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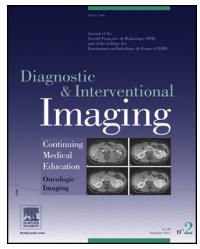

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# Prostate cancer: Review in 2014

**N. Barry Delongchamps**

*Urology Department, Cochin Hospital, 27, rue du Faubourg Saint-Jacques, 75679 Paris cedex 14, France*

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**Abstract** Recent advances need to be highlighted in the management of both localized and metastatic prostate cancer. New early detection and molecular characterization tools are being developed to improve differentiation of their progression profiles and reduce ''overdetection'' and ''overtreatment'' of clinically ''insignificant'' cancers. In addition, the development of multi-parametric MR has improved the characterization of localized cancer and introduced the new concept of focal treatment. Finally, several treatments for metastatic cancer which is resistant to castration have recently increased the therapeutic armamentarium.


Significant advances have been made recently and more will be made in the coming years in the treatment of prostate cancer. The first of these is improved detection and pretreatment characterization based on targeted multi-parametric MR-guided prostate biopsies and the development of new biomarkers. Secondly, joint advances have been made both in imaging and in focal treatments, allowing small tumors to be targeted and providing as effective curative treatment as radical therapy but without its adverse effects. Finally, new treatments for metastatic cancer which is resistant to castration have been developed.

## Detection and characterization: new RNA markers

The limitations of the screening tools, the major one of which is serum prostate-specific antigen (PSA), have been widely demonstrated. The negative predictive value of PSA is only 85% and 75% of patients investigated for a PSA level of between 2.5

*Abbreviations:* AS, Aortic Stenosis; ATU, Temporary Authorization For Use; HIFU, High Intensity Focused Ultrasound; MA, Marketing Authorization; PDT, PhotoDynamic Therapy; PSA, Prostate-Specific Antigen; VTP, Vascular Targeting PDT.

*E-mail address:* nicolasbdl@hotmail.com

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and 10 ng/mL (and/or pathological rectal examination) have negative biopsies [1]. Conversely, 10 to 35% of these patients are subsequently diagnosed with a prostatic adenocarcinoma from repeat biopsies. The use of age-related PSA velocity (PSAv) and density (PSAd), complexed PSA (PSAc) and the free/total PSA ratio have only brought marginal improvements in diagnosis. These limitations feed into the debate about the appropriateness of mass screening for prostate cancer, although this has shown to reduce disease-specific mortality by 20%, but have also highlighted the risk of overdiagnosis and overtreatment.

A number of the biomarkers currently under evaluation are markers of RNA expression. Some of these, such as the PCA3 gene or TMPRSS2 and ETS gene fusion transcripts, can be detected in urine. Others represent the ''tumor tissue expression signature'' of gene panels.

The *PCA3*, or *differential display code 3 (DD3)* gene is located on 9q21-22. It is almost invariably overexpressed in prostate tumor tissue, by a factor of 66 to 140 times more than in non-malignant prostate tissue [2] and is non-existent in non-prostatic healthy tissue and in other cancers.

Five single or multicenter prospective studies have published the results of a urinary PCA3 test in unselected patients who have undergone prostatic biopsies because of a raised PSA (threshold 2.5 to 4 ng/mL) and/or have an abnormal rectal examination [3,4]. These studies have demonstrated the PCA3 score to be superior to PSA measurement (total and/or free), in terms of predictive value (positive or negative) and specificity, at the cost of slightly lower sensitivity. The cut points of 35 appears to be the most discriminatory. The PCA3 score still performs well regardless of PSA levels (less than 4 to 10, or over 10 ng/mL) or prostate volume [3,4].

Three series have recently examined the correlation between the preoperative PCA3 score and factors relating to tumor aggression and volume on prostatectomy specimens [5,6].

The *TMPRSS2-ETS* fusion genes have been demonstrated in the majority of cases of prostate cancer. The most usual variant involves two genes located on chromosome 21, *TMPRSS2* and *ERG*. The *TMPRSS2* gene codes for transmembrane serum protease 2 which is strongly expressed by normal and malignant prostate cells and its expression is regulated by androgens. Genes belonging to the ETS family (*ERG*, *ETV1*, *ETV4*) code for transcription factors which are involved in the signaling pathways which regulate cell growth, cell differentiation and carcinogenesis. Activation of the *ERG* by fusion with *TMPRSS2* under the influence of androgen stimulation appears to be responsible for overexpression of transcription factors, which may result in epigenetic reprogramming and dysregulation of the apoptosis pathways. The different isoforms of the fusion genes and their level of expression may also influence tumor progression [7]. Detection of gene transcripts in urine is however difficult and reported detection rates are around 50%. Combined detection methods in urine before and after biopsy and in the biopsy gun rinse material are currently being assessed [8].

Combined assessment of the tissue expression of genes involved individually in cancer progression has been used to study ''gene expression signatures''. Several tools have been developed in this context and are under assessment. As an example, CPP (cell-cycle progression gene Panel) represents the expression profile of 31 genes involved in cellular proliferation [9]. Tumor tissue expression of these genes is reported as a score. Several retrospective assessment studies have suggested that the CPP score is independently associated with biologic recurrence and disease-specific survival after radical prostatectomy [9], including disease-specific survival in patients included in active monitoring protocols [10].

## Local treatments: photodynamic vaporization

Unlike in other tumor models (breast, cervix and colon etc.), the early diagnosis and screening for prostate cancer do not at present alter the treatment target which remains the entire gland. In a small, still limited tumor, the most satisfactory approach, however, theoretically, would be local treatment. The sine qua non condition for this is firstly that these small tumors are well-visualized. Diffusion-weighted MR and spectrometry currently allow cancers with a volume of 0.50 cc or more, to be diagnosed. These investigations are becoming increasingly reliable and consistent findings are generally achieved between imaging and the surgical specimens or histology results. As prostate tumors are often multifocal, the index site which determines the potential of the tumor to progress needs to be identified and targeted. This would appear sufficient to significantly reduce overall tumor volume and delay progression [11]. This is the principle on which uni- or even bifocal treatment is based. Different techniques can be used for this and are described in several recent publications [12—14]: high intensity focal ultrasound (HIFU), cryotherapy, laser phototherapy, radiofrequency ablation, local curietherapy and stereotactic radiotherapy. The aim of these is to offer relatively non-invasive treatments which do not have the adverse effects of radical surgery (impotence and incontinence), but which also do not compromise the success of subsequent treatments. The key factor is not to prevent reverting to radical or salvage treatment if required. There is as yet insufficiently long clinical experience with these methods to establish whether the local treatments impact on subsequent therapies. Photodynamic vaporization may be less prone to this, although it is still far too early to draw conclusions.

Photodynamic vaporization (or vascular targeting phototherapy, VTP) is a developing technique for the curative treatment of solid cancers. PDT is currently used and has been developed in gastroenterology, dermatology and ENT practice and in gynecology [15]. This involves light activation of an intravenously injected photosensitizing agent. Very short half-life photosensitizing agents which are activated intravascularly have recently been developed and include padoporfin or padeliporfin (WST11 or Tookad Soluble®). Activation of WST1 by a 753 nm laser light source causes tumor ischemia due to vasoconstriction and endothelial lysis. The tumor is illuminated by optical fibers with a diffusing tip which are introduced across the perineum under ultrasound guidance. The energy delivered to the tissues can be calculated based on the diffusion surface area of the tip of the optical fiber. This is the light fluency, expressed in