatic hyperplasia – around 10% of the resected patients have microscopic malignant lesions.

The method is reliable as a diagnosis method for prostate cancer, because the resected tissue has its origin in the transition zone of the prostate, where the prostate cancer incidence is three times lower than in the peripheral zone.<sup>77</sup>

## Diagnosis algorithms

After the large scale introduction of dosing of the seric PSA, a number of diagnosis algorithms were proposed, trying to detect a higher proportion of patients with localised prostate cancer, while keeping the testing costs as low as possible. Synthesizing the multitude of available diagnosis schemes, we may encounter the following possible clinical situations:<sup>78</sup>

a. If the seric PSA values are in the limits according to the age group, and digital rectal examination is without any findings, the patient is followed-up by yearly checkups;

b. If the PSA values are above normal, but digital rectal examination is normal, we should perform ultrasound guided prostate biopsies, inclusive in the transition zone;

c. If there are abnormal findings during the digital rectal examination, regardless of the PSA values, we should also perform biopsies of the lesions, followed by randomized biopsies of the rest of the prostate.

## STAGING OF PROSTATE CANCER

Accurate staging of prostate cancer influences greatly the correct therapeutic decision, and, consequently, the prognosis of the patients. Tumor extension is directly correlated with prognosis in newly diagnosed male patients. Pathological stage is the most precise prediction method of outcome after therapy in patients with clinically localized disease.<sup>79</sup> In contrast with this fortunate situation, therapy with radical intention is not improving the prognosis in patients with advanced prostate cancer, because there is no available adjuvant therapy capable to destroy completely the tumor cells. This is the main reason why accurate assessment of tumoral extension is essential for the patients with newly diagnosed prostate cancer. Currently available staging methods include: digital rectal examination, seric tumor markers, pathological grading, imaging examinations and pelvic lymph node dissection.

**Table 1.** Correlation between the Whitmore-Jewett staging system and the TNM classification.

Whitmore-Jewett classification	TNM		Description
	1992	2002	
-	T <sub>x</sub>	T <sub>x</sub>	Primary tumor cannot be assessed
-	T <sub>0</sub>	T <sub>0</sub>	No evidence of primary tumor
<b>A</b>	<b>T<sub>1</sub></b>	<b>T<sub>1</sub></b>	<b>Clinically inapparent tumor not palpable or visible by imaging</b>
A <sub>1</sub>	T <sub>1a</sub>	T <sub>1a</sub>	Tumor incidental histologic finding in less than or equal to 5% of tissue resected
A <sub>2</sub>	T <sub>1b</sub>	T <sub>1b</sub>	Tumor incidental histologic finding in greater than 5% of tissue resected
-	T <sub>1c</sub>	T <sub>1c</sub>	Tumor identified by needle biopsy (because of elevated PSA level); tumors found in 1 or both lobes by needle biopsy but not palpable or reliably visible by imaging
<b>B</b>	<b>T<sub>2</sub></b>	<b>T<sub>2</sub></b>	<b>Tumor confined within prostate</b>
B <sub>1</sub>	T <sub>2a</sub>	T <sub>2a</sub>	Tumor involving less than half a lobe
B <sub>1</sub>	T <sub>2b</sub>	T <sub>2b</sub>	Tumor involving less than or equal to 1 lobe
B <sub>2</sub>	-	T <sub>2c</sub>	Tumor involving both lobes
<b>C<sub>1</sub></b>	<b>T<sub>3</sub></b>	<b>T<sub>3</sub></b>	<b>Tumor extending through the prostatic capsule; no invasion into the prostatic apex or into, but not beyond the prostatic capsule</b>
C <sub>1</sub>	T <sub>3a</sub>	T <sub>3a</sub>	Unilateral extracapsular extension
C <sub>1</sub>	T <sub>3b</sub>	T <sub>3a</sub>	Bilateral extracapsular extension
C <sub>1</sub>	T <sub>3c</sub>	T <sub>3b</sub>	Tumor invading seminal vesicle(s)
<b>C<sub>2</sub></b>	<b>T<sub>4</sub></b>	<b>T<sub>4</sub></b>	<b>Tumor fixed or invading adjacent structures other than seminal vesicles (eg, bladder neck, external sphincter, rectum, levator muscles, pelvic wall)</b>
C <sub>2</sub>	T <sub>4a</sub>	T <sub>4a</sub>	Tumor invading bladder neck, external sphincter, and/or rectum
C <sub>2</sub>	T <sub>4b</sub>	T <sub>4b</sub>	Tumor invading levator muscles, and/or pelvic wall
<b>DO</b>	-	-	<b>Acid phosphatase elevation</b>
-	N <sub>x</sub>	N <sub>x</sub>	Regional lymph nodes cannot be assessed
-	N <sub>0</sub>	N <sub>0</sub>	No regional lymph node metastasis
<b>D<sub>1</sub></b>	<b>N<sub>1</sub></b>	<b>N<sub>1</sub></b>	<b>Metastasis in regional lymph node or nodes</b>
-	M <sub>x</sub>	M <sub>x</sub>	Distant metastasis cannot be assessed
-	M <sub>0</sub>	M <sub>0</sub>	No distant metastasis
<b>D<sub>2</sub></b>	<b>M<sub>1</sub></b>	<b>M<sub>1</sub></b>	<b>Distant metastasis</b>
D <sub>2</sub>	M <sub>1a</sub>	M <sub>1a</sub>	Non regional lymph node(s)
D <sub>2</sub>	M <sub>1b</sub>	M <sub>1b</sub>	Bone(s)
D <sub>2</sub>	M <sub>1c</sub>	M <sub>1c</sub>	Other site(s) with or without bone disease
<b>D<sub>3</sub></b>	-	-	<b>Hormone resistant prostate cancer</b>

## Staging systems

The first prostate cancer clinical staging system was introduced by Whitmore in 1956 and it was modified by Jewett in 1975. The TNM system was adopted in 1975 by the American Joint Committee for Cancer and was modified three times, in 1992, 1997 and 2002, in cooperation with International Union Against Cancer (UICC).<sup>51,80,81</sup> (Table 1)

During the last 15 years we are witnessing a significant stage migration phenomenon, manifested by increased detection of localized prostate cancer, as a consequence of PSA screening.

Regardless of the staging method, clinical staging usually underestimates tumor extension which is exactly evaluated after the radical prostatectomy.

No current diagnosis method can make the differentiation between localized prostate cancer (which is curable) and advanced cancer (non curable in a large number of cases).

## PROGNOSIS

The prognosis of the patients with prostate cancer is most significantly influenced by the tumor stage at the initial diagnosis time.

### Survival

There are actually important differences regarding the survival of patients with prostate cancer in different areas of the world. While in the United States (where a national screening program is running since the 1990's) around 55-60% of all cases of prostate cancer are diagnosed in early phase ( $T_{1-2}$  stage), with an almost 100% survival rate for this group, in Europe (where a screening program is not available everywhere) 25-30% of all cases are diagnosed in advanced phases ( $T_4$  stage), with a 5-year survival smaller than 60% for this group.<sup>82-84</sup>

In conclusion, survival is inversely proportional with tumor stage, being low in patients with prostate capsule penetration and very low in patients with metastases: almost half of the latter die in the first two years, regardless of the therapeutic methods employed.<sup>85</sup>

Table 2 presents the relationship between the clinical stage, prognosis, survival and cure rate, observed during the epidemiological study of P. Scardino et al.<sup>86</sup>

Prognosis and survival evaluation are very important especially when we take into account the patients with incipient prostate cancer, which is curable. In order to help this evaluation process, a number of clinical and paraclinical parameters are used, helping us to choose the correct therapy.

**Table 2.** Relationship between the clinical stage, survival and cure rate.

Clinical stage	Patients (%)	Prognosis	10-year survival	Estimated cure rate (%)
$T_{1a}$	10	Therapy: often "exaggerated"	95	85
$T_{1b-T_2}$	30	Curable cancer	80	65
$T_3-T_4$	10	Occasionally curable cancer	60	25
N+	40	Difficult to cure cancer	40	< 5
M+	10	Incurable cancer	10	< 1

### Prognosis factors

The most significant prognosis factors, besides the clinical stage, are the initial (pre-therapeutic) level of total seric PSA and the Gleason score. Based on their assessment, we are able to elaborate two extreme clinical scenarios:

a. The patients with localized prostate cancer, with initial PSA levels lower than 4 ng/ml and with a Gleason score lower than 5, have a very good post-therapeutic prognosis and excellent survival;

b. The patients with initially elevated PSA values and with a Gleason score higher than 7, have a less favorable prognosis, with poor survival.

The greatest challenge of the prognosis is posed between the two extremes, creating the opportunity for new algorithms, which should offer a better evolution prediction.

The most complete classification of the prognostic factors in prostate cancer was realized by the American Pathology Association, coordinated by D. Bostwick.<sup>87</sup> According to this classifications, there are three categories of prognostic factors:

1. **Category I:** factors with prognostic significance, useful in the clinical management of the patients;

2. **Category II:** extensively studied factors, which should have validation through studies on large patient populations;

3. **Category III:** factors with insufficient studies regarding their prognostic value.

Table 3 presents the most significant prognostic factors, grouped in the three described categories.<sup>88</sup>

### Pathological findings

During the pathological examination of the prostatectomy specimen we can obtain essential information on tumoral stage. If prostatic capsule

**Table 3.** Prognosis factors in prostate cancer.

<b>Category I</b>	Seric PSA
	Pathological staging
	Gleason score
	Surgical margin
<b>Category II</b>	Tumoral tissue volume
	Histological subtype
	DNA ploidy
<b>Category III</b>	Perineural invasion
	Lymph node micrometastasis
	Neuroendocrine differentiation
	Androgen receptors
	Microvascular density
	Nuclear structure, chromatin texture
	PSA-derived factors
	Proliferation markers (MIB-1, Ki-67)
	Apoptosis
	Human glandular Kallikrein 2
	Integrins
	Genetic factors (p53, bcl-2)

penetration, with seminal vesicle invasion or lymph node involvement is observed, then the postoperative recurrence rate is high (>50%); in contrast, if the tumor is localized, not spreading beyond the prostatic capsule, then the recurrence rate is generally low (<10%).<sup>87</sup>

Gleason score is a very significant prediction factor, especially in patients with localized prostate cancer, with no capsule penetration. A total Gleason score smaller than 5 means a good prognosis, while a total Gleason score greater than 7 is associated with an increased recurrence or metastasis probability. If the total Gleason score is between 5 and 7, additional prediction factors are necessary.

### Molecular and genetic prognostic factors

When we judge the cases where the PSA levels and the total Gleason score have intermediary values, we observe that an exact prognosis prediction is very difficult. This is the main reason for some recent studies, that tried to introduce new prognosis markers; the most successful so far appear to be the genetic markers, which are discovered during the mutation analysis of the tumor cells.<sup>89</sup>

a. **Tumor suppression gene p53** is a blocker of the cell cycle control, leaving time for the DNA repair before the cell division. Mutations of this gene allow tumor cells to divide before the DNA repair, increasing the genetic instability risk, which leads to further

malignant cell mutations. The presence of mutant p53 gene is a factor of bad prognosis, even in patients with a low or intermediary total Gleason score.<sup>89,90</sup>

b. **Proto-oncogene bcl-2** is implicated in the control of the programmed cell death (or apoptosis). An increased expression of bcl-2 is a marker of bad prognosis, associated with an increased Gleason score or with locally advanced or metastasized tumors.<sup>91,92</sup>

c. **Proliferation marker Ki-67** is identified only in multiplying cells, its increased expression being associated with recurrence after the radical prostatectomy and with a decrease of recurrence-free survival.<sup>89</sup>

d. **Apoptosis index** is actually considered a more valuable prediction factor of bad prognosis than tumor volume, mitotic index or prostatic capsule penetration.<sup>89</sup>

e. **Angiogenesis.** Microvascular Density (MVD), measured at the level of prostate tumor tissue, is proportionally with the tumor stage and is a prediction factor of extra-capsular extension.<sup>89</sup>

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