Diagnosis, Clinical Work Up, TNM Classification, Markers

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6.1 Diagnosis of Prostate Cancer (PCa): Clinical Work Up

6.1.1 Localized Prostate Cancer

Prostate cancer, usually affecting elderly, is now recognized as a health problem as it became in developed countries the first cancer of men over their 50 years.

Today, the diagnosis of prostate cancer results more on the realization of digital rectal examination (DRE) and PSA blood test leading to randomized transrectal ultrasonography (TRUS) biopsy than on other clinical symptoms (Parekh et al. 2007).

Usually an elevated level of PSA evokes a diagnosis of prostate cancer, especially if the rectal examination (DRE) is suspect. The level of PSA is a continuous parameter: the higher the value, the most likely the existence of prostate cancer.

Initially, most guidelines for early detection of prostate cancer used cut-off values of PSA to indicate a biopsy, with recommendations varying between PSA values of 2.5 and 4.0 ng/ml.

However, according to the Prostate Cancer Prevention Trial (PCPT) study summarized in the Table 6.1, prostate cancer may occur even with a PSA level below the upper level of 4 ng/ml, suggesting that there is no cut-off point to eliminate prostate cancer (Parekh et al. 2006).

For example, in the European Randomized Study of Screening for Prostate Cancer (ERSPC), a PSA cut-off ≥3 ng/ml was, for the Rotterdam

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Table 6.1 Incidence of PCa according to the level of PSA (Hamdy and Roupret 2008)

PSA level ng/ml	Patients number (n=2,950)	Positive predictive value for cancer (%)	Positive predictive value for aggressive cancer (%)
0–0.5	486	32 (6.6)	4 (12.5)
0.6–1	791	80 (10.1)	10 (8)
1.1–2	998	170 (17)	20 (11.8)
2.1–3	482	115 (23.9)	22 (19.1)
3.1–4	193	52 (26.9)	13 (25)

PSA level ng/ml	Positive predictive value for cancer (%)
0–1	2.8–5
1–2,5	10.5–14
2.5–4	22–30
4–10	40
>10	70

section, an indication for prostate biopsy, and the author justifies this low threshold because the overall risk or prostate cancer death is low in this cohort (Roobol 2011).

These results also showed that the value of PSA was not correlated with the tumoral aggressiveness currently identified by a Gleason score >7 on the biopsies (Teillac and Abrahamsson 2006).

At least, when a rectal examination is carried out, either on a systematic way or because of functional non-specific voiding disorders like dysuria or frequency, or minimal clinical modifications like asymmetry and irregularities of one lobe, prostate biopsy is justified, irrespectively of the PSA level, especially in young patients to eliminate the diagnosis of prostate cancer (Heidenreich et al. 2011).

While rectal examination and PSA results are fundamental because they work out the local extension of the tumor and allow the repartition of the patients according to d'Amico's Classification (Table 6.3), prostate biopsy decision must take account of other risk factors (increasing age, ethnicity, and heredity), and therapeutic choices are argued after a complete medical check-up of the patient. At least, the clinician must imperatively evaluate different functional data and take care of:

- Voiding function: it is best evaluated by an auto questionnaire which integrates question on irritative and obstructive symptoms.
- Several questionnaires are accessible and were validated in the literature, the most frequently used being score IPSS (Appendix A) (Barry et al. 1992).
- Erectile function: just as for the voiding disorders, a precise evaluation of the erectile score before any treatment and after treatment is essential for a better evaluation of the morbidity frequency, or minimal clinical modifications of the treatments. Questionnaires are accessible as IIEF5 score (Appendix B).
- Intestinal disorders that may compromise radiotherapy.

Assessment of the patient is also focused on evaluation of co-morbidities, which can be analyzed by a general score like the Charlson score (Appendix C). Complementary information as measurement of the body mass index (BMI) and explanation of toxicities of treatments will allow a clear discussion of different therapeutic choices adapted to the individual risks of the patient and his priorities during a multidisciplinary medical team discussion.

6.1.2 Advanced and Metastatic Cancer

By screening, the clinician can discover prostate cancer early, before the appearance of the clinical signs, and it is now rare to discover this tumor with inaugural metastasis.

It is nevertheless important to eliminate prostate cancer in front of any osseous pain when the

diagnosis is reluctant or in front of a neurological complication as para- or quadriplegia by spinal cord compression which represents the most dramatic entity and the most pejorative form of initial diagnosis of prostate cancer.

Therefore, any biological syndrome in relation with a tumoral extension like acute renal insufficiency or hypercalcemia is suspicious for locally advanced or metastatic prostate cancer and justifies clinical and biological evaluation for prostate cancer.

6.1.3 In Summary

Today, the dilemma is probably to find an accurate test (biological and/or radiological) to define when we really need to perform biopsy in order to limit unnecessary biopsy on asymptomatic men.

Thus, the indication of prostate biopsies leans on interpretation of PSA, urinary markers like PCA3, and the results of imaging studies especially multimodal MRI which has been developed for 10 years and nomograms combining all these results.

A better knowledge of family factors and genetic profiles will probably allow, in the near future, a better identification of the patients with an aggressive tumor, leading to improvement of screening diagnosis and adapted treatments.

6.2 Diagnosis of Prostate Cancer (PCa): Biological Evaluation

6.2.1 Blood Markers

6.2.1.1 PSA

PSA remains one of the cornerstones of biological markers of prostate cancer but due to the lack of cancer specificity, interpretation may be influenced by many factors.

For example, PSA is increased with benign prostate hypertrophy, urethral trauma, bacterial acute or chronic prostatitis, or endoscopic bladder exploration.

On the other hand, obesity, or different medications like hormonotherapy, finastéride, or dutasteride decrease the value of PSA (Payne et al. 2011).

Despite these limits, PSA remains nevertheless the marker of reference.

As there is no real threshold of PSA value below which the clinician is allowed to eliminate the back thought of prostate cancer prostate, it is advisable to interpret the value of PSA in order to limit the negative and the false-positives of the test and to optimize the indication of prostate biopsies.

This is more and more important, considering the potential morbidity of the biopsies such as infectious risk, which increases with the number of biopsies carried out, and hemorrhagic complications (hematuria, rectal hemorrhage), themselves facilitated by anticoagulant treatments started for cardiovascular diseases.

To increase PSA accuracy and interpretation, the clinician can use:

- *PSA density* (*PSA d*), described by Oesterling (Beduschi and Oesterling 2007), is interesting while adjusting with prostatic volume, in particular, with the volume of the zone of transition.
- The use of the PSA density improving specificity could avoid between 25 and 37% of biopsy. The limiting value is of 0.10 ng/ml/cm^3 of prostate.
- Multivariate analysis showed that PSA transitional zone was more powerful in prediction of prostate cancer however, we must keep in mind that PSA density measurement requires transrectal ultrasound and it is unlikely that it will replace PSA for prostate cancer screening (Benson et al. 1992).
- *PSA velocity* (*PSA v*) *or PSA doubling time* (*PSA DT*) analyses variations of PSA *measurements with time*.
- *The accurate measurement of* PSA v or PSA DT requires longitudinal checking over many years and can be calculated easily on the net (www.mskcc.org/mskcc).
- While PSA DT can be interesting for prostate cancer detection with a threshold >0.65 ng/ml, PSAv >0.75 ng/ml/year or with a threshold of 2 ng/ml the year before, prostatectomy is now recognized as a specific factor of death

(Carter et al. 1992); PSA v could be helpful in detecting aggressive cancer and in determining patients to be rescreened for early detection (Schroder et al. 2008).

- *Different thresholds, while adjusting PSA value with age*
- Interpretation of PSA according to the age would make it possible to increase the detection of cancer among young patients with a variable threshold between 40 and 80 years.
- (Steuber et al. 2008) suggests the realization of the first PSA blood test at 40 years old which must be lower than 0.7 ng/ml; interestingly, an early result would limit the number of blood controls later.
- However, all these modifications tend to correlate highly with PSA, and the few studies that appropriately evaluated their independent diagnostic contribution to PSA showed no incremental value above PSA (Steuber et al. 2008).
- *Others blood markers*, combining PSA with the result of molecular isoforms: ratio of free PSA/total PSA, pro PSA, or complexed PSA values, PHI, etc. All these biomarkers are under evaluation and discussed further.
- *Nomograms*
- Many authors also recommend determining for their patients their personal risk by using a risk calculator based on different data in order to decide with the clinician whether or not to undergo a biopsy (www.uroweb.org; http://www.prostatecancer-riskcalculator.com/via.html). We must keep in mind that these nomograms are based on different databases and that they are not completely adapted to our own patients but they are undoubtedly helpful (Ngo et al. 2011; Parekh et al. 2006).

6.2.1.2 PSA Isoforms

As t PSA has a limited specificity and sensibility in determining the presence of prostate cancer especially in the range between 2 and 10 ng/ml, several derivatives have been described (Fig. 6.1) and their performance studied (Jolivet-Reynaud et al. 2008).

- *% Free PSA* [*(f PSA/t PSA) × 100*]:
- The f PSA/tPSA ratio is suspected of cancer when this report is lower than 10 or 15%, and this was an important predictor of prostate cancer if the volume of the gland was <30 ml (Djavan et al. 2011).
- Free PSA levels below 15–25% are classically associated with an increased risk of prostate cancer, but it is estimated that only 30–50% of men with free PSA less than 15% have a positive biopsy (Catalona and Partin 1998).
- In a large review, Roddam (Roddam et al. 2005) has shown that the diagnostic performance of f/t PSA and c PSA was equivalent in both the 2–4 and 4–10 ng/ml t PSA ranges, while the performance of the f/t PSA tests in the 4–10 ng/ml range was significantly superior to that in the 2–4 ng/ml range.
- So, % free PSA can be used to increase the sensitivity when t PSA has lower values than 4 ng/ml or to increase the specificity of t PSA when it is between 4 and 10 ng/ml.
- This meta-analysis showed that the specificity of % free PSA remains low, 18% at a sensibility of 95% in the 4–10 ng/ml t PSA range, and 6% in the 2–4 ng/ml range (Guazzoni et al. 2011), thus limiting the interpretation of this blood test which can vary with kits of different manufacturers.
- *Complexed PSA*
- Complexed PSA is PSA bound to protease inhibitor.
- Complexed PSA to α_1 antichymotrypsin is augmented in patients with prostate cancer. This blood test requires immunoassay and was shown to moderately improve specificity by 6.2–7.9% compared to t PSA in the range 2.0–10.0 ng/ml, but because of the limited amount of data, diagnosis performance of c PSA is difficult to investigate (Partin et al. 2003).
- *B PSA*
- Milolacyk has found that B PSA was augmented in the transitional zone of patients with benign prostatic hyperplasia (BPH) (Mikolajczyk et al. 2000; Mikolajczyk et al. 2004), suggesting that assays could discriminate patients with BPH from those with early prostate cancer (Canto et al. 2004).
- To our knowledge, this has not been confirmed by multicentric studies.
- *p2 PSA* ([*−2*] *pro PSA*)

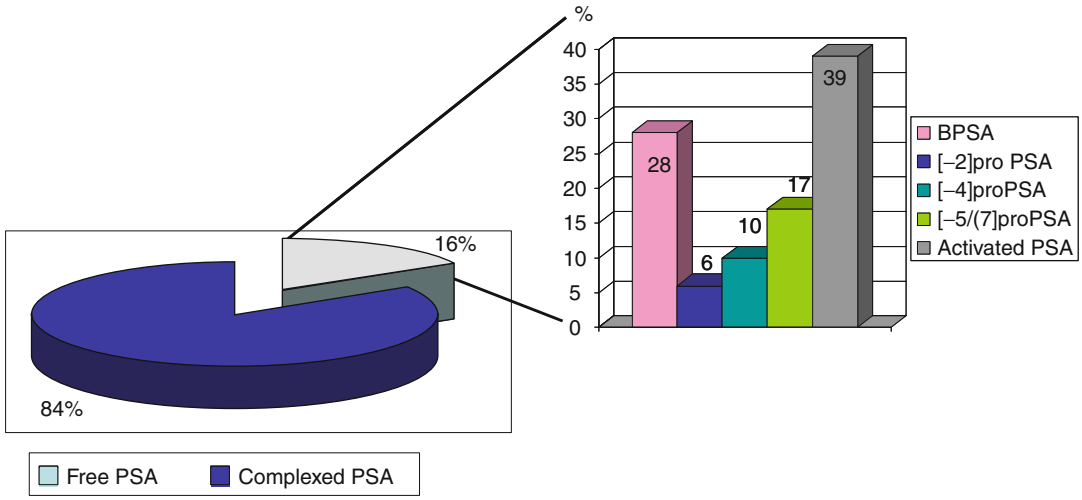

Fig. 6.1 Repartition of PSA isoforms

- Pro PSA is one of several distinct isoforms of free PSA found in serum. The primary form in PCa tissue is p2 PSA; p2 PSA is a PSA isoform, namely, % p2 PSA.
- Prostate health index (PHI) is a mathematical formula combining % p2 PSA with f PSA and PSA [p2 PSA/f PSA × t PSA $^{1/2}$]. This mathematical combination of f PSA, t PSA, and p2 PSA was recently described, and an immunoassay system (Jansen et al. 2010) seems promising because p2 PSA and PHI were significantly higher in patients with prostate cancer than in controls (Catalona et al. 2011; Sokoll et al. 2008).
- p2 PSA may improve the accuracy of t PSA and f PSA in predicting prostate cancer on biopsy of men when t PSA ranges between 4 and 10 ng/ml (Guazzoni et al. 2011), and % p2 PSA and PHI were 23% more accurate than t PSA in detecting patients with prostate cancer with sensibilities of 42.9% for PHI and 38.8% for % p2 PSA, higher than those of t PSA (5.1%), % f PSA (20%), and PSA d (26.5%) at 90% specificity.
- The usefulness of p2 PSA and its relationship with prostate cancer aggressiveness are in debate, and PHI may have a relationship with biopsy Gleason score (Catalona et al. 2011). However, due to the small number of patients included in these studies, multicentric confirmatory studies are mandatory.

- *Early prostate cancer antigen 2* (*EPCA-2*)
- Early prostate cancer antigen (EPCA) is a nuclear matrix protein that has shown promise as a diagnostic marker for PCa. A recently developed blood-based assay showed a 92% diagnostic sensitivity and a 94% diagnostic specificity in a small cohort of 12 PCa and 34 healthy patients (Paul et al. 2005). It was confirmed in a larger cohort of 385 men in which specificity and sensibility of EPCA2 blood test to detect prostate cancer were, respectively, 94% and 92% while PSA sensitivity was 65%, differentiated localized tumor from extracapsular tumor ($p < 0.0001$), and confirmed that EPCA-2 was able to differentiate localized PCa from metastatic PCa with an AUC of 0.89 (Leman et al. 2007). However, methodologic deficiencies with this marker have been identified, casting doubt on its actual validity (Diamandis 2007).
- Recently, two studies on Chinese populations were published, confirming the interest to EPCA-2. In the first one, serum EPCA-2, with a cut-off of 10 ng/ml, was measured on 449 patients with symptomatic BPH and 112 healthy men: 100% specificity for healthy men. And 98% specificity and 100% sensitivity in separating men with PCa from those without were found (Zhigang et al. 2010). In the second one, 40 healthy controls, 77 patients with localized PCa who underwent

radical prostatectomy, and 51 patients with locally advanced or metastatic disease who received androgen deprivation therapy were enrolled in a prospective study. Serum EPCA level, cut-off 15.2 ng/ml, was significantly correlated with a poor prognosis (Zhigang et al. 2011).

- In summary, EPCA-2 seems to be a specific diagnostic marker for prostate cancer, an aggressive marker of prostate cancer, but larger studies are needed to confirm these promising data.
- *Other blood markers*
- Many markers are discussed in the literature including insulin-like growth factor 1, human glandular kallikrein 2, molecular subfraction of f PSA, somatic cytochrome C, glutamate decarboxylase 1, etc.

Today, none of them is useful in clinical practice, and further prospective studies are required to evaluate their efficacy against other markers and all require specialized laboratory (Djavan et al. 2011).

6.2.2 Urinary Markers

6.2.2.1 PCA3

PCA3 measurement in urine specimens is a prostate-specific marker associated with the likelihood of biopsy prostate cancer detection, considered as a promising new biomarker under development because PCA3 codes for a messenger RNA highly overexpressed by prostate cancer cells.

Performance of PCA3 compared to or associated with other markers (PSA, free PSA) is always under evaluation, but many results suggest that there is a significant potential to combine PCA3 with other risk factors to predict biopsy outcome (Steuber et al. 2008).

Usually, PCA3 measurement is proposed as a second-line diagnostic test after a previous negative biopsy result. In this group, PCA3 score can help the decision of whether or not to rebiopsy regarding the high specificity of the test around 70%.

Different cut-offs of PCA3 score have been studied in the literature in order to predict prostate cancer in men with one or two previous negative biopsy (Haese et al. 2008; Remzi et al. 2010).

Table 6.2 Performance of PCA3 score according to different cut-offs

PCA3 score cut-off	Sensitivity (%)	Specificity (%)
>20	73	51
>35	47	72
>50	35	82
% f PSA cut-off 25%	83	23

In a multicentric European prospective study of 463 men candidate for a second or third repeat biopsy, Haese showed that with a cut-off 35, PCA3 score was significantly higher in men with significant cancer; PCA3 score was superior to % free PSA for predicting biopsy outcome. Sensibility and specificity of PCA3 assay were reported according to different cut-offs (Table 6.2).

The sensibility and specificity of the PCA3 score at a cut-off of 35 was comparable in men with one or two previous negative biopsy with an area under the receiver operating curve (ROC) of 0.66–0.87.

PCA3 score was not affected by age, prostate volume, chronic prostatitis, or total PSA (t PSA) value and confirming that PCA3 score was promised in guiding repeat biopsy decisions (Deras et al. 2008; Vlaeminck-Guillem et al. 2011).

PCA3 performance in combination with PSA was validated in the REDUCE trial (Aubin et al. 2010); in this study, PCA3 was increased in cancer with significant Gleason score greater than 6; the result was predicting biopsy outcome at 2 years and could give additional information to evaluate the cancer risk and help the clinician in biopsy decision.

PCA3 was studied as a first-line diagnostic test and compared to PSA value >3 ng/ml during rescreening of 721 men biopsied within the ERSPC trial (Roobol et al. 2010). In this study, the cut-off score of PCA3 was very low (>10) and also compared with the recommended cut-off value of 35. Based on the ROC analyses, PCA3 performs marginally better than PSA ($p = 0.143$), suggesting that in the low PSA ranges, PCA3 score was not useful in identifying aggressive cancer. Contradicting results were recently published in another study of 516 men enrolled with a total PSA of 2.5–10 ng/ml before initial biopsy decision. With a biopsy detection rate of

40%, ROC curve analysis showed a significant AUC of >0.761 for PCA3 score (>35) versus 0.577 for t PSA, 0.689 for PSA d and 0.606 for free PSA, suggesting a clinical utility for initial diagnosis especially when the result is included in a risk calculator (PCPT risk calculator available at: http://deb.uthscsa.edu/URORiskCalc/Pages/calcsPCA3.jsp).

In parallel, PCA3 score may have a clinical utility identifying patient with low-volume and low-grade tumor. PCA3 was correlated with tumor volume on 72 prostatectomy specimens and prediction of extracapsular extension (Whitman et al. 2008). Correlation with multifocality was also reported in a study of 102 patients treated by radical prostatectomy (Vlaeminck-Guillem et al. 2011) with a median PCA3 score of 96 when more than 4 cancer foci were identified compared to 32 when only one tumor foci is present.

In summary, despite heterogeneous results of the studies in terms of sensibility and specificity caused by the differences in the optimum cut-off point of the PCA3, PCA3 assay is helpful as a diagnostic tool in the decision of which men need repeat biopsy; PCA3 score may be useful as a diagnostic tool for initial biopsy, and future studies will clarify its position as a prognostic marker (Auprich et al. 2010; Chun and De la Taille 2009; De la Taille et al. 2011; Ficarra et al. 2010; Auprich et al. 2011.

6.2.2.2 Annexin A3; Sarcosine

Annexin A3 (ANXA3) belongs to a family of calcium and phospholipid binding protein that is implicated in cell differentiation, migration, and immunomodulation. Five hundred ninety-one patients from 4 European urological clinics were prospectively recruited. Urine was obtained directly after digital rectal examination and Annexin A3 was evaluated. Annexin A3 has an inverse relationship to cancer, and therefore its specificity was much better than that of prostate specific antigen (Schostak et al. 2009).

Sarcosine is an *N*-methyl derivative of the amino acid glycine. Androgen receptor and the ERG gene fusion product coordinately regulate components of the sarcosine pathway. Sarcosine was identified as a differential metabolite that was highly increased during prostate cancer progression to metastasis and can be detected non-invasively in urine. Sarcosine is considered as a potentially important metabolic intermediary of cancer cell invasion and aggressively (Sreekumar et al. 2009).

6.2.3 Fusion Genes: TMPRSS2-ERG

The recent identification of fusion gene provides new insights into the initial mechanisms of molecular events implicated in the prostate carcinogenesis (Beuzeboc et al. 2009; Perner et al. 2006). The gene TMPRSS2 was demonstrated to be upregulated by androgenic hormones in prostate cancer cells and downregulated in androgen-independent prostate cancer tissue. TMPRSS2 protein's function in prostate carcinogenesis relies on overexpression of ETS transcription factors, such as ERG (estrogen-regulated gene). ERG overexpression contributes to development of androgen independence in prostate cancer through disruption of androgen receptor signaling. The presence of TMPRSS2-ERG fusion gene in up to half of all human prostate cancer makes it one of the most common genetic rearrangements in human epithelial tumors (Demichelis et al. 2007).

A significant association was observed between TMPRSS2-ERG, identified in fluorescence *in situ* hybridization (FISH), rearranged tumors through deletions and higher tumor stage and the presence of metastatic disease involving pelvic lymph node. The deletion as cause of TMPRSS2-ERG fusion is associated with clinical features for prostate cancer progression compared with tumors that lack TMPRSS2-ERG rearrangement. The TMPRSS2-ERG fusion may contribute to a more aggressive prostate cancer phenotype and perhaps account in part to higher grade prostate cancer and support the critical role of ERG as an oncogene in prostate cancer (Perner et al. 2006).

Recently, combining urinary detection of TMPRSS2-ERG and PCA3 with serum PSA has been described as performing better than the individual biomarkers alone in predicting prostate cancer (Salami et al. 2011).

Urinary TMPRSS2-ERG in combination with PCA3 improved the performance of the

multivariate Prostate Cancer Prevention Trial (PCPT) risk calculator in predicting cancer on biopsy. Tomlins et al.'s study demonstrates that urine TMPRSS2-ERG, in combination with PCA3, enhances the utility of serum PSA for predicting prostate cancer risk and clinically relevant cancer on biopsy. The two limitations of this study are that more than 85% of patients were Caucasian and only PSA-screened cohort had been retained. Studies with other geographic cohorts of men and non-PSA-screened population will be required to determine the potential utility of these biomarkers (Tomlins et al. 2011).

In summary, the fusion gene TMPRSS2-ERG is a promising new biomarker predicting aggressive prostate cancer phenotype. Recently, a panel of urinary TMPRSS2-ERG associated with urinary PCA3 and serum PSA seems to be interesting for predicting prostate cancer risk and clinically relevant cancer on biopsy.

Evidence is pointing to the use of a multiple markers to fully characterize the heterogeneity of prostate tumor. Multiplex models PCA3, TMPRSS2, ERG, Annexin A3, and sarcosine seem to add more to the diagnostic performance for predicting PCa (Cao et al. 2010).

6.3 Classification and Prognostic Groups

6.3.1 The 2009 TNM Classification (Tumor Node Metastasis)

TNM 2009 is used throughout different guidelines for diagnosis and treatments and must be used systematically.

T – Primary tumor

TX Primary tumor cannot be assessed

T0 No evidence of primary tumor

T1 Clinically unapparent tumor not palpable or visible by imaging

T1a Tumor incidental histological finding in 5% or less of tissue resected

T1b Tumor incidental histological finding in more than 5% of tissue resected

T1c Tumor identified by needle biopsy (e.g., because of elevated PSA level)

T2 Tumor confined within the prostate

T2a Tumor involves one half of one lobe or less

T2b Tumor involves more than half of one lobe, but not both lobes.

T2c Tumor involves both lobes

T3 Tumor extends through the prostatic capsule

T3a Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement

T3b Tumor invades seminal vesicle(s)

T4 Tumor is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

N – Regional lymph nodes

NX Regional lymph nodes cannot be assessed

N0 No regional lymph node metastasis

N1 Regional lymph node metastasis

M – Distant metastasis

MX Distant metastasis cannot be assessed

M0 No distant metastasis

M1 Distant metastasis

M1a Non-regional lymph node(s)

M1b Bone(s)

M1c Other site(s)

Remarks:

1. Tumor found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.
2. Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.
3. Metastasis no larger than 0.2 cm can be designated pN1 mi.
4. When more than one site of metastasis is present, the most advanced category should be used.

6.3.2 Classifications

Using the TNM classification, different prognostic groups are useful to stratify patients and discuss treatments.

According to d'Amico, three different groups are described:

Table 6.3 Staging and risk stratification of PCa

	Low risk	Intermediate risk	High risk
Clinical stage	T1a–c N0 M0 T2a N0 M0	T2b–c N0 M0	T3 – T4 N0 M0
PSA	And <10 ng/ml	Or 10–20 ng/ml	Or >20 ng/ml
Gleason score	And ≤6	Or =7	Or >7

Table 6.4 Staging of PCa according to EAU guidelines 2011

Prognostic group	Clinical stage			PSA	Gleason score
Group I	T1a–c T2a	N0 M0		<10 <10	≤6 ≤6
Group II a	T1a–c T2a,b	N0 M0 N0 M0		<20 ≥10<20 <20	7 ≤6 ≤7
Group II b	T2c T1 – 2	N0 M0		Any PSA ≥20 Any PSA	Any Gleason Any Gleason ≥8
Group III	T3a,b	N0	M0	Any PSA	Any Gleason
Group IV	T4 Any T	N0 N1 Any N	M0 M0 M0	Any PSA	Any Gleason

In the EAU guidelines, four prognostic groups have been published (Table 6.4).

Note: When either PSA or Gleason is not available, grouping should be determined by cT category and whichever of either PSA of Gleason is available. When neither is available prognostic grouping is not possible, use stage grouping.

6.4 Diagnosis and Local Evaluation of Prostate Cancer: The Place of MRI

While MRI provides the best images of prostate, there is no definite consensus about the role of MRI in prostate cancer either for early detection or for local staging.

Traditionally, MRI for prostate cancer has been performed with an endorectal coil and a 1.5 T machine to predict the local extension of the tumor. With the introduction of higher field strength (3 T) and the development of new MR techniques, detection and characterization of prostate cancer imaging is improving.

6.4.1 MR and Early Cancer Detection

Multiparametric MRI has shown a potential value in prostate detection, and its role is now increasing.

Multiparametric MRI includes standard T2-weighted sequences, dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and diffusion-weighted imaging sequences (DWI sequences). Each of these sequences has his own interest and their combination is necessary, many data suggesting that these sequences have the potential to guide biopsy (Scherra et al. 2010).

Obviously, a radiological expertise in prostate imaging is mandatory to define tumor localization and volume. A pelvic phased array coil is commonly used; this does not require bowel preparation like endorectal coils, but a bowel relaxant is recommended.

3 T equipment is under evaluation and could improve the sensibility of the technique in cancer detection to 92% when using DW sequences (Roy et al. 2010).

However, in the literature, the reported accuracy of prostate cancer detection with MRI varies widely between 54% and 93% according to technical issues, patient groups or the experience of the reader.

The relative high specificity of multiparametric MR seems remarkable when combining more than one functional MR technique like DW + prostate spectroscopy which analyses the concentration of different metabolites (citrate, creatine, choline) within prostate voxels could reduce indications for non-useful biopsy (Sciarra et al. 2011). However, controversies are still reported because of limited data on spectroscopy.

At least, accuracy of MR for identification of cancer remains tumor volume dependant:

- Considering any tumor volume, sensibility of MR for detection of cancer foci remains low at 32% with a specificity of 95%.
- When tumor volume is >0.5 ml, for an expert radiologist, sensibility approaches 85% without any significant change of specificity.

MRI may also contribute to depict anterior cancer especially when adding DW imaging and dynamic sequences (Sciarra et al. 2011).

In a recent publication, 16 European prostate experts discussed different items related to imaging parameters for tumor detection, localization, imaging interpretation, and reporting. For disease detection, T2W, DW, and DCE sequences were appropriated for any cancer in the peripheral zone. No clear benefit of proton spectroscopy was reported for prostate localization, but combination of the different metabolite ratios was used, with promising discrimination among different aggressiveness cancers results (Kobus et al. 2011).

Different "guidelines" for prostate cancer imaging were reported (Dickinson and Ahmed 2011):

- All individual lesions and areas of prostate should be separately scored for probability of malignancy with and ADC measurement, and the maximum diameter of largest abnormal lesion should be recorded because different information are possible to be gained from each sequence in isolation.
- DW sequence should always be associated: it is the most appropriate to exclude clinically significant disease as defined neither by a lesion size <0.5 or <0.2 cm^3 nor by a peripheral lesion Gleason 7 (4 + 3).
- At least, clinical results (DRE, PSA, history of previous surgical or medical prostate treatments, time scale, and results of previous biopsy) should be transmitted to the radiologist as these informations may influence the overall score for probability of cancer given on the report (Figs. 6.2a, b, 6.3 and 6.4).

A recent study compared diagnostic accuracy of diffusion tension imaging, Dynamic Contrast Enhanced magnetic resonance imaging and their combination in diagnosing prostate cancer on 25 patients with clinical suspicion of prostate cancer with 3 T MRI before TRUS biopsies. The analysis showed that the combination of both techniques improved the accuracy in prostate cancer diagnostic with a specificity of 77% (69–83%) and a sensitivity of 100% (97–100%), but the cohort is small (Kozlowskia et al. 2010).

In summary, MRI, delivered with these standards, could be helpful for cancer localization and targeted biopsy (Dickinson and Ahmed 2011), but today, MRI cannot be routinely incorporated into clinical care before a first set of biopsy. Multimodal MRI can help the clinician to identify patients at risk for clinically significant cancer and reduce the number of non-useful biopsy. Targeted biopsy using fusion of 3D transrectal ultrasound and MRI images can optimize detection of significant cancer and different equipments are already available in order to improve biopsy strategy (Urostation®, Targetscan®). MR-targeted cores will probably play a major role in the future (Pondman et al. 2008).

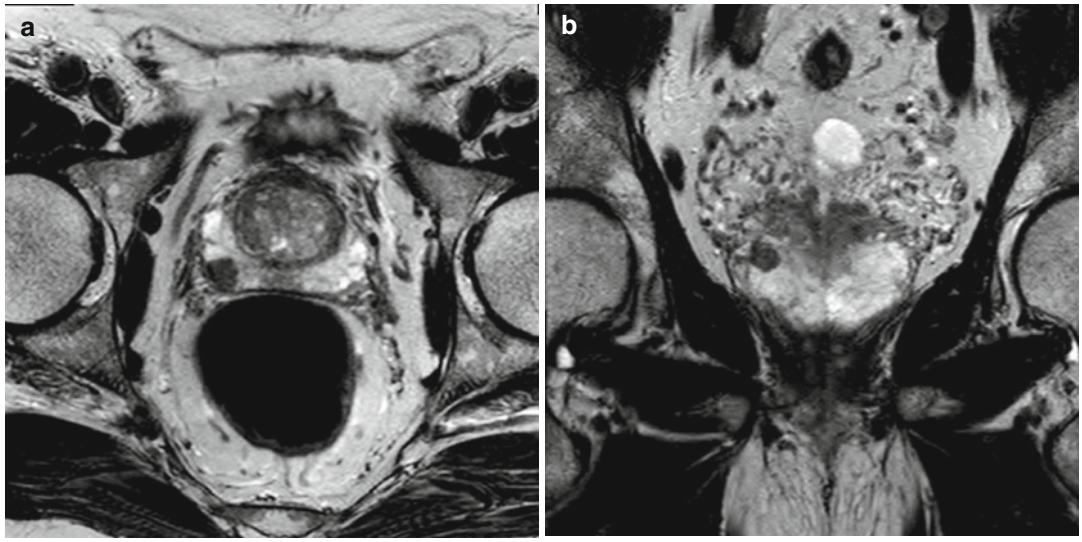

Fig. 6.2 (**a** and **b**) Axial T2-weighted and coronal images show low signal intensity in the base of the left peripheral zone

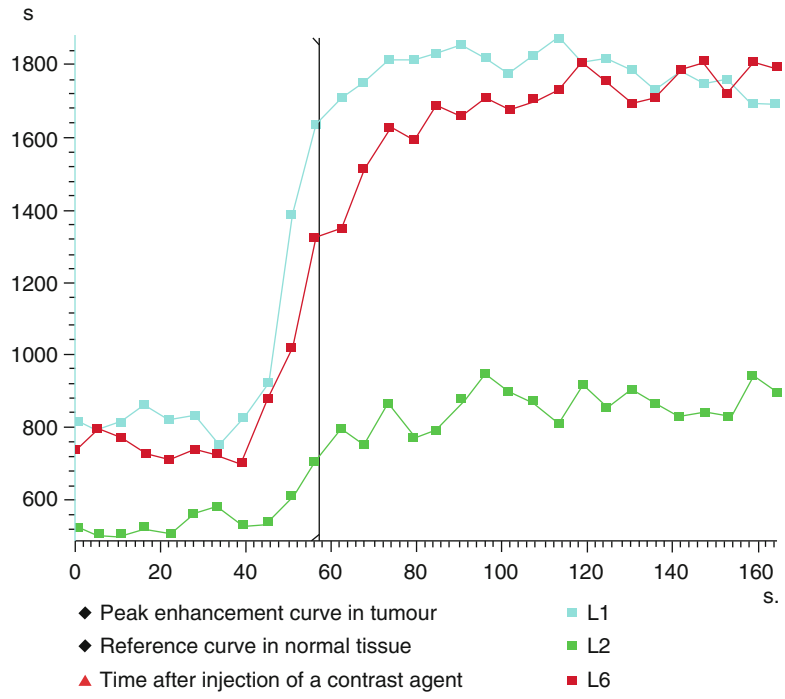

Fig. 6.3 Dynamic sequences show early enhancement in the suspected area

6.4.2 Ultrasonography, Doppler, and Elastography

Detection and localization of prostate tumors using grayscale ultrasound are poor, and transrectal ultrasound is mainly used to guide systematic biopsy. However, TRUS has several limitations for prostate detection: it is subjective, operator-dependent, and prostate echogenicity changes are often non-cancer-specific (hypo 60–70%; iso 25%; hyper less than 5%) (Gomella et al. 2001).

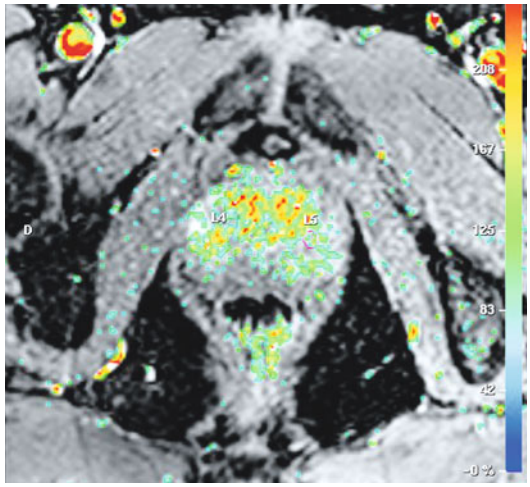

Fig. 6.4 DWI sequences show lower ADC in the suspected area, resulting in restricted water movement in PCa zone where cellular density is higher than in normal glandular tissue

As tumor growth induces neovascularization, enhanced ultrasound techniques have been investigated, such as color flow Doppler (CDI) and power Doppler studies. Although studies suggest that CDI has potential prognostic significance, CDI still has two major pitfalls: overlap with prostatitis and low sensitivity in detection of tumor blood flow within prostate cancer. Contrast-enhanced ultrasound was developed in prostate; different contrast agents were then administered intravenously because they add reflectors into the bloodstream and, as these microbubbles remain intravascular, this technique could increase the sensibility of color and power Doppler imaging (Gomella et al. 2001). Routine use of CEUS was analyzed as a first-step research program by four European centers in the period 2002–2006; additional value of contrast-enhanced ultrasound was not established in this study (Wink et al. 2008). Utilization of phosphodiesterase-5 inhibitor to increase microvascularization during power Doppler ultrasound is another approach which could increase cancer detection (Morelli et al. 2011), but today, diffusion of CEUS techniques remains limited by the availability of contrast agent, cost and a lack of prospective randomized trial demonstrating a clear benefit over standard biopsy techniques.

At least real-time elastography is also a promising tool for prostate cancer detection and targeted biopsy. This technique was analyzed for patients scheduled for radical prostatectomy, and identification of the lesions was compared with radical prostatectomy specimen; the positive predictive value, negative predictive value and accuracy were 87%, 5%, 59%, and 76%, respectively. Elastography findings correlated best with tumor lesions in the apical region, and detection rate increased with higher Gleason score, and results were reproducible on more recent study. However, more objective and reliable parameters are needed to limit the subjective estimation of electrographic colors and the inter-observer variability of elastography for systematic biopsy (Aigner et al. 2010; Salomon et al. 2008; Walz et al. 2011).

6.5 Conclusion

Research on prostate cancer markers is concerning most of developed countries.

Despite various and promising new blood, and urine biomarkers, today, PSA remains the gold standard, and guidelines to improve its utilization are frequently proposed and discussed. Other markers are always under investigation and still have to be validated to improve prostate cancer detection and limit the number of prostate biopsy on asymptomatic men.

The use of multiple markers in combination with clinical data will probably aid in predicting patients who are at risk for developing PCa, but cost will limit their utilization.

Furthermore, better visibility of malignant tissue with new imaging techniques is also improving. In the future it is likely to be able to better select patient for indications of prostate biopsies, and then to define aggressiveness of the tumour using a combination of radiological images and more specific biological tests.

6.6 Appendix A

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always
1. Over the past month, how often have you had a sensation of not emptying your bladder completely after you finished urinating?	0	1	2	3	4	5
2. Over the past month, how often have you had to urinate again less than 2 h after you finished urinating?	0	1	2	3	4	5
3. Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5
4. Over the past month, how often have you found it difficult to postpone urination?	0	1	2	3	4	5
5. Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5
6. Over the past month, how often have you had to push or strain to begin urination?	None	1 time	2 times	3 times	4 times	5 times or more
7. Over the past month, how many times did you most typically get up to urinate from the time you went to bed at night until the time you got up in the morning?	0	1	2	3	4	5

Total Symptom Score

The International Prostate Symptom Score uses the same seven questions as the AUA Symptom Index (presented above) with the addition of the following Disease Specific Quality of Life Question (bother score) scored on a scale from 0 to 6 points (delighted to terrible):

> If you were to spend the rest of your life with your urinary condition just the way it is now, how would you feel about that?

6.7 Individual Items of International Index of Erectile Function Questionnaire and Response Options (US Version)

Question/Response Options

Q1: How often were you able to get an erection during sexual activity?
0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q2: When you had erections with sexual stimulation, how often were your erections hard enough for penetration?
0 = No sexual activity
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q3: When you attempted sexual intercourse, how often were you able to penetrate (enter) your partner?
0 = Did not attempt intercourse
I = Almost never/never

2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q4: During sexual intercourse, how often were you able to maintain your erection after you had penetrated (entered) your partner?
0 = Did not attempt intercourse
I = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

Q5: During sexual intercourse, how difficult was it to maintain your erection to completion of intercourse?
0 = Did not attempt intercourse
1 = Extremely difficult
2 = Very difficult
3 = Difficult
4 = Slightly difficult
5 = Not difficult

Q6 How many times have you attempted sexual intercourse?
0 = No attempts
1 = One to two attempts
2 = Three to four attempts
3 = Five to six attempts
4 = Seven to ten attempts
5 = Eleven + attempts

Q7: When you attempted sexual intercourse, how often was it satisfactory for you?
0 = Did not attempt intercourse
1 = Almost never/never
2 = A few times (much less than half the time)
3 = Sometimes (about half the time)
4 = Most times (much more than half the time)
5 = Almost always/always

(Raymond et al. 1997)

6.8 Appendix C

Category	Weights of the comorbid conditions
Myocardial infarct	1
Congestive heart failure	1
Peripherical vascular disease	1
Cerebrovascular disease	1
Dementia	1
Chronic pulmonary disease	1
Connective tissue disease	1
Ulcer disease	1
Mild liver disease	1
Diabetes	1
Hemiplegia	2
Moderate or severe renal disease	2
Diabetes + end organ damage	2
Any tumor	2
Leukemia	2
Lymphoma	2
Moderate or severe liver disease	3
Metastatic solid tumor	6
AIDS	6

The 19 conditions contributing to conventional Charlson score

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