

How to Connect Biomarkers with Imaging in Prostate Cancer?

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ABSTRACT

Due to the clinical heterogeneity of Prostate Cancer (PC) present in clinical practice, the analysis of the metabolic profile of PC samples could offer relevant information. Compared with genomics or proteomics, metabolomics better reflects changes in phenotype and functional aspects. Metabolomic studies can be related to imaging; in particular Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR) have evolved as the most common techniques.

A relevant advantage using radiomics and artificial intelligence algorithms is the possibility to limit the discrepancies between different readers. This advantage could be particularly relevant in the use of multiparametric Magnetic Resonance (mMR) that is considered as a reader-dependent technique in qualitative evaluation. The association of genomic alteration with Multiparametric Magnetic Resonance results are likely to have a prognostic significance in PC the differential expression of genomic markers in MR-detected and undetectable lesions have been evaluated, in particular the association of Multiparametric Magnetic Resonance evaluation with the PTEN expression.

Keywords: Prostate Cancer; Mass Spectrometry; Biomarkers; Artificial intelligence algorithms.

Abbreviations: PC: Prostate Cancer; MS: Mass Spectrometry; NMR: Nuclear Magnetic Resonance; mMR: multiparametric Magnetic Resonance; PSA: Prostate Specific Antigen; BPH: Benign Prostatic Hyperplasia; RP: Radical Prostatectomy; RT: Radiotherapy; Exos: Exosomes; NFC: Nanoscale Flowcytometry; AI: Artificial Intelligence; ML: Machine Learning

INTRODUCTION

Prostate Cancer (PC) is an extremely common neoplasm in male patients, able to vary from indolent to clinically significant diseases. A correct early diagnosis of Prostate Cancer should be able to avoid indolent neoplasms whereas to early detect clinically significant tumors. Prostate Specific Antigen (PSA) continues to represent the main marker for the early diagnosis of PC. It is not a PC specific marker but it can be influenced by several factors including Benign Prostatic Hyperplasia (BPH) and prostatic inflammation. Moreover, Prostate Specific Antigen is not able to selectively detect clinically significant PC and is mainly not influenced by the tumor aggressiveness.

The definition of the correct treatment for Prostate Cancer is obtained on the basis of risk classes determined by the

combination of clinical stage, Gleason score (or ISUP grading) and PSA value. Low risk PC can be managed using an active surveillance strategy, intermediate risk tumors are mainly submitted to Radical Prostatectomy (RP) or Radiotherapy (RT) and high-risk tumors are multimodally managed. A significant percentage of first diagnosis of PC are in a metastatic stage, situation that can be related to a high aggressiveness of the tumor and suitable for combined systemic strategies.

Inside imaging, the introduction of multiparametric Magnetic Resonance (mMR) changed the strategy paradigm for the early diagnosis of Prostate Cancer. Relevant multicenter studies demonstrated that a strategy including Multiparametric Magnetic Resonance and target biopsy is able to better discriminate in favor of clinically significant PC than the old strategy considering only PSA and random biopsies [1].

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The urgency to define alternative approaches for an early detection of Prostate Cancer, discriminative from several prostatic benign pathologies, as well as indolent tumors has become clear.

Due to the clinical heterogeneity of PC present in clinical practice, the analysis of the metabolic profile of PC samples could offer relevant information. Indolent PC cases with a ISUP grading 1 can display a low aggressiveness and low propensity for growth and progression; it is possible that these tumors are associated to a metabolic profile similar to that of BPH cases. On the contrary, clinically significant ISUP 3-5 PC cases, often show rapid growth and progression, probably associated to a different metabolic profile. The analysis of new biomarkers, enclosed in extracellular nano-vesicles released in the same bio-fluids (exosomes) rather than freely circulating, associated to the new imaging with multiparametric Magnetic Resonance, could better discriminate between clinically significant neoplasms and benign prostatic modifications.

METABOLOMIC

Metabolomics, including studies on the entire small metabolite composition of a biological system, is considered as the missing link between phenotype and genotype [2]. Compared with genomics or proteomics, metabolomics better reflects changes in phenotype and functional aspects. Metabolites can represent the final products of physiological processes and their comprehension may allow a correct knowledge of disease pathogenesis and choice of intervention. Clinically, the metabolic study can help in determining a better biomarker for early diagnosis but also a prognostic indicator in terms of aggressiveness and treatment response of Prostate Cancer.

Metabolomic studies can be related to imaging, in particular Mass Spectrometry (MS) and Nuclear Magnetic Resonance (NMR) have evolved as the most common techniques. NMR spectroscopy is a quantitative technique with high reproducibility, with an increasing value in terms of sensitivity [3]. Two different metabolomic approaches are commonly used, targeted and untargeted. Targeted metabolomics is directed on the quantification of selected metabolites, involved in a particular metabolic pathway that is considered related to PC (i.e. carnitine or arginine metabolism). The untargeted approaches represent the most appropriate method to detect unexpected changes in metabolite concentrations, analyzing hundreds to thousands of metabolites.

EXOSOMES

Exosomes (Exos) are a heterogeneous group of small membrane-limited extracellular vesicles (EVs) (40–180 nm in diameter) that are released from almost all cells, in both normal and pathological processes, and can be detected in all bio-fluids, including plasma and urine [4]. For this reason, Exos can be considered specific markers of specific cells including those in the prostate gland. Normal cells from several organs as well as cancerous cells, can secrete Exos extracellularly as mediators of cell-to-cell communications. In neoplastic diseases such as Prostate Cancer, Exos can be increasingly released in biofluids

and therefore used as specific biomarkers. To date, Nanoparticle Tracking Analysis (NTA), immune captured based technologies and Nanoscale Flowcytometry (NFC) represent new technologies to analyze EVs for clinical application.

Overall, data highlight the potential role of circulating Exo levels in monitoring cancer patients either for the early diagnosis or after surgical therapies and after/during medical treatments.

In a prospective clinical trial comparing PC patients with both BPH and healthy controls, levels of Exos expressing Prostate Specific Antigen were significantly higher in plasma of PC patients, showing a significantly higher sensitivity and specificity for Exo Prostate Specific Antigen, when compared to the standard serum PSA in terms of initial diagnosis of Prostate Cancer [5].

RADIOMICS

Radiomics is the extraction of the quantitative image analysis of features provided by imaging techniques (e.g., mMR) so to improve the analysis of large datasets through semi-automatic or automatic software. Radiomics in PC has been proposed either in terms of early diagnosis or prognostic evaluation of tumor aggressiveness distinguishing favorable from unfavorable diseases through the association with Artificial Intelligence (AI) and Machine Learning (ML) algorithms [6].

A relevant advantage using radiomics and AI algorithms is the possibility to limit the discrepancies between different readers. This advantage could be particularly relevant in the use of Multiparametric Magnetic Resonance that is considered as a reader-dependent technique in qualitative evaluation.

GENOMICS

Genomics can produce molecular characterization of Prostate Cancer improving early diagnosis and prognosis evaluation. The requirement of tissue samples through biopsy or after surgery, however, limits the clinical application [7]. The heterogeneity and multifocality of PC can reduce the relevance of samples obtained at biopsy. Moreover, PC can change during the follow-up and characteristics detected at the initial diagnosis could be not representative of the present status of a metastatic or castration resistant PC. Fluid biopsy analyzing circulating cells or circulating DNA may reduce this limit. Genomic biomarkers, validated as predictors of prognosis or oncological outcomes, are recurrently used in clinical practice, such as Oncotype Dx test[®], Prolaris test[®], and Decipher test[®].

RADIOGENOMIC

The association of genomic alteration with Multiparametric Magnetic Resonance results are likely to have a prognostic significance [8]. Radiogenomics has been studied in PC investigating between quantitative imaging data and single gene expression in PC the differential expression of genomic markers in MR-detected and undetectable lesions have been evaluated, in particular the association of Multiparametric Magnetic Resonance evaluation with the PTEN expression. A significantly lower ADC was found for tumors with low PTEN expression,

both negatively correlated with Gleason score, tumor size and lymph node involvement [9].

Radiogenomic is a new section with still a low number of publication and prospective clinical trial. It can be limited by the complexity of studies and statistical evaluation but the future of radiogenomics could be its integration into everyday clinical practice through the access to large public databases of imaging and genome data. At this point, radiogenomics is an experimental field that studies the correlation between image phenotypes and genomics inside a tumor.

CONCLUSION

The biomarker field in Prostate Cancer is in continuous growth with numerous novel tests, different biomaterial sources, improved analytical measurements, and statistical processing. However, only a few of them have been approved and used in clinical practice. The combination of multiparametric Magnetic Resonance with biomarkers obtained from genomics or metabolomics would be of particular value either in the early diagnosis or in the determination of a prognostic profile of patients with Prostate Cancer.

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