April 30, 2021

PharmacologyOnLine

Special issue • 2021 • vol.1 • 59-69

MULTIMODALITY IMAGING IN PROSTATE CANCER ASSESSMENT

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Abstract

Prostate cancer (PCa) is considered a major challenge for the many medical disciplines that deal with it; despite the diagnostic and therapeutic improvement, it remains for male sex the most common neoplasm and one of the major causes of death. Clinical presentation is classically varied and can change in relation to the disease state.

The diagnostic suspicion must trigger some evaluations by a team of specialists: both biochemical and clinical. To date, despite the galaxy of new diagnostic technologies available, the first steps are still being conducted on the track that sees a central role of serum PSA levels and digito-rectal exploration (DRE). Currently an increasingly emerging role in this field is occupied by MRI, so much so that we can speak of an MRI-targeted biopsy (MRI-TB); in fact, through various methods of use, we try to improve the quality of the samples in order to have more and more accurate biopsies focused on the disease areas.

The possibility of using increasingly specific sequences such as diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE) and MR spectctroscopy (MRS) certainly places it at the center of the diagnostic step of this phase of disease.

Also from a therapeutic point of view there have been great steps forward in recent years,

for both non-metastatic and metastatic disease. In both the diagnostic and therapeutic fields, alongside conventional radiological and pharmacological techniques, nuclear medicine is in a very useful position.

In an increasingly targeted approach and in an increasingly "precise" medicine, radiopharmaceuticals such as Ra-223 dichloride and 177Lu-PSMA represent the new frontiers of prostate cancer treatment.

Keywords: *Prostate cancer; Multi-parametric magnetic resonance imaging (mpMRI); Trans-rectal ultrasound (TRUS); MRI-targeted biopsy; Prostate cancer theranostic*

INTRODUCTION

Prostate cancer (PCa) is considered a major challenge for the many medical disciplines that deal with it; despite the diagnostic and therapeutic improvement, it remains for male sex the most common neoplasm and one of the major causes of death. PCa is the most common malignacy of male sex, all over the world as well as in Italy. Its incidence shows an increasing tendence, probably due to the major lifespan and thanks to an earlier and more accurate diagnosis capacity of medical system.
In our country, about 36000 new cases of PCa are registered every year and, in agreement with other neoplasms, there are some differences between the North and the South of Italy.
It probably represents the result of a different impact of PCa risk factor, in particular concerning diet and lifestyles.

RISK FACTORS

Multifactorial etiology of PCa is the main result of interaction between genetics, hormonal and ambiental factors, in addition to age, lifestyle and some clinical and biochemical conditions, such as acute and cronic inflammation or infections.

Genetic factors include family, race and some specific gene variants.
As concerning familiarity, a small group of patients have PCa on a strictly hereditary basis (less than 15%) but a doubled risk is estimated if a first degree family member suffers from this disease. (1)
Blacks are more at risk than caucasians probably due to hormonal interactions.
In this regard, it should be emphasized that androgens play an important role in the pathogenesis of PCa: generally androgen receptor is a transcription factor which mediates the phisiological effects of its hormones (testosterone and its metabolites), but in these pathological conditions it has an aberrant functioning.
This aspect is particularly interesting in therapeutic scenario, in fact androgen deprivation therapy is already used to sensitize PCa to radiation therapy.
Age plays an important role because this type of neoplasm is described as typical of the elderly, just as an inappropriate lifestyle can be considered a risk factor. Specifically, obesity and the consumption of large quantities of red meat seem to increase the risk of PCa, due respectively to the release of inflammatory mediators and the presence of nitrites and nitrates.

More generally, activation of a pro-inflammatory circuit appears to be a mechanism underlying clinical conditions, acute or chronic, of infection and inflammation of the prostate gland or urinary tract. Specifically, Tumor Necrosis Alpha (TNF-α) and reactive oxygen species (ROS) released during acute or chronic prostatitis or cytokines and free radicals present in sexually transmitted and often asymptomatic infections (Trichomonas vaginalis, Mycoplasma) can potentially contribute to the malignant progression of the disease.

CLINICAL PRESENTATION

PCa clinical presentation varies in case of a primary tumor with more or less localized disease and a metastatic disease.
It should be noted that there are no specific signs or symptoms that directly lead to the diagnosis of prostate cancer.

The most observable symptoms in relation to the neoplastic involvement of the prostate gland are mainly of the urinary type.
Urgency, urinary frequency and nocturia are some of the most frequent.Less specific, but at the same time commonly found, is the anamnestic finding of hesitatancy. Other signs and symptoms, less frequent but important enough, are hematuria and hematospermia; these may reflect potential invasion of adjacent structures to the prostate gland, such as bladder and seminal vesicles.

In cases of locally advanced disease or metastatic disease, lymphadenomegaly (inguinal and even more rarely supra-clavicular), all painful musculoskeletal symptoms and eventually pathologic fractures must also be considered.
Peri-neural infiltration and direct bone involvement of an advanced stage disease can give rise to back pain, lumbosciatalgia or perineal pain.

Sometimes, the differential diagnosis of these painful problems, frequently present also in all benign osteoarticular pathologies, incidentally places the clinician and the patient in front of a diagnosis of prostate cancer.

PSA LEVEL

PSA is a glycoprotein product of the prostate gland, the bloodstream represents only a small part of its destination of excretion. In pathological conditions, both malignant and benign nature, as prostate cancer or prostatic hypertrophy and prostatitis, a subversion of the normal gland's architecture goes with a rising PSA level in blood. For this reason, PSA is considered a specific marker of prostate pathology.

So, PSA levels higher than the normal cut-offs can be indicative of a prostatic neoplasm or a benign pathology; moreover, some physiological situations (recent ejaculation or intense physical activity) and diagnostic procedures (cystoscopy or prostate biopsy) could cause an increase.

For these reasons, in order to improve diagnostic accuracy of the marker, measurements of PSA density, PSA rate / PSA doubling time, PSA ratio (free / total) and the various PSA isoforms were introduced. Observing the mean distribution of the marker in normal subjects, cut-off value was roughly set at 4 ng/ml but the scientific community has varying opinions about the cut-off needed to initiate the patient for biopsy In general, experts agree considering PSA level an important but not exclusive fact: the diagnostic orientation must integrate this information with the study of risk factors and clinical presentation, in addition to the clinical examination of the patient.

DRE + TRUS

The clinical examination in a suspected prostate disease consists of the digital rectal examination (DRE).
Statistically, the most common site of debut prostate cancer is the peripheral gland sector and the nodule in a good percentage of cases is already detected with palpation.
Due to the sensitivity and specificity levels, DRE cannot be considered the only diagnostic method, but its diffusion and practicality of execution certainly makes it the first diagnostic step for all patients.

Clinician's goal is to identify patients able to be studied with a biopsy exam, thanks to DRE and PSA level.
To date, the most commonly used method to guide biopsy is trans-rectal ultrasound (TRUS).

In systematic TRUS-guided biopsy, the procedure provides for a definition of the glandular regions in which it is expected to find significant lesions and directs the needle in correspondence with them. It should be noted that in this modality there is no direct tumor determination.

Initially the sampling proceeded within six definitive zones, which proved an equally subdivision of the prostate gland; however quantitatively this type of strategy randomly analyzed only a very small percentage of the prostate volume, without considering that statistically we know that there are glandular areas with a higher incidence of malignant lesions than others.

The evidence that the six core systematic biopsies omitted 30% of the significant lesions and that it did not optimize its performance in areas such as the peripheral one, which hosts most of the pathological findings, has made the method evolve by proposing an increasing number of samples. Passing from 8 to 12 and finally to 14 samples, the detection capacity has increased remarkably

Contraindications to TRUS-guided biopsy generally include anorectal pathological conditions: correlated for example with acute pain, infection or abscess, acute prostatitis; in a systemic view of the patient's clinical picture, coagulopathies, severe immunosuppression and absent rectum also represent decisive limitations to the examination.

As previously mentioned, the choice of TRUS guided biopsy in the diagnostic pathway is related to the serological marker PSA.

Over the years a dispute has arisen over the choice of the best cut-offs to be used to select

patients; the problem relates to the evidence that there is no defined PSA serum level that certainly correlates with severe disease, at the same time there is an increase in unnecessary investigations if the cut-off is lowered too cautiously.

Finding a balance, the current Prostate Cancer Risk Management Programme (PCRMP) recommends prostate biopsy in men aged 50-69 years with serum PSA levels >3 ng/ml and in those with abnormal DRE findings (nodules, induration or asymmetry). (2)
For triaging men with PSA levels >2.5 ng/ml for biopsy, other parameters including PSA velocity (>0.75 ng/ml/year), free PSA level (<20%) and PSA density (0.15) have been used. (3)

Since a large number of pathological foci are isoechoic to normal prostate parenchima, TRUS may not direct the biopsy to specific pathological targets. For this reason and to increase the diagnostic accuracy, some methods have been introduced such as contrast ultrasounds (ce-US) and real time elastography (RTE), reporting a better PCa detection rate, compared to simple TRUS. (4)

As will be described later, MRI today represents a cornerstone of PCa diagnostics. Nowadays clinician's direction is to choose a "fusion valutation" between TRUS and MRI imaging (MR-TRus guided fusion biopsy) to guide biopsy, this can give MRI an important role also in the biopsy phase as well as in the diagnostic one. (5)

HISTOPATHOLOGY AND GLEASON SCORE

Adenocarcinoma is the most common PCa histology, a malignant neoplasm originating from the basal cells of prostate acini. During cell differentiation, on the way from a stem cell to a differentiated secretory prostate cell, we can potentially observe malignant evolution.
This aspect explain prostate cancer heterogenity, of the biological and clinical side. (6)

In the 1970s, Donald F. Gleason introduced his "Gleason Score", still today the most used grading system for PCa. The idea behind this score system is to evaluate the two prevalent histologic patterns discovered by biopsy, each numbered from 1 to 5 depending on cell differentiation (1 = well differentiated; 5 = anaplastic); after that, the Gleason Score is the sum of these two evaluations, ranging from 2 to 10, and represent a succesful attempt to predict prognosis for PCa patients. (7)

It must necessarily be specified that Gleason Score is not intended as a rigid system, but as a guide that must increasingly meet the needs of clinicians and obviously ultimately patients.
This is so true that in November 2014, the International Society of Urological Pathology (ISUP) hosted a consensus conference on Gleason grading which was attended by 82 invited experts into prostate cancer from 19 countries.
The purpose of the meeting was to update the grading system for prostate cancer which had last been formally modified by the ISUP in 2005. (8)

To date and awaiting subsequent revisions, there are consolidated parts of the Gleason system and some emerging issues; these include the prognostic significance of the sub-models of the Gleason 4 grades and 5, and in particular if the presence of intraductals carcinoma and / or invasive cribriform carcinoma influence the assignment of the Gleason score and the ISUP grade.
These topics will be addressed in a future ISUP consensus conference, along with the potential of using image analysis machine learning based algorithms as decision support prostate cancer classification tools. (9)

Nowadays, thanks to Gleason Score, together with PSA serum levels and tumor stage, patients are stratified into risk groups:
very low, low, intermediate, high and very high risk.

This classification has a pivotal role in defining initial patient management. (10)

mpMRI

MRI is best used to determine the extracapsular extent of the primary tumor; multiparametrical

magnetic resonance imaging (mpMRI) is an emerging imaging based method, to diagnose PCa, in particular in case of elevated PSA levels. In contrast to conventional MR imaging data, mpMRI is able to include some functional measurements such as diffusion and perfusion imaging sequences. It represent an upgrade of multimodal MRI sequences with a complementary diagnostic point of view, for PCa detection, according to the PI-RADS (prostate imaging-reporting and data system) criteria. (11)

PI-RADS was proposed in 2012 to standardize the reading of these data;
it is based on a specific prostate gland sectors division and on a score system that summarize the probability to detect PCa. The score is obtained after reading each of the sequences employed in mpMRI.
The sensitivity/specificity of PI-RADS 1, according to a meta-analysis in 2015 (12), is reported with 79% for PCa detection; after three years was proposed a PI-RADS 2, adapting to the gained evidence on the value of different MRI sequences and their limitations depending on the location within the prostate.

It's important to underline that the mpMRI informations derives basicly from the signal of water protons in human body and are specificly related to its sequence components, comprising T2-weighted imaging (T2w), diffusion-weighted imaging (DWI), dynamic contrast-enhanced imaging (DCE) and MR spetctroscopy (MRS).

T2-weighted imaging is the sequence enable to delineate the anatomical structure of prostate gland and its surrounding scenario, including regional lymph nodes, pelvic muscles, vessels and also bladder, seminal vesicles and ductus deferens.

In principle, T2w leads the clinical T-staging searching infiltration patterns such as etracapsular extension (T3a), infiltration into seminal vesicles (T3b), or invasion of surrounding structures (T4) if the finding is evident.
Diffusion weighted imaging use the diffusive motrion of water molecole due to their thermal energy to probe tissue structure, it's a core sequence used for PCa detection and to characterize cellularity.
If DWI valutation of prostate peripheral sector shows an unclear lesion, it might be useful to study lesion's vascularization, to determine the final PI-RADS score.
Dynamic contrast-enhanced imaging fulfills this type of request, because neoangiogenesis and hypervascularization are hallmarks of malignant development, including prostate cancer.

Finally, MR spettroscopy measures the concentration of metabolites in vivo, because different metabolites feature different resonance frequencies. (13)
In particular, increase in choline and decrease of citrate depicted by spectral peaks is caracteristic for prostate cancer. (14)

MRI-targeted biopsy (MRI-TB)

Without doubt it can be said that in recent years MRI has revolutionized the approach to prostate cancer, with visible improvements. The intrinsic ability of the method to study pelvic scenario and specifically the prostate gland are increasingly placing MRI as a choice for the entire medical team (urologists, oncolygies, diagnostic urological imaging experts, etc.) in the field of guided biopsy. (15)

Even today, TRUS-guided biopsy (TRUS-GB) is the investigation of choice for detection and localization of prostate cancer in most centers because of its relative simplicity, ergonomics, and cost-effectiveness of the procedure; however, we must not forget that it is weighed down by a series of important limitations in the choice of lesions to be analyzed.
This can only represent an ever-evolving challenge, in which a brilliant method such as MRI probably represents a future but very close improvement. (16)

The recent intuition about prostate biopsy concerns the inclusion of MRI images in procedures, this type of potential strategy has allowed the current evolution of some different techniques that make up the branch of MRI-targeted biopsy (MRI-TB). To date, the best performing ones are the "in-bore MRI-TB", the "cognitive targeted biopsy"

(COG-TB and the "fusion technique" (FUS-TB).

In the direct technique -"in gantry" or "in bore"- the patient assumes a prone position for the duration of the examination and the pelvis is first studied with an mpMRI (MRI-TB). Once highly suspicious lesions are identified, those same images are used as a guide for robotic biopsy.
It should be noted that this type of technique requires high specialization and training of operators, as well as high costs deriving from the used technologies. (17)

"Cognitive" and "fusion" tecniques represent an excellent approach to the problem of pathological localizations of prostate cancer, in the glandular scenario. Both are built on the basic idea of being able to use the advantages of both imaging methods mainly skilled in the field of prostate cancer localization: TRUS approach plus MRI approach.

COG-TB provides for the targeted and detailed study of prostatic architecture through an MRI acquisition. The topographical identification of the morphologically suspected areas for neoplasia will "cognitively" become the basic know-how for the operator who, in the light of this information, will use the TRUS to perform the targeted biopsies. (18)

In opposition to this process of "union of knowledge" by various methods that are purely human and referable to the operator, there is "fusion tecnique".
Thanks to a software, FUS-TB is able to implement this concept of simultaneous use of two methods, concretely merging the images obtained by MRI technique with the TRUS ones. The real combination of two methods enhances the goodness of the results.

It is clearly not a simple technique and the learning curve for experts is challenging.
In addition to the experience of the operators, complete technical reliability must be guaranteed, both in the quality of the images and above all in their co-registration. (19)
All this to allow accurate research of the areas of interest and correct sampling, to ensure the best possible biopsy analysis.

In conclusion, in men at risk for PCa with neoplastic suspicious lesions on MRI, an MRI guided biopsy strategy of these lesions demonstrates similar overall tumour detection rates compared with systematic TRUS-GB;
at the same time, PCa incidence is increased in targeted cores when compared with systematic cores.
Hence the message that comes out renard an increased sensitivity of MRI guided biopsy tecniques for the detection of clinically significant PCa (csPCa), and decreased for clinically insignificant PCa when compared with TRUS-GB.
In a 2017 meta-analysis, *Wegelin et al.* report an "in-bore" MRI-TB superior performance in overall PCa detection when compared with COG-TB.
For overall PCa detection and detection of csPCa, FUS-TB has a similar performance compared with MRI-TB. The current number of randomised controlled trials performing a head-to-head comparison of the various techniques for MRI-GB is limited and comparative analysis is restricted by the absence of data on lesion characteristics. (20)

In addition to describing the various methods that are increasingly being used in biopsy procedures, it should be noted that the techniques of aggression of the anatomical site of the lesion are also different; at least of two types:MRI-guided and transrectal ultrasound fusion transrectal biopsy (MRI-TRUSB) and MRI-guided and transrectal ultrasound fusion transperineal biopsy (MRI-TPB). (21)
At the moment there are not many studies aimed at specifically evaluating the superiority of one of the two approaches over the other; from the partial evidence we have available, the trans-peritoneal approach would seem preferable to the classical trans-rectal one.
In fact, there are fewer complications, in particular the infectious ones seem to be minimized; furthermore, from the data emerges a greater detection for csPCa and anterior tumors. (22)

The debate and the extension of the evidence on this topic are encouraged, however, and it will be necessary to wait for several new studies to have

more solid answers. Researchers and doctors are encouraged to take a pragmatic approach update databases and internal audits, comparing these data with current evidence.

NUCLEAR MEDICINE IMAGING

Nuclear medicine and molecular imaging are playing an increasingly important role in patient with prostate cancer. (23-26). Today, nuclear and molecular diagnostic imaging studies are available for virtually every major organ system in the body. (27-32) The number of nuclear medicine–based therapies for cancer and other disorders is also expanding. (33-34). Nuclear medicine imaging non-invasively provides functional information at the molecular and cellular level that contributes to the determination of health status by measuring the uptake and turnover of target-specific radiotracers in tissue. (35-36) Functional imaging proves its value in these therapeutic implications by providing information on the biologically active volume of the cancer. (37) The currently performed functional or metabolic imaging techniques for prostate cancer evaluations are radionuclide imaging techniques such as single photon emission computed tomography (SPECT) and positron emission tomography (PET) as well as magnetic resonance imaging (MRI) techniques that provide functional and metabolic information of the cancer. (38-42) More recently, a greater interest for both diagnostic and therapeutic purposes has been associated with radiotracers directed to prostate-specific membrane antigen (PSMA), a transmembrane protein expressed on the cell surface, which showed high selective expression in PCa, metastatic lymph nodes and bone metastases. Several PSMA-targeted PET tracers have been developed many of which showing promising results for accurate diagnosis and staging of primary PCa and re-staging after biochemical recurrence, even in case of low prostate specific antigen values. These advanced imaging modalities, combined with current imaging technologies, provide more direct means of being utilized in treatment planning than before. (43-45)

THERAPY

Prostate cancer therapy represents a complex world of options for physician and patients. The treatment strategy is strongly influenced by some factors, such as the extent, the aggressiveness of the disease and the patient's life expectancy. First of all, we can distinguish between a metastatic and a non-metastatic disease, with various therapeutic options attached. (46)

Non-metastatic prostate cancer is treated with surgery, brachytherapy, radiotherapy (XRT) and hormone therapy.
Radical prostatectomy (RP) includes removal of the prostate and seminal vesicles. Limphoadenectomy is added to RP when the risk of pelvic lymph node invasion exceeds 5%
Brachytherapy admit permanent implantation, via perineal route, of 125-I or 103-Pd sealed in titanium capsules; or through the temporary use of radioactive needles with high-dose-rate (HDR) technique.
Radiotherapy with external beam technique represents another therapeutic option for localized disease, nowadays, thanks to technological evolution, it is possible to administer higher doses of radiation than in the past, with less impact on the tissues surrounding the tumor silhouette.

For low-risk patients, it should be mentioned the possibility of an "active surveillance" which offers a waiting policy through close clinical and diagnostic monitoring. Repeated prostate biopsies, measurements of PSA serum levels, mpMRI if necessary, are the weapons available to implement this path.

Metastatic disease is divided into two large groups: hormone-sensible and non hormone-sensible.
The treatment of the first one is based on a pharmacological castration of the patient, by means of androgenic deprivation (ADT). Non hormone-sensitive disease escapes this line of therapy metastatic castration-resistant prostate cancer (mCRPC) is resistant to medical or surgical castration and has limited trearment options. These patients are often treated with chemotherapy, including docetaxel and postchemotherapy androgen deprivation therapy with abiraterone acetate and enzalutamide. (47-50)

It should be noted that bone tissue is often site of metastases (over 80% of cases) in CRPC and it is frequently cause of pain and pathological fractures.

In these cases, nuclear medicine provides some bone-targeting radionuclides, such as Ra-223 dichloride which appears to be able to prolong survival as well as improv patient's quality of life; 153-Sm-EDTMP and 89-Sr instead are used only for palliative purposes. (51)

Nuclear medicine always looks to the future and in addition these bone-targeted options, we must mention the emerging role of prostate-specific membrane antigen (PSMA) ligands, coupled with radionuclide, such as 177-Lutetium (177-LuPSMA), as a novel radionuclide therapy . (52)

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