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Current status and new approaches in prostate cancer diagnosis

Abstract

Prostate adenocarcinoma, remaining among top most common cancers, is a heterogeneous group of tumors with a diverse morphological structure. Basing on the histological architecture of cancer tissue, individual cases can be classified into different therapeutic groups. Current diagnosis of prostate cancer brings many challenges. The major problem is the lack of effective and accessible diagnostic methods that would eliminate incidences of overdiagnosis and prevent unnecessary treatments of many patients. There are many efforts to determine favorable and unfavorable molecular prognostic factors. The basic marker currently used in this field is prostate-specific antigen (PSA). Increased level of PSA may suggest the presence of prostate cancer although its level is not specific for the disease and can be elevated also in certain benign hyperplastic or inflammatory conditions as well as after irritation or rectal examination. Clinical symptoms such as dysuria or hematuria are often uncharacteristic and benign prostatic diseases which cannot be confirmed on the basis of physical examination alone. Also, we often deal with the situation of false negative results of prostate needle biopsy, which require many tests to determine the final correct diagnosis. Moreover, prostate cancer can also be present in patients with non- elevated serum PSA level. Due to such difficulties, the search for new molecular markers that could be used for diagnostic purposes is underway. Evaluation of survivin level in prostate cancer tissue may serve as a new diagnostic indicator of prostate cancer progression. Other useful molecular biomarkers with good potential in prostate cancer diagnosis are AMACR (Alpha Methyl Acyl Coenzyme A Racemase), p-63 or Ki-67 or microRNAs present in body fluids.

Keywords: prostate cancer, prostate-specific antigen, new diagnostic methods, survivin.

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INTRODUCTION

Prostate cancer is the second most common cancer in Poland and the third cause of death due to cancer [1]. It affects mostly men over 65 years of age, although patients under 50 can also be affected.

Already in 1855 an article by the surgeon J. Adams was published in the medical literature describing the histopathological structure of prostate cancer. Interestingly, the author described prostate cancer as a very rare disease [2].

Currently, over 192.000 new cancer cases are recorded every year in the United States and more than 27.000 patients die from prostate cancer. In Poland, the incidence of prostate cancer is slightly above 76 per 100.000 persons and mortality is 26 per 100.000 persons. Unfortunately, in the last decades, a constant increase in morbidity and mortality due to prostate cancer has been observed and it is assumed that these numbers will grow.

Initially – in its early stages – prostate cancer develops without any symptoms. At the moment when the patient decides to seek medical help, the progression of the disease is already advanced- most often the doctors deal with the infiltration of surrounding tissues, spread of cancer along nerve trunks and bone metastases.

There are a few important risk factors that must be taken into consideration when discussing prostate cancer development. Among them, patient's age, considering its significant correlation with the cancer rates, higher than in many other cancers. The genetic background also plays an important role and increased incidence in patients with affected relatives can often be observed. Environmental risk factors include: smoking, alcohol consumption, occupational factors, exposure to cadmium, infectious agents, UV and ionizing radiation, physical activity level and diet. It is also well-established that altered hormone metabolism plays an important role in progression of prostate cancer. Elevated levels of serum prostate hormones correlate with increased risk of prostate cancer development.

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Differences in morbidity and mortality due to prostate cancer can be observed depending on the region of residence: in the United States, Australia and the Scandinavian countries, there is a high incidence. In turn, in the countries of North Africa and Asia – it is relatively low. This tendency appears to be related to the specific risk levels of certain regions and migration from low-risk (Asia) to high-risk area (e.g. the United States) can significantly increase prostate cancer incidence in migrating populations [3,4].

One of the most significant problems of modern diagnostics of prostate cancer is to provide a method that allows detecting malignant, rapidly developing and requiring aggressive, expensive treatment neoplasms, and distinguishing them from latent forms that may remain only under observation.

Screening for prostate cancer

Prostate cancer is a major healthcare problem, especially in the developed countries. Therefore, its early detection and characterization is a very important task. There are many international attempts to improve the overall outcome of the disease. The methods used in screening procedures are standards in prostate cancer diagnosis: PSA (prostate-specific antigen) level measurements, digital rectum examination and transrectal ultrasound [5].

The ERSPC trial (European Randomized Study of Screening for Prostate Cancer – the largest randomized trial of screening for prostate cancer) has demonstrated significant improvement in 9-year and 11-year follow up of the trial manifested by the reductions in prostate cancer mortality [6]. Since the introduction of PSA screening, in the United States alone there have been over a million positive results of prostate cancer.

However, there is also the other side of the coin. The further analysis of the problem suggests the risk of excessive detection of the prostate cancer. In many cases, tumors detected in screening develop so slowly that they remain clinically unreliable even for the whole course of the observation. Moreover, PSA evaluation does not bring the assessment of the character of the disease [7].

Anatomy and histology of prostate gland

The prostate gland, a structure located underneath the bladder can be anatomically divided into two lobes (right and left) and isthmus connecting them. In each of both lobes the following zones can be distinguished: the urethral part surrounding prostatic part of the urethra, the periarticular zone, the posterior transitional zone, the central zone and the peripheral zone.

Histologically, prostate is a conglomerate of 30-50 complex, tubuloalveolar exocrine glands formed into 3 layers: peri-urethral layer of mucosal glands, submucosal layer and a layer of the main glands forming a stem. The main glands – the biggest and the most numerous in prostate – produce prostatic secretion, one of major components of the sperm (30% of total volume), composed of simple sugars, lipids, acid phosphates, proteolytic enzymes, fibrinolysin and citric acid and is slightly alkaline.

The synthesis and release of prostatic secretion remains under hormonal regulation, maintained mainly by the active form of testosterone-dihydrotestosterone.

Prostatic neoplasm

Long-lasting, extensive androgen stimulation of both glandular and stromal component of the prostate plays a significant role in development of benign prostatic hyperplasia, especially common in men over 40. Almost all of the malignant prostate tumors are classified as adenocarcinomas and they are derived from epithelial cells of the prostate gland.

Among other rare malignant tumors of the prostate gland there are: sarcoma, neuroendocrine carcinoma, small cell carcinoma and urothelial carcinoma, originating from the epithelium of urethra.

In this paper, we provide an outline of the key aspects of prostate cancer diagnosis. Our paper is of a review nature, based on Polish and English literature as well as the experience in clinical practice. We have discussed commonly used conventional diagnostic methods and controversies of their efficacy. We have also presented a few modern approaches with a potential for wider application in clinical practice.

Currently used diagnostic methods in detection and characterization of prostate cancer

The early diagnosis of prostatic tumors and application of properly adjusted treatment are fundamental.

Clinical diagnosis

There are several clinical methods used in basic diagnosis of the prostate cancer. Among them:

DRE (digital rectum exam) – is a manual examination, performing in order to detect bulges and areas of changed consistency, palpable under the finger placed inside the rectum.

TRUS (transrectal ultrasound) – procedure that utilizes ultrasound where the USG transducer is inserted into the rectum – allows relatively accurate assessment of gland's size, its echogenicity and the presence of focal lesions.

In cases when TRUS is insufficient, we can use an additional technique called Color-Doppler ultrasound, which allows the assessment of vascularization level in area of interest.

A targeted biopsy under the control of TRUS or TRUS/MRI (Magnetic Resonance Imaging) is one of the standard diagnostic procedures currently performed worldwide.

PET (Positron emission tomography)- based on the use of radioactive specimen – it allows the determination of cancer spreading, the presence of metastases in various parts of the body, as well as the assessment of the effectiveness of the treatment [8].

Laboratory diagnosis

PSA (prostate-specific antigen)

The basic marker used in the diagnosis of hypertrophy and prostate cancer and monitoring the course of treatment is prostate-specific antigen (PSA), which level is determined in serum. PSA is a protein synthesized and secreted by epithelial cells of prostatic glandular lobules. In normal conditions, serum level of PSA should be lower than 4ng / ml. The increase in its secretion to serum can occur when the prostate cancer infiltrates and destroys the basal membrane of glandular lobules.

Although the PSA level is highly correlated with the presence of prostate cancer, it is now known that despite low levels of PSA, the prostatic cancer may be found in patient. The value of PSA can also be elevated in certain benign hyperplastic and inflammatory conditions and may remain high for many weeks after the DRE [9]. For such cases few modifications of plasma PSA level have been proposed including PSA density, PSA density of the transition zone, age-specific reference ranges or PSA molecular forms [10].

Histopathological diagnosis

The final diagnosis of prostate cancer is based on histopathological criteria. The three main histopathological criteria for the diagnosis of prostate cancer are: infiltrating character, presence of nucleoli in the cell nucleus and lack of basal layer cells.

In addition to the above, there are several other pathognomonic features of prostate cancer: perineural and intraneural infiltration, periglandular adipose tissue infiltration, presence of so-called "pathological" secretion inside the lumen of glandular structures of the tumor.

Gleason grading system

The system commonly used in histological assessment of prostate cancer malignancy is the Gleason scale (Gleason grading system), based on the morphological structure of the tumor.

- We use 5 stages of the histopathological diversity:
- Gleason I – cancer with predomination of glands equal in shape and size, having a clear duct lumen, so-called 'pushing-borders'.
- Gleason II – glandular ducts more diverse in size and shape, interglandular connective tissue more abundant, blurred boundaries.
- Gleason III – the shape and size of the gland ducts are even more diverse, numerous, single ducts separated from the others, the boundaries of infiltrated area is irregular, but still remains within the specified, visible borders.
- Gleason IV – the glands often confluent, cancerous epithelium forms cribriform and papillar structures, borders infiltrating with the presence of nest structures, lack of glandular lumen.
- Gleason V – bands and nests of individual cells without the formation of glandular structures, also a type of comedocarcinoma - papillar or cribriform structure with pronounced necrosis in the center.

The application of the Gleason score system is based on the Gleason sum from patterns of the two most-occurring fields with a specific differentiation level.

The use of the Gleason scale allows to determine the presumed further course of the disease, and thus – further treatment of the patient.

Immunohistochemical analysis

Ambiguous cases, where the diagnostic consensus cannot be achieved, require additional methods. Most often, we use immunohistochemical staining with the use of specific antibodies: anti-AMACR and anti-p-63 for the determination of basal layer cells or anti- Ki-67 which is a cell proliferation marker [11].

- **AMACR** – Alpha Methyl Acyl Coenzyme A Racemase – a mitochondrial and peroxisomal enzyme involved in beta-oxidation of branched chain fatty acids, currently widely used in the diagnosis of prostate cancer. The peripheral luminal overexpression of staining, characteristic of prostate cancer, may not, however, occur in some forms. It these cases the result indicates a false-negative AMACR reactivity. In about 60 cases, we can also encounter HGPIN (high-grade Prostatic Intraepithelial Neoplasia) result- a false-positive AMACR immunoreactivity.
- **p-63** belongs to the basal cell layer markers group, similarly as HMCK (high molecular weight cytokeratin-34betaE12) and CK 5/6-. For the diagnosis of prostate cancer, it is necessary to confirm the absence of these markers in the field of view.
- **Ki-67** (Marker of cell proliferation). One of the other prostate cancer indicators is Ki-67 protein, a cellular marker of proliferation, which, as in other malignant tumors, may be a good prognostic factor [12]. Easily detected by immunohistochemistry, can help in distinction between aggressive and indolent prostate cancer.

In modern cancer diagnosis the critical point is to evaluate the severity and to separate the low-risk form aggressive and live-threatening cancers. Many efforts are focused on finding new non-invasive diagnostic methods like determination of additional serum markers (e.g. Kallikrein) and urinary markers (such as PCA3 [prostate cancer antigen 3] or TMPRSS-ERG fusions- one of most common transolations for many malignancy – 50% sensitive and highly specific for prostate carcinoma) [13].

MicroRNA

New approaches in the field of enhancing prostate cancer diagnosis include precise investigation on molecular level. Studies are focused on searching for specific patterns that could help to characterize the molecular profile of cancer and improve the course of further diagnosis.

The importance of circulating microRNAs present in body fluids has been lately discovered. Isolated from both plasma and serum extracellular miRNAs can be found in healthy persons, but also in patients suffering from many types of diseases including cancer and they appear to have a strong connection with classification, diagnosis and the progression of the disease. MiR-141 has been found specifically in serum of prostate cancer patients and is now considered to have a great potential to serve as a novel diagnostic marker [14].

Survivin

Survivin (baculoviral inhibitor of apoptosis repeat-containing 5 or BIRC5) a member of IAP (inhibitors of apoptosis) group in the human body functions as a factor counteracting caspase activation and in that manner, acts as a negative apoptotic regulation agent.

Undoubtedly, the programmed cell death plays a crucial role during tissue development and differentiation processes but also in maintaining homeostasis of terminally differentiated tissues. Dysfunction in apoptotic pathways may lead to serious abnormalities such as tumor development. It is very important to differentiate and characterize such abnormal tissues.

It has been noticed that greater expression of survivin is observed in the cells of proliferative and dysplastic lesions, as is the case of the prostate gland (PIN high-grade).

The specific localization of survivin, correlated with the cell cycle phase, may also provide information of the cancer cell cycle stadium.

Nowadays, great efforts are concentrated on proper differentiation between normal and altered, pathological levels of cell sustenance mediators, e.g. growth factors.

As it was shown by Ambrosini et al., mRNA of survivin gene is present at high level in fetal tissue but undetectable in normal, mature tissues, except placenta and thymus, thus it

was reported that, survivin is prominently expressed in many human cancers such as lung, colon, pancreas, prostate and breast cancer [15].

To date survivin has been considered as a specific prognostic tumor marker in colorectal, gastric, bladder cancer. Okada et al. reported significant difference in survivin levels in cytoplasm and nuclei of gastric cancer cells which, in correlation with vascularization levels measurements and histological staining analysis, suggested prognostic potential[16].

Immunohistological analysis of prostatectomy specimens showed that prostate carcinoma is characterized by about two times higher survivin expression than normal prostate specimens. Moreover, it appeared to be correlated with higher final Gleason sum, further cancer-associated alterations such as in TGF-β pathway (significant in proliferation and apoptosis) and with overall increased risk of biochemical progression [17].

Survivin can play an important role in novel combined therapies. A small-molecule survivin suppressant has been successfully applied on tumor xenografts in experimental studies of HRPC (hormone-refractory prostate cancer) in which androgen deprivation therapy eventually fails in most patients [18].

CONCLUSION

Thanks to effective prevention and screening programs, there has been a significant improvement in the detection and treatment of prostate cancer in recent years.

However, there is still a lot of controversy about the effectiveness of prostate cancer therapies and, above all, about the need for radical treatment, due to the low correlation between morphological evaluation of the tumor and its biological course.

There is a great need to review and update the main diagnostic methods, since some of them have evolved and improved over the past few decades. There is also a great effort in searching for new approaches which could be introduced to practice in the near future complementing the gold standard techniques.

On the basis of the histopathological analysis, we cannot unequivocally assess which forms are of aggressive and rapid course and which would rather be indolent, with no particular clinical significance. This assessment is particularly difficult when the diagnostic material is fragmentary, often containing only small areas of histological structure of the cancer.

Perhaps the hope would be in the assessment of the survivin – its molecular level or intensity of the histological staining.

Survivin is a protein that can be found in cancer cells, in cells of the adult organism it is usually found in trace amounts. Perhaps demonstrating its presence in the cancer cells could allow us to assess the potential increased malignancy of the tumor.

It was noted that the higher expression of survivin can be observed in the cells of proliferative and dysplastic lesions, as it occurs in the prostate gland (PIN high-grade).

The location of survivin in a cell, depending on the phase of the cell cycle, can also provide some information – e.g. how many cells are in a given phase of the cycle.

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